National Institute for Health and Care Excellence

Final

Hyperparathyroidism (primary): diagnosis, assessment and initial management

[H] Evidence review for bisphosphonates

NICE guideline NG132

Intervention evidence review

May 2019

Final

This evidence review was developed by the National Guideline Centre

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Contents

1 Bisphosphonates

1.1 Review question: What is the clinical and cost effectiveness of bisphosphonates in people with primary hyperparathyroidism?

1.2 Introduction

People with primary hyperparathyroidism (PHPT) may have reduced bone mineral density, which increases the risk of fragility fractures. Bisphosphonates are a class of drug that reduces bone loss and increase bone mineral density. Oral bisphosphonates have no appreciable and sustained effects in lowering serum calcium. The aim of this review is to ascertain the clinical and cost-effectiveness of bisphosphonates, including in people not eligible for surgery and in people post-surgery.

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults (18 years or over) with confirmed primary hyperparathyroidism Strata (the following groups are to be reported separately): • Absence/presence of bone end-organ effects (bone end-organ effects defined as history of fragility fractures or osteoporosis (BMD T-score <-2.5 at any site) • People with normocalcaemic PHPT • Previous parathyroidectomy • Pregnant women
Interventions	Oral or IV bisphosphonates
Comparisons	Placebo; no treatment; calcimimetics; surgery; combination treatment
Outcomes	Health-related quality of life; mortality; deterioration in renal function; fractures; occurrence of kidney stones; persistent hypercalcaemia; BMD (lumbar spine or distal radius); cardiovascular events; adverse events; cancer incidence
Study design	RCTs and systematic reviews of RCTs

1.4 Clinical evidence

1.4.1 Included studies

A search was conducted for randomised controlled trials assessing the effectiveness of bisphosphonates for treatment of people with primary hyperparathyroidism. The bisphosphonates were to be compared against the following: placebo, no treatment, calcimimetics, surgery or combination treatment.

Three studies were included in the review.[4, 5, 15] These are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 3 and Table 4). See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

In the three studies, the participants were either all or mostly osteoporotic (defined as BMD T-score ≤ -2.5). All participants were women except in one study [15] in which a third of the

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participants were men. The bisphosphonates were given orally in all the studies. Two studies compared alendronate with placebo [5, 15]; one compared alendronate with vitamin D supplements against vitamin D only [4]. The participants in the study Cesareo 2015 [4] were all normocalcaemic (generally defined as serum adjusted calcium ≤ 2.6 mmol/litre); this study was analysed separately under the normocalcaemic stratum. It should be noted that all participants in this study had osteoporosis (and therefore, also had bone end-organ effects according to our protocol). All the other studies were considered together in our stratum of people with bone end-organ effects and hypercalcaemic PHPT.

No studies were identified comparing bisphosphonates to calcimimetics, surgery or combination treatment.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Follow-up	Outcomes
Cesareo 2015[4]	Alendronate + Vitamin D versus Vitamin D only	Normocalcaemic osteoporotic postmenopausal women with PHPT (inclusion criteria was BMD T score <-2.5 at ≥1 skeletal site) Stratum analysed in: normocalcaemic PHPT and presence of bone end-organ effects	12 months	Lumbar spine BMD Incidence of hypercalcaemia or hypercalciuria
Chow 2003[5]	Alendronate versus Placebo	Included participants were “generally osteoporotic” postmenopausal women with PHPT (no other details given except baseline BMD T score of −2.54 ± 1.25 at lumbar spine and −3.58 ± 1.43 at distal third of radius) Stratum analysed in: hypercalcaemic PHPT and presence of bone end-organ effects	48 weeks	Lumbar spine BMD Distal radius BMD Serious adverse events
Khan 2004[15]	Alendronate versus Placebo	Mix of men and women (≈ 1:3) with PHPT in which the majority (>60%)	12 months	Fractures Adverse events

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Study	Intervention and comparison	Population	Follow-up	Outcomes
		were osteoporotic (inclusion criteria was T score <-1.0 at ≥1 skeletal site) Stratum analysed in: hypercalcaemic PHPT and presence of bone end-organ effects		

See appendix D for full evidence tables.

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1.4.4 Quality assessment of clinical studies included in the evidence review

1.4.4.1 Results stratum: People with normocalcaemic PHPT and presence of bone end-organ effects

Table 3: Clinical evidence summary: Alendronate + Vitamin D versus Vitamin D only

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Vitamin D only	Risk difference with Alendronate + Vitamin D
Lumbar spine BMD assessed with: g/cm^2 follow up: 12 months	30 (1 RCT)	LOW [a,b]	-	The mean lumbar spine BMD was 0.759 g/cm^2	MD 0.06 higher (0.01 higher to 0.11 higher)
Incidence of hypercalcaemia or hypercalciuria follow up: 12 months	30 (1 RCT)	LOW [a,c]	Not estimable	Moderate	
				0 per 1000	0 fewer per 1000 (120 fewer to 120 more)

a. Downgraded by one increment if the majority of the evidence was at high risk of bias and downgraded by two increments if the majority of the evidence was at very high risk of bias
b. Downgraded by one increment if the confidence interval crossed one MID, and downgraded by two increments if the confidence interval crossed both MIDs
c. Outcome of interest listed in the protocol is the number of persistent hypercalcaemia cases

1.4.4.2 Results stratum: People with hypercalcaemic PHPT and presence of bone end-organ effects

Table 4: Clinical evidence summary: Alendronate versus Placebo

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Alendronate
Lumbar spine BMD assessed with: % change from baseline follow up: 48 weeks	40 (1 RCT)	LOW[a]	-	The mean change in lumbar spine BMD was +0.19 %	MD 3.6% higher (1.45 higher to 5.75 higher)

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Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Alendronate
Distal radius BMD assessed with: % change from baseline follow up: 48 weeks	40 (1 RCT)	VERY LOW[a,b]	-	The mean change in distal radius BMD was +0.07 %	MD 0.94% higher (1.68 lower to 3.56 higher)
Number of serious adverse events follow up: 48 weeks	40 (1 RCT)	VERY LOW[a,b]	RR 0.67 (0.12 to 3.57)	Moderate	
				150 per 1000	49 fewer per 1000 (132 fewer to 385 more)
Number of fractures follow up: 12 months	37 (1 RCT)	LOW[a]	Not estimable	Moderate	
				0 per 1000	0 fewer per 1000 (100 fewer to 100 more)
Number of adverse events follow up: 12 months	37 (1 RCT)	LOW[a]	Not estimable	Moderate	
				0 per 1000	0 fewer per 1000 (100 fewer to 100 more)

a. Downgraded by one increment if the majority of the evidence was at high risk of bias and downgraded by two increments if the majority of the evidence was at very high risk of bias
b. Downgraded by one increment if the confidence interval crossed one MID, and downgraded by two increments if the confidence interval crossed both MIDs

See appendix F for full GRADE tables.

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1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified for this question.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.5.3 Unit costs

The committee advised that the predominate bisphosphonates currently prescribed for treatment of PHPT are alendronic acid (oral) and zoledronic acid (intravenous). The prices for these two bisphosphonates were presented to the committee for consideration. Alendronic acid is available in a number of different formulations (e.g. sugar free) which are priced differently. For the purpose of cost effectiveness considerations the lowest priced option has been included.

