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Pharmacological interventions versus placebo, no treatment or usual care for osteoporosis in people with chronic kidney disease stages 3-5D (Review)

Hara T, Hijikata Y, Matsubara Y, Watanabe N

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[Intervention Review]

Pharmacological interventions versus placebo, no treatment or usual care for osteoporosis in people with chronic kidney disease stages 3-5D

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ABSTRACT

Background

Chronic kidney disease (CKD) is an independent risk factor for osteoporosis and is more prevalent among people with CKD than among people who do not have CKD. Although several drugs have been used to effectively treat osteoporosis in the general population, it is unclear whether they are also effective and safe for people with CKD, who have altered systemic mineral and bone metabolism.

Objectives

To assess the efficacy and safety of pharmacological interventions for osteoporosis in patients with CKD stages 3-5, and those undergoing dialysis (5D).

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 25 January 2021 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials comparing any anti-osteoporotic drugs with a placebo, no treatment or usual care in patients with osteoporosis and CKD stages 3 to 5D were included.

Data collection and analysis

Two review authors independently selected studies, assessed their quality using the risk of bias tool, and extracted data. The main outcomes were the incidence of fracture at any sites; mean change in the bone mineral density (BMD; measured using dual-energy radiographic absorptiometry (DXA)) of the femoral neck, total hip, lumbar spine, and distal radius; death from all causes; incidence of adverse events; and quality of life (QoL). Summary estimates of effect were obtained using a random-effects model, and results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) for continuous outcomes. Confidence in the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

Seven studies involving 9164 randomised participants with osteoporosis and CKD stages 3 to 5D met the inclusion criteria; all participants were postmenopausal women. Five studies included patients with CKD stages 3-4, and two studies included patients with CKD stages 5 or 5D. Five pharmacological interventions were identified (abaloparatide, alendronate, denosumab, raloxifene, and teriparatide). All studies were judged to be at an overall high risk of bias.

Among patients with CKD stages 3-4, anti-osteoporotic drugs may reduce the risk of vertebral fracture (RR 0.52, 95% CI 0.39 to 0.69; low certainty evidence). Anti-osteoporotic drugs probably makes little or no difference to the risk of clinical fracture (RR 0.91, 95% CI 0.79 to 1.05; moderate certainty evidence) and adverse events (RR 0.99, 95% CI 0.98 to 1.00; moderate certainty evidence). We were unable to incorporate studies into the meta-analyses for BMD at the femoral neck, lumbar spine and total hip as they only reported the percentage change in the BMD in the intervention group.

Among patients with severe CKD stages 5 or 5D, it is uncertain whether anti-osteoporotic drug reduces the risk of clinical fracture (RR 0.33, 95% CI 0.01 to 7.87; very low certainty evidence). It is uncertain whether anti-osteoporotic drug improves the BMD at the femoral neck because the certainty of this evidence is very low (MD 0.01, 95% CI 0.00 to 0.02). Anti-osteoporotic drug may slightly improve the BMD at the lumbar spine (MD 0.03, 95% CI 0.03 to 0.04, low certainty evidence). No adverse events were reported in the included studies. It is uncertain whether anti-osteoporotic drug reduces the risk of death (RR 1.00, 95% CI 0.22 to 4.56; very low certainty evidence).

Authors' conclusions

Among patients with CKD stages 3-4, anti-osteoporotic drugs may reduce the risk of vertebral fracture in low certainty evidence. Anti-osteoporotic drugs make little or no difference to the risk of clinical fracture and adverse events in moderate certainty evidence. Among patients with CKD stages 5 and 5D, it is uncertain whether anti-osteoporotic drug reduces the risk of clinical fracture and death because the certainty of this evidence is very low. Anti-osteoporotic drug may slightly improve the BMD at the lumbar spine in low certainty evidence. It is uncertain whether anti-osteoporotic drug improves the BMD at the femoral neck because the certainty of this evidence is very low. Larger studies including men, paediatric patients or individuals with unstable CKD-mineral and bone disorder are required to assess the effect of each anti-osteoporotic drug at each stage of CKD.

PLAIN LANGUAGE SUMMARY

Pharmacological treatments for osteoporosis in patients with chronic kidney disease

What is the issue?
Patients with chronic kidney disease (CKD) have an increased risk of osteoporosis (weakened bone strength), which can often lead to bone fracture. Several drugs are available for the treatment of osteoporosis; however, it is unknown whether these drugs are equally effective and safe in patients with CKD because bone strength impairment in these patients occurs via a different mechanism.

What did we do?
Data were collected from studies including patients with osteoporosis and CKD stages 3-5, and those undergoing dialysis (stage 5D) with data available on fracture, change in the bone mineral density (BMD; a bone strength index), and adverse events. We included seven studies with available evidence up to 25 January 2021, comparing anti-osteoporotic drugs (abaloparatide, alendronate, denosumab, raloxifene, and teriparatide) with placebo (a dummy drug), in 9,164 postmenopausal women. We performed a meta-analysis to assess the effects of these anti-osteoporotic drugs.

What did we find?
In postmenopausal women with CKD stages 3-4, anti-osteoporotic drugs may reduce vertebral fracture in low certainty evidence. Anti-osteoporotic drugs probably make little or no difference to clinical fracture and adverse events in moderate certainty evidence. In postmenopausal with CKD stages 5 or 5D, it is uncertain whether anti-osteoporotic drug reduces the risk of clinical fracture and death, and anti-osteoporotic drug may slightly improve BMD at the lumbar spine in low certainty evidence. It is uncertain whether anti-osteoporotic drug improve BMD at the femoral neck.

Conclusions
Among postmenopausal women with CKD stages 3-4, anti-osteoporotic drugs may reduce the risk of vertebral fracture. Among patients with CKD stages 5 and 5D, anti-osteoporotic drug may slightly improve bone strength. However, these conclusions are based on limited data and therefore uncertain.

SUMMARY OF FINDINGS

Summary of findings 1. Any anti-osteoporotic drugs versus placebo in postmenopausal women with osteoporosis and CKD stages 3-4

Any anti-osteoporotic drugs versus placebo in postmenopausal women**with osteoporosis and CKD stages 3-4**

Patient or population: postmenopausal women with osteoporosis and CKD stages 3-4

Settings: multinational; outpatients

Intervention: any anti-osteoporotic drugs (abaloparatide, alendronate, denosumab, raloxifene, teriparatide)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Any anti-osteoporotic drugs			
Vertebral fracture by radiography Follow up: range 19 to 54 months	73 per 1000	38 per 1000 (28 to 50)	RR 0.52 (0.39 to 0.69)	9,054 (5)	⊕⊕⊖⊖ **low** [1, 2]
Clinical fracture Follow up: range 24 to 54 months	54 per 1000	49 per 1000 (43 to 57)	RR 0.91 (0.79 to 1.05)	5,827 (4)	⊕⊕⊕⊖ **moderate** [1]
Mean change in BMD of the femoral neck Follow up: range 19 to 54 months	Included studies only reported the percentage change in the BMD in the intervention group. In the three studies the mean change in BMD of the femoral neck was reported to improve by approximately 0.5% to 5% in the intervention group.		-	6,081 (3)	⊕⊖⊖⊖ **very low** [1,3,4]
Mean change in BMD of the lumbar spine Follow up: range 19 to 54 months	Included studies only reported the percentage change in the BMD in the intervention group. In the five studies the mean change in BMD of the lumbar spine was reported to improve by approximately 1% to 15% in the intervention group.		-	9,054 (5)	⊕⊖⊖⊖ **very low** [1,3,4]
Mean change in BMD of the total hip	Included studies only reported the percentage change in the BMD in the intervention group. In the three studies the mean change in BMD		-	3,998 (3)	⊕⊖⊖⊖ **very low** [1,3,4]

Follow up: range 19 to 54 months	of the total hip was reported to improve by approximately 5% to 6% in the intervention group.				
Mean change in BMD of the distal radius	Not reported		-	-	-
Adverse events Follow up: range 19 to 54 months	946 per 1000	937 per 1000 (927 to 946)	RR 0.99 (0.98 to 1.00)	9,054 (5)	⊕⊕⊕⊖ **moderate** [1]
Death Follow up: range 36 to 54 months	Included studies only reported total death. Death ranged from 0.7% to 1.6%		Not estimable	4,973 (2)	⊕⊕⊖⊖ **low** [1, 3]
QoL	Not reported		-	-	-

*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% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CKD: chronic kidney disease; **CI:** Confidence interval; **RR:** Risk Ratio; **BMD:** bone mineral density; **QoL**: quality of life

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] Downgraded one level due to a serious risk of bias: all studies had a high overall risk of bias
[2] Downgraded one level due to inconsistency: there was substantial heterogeneity
[3]Downgraded one level due to a publication bias: there were high risk of reporting bias
[4]Downgraded one level due to indirectness: surrogate endpoint was evaluated

Summary of findings 2. Raloxifene versus placebo for postmenopausal women with osteoporosis and CKD stages 5 and 5D

Raloxifene versus placebo for postmenopausal women with osteoporosis and CKD stages 5 and 5D

Patient or population: postmenopausal women with osteoporosis and CKD stages 5 and 5D

Settings: Iran, Venezuela; in- and outpatients

Intervention: any anti-osteoporotic drugs (raloxifene)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Raloxifene			
Vertebral fracture by radiography	Not reported		-	-	-
Clinical fracture Follow up: 8 months	33 per 1000	11 per 1000 (0 to 260)	RR 0.33 (0.01 to 7.87)	60 (1)	⊕⊖⊖⊖ **very low** [1, 2]
Mean change in BMD of the femoral neck Follow up: range 8 to 12 months	The mean change in BMD of the femoral neck was 0.01 g/cm² higher with raloxifene than placebo (95% CI 0.00 to 0.02) (mean change in BMD of the femoral neck in placebo group was -0.009 to -0.002 g/cm²)		MD 0.01 (0.00 to 0.02)	110 (2)	⊕⊖⊖⊖ **very low** [1, 3, 4]
Mean change in BMD of the lumbar spine Follow up: range 8 to 12 months	The mean change in BMD of the lumbar spine was 0.03 g/cm² higher with raloxifene than placebo (95% CI 0.03 to 0.04) (mean change BMD of the lumbar in placebo group was -0.019 to -0.003 g/cm²)		MD 0.03 (0.03 to 0.04)	110 (2)	⊕⊕⊖⊖ **low** [1, 4]
Mean change in BMD of the total hip	Not reported		-	-	-
Mean change in BMD of the distal radius	Not reported		-	-	-
Adverse events Follow up: range 8 to 12 months	No adverse events were observed in the included studies		Not estimable	110 (2)	⊕⊖⊖⊖ **very low** [1, 2]
Death Follow up: range 8 to 12 months	50 per 1000	50 per 1000 (11 to 228)	RR 1.00 (0.22 - 4.56)	110 (2)	⊕⊖⊖⊖ **very low** [1, 2]
QoL	Not reported		-	-	-

*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% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CKD: chronic kidney disease; **CI:** Confidence interval; **RR:** Risk Ratio; **MD:** Mean Difference; **BMD:** bone mineral density; **QoL:** quality of life

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.

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[1]Downgraded one level due to a serious risk of bias: all studies had a high overall risk of bias
[2]Downgraded two levels due to serious imprecision: there were very few/no events and the CIs encompass both considerable benefit and considerable harm
[3]Downgraded one level due to inconsistency: there was considerable heterogeneity
[4]Downgraded one level due to indirectness: surrogate endpoint was evaluated

BACKGROUND

Description of the condition

The World Health Organization (WHO) defines osteoporosis as 'a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk' (WHO 1994). Thereafter, the National Institutes of Health (NIH) defines osteoporosis mechanistically as 'a skeletal disorder characterised by compromised bone strength predisposing to a higher risk of fracture. Bone strength reflects the integration of two main features: bone quantity and bone quality' (NIH 2001). The clinical diagnosis of osteoporosis is broadly based on bone mineral density (BMD) measurements. BMD is converted into a T-score, which indicates the number of standard deviations (SDs) above or below the mean BMD for young adults. Osteoporosis is diagnosed when the T-scores are < -2.5 SD (WHO 1994). Osteoporosis dose not manifest clinically manifestations until a fracture develops. These osteoporotic fractures are a global healthcare burden. An estimated 9.0 million osteoporotic fractures were reported worldwide in 2000 (Johnell 2006), with an estimated annual cost of 19 billion USD in the USA (Burge 2007) and 1.8 billion GBP in the UK (Burge 2001). The ability to perform activities of daily living deteriorates after a fracture, along with the quality of life (QoL). Furthermore, morbidity and death are markedly increased in patients following a major bone fracture (Browner 1996; Keene 1993). Therefore, preventive interventions are therefore needed to reduce or prevent fractures in patients with osteoporosis. Current national osteoporosis guidelines recommend pharmacological interventions with anti-osteoporotic drugs in addition to non-pharmacological interventions that include modifying nutrition, ceasing smoking, performing weight-bearing exercises, and moderating alcohol intake (Eastell 2019; Kanis 2019; Naranjo Hernandez 2018; NOGG 2017; Qaseem 2017).

The number of patients with chronic kidney disease (CKD) is increasing. In 2015, CKD was ranked the 10th most common cause of death globally, with an age-standardised annual death rate of 19.2 per 100,000 of the population (GBD 2016). Thus, CKD is a major healthcare problem. Osteoporosis is an important comorbidity in patients with CKD. The National Health and Nutrition Examination Survey indicated that osteoporosis is two times more common in patients with moderate-to-severe CKD than in the general population (Nickolas 2006). Furthermore, the prevalence of osteopenia in patients undergoing dialysis is up to 20% in skeletal structures clinically associated with fracture (Stein 1996). Fractures have been reported to occur 2 to 100 times more frequently in patients with CKD than in age-matched individuals without CKD (Alem 2000; Nickolas 2006). Patients with CKD who have fractures also develop other serious problems. Major bone fractures are associated with high rates of hospitalisation and death (Kim 2016; Tentori 2013). Healthcare–associated costs after fractures exceeded $600 million in 2010 in the USA (Kim 2016).

Conditions associated with CKD make the diagnosis and treatment of osteoporosis difficult (Cunningham 2004). Impairment of skeletal strength in patients with CKD occurs via a different mechanism. Kidney Disease: Improving Global Outcomes (KDIGO) defines CKD-mineral and bone disorder (MBD) as a systemic condition of mineral and bone metabolism resulting from CKD (KDIGO 2009). The disorder is characterised by the following: 1) abnormalities in calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism; 2) bone turnover, mineralization, volume linear growth, or strength abnormalities; or 3) vascular or another soft-tissue calcification (KDIGO 2009). The initial onset of CKD-MBD occurs in early-stage CKD (Levin 2007). Bone disorder caused by CKD-MBD is termed renal osteodystrophy (ROD); it is a form of osteoporosis and a complex heterogeneous disorder of bone quality and density. ROD is traditionally classified as follows: hyperparathyroid bone disease, mild hyperparathyroid bone disease, mixed osteodystrophy, low turnover/adynamic bone disease, and osteomalacia (Llach 2000). Although bone biopsy is the gold standard diagnostic tool of ROD, access is limited, and it is not suitable for repeated evaluations. Alternatively, bone turnover markers such as intact PTH and alkaline phosphatase, are used clinically by nephrologists; however, their predictive values for bone turnover is limited (Khairallah 2018a; Sprague 2016). The state of bone turnover should be evaluated when an anti-osteoporotic drug is used, because drug use may lead to adynamic bone disease in patients with CKD (Amerling 2010). A single cross-sectional study of 13 patients with CKD stages 2-4 suggested that the use of bisphosphonates was associated with adynamic bone disease in these patients (Amerling 2010). Although that study did not demonstrate that bisphosphonates caused adynamic bone disease, no large-scale clinical safety data are available for patients with moderate-to-severe CKD treated with bisphosphonates. In addition, the key drug used in patients with osteoporosis is contraindicated for those with severe CKD (Nitta 2017). Based on this, the CKD-MBD KDIGO guidelines were revised in 2017 to recommend the use of BMD measurements to assess fracture risk. In addition, they emphasised the importance of managing CKD-MBD by controlling of vitamin D deficiency, hyperphosphataemia, and hyperparathyroidism before initiating anti-osteoporotic drugs for CKD-associated osteoporosis (KDIGO 2017).

Description of the intervention

A number of agents are effective for the treatment of osteoporosis in the general population, including bisphosphonates, denosumab, selective oestrogen receptor modulators (SERMs), and teriparatide (Crandall 2014). In addition, abaloparatide and romosozumab, which have been recently introduced, and strontium ranelate are used to treat osteoporosis (Reginster 2019).

