APPENDIX I
PHARMACOLOGICAL INTERVENTIONS, DOSES IN THE BNF [55] AS AT MARCH 2008

1 Bisphosphonates

1.1 Alendronic acid

For the prevention of postmenopausal osteoporosis, the alendronic acid dose is 5 mg/day. For treatment of postmenopausal osteoporosis and osteoporosis in men, this is a dose of 10 mg/day or (in postmenopausal osteoporosis) 70 mg once weekly. For the prevention and treatment of corticosteroid-induced osteoporosis, the licensed dose is 5 mg/day or 10 mg/day in postmenopausal women not receiving HRT. Trade name: Fosamax.

1.2 Disodium etidronate

For the treatment of osteoporosis in postmenopausal women and for the prevention and treatment of corticosteroid-induced osteoporosis, the disodium etidronate dose is 400 mg/day for 14 days, then calcium carbonate 1.25 g/day (500 mg/day elemental calcium) for 76 days. Trade name: Didronel PMO.

1.3 Risedronate sodium

For the prevention of osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women, the risedronate dose is 5 mg/day. For the treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures, the dose is 5 mg/day or 35 mg once weekly. Trade name: Actonel.

1.4 Ibandronic acid

For the treatment of postmenopausal osteoporosis, the ibandronic acid dose is 150 mg by mouth, once a month, or 3 mg over 15–30 seconds by intravenous injection, once every 3 months. Trade names: Bonviva, Bondronat.

1.5 Zoledronic acid

For the treatment of postmenopausal osteoporosis, the zoledronic acid dose is 5 mg over at least 15 minutes by intravenous infusion, once a year. Trade name: Aclasta

2 Strontium ranelate

The strontium ranelate dose is 2 g/day in water, preferably at bedtime. Strontium ranelate is licensed only for postmenopausal women. Trade name: Protelos.

3 Calcitonin and PTH

3.1 Teriparatide

The teriparatide (PTH 1-34) dose is a 20 microgram/day subcutaneous injection, for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures; the maximum duration of treatment is 18 months. Trade name: Forsteo.

3.2 PTH (1-84)

The human recombinant PTH (1-84) dose for the treatment of osteoporosis in postmenopausal women at high risk of fractures, to reduce the risk of vertebral fractures, is a 100 microgram/day subcutaneous injection, with a maximum duration of treatment of 24 months. Trade name: Preotact.

3.3 Calcitonin

The calcitonin dose for the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures, is a dose of 200 units (one spray) into one nostril daily, with dietary calcium and vitamin D supplements. Other names: calcitonin salmon; salcatonin. Trade name: Miacalcic.

3.4 Sex hormone therapies

3.4.1 HRT (oestrogen with or without progestogen)

The following HRT regimens are licensed for osteoporosis.

Conjugated oestrogen with progestogen

Oral

- Conjugated oestrogen (equine) 0.625 mg/day and medroxyprogesterone acetate 5 mg/day in women with an intact uterus (Premique).

- Conjugated oestrogen (equine) 0.625 mg/day for 14 days then conjugated oestrogens (equine) 0.625 mg/day and medroxyprogesterone acetate 10 mg/day (Premique Cycle Calendar pack).
- Conjugated oestrogens (equine) 0.625 mg/day and 12 days (days 17–28) norgestrel 0.15 mg/day (≡ levonorgestrel 75 micrograms/day) in women with an intact uterus (Prempak-C 0.625 Calendar pack).
- Conjugated oestrogens (equine) 1.25 mg/day and 12 days (days 17–28) norgestrel 0.15 mg/day (≡ levonorgestrel 75 micrograms/day) in women with an intact uterus (Prempak-C 1.25 Calendar pack).

Oestradiol with progestogen

Oral

- Oestradiol 1 mg/day, drospirenone 2 mg/day in women with an intact uterus (Angeliq).
- Oestradiol 1 mg/day, norethisterone acetate 0.5 mg/day in women with an intact uterus (Kliovance).
- Oestradiol valerate 2 mg/day, norethisterone 0.7 mg/day in women with an intact uterus (Climesse).
- Oestradiol 2 mg/day, norethisterone acetate 1 mg/day in women with an intact uterus (Elleste-Duet Conti and Kliofem and Nuvelle Continuous).
- Oestradiol 1 mg/day for 14 days then oestradiol 1 mg/day plus dydrogesterone 10 mg/day for 14 days (Femoston 1/10 tablets).
- Oestradiol 2 mg/day for 14 days then oestradiol 2 mg/day plus dydrogesterone 10 mg/day for 14 days (Femoston 2/10 tablets).
- Oestradiol 1 mg/day plus dydrogesterone 5 mg/day (Femoston Conti tablets).
- Oestradiol valerate 1 mg, medroxyprogesterone acetate 2.5 mg in women with an intact uterus (Indivina 1 mg/2.5 mg).
- Oestradiol valerate 1 mg, medroxyprogesterone acetate 5 mg in women with an intact uterus (Indivina 1 mg/5 mg).
- Oestradiol valerate 2 mg, medroxyprogesterone acetate 5 mg in women with an intact uterus (Indivina 2 mg/5 mg).
- Oestradiol valerate 2 mg/day for 11 days then oestradiol valerate 2 mg and norgestrel 0.5mg (≡ levonorgestrel 0.25 mg) for 10 days, then 7-day interval (Cyclo-Progynova).

- Oestradiol 2 mg/day for 16 days then oestradiol 2 mg/day and norethisterone acetate 1 mg for 12 days (Elleste-Duet 2 mg).
- Oestradiol valerate 2 mg/day for 16 days then oestradiol valerate 2 mg/day and evonorgestrel 75 micrograms/day for 12 days in women with an intact uterus (FemTab Sequi and Nuvelle).
- Oestradiol 1 mg/day for 16 days then oestradiol 1 mg/day and norethisterone acetate 1 mg/day for 12 days in women with an intact uterus (Novofem).
- Oestradiol valerate 2 mg/day for 70 days then oestradiol valerate 2 mg/day and medroxyprogesterone acetate 20 mg/day for 14 days then 7 days of inactive tablets in women with an intact uterus (Tridestra).
- Oestradiol 2 mg/day for 12 days then oestradiol 2 mg and norethisterone acetate 1 mg/day for 10 days then oestradiol 1 mg/day for 6 days, in women with an intact uterus (Trisequens).

Transdermal patches

- Estraderm TTS *50* (releasing oestradiol approx. 50 micrograms/24 hours), one self-adhesive patch applied twice weekly for 2 weeks followed by Estragest TTS (releasing oestradiol approx. 50 micrograms/24 hours and norethisterone acetate 250 micrograms/24 hours), one patch applied twice weekly for 2 weeks in women with an intact uterus (Estracombi).
- One self-adhesive patch (releasing oestradiol approx. 50 micrograms/24 hours and norethisterone acetate approx. 170 micrograms/24 hours) applied twice weekly (Evorel Conti).
- Evorel *50* (releasing oestradiol approx. 50 micrograms/24 hours), one self-adhesive patch applied twice weekly for 2 weeks then Evorel *Conti* (releasing oestradiol approx. 50 micrograms/24 hours and norethisterone acetate approx. 170 micrograms/24 hours), one self-adhesive patch applied twice weekly for 2 weeks (Evorel Sequi).
- Fematrix 80 (releasing oestradiol 80 micrograms/24 hours), one patch twice weekly continuously and 14 tablets of Duphaston (dydrogesterone 10 mg on days 15–28) (Femapak 80 combination pack).

Conjugated oestrogens only

- Conjugated oestrogens (equine) 0.625–1.25 mg/day; with cyclical progestogen for 12–14 days of each cycle in women with intact uterus (Premarin).

Oestradiol only

Oral

- Oestradiol 2 mg/day in women with intact uterus (Elleste-Solo 2 mg) (with cyclical progestogen for 12–14 days of each cycle).
- Oestradiol valerate 2 mg/day (with cyclical progestogen for 12 days of each cycle in women with an intact uterus) (Progynova).
- Oestradiol 2 mg/day with cyclical progestogen for 10–14 days of each cycle in women with intact uterus (Zumenon).

Implant

- Oestradiol 25 mg implant with cyclical progestogen for 12–14 days of each cycle in women with intact uterus, 25–100 mg as required (usually every 4–8 months) according to oestrogen levels (Estradiol Implants).

Transdermal patches

- Oestradiol 80 micrograms/24 hours patch (twice weekly) (with cyclical progestogen for 12–14 days of each cycle in women with intact uterus) (Elleste Solo MX 80).
- Oestradiol 50 micrograms/24 hours patch (twice weekly) (with cyclical progestogen for 12 days of each cycle in women with intact uterus) (Estraderm MX 50).
- Oestradiol 75 micrograms/24 hours patch (twice weekly) (with cyclical progestogen for 12 days of each cycle in women with intact uterus) (Estraderm MX 75).
- Estraderm TTS *50* (releasing oestradiol approx. 50 micrograms /24 hours), one self-adhesive patch applied twice weekly continuously (with cyclical progestogen for 12 days of each cycle in women with intact uterus) (Estraderm TTS 50).
- Estradot 50 (releasing oestradiol approx. 50 micrograms/24 hours), one self-adhesive patch applied twice weekly continuously (with cyclical progestogen for 12 days of each cycle in women with intact uterus).

- Estradot 75 (releasing oestradiol approx. 75 micrograms/24 hours), one self-adhesive patch applied twice weekly continuously (with cyclical progestogen for 12 days of each cycle in women with intact uterus).
- Estradot 100 (releasing oestradiol approx. 100 micrograms/24 hours), one self-adhesive patch applied twice weekly continuously (with cyclical progestogen for 12 days of each cycle in women with intact uterus).
- Evorel 50 (releasing oestradiol approx. 50 micrograms/24 hours), one self-adhesive patch applied twice weekly continuously (with cyclical progestogen for at least 12 days of each cycle in women with intact uterus).
- Evorel 75 (releasing oestradiol approx. 75 micrograms/24 hours), one self-adhesive patch applied twice weekly continuously (with cyclical progestogen for at least 12 days of each cycle in women with intact uterus).
- Evorel 100 (releasing oestradiol approx. 100 micrograms/24 hours), one self-adhesive patch applied twice weekly continuously (with cyclical progestogen for at least 12 days of each cycle in women with intact uterus).
- Fematrix 80 (releasing oestradiol 80 micrograms/24 hours), one patch twice weekly continuously (with cyclical progestogen for 12–14 days of each cycle in women with intact uterus).
- FemSeven 50 (releasing oestradiol 50 micrograms/24 hours), one patch once weekly continuously (with cyclical progestogen for at least 10 days of each cycle in women with intact uterus).
- Progynova TS 50 (releasing oestradiol 50 micrograms/24 hours), one patch once weekly continuously (with cyclical progestogen for 10–14 days of each cycle in women with intact uterus).
- Progynova TS 100 (releasing oestradiol 100 micrograms/24 hours), one patch once weekly continuously (with cyclical progestogen for 10–14 days of each cycle in women with intact uterus).

Gel

- Oestrogel Oestradiol 0.06%, two measures to be applied over an area twice that of the template provided once daily continuously, with cyclical progesterone for 12 days of each cycle in women with intact uterus.

Oestradiol, oestriol and oestrone

- Hormonin: oestradiol 600 micrograms, oestriol 270 micrograms and oestrone 1.4 mg; 1–2 tablets daily with cyclical progesterone for 12–14 days of each cycle in women with intact uterus.

Oestropipate only

- Harmogen: oestropipate 1.5 mg continuously with cyclical progesterone for 10–13 days of each cycle in women with intact uterus.

3.4.2 Selective Estrogen (oestrogen) Receptor Modulators (SERMs) (raloxifene)

Raloxifene is licensed in the UK for the treatment and prevention of postmenopausal osteoporosis with a BNF dosage of 60 mg/day. It is not licensed for other population groups. Trade name: Evista

3.4.3 HRT (other): tibolone, testosterone, nandrolone

Nandrolone is licensed for osteoporosis in postmenopausal women at a dose of 50 mg every 3 weeks by deep intramuscular injection. Trade name: Deca-Durabolin.

3.5 Vitamin and mineral supplements

3.5.1 Vitamin D

Calcitriol is licensed for postmenopausal osteoporosis at a dose of 0.25 micrograms twice daily.

Native vitamin D is also included because it is routinely used in the UK for osteoporosis: vitamin D2 (ergocalciferol or calciferol), vitamin D3 (colecalciferol or cholecalciferol), or vitamin D unspecified.

3.5.2 Calcium

Calcium is not specifically licensed for osteoporosis treatment, but the doses and formulae used in the BNF for calcium deficiency were used for this review.

Calcium salts:

- calcium gluconate 600 mg (calcium 53.4 mg or Ca^{2+} 1.35 mmol)

- calcium gluconate 1 g (calcium 89 mg or Ca^{2+} 2.23 mmol)
- calcium lactate 300 mg (calcium 39 mg or Ca^{2+} 1 mmol)
- calcium carbonate 1.25 g, providing calcium citrate when dispersed in water (calcium 500 mg or Ca^{2+} 12.6 mmol); trade name: Cacit
- calcium carbonate 1.25 g (calcium 500 mg or Ca^{2+} 12.6 mmol); other name: calcium-500; trade name: Calcichew
- calcium carbonate 1.5 g (calcium 600 mg or Ca^{2+} 15 mmol); trade name: Adcal
- calcium carbonate 2.5 g (calcium 1 g or Ca^{2+} 25 mmol); trade name: Calcichew Forte
- calcium glubionate 1.09 g, calcium lactobionate 727 mg (calcium 108.3 mg or Ca^{2+} 2.7 mmol)/5 ml; trade name: Calcium-Sandoz
- calcium lactate gluconate 930 mg, calcium carbonate 700 mg, anhydrous citric acid 1.189 g, providing calcium 400 mg (Ca^{2+} 10 mmol); Trade name: Sandocal Sandocal-400
- calcium lactate gluconate 2.263 g, calcium carbonate 1.75 g, anhydrous citric acid 2.973 g providing 1 g calcium (Ca^{2+} 25 mmol); Trade name: Sandocal Sandocal-1000.

APPENDIX II
SEARCH STRATEGIES

The MEDLINE search strategy is given below:

No.	Search terms
1	exp osteoporosis/
2	bone diseases, metabolic/
3	osteoporo$.tw.
4	or/1-3
5	(bone adj6 densit$).tw.
6	bone density/
7	bmd.ti,ab.
8	(bone or bones).mp.
9	exp densitometry/
10	tomography, x-ray computed/
11	densit$.tw.
12	10 and 11
13	9 or 12
14	8 and 13
15	5 or 6 or 7 or 14
16	exp fractures, bone/
17	fractures, cartilage/
18	fracture$.ti,ab.
19	or/16-18
20	4 and (15 or 19)

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Adachi 2001 RCT (fracture) trial held in Multinational. Setting: mixed. Funding:Supported by grants from Merck & Co., the General Clinical Research Centres Programs, and the National Centre for Research Resources, and NIH grant	Inclusion criteria: Patients receiving at leat 7.5 mg of oral prednisone or equivalent doses of other glucocorticoids for a variety of diseases were eligible. Exclusion criteria: Not stated. Patient type: age: 21-79 years (mean 53/54 years0, All BMDs, Males and females. Glucocorticoid-induced osteoporosis . Some patients with history of fracture. Smoking: Not stated. Details: 32% men; 10-16% of participants with a vertebral fracture at baseline; 25-31% with nonvertebral fracture at baseline. Years postmeopausal: Not stated. BMD and Fracture assessment: BMD by dual x-ray absorptiometry; lateral and thoracic spine radiographs at baseline, 1 year, 2 years or at time of discontinuation. Comorbidities: Patients taking glucocorticoids for a variety of diseases (70% with rheumatologic conditions). Calcium and Vitamin D regimens: All patients received Ca and Vit D. Daily 800-1,000 mg Ca and 250-500 IU vitamin D. Other study comments: Extension study of Saag 1998 (original study included 560 patients); included both pre- and postmenopausal women; BMI, weight, height not reported; 36% patients with history of upper GI disease, 54% were taking NSAIDS, 29% received methotrexate.	1) alendronic acid; duration: 2 years; frequency per day: Once daily; amount 5 mg/day (n=63). 2) placebo; duration: 2 years; frequency per day: Once daily; amount Not stated (n=61). Other interventions: 3) alendronic acid 10 mg/day for 2 years (n=55) 4) alendronic acid 2.5/10 mg for 2 years (n=29). Intervention concurrent medications: 7.5 mg/day prednisone or equivalent. Control concurrent medications: 7.5 mg/day prednisone or equivalent. Concordance: Not stated. Washout period: Not stated.

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Study	*Participants*	*Interventions*
Black 1996 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Study funded by Merck Research Laboratories	Inclusion criteria: femoral neck BMD of 0.68 g/cm2 or less. Exclusion criteria: Peptic ulcer desease, dyspepsia, abnormal renal function, myocardial infarction ≤ 6 months ago, unstable angina, disturbed thyroid, taken oestrogen or calcitonin within 6 months previous or bisphos or sodium fluoride >1 mg daily for 2 wks at any time. Patient type: age: 55-81 years, Osteoporosis, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Some patients. Details: At baseline, 68-70% had at least one vertebral fracture at baseline; 17% had 2 fractures, and 13-15% had 3 or more. Years postmeopausal: At least 2 years. BMD and Fracture assessment: BMD: hip, post-ant spine, lateral spine & whole body. hologic QDR-2000 densitometers. Vert fracture: Lateral radiographs Clin fract written report. Comorbidities: not stated. Calcium and Vitamin D regimens: Some patients received Ca and Vit D. Patients with less than 1000 mg/d were asked to take 500mg of elemental calcium (OsCal) AND 250 IU of cholecalciferol (vitD). 83.4% PLB and 81.2% ALN took Calc and Vit D. Other study comments: Part of Fracture Intervention Trial; 97% Caucasian; Height: ALN: 159cm (6.1SD), PLB: 159cm (6.3SD); BMI (kg/cm2): ALN: 25.5 (4.2SD), PLB 25.6 (4.2SD).	1) alendronic acid with 100ml water having fasted overnight and at least 30 min before breakfast. Not to lie down within 30 min of taking the medication.; duration: 3 years; frequency per day: daily; amount 5mg for 2 yrs, 10mg for 1 yr (n=1022). 2) placebo; duration: 3 years; frequency per day: not stated; amount not applicable (n=1005). Intervention concurrent medications: not stated. Control concurrent medications: Not stated. Concordance: Assessed by pill count. Pts taking at least 75% of their pills. Washout period: Not stated.

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Alendronic acid review

Study	*Participants*	*Interventions*
Black 2003 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Contract: NIAMSD; Merck: supplemetary funds for CT. Tx provided: preotact & matching placebo by NPS; Alendronate & matching placebo by Merck; Calcium by GlaxoSmithKline. Merck/NPS: nonbinding comments. Investigators: design, accrual & writing & hold data	Inclusion criteria: T-score below -2.5 at femoral neck, total hip or spine T-score -2.0 at one of these sites; ≥ 65 years; history of post meno fract, maternal hist of hip fracture. Exclusion criteria: Ever treated with bisphos for > 12 mths or for specified shorter intervals in recent months. Patient type: age: 55-85 years, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 51 and 48% had clinical fractures since the age of 45 years. Years postmeopausal: At least 2 years. BMD and Fracture assessment: BMD by dual x-ray absorptiometry and quantitative computed tomography. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. 500mg calcium carbonate and 400IU Vit D. Other study comments: Mean BMI: 25 kg/m2; 90-97% Caucasian; BMD primary outcome. Clinical fractures: secondary outcome.	1) Parathyroid hormone (1-84) plus alendronic acid; duration: 12 months; frequency per day: Once daily; amount 100 mcg + 10mg (n=59). 2) parathyroid hormone (1-84); duration: 12 months; frequency per day: Once daily; amount 100 mcg (n=119). Other interventions: 3) alendronic acid 10 mg /day for 1 year (n=69). Intervention concurrent medications: not stated. Control concurrent medications: Not stated. Concordance: Unused cartridges were returned. Medication taken for at least 11 of the 12 months of that year and as the use of at least 80% of medication. Washout period: Two-week run-in period.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Black 2005 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Study medications provided by NPS Pharmaceuticals, Merck and GlaxoSmithKline. Supplementary funds for CT by Merck.	Inclusion criteria: T-score below -2.5 at femoral neck, total hip or spine T-score -2.0 at one of these sites;≥ 65 years; history of post meno fract, maternal hist of hip fracture. Exclusion criteria: Ever treated with bisphos for > 12 mths or for specified shorter intervals in recent months. Patient type: age: 55-85 years, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 42-51% had clinical fractures since the age of 45 years. Years postmeopausal: At least 2 years. BMD and Fracture assessment: BMD by dual x-ray absorptiometry and quantitative computed tomography. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. 500mg calcium carbonate and 400IU Vit D. Other study comments: Mean BMI: 25 kg/m2; 90-97% Caucasian; Fracture Intervention Trial; BMD primary outcome. Clinical fractures: secondary outcome.	1) Parathyroid treatment in year 1 followed by alendronic acid in year 2; duration: 2 years; frequency per day: Once daily; amount 100 mcg PTH per day, 10mg ALN per day (n=59). 2) Parathyroid treatment in year 1 followed by placebo in year 2; duration: 2 years; frequency per day: Once daily; amount PTH 100 mcg (n=60). Other interventions: 3) PTH 100 mcg plus 10 mg/day alendronic acid in year 1 followed by 10 mg/day alendronic acid in year 2 (n=59) 4) 10 mg/day alendronic acid for 2 years (n=60). Intervention concurrent medications: not stated. Control concurrent medications: Not stated. Concordance: Unused cartridges were returned. Medication taken for at least 11 of the 12 months of that year and as the use of at least 80% of medication. Washout period: Two-week run-in period.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Black 2006 (FLEX) RCT (fracture) extension trial held in USA. Setting: secondary care. Funding:Study was supported by contracts with Merck & Co and was designed partly by Merck employees	Inclusion criteria: Postmenopausal women aged 55-81 years with a low femoral neck BMD (<0.68 g/cm2); women who completed at least 3 years treatment with alendronate and subsequent 1 year open-label period were eligible for FLEX. Exclusion criteria: Women whose total hip BMD at FLEX baseline was less than 0.515 g/cm2 (T-score <-3.5) or whose total hip BMD was lower than at FIT baseline were ineligible. Patient type: age: mean 73 years, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: 34% with prevalent vertebral fractures; 60% with a history of clinical fractures since menopause. Years postmeopausal: TSM not reported. BMD and Fracture assessment: BMD by dual x-ray absorptiometry; lateral spine radiographs at baseline, 36 and 60 months; fractures by self-report and confirmed by radiographs. Comorbidities: Some women taking HRT or raloxifene (2/3%). Calcium and Vitamin D regimens: All patients received Ca and Vit D. Daily 500 mg Ca and 250 U vitamin D. Other study comments: Mean BMI: 26 kg/m2; 96/98% White; extension of the Fracture Intervention Trial (FIT): FIT Long-term Extension (FLEX); women were randomised at start of extension (all had received alendronate); alendronate dosage groups were pooled.	1) alendronic acid following 5 years alendronic acid; duration: 5 years; frequency per day: Once daily; amount 10 mg per day (n=333). 2) Placebo following 5 years alendronic acid; duration: 5 years; frequency per day: Once daily; amount not applicable (n=437). Other interventions: 3) 5 mg alendronic acid per day for 5 years (n=329). Intervention concurrent medications: some women taking HRT or raloxifene. Control concurrent medications: Some women taking HTR or raloxifene. Concordance: Adherence was assessed in the clinic by self-report and pill count. Washout period: Not clear.