Table 5: UK costs of bisphosphonates

Drug	Preparation	Recommended dose	Cost – per month	Cost – annual
Alendronic acid	Tablet	70 mg weekly[(a)]	£0.60	£7.82
Zoledronic acid	Intravenous infusion	50 mcg/ml once a year	-	£13.24

Source[s]: NHS Drug Tariff, 2017[19]; BNF[11], eMIT[6]
(a) Taken once per week as a single dose

The committee noted that there would also be a significant cost to deliver bisphosphonates intravenously, which would usually be a day-case delivery. As the NHS Reference costs do not include an entry for IV delivery of bisphosphonates, this cost is estimated using the reference cost of a day case delivery of simple parenteral chemotherapy (at first attendance), which is assumed to cover the cost of a day case admission of a drug by infusion. Therefore the delivery cost for zoledronic acid is estimated to be £260 (SB12Z).

1.6 Resource impact

The recommendations made by the committee based on this review are not expected to have a substantial impact on resources.

1.7 Evidence statements

1.7.1 Clinical evidence statements

1.7.1.1 Alendronate + Vitamin D versus Vitamin D only in people with normocalcaemic PHPT and presence of bone end-organ effects

There was a clinically important benefit of Alendronate + Vitamin D for Lumbar spine BMD (1 study, n=30; follow up 12 months; Low quality). There was no difference between

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Alendronate + Vitamin D and Vitamin D only for Incidence of hypercalcaemia or hypercalciuria (1 study, n=30; follow up 12 months; Low quality). No evidence was identified for health-related quality of life; mortality; deterioration in renal function; fractures; occurrence of kidney stones; cardiovascular events; adverse events; cancer incidence.

1.7.1.2 Alendronate versus placebo in people with hypercalcaemic PHPT and presence of bone end-organ effects

There was a clinically important benefit of Alendronate for lumbar spine BMD (1 study, n=40; follow up 48 weeks; Low quality). There was no difference between Alendronate and placebo for distal radius BMD (1 study, n=40; follow up 48 weeks; Very Low quality); number of fractures (1 study, n=37; follow up 12 months; Low quality); number of serious adverse events (1 study, n=40; follow up 48 weeks; Very Low quality) and number of adverse events (1 study, n=37; follow up 12 months; Low quality). No evidence was identified for health-related quality of life; mortality; deterioration in renal function; occurrence of kidney stones; persistent hypercalcaemia; cardiovascular events; cancer incidence.

1.7.1.3 Bisphosphonates versus calcimimetics

No evidence was identified.

1.7.1.4 Bisphosphonates versus surgery

No evidence was identified.

1.7.1.5 Bisphosphonates versus combination treatment (calcimimetics and bisphosphonates)

No evidence was identified.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The committee considered the outcomes of health-related quality of life and mortality as critical outcomes for decision making. Other important outcomes included deterioration in renal function, fractures, occurrence of kidney stones, persistent hypercalcaemia, BMD (lumbar spine or distal radius), cardiovascular events, adverse events and cancer incidence.

No evidence was identified for the critical outcomes of HRQOL and mortality and the important outcomes of deterioration in renal function; occurrence of kidney stones; cardiovascular events; and cancer incidence.

1.8.1.2 The quality of the evidence

Three studies were identified in total, all comparing oral bisphosphonates to no bisphosphonate administration. Two studies compared alendronate with placebo and the other study compared alendronate plus vitamin D supplements against vitamin D alone. No studies were identified comparing bisphosphonates to calcimimetics, surgery or combination treatment. No evidence was found for the use of IV bisphosphonates in people with primary hyperparathyroidism.

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The evidence was split into strata according to the protocol. The first stratum was people with normocalcaemic primary hyperparathyroidism and the presence of bone end-organ effects. The second stratum was people with hypercalcaemic primary hyperparathyroidism and the presence of bone end-organ effects. The protocol definition for someone having bone end-organ effects was either a history of fragility fractures or osteoporosis (BMD T-score <-2.5 at any site). The evidence for the normocalcaemic primary hyperparathyroidism stratum completely matched this protocol definition, as people were only included in the study if they had osteoporosis. However, the evidence for the hypercalcaemic primary hyperparathyroidism stratum was less clear as to the proportion of people who had bone end-organ effects. One study stated that the included participants were 'generally osteoporotic' with no other details given except for a mean baseline BMD T-score of −2.54 ± 1.25 at lumbar spine and −3.58 ± 1.43 at distal third of radius. The other study included people with a T-score <-1.0 at ≥1 skeletal site, and stated that >60% had osteoporosis. The committee agreed that this evidence should be analysed in the 'presence of end-organ effects' stratum, but this uncertainty decreased the committee's confidence in the evidence. No evidence was identified in people without bone end-organ effects, nor was any evidence identified for the protocol strata of pregnant women or people who have had previous parathyroidectomy.

All of the evidence was of Low or Very Low quality due to risk of bias and imprecision, decreasing the confidence that the effect estimate represents the true effect that would be seen in the guideline population.

1.8.1.3 Benefits and harms

For people with normocalcaemic primary hyperparathyroidism and the presence of bone end-organ effects, there was a clinical benefit of bisphosphonates on the lumbar spine BMD. No person in either arm developed a change in hypercalcaemia during the study and therefore there was no clinical difference of bisphosphonates on this outcome. No other outcomes were reported for this stratum.

For people with hypercalcaemic primary hyperparathyroidism and the presence of bone end-organ effects, there was a clinical benefit of bisphosphonates on the lumbar spine BMD. There was no clinical difference for the outcomes of the distal radius BMD, number of fractures, number of serious adverse events and number of adverse events.

The committee highlighted that alendronate is often associated with upper GI events and even hospitalisation, but that this was not reflected in the available evidence. From clinical experience the committee agreed that alendronate can cause problematic GI side effects. The committee noted that taking oral alendronate can be inconvenient for people as they need to take the drug in the morning and remain in an upright position for half an hour. IV administration of bisphosphonates is sometimes used immediately before surgery. No evidence was found in this review for the use of IV bisphosphonates in people with primary hyperparathyroidism looking at bone density and fracture outcomes. However, the committee was aware of cohort studies for their use perioperatively to control calcium homeostasis, which is not within our scope. The committee noted that the included study sample sizes were small and that the studies would not have been powered to detect a difference in fractures.

The committee discussed that the lumbar spine BMD often sees a greater response to bisphosphonates due to the proportion of trabecular bone within the vertebrae. This is reflected in the evidence, with a clinical benefit of bisphosphonates on the lumbar spine BMD but not the distal radius BMD.

The committee agreed that bisphosphonates should be considered in people with primary hyperparathyroidism and bone end organ effects, to reduce fracture risk in line with NICE guideline on osteoporosis: assessing the risk of fragility fracture. The committee agreed that the use of bisphosphonates should be considered in both people who will and will not go on

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to have surgery. The committee from their experience noted that in people with primary hyperparathyroidism, both oral and intravenous bisphosphonates lower serum calcium levels transiently and are sometimes used in acute treatment, but are inefficient in maintaining lower serum calcium-levels in the long term. The committee from their clinical experience discussed the pre-operative use of intravenous bisphosphonate therapy to reduce hypercalcaemia. While this may help reduce serum calcium if the level is very high, the committee did not advocate this approach.

The committee discussed that fracture risk may remain elevated in people after successful parathyroidectomy and felt that bisphosphonates would be appropriate to help improve BMD and reduce fracture risk in these patients.

Bisphosphonates have shown benefit in postmenopausal women with osteoporosis, and the committee agreed that there is no reason this benefit would be any different in people with primary hyperparathyroidism. The committee was aware of the recommendations in NICE's technology appraisal guidance on bisphosphonates for treating osteoporosis.