Bisphosphonates

Bisphosphonates are analogues of inorganic pyrophosphates that inhibit osteoclast function. They are typically administered orally in pill form, although intravenous (IV) bisphosphonates are also available. Oral regimes involve daily or weekly administration, whereas IV bisphosphonates are administered monthly or yearly. The first-line treatment for osteoporosis is usually bisphosphonates when pharmacological intervention is recommended. However, the use of bisphosphonates may lead to bisphosphonate-related osteonecrosis of the jaw (Ruggiero 2004) and atypical femoral fracture (Donnelly 2012). In addition, oral bisphosphonates may cause erosive oesophagitis when patients fail to maintain an upright posture for approximately 30 minutes after taking the medicine with a glass of water (De Groen 1996).

Denosumab

Denosumab is a fully humanised monoclonal antibody specific to the receptor activator of nuclear factor kappa B ligand (RANKL), which mainly regulates osteoclasts. The recommended dosage of denosumab is 60 mg administered by subcutaneous(SC)

injection by every 6 months (Bone 2008). The discontinuation of denosumab may lead to a rebound in bone turnover and rapid BMD loss and increased risk of fracture (Miller 2008). This is an important difference from bisphosphonates. Conversely, treatment adherence and patient preferences may be better with denosumab than with bisphosphonates (Eliasaf 2016; Morizio 2018). Major adverse effects associated with denosumab include cellulitis, urinary tract infections, hypocalcaemia, osteonecrosis of the jaw, and atypical femoral fracture. Denosumab does not depend on kidney clearance for its metabolism and excretion. However, the low kidney function is associated with more frequent hypocalcaemia (Block 2012; Dave 2015).

selective oestrogen receptor modulators (SERMs)

SERMs (bazedoxifene, raloxifene) are synthetic non-steroidal compounds that interact with oestrogen receptors. Differing from oestrogen, these medicines act as either receptor agonists or antagonists in the target sites. They are associated with a lower cancer risk than oestrogen, and they have beneficial effects on the bone. SERMs have been shown to reduce the risk of only vertebral fractures (Crandall 2014). They are typically administered orally in pill form once a day. Serious adverse effects associated with SERMs include deep venous thrombosis (DVT), pulmonary embolism, and stroke (Adomaityte 2008; Barrett-Connor 2006).

Teriparatide

Teriparatide is a recombinant human PTH (1-34). It is administered by SC injection, either daily or weekly. PTH generally stimulates osteoclast activity to release more ionic calcium into the blood, subsequently elevating the serum calcium levels. Teriparatide has anabolic effects on the skeleton, with the most pronounced effects on cancellous bone. The adverse effects include temporary elevation of the serum calcium levels, postural hypotension, dizziness, headache, and nausea (Neer 2001).

Abaloparatide

Abaloparatide is an analogue of a PTH; it was approved by the United States Food and Drug Administration (US FDA) to treat osteoporosis in 2017. It has a relatively greater affinity for PTH/PTHrP receptor type 1 (or PTHR1) in the transient state and is an anabolic agent. The recommended dose of abaloparatide is 80 µg, administered via SC injection once a day. Adverse effects include hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo (Miller 2016).

Romosozumab

Romosozumab is a humanised monoclonal antibody that binds and inhibits the activity of the protein sclerostin. It has a dual effects on the bone; it increases bone formation and decreases bone breakdown. The recommended dose of romosozumab is 210 mg, administered via SC injection once a month; it should be limited to 12 doses. Serious adverse effects are cardiac death, heart attack, and stroke (Saag 2017). Other adverse effects include headache, joint pain, and pain at the injection site (Cosman 2016). The approval of romosozumab was on hold owing to its serious adverse effects, but it was finally approved by the US FDA for the treatment of osteoporosis in 2019 with a black box warning.

Strontium ranelate

Strontium ranelate consists of two divalent cation atoms. Strontium has pharmacological actions and its structure is closely related to calcium, an active component of the bone. This agent has been suggested to decrease bone resorption and stimulate bone formation. The recommended oral daily dose of strontium ranelate is 2 g (Meunier 2004). Adverse effects include nausea and diarrhoea. The use of this agent may lead to DVT, heart attack, and severe allergic reaction (Abrahamsen 2014; Osborne 2010).

How the intervention might work

Available anti-osteoporotic drugs are antiresorptive and/or anabolic agents. In the general population, these drugs improve the BMD and reduce the risk of some fractures. A systematic review reported that bisphosphonates, denosumab, and teriparatide reduced the risk of fractures compared with the placebo in postmenopausal women with osteoporosis. These interventions were found to reduce vertebral fractures (relative risk (RR) reduction range: 0.40 to 0.60) and nonvertebral fractures (RR reduction range: 0.60 to 0.80). Raloxifene, which is a SERMs, reduced the risks of only vertebral fractures (Crandall 2014). A more recent systematic review indicated that abaloparatide, romosozumab, and strontium ranelate also reduce the incidence of fractures compared with placebo in postmenopausal women with osteoporosis. This review showed that abaloparatide, romosozumab, and strontium ranelate reduces the incidence of vertebral fractures (RR: 0.13 (95% credible interval (CrI) 0.04 to 0.34); 0.31 (95% CrI 0.2 to 0.37); and 0.71 (95% CrI 0.63 to 0.80), respectively) and nonvertebral fractures (RR: 0.50 (95% CrI 0.28 to 0.85); 0.64 (95% CrI 0.49 to 0.81); and 0.87 (95% CrI 0.76 to 0.99), respectively) (Reginster 2019). Anti-osteoporotic drugs may also be indicated for patients with CKD who have a stable CKD-MBD and undergoing bone turnover assessment.

Why it is important to do this review

According to the WHO, the elderly population is continuing to grow globally at an unprecedented rate (He 2016). Clinical and epidemiological evidence indicates that ageing is a major factor associated with the incidence of CKD and osteoporosis (Glassock 2012; Kanis 2005). Osteoporotic fractures are highly co-prevalent with CKD in the elderly population (Klawansky 2003). Treatment for osteoporosis in patients with CKD is therefore an area of high unmet need. The publication of the CKD-MBD KDIGO guidelines in 2017 represented a dramatic change in the previous paradigm regarding the diagnosis and treatment of osteoporosis in patients with CKD. These guidelines have changed the view of the nephrologists in terms of the management of osteoporosis and its treatment in patients with CKD. However, it remains unclear how nephrologists should manage their patients (Khairallah 2018a; Khairallah 2018b). Cochrane systematic review has evaluated interventions for bone disease in only kidney transplant recipients (Palmer 2019). Only one other systematic review has evaluated interventions for osteoporosis in patients with CKD, and this study was not comprehensive (Wilson 2017). Wilson 2017 searched only published studies in PubMed and the Cochrane Central Register of Controlled Studies (CENTRAL). Meta-analyses that exclude unpublished studies and outcomes are likely to overestimate the effects of the evaluated interventions or miss important adverse events, as reflected in Chapters 8.14.1 and 10.2.1 of the Cochrane

Handbook (Higgins 2011). Additionally, limiting the review to only English-language articles may introduce a bias.

OBJECTIVES

To assess the efficacy and safety of pharmacological interventions for osteoporosis in patients with CKD stages 3-5, and those undergoing dialysis (5D).

METHODS

Criteria for considering studies for this review

Types of studies

We included all published, unpublished, and ongoing randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which treatment allocation was determined by alternation, use of alternate medical records, date of birth, or other predictable methods).

Types of participants

Participants of any age with CKD stages 3–5D as defined by the K/DOQI (Levey 2003) or the KDIGO guidelines (Eknoyan 2013) were considered for inclusion. The review excluded patients who had a functioning kidney transplant or were those treated with corticosteroids, because corticosteroids strongly contribute to the progression of osteoporosis. Additionally, two Cochrane reviews have already evaluated these populations (Allen 2016; Palmer 2019). The target population included patients with evidence of severe osteopenia or osteoporosis according to WHO criteria (T score < −2.0 SD). The International Society for Clinical Densitometry suggests that the diagnosis of osteoporosis in children and adolescents should not be made based on densitometric criteria alone (ISCD 2019). Thus, based on a previous study (Ward 2007), children who had at least one low-trauma fracture and/or reduced BMD were included.

Types of interventions

Patients receiving anti-osteoporotic drugs were compared with individuals receiving a placebo, no treatment, or usual care. The primary intervention was treatment with anti-osteoporotic drugs, including the following:

1. Bisphosphonates (etidronate, clodronate, tiludronate, alendronate, risedronate, ibandronate, pamidronate, zoledronate)
2. Denosumab
3. SERMs (bazedoxifene, raloxifene)
4. Teriparatide
5. Abaloparatide
6. Romosozumab
7. Strontium ranelate

Other treatments (e.g., vitamin D, phosphate binders, calcium supplements, calcimimetics, dialysate calcium adjustment, and dietary calcium or phosphate manipulation) were excluded from primary comparisons but were listed as co-interventions. This approach was used as these interventions were included in three previous Cochrane reviews (Palmer 2007b; Palmer 2009; Ruospo 2018). We did not place any restrictions on the doses of therapy. All studies had a follow-up period of at least six months.

Types of outcome measures

Primary outcomes

The primary outcomes at final follow-up were as follows.

- Incidence of fracture at any sites (clinical or radiographic)
- Mean change in the BMD measured using dual-energy radiographic absorptiometry (DXA) at the femoral neck, total hip, lumbar spine, or distal radius.
- Adverse events: osteonecrosis of the jaw that delays dental healing, atypical femoral fracture, any gastroesophageal disorder (oesophagitis, oesophageal ulcer, oesophageal stricture, oesophageal erosions, dysphagia, gastric bleeding, duodenitis, or ulceration), nausea, diarrhoea, any musculoskeletal disorders (bone pain, arthralgia, myalgia, and muscle cramps), fever, hypersensitivity reactions, cellulitis, venous thromboembolism, stroke, oedema, hot flushes, acute kidney injury (AKI), histological osteomalacia or low-bone turnover renal osteodystrophy, urinary tract infections (UTI), sepsis, and any other complication that may occur.

Secondary outcomes

The secondary outcomes at maximal follow-up were as follows:

- SONG core outcomes: the SONG core outcomes, as specified by the Standardised Outcomes in Nephrology initiative (SONG 2017). We evaluated the following:
  - Death (any cause, including cardiovascular)
  - Cardiovascular and cerebrovascular morbidity
  - Life participation (only in participants undergoing peritoneal dialysis (PD))
  - Fatigue score (only in participants undergoing haemodialysis (HD))
  - Vascular access failure (only in participants undergoing HD)
  - PD-related infections (only in participants undergoing PD)
  - PD failure (only in participants undergoing PD)
- QoL as reported in individual studies
- Serum levels of intact PTH, calcium, phosphorus, and alkaline phosphatase (total or bone-specific).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 25 January 2021 through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources:

1. Monthly searches of CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register were identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website under CKT Register of Studies.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies, and clinical practice guidelines
2. Experts/organisations in the field seeking information about unpublished or incomplete studies
3. Grey literature sources (e.g., abstracts, dissertations, and theses), in addition to those already included in the Cochrane Kidney and Transplant Register of Studies

Data collection and analysis

Selection of studies

Two review authors independently screened the titles and abstracts from search results and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full text of study reports or publications, which were then independently assessed by two review authors for inclusion. The reason for excluding ineligible studies was recorded. We resolved any disagreement through discussion or, if required, by consultation with a third author. We identified and excluded duplicates studies and collated multiple reports of the same study; this enabled each study rather than each report, to act as a unit of interest in the review. The selection process was recorded in sufficient detail to the enable completion of the PRISMA flow diagram and to generate a table detailing the 'Characteristics of excluded studies' (Moher 2009).

Data extraction and management

A data collection form for was used to document study characteristics and outcome data; this form was piloted on at least one study included in the review. The data extraction form included the following items.

- Methods: study design, total duration of study, number of study centres and location, study setting, withdrawals, and date of study
- Participants: number (N), mean age, age range, sex, baseline CKD stage, diagnostic criteria, follow-up duration, inclusion criteria, and exclusion criteria
- Interventions: intervention, comparison, concomitant medications, and intervention dosage
- Outcomes: primary and secondary outcomes specified and collected, and time points reported
- Notes: funding for studies and notable conflicts of interest reported by study authors, and any other necessary information

Two review authors independently extracted outcome data from the included studies. In the 'Characteristics of included studies', we noted if the study authors did not report outcome data in a usable way. We resolved disagreements by consensus or by involving a third author. One review author transferred data into Review Manager. Double data entry was used to confirm that the data were entered correctly data were entered correctly. A second review author spot-checked study characteristics for accuracy against study reports.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Were reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

We judged each potential source of bias as high, low, or unclear, and included text from the study report and justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across studies for each of the domains listed. Blinding was considered for different key outcomes where necessary (e.g., for unblinded outcome assessment, the risk of bias for death (any cause) may be differ from that for a participant-reported health-related QoL scale). We contacted study authors for additional information to clarify any risk of bias when the study reports did not provide enough detail to allow for a clear judgement. We considered the risk of bias for studies that contribute to a particular outcome when considering treatment effects.

We assessed the overall risk of bias based on the following bias domains: allocation concealment, blinding of outcome assessors, and incomplete outcome data.

- Low risk of bias: all the above domains are at a low risk of bias
- High risk of bias: one or more of the above domains are at a high or unclear risk of bias

Measures of treatment effect

We analysed dichotomous outcomes as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment, the mean difference (MD) or the standardised mean difference (SMD) were used if different scales were used. For outcomes provided as rates, the results were expressed as rate ratios with 95% CIs. If studies included a mixture of change-from-baseline and final value scores, we used the (unstandardised) MD method in RevMan according to Chapter 9.4.5.2 of the Cochrane handbook (Higgins 2011). However, the change-from-baseline and final value scores were not combined as the SMD, as the SD would reflect the differences in the reliability of the measurements rather than the differences in the measurement scale (Higgins 2011). If a study reported outcomes at multiple time points, we used the last time point recorded. We performed meta-analyses only when this approach was meaningful; that is, if treatments, participants, and the underlying clinical questions were sufficiently similar to allow

for pooling. Skewed data were to be presented descriptively (for example, as medians and interquartile ranges for each group).

Unit of analysis issues

We did not anticipate the inclusion of studies with non-standard designs, such as cross-over studies and cluster-RCTs, in the review. However, studies with multiple arms could be identified and included. In such cases, all intervention groups that were relevant to the review were included. To avoid double counting of the comparator, the number of patients in the comparator group was divided across the number of eligible intervention arms.

Dealing with missing data

Any further information required from the original author was requested in writing by (e.g. emailing the corresponding author), and any relevant information obtained in this manner was included in the review. Important numerical data, such as the number of screened and randomised patients, as well as the intention-to-treat (ITT), as-treated, and per-protocol populations, were carefully evaluated. Attrition rates, including dropouts, losses to follow-up, and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was initially assessed by the visual inspection of the forest plots. Thereafter, statistical heterogeneity was quantified using the I^2 statistic, which described the percentage of total variation across studies that was due to heterogeneity rather than sampling error (Higgins 2003). I^2 values can be interpreted as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed I^2 value depended on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a CI for I^2) (Higgins 2011).

Assessment of reporting biases

If possible, funnel plots were used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Different CKD patient populations (patients with CKD stage 3-5, and patients undergoing dialysis (5D)) were analysed separately. When the selected relevant studies were sufficiently similar, a meta-analysis was performed. Considering substantial heterogeneity between studies, we used the random-effects model. If substantial or considerable heterogeneity (I^2> 60%) was present, we did not perform a meta-analysis (see Assessment of heterogeneity).

Subgroup analysis and investigation of heterogeneity

If sufficient data were available, we conducted the following subgroup analyses for the primary outcomes.

- Age (< 18 years and ≥ 18 years)
- Sex
- Types of interventions
- intact PTH (< 50, 50 to 300, and > 300 pg/mL)
- Concomitant use of vitamin D

Sensitivity analysis

Sensitivity analyses, defined a priori, were performed to assess the robustness of our conclusions. We performed the following sensitivity analyses for the primary outcomes.

- Excluding studies judged to be at a high overall risk of bias
- Excluding studies judged to be at a high or unclear risk of bias for at least one of the overall risk of bias domains.

Summary of findings and assessment of the certainty of the evidence

The main results of the review are presented in the 'Summary of findings' tables. These tables presented key information related to the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also included an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). This approach defined the quality of a body of evidence as the extent to which one could be confident that an estimate of effect or association was close to the true quantity of specific interest. The quality of a body of evidence involved consideration of the within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias (Schunemann 2011b). We planned to present the following outcomes in the 'Summary of findings' tables.

- Incidence of fracture at any sites
- Mean change in the BMD measured using DXA at the femoral neck, total hip, lumbar spine, and distal radius
- Death (any cause)
- Incidence of adverse events
- QoL.