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Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Bone 1997 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Study monitors, program co-ordinators, and statisticians provided by Merck Research Laboratories researchers	Inclusion criteria: Generally of good health; lumbar spine BMD 2.0 SD below mean peak levels. Exclusion criteria: More than 1 lumbar crush fracture; history of recent major gastrointestinal disease, used a drug to inhibit gastric acid secretion; chronic nonsteroidal antiiflamatory therapy or agents known to affect bone metabolism; vit D deficiency. Patient type: age: 60-85 years (mean 71 years), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 38% had a prevalent vertebral fracture in ALN group and 34.1% in placebo group. Years postmeopausal: mean TSM 22-25 years. BMD and Fracture assessment: BMD by dual x-ray absorptiometry; lateral thoracic and lumbar spine radiographs; nonvertebral fractures based on clinical examination and radiographs. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. Daily 500 mg Ca. Other study comments: Meaan height and weight: 159/161 cm and 61/62 kg; 97-99% Caucasian.	1) alendronic acid; duration: 2 years; frequency per day: Once daily; amount 5 mg per day (n=93). 2) Placebo; duration: 2 years; frequency per day: Once daily; amount Not applicable (n=91). Other interventions: 3) alendronic acid 1 mg/day for 2 years (n=86) 4) alendronic acid 2.5 mg/day for 2 years (n=89). Intervention concurrent medications: not stated. Control concurrent medications: Not stated. Concordance: Assessed at each clinic visit through patient reports and tablet counts. Washout period: Not stated.

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CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Carfora 1998 RCT (fracture) trial held in Italy. Setting: secondary care. Funding:Not stated	Inclusion criteria: Postmenopausal women with a bone mineral density of the lumbar spine at least 2.5 SD below the mean value. Exclusion criteria: Women with other cayses of Osteoporosis (treatment with glucorticoids) or vit D deficiency, Paget's disease, or hyperparathyroidism; active peptice ulcer disease, abnomal renal function or abnormal hepatic function. Abnomalities of the lumbar spine. Patient type: age: 44-73 years, Osteoporosis, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: No details given. Years postmeopausal: 5 years. BMD and Fracture assessment: BMD: dual energy x-ray absorptiometry. Fractures: x-rays of thoracic and lumbar region in lateral projection. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. 500mg elemental calcium, daily, at least 4 hours after the assumption of the drug. Other study comments: height/weight/BMI; ethnicity not given.	1) alendronic acid each morning with water each morning at least 1 1/2 hours before breakfast; duration: 30 months; frequency per day: Once daily; amount 10 mg per day (n=34). 2) Placebo orally each morning with water each morning at least 1 1/2 hours before breakfast; duration: 30 mths; frequency per day: Once daily; amount not applicable (n=34). Other interventions: 3) 5 mg alendronic acid for 30 months (n=34) 4) 20 mg alendronic acid for 15 months followed by placebo for 15 months (n=34). Intervention concurrent medications: not stated. Control concurrent medications: Not stated. Concordance: Pts evaluated after one week, one month and then every five months. Tolerance to drug evaluated by clinical surveillance and biochemical markers.. Washout period: Not stated.

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Alendronic acid review

Study	*Participants*	*Interventions*
Cummings 1998 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Funding from Merck Research Laboratories	Inclusion criteria: 55-90 years of age; postmenopausal for at least 2 years; BMD of 0.68 g/cm2 or less; no vertebral fractures. Exclusion criteria: Recent peptic ulcers or ulcers that needed hospitalisation, dyspepsia, renal or hepatic dysfunction, severe malabsorption, blood pressure exceeding 210 mm Hg sys or 105 mm Hg diasm, myocardial infarction with in 6 mths, unstable angina, hypperparathy-roid. Patient type: age: mean (SD): ALN 67.6(6.2), Placebo 67.7 (6.1), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: Did not have fractures at baseline; but fractures since age 45y: ALN: 797(36%), Placebo: 710(35%).. Years postmeopausal: ≥ 2 years. BMD and Fracture assessment: BMD: Hologic QDR 2000 densitometers. Fractures: Clinical: Lateral spine radiographs at baseline and at 4 years. Comorbidities: not stated. Calcium and Vitamin D regimens: Some patients received Ca and Vit D. Patients with less than 1000 mg/d were asked to take 500mg of elemental calcium (OsCal) AND 250IU of cholecalciferol (vitD). 82% in each group. Other study comments: Part of FIT, clinical fracture arm, for low BMD but no vertebral fracture. Height: mean (SD) ALN: 161(6), Placebo: 160(6), BMI: mean(SD) kg/m2 ALN: 24.9(3.9), Placebo: 25(4).	1) alendronic acid with 120ml water in fasting state, not to lie down or eat/drink for at least half hour; duration: Avg 4.2 years; frequency per day: daily; amount 5mg/d for 2 years followed by 10mg/day for 2 years (n=2214). 2) placebo; duration: 4 years; frequency per day: not stated; amount not stated (n=2218). Intervention concurrent medications: not stated. Control concurrent medications: Not stated. Concordance: ptcs taking at least 75% of their pills. Washout period: not stated.