The committee discussed that bisphosphonates do not act to reduce hypercalcaemia in the long term and hence agreed that a bisphosphonate should not be offered for long-term management of hypercalcaemia in primary hyperparathyroidism.

The committee discussed that, in people who are cured after parathyroid surgery, skeletal recovery can take some time and the use of bisphosphonates in this population needs to be carefully considered on an individual case basis.

Although there was no evidence available for intravenous bisphosphonates, the committee was comfortable in extrapolating evidence from oral bisphosphonates to intravenous bisphosphonates, as oral bisphosphonates are considered to be less potent and cause fewer adverse effects than intravenous bisphosphonates.

The committee noted that serum-calcium concentration needs to be monitored during treatment [11].

The committee noted that there was a very rare risk of bisphosphonate-related osteonecrosis of the jaw (ONJ) and/or atypical femoral fracture (AFF). ONJ and AFF are associated with both oral and IV bisphosphonates (more notable with IV) and are thought to be caused by trauma to bones that have a limited capacity for healing due to the effects of bisphosphonate therapy retained within the skeleton. The committee hence discussed the importance of warning patients about these risks, as this may have an impact on quality of life and future care.

1.8.2 Cost effectiveness and resource use

No relevant health economic evaluations were identified for this question. Unit costs were presented to the committee to aid their consideration of cost effectiveness.

The majority of bisphosphonates are taken via oral delivery. The annual cost of oral bisphosphonates (alendronic acid) in the UK is estimated to be around £7.82, given the recommended weekly dose of 70 mg. IV bisphosphonates (zoledronic acid) are given once annually, and have an annual drug cost of around £13.24. Delivery of IV bisphosphonates usually takes place as a day case in hospital. The cost of delivery for IV bisphosphonates was estimated to be around £260, using a proxy measure of the NHS reference cost for day case delivery of simple parenteral chemotherapy as the cost of delivering a drug by intravenous infusion. However, the committee noted that actual costs may vary significantly depending on the location and type of clinic where the drug is delivered, and could range from £130 to £800. Hence, the impact on healthcare resource is highly dependent on where IV delivery takes place.

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While evidence on the clinical effectiveness of bisphosphonates is uncertain from this review, the committee noted that both oral and IV bisphosphonates are recommended in TA464 for treating osteoporosis, and hence have previously been assessed as being a cost effective treatment. Bisphosphonates are currently recommended for people eligible for a risk assessment for osteoporosis and who have a risk of fracture greater than 1% (for oral bisphosphonates) or 10% (for IV bisphosphonates). In accordance with this guidance, people with primary hyperparathyroidism are eligible for risk assessment for osteoporosis as primary hyperparathyroidism is listed as a risk factor for 'other causes of secondary osteoporosis'. The committee considered that under this guidance the majority of the primary hyperparathyroidism population are likely to be eligible for bisphosphonates.

As also reflected in TA464, the committee discussed that due to the high administration cost of IV bisphosphonates this treatment should be limited to those who are intolerant to oral bisphosphonates. It is estimated that around one-third of patients will experience side effects of alendronic acid, however it is unclear what proportion of these patients will receive IV delivery. While the committee acknowledges that the cost associated with IV bisphosphonates is potentially high, this cost is likely to be outweighed by costs associated with clinical events such as fragility fractures, which the patient is at risk of experiencing in the absence of treatment via bisphosphonates. Hence, the committee is of the opinion that bisphosphonates in either form of delivery are a cost effective intervention.

The committee discussed that bisphosphonates are also likely to be an effective and cost effective treatment for reducing fracture risk associated with the loss of bone density as a result of hypercalcaemia in people with primary hyperparathyroidism. This is due to the low cost of treatment and the avoided costs and disutility associated with the reduced fracture risk, which is likely to be sufficiently large for bisphosphonates to be considered cost effective.

Overall, bisphosphonates are a low-cost drug, and the recommendation in this guideline is in line with current standard practice. Consequently, this recommendation is not expected to have a significant resource impact.

1.8.3 Other factors the committee took into account

As bisphosphonates do not provide a cure for the underlying condition of primary hyperparathyroidism, it was emphasised that they should not be considered as an alternative to curative measures such as surgery. Therefore it is important that patients are given the full context of this treatment to ensure that bisphosphonates are not considered by the patient as an alternative to surgery.

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Appendices

Appendix A: Review protocols

Table 6: Review protocol: Bisphosphonates

Field	Content
Review question	What is the clinical and cost effectiveness of bisphosphonates in people with primary hyperparathyroidism?
Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To assess the effectiveness of bisphosphonates for treatment of people with primary hyperparathyroidism
Eligibility criteria – population	Adults (18 years or over) with confirmed primary hyperparathyroidism Strata (report the following groups separately): • Absence/presence of bone end-organ effects (bone end-organ effects defined as history of fragility fractures or osteoporosis (BMD T-score <-2.5 at any site) • People with normocalcaemic PHPT (serum adjusted calcium ≤2.6 mmol/L and an elevated PTH that cannot be explained by abnormal renal function or low 25OHD) • Previous parathyroidectomy • Pregnant women Exclude people: • with secondary and tertiary HPT • with multiple endocrine neoplasia (MEN) • with familial hyperparathyroidism • with parathyroid carcinoma • on medications interfering with calcium metabolism (for example, lithium). Studies including mixed populations of people with primary and secondary or tertiary hyperparathyroidism will be excluded unless subgroups reported separately by type of hyperparathyroidism.
Eligibility criteria – intervention(s)	• Oral bisphosphonates (alendronic acid/alendronate, ibandronic acid, risedronate/ risedronate sodium, sodium clodronate, etidronate) • IV bisphosphonates (ibandronic acid, pamidronate disodium, zoledronic acid)
Eligibility criteria – comparator(s)	• Placebo • No treatment (surveillance/conservative management) • Surgery (see protocol in evidence report C) • Calcimimetics (see protocol in evidence report G) • Combination treatment (calcimimetics and bisphosphonates) The above comparators will not be pooled in the analysis
Outcomes and prioritisation	Report all outcomes separately for <6 months and ≥6 months (for fractures and BMD only report outcomes ≥12 months)

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	Critical outcomes: • HRQOL (continuous outcome) • Mortality (dichotomous outcome) **Important outcomes:** • Deterioration in renal function (dichotomous – study may also report renal replacement) • Fractures (vertebral or long bone) (dichotomous outcome) • Occurrence of kidney stones (dichotomous outcome) • Persistent hypercalcaemia (dichotomous outcome) • BMD (continuous) of the distal radius or the lumbar spine • Cardiovascular events (dichotomous outcome) • Adverse events (to include discontinuation due to side effects; dichotomous outcome) • Cancer incidence (dichotomous outcome)
Eligibility criteria – study design	RCTs and systematic reviews of RCTs In the absence of RCT evidence NRSs will be included (only if the following key confounders are matched for or adjusted for in the analysis) Key confounders: • Age • Absence/presence of end-organ effects • Adjusted serum calcium level
Other inclusion exclusion criteria	• Non-English language articles • Conference abstracts
Proposed sensitivity / subgroup analysis, or meta-regression	IV versus oral bisphosphonates Sensitivity analysis: if there is still heterogeneity in the data following subgroup analysis, remove any studies from the analysis that use the Z-score to recruit people with a low BMD, rather than the T-score to recruit people with osteoporosis.
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). • GRADEpro was used to assess the quality of evidence for each outcome. • Endnote for bibliography, citations, sifting and reference management Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library, CINAHL, PsycINFO Date: all years Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2002 NHSEED, HTA – all years

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	Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10051
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B.
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jonathan Mant in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.