RESULTS

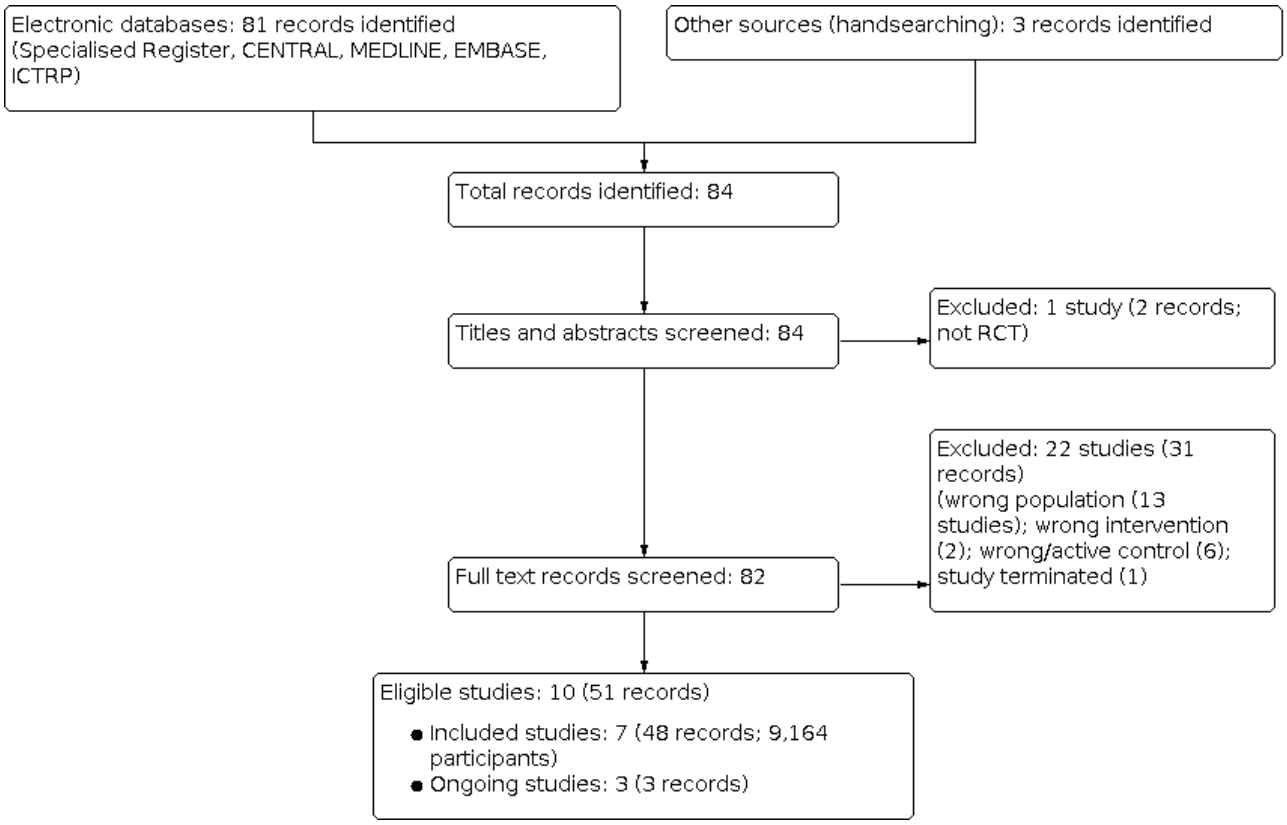
Description of studies

Detailed descriptions of the studies covered in this review are provided in the following tables: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

After searching the Specialised Register, contacting pharmaceutical companies, an additional web search, and removing duplicates, a total of 84 records were identified. After title and abstract screening and full-text review, seven studies (48 records) were included (ACTIVE 2016; FIT 1993; FREEDOM 2009; FTP 2001; Haghverdi 2014; Hernandez 2003; MORE 1999), and 23 studies (33 records) were excluded. Three ongoing studies were identified (NCT02792413; IRCT20180506039549N1; NCT02440581) and these will be assessed in a future update of this review (Figure 1).

Figure 1. Flow diagram.



Included studies

The seven studies (48 records) included in this systematic review are summarised in the Characteristics of included studies.

Study design

All studies were parallel RCTs.

Sample size

A total of 9,164 randomised participants were included in this review. The sample sizes ranged from 50 to 4,973. Five studies were included in the subgroup of large studies (ACTIVE 2016; FIT 1993; FREEDOM 2009; FTP 2001; MORE 1999).

Setting

We included four multinational studies (ACTIVE 2016; FREEDOM 2009; FTP 2001; MORE 1999), two single-country multicentre studies (FIT 1993; Hernandez 2003), and one single-centre study (Haghverdi 2014).

Participants

All studies were conducted in postmenopausal women. The mean age ranged from 62.5 to 77.6 years. Five studies (ACTIVE 2016; FIT 1993; FREEDOM 2009; FTP 2001; MORE 1999) included patients with CKD stages 3a-4. Two studies (Haghverdi 2014; Hernandez 2003) included patients undergoing HD or with CKD stage 5 not yet receiving dialysis. Patients receiving PD were not included. FREEDOM 2009 reported data separately for CKD stages 3 and 4, and MORE 1999 reported data for stages 3a and 3b-4.

Interventions

Five agents were identified: abaloparatide, alendronate, denosumab, raloxifene, and teriparatide. One study compared abaloparatide with placebo and the active control teriparatide (ACTIVE 2016); one study compared alendronate with placebo (FIT 1993); one study compared denosumab with placebo (FREEDOM 2009); one study compared teriparatide with placebo (FTP 2001); and three studies compared raloxifene with placebo (Haghverdi 2014; Hernandez 2003; MORE 1999).

Outcomes

The duration of follow-up ranged from 8 to 54 months. The following reported outcomes included data based on paired comparisons.

- Fracture was reported in six studies (9,114 participants) (ACTIVE 2016; FIT 1993; FREEDOM 2009; FTP 2001; Haghverdi 2014; MORE 1999). Five studies assessed radiographic vertebral fracture assessed by a blinded, independent assessor (ACTIVE 2016; FIT 1993; FREEDOM 2009; FTP 2001; MORE 1999). Five studies assessed non-vertebral or clinical fracture (FIT 1993; FREEDOM 2009; FTP 2001; Haghverdi 2014; MORE 1999).
- BMD was assessed in all studies.
  - BMD at femoral neck: ACTIVE 2016; FIT 1993; Haghverdi 2014; Hernandez 2003; MORE 1999
  - BMD at lumbar spine: ACTIVE 2016; FIT 1993; FREEDOM 2009; FTP 2001; Haghverdi 2014; Hernandez 2003; MORE 1999
  - BMD at total hip: ACTIVE 2016; FIT 1993; FREEDOM 2009

- Adverse events were reported in all studies
- SONG outcomes
  - Death was reported in four studies (5,664 participants) (FIT 1993; Haghverdi 2014; Hernandez 2003; MORE 1999)
  - Cardiovascular and cerebrovascular morbidity were reported in two studies (3,471 participants) reported (FIT 1993; FREEDOM 2009)
  - Life participation was not reported
  - Fatigue score was not reported
  - Vascular access failure was reported in two studies (110 participants) (Haghverdi 2014; Hernandez 2003)
  - PD-related infections were not reported
  - PD failure was not reported
  - QoL was not reported
- Serum levels of intact PTH, calcium, phosphorus, and alkaline phosphatase (total) were reported by one study (60 participants) (Haghverdi 2014).

Excluded studies

The characteristics of the excluded studies based on full-text assessment are shown in the Characteristics of excluded studies table.

Risk of bias in included studies

The results of risk of bias assessment of the seven included studies are summarised in Figure 2 and Figure 3. Two authors independently assessed the included studies for each checklist item as having a high, low, or unclear risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

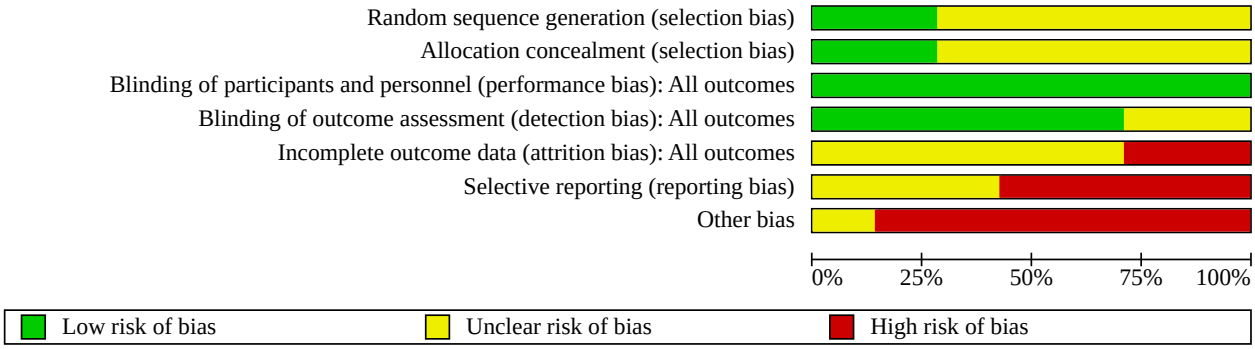
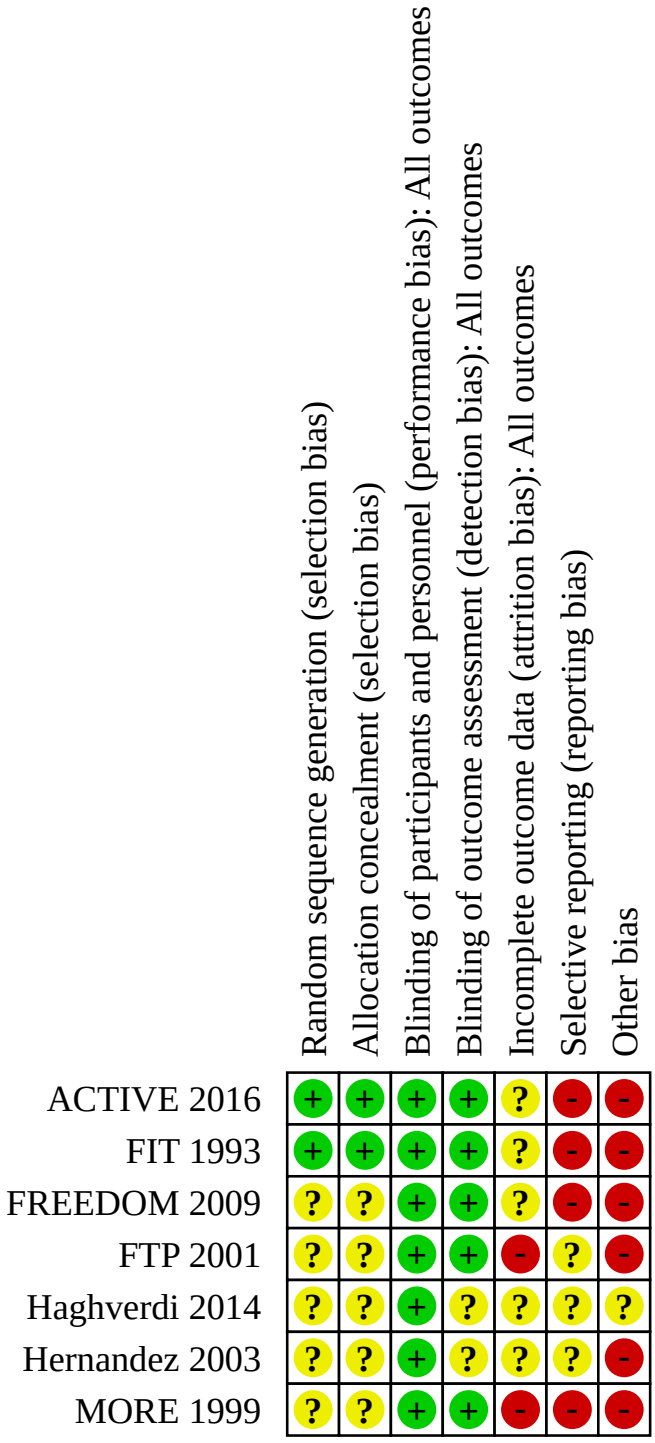


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

Two studies (ACTIVE 2016; FIT 1993) used a computer-generated random sequence. The remaining five studies (FREEDOM 2009; FTP 2001; Haghverdi 2014; Hernandez 2003; MORE 1999) did not indicate the randomisation methods and were therefore categorised as unclear.

We used a subset of data from these five studies (ACTIVE 2016; FIT 1993; FREEDOM 2009; FTP 2001; MORE 1999), which also enrolled postmenopausal women with normal kidney function. The number of patients with CKD in each study was as follows.

- ACTIVE 2016: 527/2,463 (21.4%)
- FIT 1993: 581/2,027 (28.7%)
- FREEDOM 2009: 2,890/7,868 (36.7%)
- FTP 2001: 83/1,637 (5.1%)
- MORE 1999: 4,973/7,705 (64.5%).

ACTIVE 2016 and FIT 1993 determined that the balance of the allocated groups was maintained because the number of extracted participants from each study was acceptable.

Allocation concealment

Two studies (ACTIVE 2016; FIT 1993) used central randomisation, whereas no information was included in the other five studies, which were categorised as unclear.

Blinding

Performance bias

All studies reported adequate double-blinding procedures (ACTIVE 2016; FIT 1993; FREEDOM 2009; FTP 2001; Haghverdi 2014; Hernandez 2003; MORE 1999).

Detection bias

Outcome assessors were blinded in five studies (ACTIVE 2016; FIT 1993; FREEDOM 2009; FTP 2001; MORE 1999). Other studies (Haghverdi 2014; Hernandez 2003) included no description and were categorised as unclear.

Incomplete outcome data

For the primary efficacy outcome of fracture events, four studies (ACTIVE 2016; FIT 1993; FREEDOM 2009; MORE 1999) reported results of the ITT analyses. Two studies (FTP 2001; MORE 1999) were classified as high risk because missing outcome data did not balance the numbers across intervention groups, and these studies excluded more than 10% of participants from the final analysis. The other five studies (ACTIVE 2016; FIT 1993; FREEDOM 2009; Haghverdi 2014; Hernandez 2003) were classified as unclear because there was insufficient information for judgement.

Selective reporting

Two studies (ACTIVE 2016; FIT 1993) defined the primary efficacy and safety outcomes in the protocols associated with the published manuscripts. Protocols were not available for the other five studies (FREEDOM 2009; FTP 2001; Haghverdi 2014; Hernandez 2003; MORE 1999). Only the percent improvement in the treatment groups (no control group data) were reported in four studies for death (FIT 1993; MORE 1999) and BMD (ACTIVE 2016; FIT 1993; FREEDOM 2009) Four studies were judged to be at high risk of reporting bias (ACTIVE 2016; FIT 1993; FREEDOM 2009; MORE 1999) and three studies were judged to have unclear risk of bias (FTP 2001; Haghverdi 2014; Hernandez 2003).

Other potential sources of bias

Six studies were sponsored by pharmaceutical companies (ACTIVE 2016; FIT 1993; FREEDOM 2009; FTP 2001; Hernandez 2003; MORE 1999).

Effects of interventions

See: **Summary of findings 1** Any anti-osteoporotic drugs versus placebo in postmenopausal women with osteoporosis and CKD stages 3-4; **Summary of findings 2** Raloxifene versus placebo for postmenopausal women with osteoporosis and CKD stages 5 and 5D

We were unable to perform the qualitative analysis as planned for the following reasons:

- We could not obtain sufficient information on each CKD stage, despite contacting the corresponding authors.
- Most of the studies reported both vertebral and non-vertebral or clinical fracture.

These were handled as follows:

- Stage of CKD was divided into 2 groups: 1) stages 3-4, and 2) stages 5 and 5D, based on the study's description/definition.
  - FREEDOM 2009 reported data separately for stages 3 and 4
  - MORE 1999 reported data separately for stages 3a and 3b-4.
- We divided “the Fracture at any sites” into “Vertebral fracture by radiography” and “Clinical fracture”. Clinical fracture was defined as any site fractures with fracture-related symptoms(FIT 1993).

See: Summary of findings 1; Summary of findings 2.

1. Patients with osteoporosis and CKD stages 3-4

Five studies were eligible (ACTIVE 2016; FIT 1993; FTP 2001; FREEDOM 2009; MORE 1999). The anti-osteoporotic drugs included were abaloparatide, alendronate, denosumab, teriparatide, and raloxifene.

Fracture: vertebral fracture by radiography

In the meta-analysis using the inverse variance random-effects model, anti-osteoporotic drugs may reduce the risk of vertebral fracture (Analysis 1.1 (5 studies): RR 0.52, 95% CI 0.39 to 0.69; low certainty evidence). Heterogeneity was moderate (I^2 = 40%).

Fracture: clinical fracture

In the meta-analysis using the inverse variance random-effects model, anti-osteoporotic drugs probably makes little or no difference to the risk of clinical fracture (Analysis 1.2 (4 studies): RR 0.91, 95% CI 0.79 to 1.05; moderate certainty evidence). However, we could not incorporate the study of FTP 2001 into the meta-analysis because no clinical fractures occurred in either the treatment and placebo groups. Heterogeneity was low (I^2 = 0%).