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Alendronic acid review

Study	*Participants*	*Interventions*
Dursun 2001 RCT (fracture) trial held in Turkey. Setting: secondary care. Funding:Not stated	Inclusion criteria: BMD of 2 SD or more below young adult mean at either posteroanterior lumbar spine or the femoral neck. Exclusion criteria: Hx of drug /alc abuse. Evidence of bone meta disorder. Active gastrointestinal or lever desease, renal failure, renal calculi, Rx of osteo with syst corticosteroid therapy, malignancy, disorder of calcium meta and lumb vert abnorm preventing BMD evaluatio. Patient type: age: Mean ALN: 60.26, Calcitonin: 63.22, Calc 60.26, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: Female patients. Fractures not stated. Years postmeopausal: Mean ALN: 14.32, Calcitonin: 17.56, Calc 14.88. BMD and Fracture assessment: BMD: Dual energy xray absorbtiometry. Fracture: Lateral and anteroposterior x-rays of thoracic and lumbar vertebrae. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. Intervention and Control had additional 1000mg Calcium. Other study comments: Mean (SD) height; 154.10(4.78) weight; ALN and Calc;66.41(11.53), Calcit;67.18 (8.56) BMI kg/m2; ALN and Calc;28.62 (5.52), Calcit;29.13(4.40).	1) alendronic acid (taken in morning at least 30 mins before breakfast - remain upright) PLUS Calcium; duration: 1 year; frequency per day: daily; amount 10mg (n=51). 2) Calcium only; duration: 1 year; frequency per day: daily; amount 1000 mg (n=50). Other interventions: 3) (n=50) calcitonin 100 IU daily for 1 year PLUS Calcium. Intervention concurrent medications: not stated. Control concurrent medications: Not stated. Concordance: not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Greenspan 2002 RCT (fracture) trial held in USA. Setting: nursing home. Funding:Study of Merck & Co Inc	Inclusion criteria: T-score to be lower than -2.0 SD at the posterior-anterior lumbar spine or total hip. Exclusion criteria: Disorders of bone mineralisation; 25-hydroxycholecalciferol level < 25 nmol/ml; untreated hyperthyroidism; recent major GI mucosal erosive disease; use of bone-active agents. Patient type: age: 78.5 years (65 to 91), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 55% had a history of fracture. Years postmeopausal: not stated. BMD and Fracture assessment: BMD by DXA of hip and spine. Clinical fracture data collected. Comorbidities: none stated. Calcium and Vitamin D regimens: Some patients received Ca and Vit D. All patients received 400 IU/day. Calcium carbonate given to patients whose dietary intake was less than 1500mg. Other study comments: Overall 64% used either aspirin or NSAID; 97% of patients were white.	1) Alendronic acid; duration: 2 years; frequency per day: once; amount 10mg (n=not stated). 2) Placebo; duration: 2 years; frequency per day: once; amount (n=not stated). Concordance: not stated. Washout period: none stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Greenspan 2003 RCT (fracture) trial held in USA. Setting: primary care. Funding:NIH grants	Inclusion criteria: 65 years or older. Exclusion criteria: disease or drugs affecting bone metabolism; osteoporosis drug within 1 yr; contraindication to HRT or alendronate; BMD 0.9g/cm2 or more (i.e. T score =0). Patient type: age: mean around 72yr (65-90yr), All BMDs, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Some patients. Details: 33-39% had a fracture after age 50y; 35% had had a hysterectomy. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed by DXA (total hip, lumbar spine, radius); clinical fractures reported. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. All patients given 400IU vitamin D. If calcium intake <1000mg/day, patients given tablets containing 600mg calcium +200IU vitamin D. Other study comments: mean BMI around 27.5 kg/m2.	1) alendronic acid; duration: 3 years; frequency per day: once; amount 10mg (n=93). 2) placebo; duration: 3 years; frequency per day: once; amount (n=93). Other interventions: 3) HRT (conjugated oestrogen + medroxyprogesterone 2.5mg/day (if uterus) (n=93) 4) HRT+alendronic acid (n=94). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: not stated how assessed. Washout period: 3 month run-in on HRT, alendronic acid placebo, calcium and multivitamin as necessary.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Liberman 1995 RCT (fracture) trial held in Multinational. Setting: not stated. Funding:Supported by a grant from Merck Research laboratories	Inclusion criteria: Postmenopausal women (for at least 5 years); age 45 to 80; at least 2.5 SD below the mean value. Exclusion criteria: Other disorders of BMD, abnormal hepatic function, abnormality of lumbar spine precluding assess of BMD, history of hip fracture, prior bisphos treat within 12 mths. Patient type: age: 45-80: Mean age yr: ALN: 64, PLB: 64, Osteoporosis, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: Vert fractures at baseline in ALN: 106 (20.2%), PLB 75 (21.2%). Years postmeopausal: ≥5. BMD and Fracture assessment: BMD of lumbar spine, femoral neck, trochanter, forearm and body by dual-energy x-ray absorptiometry densitometers. Vert fracts by Lateral spine films. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. 500mg elemental calcium. Other study comments: height/weight/ethnicity not stated. BMI mean: ALN:24.2, PLB:24.1. Mean yr since meno: ALN: 16, PLB: 17. Multicentre study in USA, Australia, Canada, Europe, Isreal, Mexico, New Zealand and S Africa. Data pooled from 2 identical trials and from 3 ALN Grps.	1) alendronic acid; duration: 3 years; frequency per day: Once daily; amount 5 or 10 mg/day, or 20 mg/day for 2 yrs+5mg for 1 y (n=597). 2) placebo; duration: 3 years; frequency per day: daily; amount Not applicable (n= 397). Intervention concurrent medications: not stated. Control concurrent medications: Not stated. Concordance: Not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Lindsay 1999 RCT (fracture) trial held in USA. Setting: not stated. Funding:Work supported by grant from Merck & co. One author was employed by them.	Inclusion criteria: At least 40 years or at least 25 years if surgical menopause; postmenopausal ≥ 5 y and receiving HRT ≥ 1y, with oestrogen content at least lowest dose for osteoprorosis treatment. T score ≤ -2.0 SD; at least 80% compliant in run-in period. Exclusion criteria: Contraindications to HRT; other osteoporosis treatments; untreated hyperthyroidism; disorders of bone mineralisation; conditions affecting oesophageal emptying; drugs that might affect Ca metabolism. Patient type: age: ALN+HRT: 61.9 years (SD 7.2); HRT: 61.5 (SD 8.8), Mixed osteoporosis/osteopenia, Postmenopausal women only. Bilateral oophorectomy . Some patients with history of fracture. Smoking: Some patients. Details: Prior fracture: ALN+HRT 57.5%; HRT 55.6%; some with surgical menopause (29% bilateral oophorectomy); over half had not had a hysterectomy; 36 and 47% smokers; 57% alcohol use. Years postmeopausal: mean-15.4 years. BMD and Fracture assessment: BMD: Lumbar spine, femoral neck, Lumbar spine / femoral neck BMD by Hologic or Lunar DXA. Fracture: adverse events reporting only. Comorbidities: none stated. Calcium and Vitamin D regimens: Some patients received Ca and Vit D. All patients received vitamin D at 400 IU/day; calcium carbonate supplements were given to patients with a baseline intake of < 1000 mg/day to achieve at least 1000 mg/day. Other study comments: BMI mean 23.1 and 24.2 kg/m2; 98.1 and 95.3% Caucasian; randomisation stratified by HRT use above and below 2 years.	1) Alendronic acid + previous HRT (oestrogen equivalent to 0.625mg/day; medroxyprogesterone acetate for those with intact uterus); duration: 12 months; frequency per day: once; amount 10mg (n=214). 2) Placebo + previous HRT (oestrogen equivalent to 0.625mg/day; medroxyprogesterone acetate for those with intact uterus); duration: 12 months; frequency per day: once; amount (n=214). Intervention concurrent medications: HRT (duration mean 9.7 y). Control concurrent medications: HRT (duration mean 9.5y). Concordance: method not stated. Washout period: 2 weeks on placebo.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Miller 2004 RCT (fracture) trial held in USA. Setting: not stated. Funding:Funding for the clinical trial was provided by Merck Research Laboratories, USA	Inclusion criteria: Men with hypogonadal or idiopathic osteoporosis; BMD at least 2 SD below the mean at the femoral neck or at least 1 SD below the mean at the lumbar spine for young normal white males; documented non-traumatic (osteoporotic) fracture. Exclusion criteria: Osteoporosis secondary to corticosteriods; metabolic bone disorders; vitamin D or testosterone deficiency, any prior use of bisphosphonates, calcitonin, or fluoride; history of major upper GI disease; oesophageal conditions; prostrate cancer. Patient type: age: 25-90 years (mean 65.8 and 66.7 years), Mixed osteoporosis/osteopenia, Males only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: 62% in treatment and 66% in placebo group with pre-existing vertebral fracture and 59% and 67% with prior osteoporotic fracture. Years postmeopausal: not applicable. BMD and Fracture assessment: BMD by dual x-ray absorptiometry; vertebral fractures by lateral radiographs at baseline and 12 months; decrease >20% and >4mm. Comorbidities: 24% reported a history of upper GI disease. Calcium and Vitamin D regimens: All patients received Ca and Vit D. 500 mg of calcium as carbonate plus 200 IU vitamin D twice daily. Other study comments: mean height., weight and BMI in treatment group: 174.4 cm, 78.7 kg, 25.8 kg/m2; placebo group: 171.4 cm, 79.1 kg, 26.9 kg/m2; 97/98% were white; 41% of all men were hypogonadal.	1) Alendronic acid; duration: 12 months; frequency per day: Once weekly; amount 70 mg once-weekly tablets (n=109). 2) Placebo; duration: 12 months; frequency per day: not stated; amount not stated (n=58). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Orwoll 2000 RCT (fracture) trial held in Multinational. Setting: not stated. Funding:Spported by grants from Merck; a number of the authors served as consultants to Merck; second author owns stock in Merck	Inclusion criteria: BMD at femoral neck <2 SD below the mean value in normal young men and BMD at the lumbar spine <1 SD below the mean or a BMD of at leat 1 SD below the mean at the femoral neck and at lease 1 vertebral deformity or a history of osteoporotic fracture. Exclusion criteria: Secondary causes of osteoporosis other than low serum free testosterone concentrations; other bone diseases, vit D deficiency, renal disease, severe cardiac disease, cancer, peptic ulcer or esophageal disease; men unable to follow drug instructions. Patient type: age: 31-87 years (mean 63 years), Mixed osteoporosis/osteopenia, Males only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: 49% in treatment group and 52% in placebo group with vertebral fractures. Years postmeopausal: not applicable. BMD and Fracture assessment: BMD by dual x-ray absorptiometry; posteroanterior and lateral radiographs of lumbar and thoracic spine at baseline and after 2 years. Comorbidities: 10 men considered to be eugonadal. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Calcium 500 mg daily in the form of calcium carbonate and vit D (400 IU in the USA and 400-450 IU daily in the other countries). Other study comments: mean BMI 25 (3 SD); height and weight not reported; 97-99% white; 36% of men had low serum free testosterone concentrations.	1) alendronic acid; duration: 2 years; frequency per day: Once daily; amount 10 mg per day (n=146). 2) Placebo; duration: 2 years; frequency per day: not stated; amount not stated (n=95). Intervention concurrent medications: 3 men received doses of testosterone. Control concurrent medications: 7 men received doses of testosterone. Concordance: not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Participants*	*Interventions*
Pols 1999 RCT (fracture) trial held in Multinational. Setting: not stated. Funding:Study was supported by Merck & Co., Inc.	Inclusion criteria: Postmenopausal women ≥ 3yrs, BMD of lumbar spine (L2-4) ≥ 2SD below mean for post meno woman. Good health, between 20% and 50% above ideal weight. Exclusion criteria: Metabolic bone desease other than osteo, disturbed parathyroid or thyroid function; gastrointestinal disease, myocardial infarction, hypertension or angina, end organ disease, treat with >8mg/day bisphos or floride, vit A > 10000 U/day, vit D > 1000 U/day. Patient type: age: Mean (SD), ALN: 62.8 (7.5), PLB: 62.8 (7.4), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: Fracture at baseline not stated. Years postmeopausal: ≥3 yrs. BMD and Fracture assessment: BMD: Lumbar spine, femoral neck, trochanter, hip DXA by Hologic QDR densitometry or by Lunar DPX densitometry. Fracture by adverse events reporting only. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. 500mg of elemental calcium as the carbonate or citrate salt. One tablet daily at the evening meal. Other study comments: Mean (SD) height in cm: ALN: 158.6 (7.0), PLB 158.5 (6.8), weight in kg: ALN: 63.8 (9.6), PLB 63.6 (9.7) yrs postmeno: ALN:15.8 (8.5), PLB 15.9 (8.4), BMI, ethnicity not stated. Spine radiographs not obtained, vertebral fracture could not be evaluated.	1) alendronic acid with a glass of water each morning after overnight fast. Not to eat drink or lay down for 30 mins after; duration: 1yr; frequency per day: Once daily; amount 10mg per day (n=950). 2) Placebo with a glass of water each morning after overnight fast. Not to eat drink or lay down for 30 mins after; duration: 1yr; frequency per day: Once daily; amount matching image (n=958). Intervention concurrent medications: not stated. Control concurrent medications: Not stated. Concordance: not stated. Washout period: 2- to 4-week basline period.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Participants*	*Interventions*
Adachi 1997 RCT (fracture) trial held in Canada. Setting: primary care. Funding:Supported by a grant-in-aid from Procter & Gamble Pharmaceuticals, Canada.	Inclusion criteria: Ambulatory 18-90 years with a variety of diseases; started high-dose prednisone or equiv therapy within previous 100 days & expected to continue for 1y. Exclusion criteria: Abnormalities on spinal radiographs, meds known to affect bone metabolism within the preceding year. Patient type: age: 62 years (31-83): and 60 (19-87), All BMDs, Males and females. Glucocorticoid-induced osteoporosis . Some patients with history of fracture. Smoking: Not stated. Details: M:F 54:87 [premenopausal 17; postmenopausal 70]; Vertebral fractures:45-49%. Years postmeopausal: Not stated. BMD and Fracture assessment: DXA at lumbar spine and hip scans; Vert #: increase in vertebral-deformity score from b/l; grade 0:normal; 1: 20-25% reduction; 2:26-40% reduction; 3: reduction >40%. Comorbidities: mainly polymyalgia rheumatica and rheumatoid arthritis. Calcium and Vitamin D regimens: Not stated or Unclear. All patients received 76 days of calcium carbonate (500 mg of elemental Ca) as part of the intervention. Serum 25-hydroxy vitamin D 31 ng/ml (normal levels). Other study comments: No pts had corticosteroids in the past. Pts were expected to take a mean daily dose of 7.5mg or more for 90 days with subsequent ongoing Rx at a mean daily dose of 2.5mg or more; pts were stratified according to sex & menopausal status then randomised.	1) Etidronate disodium followed by calcium carbonate; duration: 12 months; frequency per day: once; amount 400 mg etidronate for 14 days then 500mg elemental calcium for 76 days (n=67). 2) Placebo then calcium carbonate; duration: 12 months; frequency per day: placebo/14 days repeated for 3 times; amount Placebo for 14 days then 500mg elemental calcium for 76 days (n=74). Intervention concurrent medications: mean dose of prednisone or equiv: 21mg/day. Control concurrent medications: Mean dose of prednisone or equiv: 23mg/day. Concordance: Not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Participants*	*Interventions*
Campbell 2004 RCT (fracture) trial held in UK. Setting: primary care. Funding:Funded with an unrestricted grant to the Research Committee from Allen and Hanburys and Glaxo	Inclusion criteria: asthma, taking oral &/or inhaled GCO Rx for at least 1 year; Postmenopausal women (50-70 years) eligible unless had hysterectomy. Patient type: age: 58.7 (SD 7.7): 60.2 (SD 7.6) years, All BMDs, Males and females. Glucocorticoid-induced osteoporosis . Some patients with history of fracture. Smoking: Not stated. Details: men:postmenopausal women 100:76; previous osteoporotic fractures 9-11%. Years postmeopausal: Not stated. BMD and Fracture assessment: DXA at lumbar spine & proximal femur; Vert # defined by quantitative morphometry as a loss of vert ht of 20% or more at the anterior, mid or posterior. Comorbidities: all patients had asthma. Calcium and Vitamin D regimens: No patients. No patients received additional calcium or vitamin D outside the study interventions. Other study comments: Weight:74.8kg (SD 15):72.4(12.8); Patients stratified according to use of GCO: A) oral prednisolone & inhaled GCO; B) inhaled GCO & intermittent prednisolone (>30days ever); C)inhaled GCO & no more than 30 days prednisolone ever.	1) Etidronate then calcium carbonate; duration: 5 years; frequency per day: once; amount 400 mg/day 2 weeks in 3 months then calcium 500mg/d for rest of 3 months (n=88). 2) no treatment; duration: 5 years; frequency per day: ; amount (n=95). Other interventions: 3) Etidronate 400 mg/day 2 weeks in 3 months then no treatment for rest of 3 months (n=81) 4) calcium 500 mg/day (n=85). Concordance: Not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Participants*	*Interventions*
Cortet 1999 RCT (fracture) trial held in France. Setting: secondary care. Funding:Not stated	Inclusion criteria: Patients receiving long-term glucocorticoid therapy for an anticipated duration of more than 1 year for inflammatory rheumatic diseases. Starting dose of glucocorticoid > 7.5 mg/day for at least 3 months then maintenance at least 2.5 mg/day. Exclusion criteria: Medications known to modify bone metabolism or the metabolism of calcium and phosphate; bisphosphonates, fluoride, oestrogens and/or progestogens within the last year; calcitonin or vitamin D derivatives within the last 6 months; pregnancy. Patient type: age: mean 62 years, All BMDs, Males and females. Glucocorticoid-induced osteoporosis . History of fracture unclear or not stated. Smoking: Not stated. Details: men 43: women 55 [9 premenopausal, 46 postmenopausal]; proportion of patients with a fracture: not stated. Years postmeopausal: . BMD and Fracture assessment: Radiographically confirmed symptomatic fractures recorded. Comorbidities: inflammatory rheumatic diseases (RA, polymyalgia rheumatica, giant cell arteritis). Calcium and Vitamin D regimens: Some patients received Vit D only. Vitamin D supplementation of no more than 1000 IU/day was permitted. Other study comments: Insufficient detail (used data from HTA review).	1) Etidronate then calcium; duration: 1 year; frequency per day: once; amount 400 mg/day etidronate for 14 days then 500 mg/day elemental calcium for 76 days (n=44). 2) placebo then calcium; duration: 1 year; frequency per day: once; amount placebo for 14 days then 500 mg/day elemental calcium for 76 days (n=39). Concordance: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Participants*	*Interventions*
Geusens 1998 RCT (fracture) trial held in Belgium. Setting: not stated. Funding:Supported by a grant from Procter & Gamble Pharmaceuticals, UK	Inclusion criteria: not stated. Exclusion criteria: not stated. Patient type: age: 65 years (SD19) and 63 (SD18), All BMDs, Postmenopausal women only. Glucocorticoid-induced osteoporosis . History of fracture unclear or not stated. Smoking: Not stated. Details: all postmenopausal women; proportion of patients with a fracture not stated.. Years postmeopausal: 19years (SD11):13(SD9). BMD and Fracture assessment: BMD assessed with DXA at lumbar spine in vert L2-L4; left femoral neck & left femoral trochanter;Radiographically confirmed symptomic #s recorded. Comorbidities: rheumatoid arthritis; polymyalgia rheumatica; chronic bronchitis. Calcium and Vitamin D regimens: Not stated or Unclear. Other study comments: Ht:157cm(SD6):160(SD6);Wt:63kg(SD7):69(SD11); Ethnicity: not stated; Duration of corticosteroid Rx: 45 months(3-503):31(3-108) All received long-term corticosteroids equiv 5-20mg prednisolone/day for >3mo..	1) etidronate then calcium (salt not specified); duration: 2 years; frequency per day: once; amount 400 mg/day etidronate for 2 weeks then 500mg/day elemental calcium for 11 weeks (n=18). 2) placebo then calcium; duration: 2 years; frequency per day: once; amount placebo for 2 weeks then 500mg/day elemental calcium for 11 weeks (n=19). Intervention concurrent medications: not stated. Control concurrent medications: Not stated. Concordance: not reported.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Participants*	*Interventions*
Herd 1997 RCT (BMD only) trial held in UK. Setting: primary care. Funding:Carried out in association with Proctor and Gamble Pharmaceuticals.	Inclusion criteria: All white, ambulatory, postmenopausal women. Exclusion criteria: osteoporotic fractures at any site; generalised bone disease incl hyperparathyroidism. Cancer within last 5 years, Paget's disease. Corticosteroids, anabolic drugs, calcitonin, vitamin D > 400IU; previous treatment with fluoride or bisphosphonate. Patient type: age: 55 years (37-66), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . No patients with history of fracture. Smoking: Not stated. Details: no prevalent fractures. Years postmeopausal: mean 5.4 - 5.6 y (SD 3). BMD and Fracture assessment: Dual x-ray absorptiomtery. Comorbidities: None. Calcium and Vitamin D regimens: No patients. Calcium and vitamin D intake not stated apart from exclusion criteria and calcium in study drugs. Other study comments: Height 161 cm; weight 61-63 kg; ethnicity: white; Pts stratified into 3 groups, according to years since menopause [1-3y; 4-6y; & 7-10y] then randomly allocated.	1) Etidronate then calcium supplements (type not stated); duration: 2 years; frequency per day: once; amount 400 mg/day etidronate for 2 weeks followed by 500 mg/day elemental Ca for 76 days (n=75). 2) placebo etidronate 400 mg/day for 2 weeks followed by 500 mg/day elemental Ca for 76 days; duration: 2 years; frequency per day: once; amount (n=77). Concordance: Assessed by pill count. Washout period: None stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Participants*	*Interventions*
Jenkins 1999 RCT (fracture) trial held in UK. Setting: primary care. Funding:Supported by grants from the Southampton Rheumatology Trust & Wessex Regional Health Authority. Procter & Gamble provding the drugs.	Inclusion criteria: polymyaglia rheumatism or rheumatioid arthritis with clinical indication to commence corticosteroids for 1st time. Exclusion criteria: coexistent diseases likely to impair interpretation of the results, taking concomitant medication known to influence bone mineral metabolism. Patient type: age: 68.7 (SD 10.9): 65.9 (SD 9.7) years, Mixed osteopenia/normal BMD, Males and females. Glucocorticoid-induced osteoporosis . History of fracture unclear or not stated. Smoking: Not stated. Details: M:F 11:17. Years postmeopausal: Not stated. BMD and Fracture assessment: BMD at lumbar spine & proximal femur: DXA; fractures assessed by lateral radiographs. Comorbidities: polymyaglia rheumatism or rheumatioid arthritis. Calcium and Vitamin D regimens: Not stated or Unclear. Additional calcium and vitamin D not stated apart from study drugs. Other study comments: Height: 159.3cm (SD10.0):166.9(SD 11.1) stat sig;Weight:65.5kg (SD 12.8):71.9 (12.1);BMI: not stated; Ethnicity: not stated; All pts recd prednisolone for 1 yr 15mg/day for 1month, 10 mg/day for the third month and dosage altered to clinical response.	1) etidronate then calcium (salt not stated); duration: 1 year; frequency per day: once; amount 400 mg/day etidronate for 2 weeks then 500mg Ca/day for 11 weeks (n=15). 2) Intermittent cyclical placebo; duration: 1 year; frequency per day: not stated; amount placebo for 2 weeks then 500mg Ca/day for 11 weeks (n=13). Intervention concurrent medications: median prenisolone dose: 8.75mg. Control concurrent medications: Median prednisolone dose: 10 mg. Concordance: recording all medication in a daily diary.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Participants*	*Interventions*
Meunier 1997 RCT (fracture) trial held in France. Setting: primary care. Funding:Supported by Procter & Gamble Pharmaceuticals (UK) Ltd	Inclusion criteria: weight within 15% of normal BMI; natural menopause 6-60 months before the study and normal BMD. Exclusion criteria: Any disease known to affect bone metabolism; bilateral oophorectomy or hysterectomy; prolong Rx with calcitonin, vit D (>400 U/day), Ca (>500mg/day), corticosteroids or anabolic steroids within past 6mo or BR or a therapeutic dose of Flouride. Patient type: age: 52.7 years (45-75 years), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Some patients. Details: all female. Years postmeopausal: mean 2.3-2.4 years. BMD and Fracture assessment: BMD assessed at lumbar spine & femoral neck with DXA. Comorbidities: none stated; ambulatory and active. Calcium and Vitamin D regimens: Not stated or Unclear. Only calcium as a study drug was reported. Other study comments: Ethnicity: Caucasian; Height: 160 cm; Weight: 45- 90kg; BMI: Not stated; 37 pts followed up [21Eti: 16 from placebo]; 2 withdrew. Participants recruited form GPs and gynae referral.	1) Etidronate followed by calcium supplement (type not stated); duration: 2 years; frequency per day: once; amount 400 mg/day etidronate for 2 weeks followed by 500mg/day elemental Ca for 11 weeks (n=27). 2) placebo (lactose (0.48g) + sodium chloride (0.25g) + magnesium stearate (0.005g)) then calcium; duration: 2 years; frequency per day: once; amount placebo for 2 weeks followed by 500mg/day elemental Ca for 11 weeks (n=27). Concordance: Assessed by pill count; compliant if >80% taken.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Participants*	*Interventions*
Montessori 1997 RCT (fracture) trial held in Netherlands. Setting: primary care. Funding:grant from Proctor and Gamble Pharmaceuticals	Inclusion criteria: <75 years old ambulant and active, postmenopausal (naturally or by bilateral oophorectomy) for at least 1 year, with a BMD of the lumbar spine >1SD below that of age matched controls (Z score <-1SD). Exclusion criteria: Seconday osteoporosis, acute disease, medications. Patient type: age: mean 62.5 years (45-73), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 11/40 (28%) etidronate and 17/40 (43%) placebo had fracture at baseline (not significant). Years postmeopausal: 15.08 years. BMD and Fracture assessment: BMD: (DXAscan) of lumbar spine L1-4, greater trochanter, femoral neck, Wards triangle right hip. Vertebral fracture:Xrays thoracic and lumbar spine. Comorbidities: None. Calcium and Vitamin D regimens: Not stated or Unclear. Calcium as study drugs. Estimated dietary intake was 322-2865 mg/day; serum osteocalcin levels in normal range. Other study comments: Ethnicity: White.	1) etidronate then calcium citrate; duration: 3 years; frequency per day: once; amount 400mg/day etidronate for 14 days then 500mg elemental Calcium for 76 days (n=40). 2) calcium citrate; duration: 3 years; frequency per day: 500 mg/day continuously; amount once (n=40). Concordance: Every 3 months at hospital visit, telephone, GP; 79/80 patients took >75% medication. Washout period: None.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Participants*	*Interventions*
Pouilles 1997 RCT (fracture) trial held in France. Setting: primary care. Funding:Not stated	Inclusion criteria: women [not taking HRT]who had spontaneously or after bilateral oophorectomy ceased menstruating 6-60mo before enrollment with biochem evi of menopause required. Exclusion criteria: history of alcoholism or with evidence from physical exam, lab tests or radiography of any bone metabolism disorder.Women undergoing Rx which might interfere with bone metabolism. Patient type: age: 53.9 years (45-60), Unclear, Postmenopausal women only. Mixed . History of fracture unclear or not stated. Smoking: Not stated. Details: some had bilateral oophorectomy. Years postmeopausal: mean 30-31months (SD 17). BMD and Fracture assessment: BMD at lumbar spine & hip assessed by DXA. Comorbidities: none stated. Calcium and Vitamin D regimens: Not stated or Unclear. Not stated apart from study drugs. Other study comments: Caucasian women. Not undergoing HRT.	1) Etidronate then calcium citrate; duration: 2 years; frequency per day: once; amount 400 mg/day etidronate for 14 days then 500mg day elemental calcium for 77 days (n=54). 2) placebo then calcium citrate; duration: 2 years; frequency per day: ; amount Placebo for 14 days then 500mg day elemental calcium for 77 days (n=55). Concordance: assessed by pill count; compliant if >80% pills. Washout period: Not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Participants*	*Interventions*
Roux 1998 RCT (fracture) trial held in Multicentre[Belgium,France,GB,Germany,Italy,Nether. Setting: primary care. Funding:Not stated	Inclusion criteria: high-dose corticosteroids initiated within 90 days of study entry and cont for at least 12 mo; initial 90 days (during study) of mean daily dose of at least 7.5mg prednisone or its equiv and subsequent Rx 2.5mg/day. Exclusion criteria: Pts taking medications or presenting with diseases affecting bone or calcium metabolism. Bisphosphonates, fluoride, oestrogen or progestogen within 1y; calcitonin or vitamin D within 6 months. Pregnancy. Patient type: age: 59 years, Mixed osteopenia/normal BMD, Males and females. Glucocorticoid-induced osteoporosis . Some patients with history of fracture. Smoking: Not stated. Details: M:F 42:75 [57 women were postmeopausal]; proportion of patients with a fracture: 2/59 and 1/58. Years postmeopausal: 17.5 years (SD 9.9): 15.9 (SD 9.1). BMD and Fracture assessment: BMD assessed at lumbar spine with DXA& fracture assessed with lateral radiographs. Comorbidities: vasculitis, rheumatoid arthritis; polymyalgia rheumatica. Calcium and Vitamin D regimens: Some patients received Vit D only. Patients were allowed Vitamin D up to 1000UI/day. Other study comments: height:163.8cm (SD 9.7); weight:67.7 kg (SD 13.3). HTA report of personal comm. stated that number with vertebral fractures was 2 (Et) and 3 (pl) and with nonvertebral fractures was 2 and 4.	1) Etidronate disodium followed by calcium carbonate; duration: 12 months; frequency per day: once; amount 400mg/day etidronate for 14 days then 500mg/day elemental calcium for 76 days (n=59). 2) placebo then calcium carbonate; duration: 12 months; frequency per day: once; amount placebo for 14 days then 500mg/day elemental calcium for 76 days (n=58). Concordance: Regular pill counts and review of pts' meds diary. Washout period: Not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Participants*	*Interventions*
Watts 1990 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Norwich Eaton Pharmaceuticals provided medication	Inclusion criteria: White and Asian women with osteoporosis (1-4 vertebral fractures) plus radiographic evidence of vertebral osteopaenia. Postmenopausal at least 12 months, generally healthy. Exclusion criteria: >75 years, weight below 40kg or above 80kg; active rheumatoid arthritis, GI or liver disease, chronic alcoholism, renal impairment. Prior treatment with oestrogens, steroids, phosphate, calcium, vitaming D, diuretic in preceding 6 months. Patient type: age: means 64.7 - 65.7 years, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: all had 1-4 vertebral compression fractures + radiological evidence osteopaenia. Years postmeopausal: At least 12 months. BMD and Fracture assessment: BMD femoral neck by dual photon absorptiometry. Vertebral #s by lateral radiographs of spine at entry and 12 and 24 months. Comorbidities: None stated. Calcium and Vitamin D regimens: Not stated or Unclear. calcium as part of intervention cycle. Patients counselled to include at least 700 mg/day calcium in diet; mean was 743 and 807 mg/day. .	1) etidronate followed by calcium carbonate; duration: 2 years; frequency per day: once; amount placebo phosphate for 3 days then 400mg/day etidronate for 2 weeks then 500mg/day elemental calcium for 74 days (n=105). 2) Placebo followed by calcium carbonate; duration: 2 years; frequency per day: once; amount placebo phosphate for 3 days then placebo etidronate for 2 weeks then 500mg/day elemental calcium for 74 days (n=104). Other interventions: 3) 1.0 g/day phosphate for 3 days then etidronate then calcium (n=107) 4) phosphate then placebo then calcium (n=107). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Not stated. Washout period: None.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Participants*	*Interventions*
Cohen 1999 RCT (fracture) trial held in USA and Canada. Setting: not stated. Funding:Grant from Procter and Gamble Pharmaceuticals and Hoechst Marion Roussel	Inclusion criteria: Corticosteroids ≥ 7.5mg/day within 3 months; women at least 1 year postmenopausal or surgical menopause or birth control methods. Exclusion criteria: History of hyperparthyroidism, hyperthyroidism or osteomalacia within 1 year. Drugs known to affect bone metabolism within 1 year. Conditions that interfere with evaluation of lumbar spine BMD. Patient type: age: RSD 61.9 and PL 57.2 years (SD 14.5) (sig different), Mixed osteopenia/normal BMD, Males and females. Glucocorticoid-induced osteoporosis . Some patients with history of fracture. Smoking: Not stated. Details: 25-27% men; 14-15% premenopuasal women; 35-37% postmenopausal. 27 and 22% with a vertebral fracture. Years postmeopausal: at least 1 year. BMD and Fracture assessment: BMD assessed by DXA of lumbar spine and proximal femur. Fracture assessed using quantitative morphometry (vertebral height decrease ≥15%). Comorbidities: Rheumatoid arthritis (30%), polymyalgia rheumatica, pulmonary and skin conditions. Calcium and Vitamin D regimens: Some patients received Ca and Vit D. All patients received 500mg as CaCO3 supplements. Patients with 25-hydroxy vitamin D levels below normal given up to 500 IU vitamin D / day. Other study comments: BMI and ethnicity not stated. Some patients had surgical menopause. Stratified into men / pre- and postmenopausal women before randomisation.	1) Risedronate; duration: 12 months; frequency per day: once; amount 5mg (n=76). 2) placebo; duration: 12 months; frequency per day: once; amount (n=77). Other interventions: 3) risedronate 2.5 mg/day (n=75). Concordance: not stated how assessed. Washout period: not stated, but patients ineligible if they had taken osteoporosis drugs in last 12 m.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Participants*	*Interventions*
Fogelman 2000 RCT (fracture) trial held in Multicentre (Europe). Setting: not stated. Funding:Procter & Gamble and Aventis provided support, no further details.	Inclusion criteria: Women up to 80 years of age. Postmenopausal for at least 1 year; mean lumbar spine (L1-L4) T score of -2 or less. Exclusion criteria: Hyperparathyroidism, hyperthyroidism, or osteomalacia within a year before the study. History of cancer. Patient type: age: Mean placebo 64 (SD 6.7); risedronate 65 (SD 6.7), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: female. Years postmeopausal: at least 1 year. BMD and Fracture assessment: DXA at lumbar spine, femoral neck and trochanter; fracture assessed by radiograph. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. One gram of calcium per/day, taken a different times to the study drug. .	1) Risedronate taken on an empty stomach with at least 240ml of water, 30-60 min before breakfast in an upright position; duration: 2 years; frequency per day: once per day; amount 5 mg 179. 2) Placebo; duration: 2 years; frequency per day: once per day; amount 180. Other interventions: 3) Risedronate 2.5mg per day (n=184). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Participants*	*Interventions*
Harris 1999 RCT (fracture) trial held in Multicentre (North America). Setting: not stated. Funding:Grants by Procter & Gamble, and Hoechst Marion Roussel, no further details.	Inclusion criteria: At least 1 vertebral fracture at baseline. Ambulatory women no older than 85 years. Exclusion criteria: Conditions that might interfer with the evaluation of spine bone loss, or if they had recevied drugs known to affect bone metabolism. Patient type: age: risedronate mean 69 yrs (SD 7) placebo 68 (SD 7), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Some patients. Details: female all with at least one fracture. Years postmeopausal: mean 24 years (SD ~10). BMD and Fracture assessment: BMD assessed by DXA at lumbar & femoral neck; fracture assessed by radiograph. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. All patients given Ca 1000 mg/day; also given Vit-D up to 500 IU/day if baseline levels were low. Other study comments: 96% were white. Participants stratified at baseline according to the number of vertebral fractures The VERT North America trial.	1) Risedronate on an empty stomach 30-60 min before breakfast with water and to remain upright; duration: 3 years; frequency per day: once per day; amount 5 mg 813. 2) Placebo; duration: 3 years; frequency per day: once per day; amount 815. Other interventions: 3) Risedronate 2.5 mg (n=811); 2.5 mg group later discontinued. Intervention concurrent medications: none. Control concurrent medications: none. Concordance: not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Participants*	*Interventions*
Hooper 2005 RCT (fracture) trial held in Multicentre Australia. Setting: not stated. Funding:Authors received funding, honoraria or grants from industry sources. Research grant support from Procter & Gamble, and Sanofi-aventis.	Inclusion criteria: Postmenopausal for 6 to 36 months, with FSH of at least 50 mIU/ml and serum estradiol of no more than 20 pg/ml. Exclusion criteria: No history of hyperparathyroidism, hyperthyroidism, or osteomalacia, or treatment with bone agents likely to affect bone metabolism. Patient type: age: 42-63 years, mean 53 years., Mixed osteopenia/normal BMD, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Some patients. Details: not stated. Years postmeopausal: 6 months to 3 years. BMD and Fracture assessment: BMD determined by DXA at lumbar spine and proximal femur; fracture assessed radiographically. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Ca 1000 mg/day taken with midday or evening meal. Other study comments: 98% Caucasian.	1) Risedronate taken with 240ml of water on an empty stomach 30-60 min before breakfast; duration: 2 years; frequency per day: once per day; amount 5 mg 129. 2) Placebo; duration: 2 years; frequency per day: ; amount once per day 126. Other interventions: 3) Risedronate 2.5 mg (n=128). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: no stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Participants*	*Interventions*
McClung 2001 RCT (fracture) trial held in Multicentre (USA, Canada, Europe, Australia, NZ). Setting: not stated. Funding:Authors received grants or act as consultants to either Procter & Gamble, or Aventis Pharma.	Inclusion criteria: Low BMD at the femoral neck T score lower than -4 or lower than -3 with at least 1 non-skeletal risk factor for hip fracture. Exclusion criteria: Any major illness, recent history of cancer, another metabolic bone disease within the previous year, history of bilateral hip fracture. Patient type: age: 70 to >80 years, Likely to be mixed, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: not clear. Years postmeopausal: not stated. BMD and Fracture assessment: DXA BMD, and radiographic determination of fracture. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Ca 1000 mg/day; Vit-D =/< 500 IU/day if vit-D concentrations were low. Other study comments: Women enrolled into 2 groups, 70-79 years with osteoporosis (n= 5445) and 80+ years with at least 1 nonskeletal risk factor or osteoporosis (n= 3886). These groups were randomised separately 98% of women were white..	1) Risedronate 5 mg taken with 240 ml water on an empty stomach in upright position; duration: 3 years; frequency per day: once per day; amount 5.0 mg (n=3104). 2) Placebo; duration: 3 years; frequency per day: once per day; amount 3134. Other interventions: 3) Risedronate 2.5 mg (n=3093). Combined data reported for 2.5 and 5.0mg. Intervention concurrent medications: none. Control concurrent medications: none. Concordance: not stated. Washout period: Not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Participants*	*Interventions*
Mortensen 1998 RCT (fracture) trial held in 2 centres, USA, Denmark. Setting: secondary care. Funding:Financial support provided by Procter & Gamble, no further details.	Inclusion criteria: Estradiol at least 40 pg/mL and FSH at least 20 U/L and patients had to be ambulatory and active. Exclusion criteria: Used any bisphosphonate, thyroid hormone therapy, glucocorticoids, anabolic agents, calcitonin, vitamin D, high dose calcium, diuretics or anticonvulsants. Evidence of osteoporosis. Patient type: age: mean age risedronate 52.1; placebo 51.2 years, All BMDs, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: not stated. Years postmeopausal: 6 to 60 months postmenopausal. BMD and Fracture assessment: DXA for BMD and radiographs to determine fractures. Comorbidities: not stated. Calcium and Vitamin D regimens: No patients. Not required. Other study comments: Patients stratified according to calcium intake. All participant were caucasian. Treated for 2 years with additional 1 year follow-up without interventions.	1) Risedronate to be taken with 8oz of water 2h before bedtime or 2h after a meal; duration: 3 year; frequency per day: once per day; amount 5 mg (n=37). 2) Placebo; duration: 3 year; frequency per day: twice per day; amount (n=36). Other interventions: 3) Cyclic risedronate (n=38). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: not stated. Washout period: no stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Participants*	*Interventions*
Reginster 2000 RCT (fracture) trial held in 80 centres (Europe & Australia). Setting: not stated. Funding:Grants by Procter & Gamble, and Hoechst Marion Roussel, no further details.	Inclusion criteria: Ambulatory women up to 85 years and at least 5 years postmenopausal were eligible if they had at least 2 radiographically confirmed vertebral fractures. Exclusion criteria: Conditions that might interfer with evaluation of spinal osteoporosis, and use of calcitonin, calcitriol or vitamin D supplements within 6 months. Patient type: age: risedronate mean 71 yrs (SD 7); placebo 71 (SD 7), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: all had fracture. Years postmeopausal: at least 5 years postmenopausal. BMD and Fracture assessment: DXA used for BMD and radiographic determination of fractures. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Ca 1000 mg/day and up to 500 IU/day where necessary (35%) required Vit-D supplementation. Other study comments: 256 women (135) risedronate and (130) placebo continued with study medication for a further 2 years extension phase The VERT Multinational study.	1) Risedronate to be taken with 240ml of water 30-60 min before breakfast; duration: 3 years; frequency per day: once a day; amount 5 mg (n=408). 2) Placebo; duration: 3 years; frequency per day: once a day; amount (n=408). Other interventions: 3) Risedronate 2.5 mg per day (n=410). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: 86% were compliant according to tablet counts. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Participants*	*Interventions*
Reid 2000 RCT (fracture) trial held in Multicenter (Europe). Setting: not stated. Funding:Grants by Procter & Gamble, and Hoechst Marion Roussel, and participated in the study design, data analysis and writing the report.	Inclusion criteria: Ambulatory women 18-85 years, who had taken corticosteroids for at least 6 months. Exclusion criteria: Participants excluded if they had history of hyperparathyroidism, hyperthyroidism, or osteomalacia, within a year before the study; sarcoidosis or cancer; taken medication known to affect bone metabolism. Patient type: age: 18-85 male and female. Mean age 59 years, All BMDs, Males and females. Mixed high risk patients . Some patients with history of fracture. Smoking: Not stated. Details: 36% men, 7-9% premenopausal women, 53-55% postmenopausal. Vertebral fracture at baseline risedronate 34; placebo 35. Years postmeopausal: at least one year where applicable. BMD and Fracture assessment: BMD assessed with DXA at femoral neck trochanter and forearm. Fracture assessed radiographically. Comorbidities: Yes, RA, asthma, polymyalgia rheumatica, SLE, temporal arteritis, vasculitis, COPD, polymyositis, chronic interstitial lung disease, other. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Ca 1000 mg/day and Vit-D 400 IU/D. Other study comments: Patients had received high dose oral corticosteriod for at least 6 months prior to study entry. Participants stratified to men, premenopausal women, using birth control or sterile, and postmenopausal (for at least 1 year) women.	1) Risedronate taken with 240ml of water on an empty stomach 30-60 min before breakfast; duration: 1 year; frequency per day: once per day; amount 5 mg (n=100). 2) Placebo; duration: 1 year; frequency per day: ; amount once per day (n=96). Other interventions: 3) Risedronate 2.5 mg / day (n=94). Intervention concurrent medications: Prednisone (or equivalent). Control concurrent medications: Prednisone (or equivalent). Concordance: How assessed?. Washout period: none.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Ibandronic Acid review