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Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 7: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations (recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered). • Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[18] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and

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Review question	All questions – health economic evidence
	the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 06 August 2018	Exclusions
Embase (OVID)	1974 – 06 August 2018	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 8 of 12 CENTRAL to 2018 Issue 7 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 06 August 2018	Exclusions
PsycINFO (ProQuest)	Inception – 06 August 2018	Exclusions

Medline (Ovid) search terms

1.	hyperparathyroidism/ or hyperparathyroidism, primary/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	Parathyroid Neoplasms/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14

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16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language

Embase (Ovid) search terms

1.	hyperparathyroidism/ or primary hyperparathyroidism/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	parathyroid tumor/ or parathyroid adenoma/ or parathyroid carcinoma/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Hyperparathyroidism] explode all trees
#2.	MeSH descriptor: [Hyperparathyroidism, Primary] explode all trees
#3.	((primary or asymptomatic or symptomatic or mild or familial or maternal) near/6 (HPT or hyperparathyroidis*)):ti,ab
#4.	PHPT:ti,ab
#5.	MeSH descriptor: [Parathyroid Neoplasms] explode all trees

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#6.	(parathyroid* near/3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)):ti,ab
#7.	(or #1-#6)

CINAHL (EBSCO) search terms

S1.	(MH "Hyperparathyroidism")
S2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) n6 HPT) OR ((primary or asymptomatic or symptomatic or mild or familial or maternal) n6 hyperparathyroidis*)
S3.	PHPT
S4.	(MH "Parathyroid Neoplasms")
S5.	(parathyroid* n3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumor* or tumour* or cancer* or metasta* or hypercalcemi* or hypercalcaemi*))
S6.	S1 OR S2 OR S3 OR S4 OR S5
S7.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S8.	S6 NOT S7

PsycINFO (ProQuest) search terms

1.	su.Exact("parathyroid neoplasms" OR "hyperparathyroidism" OR "hyperparathyroidism, primary")
2.	PHPT
3.	((primary or asymptomatic or symptomatic or mild or familial or maternal) Near/6 (HPT or hyperparathyroidis*))
4.	(parathyroid* near/3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumor* or tumour* or cancer* or metasta* or hypercalcaemi* or hypercalcemi*))
5.	1 or 2 or 3 or 4
6.	(su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice))
7.	(s1 or s2 or s3 or s4) NOT (su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to primary hyperparathyroidism population in the NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. The NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics papers published since 2002.

Table 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2002 – 06 August 2018	Exclusions Health economics studies
Embase	2002 – 06 August 2018	Exclusions Health economics studies

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Database	Dates searched	Search filter used
Centre for Research and Dissemination (CRD)	HTA - Inception – 06 August 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	hyperparathyroidism/ or hyperparathyroidism, primary/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	Parathyroid Neoplasms/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.

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38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

Embase (Ovid) search terms

1.	hyperparathyroidism/ or primary hyperparathyroidism/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	parathyroid tumor/ or parathyroid adenoma/ or parathyroid carcinoma/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.

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32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Hyperparathyroidism EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Hyperparathyroidism, Primary EXPLODE ALL TREES
#3.	(((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)))
#4.	(PHPT)
#5.	MeSH DESCRIPTOR Parathyroid Neoplasms EXPLODE ALL TREES
#6.	((parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)))
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8.	* IN NHSEED
#9.	* IN HTA
#10.	#7 AND #8
#11.	#7 AND #9

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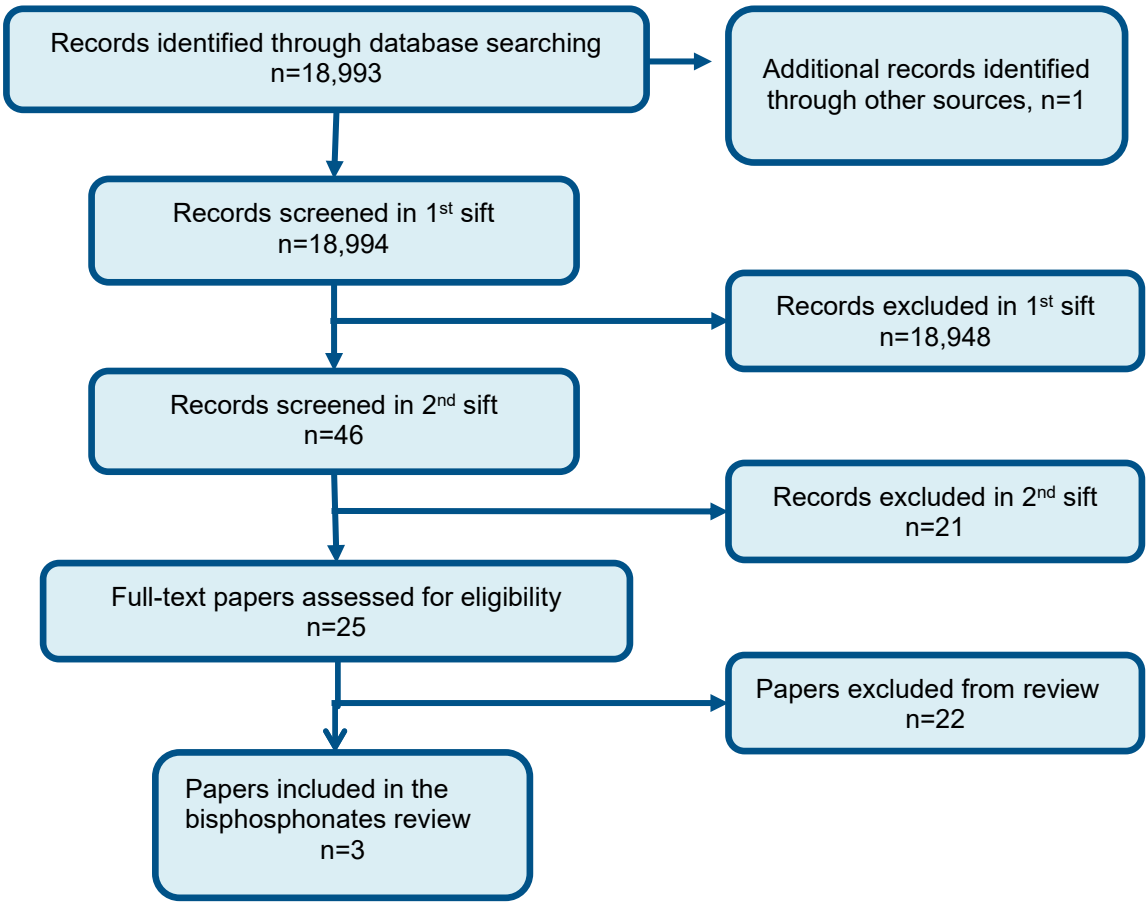
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of pharmacological management (sifted for both calcimimetics and bisphosphonates reviews)



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Appendix D: Clinical evidence tables