Mean change in BMD

Femoral neck

Three studies (ACTIVE 2016; FIT 1993; MORE 1999) (6,081 patients) described the assessment of the BMD at the femoral neck. However, we were unable to incorporate these studies into the meta-analysis because only the percentage change in the BMD in the treatment group was reported. In the three studies the mean change in BMD of the femoral neck was reported to improve by approximately 0.5% to 5% in the intervention group. The certainty of evidence was very low.

Lumbar spine

All five studies (9,054 patients) described the assessment of the BMD at the lumbar spine. However, we were unable to incorporate these studies into the meta-analysis because only the percentage change in the BMD in the treatment group was reported. In the five studies the mean change in BMD of the lumbar spine was reported to improve by approximately 1% to 15% in the intervention group. The certainty of evidence was very low.

Total hip

Three studies (ACTIVE 2016; FIT 1993; FREEDOM 2009) (3,998 patients) described the assessment of the BMD at the total hip. However, these studies could not be incorporated into the meta-analysis because only the percentage change in the BMD in the treatment group was reported. In the three studies the mean change in BMD of the total hip was reported to improve by approximately 5% to 6% in the intervention group. The certainty of evidence was very low.

Radius

This outcome was not reported by the included studies.

Adverse events

In the meta-analysis using the inverse variance random-effects model, the use of anti-osteoporotic drug probably makes little or no difference to adverse events (Analysis 1.3 (4 studies): RR 0.99, 95% CI 0.98 to 1.00; moderate certainty evidence). Heterogeneity was low (I^2 = 2%). FTP 2001 could not be incorporated into the meta-analysis but reported adverse events were observed in 99.1% of all study patients (576/581).

Death (any cause)

FIT 1993 and MORE 1999 (5,554 patients) reported death, however they could not be incorporated into the meta-analysis because only the total number of deaths was reported. The death in these studies ranged from 0.7% to 1.6%. The certainty of evidence was low.

Cardiovascular and cerebrovascular morbidity

FIT 1993 and FREEDOM 2009 (3,471 patients) assessed cardiovascular and cerebrovascular morbidity. However, FIT 1993 could not be incorporated into the meta-analysis because it only reported total cardiovascular or cerebrovascular events (cardiovascular events 2.6% and cerebrovascular events 2.2%). Denosumab probably makes little or no difference to cardiovascular and cerebrovascular morbidity (Analysis 1.4 (1 study, 8,281 participants): RR 1.00, 95% CI 0.75 to 1.32; moderate certainty evidence).

Quality of life

QoL was not reported by the included studies.

Bone markers

Bone markers were not reported by the included studies.

2. Patients with osteoporosis and CKD stages 5 and 5D

Two eligible studies were identified (Haghverdi 2014; Hernandez 2003), both evaluated raloxifene.

Fracture: vertebral fracture evidenced by radiography

Vertebral fracture identified by radiography was not reported by the included studies.

Fracture: clinical fracture

Haghverdi 2014 reported it is uncertain whether raloxifene reduces the risk of clinical fracture (Analysis 2.1: RR 0.33, 95% CI 0.01 to 7.87; very low certainty evidence).

Mean change in the BMD

Femoral neck

It is uncertain whether raloxifene improves the BMD at the femoral neck (Analysis 2.2 (2 studies, 110 participants): MD 0.01, 95% CI 0.00 to 0.02; very low certainty evidence). Heterogeneity was high (I^2 = 91%).

Lumbar spine

Raloxifene may increase the BMD at the lumbar spine (Analysis 2.3 (2 studies, 110 participants): MD 0.03, 95% CI 0.03 to 0.04; low certainty evidence). Heterogeneity was low (I^2 = 0%).

Total hip

BMD in the total hip was not reported by the included studies.

Radius

BMD in the radius was not reported by the included studies.

Adverse events

Both studies (Haghverdi 2014; Hernandez 2003) reported no adverse events. The certainty of evidence was very low.

Death

It is uncertain whether raloxifene reduces the risk of death (Analysis 2.5 (2 studies, 110 participants): RR 1.00, 95% CI 0.22 to 4.56; very low certainty evidence).

Vascular access failure

Vascular access failure was not reported by the included studies.

Life participation, fatigue score, PD-related infections, or PD failure

Life participation, fatigue scores, PD-related infections, or PD failure were not by the included studies.

Quality of life

QoL was not reported by the included studies.

Bone markers

Haghverdi 2014 reported some differences in bone markers between raloxifene and placebo (Analysis 2.7; Analysis 2.8; Analysis 2.9; Analysis 2.10). However, the baseline data were not balanced, and no marked changes were observed between the treatment and placebo groups.

Subgroup analyses

Subgroup analyses based on age (< 18 years and ≥ 18 years) and sex were not possible as all patients were postmenopausal women.

Types of interventions

Five drugs were identified (abaloparatide, alendronate, denosumab, teriparatide, and raloxifene). Meta-analysis could be only conducted about teriparatide. The results are provided below.

Abaloparatide

ACTIVE 2016 reported it is uncertain whether abaloparatide reduces the risk of vertebral fracture because the certainty of this evidence is very low (Analysis 3.1: RR 0.25, 95% CI 0.03 to 2.20) and abaloparatide probably makes little or no difference to adverse events (Analysis 3.5: RR 1.01, 95% CI 0.94 to 1.10; moderate certainty evidence).

Alendronate

FIT 1993 reported alendronate may make little or no difference to the risk of vertebral fracture (Analysis 4.1: RR 0.74, 95% CI 0.33 to 1.66; low certainty evidence) and the risk of clinical fracture (Analysis 4.2: RR 0.79, 0.52 to 1.20; low certainty evidence).

Denosumab

FREEDOM 2009 reported denosumab probably reduces the risk of vertebral fracture (Analysis 5.1: RR 0.41, 95% CI 0.28 to 0.58; moderate certainty evidence), may make little or no difference to the risk of clinical fracture (Analysis 5.2: RR 0.86, 95%CI 0.66 to 1.12; low certainty evidence), and probably makes little or no difference to adverse events (Analysis 5.6: RR 0.99, 95% CI 0.97 to 1.01; moderate certainty evidence), and cardiovascular and cerebrovascular morbidity (Analysis 5.7: RR 1.00, 95% CI 0.75 to 1.32; moderate certainty evidence).

Teriparatide

Teriparatide probably reduces the risk of vertebral fracture (Analysis 6.1: RR 0.31, 95% CI 0.10 to 0.90; moderate certainty evidence). Heterogeneity was low (I^2 = 0%). Teriparatide may make little or no difference to adverse events (Analysis 6.5: RR 0.95, 95% CI 0.74 to 1.14; low certainty evidence). Heterogeneity was high (I^2 = 79%).

Raloxifene

MORE 1999 reported that raloxifene probably reduces the risk of vertebral fracture (Analysis 7.1: RR 0.60, 95% CI 0.36 to 1.00; moderate certainty evidence), may make little or no difference to the risk of clinical fracture (Analysis 7.2: RR 0.96, 95% CI 0.80 to 1.16; low certainty evidence) and probably makes little or no difference to adverse events (Analysis 7.5: RR 0.99, 95% CI 0.98 to 1.00; moderate certainty evidence).

Intact PTH level (< 50, 50-300, and > 300 pg/mL)

Most eligible patients were likely to have stable intact PTH levels. We contacted the relevant study authors to request further details; however, they were unable to provide further information.

Concomitant use of vitamin D

Most eligible patients were likely to use vitamin D. We contacted the relevant study authors to request further details; however, they were unable to provide further information.

Sensitivity analyses

All eligible studies were considered to be at a high risk for bias. In the sensitivity analysis, we excluded studies judged to be at a high risk of bias for at least one of the overall risk of bias domains. FTP 2001 and MORE 1999 were excluded from this analysis (Analysis 8.1; Analysis 8.2; Analysis 8.3). The results were similar to Analysis 1.1, Analysis 1.2, and Analysis 1.3.

Funnel plots

No funnel plots were generated to evaluate potential publication bias because less than 10 eligible RCTs were available for each pooled analysis.

DISCUSSION

Summary of main results

Seven studies randomising 9,164 patients were included in our meta-analyses of the main outcomes. All participants were postmenopausal women. Five studies included patients with CKD stages 3-4, and two studies included patients with CKD stages 5 or 5D. Five anti-osteoporotic agents were identified: abaloparatide, alendronate, denosumab, raloxifene, and teriparatide.

Among patients with CKD stages 3-4, anti-osteoporotic drugs may reduce the risk of vertebral fracture. Anti-osteoporotic drugs probably makes little or no difference to the risk of clinical fracture or adverse events. The efficacy and safety of anti-osteoporotic drugs were similar during sensitivity analysis, which excluded studies with a high risk of bias for at least one of the overall risk of bias domains.

Among patients with CKD stages 5 and 5D, it is uncertain whether raloxifene reduces the risk of clinical fracture and death. Raloxifene may slightly improve the BMD at the lumbar spine, and uncertain effects on BMD at the femoral neck.

We could not perform a meta-analysis of each type of intervention because each drug was assessed in individual studies.

Overall completeness and applicability of evidence

Both published and unpublished data were included in this review. We contacted the relevant corresponding authors to acquire the data that were not reported in the published articles. However, the information obtained was insufficient. All study participants were postmenopausal women; therefore, the evidence obtained cannot be directly applied to men and paediatric patients. Importantly, the CKD-BMD of all study participants was stable at baseline; therefore, the evidence cannot be applied to patients with insufficient control of CKD-BMD.

Quality of the evidence

The certainty of the evidence was graded using the GRADE approach (GRADE 2008). As shown in the Summary of findings 1, among patients with CKD stages 3-4, vertebral fracture was assessed to be of low certainty owing to concerns of serious risks of bias and inconsistency. We assessed clinical fracture and adverse events to be of moderate certainty owing to concerns of serious risks of bias.

As shown in the Summary of findings 2, among patients with CKD stages 5 and 5D, we assessed clinical fracture and death to be of very low certainty owing to concerns of serious risks of bias and serious imprecision. We assessed the mean change in the BMD at the lumbar spine to be of low certainty owing to concerns of serious risks of bias and indirectness.

We assessed the mean change in the BMD at the femoral neck to be of very low certainty owing to concerns of serious risks of bias, inconsistency, and indirectness.

Potential biases in the review process

We performed a comprehensive search using several different databases; however, we cannot rule out the possibility that smaller studies were missed. In addition, although we contacted the corresponding authors and conducted web searches to collect additional data, we were unable to obtain sufficient information. There might be a potential bias due to data availability or publication status.

Agreements and disagreements with other studies or reviews

This review differed from the review by Wilson 2017 in several aspects. Toussaint 2010 was excluded because most of the patients did not have osteoporosis, and the ACTIVE 2016 study was newly included. In addition, this review demonstrated an effect that included all drug subtypes. The primary results of this review were consistent with those of Wilson 2017. However, the evidence is limited to patients with CKD stages 3-5D.

The effects of each drug were consistent with findings in the general population (Crandall 2014; Reginster 2019). Regarding the five large studies identified (ACTIVE 2016; FIT 1993; FREEDOM 2009; FTP 2001; MORE 1999), we used a subset of data from these five studies in our meta-analysis. The each subset result was consistent with the overall results of each study. However, the 95% CIs for the estimates were wide owing to the smaller sample sizes.

AUTHORS' CONCLUSIONS

Implications for practice

Among patients with CKD stages 3-4, anti-osteoporotic drugs may reduce the risk of vertebral fracture in low certainty evidence. Anti-osteoporotic drugs probably make little or no difference to the risk of clinical fracture and adverse events in moderate certainty evidence.

In low certainty evidence, patients with CKD stages 5 and 5D, it is uncertain whether anti-osteoporotic drug reduces the risk of clinical fracture and death because the certainty of this evidence is very low. Anti-osteoporotic drug may slightly improve the BMD at the lumbar spine in low certainty evidence. It is uncertain whether anti-osteoporotic drug improves the BMD at the femoral neck because the certainty of this evidence was very low.

Implications for research

Several concerns remain, and future studies should address the following points.

1. This review could not assess the effectiveness or safety of anti-osteoporotic drugs in patients with unstable CKD-MBD; it is important to establish the recommendations for these patients.
2. This review could not assess the effectiveness or safety of anti-osteoporotic drugs in men or paediatric patients; it is also important to establish the recommendations for these patients.
3. We could not sufficiently assess the effectiveness or safety of anti-osteoporotic drugs in patients with each CKD stage. Therefore, these analyses should be repeated when more data become available.
4. We could not sufficiently assess the effect of each anti-osteoporotic drug. Therefore, these analyses should be repeated after the publication of more data.
5. Future studies should compare the subtypes of anti-osteoporotic drugs in order to provide clinicians with information on the comparative effectiveness of available therapies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ACTIVE 2016

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: March 2011 to October 2014 • Duration of study follow-up: 19 months (18 months of treatment plus 1 month of follow-up)
Participants	• Country: multinational (Argentina, Brazil, China, Czech Republic, Denmark, Estonia, Lithuania, Poland, Romania, USA) • Setting: multicentre (28 sites) • Inclusion criteria: postmenopausal women; CKD stage 3; osteoporosis or past fracture and osteopenia; normal bone markers • Number: total (527); treatment group (168); control group 1 (167); control group 2 (192) • Mean age ± SD: 74.0 ± 5.5 years • Sex: women only • CKD stage: CKD stages 3-4 (eGFR < 60 mL/min) • BMI: not reported • Diabetes: not reported • Current smoker: not reported • Exclusion criteria: bone disorder other than postmenopausal status; use of corticosteroids; prior treatment with other anti-osteoporotic drugs
Interventions	Treatment group • Abaloparatide: 80 µg/day self-administered by SC injection Control group 1 • Placebo Control group 2 (active comparator) • Teriparatide: 20 µg/day self-administered by SC injection Co-interventions • Calcium: 500 to 1000 mg • Vitamin D: 400 to 800 IU

ACTIVE 2016 *(Continued)*

	○ Actual use of calcium or vitamin D: not reported
Outcomes	Primary outcome • New vertebral fractures Secondary outcomes • Nonvertebral fractures • Moderate and severe vertebral fractures • Percentage change in the BMD of the lumbar spine, total hip, and femoral neck from baseline compared with teriparatide • Change in bone turnover biomarkers (s-PINP, s-CTX) • Adverse events
Notes	• Funding source: The study was funded by Radius Health • Further information was requested, but no response was received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to each treatment groups by means of a central, interactive, automated telephone system
Allocation concealment (selection bias)	Low risk	Allocation was concealed because participants were assigned to each group using a central, interactive, automated telephone system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active comparator (teriparatide) could not be repackaged and blinded. However, the comparison between abaloparatide and placebo, which was main purpose of this study, could be blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Efficacy and safety outcomes were assessed by blinded and independent assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data were balanced in numbers across intervention groups; however, the reasons for missing data were not stated
Selective reporting (reporting bias)	High risk	All predefined efficacy and safety outcomes were reported, however BMD was reported incompletely so that these data could not be entered in a meta-analysis (no control group data)
Other bias	High risk	The study was funded by Radius Health

FIT 1993

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study follow-up: 48 to 54 months
Participants	• Country: USA

FIT 1993 *(Continued)*

- Setting: multicentre (11 sites)
- Inclusion criteria: postmenopausal women; serum creatinine ≤ 1.27 mg/dL; osteoporosis or osteopenia; normal bone markers
- Number: total (581); treatment group (not reported); control group (not reported)
- Mean age ± SD: 74.6 ± 4.4 years
- Sex: women only
- CKD stage: CKD stages 3-4
- BMI: 21.8 ± 2.6
- Diabetes: not reported
- Current smoker: not reported
- Exclusion criteria: bone disorder other than postmenopausal status, use of corticosteroids, prior treatment with other anti-osteoporotic drugs

Interventions	Treatment group • Oral alendronate: 5 mg/day for 2 years; dose was increased to 10 mg/day over the subsequent 2 years Control group • Placebo Co-interventions • Participants with an average calcium intake < 1000 mg/day were asked to take a daily supplement containing 500 mg of $CaCO_3$ and 400 IU of vitamin D3 per day (82% of participants in each treatment group)
Outcomes	Primary outcome • New vertebral deformities Secondary outcomes • Clinical fractures • Change in BMD at femoral neck, lumbar spine and total hip • Change in height • Bone biochemistry • Bone quality
Notes	• Funding source: Merck Research Laboratories. • Further information was requested, but no response was received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to each treatment group by means of a central system by computer-generated codes
Allocation concealment (selection bias)	Low risk	Allocation was concealed because participants were assigned to each group using a central system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blind study
Blinding of outcome assessment (detection bias)	Low risk	Efficacy and safety outcomes were assessed by blinded and independent assessors

FIT 1993 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	All predefined efficacy and safety outcomes were reported however BMD and death were reported incompletely so that these data could not be entered in a meta-analysis (no control group data)
Other bias	High risk	The study was funded by Merck Research Laboratories