Study	*Participants*	*Interventions*
Chesnut 2004 RCT (fracture) trial held in Multinational. Setting: not stated. Funding:Research grants provided by Roche; three authors were/had been employees of Roche	Inclusion criteria: BMD T score -2 to -5 in at least one vertebrae (L1-L4); at least 5 years menopausal; participants with upper GI disorders or receiving medications with a potential GI irritation were included. Exclusion criteria: BMD <5.0 at the lumbar spine; more than 2 prevalent fractures at lumbar spine; diseases, disorders, or therapy affecting bone metabolism; previous treatment with bisphosphonates; flouride treatment; renal impairment; hyper- or hypocalcemia. Patient type: age: mean 69 years (SD 6), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 93-94% of patients with at least one fracture; 42-44% with two fractures. Years postmeopausal: at least 5 years (mean TSM 21 years). BMD and Fracture assessment: BMD by dual x-ray absorptiometry; lateral radiographs of thoraco-lumbar spine annually; height reduction in vertebral body >20% and >4mm. Comorbidities: 25-28% with pre-existing GI disorders. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Daily 500mg Ca and 400 IU vitamin D. Other study comments: Mean height, weight and BMI: 160 cm, 67 kg, 26 kg/m2; n=995 in North America and n=1934 in Europe.	1) Ibandronic acid; duration: 3 years; frequency per day: Once; amount 2.5 mg orally (n=982). 2) Placebo; duration: 3 years; frequency per day: Once; amount not stated (n=982). Other interventions: 3) Ibandronate orally 20 mg every other day for 12 doses every 3 months (placebo on days with no active medication) (n=982). Intervention concurrent medications: 35-37% NSAIDS and 61-63% antacids. Control concurrent medications: 35-37% NSAIDS and 61-63% antacids. Concordance: not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Ibandronic Acid review

Study	*Participants*	*Interventions*
Eisman 2008 RCT (fracture) trial held in Mutlinational. Setting: not stated. Funding:Research supported by F. Hoffmann-La Roche Ltd and GlaxoSmithKline (they also had a role in study design and interpretation of data); 3 authors worked for Hoffmann-La Roche	Inclusion criteria: Women 55-80 years; at least 5 years postmenopausal; mean lumbar spine BMD T-score <-2.5 but ≥ -5. Exclusion criteria: Women who had received previous IV or oral bisphosphonates, or any other drug affecting bone metabolism were excluded; renal impairment, a history of major upper GI disease, or allergy to bisphosphonates. Patient type: age: mean 65.6 years, Osteoporosis, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 43-44% of patients with a prevalent fracture. Years postmeopausal: at least 5 years (mean TSM 18/19 years). BMD and Fracture assessment: BMD by dual x-ray absorptiometry; clinical and nonvertebral fractures were monitored from adverse event reporting and confirmed radiographically. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Daily 500 mg Ca and 400 IU vitamin D. Other study comments: Mean height, weight, BMI: 158 cm, 63/64 kg, 25/26 kg/m2; Dosing IntraVenous Administration (DIVA) study; data reported at 1 year only. Statified by centre and BMD.	1) Ibandronic acid plus daily oral placebo; duration: 2 years; frequency per day: Once every 3 months; amount 3 mg iv injections every 3 months (n=471). 2) Ibandronic acid plus placebo IV (either 3 monthly or 2 monthly); duration: 2 years; frequency per day: Once; amount 2.5 mg oral tablet (n=470). Other interventions: 3) 2 mg iv injections every 2 months plus daily placebo for 2 years (n=454). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Ibandronic Acid review

Study	*Participants*	*Interventions*
Reginster 2006 RCT (fracture) trial held in Multinational. Setting: not stated. Funding:Research supported by F Hoffmann-La Roche Ltd and GlaxoSmithKline; 1 author was employed by Hoffmann-La Roche	Inclusion criteria: Postmenopausal women; aged 55-80 years; at least 5 years since the menopause, with mean lumbar spine BMD T-score between <-2.5 and >-5.0 (L2 to L4); patients with controlled dyspeptic symptoms, history of nonrecurring peptic ulcers were included. Exclusion criteria: Patients with uncontrolled active or recurrent peptic ulcer disease; disease, disorder or therapy known to influence bone metabolism, treatment with bisphosphates, fluoride treatment; renal impairment, and contraindications to Ca or vit D therapy. Patient type: age: mean 66.2 and 65.8 years, Osteoporosis, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 47-49% of patients with a history of previous fractures. Years postmeopausal: at least 5 years (mean TSM 18/19 years). BMD and Fracture assessment: BMD by dual x-ray absorptiometry; clinical fractures were identified symptomatically and confirmed radiographically. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Daily 500 mg Ca and 400 IU vitamin D. Other study comments: Mean height, weight, BMI: 157cm, 64 kg, 26 kg/m2; Monthly Oral iBandronate In LadiEs (MOBILE) study. Statified by centre and BMD.	1) Ibandronic acid plus daily placebo; duration: 2 years; frequency per day: Once monthly; amount 150 mg per month (n=401). 2) Ibandronic acid plus once-monthly placebo; duration: 2 years; frequency per day: Once; amount 2.5 mg daily (n=402). Other interventions: 3) 50 mg + 50 mg (single doses on 2 consecutive days) monthly ibandronate (n=404) 4) 100 mg Ibandronate monthly (n=402); participants also received placebo to maintain blinding. Intervention concurrent medications: none. Control concurrent medications: None. Concordance: not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Zoledronic acid review

Study	*Participants*	*Interventions*
Black 2007 RCT (fracture) trial held in Mulitcentre, International. Setting: not stated. Funding:Authors had research grants or consultancies from industry, and received support from Novartis Pharma	Inclusion criteria: Postmenopausal women aged between 65-89 years, with a bone mineral density T score of -2.5 or less at the femoral neck, with or without evidence of vertebral fracture; or a T score of -1.5 or less with radiological evidence of at least two mild verte. Exclusion criteria: Previous use of parathyroid hormone or sodium fluoride, use of anabolic steroids or growth hormone within 6 months of trial; oral or IV corticosteroids within 12 months of trial. Patients with calcium levels >2.75 mmol per litre or < 2.2 mmol per l. Patient type: age: Mean (73) range (65-89) years, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: Female. Years postmeopausal: not stated. BMD and Fracture assessment: Spinal lateral radiographs. Vertebrae from T4 to L4 were evaluated by an expert reader (Synarc) with the use of morphometry and standard methods. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Oral Calcium 1000-1500 mg/day and Vit-D 400-1200 IU/day. Other study comments: BMI 25%. Participants stratified according to whether they were taking osteoporosis medication at baseline, and then randomised. Approximately half were from Europe and half from North and South America and Asia.	1) zoledronic acid; duration: 3 years; frequency per day: 5 mg 15 minute intravenous administration; amount baseline, 12 months and 24 months (n=3889). 2) Placebo infusion; duration: 3 years; frequency per day: baseline, 12 & 24 months; amount 15 min iv infusion (n=3876). Other interventions: None. Intervention concurrent medications: none. Control concurrent medications: none. Concordance: Not stated. Washout period: variable, up to 2 years, depending on duration of previous medication.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Zoledronic acid review

Study	*Participants*	*Interventions*
Lyles 2007 RCT (fracture) trial held in Multinational (Europe, N America, Latin America). Setting: not stated. Funding:study supported by Novartis	Inclusion criteria: Had undergone repair of hip fracture and unwilling/unable to take oral bisphosphonates. 50y & older; received infusion within 90d of non-trauma hip fracture surgical repair; ambulatory before fracture and having both legs. Exclusion criteria: previous hypersenstivity to bisphosphonate, potential for pregnancy, creatinine clearance <30ml/min; corrected serum Ca level > 11 mg/dl or <8mg/dl; active cancer, metabolic bone disease other than OP; life expectancy < 6 mo. Patient type: age: mean 74.5 years (SD 9.6); 18% under 65y;14% 85y and older, Mixed osteoporosis/osteopenia, Males and females. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: 76-77% females; all patients had had a recent hip fracture. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed at hip or spine by DXA; lateral radiographs of chest and spine taken, but, for vertebral fractures, only evaluated if symptoms present. Comorbidities: hypertension, coronary artery disease, osteoarthritis, stroke, depression, diabetes. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Most pts received 50,000-125,000 IU vitamin D2 or D3 2w before infusion; then all pts received calcium (1-1.5g/day) and vitamin (800 IU/day). Other study comments: BMI 24.8 kg/m2 (SD 4.5); 91% white, 7% Hispanic, 1% Black; some with delirium/dementia. If BMD >8% decline in y1 or >10% in y1-2, pts could choose to (1) continue (2) add calcitonin/HRT/raloxifene + continue (3) have oral bisphos/Tpd + F-U (4) stop+FU.	1) zoledronic acid infusion over 15 min; duration: median 1.9 years; frequency per day: once annually; amount 5 mg / year (n=1065). 2) placebo infusion; duration: median 1.9 years; frequency per day: once annually; amount NA (n=1062). Intervention concurrent medications: 9% received concomitant HRT, calcitonin, tibolone, raloxifene); some had bisphophonate/teriparatide. Control concurrent medications: 12% received concomitant HRT, calcitonin, tibolone, raloxifene); some had bisphophonate/teriparatide. Concordance: If BMD declined >8-10%, patients could opt to discontinue infusions. Washout period: varied according to nature of drug (bisphosphonates or PTH) and duration of use.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Cross biphosphonates review

Study	*Participants*	*Interventions*
Miller 2008 (MOTION) RCT (fracture) trial held in Multinational (65 centres in N America, Latin America, Europe and S Africa). Setting: not stated. Funding:Study sponsored by Hoffmann-La Roche and GlaxoSmithKline	Inclusion criteria: Postmenopausal women, ambulatory, aged 55-84, with mean lumbar spine T-score less than -2.5 and ≥ -5.0. Exclusion criteria: Signif medical disease, inability to stand/sit upright for 60min, hypersensitivity to bisphosphonates; contraindications calcium/vit D, renal impairment, history of major upper GI disease, any active disease/recent drugs, known to affect bone metabolism. Patient type: age: mean 65.6 years, Osteoporosis, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: proportion of patients with a fracture was 38-39% (mean). Years postmeopausal: 18.5 years mean. BMD and Fracture assessment: BMD assessed by DXA scan of proximal femur and lumbar spine. Comorbidities: none stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Vitamin D 400 IU/day; elemental calcium 500 mg/day as dietary supplements. Other study comments: height mean 155 cm; weight mean 62 kg; ethnicity: 81-83% Caucasian; stratified by country, history of clinical fractures, total hip BMD.	1) Ibandronic acid plus placebo alendronic acid; duration: 12 months; frequency per day: once monthly; amount 150 mg/month (n=887). 2) Alendronic acid plus placebo ibandronic acid; duration: 12 months; frequency per day: 70 mg/week; amount once weekly (n=873). Concordance: not reported.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Cross biphosphonates review

Study	*Participants*	*Interventions*
Muscoso 2004 RCT (fracture) trial held in Italy. Setting: secondary care. Funding:Not stated	Inclusion criteria: female patients with osteoporosis. Exclusion criteria: Not stated. Patient type: age: 71years (SD 19):66 years (SD 9), Osteoporosis, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: history of fractures not stated. Years postmeopausal: Not stated. BMD and Fracture assessment: Details on how fracture was assessed not provided; BMD of lumbar vertebrae by DXA. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. All patients received 1g of Ca and 800 IU of Vitamin D daily. Other study comments: height/weight/BMI: not stated; Age groups: 50-59 years: 300 cases; 60-69 years: 702 cases; 70-79 years:820 cases; >80 years: 178 cases; 14/18#s >80yr; 4#s:70-79 years; no #s: in the remaing group.	1) Alendronic acid; duration: 2 years; frequency per day: once; amount 10 mg (n=1000). 2) Risedronate; duration: 2 years; frequency per day: 5 mg; amount once (n=100). Other interventions: 3) Raloxifene 60 mg/day (n=100); 4) Clodronate 100 mg/day i.m. (n=800). Concordance: Not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Cross biphosphonates review

Study	*Participants*	*Interventions*
Reid 2006b (FACTS) RCT (fracture) trial held in Multinational; 27 sites in Europe, Middle East, Americas, Asia-Pacific. Setting: primary care. Funding:Funded by Merck & co.	Inclusion criteria: Postmenopausal women; good general health; ≥40years or ≥25y if surgically menopausal. Spine anatomy suitable for measurement with DXA. T-score ≤ -2.0. Oestrogen use for ≤1wk at least 3mo before study & use of vaginal oestrogen cream (≤2g, 2xwkly) allowed. Exclusion criteria: Abnormality of oesophagus that delayed emptying, e.g. stricture or achalasia. Pts unable to remain upright for 30 min. Hypocalcaemia, hypovitaminosis D, metabolic bone disease. Bisphosphonates w/in 1y or for ≥2y w/in 5y; use of PTH w/in1y. Patient type: age: mean 64.2 years (SD 8.2), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: History of fracture 33.7%. Years postmeopausal: mean 16.8 years (SD 9.5). BMD and Fracture assessment: BMD assessed at posterior-anterior lumbar spine & proximal femur with DXA. Not stated how fracture assessed. Comorbidities: hypertension 32%; osteoarthritis 18%; hypercholesterolaemia 15%. Calcium and Vitamin D regimens: All patients received Ca and Vit D. All patients instructed to take 1000mg of elemental Calcium & 400 IU Vitamin D daily either from dietary sources or as a supplement. Other study comments: Excl(contd):use of oestrogen or oestrogen analogues, tibolone or anabolic steroids w/in 6mo. Height/weight/BMI: not stated; Ethnicity:white:(78.5%);Hispanic (8.8%);Asian (7.6%);Other (5.1%); 28% reported use of an NSAID during the study.	1) Alendronic acid and risedronate placebo; duration: 1 year; frequency per day: once weekly; amount 70 mg/week (n= 468). 2) Risedronate and alendronic placebo; duration: 1 year; frequency per day: once weekly; amount 35 mg/week (n=468). Intervention concurrent medications: 29.3% used an NSAID during study. Control concurrent medications: 27.4% used an NSAID during study. Concordance: Not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Cross biphosphonates review

Study	*Participants*	*Interventions*
Rosen 2005 (FACT) RCT (fracture) trial held in USA. Setting: primary care. Funding:Authors received funding from Aventis, Eli Lilly Merck, Novartis, NPC Pharmaceuticals, & Wyeth. Industry assisted with co-ordination of data processing.	Inclusion criteria: Postmenopausal women; good general health; ≥40years or ≥25y if surgically menopausal. Spine anatomy suitable for measurement with DXA. T-score ≤ -2.0. Oestrogen use for ≤1wk at least 3mo before study & use of vaginal oestrogen cream (≤2g, 2xwkly) allowed. Exclusion criteria: Abnormality of oesophagus that delayed emptying, e.g. stricture or achalasia. Pts unable to remain upright for 30 min. Hypocalcaemia, hypovitaminosis D, metabolic bone disease. Bisphosphonates w/in 1y or for ≥2y w/in 5y; use of PTH w/in1y. Patient type: age: Mean 64.5 years (SD 9.8), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: history of hip,spine or wrist after age 45 years was 12% (mean); 13.5-14.4% women were current smokers. Years postmeopausal: mean 18.5 years. BMD and Fracture assessment: BMD measured by DXA at the PA lumbar spine and proximal femur. Comorbidities: 25% of pts had a prior history of any upper GI disorder at b/l. Calcium and Vitamin D regimens: All patients received Ca and Vit D. All patients were instructed to consume 1000mg of elemental Ca & 400 IU of Vit D daily either from dietary sources or a supplement. Other study comments: Excl(contd):use of oestrogen or oestrogen analogues, tibolone or anabolic steroids w/in 6mo. Ethnicity: White (95%); Black (0.9%); Asian (1.4%); Other (2.4%); BMI: 25.2(4.7): 25.5(4.5) kg/m2.	1) Alendronic acid +risedronate-matching placebo; duration: 12 months; frequency per day: once weekly (same day each week); amount 70 mg/week (n=520). 2) Risedronate + alendronic acid-matching placebo; duration: 12 months; frequency per day: once weekly; amount 35mg/day (n=533). Intervention concurrent medications: 41% used concomitant NSAIDs during the study. Control concurrent medications: 41% used concomitant NSAIDs during the study. Concordance: Patients recorded medication use over the 12mo of treatment & validated with tablet counts of returned medication at each study visit.. Washout period: not specified, but see exclusion criteria.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Bisphosphonate