	Cesareo 2017[4]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Italy
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Normocalcaemia was defined as an adjusted plasma calcium level below the upper limit of reference range (10.5 mg/dL). A state of hyperparathyroidism was defined as parathyroid hormone levels in the upper third of the reference interval or above (>65 pg/mL).
Stratum	People with normocalcaemic PHPT: All the participants were normocalcaemic (see method of assessment/diagnosis).
Subgroup analysis within study	Not applicable
Inclusion criteria	Menopausal state of ≥5 years; presence of osteoporosis (BMD T-score <-2.5SD at ≥1 skeletal sites); elevated serum parathyroid hormone (normal values of calcium after adjustment for serum albumin); normal serum vitamin levels (>30 ng/mL)
Exclusion criteria	Secondary HPT; concurrent systematic illness; thyroid disease; hepatic/renal dysfunction; disorders known to influence BMD; treatment in the past year with oestrogens, bisphosphonates, calcium/vitamin D supplements or any other drugs that could interfere with bone/mineral metabolism; personal/familial history of recurrent kidney stone disease.
Age, gender and family origin	Age - Mean (SD): 57 (4). Gender (M:F): All women. Family origin: Not reported
Further population details	N/A
Extra comments	Normocalcaemic postmenopausal women with PHPT
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Bisphosphonates - oral Alendronate. Weekly Fosavance® tablets (70 mg/28,000IU): all the participants were instructed to take tablets at the same time in the morning in a fasting state (30 minutes before breakfast). Duration 12 months. Concurrent medication/care: Weekly cholecalciferol (Dibase® 10,000IU) 2800IU drops (=11 drops). Indirectness: No indirectness Further details: 1. Route of administration: oral Comments: Overall, dietary calcium intake was not adequate (Alendronate = 685±89mg versus Control = 703±12mg; p=n.s.)

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	(n=15) Intervention 2: Conservative management. Weekly cholecalciferol (Dibase® 10,000IU) drops (=11 drops) taken at the same time every morning in a fasting state (30 minutes before breakfast). Duration 12 months. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. Route of administration: oral
Funding	Other ("Tendi la mano-AIPOM Onlus" (an independent Italian non-profit association) paid for the laboratory tests.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALENDRONATE + VITAMIN D versus VITAMIN D ONLY Protocol outcome 1: Persistent hypercalcaemia - Actual outcome for People with normocalcaemic PHPT: Incidence of hypercalcaemia or hypercalciuria at 12 months; Group 1: 0/15, Group 2: 0/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing; Group 2 Number missing Protocol outcome 2: Bone mineral density (BMD; distal radius or lumbar spine) at ≥12 months only - Actual outcome for People with normocalcaemic PHPT: Lumbar (L1-L4) BMD at 12 months; Group 1: mean 0.819 g/cm² (SD 0.074); n=15, Group 2: mean 0.759 g/cm² (SD 0.072); n=15; Comments: At baseline: Alendronate = 0.781±0.071g/cm² (Change after 12 months = 4.7% increase) versus Vitamin D = 0.772±0.074g/cm² (Change after 12 months = 1.6% decrease) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness; Group 1 Number missing: NR; Group 2 Number missing: NR	
Protocol outcomes not reported by the study	Quality of life; Mortality; Deterioration in renal function; Fractures (vertebral or long bone) at ≥12 months only; Occurrence of kidney stones; Cardiovascular events; Adverse events (including discontinuation due to side effects); Cancer.

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Study	Chow 2003[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Hong Kong (China)
Line of therapy	Mixed line
Duration of study	Intervention + follow up: Intervention for 48 weeks + Follow-up at 60 and 72 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: PHPT was diagnosed by a trained endocrinologist based on a serum albumin-adjusted calcium concentration greater than 2.62 mmol/L (normal range, 2.15–2.55 mmol/l) with an inappropriately normal or raised serum parathyroid hormone concentration.
Stratum	Presence of bone end-organ effects (bone end-organ effects defined as history of fragility fractures or osteoporosis (BMD T-score <-2.5 at any site): included participants were generally osteoporotic.
Subgroup analysis within study	Not applicable
Inclusion criteria	Post-menopausal women with PHPT who (1) did not reach criteria for surgery according to the NIH guideline, (2) preferred not to have surgery, (3) were considered to be at too high surgical risk, or (4) were on the waiting list for surgery.
Exclusion criteria	Received bisphosphonates, calcitonin, gallium nitrate, mithramycin or fluoride treatment within 1 year of recruitment; on sex hormone therapy (HRT) or on medications that will affect bone metabolism (e.g. steroid, anticonvulsants, vitamin D > 1,000U/d, vitamin A > 10,000U/d); presence of underlying diseases that may affect bone metabolism (e.g. Paget's disease, osteogenesis imperfecta, rheumatoid arthritis, systemic lupus erythematosus and other collagen vascular diseases); unstable angina or myocardial infarction within 1 year before study entry; malignancy within the past 10 years, significant renal impairment (defined as serum creatinine > 150μmol/l or other end organ damage.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 70 (9.3). Gender (M:F): All women. Ethnicity: Not reported
Further population details	N/A
Extra comments	Post-menopausal women with PHPT
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Bisphosphonates - oral Alendronate. 10 mg/day (all patients were instructed to take the study drug each morning while fasting, at least 30 minutes before the first meal, with at least 125 ml of plain water). Duration 48 weeks. Concurrent medication/care: The patients were instructed on normal calcium diet and to avoid extra vitamin D supplement. Indirectness: No indirectness Further details: 1. Route of administration: oral

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	(n=20) Intervention 2: Conservative management. Placebo tablets 10 mg/day (all patients were instructed to take the study drug each morning while fasting, at least 30 minutes before the first meal, with at least 125 ml of plain water). Duration 48 weeks. Concurrent medication/care: The patients were instructed on normal calcium diet and to avoid extra vitamin D supplement. Indirectness: No indirectness Further details: 1. Route of administration: oral
Funding	Study funded by industry (Medical School Grant Program from Merck & Co., Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL ALENDRONATE versus PLACEBO

Protocol outcome 1: Bone mineral density (BMD; distal radius or lumbar spine) at ≥12 months only
- Actual outcome for Presence of bone end-organ effects (bone end-organ effects defined as history of fragility fractures or osteoporosis (BMD T-score <-2.5 at any site): Change in femoral neck BMD at 48 weeks (% change from baseline); Group 1: mean 4.17 % (SD 6.01); n=20, Group 2: mean -0.25 % (SD 3.35); n=20; Comments: p = 0.011
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Whether the statistical analyses were performed on an intention-to-treat basis was not specified by the study. It is reported that "four "participants did not complete the study but it is unclear at which point they withdrew and whether their data were included in the analyses or not. In the adverse events section, it is indicated that all "five" participants who experienced serious adverse events were withdrawn from the study. It is unclear whether the first "four" and second "five" participants were the same or different, therefore, it is not possible to establish exactly how many people were withdrawn from the study and how many were analysed ultimately. Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: Anxiety about the test drug after discussion with family members; Group 2 Number missing: 3, Reason: Beta-blocked induced heart block; ibuprofen-induced gastric ulcer; protocol compliance impossible due to poor mobility associated with Parkinsonism.
- Actual outcome for Presence of bone end-organ effects (bone end-organ effects defined as history of fragility fractures or osteoporosis (BMD T-score <-2.5 at any site): Change in lumbar spine BMD at 48 weeks (% change from baseline); Group 1: mean 3.79 % (SD 4.04); n=20, Group 2: mean 0.19 % (SD 2.8); n=20; Comments: p = 0.016
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Whether the statistical analyses were performed on an intention-to-treat basis was not specified by the study. It is reported that "four "participants did not complete the study but it is unclear at which point they withdrew and whether their data were included in the analyses or not. In the adverse events section, it is indicated that all "five" participants who experienced serious adverse events were withdrawn from the study. It is unclear whether the first "four" and second "five" participants were the same or different, therefore, it is not possible to establish exactly how many people were withdrawn from the study and how many were analysed ultimately. Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: Anxiety about the test drug after discussion with family members; Group 2 Number missing: 3, Reason: Beta-blocked induced heart block; ibuprofen-induced gastric ulcer; protocol compliance impossible due to poor mobility associated with Parkinsonism.
- Actual outcome for Presence of bone end-organ effects (bone end-organ effects defined as history of fragility fractures or osteoporosis (BMD T-score <-2.5 at any site): Change in distal radius BMD at 48 weeks (% change from baseline); Group 1: mean 1.01 % (SD 2.32); n=20, Group 2: mean 0.07 % (SD 5.5); n=20; Comments: p = 0.573
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Whether the statistical analyses were performed on an intention-to-treat basis was not specified by the study. It is reported