FREEDOM 2009

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study follow-up: 36 months
Participants	• Country: multinational (USA, Canada, Argentina, Brazil, Mexico, Australia, New Zealand, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland, UK Czech Republic, Greece, Hungary, Latvia, Malta, Slovak Republic, Romania, Serbia) • Setting: multicentre • Inclusion criteria: postmenopausal women; CKD stages 3-4; osteoporosis • Number: CKD stage 3 (2,817); CKD stage 4 (73); treatment group (not reported); control group (not reported) • Mean age ± SD (years): CKD stage 3 (75.1 ± 4.9); CKD stage 4 (80.0 ± 5.5) • Sex: women only • CKD stage: CKD stages 3-4 • BMI: not reported • Diabetes: not reported • Current smoker: CKD stage 3: (263); CKD stage 4 (9) • Exclusion criteria: bone disorder other than postmenopausal status; use of corticosteroids; prior treatment with other anti-osteoporotic drugs

Interventions	Treatment group
	• Denosumab (SC): 60 mg every 6 months
	Control group
	• Placebo
	Co-intervention
	• Calcium (1,000 mg/day)
	  ○ Actual use of calcium supplementation: CKD stage 3 (2798), CKD stage 4 (73)
	• Vitamin D (400 to 800 IU/day)
	  ○ Actual use of vitamin D supplementation: not reported

Outcomes	Primary outcome • New vertebral fracture Secondary outcomes

FREEDOM 2009 *(Continued)*

- Nonvertebral fracture
- Hip fracture
- New clinical vertebral fracture
- Multiple (≥ 2) new vertebral fractures
- Percentage change in the BMD of the lumbar spine and total hip from baseline
- Bone turnover marker: serum C-telopeptide of type I collagen (CTX); intact serum procollagen type I N-terminal
- Propeptide (PINP)
- Adverse events

Notes	• Funding source: Amgen • Further information was requested, but no response was received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported; however "Randomization was stratified according to 5-year age group"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Efficacy and safety outcomes were assessed by blinded and independent assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data balanced between intervention groups; reasons for missing data were not reported
Selective reporting (reporting bias)	High risk	BMD was reported incompletely so that these data could not be entered in a meta-analysis (no control group data)
Other bias	High risk	The study was funded by Amgen

FTP 2001

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study follow-up: 24 months
Participants	• Country: multinational (Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, Hungary, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Sweden, USA) • Setting: multicentre (99 sites) • Inclusion criteria: postmenopausal women; SCr ≤ 2 mg/dL; past fracture and/or osteopenia; normal bone maker

FTP 2001 *(Continued)*

- Number: total (83); treatment group 1 (29); treatment group 2 (34); control group (20)
- Mean age ± SD (years): treatment group 1 (77.2 ± 5.2); treatment group 2 (77.8 ± 3.5); control group (77.8 ± 5.3)
- Sex: women only
- CKD stage: CKD stage 3
- BMI: not reported
- Diabetes: not reported
- Current smoker: not reported
- Exclusion criteria: bone disorder other than postmenopausal, use of corticosteroids, prior treatment with other anti-osteoporotic drugs

Interventions	Treatment group 1 • Teriparatide (SC): 20 µg/day by self-administered injection Treatment group 2 • Teriparatide (SC): 40 µg/day by self-administered injection Control group • Placebo Co-intervention • Calcium (1,000 mg/day) and vitamin D (400 to 1200 IU/day) supplementation ○ Actual use of calcium or vitamin D: not reported
Outcomes	• Vertebral fractures • Changes in height from baseline • Nonvertebral fractures (clavicle, scapula, ribs, sacrum, humerus, forearm, carpus, pelvis, femur, patella, tibia, fibula, ankle, calcaneus, tarsus, and metatarsal) • Change percentage of BMD of the lumbar spine, proximal femur, and radius and the total-body from baseline • Adverse events
Notes	• Funding source: funded by Eli Lilly • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Efficacy and safety outcomes were assessed by blinded and independent assessors

FTP 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data did not balance in numbers across intervention groups, and reasons for missing data was not reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	The study was funded by Eli Lilly

Haghverdi 2014

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study follow-up: 8 months
Participants	• Country: Iran • Setting: single centre • Inclusion criteria: postmenopausal women; CKD stages 5 or 5D (HD); osteoporosis, or severe osteopenia • Number: total (60); treatment group (CKD stage 5 (4); CKD stage 5D (26)); control group (CKD stage 5 (5); CKD stage 5D (25)) • Mean age ± SD (years): treatment group (63.5 ± 11.9); control group (62.1 ± 11.8) • Sex: women only • CKD stage: CKD stages 5 or 5D (HD) • BMI: not reported • Diabetes: not reported • Current smoker: not reported • Exclusion criteria: bone disorder other than postmenopausal status; use of corticosteroids; prior treatment with other anti-osteoporotic drugs
Interventions	Treatment group • Raloxifene (oral): 60 mg/day Control group • Placebo Co-interventions • Calcium and rocaltrol ○ Actual use of calcium or rocaltrol: not reported
Outcomes	• Change in serum levels of total calcium, phosphorus, alkaline phosphatase and intact PTH • Change in BMD of the lumbar spine and femoral neck as determined by dual x-ray absorptiometry • Adverse events
Notes	• Funding source: not reported • Further information was requested, but no response was received
Risk of bias	

Haghverdi 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data balanced in numbers across intervention groups, and reasons for missing data was stated. However, insufficient information to permit judgement because of not mention about ITT
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: the protocol was not available
Other bias	Unclear risk	Insufficient information to permit judgement

Hernandez 2003

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study follow-up: 12 months
Participants	• Country: Venezuela • Setting: multicentre • Inclusion criteria: postmenopausal women; CKD stage 5D (HD); osteoporosis or severe osteopenia • Number: treatment group (25); control group (25) • Mean age ± SD (years): treatment group (63.1 ± 8.6); control group (61.9 ± 8.7) • Sex: women only • CKD stage: CKD stage 5D (HD) • BMI: not reported • Diabetes: treatment group (0); control group(0) • Current smoker: not reported • Exclusion criteria: bone disorder other than postmenopausal; use of corticosteroids; prior treatment with other anti-osteoporotic drugs
Interventions	Treatment group • Raloxifene (oral): 60 mg/day Control group • Placebo

Hernandez 2003 *(Continued)*

	Co-interventions • Not reported
Outcomes	• Change of the BMD of the lumbar spine and femoral neck • Change of serum lipids: total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides • Adverse events

Notes	• Funding source
	  ○ Funded by Grant G-97-008808 of the Fondo Nacional de Ciencia, Tecnolog ía y Innovacio ´n de Venezuela (FONACIT) and Fundarenal-HUC
	  ○ Eli Lilly and Co. provided the study drug
	• We requested further information but there was no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants were followed up. However, insufficient information to permit judgement because of not mention about ITT
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	The study was supported by Eli Lilly

MORE 1999

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study follow-up: 36 months
Participants	• Country: multinational (Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Mexico, The Netherlands, New Zealand, Norway, Poland, Slovak Republic, Singapore, Slovenia, Spain, Sweden, UK, USA) • Setting: multicentre (180 cites)

MORE 1999 *(Continued)*

- Inclusion criteria: postmenopausal women; CKD stages 3-4; osteoporosis
- Number: total (4,973); treatment group (CKD stage 3a (2,323); CKD stages 3b-4 (970)); control group (CKD stage 3a (1,170); CKD stages 3b-4 (510))
- Mean age ± SD (years)
  - Treatment group: CKD stage 3a (66.9 ± 6.2); CKD stages 3b-4 (71.7 ± 5.3)
  - Control group: CKD stage 3a (67.3 ± 6.1); CKD stages 3b-4 (71.7 ± 5.3)
- Sex: women only
- CKD stage: CKD stages 3-4
- BMI
  - Treatment group: CKD stage 3a (24.6 ± 3.2); CKD stages 3b-4 (22.7 ± 3.2)
  - Control group: CKD stage 3a (24.7 ± 3.2); CKD stages 3b-4 (22.7 ± 3.3)
- Diabetes
  - Treatment group: CKD stage 3a (74); CKD stages 3b-4 (29)
  - Control group: CKD stage 3a (45); CKD stages 3b-4 (19)
- Current smoker
  - Treatment group: CKD stage 3a (402); CKD stages 3b-4 (197)
  - Control group: CKD stage 3a (146); CKD stages 3b-4 (78)
- Exclusion criteria: bone disorder other than postmenopausal, use of corticosteroids, prior treatment with other anti-osteoporotic drugs

Interventions	Treatment group 1 • Raloxifene (oral): 60 mg/day Treatment group 2 • Raloxifene (oral): 120 mg/day Control group • Placebo Co-interventions • Calcium (500 mg/day) and vitamin D (400 to 600 IU/day) supplementation ◦ Actual use of calcium or vitamin D: not reported
Outcomes	Primary outcome • Vertebral fractures Secondary outcomes • Nonvertebral fractures • Change percentage of BMD of the lumber spine and femoral neck • Adverse events
Notes	• Funding source: the study was funded by Eli Lilly • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

MORE 1999 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Efficacy and safety outcomes were assessed by blinded and independent assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data did not balance in numbers across intervention groups, and reasons for missing data was not reported
Selective reporting (reporting bias)	High risk	The protocol was not available. BMD and death were reported incompletely so that these data could not be entered in a meta-analysis (no control group data)
Other bias	High risk	The study was funded by Eli Lilly

BMD - bone mineral density; BMI - body mass index; CKD - chronic kidney disease; (e)GFR - (estimated) glomerular filtration rate; HD - haemodialysis; PTH - parathyroid hormone; RCT - randomised controlled trial; SC - subcutaneous

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ariyoshi 2006	Wrong population: most patients had normal bone condition
DIVINE 2011	Wrong control: compared to an active control (ibandronate versus alendronate)
Fukunaga 2002	Wrong control: compared to an active control (risedronate versus etidronate)
Grotz 1998	Wrong population: kidney transplant recipients
Hagino 2014	Wrong control: compared to an active control (75 mg risedronate/month versus 2.5 mg risedronate/day)
Hashiba 2004	Wrong population: most patients had normal bone condition
Hashiba 2006	Wrong population: most patients had normal bone condition
Iseri 2019	Wrong control: compared to an active control (denosumab versus alendronate)
JPRN-C000000390	Not RCT
Kishimoto 2006	Wrong control: compared to an active control (17.5 mg risedronate/week versus 2.5 mg risedronate/day)
Kleinstueck 2001	Wrong population: most the patients were not osteoporotic
Kushida 2006	Wrong control: compared to an active control (risedronate versus etidronate)
NCT00261625	Wrong population: no mention of the patients' bone condition
NCT00299572	wrong population: no mention of the patients' bone condition

Study	Reason for exclusion
Omidvar 2011	wrong population: kidney transplant recipients
Ruzhytska 2015	Wrong population: inclusion of patients with CKD stages 1 and 2. Further information was requested, but no response was received
Saito 2012	Wrong population: patients' bone condition was not sufficiently evaluated
Sirsat 2010	Wrong population: kidney transplant recipients
Toussaint 2010	Wrong population: most patients were not osteoporotic
UMIN00001829	This study was not terminated prior to commencement
Wang 2008b	Wrong intervention: salmon calcitonin
Wang 2008c	Wrong intervention: salmon calcitonin
Wetmore 2005	Wrong population: most patients were not osteoporotic

RCT - randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

IRCT20180506039549N1

Study name	Effect of alendronate in patents with osteoporosis and chronic kidney disease
Methods	• Allocation: randomised • Intervention Model: parallel assignment • Masking: patients, assessor, and analyser
Participants	Inclusion criteria • Osteoporotic patients with CKD • Patients aged > 18 years Exclusion criteria • Patients with hyperparathyroidism • Patients with hypoparathyroidism • Patients with normal densitometry
Interventions	Intervention • Alendronate: 70 mg tablet once a week before meals, with a glass of water for 6 months Control • Placebo
Outcomes	• Bone density in patients with CKD stages 3a-3b after 6 months of follow-up
Starting date	August 6, 2018
Contact information	Shokouh Shayanpour Golestan St, Ahvaz 61357-12794 Ahvaz Iran (Islamic Republic of)

IRCT20180506039549N1 *(Continued)*

	+98 61 3333 7077 shayanpor.sh@ajums.ac.ir Ahvaz University of Medical Sciences
Notes	Further information was requested, but no response was received.

NCT02440581

Study name	Renal osteodystrophy: A fresh approach
Methods	• Allocation: randomised • Intervention model: parallel assignment • Masking: none (open-label study)
Participants	Inclusion criteria • Aged ≥ 21 years • Chronic maintenance dialysis of at least 3 months' duration • Osteoporosis on DXA of either the spine or total hip (women: post-menopausal or aged ≥ 50 with T-score ≤ -2.5; men: aged ≥ 50 with T-score ≤ -2.5; all others, Z-score ≤ -2.5) • Normal serum calcium Exclusion criteria • Systemic illnesses or organ diseases that may affect bone, except type 1 or type 2 diabetes mellitus • Known Paget 's disease of bone • BMD t-score of the radius less than -3.5 by DXA • Abnormalities of the oesophagus that delay oesophageal emptying, such as stricture or achalasia • Treatment within the last 6 months with drugs that may affect bone metabolism, including bisphosphonates and teriparatide, except for treatment with calcitriol, vitamin D analogues and/or calcimimetics • Calcidiol level below the normal range
Interventions	Intervention group • Low turnover osteoporosis group: teriparatide and cinacalcet • High turnover osteoporosis group: alendronate Control • Low turnover osteoporosis group: no intervention • High turnover osteoporosis group: no intervention
Outcomes	Primary outcome • Change in quantitative computed tomography BMD of the hip in 1 year Secondary outcomes • Changes in coronary artery calcifications by multiple detector computed tomography (MDCT) in 1 year • Change in serum biochemical bone markers of bone activity at 6 months and 1 year
Starting date	July, 2015
Contact information	Hartmut Malluche, MD

NCT02440581 *(Continued)*

	University of Kentucky Lexington, Kentucky, United States, 40536 859-323-5049 hhmall@uky.edu
Notes	Further information was requested. The corresponding author responded that the study is in the final year and the first results will be available at the end of this year

NCT02792413

Study name	Randomised controlled study evaluating the effect of a biotherapy treatment (Anti-RANKL ligand antibody: Denosumab) on bone and vascular metabolism in osteoporotic chronic kidney disease
Methods	• Allocation: randomised • Intervention model: parallel assignment • Masking: participant, care provider and investigator
Participants	Inclusion criteria • Patients aged ≥ 65 years • CKD stage 5 patient, HD with extracorporeal treatment for ≥ 3 months • Patients with osteoporosis (history of bone fracture or T-scoring < -2.5 SD) • Serum PTH levels consistent with the KDIGO guidelines Exclusion criteria • Cinacalcet treatment • Calcium parameters (PTH, 25(OH) vitamin D3, calcium) outside the KDIGO guidelines • Suspicion of lower bone remodelling • Patients with a cancer or myeloma • Patients with severe hepatic cytolysis • Patients with severe teeth problems • Patient positive for human immunodeficiency virus
Interventions	Intervention • Denosumab (SC): 60 mg injection every 6 months and the standard treatment (vitamin D and calcium) Control • NaCl 0.9% (SC): injection every 6 months and the standard treatment (vitamin D and calcium)
Outcomes	Primary outcome • Relative variation in femoral bone mineral density after 24 months of follow-up Secondary outcomes • Relative variation in lumbar BMD after 24 months of follow-up • Relative variation in coronary calcification scores after 24 months of follow-up • Relative variation in abdominal aorta calcification scores after 24 months of follow-up • Variation in calcium levels after 6, 12, 18, and 24 months of follow-up • Variation in phosphorus levels after 6, 12, 18, and 24 months of follow-up • Morbi-death after 24 months of follow-up • Adverse events occurring during the entire study period

NCT02792413 *(Continued)*

Starting date	November 19, 2018
Contact information	Prof Jean-Paul CRISTOL CHU Lapeyronie, Department of Biochemistry and Hormonology, Montpellier, FRANCE +33(0)4 67 33 83 15 jp-cristol@chu-montpellier.fr
Notes	Recruitment may be ongoing or complete

BMD - bone mineral density; CKD - chronic kidney disease; HD - haemodialysis; PTH - parathyroid hormone; SC - subcutaneous

DATA AND ANALYSES

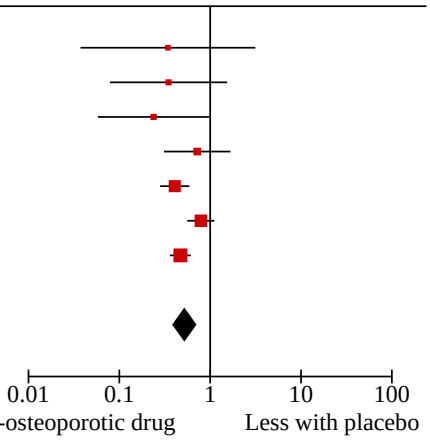
Comparison 1. Any anti-osteoporotic drug versus placebo for patients with osteoporosis and CKD stages 3-4