Cross biphosphonates review

Study	*Participants*	*Interventions*
Sarioglu 2006 RCT (BMD only) trial held in Turkey. Setting: not stated. Funding:Not stated	Inclusion criteria: Postmenopausal women with osteoporosis. Exclusion criteria: Pts >75yrs, taking oestrogen, calcitonin, anabolic steroids; presence of any disease which interferes with bone metabolism, recent use of drugs known to affect bone metabolism, history of esophagitis & peptic ulcer. Patient type: age: 60.3 (SD 7.1): 57.3 (SD6.6), All BMDs, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 3/25 (12%) pts in the alendronic acid grp & 2/25 (8%) in the risedronate group had previous compression fractures in lumbar vertebrae.. Years postmeopausal: 14.7(SD2.7):12.1(SD2.4). BMD and Fracture assessment: BMD: DXA at the lumbar spine,LH femoral neck,trochanter,Wards,TH & Lateral and anterior thoracic & lumbar spine radiographs evaluated for vertebral #s. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Both groups received 1000mg/d calcium & 400 IU Vit D as supplemental therapy throughout the study. Other study comments: height/weight/ ethnicity: not stated; BMI: 27.7(SD 3): 27(SD 4.5) kg/m2.	1) Alendronic acid; duration: 12 months; frequency per day: once weekly; amount 70 mg/week (n=25). 2) Risedronate; duration: 12 months; frequency per day: 5 mg; amount once (n=25). Concordance: Not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Strontium ranelate

Strontium ranelate review

Study	*Participants*	*Interventions*
Adami 2006 (TROPOS) RCT (fracture) trial held in Multi-centre, 75 centres in 11 european and in Au. Setting: secondary care. Funding:The TROPOS study supported by funding from Servier	Inclusion criteria: Postmenopausal ambulatory women age 74 or more, or 70-74 with an additional risk factor (i.e.history of osteoporotic fracture after menopause, resident in a retirement home, frequent falls or a maternal history of osteoporotic fractures of the hip, spine). Exclusion criteria: Women with diseases interfering with bone metabolism and those using antisteroporotic agents (bisphosponates taken for more than 14 days within the previous year , oestrogen, calcitonin, fluoride salts, calcitriol). Patient type: age: 74 or more, or 70-74 with additional risk factors, Osteoporosis, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: N/A. Years postmeopausal: average 28 years. BMD and Fracture assessment: BMD via DXA; radiographic determination of non-vertebral fractures. Radiographic determination of Vert. fractues were not mandatory but were obtained where possible. Comorbidities: None reported. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Participants undertook a run in period of between 2 weeks an 6 months to normalise Ca & Vit-D levels. Daily intake of Ca given to ensure intake was above 1000mg, and Vit-D given 400-800 IU/day.Supplementation was continued throughout the study. .	1) Strontium ranelate taken once daily at bedtime or twice a day, one sachet before breakfast and one at bedtime; duration: 3 years; frequency per day: once or twice per day; amount 2 gram per day (n=2554). 2) Placebo powder; duration: 3 years; frequency per day: once or twice per day; amount (n=2537). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Mean global compliance of 82%, no further data. Washout period: not reported.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Strontium ranelate

Strontium ranelate review

Study	*Participants*	*Interventions*
Meunier 2002 (STRATOS) RCT (fracture) trial held in Multicentre, 31 centres in 9 European countries. Setting: secondary care. Funding:STRATOS study. Funding provided by Servier	Inclusion criteria: Non-obese menopausal women who were at least 12 months postmenopausal with established osteoporosis. Exclusion criteria: More than 2 X-ray documented vertebral crushed fractures between L1 and L4 documented secondary osteoporosis; osteomalacia; severe scoliosis. Treatment with calcitonin, oestrogen, corticosteroids. Patient type: age: 45-78 years, Osteoporosis, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: N/A. Years postmeopausal: Approx 18 years on average. BMD and Fracture assessment: BMD assessed by DXA at lumbar spine. Spinal radiographs used to determine fracture and a decrease of at least 20% was taken in indicate vertebral deformity. Comorbidities: None. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Calcium 500 mg/day and Vitamin D 800 IU/day throughout the study. Other study comments: mean BMI 25.4 kg/m2; mean weight 63.6 - 65.1kg.	1) Strontium ranelate; duration: Two years; frequency per day: Twice per day; amount 2 gram (n=87). 2) Placebo; duration: Two years; frequency per day: Twice per day; amount (n=91). Other interventions: SR given at 0.5, 1.0 and 2.0 grams i.e. 4 arm study. Only 2 gram SR reported. Intervention concurrent medications: none. Control concurrent medications: None. Concordance: by unused tablets returned at study visits, and by drug concentration measurements. Washout period: Not reported.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Strontium ranelate

Strontium ranelate review

Study	*Participants*	*Interventions*
Meunier 2004 (SOTI) RCT (fracture) trial held in Multicentre (72) 11 European countries & Australi. Setting: secondary care. Funding:Trial supported by Servier and authors received consultant fees from Servier.	Inclusion criteria: At least 50 years old, had been postmenopausal for at least 5 years, had had at least one fracture confirmed by X-ray and lumbar spine BMD of 0.840g per cm2 or less. Exclusion criteria: Severe disease or conditions that could interfere with bone metabolism, or if they used anti-osteoporotic treatments (fluoride salts and biphosponates taken for more than 12 days within the previous 12 months, oestrogen, calcitonin, calcitriol in past 12. Patient type: age: Mean age 69 years, range not reported, Osteoporosis, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Some patients. Details: N/A. Years postmeopausal: average 22 years. BMD and Fracture assessment: BMD assessed by DXA at lumbar spine; vertebral fractures assessed radiographically. Comorbidities: None reported. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Calcium up to 1000 mg and vitamin D 400-800 IU. Other study comments: BMI 26.2 kg/m2; 11-12% smoking; ITT analysis performed on participants who had at least one packet of treatment and for whom at least one spinal radiograph was obtained after baseline.	1) Strontium ranelate two packets of powder mixed with water taken am and nolte or at bedtime; duration: 3 years; frequency per day: either once or twice/day; amount 2 gram per day (n=828). 2) Placebo; duration: 3 years; frequency per day: either once or twice/day; amount (n=821). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: not stated. Washout period: not reported.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Parathyroid hormone

Teriparatide review

Study	*Participants*	*Interventions*
Cosman 2001 RCT (fracture) trial held in USA. Setting: mixed. Funding:National Institutes of Health (NIH)	Inclusion criteria: primary osteoporosis, T-score of 2.5 below normal premenopausal mean in spine or hip region &/or X-ray documented osteoporotic vertebral fracture;no exclusions due to bone loss; on HRT for 2y (1y before study & 1y FUP)before randomisation to stabilise BMD. Exclusion criteria: (n=13) secondary causes of osteoporosis or medications affecting bone metabolism; (n=2)active renal calculus with 10y or multilple renal stone. Patient type: age: 57.7 (1.7 SE); 62.9 (1.5 SE), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 100% women; Prevalent vertebral fracture at baseline: PTH/Placebo 58%/46%. Years postmeopausal: 14.6 (2.0 SE); 17.8 (1.8 SE). BMD and Fracture assessment: BMD by QDR on spine & hip; Fracture 15% height reduction; incident fractures by 15-20% reduction; BMD spine PTH/Placebo 0.738(0.016 SE)/0.762 (0.016 SE); BMD totalhip 0.726(0.019)/0.71(0.017). Calcium and Vitamin D regimens: All patients received Vit D. Nutritional advice on mantainance of daily calcium intakes of 1500 mg using 3 food diaries to assess dietary intakes; Vit D given as single multivitamin containing 400 IU/day. Other study comments: on HRT => 2 years before randomisation height 160/160cm; weight 63/61kg(1.8).	1) PTH (1-34) subcutaneous daily self injection + HRT; duration: 36 months; frequency per day: once daily; amount 25 mcg/day (n=27). 2) HRT (as prescribed); duration: 36 months; frequency per day: Not stated; amount Not stated (n=25). Intervention concurrent medications: not stated. Control concurrent medications: not stated. Concordance: Assessed by returned of unused undiluted PTH vials, at least 90% of distributed PTH completed; at least 90% completed hormone therapy in both groups. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Parathyroid hormone

Teriparatide review

Study	*Participants*	*Interventions*
Cosman 2005 RCT (fracture) trial held in USA. Setting: mixed. Funding:sponsors' influence limited to data&safety monitoring (DSM) board only; DSM designated by NIH to conduct, safety & progress; Non-pharma sponsors (NIAMSD)&other (Eli Lilly, Merck, Roche-GlaxoSmithKline, Novartis, Pfizer, NPS, Procter&Gamble, Aventis, Wyeth	Inclusion criteria: BMD Tscore of -2.5 or less at the lumbar spine, femoral neck or total hip; or T-score of -2 or less at any of the same sites plus history of fracture in adulthood (at least 40 year), or vertebral fracture identified by radiography; overnight fast. Exclusion criteria: rheumatoid arthritis, multiple prior renal stones, kidney stone within preceding 5 years, current use of glucocorticoids, antiepileptic medications, estrogen; excluded fractures caused by trauma (motor vehicle accidents), finger, toe and skull fractures. Patient type: age: 57.7 (1.7 SE); 62.9 (1.5 SE), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 100% women; prior nonspinal fracture in adulthood % dailyPTH/cyclicPTH/Placebo: 60/58/30; prevalent vertebral fractures % dailyPTH/cyclicPTH/Placebo: 51/54/49. Years postmeopausal: 19.5(10.6 SD); 20.7 (8.7 SD); 22.1 (8.9 SD). BMD and Fracture assessment: BMD by Lunar Prodigy at spine hip & total body; BMD (SD), spine 0.838 (0.11), 0.847 (0.08), 0.83 (0.1); hip 0.76 (0.11), 0.739 (0.09), 0.768 (0.01). Calcium and Vitamin D regimens: Some patients received Ca and Vit D. In all patients and when necessary by supplements: Ca intake was mantained between 1200-1500 mg/day and assessed by food frequency questionnaire; 25-hydroxyvitamin D intake achieved and mantained at more than 20 ng/m (normal). Other study comments: height 160/157cm; weight 63/62 kg.	1) Daily PTH (1-34) subcutaneous daily self injection+ alendronic acid; duration: 15 months; frequency per day: 1/day + 1/week; amount 25 mcg/day + 70 mg/day (n=43). 2) Nothing + alendronic acid; duration: 1.25 years; frequency per day: 1/week; amount 70 mg/week (n=43). Other interventions: 3) Cyclic Teriparatide subcutaneous + alendronic acid, 25 mcg/day + 70 mg/week, n=40; tx cycle=3months and followed for 3 months without PTH. Intervention concurrent medications: not stated. Control concurrent medications: not stated. Concordance: PTH therapy assessed by returned PTH vials & review of diaries; Alendronate assessed by patients interview; rate for all tx exceeded 90%; 107/108 (99%) completed 100% of study visits. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Parathyroid hormone

Teriparatide review

Study	*Participants*	*Interventions*
Kurland 2000 RCT (fracture) trial held in USA, two centres. Setting: secondary care. Funding:FDA, NIH and Biomeasure Inc supported the study	Inclusion criteria: Men with idiopathic osteoporosis; T-score <-2.5 at the femoral neck or lumbar spine (using male reference); men on stable testosterone were eligible. Exclusion criteria: Secondary causes of osteoporosis; hypogonadism; no treatment for osteoporosis within 6 months previous to randomisation. Patient type: age: 30-68 years (mean 50 SD 1.9 years), Mixed osteoporosis/osteopenia, Males only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: 78% had sustained fractures. Years postmeopausal: not applicable. BMD and Fracture assessment: BMD by dual x-ray absorptiometry; radiographs of thoracolumbar spine at baseline and 12 months; fractures: 20-25% reduction in vertebral heights. Comorbidities: 20 men were eugonadal. Calcium and Vitamin D regimens: All patients received Ca and Vit D. 1500 Ca plus 400 IU vit D daily. Other study comments: mean BMI kg/m2: total 25(SD1.5), PTH: 25.9 (SD1.5) & placebo:24.3 (SD1); mean Height & Wt 177 cm: 81.6kg in PTH group & 178cm, 77 kg in placebo gp; 7 men previously treated; mean cigarette use: PTH:1400 and placebo:992.	1) PTH (1-34) subcutaneous daily self injection; duration: 12-15 months; frequency per day: Once daily; amount 25 mcg subcutaneous self-injection (n=10). 2) mannitol and citric acid; duration: 12-15 months; frequency per day: Once daily; amount not stated (n=13). Intervention concurrent medications: not stated. Control concurrent medications: not stated. Concordance: Medication diaries and vial counts; one patient in the treatment group was poorly compliant in the first year and missed the equivalent of four months of therapy but compliance improvedin the final six months of the treatment protocol. Washout period: 1500 mg daily Ca plus 400 IU vit D for 12-15 months.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Parathyroid hormone

Teriparatide review

Study	*Participants*	*Interventions*
Lane 1998 RCT (fracture) trial held in USA. Setting: primary care. Funding:study supported by Public Health Service Grant, Rosalind Russell Arthritis Research Centre and UCSF Program in Osteoporosis and Bone Biology	Inclusion criteria: with chronic noninfectious inflammatory diseases, taking HRT for at least a year, treated with prednisone or its equivalent for 12 months before study at a mean 5-20mg/day & expected to continue corticosteroid Rx for at least 1 year. Exclusion criteria: secondary osteop other than from rheumatic diseases, corticosteroids, renal or hepatic dysfunction, or abnormalities on spinal radiographs precluding accurate measurements. Patient type: age: 63 SD10 (50-82), Mixed osteoporosis/osteopenia, Postmenopausal women only. Glucocorticoid-induced osteoporosis . Some patients with history of fracture. Smoking: No patients. Details: F: 100%; 29% PTH+HRT & 26% HRT with a fracture. Years postmeopausal: 18 years (SD10). BMD and Fracture assessment: BMD by dual x-ray absorptiometry of lumbar spine, total hip region & forearm; vertebral fractures by thoracolumbar spine radiographs assessed by standard technique. Fractures secondary outcomes. Comorbidities: chronic noninfectious inflammatory: rheumatoid arthritis, systemic lupus erythematosus, vasculitis, polymialgia rheumatica, asthma, kidney transplant. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Ca Supplementation (Ca carbonate) of 1500 mg/day added to individual Ca dietary; two multivitamins a day with 800 IU Vitamin D3. Other study comments: BMI 26SD1kg/m2; corticosteroid Rx for at least 1y; use of disease modifying agents similar in both groups.	1) PTH (1-34) subcutaneous daily self injection + HRT (Oestrogen); duration: 12 months; frequency per day: once daily; amount 25 mcg/day (n=28). 2) Oestrogen; duration: 12 months; frequency per day: once daily; amount 0.625mg/day (n=23). Intervention concurrent medications: overall 63% on disease modifying agents for rheumatoid arthritis (eg methotrexate). Control concurrent medications: overall 63% on disease modifying agents for rheumatoid arthritis. Concordance: estimated by measuring the remaining volume in returned medication vials at each visit; ranged from 80-90% of daily doses. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Parathyroid hormone

Teriparatide review

Study	*Participants*	*Interventions*
Neer 2001 (FPT) RCT (fracture) trial held in USA, multinational & multicentre. Setting: primary care. Funding:Eli Lilly supported trial, 3 authors from Eli Lilly & another had stock	Inclusion criteria: Ambulatory patients with at least 5 years postmenopausal, free of other major diseases. Exclusion criteria: bone/calcium metabolism diseases urolithiasis, etc. Patient type: age: 69 years(SD3) (42-86), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Some patients. Details: 100% female; all subjects with at least 1 moderate or 2 mild atraumatic vertebral fractures on radiographs of the thoracic and lumbar spine; data discrepancy from two reports on TPTD 20mcg vs Placebo. Years postmeopausal: 21-24 years. BMD and Fracture assessment: BMD: lumbar spine & femoral neck by DXA absorptiometry; fractures: radiographically semiquantitatively graded. Comorbidities: free of other major diseases. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Calcium 1000 mg; Vit D 400-1,200 IU/day; oral supplementation. Other study comments: White race 98-99%; Smoking: PTH 18.5% Placebo 15.8%; 15-20%; BMI: PTH 26.7 kg/m2 (5SD) Placebo 26.8 (4SD); sponsor terminated original trial early due to evidence from animal studies showing osteosarcoma.	1) Teriparatide subcutaneous self injection; duration: 18 (SD6) months; frequency per day: once daily; amount 20 mcg/day (n=541). 2) Placebo; duration: 18 (SD5) months; frequency per day: once; amount Not stated (n=544). Other interventions: 3) Teriparatide 40mcg/day once, mean duration 17 (SD6) months, n=552. Intervention concurrent medications: not stated. Control concurrent medications: not stated. Concordance: Assessed by returned medication, mean rate 79-83%. Washout period: 2 weeks on placebo.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Parathyroid hormone

Teriparatide review

Study	*Participants*	*Interventions*
Orwoll 2003 RCT (fracture) trial held in USA, multinational & multicentre. Setting: primary care. Funding:Eli Lilly and Company; two of the authors are consultants for Eli Lilly & Co.; other four authors are employees of Eli Lilly & Co.; two more different authors have no conflicts of interest	Inclusion criteria: Ambulatory men with idiopathic or hypogonadal osteoporosis; lumbar spine or proximal femur BMD at least 2 SD below the young healthy adult mean for men. Exclusion criteria: Chronic disabling conditions other than osteop, secondary causes of metabolic bone disease including glucocorticoid excess, estrogen agonists or antagonists use; metabolic disorders other than osteop in 1st y randomisation; tx within 6mo w/androgen, etc. Patient type: age: 30-85 years (mean 58.6 SD12.9 years), Mixed osteoporosis/osteopenia, Males only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: % of prevalent vertebral fractures not stated; no definition or method to measure vertebral and non-verterbral fractures. Years postmeopausal: not applicable. BMD and Fracture assessment: BMD by dual x-ray absorptiometry; vertebral fractures by lateral thoracic lumbar spine radiographs. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Vit D (400-1,200 IU daily); Ca (1,000 mg daily). Other study comments: Rx exposure=11mo (2-15 mo), 71% had Rx for ≥ 9mo; stopped before 24 mo due to osteosarcomas findings in rats; BMI 25(SD4); smoking 30% TPTD & 32% Placebo; alcohol 76% & 69%respectively; no osteosarcoma cases; NonVF reported as AE; white: 99% TPTD & 100%.	1) Teriparatide; duration: 11 months of exposure; frequency per day: Once daily; amount 20 mcg subcutaneous self-injection (n=151). 2) Placebo; duration: not stated; frequency per day: not stated; amount not stated (n=147). Other interventions: 3) Teriparatide 40 mcg subcutaneous self-injection, once daily, duration 11 months (androgen n=7). Intervention concurrent medications: Androgen (n=5). Control concurrent medications: Androgen (n=9). Concordance: Assessed by counting number of unused doses returned at study visits. Average medication taken = 79%. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Parathyroid hormone

Parathyroid hormone (1-84) review

Study	*Participants*	*Interventions*
Black 2003 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Contract: NIAMSD; Merck: supplemetary funds for CT. Tx provided: preotact & matching placebo by NPS; Alendronate & matching placebo by Merck; Calcium by GlaxoSmithKline. Merck/NPS: nonbinding comments. Investigators: design, accrual & writing & hold data	Inclusion criteria: T-score below -2.5 at femoral neck, total hip or spine T-score -2.0 at one of these sites; ≥65 years; history of post meno fracture, maternal history of hip fracture. Exclusion criteria: Ever treated with bisphos for > 12 mths or for specified shorter intervals in recent months. Patient type: age: 55-85 years (mean 70.7 and 70.2 years, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 51 and 42% had clinical fractures since the age of 45 years. Years postmeopausal: At least 2 years. BMD and Fracture assessment: BMD by dual x-ray absorptiometry and quantitative computed tomography. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. 500mg calcium carbonate and 400IU Vit D. Other study comments: Mean BMI: 25 kg/m2; 90-97% Caucasian; Clinical fractures: secondary outcome.	1) Parathyroid hormone (1-84) plus alendronic acid; duration: 12 months; frequency per day: Once daily; amount 100 mcg + 10mg (n=59). 2) Alendronic acid; duration: 12 months; frequency per day: Once daily; amount 10mg (n=60). Other interventions: 3) PTH 100 mcg /day for 1 year (n=119). Intervention concurrent medications: not stated. Control concurrent medications: Not stated. Concordance: Unused cartridges were returned. Medication taken for at least 11 of the 12 months of that year and as the use of at least 80% of medication. Washout period: Two-week run-in period.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Parathyroid hormone

Parathyroid hormone (1-84) review

Study	*Participants*	*Interventions*
Greenspan 2007 (TOP) RCT (fracture) trial held in USA, international multicentre. Setting: primary care. Funding:NPS pharmaceuticals supported, designed & conducted trial; most authors employed by NPS & some employed by NPS, Roche Labs, GlaxoSmithKline, Merck&Co, P&GP-Aventis, Pfizer. 3 authors have ownership/options other than mutual funds in NPS & Pfizer	Inclusion criteria: patients 45-54 years old: T-score≤ -3 SD w/no prevalent VF & T-score=-2.5 w/1-4 VF before enrollment; patients≥55 years old: T-score=-2.5 w/no VF & T-score=-2 w/1-4 VF; patients w/mild hypercalcemia & hypercalciuria. Exclusion criteria: baseline se-Ca>66, urinary Ca-creatinine≥1, bisphosphanates≥1y or >90 days in 1y before enrollment, receiving PTH/PTH-related protein, fluoride, stronioum, history of metabolic bone disease, nephrolitiasis, hepatic/renal, Rx affecting bone metabolism. Patient type: age: overall (45 to >55); PTH 64.4(SD7.4); Placebo 64.5 (SD7.9), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: 100% female; 81% had no prevalent fractures. Years postmeopausal: Overall: 18.6 (SD9.7); PTH 18.6 (SD9.8); Placebo 18.5 (SD9.6). BMD and Fracture assessment: BMD: lumbar spine, hip, whole body & forearm by DXA absorptiom etry; fractures: radiographically semiquantitatively in a 4-point grading scale; BMD(SD) spine/hip/neck PTH: -3(0.8)/-1.9(0.8)/-2.2(0.7) vs Placebo: -2.96(0.8)/-1.9(0.8)/-2.2(0.7). Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Patients stabilised for at least 2 weeks with supplemental calcium 700 mg/day citrate salt and Vit D3 400 U/day; patients continued with Ca & Vit D3 supplementation during the 1.6 y intervention time. Other study comments: White 85%; BMI PTH 25.6 & 25.7. Non vertebral fractures reported as AE.	1) PTH (1-84) daily self subcutaneous injection; duration: 18 months; frequency per day: 1/day; amount 100 mcg (n=1286). 2) Placebo daily self subcutaneous injection; duration: 1.6 years; frequency per day: 100 mcg; amount 1/day (n=1246). Intervention concurrent medications: not stated. Control concurrent medications: not stated. Concordance: Assessed by returned medication, mean rate 79-83%. Washout period: Two-weeks on supplemental calcium, 700 mg/day citrate and 400 IU/day vitamin D3.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcitonin

Calcitonin review

Study	*Participants*	*Interventions*
Chesnut 2000 RCT (fracture) trial held in Multinational. Setting: not stated. Funding:Novartis Pharmaceuticals sponsored the study	Inclusion criteria: White, Asian, Hispanic women postmenopausal for at least 1 year; 1 to 5 prevalent thoracic or lumbar vertebral compression fractures; lumbar spine BMD at least 2 SD below normal. Exclusion criteria: History of hip fracture; women with a history of diseases, conditions or chronic usage of medications that could affect bone metabolism or bone mass; women recently treated with calcitonin, estrogens, fluorides or bisphosphonates. Patient type: age: mean 68-69 years, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: 71-75% with 1-5 fractures in all groups. Years postmeopausal: Mean TSM 22/23 years. BMD and Fracture assessment: BMD by dual x-ray absorptiometry; lateral thoracic and lumbar radiographs; fractures defined as >20% and >4mm decrease in any vertebral height. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Two 500 mg OS-CAL tablets (1,000 mg oral Ca) and one Centrum tablet daily (400 IU Vit D). Other study comments: Mean BMI: 25 kg/m2; data at 3 years presented in an abstract (Stock et al., 1997).	1) Calcitonin nasal spray; duration: 5 years; frequency per day: Once daily; amount 200 IU spray per day (n=316). 2) placebo nasal spray; duration: 5 years; frequency per day: not stated; amount not stated (n=311). Other interventions: 3) 100 IU calcitonin nasal spray per day for 5 years (n=316) 4) 400 IU calcitonin nasal spray per day for 5 years (n=312). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Adherence estimated by counting used and unused bottles of study medication. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcitonin

Calcitonin review

Study	*Participants*	*Interventions*
Luengo 1994 RCT (fracture) trial held in Spain. Setting: secondary care. Funding:None stated	Inclusion criteria: All had received oral glucocorticoids for at least 1 year. Exclusion criteria: People receiving drugs (hormones, diuretics, vitamin D, anticonvulsants) or suffering from diseases known to affect bone metabolism. Patient type: age: mean 58.8 (SD 7.0) years, Not stated, Males and females. Glucocorticoid-induced osteoporosis . Some patients with history of fracture. Smoking: No patients. Details: M:F 6:38; 4/22 (18%) in each group had prior fractures. Years postmeopausal: not stated. BMD and Fracture assessment: BMD by dual x-ray absorptiometry at the lumbar spine; vertebral and non-vertebral fractures assessed by radiographs. Comorbidities: All were glucocorticoid-dependent asthmatic patients. Calcium and Vitamin D regimens: All patients received Ca. All patients had calcium (1g elemental) as calcium lactate gluconate. Other study comments: Duration of steroid treatment 9.7 (calcitonin) and 11.6 years (control); mean dose prednisone 10 mg/day. No patient drank more than 20g ethanol /day. Pairwise randomisation (paired by age and gender).	1) salmon calcitonin nasal spray; duration: 2 years; frequency per day: once; amount 200 IU (n=22). 2) No treatment; duration: 2 years; frequency per day: ; amount (n=22). Concordance: not stated. Washout period: none stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcitonin

Calcitonin review

Study	*Participants*	*Interventions*
Overgaard 1992 RCT (fracture) trial held in Denmark. Setting: not stated. Funding:Study was supported by a grant from the Danish Medical Research Council	Inclusion criteria: Elderly women. Exclusion criteria: Women with immobility; coronary infarction, stroke or malignancy, women taking sex hormones or other drugs affecting Ca metabolism. Patient type: age: 68-72 years (mean 70 years), Osteoporosis, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: Proportion of patients with a fracture ranged from 4 to 14% (at least 25% reduction in height) or 8-15% (at least 20% reduction). Years postmeopausal: mean TSM 22/23 years. BMD and Fracture assessment: Lateral thoracic and lumbar spine radiographs; two methods were used to assess fractures: Kleerekoper et al., and Melton et al. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. Daily 500 mg Ca. Other study comments: Mean height and weight: 157-160 cm, 61/63 kg.	1) Intranasal salcatonin; duration: 2 years; frequency per day: Once daily; amount 200 IU nasal spray (n=52). 2) Placebo; duration: 2 years; frequency per day: not stated; amount not stated (n=52). Other interventions: 3) Intranasal salcatonin 50 IU per day for 2 years (n=52) 4) Intranasal salcatonin 100 IU per day for 2 years (n=52). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Patients were required to return all dispensed bottles at each clinic visit and end of study. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcitonin

Calcitonin review

Study	*Participants*	*Interventions*
Toth 2005 RCT (fracture) trial held in Hungary. Setting: secondary care. Funding:not stated	Inclusion criteria: BMD T-score at the lumbar spine/or femoral neck of <-2.5 SD; men with a history of low trauma nonvertebral fractures were included. Exclusion criteria: Presence of any vertebral deformity; risk or signs of secondary osteoporosis; hepatic, renal, haematological or malignant diseases, diabetes mellitus, or other endocrine disorders; major GI disease or dyspepsia; bisphosphonates, flouride, vit D, steroid. Patient type: age: 40-76 years (mean 59 SD 6 years), Osteoporosis, Males only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 81% of patients with a history of nonvertebral fracture. Years postmeopausal: not applicable. BMD and Fracture assessment: BMD by dual x-ray absorptiometry; thoracic and lumbar spine fractures by lateral x-rays; vertebral fracture: at least 20% reduction in height. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. 400 IU vitamin D plus 1000 mg effervescent tablet once daily for 18 months. Other study comments: mean height and weight of treatment group: 169.9 cm, 74.5 kg; control group: 168.8 cm, 74.6 kg.	1) Salmon calcitonin, Miacalcic 200 nasal spray; duration: 18 months; frequency per day: Once daily for 1 mo, followed by 1 mo interrruptio; amount 200 IU per day (n=40). 2) Vitamin supplementation only; duration: 18 months; frequency per day: ; amount (n= 31). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Every 3 months follow-up exams were conducted which included a discussion of the medication according to the study plan. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Participants*	*Interventions*
Anderson 2004 RCT (fracture) trial held in USA. Setting: primary care. Funding:National Heart, Lung and Blood Institute. Wyeth provided drugs	Inclusion criteria: postmenopausal women with hysterectomy. Exclusion criteria: Any medical likely to be associated with a predicted survival<3yr, safety (e.g. prior breast cancer or prior cancer within the last 10 years except nonmelanoma skin cancer), need HRT, adherence and retention concerns. Patient type: age: 50-79yr (mean 64yr), Not stated, Postmenopausal women only. Mixed . Some patients with history of fracture. Smoking: Some patients. Details: all with hysterectomy; 14.5% with fracture; 40% with bilateral oophorectomy. Years postmeopausal: not stated. BMD and Fracture assessment: Clinical fracture validated by x-ray. Not stated if trauma fractures included. Comorbidities: not stated. Calcium and Vitamin D regimens: Not stated or Unclear. Other study comments: 75% white; 23% minority ethnic groups; BMI around 30 kg/m2. Fracture secondary outcome.	1) conjugated equine oestrogen; duration: 6.8 years; frequency per day: once; amount 0.625mg/day (n=5310). 2) placebo; duration: 6.8 years; frequency per day: once; amount n/a (n=5429). Concordance: not stated. Washout period: 3 months.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Participants*	*Interventions*
Bone 2000 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Merck	Inclusion criteria: postmeno osteop women with hysterectomy; BMD<0.862g/cm2, no drugs affecting bone, renal insuff, severe cardiac disease, GI erosion, thrombophlebitis/ thromboembolic disease, genital bleed, raised risk breast cancer, fast triglyceride>400mg/dL. Exclusion criteria: metabolic bone disease, vit D<10ng/mL, HRT 6 mo. Patient type: age: mean 61 years (42-82), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: all had hysterectomy. Years postmeopausal: 21-23 (mean range). BMD and Fracture assessment: BMD assessed by DXA (lumbar spine); fracture assessment not stated. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. 500 mg elemental calcium / day. Other study comments: Ethnicity 87-92% white. Fractures reported but most as a result of trauma.	1) conjugated equine oestrogen (Premarin); duration: 2 years; frequency per day: once; amount 0.625mg/d (n=143). 2) placebo; duration: 2 years; frequency per day: once; amount n/a (n=50). Other interventions: 3) alendronic acid 10mg/day and placebo HRT (n=92); 4) alendronic acid 10mg/day + HRT (n=140). Concordance: not assessed.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Participants*	*Interventions*
Bush 1996 [Mebane 1996] RCT (fracture) trial held in USA. Setting: not stated. Funding:National Heart, Lung and Blood Institute & Nat. Inst of Child Health/Human Devmt, Arthritis, Diabetes, & Aging. Universities. Drugs provided by Wyeth-Ayerst, Upjohn & Schering-Plough	Inclusion criteria: no extreme hyperlipidaemia, obesity,drug for arrhythmia, DM needing insulin, elevated TSH, trauma to lower spine, hip fracture, chronic steroids, severe menop symptoms. Exclusion criteria: HT, MI, CHF, stroke, TIA, breast or endometrial cancer, skin cancer. Patient type: age: 45-64yr (mean around 56yr), Mixed osteopenia/normal BMD, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Some patients. Details: proportion with fracture not stated. 31-33% had had a hysterectomy. Years postmeopausal: 1-10yr. BMD and Fracture assessment: BMD assessed by DXA (lumbar spine, hip) & how fracture assessed. Comorbidities: not stated. Calcium and Vitamin D regimens: No patients. Other study comments: Results for BMD given for each group but fracture results collapsed into all HRT vs placebo. Secondary outcome.	1) conjugated equine oestrogen; duration: 3 yr; frequency per day: once; amount 0.625mg/d (n=175). 2) placebo; duration: 3 yr; frequency per day: once; amount n/a (n=174). Other interventions: 3) cyclic oestrogen +MPA 10mg/d x 12d/month (n=175); 4) oestrogen +MPA 2.5mg/d (n=174); 5) oestrogen + progesterone 12d/month (n=178). Intervention concurrent medications: +/- MPA or Progesterone. Concordance: pill count. Washout period: 4mo for HRT.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Participants*	*Interventions*
Herrington 2000 RCT (fracture) trial held in USA. Setting: secondary care. Funding:National Heart, Lung and Blood Institute & National Center for Research Resources. Drug provided by Wyeth-Ayerst	Inclusion criteria: postmeno women with coronary disease, no HRT, breast/endo cancer, CABG, DVT, PE, gallstones, serum AAT>1.5x normal, triglycerides 400mg/dL, creatinine>2mg/dL, >70% stenosis left main cor art, HT, DM. Patient type: age: 41.8-79.9yr (mean around 66yr), Not stated, Postmenopausal women only. Mixed . History of fracture unclear or not stated. Smoking: Some patients. Details: proportion of patients with a fracture not stated; 56-66% had had hysterectomy; 25-36% had had oophorectomy. Years postmeopausal: at least 1yr. BMD and Fracture assessment: BMD not measured; fractures at all sites (not stated how measured). Comorbidities: coronary disease. Calcium and Vitamin D regimens: Not stated or Unclear. Other study comments: RCT in women with coronary disease - outcomes cholesterol levels, atherosclerosis and fracture but not BMD. Around 18% smokers. Fracture as adverse events.	1) conjugated oestrogen; duration: 3.2yr; frequency per day: once; amount 0.625mg/d (n=100). 2) placebo; duration: 3.2yr; frequency per day: once; amount n/a (n=105). Other interventions: 3) oestrogen + medroxyprogesterone acetate (n=104). Intervention concurrent medications: range of medications. Control concurrent medications: range of medications. Concordance: not assessed. Washout period: 3 months for women already on oestrogen.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Participants*	*Interventions*
Lufkin 1992 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Ciba-Geigy	Inclusion criteria: 1 or more vertebral fractures; ambulatory white women; postmeno osteoporosis - no known drug/disease causing osteoporosis. Patient type: age: 47-75yr (median around 65yr), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Some patients. Details: all with a fracture; 36-47% had had hysterectomy. Years postmeopausal: around 15 yr. BMD and Fracture assessment: DXA of the lumbar spine and proximal femur; lateral radiographs used to measure vertebral fractures (based on at least 15% height reduction). Comorbidities: not stated. Calcium and Vitamin D regimens: No patients. Women with <800mg/d Ca in diet instructed to take this amount in diet. Other study comments: Ethnicity - all white. 28-33% non-smokers. 38 women receiving oestrogen, Ca or vit D at recruitment; Ca stopped for 3 mo; vit D or oestrogen stopped for 6 mo before study. Fracture was secondary outcome.	1) dermal patches 17beta estradiol day 1-21 of 28 day cycle and oral MPA days 11-21; duration: 1 year; frequency per day: ; amount 0.1mg/d (n=36). 2) placebo; duration: 1 year; frequency per day: once; amount n/a (n=39). Concordance: Not assessed. Washout period: 3-6 months depending on current treatments.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Participants*	*Interventions*
Mosekilde 2000 RCT (fracture) trial held in Denmark. Setting: primary care. Funding:Karen EliseJensen's Foundation, Danish Medical Research Council. Novo Nordisk, Novartis and Leo Denmark provided drugs	Inclusion criteria: women with intact uterus 45-58yr 3-24 mo postmeno or perimenopausal symptoms + raised FSH, or hysterectomy in women 45-52yr with raised FSH, no HRT last 3 mo, no steroid 6 mo, no chron dis/alc/drug addiction. Exclusion criteria: metabolic bone disease including osteoporosis (vert fracture), cancer. Patient type: age: 45-58 yr (mean around 51yr), Mixed osteopenia/normal BMD, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: postmeno women; no vert fracture; 21% with prior fracture other; 19% had had a hysterectomy. Years postmeopausal: 3-24 months. BMD and Fracture assessment: BMD assessed by DXA (lumbar spine, femoral neck, ultradistal forearm); fracture assessed by report/x-ray. Comorbidities: not stated. Calcium and Vitamin D regimens: Not stated or Unclear. Other study comments: BMI around 25; 2 groups randomised to HRT/no treatment; further 2 groups on HRT or no HRT by own choice (not included here). Fracture may be primary outcome. Fragility fractures reported separately for some outcomes.	1) sequential oestradiol/norethisterone or continuous oestradiol (2mg) if hysterectomy; duration: 5 yr; frequency per day: once; amount 2mg oest 12 d; 2mg oes+1mg Noreth 10d; 1mg oes 6d (n=502). 2) no treatment; duration: 5 yr; frequency per day: n/a; amount n/a (n=504). Concordance: questioned at clinic visit.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Participants*	*Interventions*
Pacifici 1988 RCT (fracture) trial held in USA. Setting: secondary care. Funding:not stated	Inclusion criteria: white osteoporotic women with 1 or more vert frac or spinal demineralisation. Exclusion criteria: disease affecting bone metab, CI to trial drug. Patient type: age: 26-80yr (mean 58yr), Osteoporosis, Females only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: pre- and postmenopausal women; either had fracture or evidence of spinal demineralisation. Years postmeopausal: around 13yr. BMD and Fracture assessment: BMD assessed by QCT (spine); fracture assessed by x-ray. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. 1000mg calcium carbonate. Other study comments: Ethnicity: all were white. Sample selected from women attending clinic for osteoporosis screening (not necessarily postmenopausal). Preliminary data (2nd year not fully completed).	1) conjugated oestrogens (25d/mo)+MPA (10d/mo; days 15 to 25); duration: 2yr; frequency per day: once; amount 0.625mg/d+10mg/d (n=36). 2) no treatment; duration: 2yr; frequency per day: ; amount (n=27). Other interventions: 3) K-phosphate, etidronate 200mg and calcium (n=30). Concordance: not assessed.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Participants*	*Interventions*
Ravn 1999 RCT (fracture) trial held in International. Setting: not stated. Funding:Merck in part	Inclusion criteria: postmeno women at least 6 months postmeno. Exclusion criteria: not stated. Patient type: age: 45-59yr, Mixed osteopenia/normal BMD, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: proportion with fracture not stated. Years postmeopausal: at least 6 mo. BMD and Fracture assessment: BMD assessed by QDR 2000 (lumbar spine, total hip, total body, one third distal forearm); fracture assessed by report. Comorbidities: not stated. Calcium and Vitamin D regimens: Some patients received Ca only. All women with dietary Ca lower than local standard of care advised to increase by diet or supplements. .	1) continuous oestrogen+MPA or cyclic 17β-oestradiol (22d), NETA (10d), oestradiol (6d); duration: 4 yr; frequency per day: once; amount 0.625mg/d+5mg/d or 2mg/d+1mg/d + 1mg/d (n=110). 2) placebo; duration: 4 yr; frequency per day: once; amount n/a (n=502). Other interventions: alendronic acid 5mg/dL; alendronic acid 2.5mg/dL; both groups either for 4 yr (n=333; 330) or for 2 yr and then 2 yr placebo (n=165; 169). Concordance: not assessed.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Participants*	*Interventions*
Weiss 1999 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Berlex Laboratories	Inclusion criteria: women with hysterectomy (if still had ovaries, had to be at least 45yr with vasomotor symptoms 1-5yr; if no ovaries, at least 40yr & 4weeks-5yr post oophrectomy). No immobility, need for HRT, skin irritation, bisphos, F, calcitonin, steroids, bone-act dr. Exclusion criteria: bone disease, hypo/hyperca, vit D deficiency, fracture <6mo. Patient type: age: mean around 51yr, Unclear, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: women with hysterectomy. Years postmeopausal: 0-5yr. BMD and Fracture assessment: BMD assessed (lumbar spine, nondominant radius, ipsilateral total hip, femoral neck); fracture reported but method not given. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. To total daily dose of 1500mg. Other study comments: Also no recent HRT, lipid-lowering drugs or other clinical trial in 3 months. Final nos not given for each group. Ethnicity: 83-91% white. No non-traumatic fractures in any group. Fractures as adverse events.	1) transdermal 17beta oestradiol; duration: 2yr; frequency per day: weekly patch; amount 0.1mg/day (n=35). 2) placebo; duration: 2yr; frequency per day: weekly patch; amount n/a (n=46). Other interventions: other doses transdermal 17beta oestradiol: 0.05, 0.06, 0.025mg/d. Concordance: not assessed.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Participants*	*Interventions*
Wimalawansa 1998 RCT (fracture) trial held in UK. Setting: secondary care. Funding:not stated	Inclusion criteria: postmeno women; all patients had 1-4 thoracic vertebral fractures; no HRT, steroid, calcitonin, F, bisphosphonates. Exclusion criteria: oophorectomy, 2ry osteo, bone disease, drugs affect Ca. Patient type: age: 58-72 yr (mean around 65yr), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: all patients had 1-4 thoracic vert fractures. Years postmeopausal: median 15yr. BMD and Fracture assessment: BMD assessed by DXA (lumbar spine, hip); fracture assessed by x-ray. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. 1g Ca + 400U vit D/day. Other study comments: No patients had had a surgical menopause (i.e. oophorectomy). Secondary outcome. Not stated if trauma fractures included.	1) cyclical premarin and norgestrel (12 d /month); duration: 4yr; frequency per day: once; amount 0.625mg/d+150microg (n=18). 2) no treatment; duration: 4yr; frequency per day: once; amount (n=18). Other interventions: 3) etidronate 400mg (n=17); 4) etidronate + HRT (n=19). Concordance: not assessed.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Selective Estrogen Receptor Modulators

Raloxifene review

Study	*Participants*	*Interventions*
Ettinger 1999 RCT (fracture) trial held in Multicentre 25 countries. Setting: primary care. Funding:Authors received industry funding, and honoraria from Eli Lilly & Co.	Inclusion criteria: Women ≤80 years with at least 2 years postmenopaual. No severe or long term disabling conditions. Exclusion criteria: Participants excluded if they had bone disease other than osteoporosis, substantial postmenopausal symptoms or abnormal uterine bleeding, endometrial carcinoma, suspected history of breast carcinoma. Patient type: age: 31 to 80 years; mean age 66.4 years (SD 7), Osteoporosis, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: female; Fracture at baseline: group 1: 10-11%; group 2: 88-90%. Years postmeopausal: at least 2 years. BMD and Fracture assessment: BMD assessed with DXA. Vertebral fractures determined radiographically. Non-vertebral fractures determined by direct questioning. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. Ca 500 mg/day plus cholecalciferol 400-600 IU/day. Other study comments: Participants divided into 2 study groups then randomised. Study group 1 included those with femoral neck or lumbar spine BMD T score < -2.5. Study group 2 had low BMD & 1 or more moderate or severe vert. fractures. 95.7% were white.	1) Raloxifene; duration: 3 years; frequency per day: once per day; amount 60 mg (n=2557). 2) Placebo; duration: 3 years; frequency per day: once per day; amount (n=2576). Other interventions: 3) Raloxifene 120 mg/day (n=2572). Intervention concurrent medications: Concomittant bone agents allowed in year 4. Control concurrent medications: Concomittant bone agents allowed in year 4. Concordance: 92% of women took > 80% of study meds with no difference between groups. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Selective Estrogen Receptor Modulators

Raloxifene review

Study	*Participants*	*Interventions*
Lufkin 1998 RCT (fracture) trial held in USA. Setting: not stated. Funding:Authors received industry support grant from Eli Lilly & Co.	Inclusion criteria: Free from any serious acute or chronic medical condition that might affect bone or calcium metabolism, fully ambulatory, between the ages of 45-75 years. Exclusion criteria: History of deep vein thrombosis, thromboembolic disorders, cerebral vascular accident; history of cancer within last 5 years, except for superficial skin cancer. Patients treated with sodium flouride or biphosphonates. Patient type: age: mean 68.4 years (SD 5), Osteoporosis, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: Female. Years postmeopausal: *5 years without menses. BMD and Fracture assessment: BMD from the lumber spine or proximal femur of ≤10th percentile for normal premenopausal females and 1 or more vertebral fracture (non traumatic). Radiographs used to determine vertebral fractures. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Calcium 750 mg/day and Vit-D to bring intake up to 800 IU/day. Other study comments: Participants had at least one prevalent vertebral fracture and low bone mineral density *5 years without menses or levels of serum estradiol <73 pmol/l and FSH>30 IU/l..	1) Raloxifene; duration: 12 months; frequency per day: once per day; amount 60 mg (n=48). 2) Placebo; duration: 12 months; frequency per day: once per day; amount (n=48). Other interventions: 3) Raloxifene 120 mg/day (n=47). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Selective Estrogen Receptor Modulators