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that "four "participants did not complete the study but it is unclear at which point they withdrew and whether their data were included in the analyses or not. In the adverse events section, it is indicated that all "five" participants who experienced serious adverse events were withdrawn from the study. It is unclear whether the first "four" and second "five" participants were the same or different, therefore, it is not possible to establish exactly how many people were withdrawn from the study and how many were analysed ultimately. Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: Anxiety about the test drug after discussion with family members; Group 2 Number missing: 3, Reason: Beta-blocked induced heart block; ibuprofen-induced gastric ulcer; protocol compliance impossible due to poor mobility associated with Parkinsonism.

Protocol outcome 2: Adverse events (including discontinuation due to side effects)
- Actual outcome for Presence of bone end-organ effects (bone end-organ effects defined as history of fragility fractures or osteoporosis [BMD T-score <-2.5 at any site]): Number of adverse events at 48 weeks; Group 1: 25/20, Group 2: 24/20; Comments: Most were upper respiratory tract infections. Serious adverse events: alendronate = 2 versus placebo = 3.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Whether the statistical analyses were performed on an intention-to-treat basis was not specified by the study. It is reported that "four "participants did not complete the study but it is unclear at which point they withdrew and whether their data were included in the analyses or not. In the adverse events section, it is indicated that all "five" participants who experienced serious adverse events were withdrawn from the study. It is unclear whether the first "four" and second "five" participants were the same or different, therefore, it is not possible to establish exactly how many people were withdrawn from the study and how many were analysed ultimately. Overall there were 24 adverse events (including serious cases) in the alendronate group and 25 adverse events (including serious cases) in the placebo group. Indirectness of outcome: No indirectness; Blinding details: The serious adverse events were likely objectively judged by the researchers, nevertheless, adverse events were subjectively reported by the participants "in an open fashion manner"; Group 1 Number missing: 2, Reason: Serious adverse events: hospitalisation following a fall due to dizziness; methyldopa-induced haemolytic anaemia; Group 2 Number missing: 3, Reason: Serious adverse events: fractured right humerus following a fall; first-degree heart block due to beta-blocker treatment; ibuprofen-induced gastric ulcer.

Fractures not included as an outcome for this study as it was not reported fully.

Note:
Serious adverse events: 2 in alendronate groups, 3 in placebo. Alendronate: 1 patient was hospitalized because of dizziness and had a fall, another patient developed methyldopa-induced haemolytic anaemia. Placebo: 1 patient sustained a fractured right humerus after a fall, 1 developed first-degree heart block due to β-blocker treatment, 1 ibuprofen-induced gastric ulcer.

Adverse events: No patient developed gastroesophageal symptoms requiring a change in therapy. There were no other adverse effects seen in the treatment or placebo groups.

Protocol outcomes not reported by the study	Quality of life; Mortality; Deterioration in renal function; Fractures (vertebral or long bone) at ≥12 months only; Occurrence of kidney stones; Persistent hypercalcaemia; Cardiovascular events; Cancer

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Study	Khan 2004[15]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in Canada, Hong Kong (China), USA; Setting: University hospital
Line of therapy	Mixed line
Duration of study	Intervention + follow up: Intervention period for 12 months comparing study drug versus placebo, then placebo group received the study drug in the following 12 months. Follow-up at 12 and 24 months.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All subjects had to meet the inclusion criteria (see inclusion criteria box) which are effectively diagnostic criteria.
Stratum	Presence of bone end-organ effects (bone end-organ effects defined as history of fragility fractures or osteoporosis (BMD T-score <-2.5 at any site): majority (>60%) of included participants were osteoporotic Stratification by gender, ensuring equal proportions in each study arm.
Subgroup analysis within study	Not applicable
Inclusion criteria	Confirmed hypercalcaemia and elevated levels of parathyroid hormones by immunoradiometric assay on 3 separate occasions; reduced bone density, T<-1.0, at ≥1 skeletal sites (lumbar spine / hip / radius). Patients with T<-3.5 were advised to undergo parathyroid surgery and were included only if they declined that advice and still wished to participate.
Exclusion criteria	Any guideline for surgery; concomitant antiresorptive therapy; premenopausal women planning future pregnancy and/or not using effective birth control; other metabolic bone disease; use of hormone replacement therapy for < 2 years; impaired renal function (serum creatinine of >177µmol/L); familial hypocalciuric hypercalcaemia; history of allergy/intolerance to bisphosphonates; active upper gastrointestinal symptoms; severe PHPT with a serum calcium of >3.12µmol/L.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): Alendronate 63.73 (9.36) versus Placebo 70.09 (10.36). Gender (M:F): 9:28. Ethnicity: % in intervention group versus % in placebo group: Caucasians (55.6 versus 42.1); Chinese (38.9 versus 47.4); African-Americans (5.5 versus 10.5)
Further population details	N/A
Extra comments	Patients with confirmed PHPT at McMaster University, Columbia University and the University of Hong Kong
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Bisphosphonates - oral Alendronate. 10 mg/day. Duration 12 months. Concurrent medication/care: Recommendation of moderate calcium intake, adequate hydration and ambulation. Indirectness: No indirectness Further details: 1. Route of administration: oral

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	(n=22) Intervention 2: Conservative management. 10 mg/day. Duration 12 months. Concurrent medication/care: Recommendation of moderate calcium intake, adequate hydration and ambulation. Indirectness: No indirectness Further details: 1. Route of administration: oral
Funding	Study funded by industry (In part by the Merck Medical School Grants Program and also by the National Institutes of Health Grant DK32333)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL ALENDRONATE versus PLACEBO Protocol outcome 1: Fractures (vertebral or long bone) at ≥12 months only - Actual outcome for Presence of bone end-organ effects (bone end-organ effects defined as history of fragility fractures or osteoporosis [BMD T-score <-2.5 at any site]): Number of fractures at 12 months; Group 1: 0/18, Group 2: 0/19 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4, Reason: None given; Group 2 Number missing: 3, Reason: None given Protocol outcome 2: Adverse events (including discontinuation due to side effects) - Actual outcome for Presence of bone end-organ effects (bone end-organ effects defined as history of fragility fractures or osteoporosis (BMD T-score <-2.5 at any site): Number of adverse events at 12 months; Group 1: 0/18, Group 2: 0/19 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4, Reason: None given; Group 2 Number missing: 3, Reason: None given	
Protocol outcomes not reported by the study	Quality of life; Mortality; Deterioration in renal function; Occurrence of kidney stones; Persistent hypercalcaemia; Bone mineral density (BMD; distal radius or lumbar spine) at ≥12 months only; Cardiovascular events; Cancer