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Vertebral fracture by radiography	5		Risk Ratio (IV, Random, 95% CI)	0.52 [0.39, 0.69]
1.2 Clinical fracture	4		Risk Ratio (IV, Random, 95% CI)	0.91 [0.79, 1.05]
1.3 Adverse events	4		Risk Ratio (IV, Random, 95% CI)	0.99 [0.98, 1.00]
1.4 Cardiovascular and cerebrovascular morbidity	1	2890	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.75, 1.32]

Analysis 1.1. Comparison 1: Any anti-osteoporotic drug versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 1: Vertebral fracture by radiography

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
FREEDOM 2009 (1)	-1.0712	1.1307	1.6%	0.34 [0.04 , 3.14]
ACTIVE 2016	-1.0558	0.758	3.3%	0.35 [0.08 , 1.54]
FTP 2001	-1.4351	0.7193	3.7%	0.24 [0.06 , 0.98]
FIT 1993	-0.3285	0.4299	8.9%	0.72 [0.31 , 1.67]
FREEDOM 2009 (2)	-0.8977	0.1891	24.8%	0.41 [0.28 , 0.59]
MORE 1999 (3)	-0.2357	0.1756	26.4%	0.79 [0.56 , 1.11]
MORE 1999 (4)	-0.755	0.136	31.4%	0.47 [0.36 , 0.61]
Total (95% CI)			**100.0%**	**0.52 [0.39 , 0.69]**

Heterogeneity: Tau² = 0.05; Chi² = 10.05, df = 6 (P = 0.12); I² = 40%
Test for overall effect: Z = 4.56 (P < 0.00001)
Test for subgroup differences: Not applicable

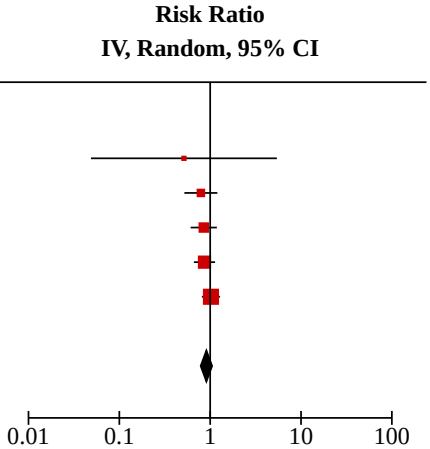


Footnotes
(1) CKD stage 4
(2) CKD stage 3
(3) CKD stage 3a
(4) CKD stage 3b-4

Analysis 1.2. Comparison 1: Any anti-osteoporotic drug versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 2: Clinical fracture

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
FTP 2001	0	0		Not estimable
FREEDOM 2009 (1)	-0.6657	1.2022	0.4%	0.51 [0.05 , 5.42]
FIT 1993	-0.2357	0.2134	12.0%	0.79 [0.52 , 1.20]
MORE 1999 (2)	-0.1625	0.1693	19.1%	0.85 [0.61 , 1.18]
FREEDOM 2009 (3)	-0.1443	0.137	29.1%	0.87 [0.66 , 1.13]
MORE 1999 (4)	0.0198	0.1176	39.5%	1.02 [0.81 , 1.28]
Total (95% CI)			**100.0%**	**0.91 [0.79 , 1.05]**

Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 4 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable

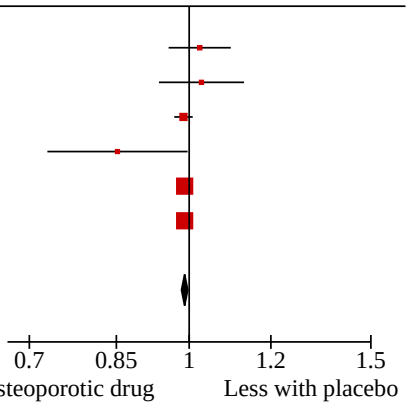


Footnotes
(1) CKD stage 4
(2) CKD stage 3b-4
(3) CKD stage 3
(4) CKD stage 3a

Analysis 1.3. Comparison 1: Any anti-osteoporotic drug versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 3: Adverse events

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
ACTIVE 2016	0.0235	0.0354	1.0%	1.02 [0.96 , 1.10]
FREEDOM 2009 (1)	0.0274	0.0484	0.5%	1.03 [0.93 , 1.13]
FREEDOM 2009 (2)	-0.0127	0.0105	11.2%	0.99 [0.97 , 1.01]
FTP 2001	-0.16	0.0798	0.2%	0.85 [0.73 , 1.00]
MORE 1999 (3)	-0.0101	0.0052	43.5%	0.99 [0.98 , 1.00]
MORE 1999 (4)	-0.0101	0.0052	43.5%	0.99 [0.98 , 1.00]
Total (95% CI)			**100.0%**	**0.99 [0.98 , 1.00]**

Heterogeneity: Tau² = 0.00; Chi² = 5.09, df = 5 (P = 0.40); I² = 2%
Test for overall effect: Z = 2.87 (P = 0.004)
Test for subgroup differences: Not applicable

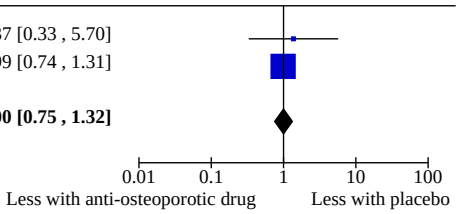


Footnotes
(1) CKD stage 4
(2) CKD stage 3
(3) CKD stage 3a
(4) CKD stage 3b-4

Analysis 1.4. Comparison 1: Any anti-osteoporotic drug versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 4: Cardiovascular and cerebrovascular morbidity

Study or Subgroup	Anti-osteoporotic drugs Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
FREEDOM 2009 (1)	4	36	3	37	3.9%	1.37 [0.33 , 5.70]
FREEDOM 2009 (2)	88	1418	88	1399	96.1%	0.99 [0.74 , 1.31]
Total (95% CI)		**1454**		**1436**	**100.0%**	**1.00 [0.75 , 1.32]**
Total events:	92		91			

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.01 (P = 1.00)
Test for subgroup differences: Not applicable



Footnotes
(1) CKD stage 4 patients
(2) CKD stage 3 patients

Comparison 2. Raloxifene versus placebo for patients with osteoporosis and CKD stage 5D

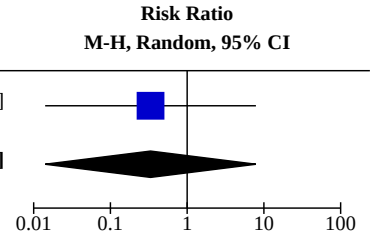
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Clinical fracture	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]
2.2 Mean change in femoral neck BMD (DXA)	2	110	Mean Difference (IV, Random, 95% CI)	0.01 [0.00, 0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Mean change in lumbar spine BMD (DXA)	2	110	Mean Difference (IV, Random, 95% CI)	0.03 [0.03, 0.04]
2.4 Adverse events	2	110	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.5 Death	2	110	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.22, 4.56]
2.6 Vascular access failure	2	110	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.7 Serum intact PTH	1	60	Mean Difference (IV, Random, 95% CI)	80.50 [-82.73, 243.73]
2.8 Serum calcium	1	60	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.81, -0.19]
2.9 Serum phosphorus	1	60	Mean Difference (IV, Random, 95% CI)	0.20 [-0.51, 0.91]
2.10 Serum alkaline phosphatase (total)	1	60	Mean Difference (IV, Random, 95% CI)	213.70 [-170.98, 598.38]

Analysis 2.1. Comparison 2: Raloxifene versus placebo for patients with osteoporosis and CKD stage 5D, Outcome 1: Clinical fracture

Study or Subgroup	Raloxifene Events	Raloxifene Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Haghverdi 2014	0	30	1	30	100.0%	0.33 [0.01 , 7.87]
Total (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			

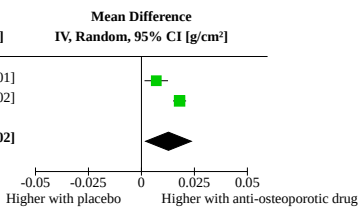
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Raloxifene versus placebo for patients with osteoporosis and CKD stage 5D, Outcome 2: Mean change in femoral neck BMD (DXA)

Study or Subgroup	Raloxifene Mean [g/cm²]	Raloxifene SD [g/cm²]	Raloxifene Total	Placebo Mean [g/cm²]	Placebo SD [g/cm²]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [g/cm²]
Hernandez 2003	0.005	0.01	25	-0.002	0.01	25	47.7%	0.01 [0.00 , 0.01]
Haghverdi 2014	0.009	0.005	30	-0.009	0.007	30	52.3%	0.02 [0.01 , 0.02]
Total (95% CI)			**55**			**55**	**100.0%**	**0.01 [0.00 , 0.02]**

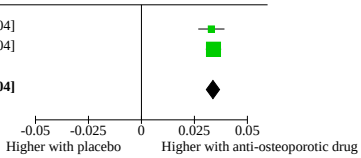
Heterogeneity: Tau² = 0.00; Chi² = 11.56, df = 1 (P = 0.0007); I² = 91%
Test for overall effect: Z = 2.32 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Raloxifene versus placebo for patients with osteoporosis and CKD stage 5D, Outcome 3: Mean change in lumbar spine BMD (DXA)

Study or Subgroup	Raloxifene Mean [g/cm²]	Raloxifene SD [g/cm²]	Raloxifene Total	Placebo Mean [g/cm²]	Placebo SD [g/cm²]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [g/cm²]
Haghverdi 2014	0.014	0.003	30	-0.019	0.017	30	25.5%	0.03 [0.03 , 0.04]
Hernandez 2003	0.031	0.002	25	-0.003	0.009	25	74.5%	0.03 [0.03 , 0.04]
Total (95% CI)			**55**			**55**	**100.0%**	**0.03 [0.03 , 0.04]**

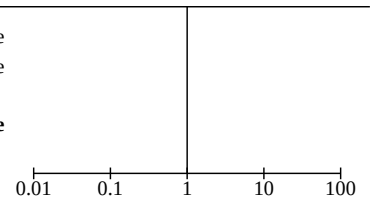
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 21.20 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Raloxifene versus placebo for patients with osteoporosis and CKD stage 5D, Outcome 4: Adverse events

Study or Subgroup	Raloxifene Events	Raloxifene Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Haghverdi 2014	0	30	0	30		Not estimable
Hernandez 2003	0	25	0	25		Not estimable
Total (95% CI)		**55**		**55**		**Not estimable**
Total events:	0		0			

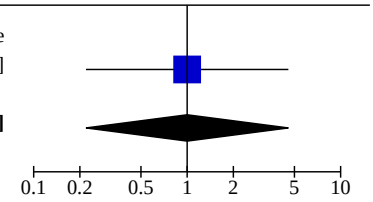
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Raloxifene versus placebo for patients with osteoporosis and CKD stage 5D, Outcome 5: Death

Study or Subgroup	Raloxifene Events	Raloxifene Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hernandez 2003	0	25	0	25		Not estimable
Haghverdi 2014	3	30	3	30	100.0%	1.00 [0.22 , 4.56]
Total (95% CI)		**55**		**55**	**100.0%**	**1.00 [0.22 , 4.56]**
Total events:	3		3			

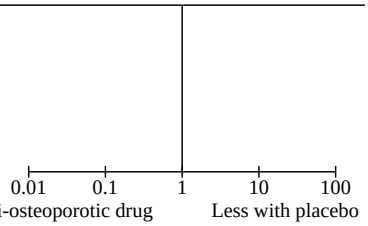
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Raloxifene versus placebo for patients with osteoporosis and CKD stage 5D, Outcome 6: Vascular access failure

Study or Subgroup	Raloxifene Events	Raloxifene Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Haghverdi 2014	0	30	0	30		Not estimable
Hernandez 2003	0	25	0	25		Not estimable
Total (95% CI)		**55**		**55**		**Not estimable**
Total events:	0		0			

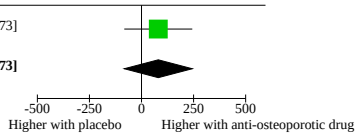
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Raloxifene versus placebo for patients with osteoporosis and CKD stage 5D, Outcome 7: Serum intact PTH

Study or Subgroup	Raloxifene Mean [pg/mL]	Raloxifene SD [pg/mL]	Raloxifene Total	Placebo Mean [pg/mL]	Placebo SD [pg/mL]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [pg/mL]
Haghverdi 2014	431.5	280.9	30	351	359.4	30	100.0%	80.50 [-82.73 , 243.73]
Total (95% CI)			**30**			**30**	**100.0%**	**80.50 [-82.73 , 243.73]**

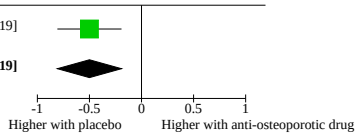
Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Raloxifene versus placebo for patients with osteoporosis and CKD stage 5D, Outcome 8: Serum calcium

Study or Subgroup	Raloxifene Mean [mg/dL]	Raloxifene SD [mg/dL]	Raloxifene Total	Placebo Mean [mg/dL]	Placebo SD [mg/dL]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [mg/dL]
Haghverdi 2014	8.9	0.5	30	9.4	0.7	30	100.0%	-0.50 [-0.81 , -0.19]
Total (95% CI)			**30**			**30**	**100.0%**	**-0.50 [-0.81 , -0.19]**

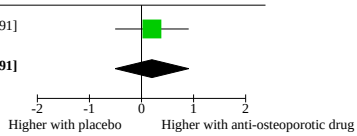
Heterogeneity: Not applicable
Test for overall effect: Z = 3.18 (P = 0.001)
Test for subgroup differences: Not applicable



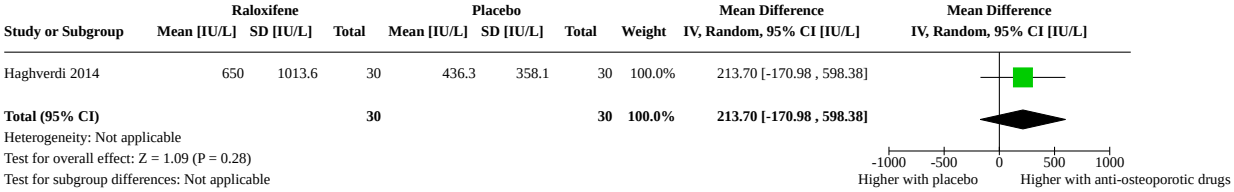
Analysis 2.9. Comparison 2: Raloxifene versus placebo for patients with osteoporosis and CKD stage 5D, Outcome 9: Serum phosphorus

Study or Subgroup	Raloxifene Mean [mg/dL]	Raloxifene SD [mg/dL]	Raloxifene Total	Placebo Mean [mg/dL]	Placebo SD [mg/dL]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [mg/dL]
Haghverdi 2014	5.3	1.7	30	5.1	1	30	100.0%	0.20 [-0.51 , 0.91]
Total (95% CI)			**30**			**30**	**100.0%**	**0.20 [-0.51 , 0.91]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable



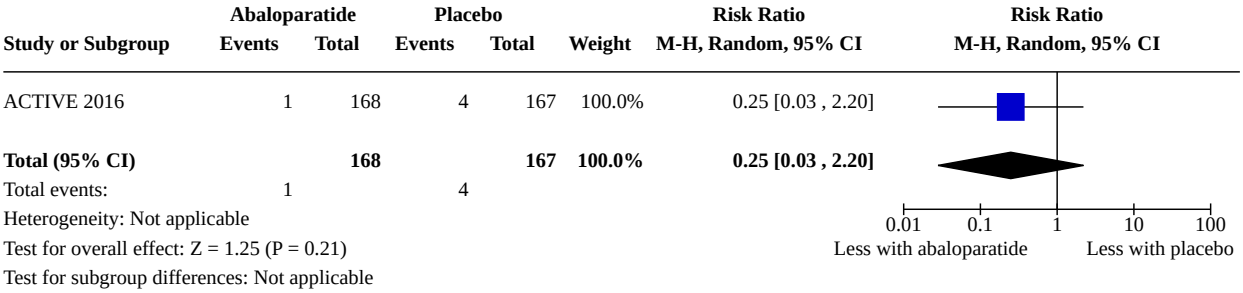
Analysis 2.10. Comparison 2: Raloxifene versus placebo for patients with osteoporosis and CKD stage 5D, Outcome 10: Serum alkaline phosphatase (total)