Raloxifene review

Study	*Participants*	*Interventions*
Michalska 2006 RCT (fracture) trial held in not stated. Setting: not stated. Funding:Authors received industry funding from Eli Lilly and Co.	Inclusion criteria: Ambulatory postmenopausal women, 50-89 years, with previous treatment alendronate and filled their prescriptions, and were reportedly compliant. Exclusion criteria: Bone disorders except for osteoporosis, endocrine and malignant diseases, uterine and ovarian abnormalities, thromboembolic disorders, severe chronic disease. Patient type: age: Mean age 65 years., Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: Female. Years postmeopausal: not reported. BMD and Fracture assessment: Femoral neck BMD assessed with densitometry. Comorbidities: not stated.. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Ca 500 mg/day; Vit-D 800 IU/day. Other study comments: All participants treated with alendronate 10 mg/day for at least 3 years prior to trial.	1) Raloxifene for 1 year blinded, following alendronic acid for up to 3 years, then 1 year open label extension; duration: 2 years; frequency per day: once per day; amount 60 mg (n=34). 2) Placebo for 1 year blinded, following alendronic acid for up to 3 years, then 1 year open label extension; duration: 2 years; frequency per day: Once per day; amount (n=33). Other interventions: 3) alendronic acid (n=33). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Two completers showed low compliance (<30%) with raloxifene. All others were 80% compliant with study medication.. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Selective Estrogen Receptor Modulators

Raloxifene review

Study	*Participants*	*Interventions*
Reginster 2003 RCT (fracture) trial held in Multicentre (Europe). Setting: not stated. Funding:Authors received industry support from Eli Lilly & Co.	Inclusion criteria: Women aged up to 72 years, menopausal for at least 2 years. BMD at least 2 SD or more below the normal peak bone mass for healthy menopausal women. Exclusion criteria: More than 2 fractured lumbar verebrae or more than 3 fractured vertebrae of any kind. Bone disorders other than osteoporosis, endocrine and malignant diseases. Menopause requiring oestrogen therapy. Patient type: age: Mean raloxifene 61.9 (SD 6); control 61.8 (SD 6), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: Female. Years postmeopausal: At least 2 years. BMD and Fracture assessment: Densitometer measurements at lumbar and femoral neck compared with normal population reference range. X-ray used to determne fracture. Comorbidities: None. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Calcium 100 mg/day and Vit-D 500 IU/day. Other study comments: Ethnicity: 595 participants Caucasian.	1) Raloxifene plus monofluorophosphate; duration: 18 months; frequency per day: Once a day; amount 60 mg raloxifene + 152mg MFP 300. 2) placebo plus MFP; duration: 18 months; frequency per day: Once a day; amount placebo + 152mg MFP 296. Other interventions: None. Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Sex hormone therapies

Nandrolone review

Study	*Participants*	*Interventions*
Frisoli 2005 RCT (fracture) trial held in Brazil. Setting: not stated. Funding:Part funded by FAPESP	Inclusion criteria: 70 years or older, Caucasian race, have no difficulty walking, no bilateral hip prosthesis, no disease which might limit movement. All with at least one bone site BMD equivalent to or lower than -2.5 SD at T score. Osteoporosis based on WHO 1994 criteria. Exclusion criteria: Mentally disabled; use of drugs that would interfer with bone remodeling; having chronic disease that might interfere with study follow up,smoking more that 20 cigarettes per day; alcohol consumption of more than 2 drinks a day; history of cancer in past. Patient type: age: mean ages ND 74 (SD 4) and placebo 77 (SD 4) years; significantly different, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: vertebral fractures: 68% ND and 52% placebo baseline data for completers. Years postmeopausal: not stated. BMD and Fracture assessment: DXA assessed BMD at various sites and fracture assessed with x-ray. Comorbidities: not stated, tried to screen out serious co-mobidities. Calcium and Vitamin D regimens: All patients received Ca. 500 mg/day calcium given to all patients. Other study comments: All Caucasian. Height 149.1 (SD 6.8) cm; Weight 55.4 (SD 7.5) kg.	1) Nandrolone; duration: 2 years; frequency per day: every 3 weeks; amount 50 mg intramuscular (n=32). 2) Placebo; duration: 2 years; frequency per day: every 3 weeks; amount (n=33). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: method of assessment not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Sex hormone therapies

Nandrolone review

Study	*Participants*	*Interventions*
Geusens 1986 RCT (fracture) trial held in Belgium. Setting: secondary care. Funding:Drugs supplied by Organon, Leo Pharmaceuticals and Sandoz	Inclusion criteria: Vertebral collapse without trauma. Exclusion criteria: Participants with other diseases that might cause osteoporosis were excluded. Patient type: age: For completers:nandrolone median 63 (IQR 25-69); calcium 75 (IQR 70-76); i.e. significant difference, Unclear, Males and females. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: Women 48 and men 12 all with vertebral collapse without trauma. Women likely to be postmenopausal (from IQR for age). Years postmeopausal: not stated. BMD and Fracture assessment: BMC assessed at left radius with gamma photon absorptiometry; spinal fracture assessed by X-ray. Comorbidities: none stated. Calcium and Vitamin D regimens: Not stated or Unclear. Dietary content estimated by dietitian. Other study comments: patient characteristics given only for completers.	1) Nandrolone + placebo calcium + placebo vitamin D; duration: 2 years; frequency per day: Every three weeks; amount 50 mg intramuscular (n=20 estimated). 2) Calcium gluconate infusions + placebo nandrolone + placebo vitamin D; duration: 2 years; frequency per day: daily for 12 consecutive days per year; amount 15 mg /kg of body weight (n=20 estimated). Other interventions: 3) Alphacalcidol (not licensed) (n=20 estimated). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Sex hormone therapies

Nandrolone review

Study	*Participants*	*Interventions*
Passeri 1993 RCT (fracture) trial held in Italy. Setting: not stated. Funding:not stated	Inclusion criteria: not stated. Exclusion criteria: Concurrent treatment or diseases known to influence bone or mineral metabolis. Patient type: age: range: 46-68 years, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: . Years postmeopausal: For completers: ND mean 10.6 (SD 6); placebo 15.3 (SD 9). BMD and Fracture assessment: BMD (vertebral) assessed by DXA; radial BMD by single photon absorptiometry; inspection of X-rays used to determine fracture. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca. 1000 mg/day of oral calcium supplements to all participants. Other study comments: No details on ethnicity; height and weight recorded only for completers.	1) Nandrolone; duration: 18 months; frequency per day: ; amount 50 mg IM (n=25). 2) Placebo IM; duration: 18 months; frequency per day: once every 3 weeks; amount (n=21). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: not reported. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Adachi 1996 RCT (fracture) trial held in Canada. Setting: secondary care. Funding:not stated	Inclusion criteria: Ambulatory, >18yr, on prednisolone>10mg/day. Exclusion criteria: prior prednisone, bone active drug, diseases known to affect bone metabolism; unstable medical conditions; current/previous alcohol/drug abuse; vit D/Ca in last 4 weeks. Patient type: age: mean around 65 years (SD 11.7), All BMDs, Males and females. Glucocorticoid-induced osteoporosis . Some patients with history of fracture. Smoking: Not stated. Details: 20 M:42 F; 6/31 patients with a fracture on placebo + 8/31 on treatment. Years postmeopausal: . BMD and Fracture assessment: BMD assessed by dual photon absorptiometry or DXA (lumbar spine); fracture assessed by x-ray. Comorbidities: polymyalgia rheumatica, temporal arteritis, asthma, vasculitis or SLE. Vitamin D and calcium details: Baseline Ca around 2.36mmol/L (vit D not stated). Other study comments: mean baseline dose of prednisone around 19mg. Intervention discontinued once corticosteroid medication discontinued and reduced in those with persistent hypercalcuria / hypercalcaemia (occurred for 1/62 patients).	1) vitamin D (type not stated) and calcium carbonate; duration: 3 years; frequency per day: Ca once; vit D weekly; amount 50,000 IU vitamin D+Ca 1g (n=31). 2) placebo vitamin D and placebo calcium; duration: 3 years; frequency per day: Ca once; vit D weekly; amount (n=31). Concordance: not reported. Washout period: not stated, but inclusion criterion was no vitamin D/Ca for 4 weeks.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Avenell 2004 RCT (fracture) trial held in UK. Setting: secondary care. Funding:UK MRC; Shire Pharmaceuticals aupplied the drugs (co-funded & supplied by Nycomed)	Inclusion criteria: Age 70 or older with low trauma osteoporotic fracture in previous 10 y, ambulatory. Exclusion criteria: cancer, bone abnormality, hypercalcaemia, renal stone in past 10 years; cognitive impairment, life expectancy less than 6 mo, known to be leaving UK, bone active drug in past 5y, >200IU vit D or >500mg Ca/day. Patient type: age: mean 77-78 years (SD 6), Not stated, Males and females. Not higher risk . All patients with history of fracture. Smoking: Some patients. Details: 83% F; all had prior osteoporotic fracture in previous 10 years. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed; fracture assessed by questionnaires, hospitals, GPs and national routine data collection. Comorbidities: not stated. Vitamin D and calcium details: 1 participant was prescribed vitamin D and 3 were prescribed calcium: not stated which groups. Further details provided from the Cochrane review. Other study comments: Further details obtained from Cochrane review (from authors).	1) vitamin D3; duration: up to 46 mo; frequency per day: once; amount 800 IU vit D3 (n=35). 2) no treatment; duration: up to 46 mo; frequency per day: ; amount n/a (n=35). Other interventions: 3) calcium alone (n=29). 4) Vitamin D + calcium (n=35). Concordance: Questionnaire & pill count; of those randomised, 65% took tablets >80% of days at 1 year.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Chapuy 1992 RCT (fracture) trial held in France. Setting: nursing home. Funding:Ministry of Research. Duphar and Co provided Vit D and Merck calcium	Inclusion criteria: healthy ambulatory women; life expectancy at least 18 months; no serious medical conditions. Oestrogen and thiazides allowed. Exclusion criteria: drugs known to alter bone metabolism within past year; fluoride treatment within 3 months; vit D or Ca within last 6 months. Patient type: age: mean 84 years (69-106y), Not stated, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: proportion of patients with a fracture not stated. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed by DXA in sub-group (hip); fracture assessed by interview, clinical symptoms, x-rays. Comorbidities: no serious medical conditions. Vitamin D and calcium details: Other study comments: nursing home or apartment for elderly people; prior fracture not excluded but no. with prior fracture not given; actuarial method used for censored data.	1) vitamin D3 plus calcium as tricalcium phosphate (1.2g elemental Ca) in aqueous suspension; duration: 18 months; frequency per day: once; amount 800 IU vit D + 1.2g calcium (n=1634). 2) lactose placebo plus suspension of lactose, kaolin and starch; duration: 18 months; frequency per day: once; amount n/a (n=1636). Concordance: number pills remaining at each visit; compliance 83-84% (70% level). Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Chapuy 2002 RCT (fracture) trial held in France. Setting: nursing home. Funding:Merck	Inclusion criteria: ambulatory institutionalised women with life expectancy at least 2 years. Exclusion criteria: malabsorption, hypercalcaemia, chronic renal failure; drugs altering bone metabolism in last year; treatments with bisphosphonates/calcitonin (< 1 mo), fluoride (<3 mo); vitamin D/Ca (<12 mo). Patient type: age: mean 85.2 years (range 64-99y), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: proportion of patients with a fracture not stated. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed by single x-ray absorptiometry (total femoral, , femoral neck, distal forearm); hip & non-vert fracture assessed but no method stated. Comorbidities: not stated. Vitamin D and calcium details: This was study intervention. Baseline calcium around 9.2mg/dl and serum 25-hydroxyvitamin D 8.9ng/ml. Other study comments: Mean dietary intake of Ca/vit D very low.	1) vitamin D3 plus calcium as tricalcium phosphate (1.2g elemental Ca) in aqueous suspension; duration: 2 years; frequency per day: once; amount 800 IU vitamin D3 plus Ca 1.2g (n=393 PP). 2) placebo calcium and placebo vitamin D; duration: 2 years; frequency per day: once; amount n/a (n=190 PP). Concordance: Supervised consumption; mean compliance >95%.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Dawson-Hughes 1997 RCT (fracture) trial held in USA. Setting: primary care. Funding:NIH grant, Human Nutrition Research Center	Inclusion criteria: 65 y or older living at home, ambulatory, no bone active drugs. Exclusion criteria: Cancer, hyperparathyroidism, renal stone/dis, bilateral hip surg; therapy with bisphosphonates, calcitonin, oestrogen in past 6 months; Tscore <-2; dietary Ca >1500mg/day. Patient type: age: mean around 71years (SD 5), Mixed osteopenia/normal BMD, Males and females. Not higher risk . History of fracture unclear or not stated. Smoking: Some patients. Details: 176 M: 213 F; proportion of patients with a fracture not stated. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed by DXA (hip, spine, total body); fracture assessed by interview verified by x-ray or hospital report. Comorbidities: not stated. Vitamin D and calcium details: Patients advised to avoid Ca/vit D supplements but have usual diet. .	1) vitamin D3 (cholecalciferol) plus calcium citrate malate (500g elemental Ca); duration: 3 years; frequency per day: once; amount 700 IU vit D3 + Ca 500mg (n=187). 2) placebo tablets containg microcrystalline cellulose; duration: 3 years; frequency per day: once; amount n/a (n=202). Concordance: Pill count; 92-93% amongst completers.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Ebeling 2001 RCT (fracture) trial held in Australia. Setting: not stated. Funding:Supported by Roche products, D.W. Keir Fellowship and The Royal Melbourne hospital	Inclusion criteria: Presence of low trauma fracture. Exclusion criteria: not stated. Patient type: age: 27-77 years, Mixed osteoporosis/osteopenia, Males only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: all had at least 1 fragility fracture. Years postmeopausal: N/A. BMD and Fracture assessment: BMD assessed at femoral neck using DXA scan; fractures assessed with X-ray. Comorbidities: not stated. Vitamin D and calcium details: No supplements given. Baseline dietary levels of calcium were 697 mg/day (Ca grp) and 675 mg/day (vit-D grp); dietary vitamin-D levels not reported. Other study comments: Caucasian males. No man had any disease known to affect bone or mineral metabolism No of patients randomised into group from outset is not clear as 2 participants are unaccounted for..	1) Vitamin-D (calcitriol) plus placebo; duration: 2 years; frequency per day: twice; amount 0.50 microg 20. 2) Calcium plus placebo (salt not stated); duration: 2 years; frequency per day: twice; amount 1000 mg 19. Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Not reported. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Falch 1987 RCT (fracture) trial held in Norway. Setting: secondary care. Funding:not stated	Inclusion criteria: 50-65 years who had sustained a fracture of distal left forearm. Exclusion criteria: other fracture right forearm, endocrine disease,malabsorption, gastric surgery, nephrolothiasis, renal failure, bone active drugs, regular intake of oestrogens. Patient type: age: mean around 60 years (50-65yr), Osteoporosis, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: all with a fracture of distal forearm. Years postmeopausal: around 12 yr. BMD and Fracture assessment: bone mass assessed by dual photon absorptiometry (right radius & ulna); fracture assessed by x-ray. Comorbidities: none stated. Vitamin D and calcium details: No Ca given. Baseline Ca around 2.4mmol/l, vitamin D not given. .	1) calcitriol; duration: 3 years; frequency per day: twice; amount 0.5 microg reducing to 0.25 microg if serum Ca >2.65 mmol/l (n=47). 2) colecalciferol; duration: 3 years; frequency per day: once; amount 400 IU (n=39). Concordance: assessed by direct questioning; level not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Gallagher 1989 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Hoffman-La-Roche, NIH grants	Inclusion criteria: normal liver/renal function; evidence of at least 1 vertebral fracture with no history of trauma. Exclusion criteria: disease/drug history associated with a disturbance of calcium metabolism; osteomalacia. Patient type: age: Mean around 63 years, Osteoporosis, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: all patients with a fracture. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed ; vertebral fracture assessed by x-ray. Comorbidities: not stated. Vitamin D and calcium details: All patients had free Ca intake. Other study comments: patients on placebo crossed over to active treatment after 1 yr; only 1 yr results used. But did not report number of patients with fractures in intervention group.	1) Calcitriol; duration: 1 year; frequency per day: twice; amount 0.5 microg (could be increased to 0.75 or 1 microg) (n=38). 2) placebo; duration: 1 year; frequency per day: twice; amount (n=33). Concordance: Not reported.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Gallagher 2001 RCT (fracture) trial held in USA. Setting: primary care. Funding:NIH grants, Wyeth-Ayerst, Hoffman-LaRoche, Pharmacia & Upjohn	Inclusion criteria: femoral neck BMD within +/- 2 SD for their age. Exclusion criteria: severe chronic illness, hyperparathyroidism, renal stone disease; bisphosphonates, oestrogen, thiazide, fluoride in last 6 months.. Patient type: age: Mean 71 years (range 65-77y), All BMDs, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: proportion of patients with a fracture: 28% and 14% calcitriol and placebo respectively. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed by DXA (spine, prox femur, total body, radial mid-shaft); fracture reports confirmed by x-ray. Comorbidities: not stated. Vitamin D and calcium details: Dietary advice to increase Ca if intake below 500mg/d & decrease if >1000mg/d. Baseline 25OHDaround 78nmol/L, baseline Ca not given. Other study comments: Stratified by hysterectomy status before randomisation.	1) Calcitriol; duration: 3 years; frequency per day: twice; amount 0.5 microg (n=123). 2) placebo; duration: 3 years; frequency per day: twice; amount n/a (n=123). Other interventions: 3) Calcitriol + HRT for 3 years (n=122). 4) HRT: conjugated oestrogen 0.625 mg/day (plus medroxyprogesterone acetate 2.5mg/day in women with a uterus)for 3 years (n=121). Concordance: Pill count; adherence was 70 and 78% respectively for calcitriol and placebo.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Harwood 2004 RCT (fracture) trial held in UK. Setting: secondary care. Funding:Provalis Healthcare	Inclusion criteria: Independent community living elderly women post hip fracture. Exclusion criteria: diseases/drugs affecting bone, low mental test score. Patient type: age: Mean 81.2 years (range 67-92yr), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: all had had surgery for hip fracture. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed by DXA (lumbar spine, contralateral proximal femur); fracture assessed by pt report only. Comorbidities: not stated. Vitamin D and calcium details: Study drug. Mean baseline Ca 2.36mmol/l (range 2.0-2.6), 25(OH)vit D mean 29nmol/l, range 6-85. Other study comments: Mean BMI 24.2kg/m2.	1) Vitamin D3 + calcium carbonate (1g as elemental Ca) in combined oral tablets; duration: 1 year; frequency per day: once; amount 800 IU vit D + Ca 1g (n=39). 2) no treatment; duration: 1 year; frequency per day: n/a; amount n/a (n=37). Other interventions: 3) vitamin D2 300,000 units single injection plus oral calcium for 1 year (n=36). 4) vitamin D2 300,000 units single injection for 1 year (n=38). Concordance: Not reported.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Jackson 2006 RCT (fracture) trial held in USA. Setting: primary care. Funding:National Heart Lung & Blood Institute	Inclusion criteria: community dwelling postmenopausal women; predicted survival at least 3 yr. Exclusion criteria: hypercalcaemia, renal stone, steroids, calcitriol. Patient type: age: mean 62 years (range 50-79y), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: 34% of patients had had fracture. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed by DXA in subset of women (lumbar spine, total hip, total body); fracture assessed by report + x-ray. Comorbidities: not stated. Vitamin D and calcium details: Study drug; calcium up to 1000mg/day and vitamin D up to 1000IU/day were allowed in addition to study drug. Mean Ca intake 1150mg/day+vit D 366IU/day. Baseline values not given. Other study comments: 52% of the women also received HRT during the trial; bisphosphonate & calcitonin were allowed (1% used these medications, increasing to 17% during follow up); mean BMI 29kg/m2. Stratified by clinical centre and age before randomisation.	1) vitamin D3 + Calcium carbonate; duration: 7 years; frequency per day: twice; amount 400 IU + 1g elemental Ca (n=18,176). 2) placebo; duration: 7 years; frequency per day: once; amount n/a (n=18,106). Intervention concurrent medications: during trial 17% had osteoporosis medication (mainly bisphosphonates) - overall. Control concurrent medications: during trial 17% had osteoporosis medication (mainly bisphosphonates) - overall. Concordance: weighing returned pill bottles; rate of adherence (>80% medication) 59% at end of trial.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Komulainen 1998 RCT (fracture) trial held in Finland. Setting: primary care. Funding:Leiras Oy, Schering AG	Inclusion criteria: 47-56 years, 6-24 months since last menstruation. Exclusion criteria: Contraindications to HRT, breast or endometrial cancer, thromboembolic diseases, medication resistant hypertension. Patient type: age: mean around 52 years, Normal BMD (within 1SD), Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: around 15% with a previous fracture in last 15 years. Years postmeopausal: 6-24 months. BMD and Fracture assessment: BMD assessed by DXA (lumbar spine & femoral neck); symptomatic non-vertebral fracture confirmed by x-ray. Comorbidities: not stated. Vitamin D and calcium details: Other study comments: BMI around 26 kg/m2.	1) vitamin D3 plus calcium lactate; duration: 5 years; frequency per day: once; amount 300 IU vit D (100 IU in 5th year) + 500mg Ca for 10 mo (ie 93mg elemental Ca/day) (n=116). 2) calcium lactate; duration: 5 years; frequency per day: once; amount 500mg Ca for 10 mo (ie 93mg elemental Ca/day) (n=116). Other interventions: 3) vitamin D3 + HRT (n=116). 4) HRT only (n=116). Concordance: questioned annually; compliance (of those randomised): vit D 89%, plac 91%. Washout period: none stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Larsen 2004 RCT (fracture) trial held in Denmark. Setting: primary care. Funding:Danish Osteoporosis Association, local health service, Pharmacy Association, Danish Health Foundation, Nycomed DAK	Inclusion criteria: community-dwelling residents aged 66+. Exclusion criteria: nursing homes, severely impaired people, mental retardation. Patient type: age: median 74yr (range 66-103yr), Not stated, Males and females. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: M 3834: F 5771; proportion of patients with a fracture around 26%. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed; fracture assessed from hospital registry. Comorbidities: not stated. Vitamin D and calcium details: Pragmatic population-based trial. Originally 4 groups: Ca+vit D; environmental change program; both; neither. But Ca/Vit D groups combined in analysis & compared with no Ca/Vit D. Other study comments: both programs included revision of patient's medication. Cluster randomisation of 4 comparable blocks of the municipality of Randers. Outcome was fractures leading to acute hospital admission.	1) Vit D3 400IU + 1 g calcium carbonate; duration: unclear - follow up 42 months; frequency per day: once; amount 400 IU Vit D3 + 1g calcium carbonate (n=2531). 2) no Ca or Vitamin D; duration: unclear - follow up 42 months; frequency per day: n/a; amount n/a (n=2532). Intervention concurrent medications: nurse led environmental health programme. Control concurrent medications: nurse led environmental health programme. Concordance: those recruited were offered interventions; participation was: 48% in Environment programme; 56% in Ca/Vit D and 45% for both.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Lips 1996 RCT (fracture) trial held in Holland. Setting: primary care. Funding:part funding from the Praeventiefonds, The Hague. Solvay-Duphar Inc provided the drugs	Inclusion criteria: 70 years and older living independently, and reasonably healthy. Exclusion criteria: history of hip fracture / total hip arthroplasty, hypercalcaemia, sarcoidosis, recent urolithiasis (in last 5 y). Patient type: age: mean 80 years, range 70-97 years, Not stated, Males and females. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: 662M:1916F; proportion of patients with a fracture not stated. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed; fracture assessed by GP report. Comorbidities: not stated. Vitamin D and calcium details: 133 participants were taking supplements containing vitamin D at baseline.During the study 36[VitD] & 37 patients had a vitamin/multivit supplement containing vit D. Median calcium intake at baseline 859 and 876 mg/day. Dietary Ca advised by letter. .	1) vitamin D3; duration: 3.5 years; frequency per day: once; amount 400 IU (n=1291). 2) placebo; duration: 3.5 years; frequency per day: once; amount n/a (n=1287). Concordance: tablet containers, questionnaire, serum 25(OH)D; 18% in each group stopped taking medication.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Lyons 2007 RCT (fracture) trial held in UK. Setting: nursing home. Funding:Wales Office	Inclusion criteria: nursing home/residential home/sheltered housing. Exclusion criteria: on 400IU vit D or more / day or contraindications to vit D. Patient type: age: mean 84 years (62-107y), Not stated, Males and females. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: 816M:2624F; proportion of patients with a fracture. Years postmeopausal: . BMD and Fracture assessment: BMD not assessed; fracture assessed by interview, records, A&E & patient episodes databases. Comorbidities: some had mobility, cognitive, hearing or communication impairments. Vitamin D and calcium details: Baseline levels not measured. Other study comments: pragmatic trial.	1) vitamin D2 (ergocalciferol); duration: 3 years; frequency per day: 2 tablets every 4 months; amount 100,000 IU every 4 months (n=1725). 2) placebo; duration: 3 years; frequency per day: once every 4 months; amount n/a (n=1715). Concordance: supervised consumption; compliance 78% vit D, 81% placebo.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Meyer 2002 RCT (fracture) trial held in Norway. Setting: nursing home. Funding:Peter Moller, avd. Av Orkla ASA, Norwegian Dairies, City Council of Oslo, Odd Fellow.	Inclusion criteria: Life expectancy of more than 6 months. Exclusion criteria: permanently bedridden; difficulties in taking medicine.. Patient type: age: mean 84.7 y (SD 7.4), Not stated, Males and females. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 75-77% female; proportion of patients with a fracture: 26-29%. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed; fractures verified by hospital discharge letters or X-ray descriptions. Comorbidities: none stated. Vitamin D and calcium details: People taking vitamin D supplements included provided did not exceed 10 microg/day (40-43%). Calcium supplementation 2.4-3.4%. Ca dietary intake 446-456mg/day. Other study comments: BMI 22.3 kg/m2.	1) Cod liver oil (vitamin D3); duration: 3 years; frequency per day: once; amount 11.0 microg (5 ml containing 2.2 microg/ml); i.e. 400 IU (n=569). 2) Cod liver oil with vitamin D extracted chemically (vitamin A re-added afterwards); duration: 3 years; frequency per day: once; amount 0.5-1.0 microg (5 ml containing 0.1-0.2 microg/ml) (n=575). Concordance: delivered by nursing staff; cessation of treatment: 36% vit D and 39% plac.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Pfeifer 2000 RCT (fracture) trial held in Gernany. Setting: primary care. Funding:Strathmann AG Hamburg, which markets vitamin D and calcium, funded the study. Some authors worked for company.	Inclusion criteria: 25-hydroxycholecalciferol serum level below 50 nmol/liter; 70 years or older. Exclusion criteria: hypercalcemia /primary HPT; osteoporotic fractures; bisphosphonate, calcitonin, vitamin D / its metabolites, oestrogen, tamoxifen in the past 6 mo, fluoride in past 2 y. Intolerance to medication; chronic renal failure; drug/alcohol/nicotine abuse. Patient type: age: Mean 74.8 years (range 70-86), Not stated, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: exclusion criterion was fractures of the extremities caused by osteoporosis. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed; fractures were verified by X-ray and medical reports. Comorbidities: 20% concomitant cardiovascular disease, 11% musculoskeletal; said to be healthy. Vitamin D and calcium details: Participants advised to avoid taking supplemental calcium and vitamin D on their own. Other study comments: 162-163 cm height; 65 kg weight Study was designed to investigate the effect of a short-term treatment with calcium and vitamin D..	1) cholecalciferol (vitamin D3) plus calcium carbonate; duration: given for 8 weeks then followed for 1y; frequency per day: twice; amount 800 IU of cholecalciferol + 1.2 g of elemental calcium (n=74). 2) calcium carbonate; duration: given for 8 weeks then followed for 1y; frequency per day: twice; amount 1.2g of elemental calcium (n=74). Intervention concurrent medications: 36% had Cv drugs. Control concurrent medications: 32% had Cv drugs. Concordance: assessed on the basis of pill counts (95-96%). Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Porthouse 2005 RCT (fracture) trial held in UK. Setting: primary care. Funding:R&D grants plus Shire, Nycomed	Inclusion criteria: women aged 70 and over with at least 1 risk factors for fracture (bodyweight < 58kg; prior fracture; maternal history; smoker; poor/fair health). Exclusion criteria: Ca > 500mg/day, kidney/bladder stone, renal failure; hypercalcaemia. Patient type: age: mean 77years (SD 5), Not stated, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: 58% patients with a fracture; 7-9% smokers. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed; fracture assessed by self report & medical record. Comorbidities: not stated. Vitamin D and calcium details: Baseline values not measured. Control group: 6% used supplements at 18 months. Other study comments: Pragmatic community based trial. Both groups had leaflet on dietary calcium intake and prevention of falls.	1) vitamin D3 (cholecalciferol) +calcium carbonate; duration: 18 months; frequency per day: once; amount 800 IU vit D + 1g Ca (n=1321). 2) no treatment; duration: n/a; frequency per day: n/a; amount n/a (n=1993). Intervention concurrent medications: advice from practice nurse + leaflet. Control concurrent medications: advice from leaflet. Concordance: Asked if wished to continue every 6 months. Adherence at 18 months 59%.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
RECORD 2005 RCT (fracture) trial held in UK. Setting: secondary care. Funding:UK MRC; Shire Pharmaceuticals supplied the drugs (co-funded & supplied by Nycomed)	Inclusion criteria: Age 70 or older with low trauma osteoporotic fracture in previous 10 y, ambulatory. Exclusion criteria: cancer, bone abnormality, hypercalcaemia, renal stone in past 10 years; cognitive impairment, life expectancy less than 6 mo, known to be leaving UK, bone active drug in past 5y, >200IU vit D or >500mg Ca/day. Patient type: age: mean 77-78 years (SD 6), Not stated, Males and females. Not higher risk . All patients with history of fracture. Smoking: Some patients. Details: 85% F; all had prior osteoporotic fracture in previous 10 years. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed; fracture assessed by questionnaires, hospitals, GPs and national routine data collection. Comorbidities: not stated. Vitamin D and calcium details: Study drugs. .	1) vitamin D3; duration: 2-5yr; frequency per day: once; amount 800 IU vit D3 (n=1343). 2) placebo; duration: 2-5yr; frequency per day: once; amount n/a (n=1332). Other interventions: 3) calcium alone (n=1311). 4) Vitamin D + calcium (n=1306). Concordance: Questionnaire & pill count; 42-53% took tablets on >80% days (vit D/Ca and Ca 42%; vit D 53%; plac 50%).