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Appendix E: Forest plots

E.1 People with normocalcaemic PHPT and presence of bone end-organ effects

E.1.1 Alendronate + Vitamin D versus Vitamin D only

Figure 2: Lumbar spine BMD (g/cm^2) at 12 months

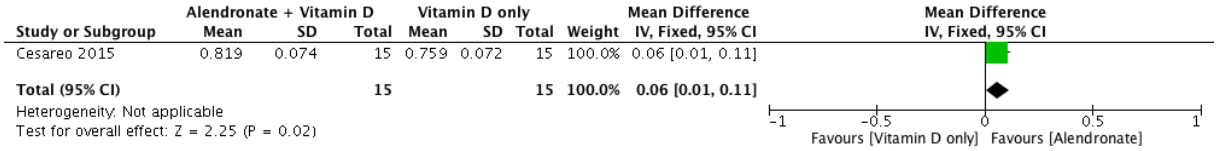
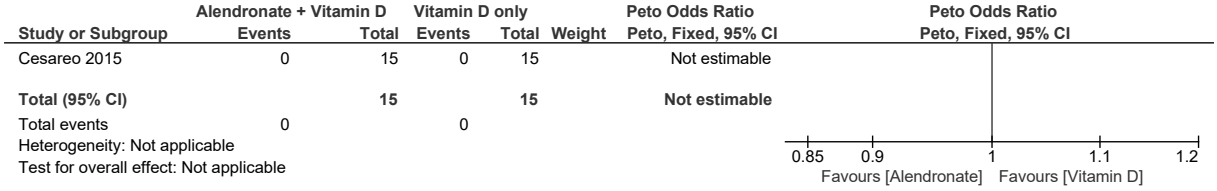


Figure 3: Incidence of hypercalcaemia or hypercalciuria in 12 months



E.2 People with hypercalcaemic PHPT and presence of bone end-organ effects

E.2.1 Alendronate versus Placebo

Figure 4: Change in lumbar spine BMD (% change from baseline) over 48 weeks

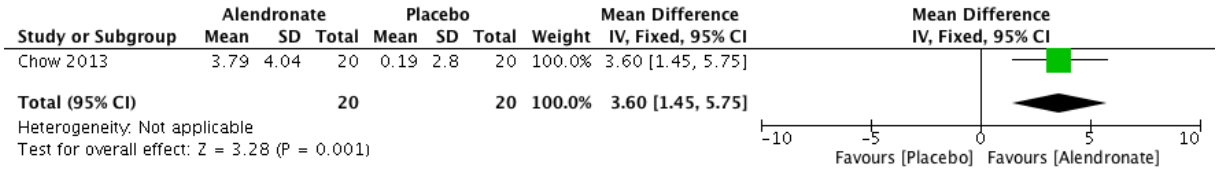


Figure 5: Change in distal radius BMD (% change from baseline) over 48 weeks

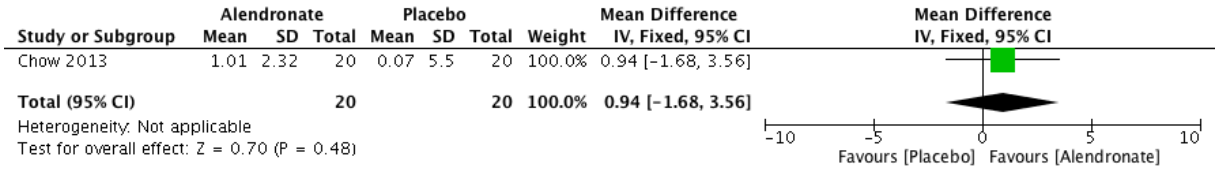


Figure 6: Number of serious adverse events in 48 weeks

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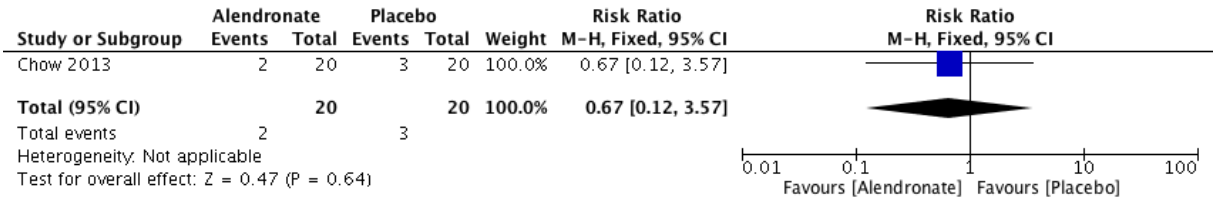


Figure 7: Number of fractures in 12 months

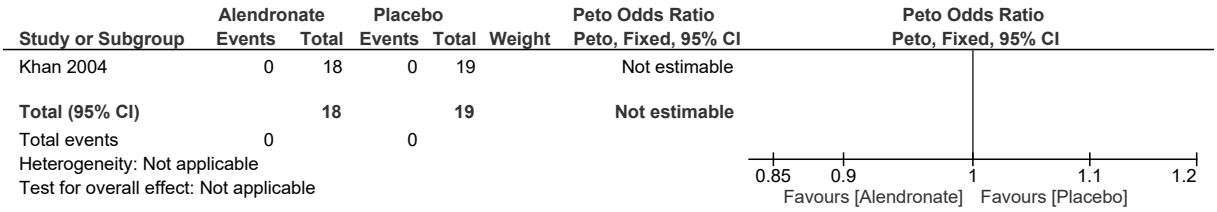
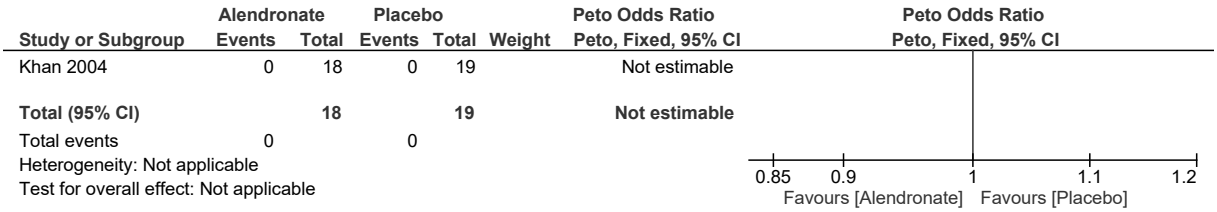


Figure 8: Number of adverse events in 12 months



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Appendix F: GRADE tables

F.1 People with normocalcaemic PHPT and presence of bone end-organ effects

Table 10: Clinical evidence profile: Alendronate + Vitamin D versus Vitamin D only

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alendronate + Vitamin D	Vitamin D only	Relative (95% CI)	Absolute (95% CI)		
Lumbar spine BMD (follow up: 12 months; assessed with: g/cm2)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	Mean (SD) 0.819 (0.0714)	Mean (SD) 0.759 (0.072)	-	MD **0.06 higher** (0.01 higher to 0.11 higher)	⊕⊕◯◯ LOW	IMPORTANT
Incidence of hypercalcaemia or hypercalciuria (follow up: 12 months)												
1	randomised trials	serious [a]	not serious	serious [c]	not serious	none	0/15 (0.0%)	0/15 (0.0%)	not estimable	**0 fewer per 1000** (from 120 more to 120 fewer)	⊕⊕◯◯ LOW	IMPORTANT

a. Downgraded by one increment if the majority of the evidence was at high risk of bias and downgraded by two increments if the majority of the evidence was at very high risk of bias
b. Downgraded by one increment if the confidence interval crossed one MID, and downgraded by two increments if the confidence interval crossed both MIDs
c. Outcome of interest listed in the protocol is the number of persistent hypercalcaemia cases