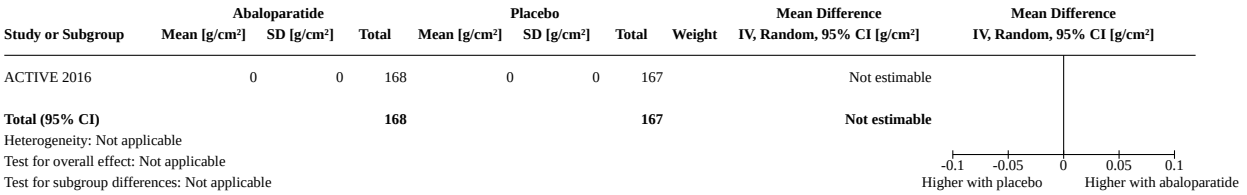
Comparison 3. Abaloparatide versus placebo for patients with osteoporosis and CKD stages 3-4

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Vertebral fracture by radiography	1	335	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.20]
3.2 Mean change in femoral neck BMD (DXA)	1	335	Mean Difference (IV, Random, 95% CI)	Not estimable
3.3 Mean change in lumbar spine BMD (DXA)	1	335	Mean Difference (IV, Random, 95% CI)	Not estimable
3.4 Mean change in total hip BMD (DXA)	1	335	Mean Difference (IV, Random, 95% CI)	Not estimable
3.5 Adverse events	1	335	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.10]

Analysis 3.1. Comparison 3: Abaloparatide versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 1: Vertebral fracture by radiography



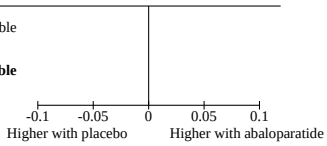
Analysis 3.2. Comparison 3: Abaloparatide versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 2: Mean change in femoral neck BMD (DXA)



Analysis 3.3. Comparison 3: Abaloparatide versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 3: Mean change in lumbar spine BMD (DXA)

Study or Subgroup	Abaloparatide Mean [g/cm²]	Abaloparatide SD [g/cm²]	Abaloparatide Total	Placebo Mean [g/cm²]	Placebo SD [g/cm²]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [g/cm²]	Mean Difference IV, Random, 95% CI [g/cm²]
ACTIVE 2016	0	0	168	0	0	167		Not estimable	
Total (95% CI)			**168**			**167**		**Not estimable**	

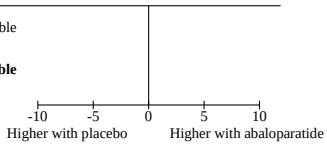
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Abaloparatide versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 4: Mean change in total hip BMD (DXA)

Study or Subgroup	Abaloparatide Mean [g/cm²]	Abaloparatide SD [g/cm²]	Abaloparatide Total	Placebo Mean [g/cm²]	Placebo SD [g/cm²]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [g/cm²]	Mean Difference IV, Random, 95% CI [g/cm²]
ACTIVE 2016	0	0	168	0	0	167		Not estimable	
Total (95% CI)			**168**			**167**		**Not estimable**	

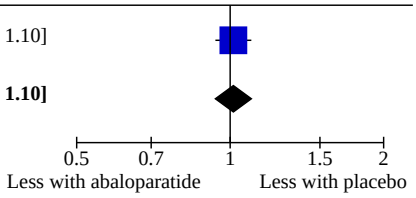
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Abaloparatide versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 5: Adverse events

Study or Subgroup	Abaloparatide Events	Abaloparatide Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
ACTIVE 2016	148	168	145	167	100.0%	1.01 [0.94 , 1.10]	
Total (95% CI)		**168**		**167**	**100.0%**	**1.01 [0.94 , 1.10]**	
Total events:	148		145				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



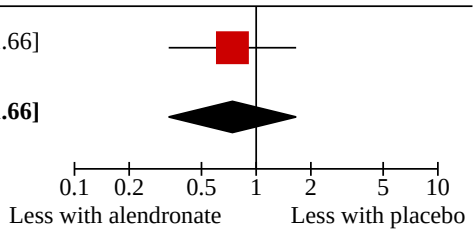
Comparison 4. Alendronate versus placebo for patients with osteoporosis and CKD stages 3-4

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Vertebral fracture by radiography	1		Risk Ratio (IV, Random, 95% CI)	0.74 [0.33, 1.66]
4.2 Clinical fracture	1		Risk Ratio (IV, Random, 95% CI)	0.79 [0.52, 1.20]

Analysis 4.1. Comparison 4: Alendronate versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 1: Vertebral fracture by radiography

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
FIT 1993	-0.3011	0.412	100.0%	0.74 [0.33 , 1.66]
Total (95% CI)			**100.0%**	**0.74 [0.33 , 1.66]**

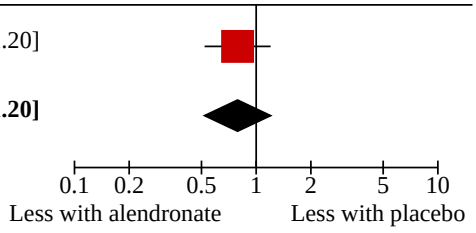
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Alendronate versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 2: Clinical fracture

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
FIT 1993	-0.2357	0.2134	100.0%	0.79 [0.52 , 1.20]
Total (95% CI)			**100.0%**	**0.79 [0.52 , 1.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



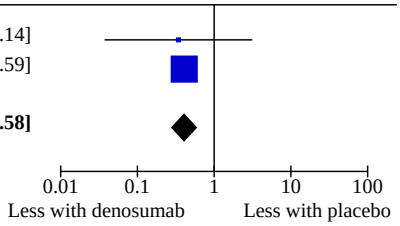
Comparison 5. Denosumab versus placebo for patients with osteoporosis and CKD stages 3-4

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Vertebral fracture by radiography	1	2890	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.28, 0.58]
5.2 Clinical fracture	1	2890	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.66, 1.12]
5.3 Mean change in femoral neck BMD (DXA)	1	2890	Mean Difference (IV, Random, 95% CI)	Not estimable
5.4 Mean change in lumbar spine BMD (DXA)	1	2890	Mean Difference (IV, Random, 95% CI)	Not estimable
5.5 Mean change in total hip BMD (DXA)	1	2890	Mean Difference (IV, Random, 95% CI)	Not estimable
5.6 Adverse events	1	2890	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.97, 1.01]
5.7 Cardiovascular and cerebrovascular morbidity	1	2890	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.75, 1.32]

Analysis 5.1. Comparison 5: Denosumab versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 1: Vertebral fracture by radiography

Study or Subgroup	Denosumab Events	Denosumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
FREEDOM 2009 (1)	1	36	3	37	2.7%	0.34 [0.04 , 3.14]
FREEDOM 2009 (2)	38	1418	92	1399	97.3%	0.41 [0.28 , 0.59]
Total (95% CI)		**1454**		**1436**	**100.0%**	**0.41 [0.28 , 0.58]**
Total events:	39		95			

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 4.84 (P < 0.00001)
Test for subgroup differences: Not applicable

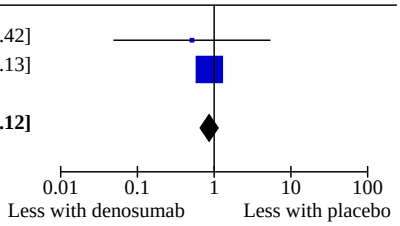


Footnotes
(1) CKD stage 4
(2) CKD stage 3

Analysis 5.2. Comparison 5: Denosumab versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 2: Clinical fracture

Study or Subgroup	Denosumab Events	Denosumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
FREEDOM 2009 (1)	1	36	2	37	1.3%	0.51 [0.05 , 5.42]
FREEDOM 2009 (2)	93	1418	106	1399	98.7%	0.87 [0.66 , 1.13]
Total (95% CI)		**1454**		**1436**	**100.0%**	**0.86 [0.66 , 1.12]**
Total events:	94		108			

Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable

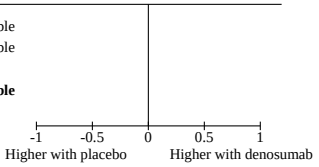


Footnotes
(1) CKD stage 4
(2) CKD stage 3

Analysis 5.3. Comparison 5: Denosumab versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 3: Mean change in femoral neck BMD (DXA)

Study or Subgroup	Denosumab Mean [g/cm²]	Denosumab SD [g/cm²]	Denosumab Total	Placebo Mean [g/cm²]	Placebo SD [g/cm²]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [g/cm²]
FREEDOM 2009 (1)	0	0	36	0	0	37		Not estimable
FREEDOM 2009 (2)	0	0	1418	0	0	1399		Not estimable
Total (95% CI)			**1454**			**1436**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

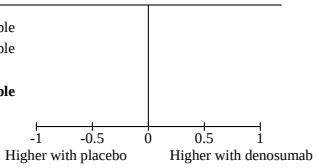


Footnotes
(1) CKD stage 4
(2) CKD stage 3

Analysis 5.4. Comparison 5: Denosumab versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 4: Mean change in lumbar spine BMD (DXA)

Study or Subgroup	Denosumab Mean [g/cm²]	Denosumab SD [g/cm²]	Denosumab Total	Placebo Mean [g/cm²]	Placebo SD [g/cm²]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [g/cm²]	Mean Difference IV, Random, 95% CI [g/cm²]
FREEDOM 2009 (1)	0	0	1418	0	0	1399		Not estimable	
FREEDOM 2009 (2)	0	0	36	0	0	37		Not estimable	
Total (95% CI)			**1454**			**1436**		**Not estimable**	

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

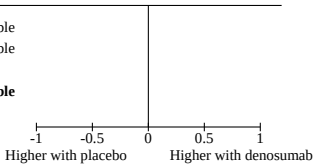


Footnotes
(1) CKD stage 3
(2) CKD stage 4

Analysis 5.5. Comparison 5: Denosumab versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 5: Mean change in total hip BMD (DXA)

Study or Subgroup	Denosumab Mean [g/cm²]	Denosumab SD [g/cm²]	Denosumab Total	Placebo Mean [g/cm²]	Placebo SD [g/cm²]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [g/cm²]	Mean Difference IV, Random, 95% CI [g/cm²]
FREEDOM 2009 (1)	0	0	36	0	0	37		Not estimable	
FREEDOM 2009 (2)	0	0	1418	0	0	1399		Not estimable	
Total (95% CI)			**1454**			**1436**		**Not estimable**	

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

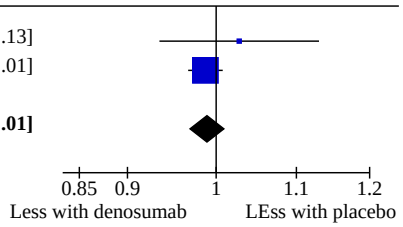


Footnotes
(1) CKD stage 4
(2) CKD stage 3

Analysis 5.6. Comparison 5: Denosumab versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 6: Adverse events

Study or Subgroup	Denosumab Events	Denosumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FREEDOM 2009 (1)	35	36	35	37	4.5%	1.03 [0.93 , 1.13]	
FREEDOM 2009 (2)	1308	1418	1307	1399	95.5%	0.99 [0.97 , 1.01]	
Total (95% CI)		**1454**		**1436**	**100.0%**	**0.99 [0.97 , 1.01]**	
Total events:	1343		1342				

Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.29)
Test for subgroup differences: Not applicable

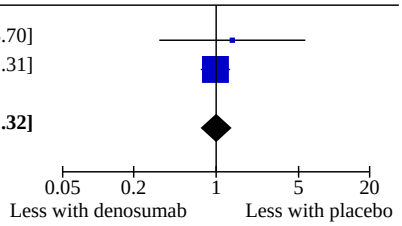


Footnotes
(1) CKD stage 4
(2) CKD stage 3

Analysis 5.7. Comparison 5: Denosumab versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 7: Cardiovascular and cerebrovascular morbidity

Study or Subgroup	Denosumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
FREEDOM 2009 (1)	4	36	3	37	3.9%	1.37 [0.33 , 5.70]
FREEDOM 2009 (2)	88	1418	88	1399	96.1%	0.99 [0.74 , 1.31]
Total (95% CI)		**1454**		**1436**	**100.0%**	**1.00 [0.75 , 1.32]**
Total events:	92		91			

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.01 (P = 1.00)
Test for subgroup differences: Not applicable



Footnotes
(1) CKD stage 4
(2) CKD stage 3

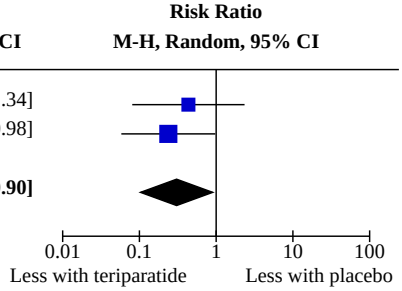
Comparison 6. Teriparatide versus placebo for patients with osteoporosis and CKD stages 3-4

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Vertebral fracture by radiography	2	442	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.10, 0.90]
6.2 Clinical fracture	1	83	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.3 Mean change in femoral neck BMD (DXA)	2	442	Mean Difference (IV, Random, 95% CI)	Not estimable
6.4 Mean change in lumbar spine BMD (DXA)	2	442	Mean Difference (IV, Random, 95% CI)	Not estimable
6.5 Adverse events	2	442	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.14]

Analysis 6.1. Comparison 6: Teriparatide versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 1: Vertebral fracture by radiography

Study or Subgroup	Teriparatide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTIVE 2016	2	192	4	167	41.2%	0.43 [0.08 , 2.34]
FTP 2001	3	63	4	20	58.8%	0.24 [0.06 , 0.98]
Total (95% CI)		**255**		**187**	**100.0%**	**0.31 [0.10 , 0.90]**
Total events:	5		8			

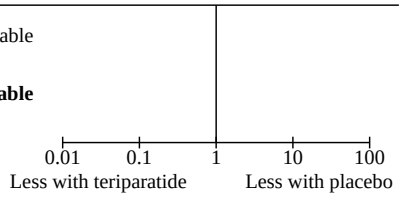
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Teriparatide versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 2: Clinical fracture

Study or Subgroup	Teriparatide Events	Teriparatide Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
FTP 2001	0	63	0	20		Not estimable
Total (95% CI)		**63**		**20**		**Not estimable**
Total events:	0		0			

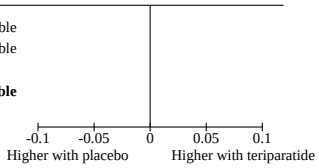
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6: Teriparatide versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 3: Mean change in femoral neck BMD (DXA)

Study or Subgroup	Teriparatide Mean [g/cm²]	Teriparatide SD [g/cm²]	Teriparatide Total	Placebo Mean [g/cm²]	Placebo SD [g/cm²]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [g/cm²]
FTP 2001	0	0	63	0	0	20		Not estimable
ACTIVE 2016	0	0	192	0	0	167		Not estimable
Total (95% CI)			**255**			**187**		**Not estimable**

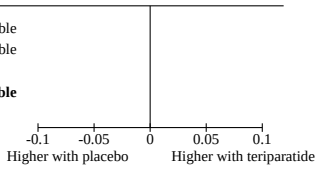
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6: Teriparatide versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 4: Mean change in lumbar spine BMD (DXA)

Study or Subgroup	Teriparatide Mean [g/cm²]	Teriparatide SD [g/cm²]	Teriparatide Total	Placebo Mean [g/cm²]	Placebo SD [g/cm²]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [g/cm²]
FTP 2001	0	0	63	0	0	20		Not estimable
ACTIVE 2016	0	0	192	0	0	167		Not estimable
Total (95% CI)			**255**			**187**		**Not estimable**

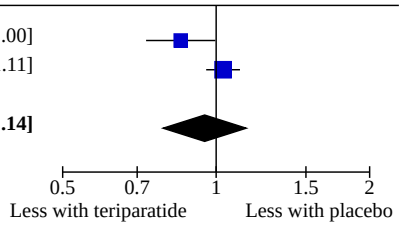
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 6.5. Comparison 6: Teriparatide versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 5: Adverse events

Study or Subgroup	Teriparatide Events	Teriparatide Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
FTP 2001	51	63	19	20	43.5%	0.85 [0.73 , 1.00]
ACTIVE 2016	172	192	145	167	56.5%	1.03 [0.96 , 1.11]
Total (95% CI)		**255**		**187**	**100.0%**	**0.95 [0.79 , 1.14]**
Total events:	223		164			

Heterogeneity: Tau² = 0.01; Chi² = 4.71, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable



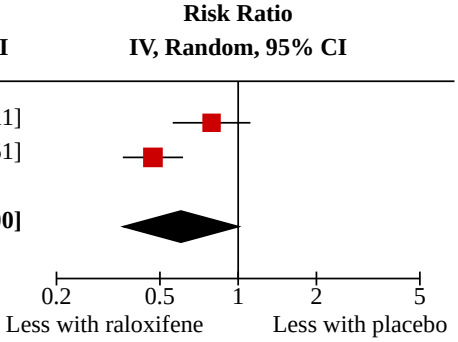
Comparison 7. Raloxifene versus placebo for patients with osteoporosis and CKD stages 3-4