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F.2 People with hypercalcaemic PHPT and presence of bone end-organ effects

Table 11: Clinical evidence profile: Alendronate versus Placebo

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alendronate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Lumbar spine BMD (follow up: 48 weeks; assessed with: % change from baseline)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	Mean (SD) 3.79 (4.04)	Mean (SD) 0.19 (2.8)	-	MD **3.6 higher** (1.45 higher to 5.75 higher)	⊕⊕◯◯ LOW	IMPORTANT
Distal radius BMD (follow up: 48 weeks; assessed with: % change from baseline)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	Mean (SD) 1.01 (2.32)	Mean (SD) 0.07 (5.5)	-	MD **0.94 higher** (1.68 lower to 3.56 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Number of serious adverse events (follow up: 48 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	2/20 (10.0%)	3/20 (15.0%)	**RR 0.67** (0.12 to 3.57)	**49 fewer per 1000** (from 132 fewer to 385 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Number of fractures (follow up: 12 months)												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Alendronate**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	0/18 (0.0%)	0/19 (0.0%)	not estimable	**0 fewer per 1000** (from 100 more to 100 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Number of adverse events (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	0/18 (0.0%)	0/19 (0.0%)	not estimable	**0 fewer per 1000** (from 100 more to 100 fewer)	⨁⨁◯◯ LOW	IMPORTANT

a. Downgraded by one increment if the majority of the evidence was at high risk of bias and downgraded by two increments if the majority of the evidence was at very high risk of bias
b. Downgraded by one increment if the confidence interval crossed one MID, and downgraded by two increments if the confidence interval crossed both MIDs

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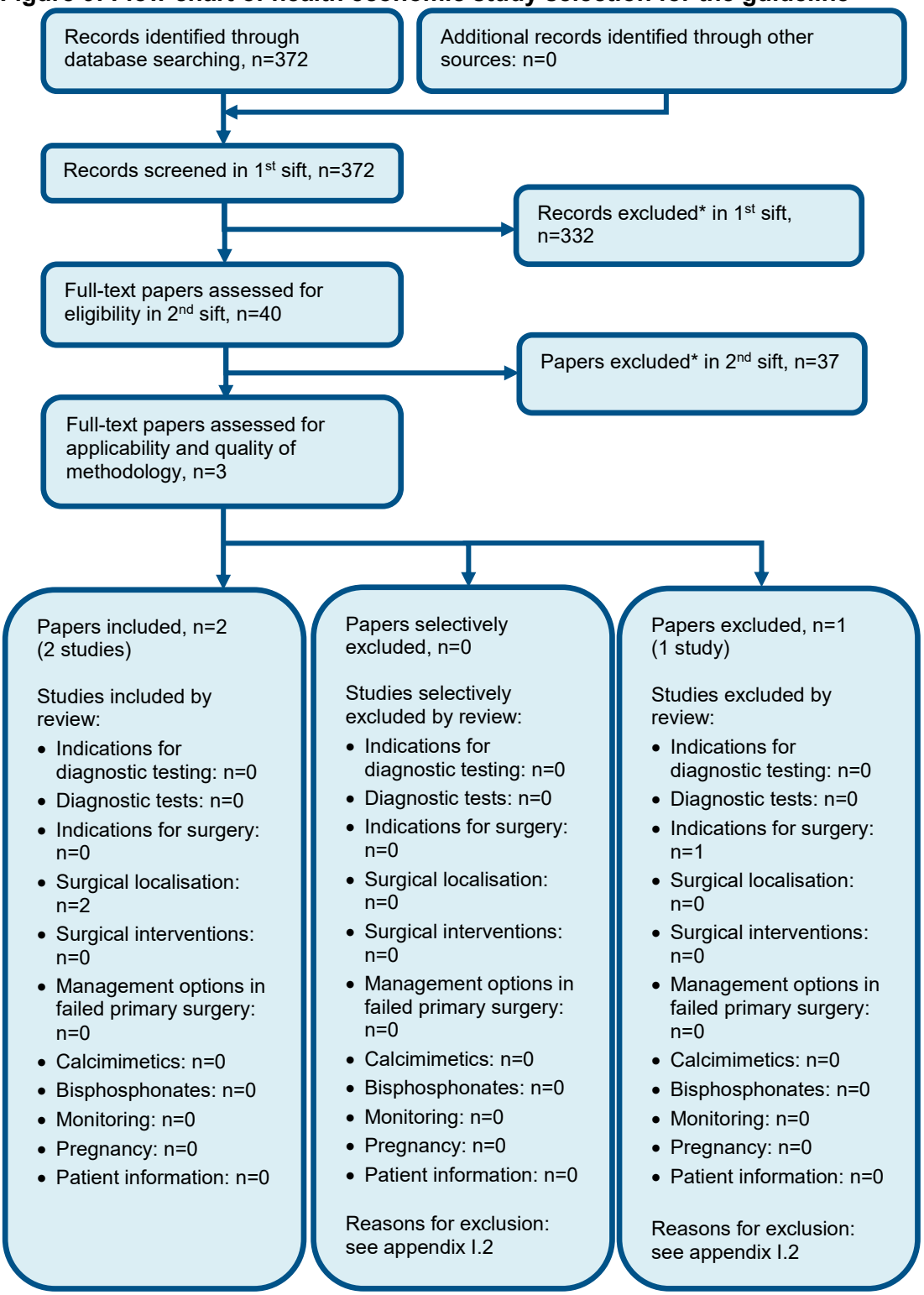
Appendix G: Health economic evidence selection

Figure 9: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

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Appendix H: Health economic evidence tables

No relevant health economic studies were identified for this question.

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Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 12: Studies excluded from the clinical review

Study	Exclusion reason
Akbaba 2013[1]	Incorrect comparator (raloxifene)
Brardi 2015[2]	Incorrect interventions
Casez 2003[3]	Incorrect interventions
Eller-Vainicher 2018 [7]	Not a randomised controlled trial
Hamdy 1987[8]	Non-comparative study
Hassani 2001[9]	Not a randomised controlled trial
Horiuchi 2002[10]	Inappropriate intervention – 2 week administration only of oral etidronate. This bisphosphonate is no longer used.
Khan 2009[14]	Post-hoc subgroup analysis of a previously published study
Khan 2014[13]	Conference abstract
Khan 2015[12]	Incorrect interventions (calcimimetics)
Martin 2010[16]	Conference abstract
Narayan 2007[17]	Incorrect population (end stage renal disease)
Parker 2002[20]	Not a randomised controlled trial
Peacock 2005[22]	Incorrect interventions (calcimimetics)
Peacock 2009[23]	Open label non-comparative extension study of an RCT
Peacock 2011[21]	Pooled analysis of 3 clinical trials (checked for references)
Reasner 1993[24]	Dose study
Rossini 2001[25]	Comparative outcomes not available
Sankaran 2010[26]	Non-systematic literature review
Schwarz 2014[27]	Incorrect interventions (calcimimetics)
Shoback 2003[28]	Incorrect interventions (calcimimetics)
Szczech 2004[29]	Non-systematic literature review

I.2 Excluded health economic studies

None.

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