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Vertebral fracture by radiography	1		Risk Ratio (IV, Random, 95% CI)	0.60 [0.36, 1.00]
7.2 Clinical fracture	1		Risk Ratio (IV, Random, 95% CI)	0.96 [0.80, 1.16]
7.3 Mean change in femoral neck BMD (DXA)	1	4973	Mean Difference (IV, Random, 95% CI)	Not estimable
7.4 Mean change in lumbar spine BMD (DXA)	1	4973	Mean Difference (IV, Random, 95% CI)	Not estimable
7.5 Adverse events	1		Risk Ratio (IV, Random, 95% CI)	0.99 [0.98, 1.00]

Analysis 7.1. Comparison 7: Raloxifene versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 1: Vertebral fracture by radiography

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
MORE 1999 (1)	-0.2357	0.1756	47.7%	0.79 [0.56 , 1.11]
MORE 1999 (2)	-0.755	0.136	52.3%	0.47 [0.36 , 0.61]
Total (95% CI)			**100.0%**	**0.60 [0.36 , 1.00]**

Heterogeneity: Tau² = 0.11; Chi² = 5.47, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 1.96 (P = 0.05)
Test for subgroup differences: Not applicable



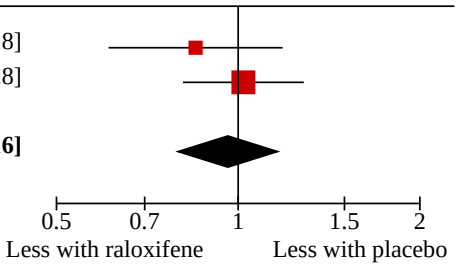
Footnotes

(1) CKD stage 3b-4
(2) CKD stage 3a

Analysis 7.2. Comparison 7: Raloxifene versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 2: Clinical fracture

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
MORE 1999 (1)	-0.1625	0.1693	32.5%	0.85 [0.61 , 1.18]
MORE 1999 (2)	0.0198	0.1176	67.5%	1.02 [0.81 , 1.28]
Total (95% CI)			**100.0%**	**0.96 [0.80 , 1.16]**

Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable

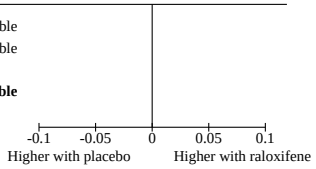


Footnotes
(1) CKD stage 3b-4
(2) CKD stage 3a

Analysis 7.3. Comparison 7: Raloxifene versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 3: Mean change in femoral neck BMD (DXA)

Study or Subgroup	Raloxifene Mean [g/cm²]	Raloxifene SD [g/cm²]	Raloxifene Total	Placebo Mean [g/cm²]	Placebo SD [g/cm²]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [g/cm²]
MORE 1999 (1)	0	0	2323	0	0	1170		Not estimable
MORE 1999 (2)	0	0	970	0	0	510		Not estimable
Total (95% CI)			**3293**			**1680**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

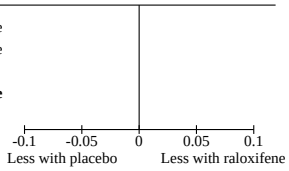


Footnotes
(1) CKD stage 3a
(2) CKD stage 3b-4

Analysis 7.4. Comparison 7: Raloxifene versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 4: Mean change in lumbar spine BMD (DXA)

Study or Subgroup	Raloxifene Mean [g/cm²]	Raloxifene SD [g/cm²]	Raloxifene Total	Placebo Mean [g/cm²]	Placebo SD [g/cm²]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [g/cm²]
MORE 1999 (1)	0	0	970	0	0	510		Not estimable
MORE 1999 (2)	0	0	2323	0	0	1170		Not estimable
Total (95% CI)			**3293**			**1680**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

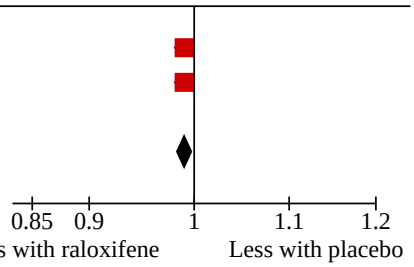


Footnotes
(1) CKD stage 3b-4
(2) CKD stage 3a

Analysis 7.5. Comparison 7: Raloxifene versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 5: Adverse events

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
MORE 1999 (1)	-0.0101	0.0052	50.0%	0.99 [0.98 , 1.00]
MORE 1999 (2)	-0.0101	0.0052	50.0%	0.99 [0.98 , 1.00]
Total (95% CI)			**100.0%**	**0.99 [0.98 , 1.00]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 2.75 (P = 0.006)
Test for subgroup differences: Not applicable



Footnotes
(1) CKD stage 3b-4
(2) CKD stage 3a

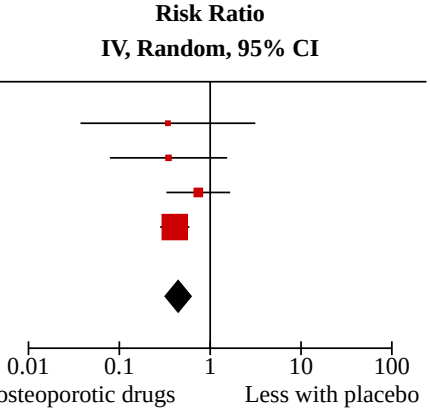
Comparison 8. Sensitivity analysis: any anti-osteoporotic drugs versus placebo for patients with osteoporosis and CKD stages 3-4

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Vertebral fracture by radiography	3		Risk Ratio (IV, Random, 95% CI)	0.44 [0.32, 0.61]
8.2 Clinical fracture	2		Risk Ratio (IV, Random, 95% CI)	0.84 [0.67, 1.05]
8.3 Adverse events	2	3417	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.97, 1.01]

Analysis 8.1. Comparison 8: Sensitivity analysis: any anti-osteoporotic drugs versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 1: Vertebral fracture by radiography

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
FREEDOM 2009	-1.0712	1.1307	2.2%	0.34 [0.04 , 3.14]
ACTIVE 2016	-1.0558	0.758	4.8%	0.35 [0.08 , 1.54]
FIT 1993	-0.3011	0.412	16.2%	0.74 [0.33 , 1.66]
FREEDOM 2009	-0.8977	0.1891	76.9%	0.41 [0.28 , 0.59]
Total (95% CI)			**100.0%**	**0.44 [0.32 , 0.61]**

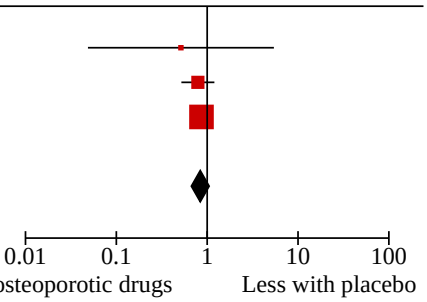
Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 4.90 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8: Sensitivity analysis: any anti-osteoporotic drugs versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 2: Clinical fracture

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
FREEDOM 2009	-0.6657	1.2022	0.9%	0.51 [0.05 , 5.42]
FIT 1993	-0.2357	0.2134	28.9%	0.79 [0.52 , 1.20]
FREEDOM 2009	-0.1443	0.137	70.2%	0.87 [0.66 , 1.13]
Total (95% CI)			**100.0%**	**0.84 [0.67 , 1.05]**

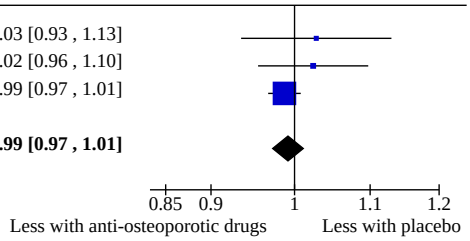
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.53 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 8.3. Comparison 8: Sensitivity analysis: any anti-osteoporotic drugs versus placebo for patients with osteoporosis and CKD stages 3-4, Outcome 3: Adverse events

Study or Subgroup	Anti-osteoporotic drugs Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
FREEDOM 2009	35	36	35	37	4.1%	1.03 [0.93 , 1.13]
ACTIVE 2016	320	360	145	167	7.7%	1.02 [0.96 , 1.10]
FREEDOM 2009	1308	1418	1307	1399	88.2%	0.99 [0.97 , 1.01]
Total (95% CI)		**1814**		**1603**	**100.0%**	**0.99 [0.97 , 1.01]**
Total events:	1663		1487			

Heterogeneity: Tau² = 0.00; Chi² = 1.54, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Kidney Diseases] explode all trees 2. MeSH descriptor: [Renal Replacement Therapy] explode all trees 3. MeSH descriptor: [Renal Insufficiency] this term only 4. MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees 5. MeSH descriptor: [Diabetic Nephropathies] this term only 6. (diabetic kidney disease*):ti,ab,kw 7. (Diabetic nephropath*):ti,ab,kw 8. dialysis:ti,ab,kw (Word variations have been searched) 9. hemodialysis or haemodialysis:ti,ab,kw (Word variations have been searched) 10. hemofiltration or haemofiltration:ti,ab,kw (Word variations have been searched) 11. hemodiafiltration or haemodiafiltration:ti,ab,kw (Word variations have been searched) 12. kidney disease* or renal disease* or kidney failure or renal failure:ti,ab,kw (Word variations have been searched)

(Continued)

	13.ESRF or ESKF or ESRD or ESKD:ti,ab,kw (Word variations have been searched) 14.CKF or CKD or CRF or CRD:ti,ab,kw (Word variations have been searched) 15.CAPD or CCPD or APD:ti,ab,kw (Word variations have been searched) 16.predialysis or pre-dialysis:ti,ab,kw (Word variations have been searched) 17.{or #1-#16} 18."Chronic Kidney Disease-Mineral and Bone Disorder" 19.MeSH descriptor: [Osteoporosis] this term only 20.MeSH descriptor: [Osteoporosis, Postmenopausal] explode all trees 21.(osteoporosis):ti,ab,kw 22.("mineral and bone disorder"):ti,ab,kw 23.{or #18-#22} 24.MeSH descriptor: [Bone Density Conservation Agents] explode all trees 25.MeSH descriptor: [Diphosphonates] explode all trees 26.(etidronate or clodronate or tiludronate):ti,ab,kw 27.(alendronate or risedronate or ibandronate):ti,ab,kw 28.(pamidronate or zoledronate):ti,ab,kw 29.MeSH descriptor: [Denosumab] this term only 30.(denosumab or prolia or xgeva):ti,ab,kw 31.("amg 162" or amg162):ti,ab,kw 32.MeSH descriptor: [Raloxifene Hydrochloride] this term only 33.(raloxifene):ti,ab,kw 34.MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees 35.(bazedoxifene):ti,ab,kw 36.MeSH descriptor: [Teriparatide] this term only 37.(teriparatide):ti,ab,kw 38.abaloparatide:ti,ab,kw 39.romosozumab:ti,ab,kw 40.strontium renalate:ti,ab,kw 41.{or #24-#40} 42.{and #17, #23, #41}
MEDLINE	1. Kidney Diseases/ 2. exp Renal Replacement Therapy/ 3. Renal Insufficiency/ 4. exp Renal Insufficiency, Chronic/ 5. Diabetic Nephropathies/ 6. diabetic kidney disease$.tw. 7. diabetic nephropath$.tw. 8. exp Hypertension, Renal/ 9. dialysis.tw. 10.(hemodialysis or haemodialysis).tw. 11.(hemofiltration or haemofiltration).tw. 12.(hemodiafiltration or haemodiafiltration).tw. 13.(kidney disease* or renal disease* or kidney failure or renal failure).tw. 14.(ESRF or ESKF or ESRD or ESKD).tw. 15.(CKF or CKD or CRF or CRD).tw. 16.(CAPD or CCPD or APD).tw. 17.(predialysis or pre-dialysis).tw. 18.Uremia/ 19.(uremic or ur?emia).tw. 20.or/1-19 21."Chronic Kidney Disease-Mineral and Bone Disorder"/

(Continued)

	22.Bone Diseases, Metabolic/ 23.OSTEOPOROSIS/ 24.OSTEOPOROSIS, POSTMENOPAUSAL/ 25.osteoporosis.tw. 26."mineral and bone disorder".tw. 27.or/21-26 28.Bone Density Conservation Agents/ 29.exp Diphosphonates/ 30.(etidronate or clodronate or tiludronate).tw. 31.(alendronate or risedronate or ibandronate).tw. 32.(pamidronate or zoledronate).tw. 33.Denosumab/ 34.denosumab.tw. 35.prolia.tw. 36.xgeva.tw. 37.("amg 162" or amg162).tw. 38.Raloxifene Hydrochloride/ 39.raloxifene.tw. 40.exp Selective Estrogen Receptor Modulators/ 41.bazedoxifene.tw. 42.Teriparatide/ 43.teriparatide.tw. 44.abaloparatide.tw 45.romosozumab.tw 46.strontium renalate.tw 47.or/28-45 48.and/20,27,47
EMBASE	1. exp renal replacement therapy/ 2. kidney disease/ 3. chronic kidney disease/ 4. kidney failure/ 5. chronic kidney failure/ 6. mild renal impairment/ 7. stage 1 kidney disease/ 8. moderate renal impairment/ 9. severe renal impairment/ 10.end stage renal disease/ 11.renal replacement therapy-dependent renal disease/ 12.diabetic nephropathy/ 13.kidney transplantation/ 14.renovascular hypertension/ 15.(hemodialysis or haemodialysis).tw. 16.(hemofiltration or haemofiltration).tw. 17.(hemodiafiltration or haemodiafiltration).tw. 18.dialysis.tw. 19.(CAPD or CCPD or APD).tw. 20.(kidney disease* or renal disease* or kidney failure or renal failure).tw. 21.(CKF or CKD or CRF or CRD).tw. 22.(ESRF or ESKF or ESRD or ESKD).tw. 23.(predialysis or pre-dialysis).tw. 24.((kidney or renal) adj (transplant* or graft* or allograft*)).tw.

(Continued)

25.or/1-24
26.exp osteoporosis/
27.osteoporosis.tw.
28."chronic kidney disease-mineral and bone disorder"/
29.renal osteodystrophy/
30.or/26-29
31.exp Diphosphonates/
32.(etidronate or clodronate or tiludronate).tw.
33.(alendronate or risedronate or ibandronate).tw.
34.(pamidronate or zoledronate).tw.
35.Denosumab/
36.denosumab.tw.
37.prolia.tw.
38.xgeva.tw.
39.("amg 162" or amg162).tw.
40.Raloxifene Hydrochloride/
41.raloxifene.tw.
42.exp Selective Estrogen Receptor Modulators/
43.bazedoxifene.tw.
44.Teriparatide/
45.teriparatide.tw.
46.abaloparatide/
47.abaloparatide.tw
48.romosozumab/
49.romosozumab.tw.
50.strontium ranelate/
51.strontium renalate.tw.
52.or/31-51
53.and/25,30,52

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).

(Continued)

	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they can-

(Continued)

	not be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

HISTORY

Protocol first published: Issue 9, 2019

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: TH, NW
2. Study selection: TH, YH, YM
3. Extract data from studies: TH, YH, YM, NW
4. Enter data into RevMan: TH, YH, YM
5. Carry out the analysis: TH, NW
6. Interpret the analysis: TH, NW
7. Draft the final review: TH, NW
8. Disagreement resolution: TH, YH, YM, NW
9. Update the review: TH

DECLARATIONS OF INTEREST

- TH: no known conflicts of interest
- YH: no known conflicts of interest
- YM: no known conflicts of interest
- NW: no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- New Source of support, Other

External sources

- New Source of support, Other

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We could not obtain sufficient information on each CKD stage, despite contacting the corresponding authors.
- Most of the studies reported both vertebral and non-vertebral or clinical fracture.

These were handled as follows:

- Stage of CKD was divided into 2 groups: 1) stages 3-4 and 2) stages 5 and 5D.
- We divided “the Fracture at any sites” into “Vertebral fracture by radiography” and “Clinical fracture”. Clinical fracture was defined as any site fractures with fracture-related symptoms (FIT 1993).

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [adverse effects] [therapeutic use]; Bias; Bone Density [drug effects]; Bone Density Conservation Agents [adverse effects] [*therapeutic use]; Denosumab [adverse effects] [therapeutic use]; Femur Neck [drug effects]; Fractures, Spontaneous [epidemiology] [prevention & control]; Hip; Indoles [adverse effects] [therapeutic use]; Lumbar Vertebrae [drug effects]; Osteoporosis, Postmenopausal [drug therapy] [mortality] [*therapy]; Parathyroid Hormone-Related Protein [adverse effects] [therapeutic use]; Raloxifene Hydrochloride [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Renal Dialysis; Renal Insufficiency, Chronic [*complications] [therapy]; Spinal Fractures [diagnostic imaging] [prevention & control]; Teriparatide [adverse effects] [therapeutic use]; Thiophenes [adverse effects] [therapeutic use]; *Watchful Waiting

MeSH check words

Female; Humans