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Smith 2007 RCT (fracture) trial held in UK. Setting: primary care. Funding:study supported by MRC, NHS R&D, NOS, Celltech UK plc (manufacturers). One author received honoraries from Shire Pharmaceuticals	Inclusion criteria: over 75 years. Exclusion criteria: current cancer, history of untreated osteoporosis, bilateral total hip replacement, renal failure, renal stones, hypercalcaemia, sarcoidosis; people taking 400 IU/day or more vitamin D. Patient type: age: median 79.1 years (IQR 76.9-82.7), Not stated, Males and females. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: 46% men; 37-39% had a fracture. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed; fracture assessed by patient report and confirmation from hospital and practice records. Comorbidities: none stated. Vitamin D and calcium details: People taking 400 IU/day or more of vitamin D excluded. Mean dietary calcium in a random sample of 200 was 625mg/day (SD 231). Other study comments: Pragmatic community based trial. Random sample of 200 participants: 37% ever smokers, 4/200 consumed more than 20 units alcohol /week. Height/weight/BMI; ethnicity; not reported.	1) vitamin D2 (ergocalciferol) IM injection; duration: 3 years; frequency per day: once per year; amount 300,000 IU / year (n=4727). 2) placebo injection; duration: 3 years; frequency per day: once per year; amount (n=4713). Concordance: unclear, but only 30/4713 (0.6%) did not receive injections.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Tilyard 1992 RCT (fracture) trial held in New Zealand. Setting: secondary care. Funding:Roche	Inclusion criteria: ambulatory postmenopausal white women. Exclusion criteria: major medical problems, drugs affecting bone. Patient type: age: mean 64 years (SD 7), Osteoporosis, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: all with a fracture. Years postmeopausal: 15 years. BMD and Fracture assessment: BMD not assessed; fracture assessed by x-ray. Comorbidities: not stated. Vitamin D and calcium details: Study drug. Baseline vitamin D not given and no other calcium supplements. Daily Ca intake 885-899 mg/day at baseline. Other study comments: no history of using any drug known to ameliorate or cause osteoporosis; none were taking oestrogen.	1) calcitriol; duration: 3 years; frequency per day: twice; amount 0.5 microgr (n=314). 2) 5.2 g calcium gluconate; duration: 3 years; frequency per day: twice; amount 1g elemental Ca (n=308). Concordance: unclear how assessed; compliance: 84% for each group.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Vitamin D

Vitamin D review

Study	*Participants*	*Interventions*
Trivedi 2003 RCT (fracture) trial held in UK. Setting: primary care. Funding:MRC	Inclusion criteria: community dwelling aged 65-85 years. Exclusion criteria: already on or contraindicated to vit D (eg history of renal stones, sarcoidosis, malignancy). Patient type: age: mean around 75 y (65-85y), Not stated, Males and females. Mixed . History of fracture unclear or not stated. Smoking: Some patients. Details: 2037 M: 649F; proportion of patients with a fracture not stated. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed; fracture assessed by questionnaire & mortality reports. Comorbidities: 16% heart disease, 4% stroke, 6% cancer, 5% on steroids. Vitamin D and calcium details: Advised that if they started vit D supplements of >200IU/day, they stopped study medication, but continued to be followed. Other study comments: Mean BMI around 24. Patients continued any usual drug treatment and any new drugs advised during routine care. Stratification and then randomisation by age and gender.	1) cholecalciferol; duration: 5 years; frequency per day: once every 4 months; amount 100000 IU orally every 4 months (n=1345). 2) placebo; duration: 5 years; frequency per day: once tablet every 4 months; amount n/a (n=1341). Concordance: self report; 76% had >80% compliance.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcium

Calcium review

Study	*Participants*	*Interventions*
Avenell 2004 RCT (fracture) trial held in UK. Setting: secondary care. Funding:UK MRC; Shire Pharmaceuticals funded the drugs (co-funded & supplied by Nycomed)	Inclusion criteria: Age 70 or older with low trauma osteoporotic fracture in previous 10 y, ambulatory. Exclusion criteria: cancer, bone abnormality, hypercalcaemia, renal stone in past 10 years; cognitive impairment, life expectancy less than 6 mo, known to be leaving UK, bone active drug in past 5y, >200IU vit D or >500mg Ca/day. Patient type: age: mean 77-78 years (SD 6), Not stated, Males and females. Not higher risk . All patients with history of fracture. Smoking: Some patients. Details: 85% F; all had prior osteoporotic fracture in previous 10 years. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed; fracture assessed by questionnaires, hospitals, GPs and national routine data collection. Comorbidities: not stated. Vitamin D and calcium details: Study drugs. .	1) calcium carbonate; duration: 2-5 years; frequency per day: twice; amount 1000mg (n=29). 2) no treatment; duration: 2-5 years; frequency per day: twice; amount n/a (n=35). Other interventions: 3) vitamin D3 800 IU/day (n=35). 4) Vitamin D + calcium (n=35). Concordance: Questionnaire & pill count.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcium

Calcium review

Study	*Participants*	*Interventions*
Chevalley 1994 RCT (fracture) trial held in Switzerland. Setting: not stated. Funding:Swiss National Science Foundation grand & by Robapharm AG	Inclusion criteria: Not stated. Exclusion criteria: Patients with parathyroid, thyroid, hepatic or cardiac disorders, Paget's disease of bone, plasma creatinine, received coriticosteroids, oestrogens, anticonvulsants, calcitonin or fluoride were excluded. Patient type: age: mean age 72 years (SD 0.6), All BMDs, Males and females. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: Mixed, 82 F and 11 M; all the women were postmenopausal; 44-59% of patients had prevalent vertebral fracture. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed at femoral neck with DPA; fracture assessment not stated. Comorbidities: not stated. Vitamin D and calcium details: All given a single oral dose of 300,000 IU vitamin-D at the beginning of the study. Mean dietary calcium intake 619 mg/day. Other study comments: Not licensed dose, but included still (& half Ca pts had unlicensed Ca). < 5% were smokers Only results for participants with no fractures at baseline were used..	1) Calcium carbonate; duration: 18 months; frequency per day: per day; amount 800 mg (elemental Ca) (n=31). 2) Placebo; duration: 18 months; frequency per day: ; amount 31. Other interventions: 3) calcium as osseino-mineral complex; 800 mg/day, 18 months (n=31). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: tablet counting - 95% compliance. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcium

Calcium review

Study	*Participants*	*Interventions*
Hansson 1987 RCT (fracture) trial held in Sweden. Setting: not stated. Funding:Swedish Medical Research Council and Asker's Foundation.	Inclusion criteria: At least 1 and maximum of 3 vertebral compression fractures. Exclusion criteria: None had known diseases or was taking medication that could directly influence the normal skeletal metabolism. Patient type: age: mean: 66 years (SD 6)., Osteoporosis, Postmenopausal women only. Not higher risk . All patients with history of fracture. Smoking: Not stated. Details: all had 1-3 vertebral fractures at baseline. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed with DXA at lumbar spine, but values not stated; fracture assessment method not reported. Comorbidities: not stated. Vitamin D and calcium details: No Vit-D given. No supplements given. Baseline mean dietary calcium intake not stated. .	1) Calcium (as bicarbonate, lactate and gluconate); duration: 3 years; frequency per day: once; amount 1g (n=25). 2) Placebo (starch); duration: 3 years; frequency per day: once; amount (n=25). Other interventions: 3) Fluoride 30mg + Calcium (n=25) 4) Fluoride 10mg + Calcium (n=25). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcium

Calcium review

Study	*Participants*	*Interventions*
Peacock 2000 RCT (fracture) trial held in USA. Setting: not stated. Funding:Not reported	Inclusion criteria: age 60 years and over. Exclusion criteria: Terminal illness, Paget's disease, recurrent urinary stone disease, had been treated with sodium fluoride, bisphosphonate, steroids, or dilantin, renal disease. Patient type: age: Age over 60 years; mean age women 74, men 76 yrs., All BMDs, Males and females. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: M:F:122:316; all women postmenopausal. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed by DXA at femoral neck; fracture assessed by X-ray. Comorbidities: No stated. Vitamin D and calcium details: Baseline dietary calcium 670 mg/day (Ca) and 629mg/day. Other study comments: not licensed dose, but still included All participants "white". Compliace was 80% (SD 205) for calcium; 85% (SD 19%) for placebo..	1) Calcium citrate plus placebo; duration: 4 years; frequency per day: 3 times; amount 750 mg (250mg elemental Ca x 3) (n=126). 2) Placebo; duration: 4 years; frequency per day: ; amount (n=135). Other interventions: 3) 25-OH Vitamin D, 15mcg (n=132). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcium

Calcium review

Study	*Participants*	*Interventions*
Prince 2007 RCT (fracture) trial held in Australia. Setting: not stated. Funding:Grant from Healthway Health Promotion Foundation, and National Health and Medical Research Council of Australia.	Inclusion criteria: participants over 70 years. Exclusion criteria: taking medication that could affect bone mass; medical conditions that meant they were unlikely to survive 5 years. Patient type: age: mean age 75 years (3 SD), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: prevalent fractures since age 50: 25-32%. Years postmeopausal: mean 26 years. BMD and Fracture assessment: BMD assessed by DXA at femoral neck; fracture assessed by X-ray. Comorbidities: no details. Vitamin D and calcium details: Supplements not given. Dietary calcium intake 915 mg/day (Ca) and 897 mg/day (p). Other study comments: Not licensed dose, but still included Height 158-159 cm mean; weight 68-69 kg; smoking 34-42%.	1) Calcium carbonate; duration: 5 years; frequency per day: twice; amount 1.2 g (2 x 0.6g) (n=730). 2) Placebo; duration: 5 years; frequency per day: ; amount (n=730). Intervention concurrent medications: none. Control concurrent medications: None. Concordance: tablet counting. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcium

Calcium review

Study	*Participants*	*Interventions*
Recker 1996 RCT (fracture) trial held in USA. Setting: not stated. Funding:Grant from National Dairy Promotion and Research Board, and NIH	Inclusion criteria: Healthy postmenopausal women aged over 60 years whose calcium intakes were estimated to be <1 gram per day. Exclusion criteria: Participants with other diagnoses or with treatment known to affect skeleton were excluded. Patient type: age: Mean age 74 years (SD 7), Not stated, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: prevalent fractures: 44% Ca, 59% placebo. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed with SPA at radius; fracture assessed by X-ray. Comorbidities: not stated. Vitamin D and calcium details: None other than in intervention group. Dietary supplements not given. Baseline calcium dietary intake estimated at 386 mg/day (Ca) and 442 mg/day (p). Other study comments: Not licensed dose, but still included White women of European ancestry. Participants were split into 4 group according to frature history. Data added together to form two groups for this review..	1) Calcium carbonate; duration: ~ 4 years; frequency per day: twice; amount 1.2g (2 x 600mg elemental calcium) (n=95). 2) placebo; duration: ~4 years; frequency per day: twice; amount 102. Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Tablet counting. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcium

Calcium review

Study	*Participants*	*Interventions*
RECORD 2005 RCT (fracture) trial held in UK. Setting: secondary care. Funding:UK MRC; Shire Pharmaceuticals funded the drugs (co-funded & supplied by Nycomed)	Inclusion criteria: Age 70 or older with low trauma osteoporotic fracture in previous 10 y, ambulatory. Exclusion criteria: cancer, bone abnormality, hypercalcaemia, renal stone in past 10 years; cognitive impairment, life expectancy less than 6 mo, known to be leaving UK, bone active drug in past 5y, >200IU vit D or >500mg Ca/day. Patient type: age: mean 77-78 years (SD 6), Not stated, Males and females. Not higher risk . All patients with history of fracture. Smoking: Some patients. Details: 85% F; all had prior osteoporotic fracture in previous 10 years. Years postmeopausal: not stated. BMD and Fracture assessment: BMD not assessed; fracture assessed by questionnaires, hospitals, GPs and national routine data collection. Comorbidities: not stated. Vitamin D and calcium details: Study drugs. .	1) calcium carbonate; duration: 2-5 years; frequency per day: twice; amount 1000mg (n=1343). 2) placebo; duration: 2-5 years; frequency per day: twice; amount n/a (n=1332). Other interventions: 3) vitamin D3 800 IU/day (n=1343). 4) Vitamin D + calcium (n=1306). Concordance: Questionnaire & pill count.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcium

Calcium review

Study	*Participants*	*Interventions*
Reid 1993 RCT (fracture) trial held in New Zealand. Setting: not stated. Funding:Not reported	Inclusion criteria: menopause more than 3 years. Exclusion criteria: History of disorders of calcium metabolism, including symptomatic vertebral fractures; renal, thyroid, or hepatic dysfunction; current systemic disease; the use of hormone-replacement therapy within the previous three years. Patient type: age: 58 years (SD 5), Mixed osteopenia/normal BMD, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Some patients. Details: 7-11% smokers. Years postmeopausal: mean 9-10 years (SD 5). BMD and Fracture assessment: BMD assessed at femoral neck by DXA; fracture assessment not stated. Comorbidities: not stated. Vitamin D and calcium details: None other than in intervention group. No supplements given. Baseline mean dietary calcium intake 750 mg/day. Other study comments: The mean (+/- SD) rate of compliance during the two-year study period was 84 +/- 7 percent in the calcium group and 83 +/- 10 percent in the placebo group.	1) calcium lactate-gluconate (5.24g) and calcium carbonate (0.8g); duration: 2 years; frequency per day: once; amount 1g elemental calcium (n=61). 2) Placebo; duration: 2 years; frequency per day: once; amount 61. Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Assessed by tablet counts. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcium

Calcium review

Study	*Participants*	*Interventions*
Reid 2006 RCT (fracture) trial held in New Zealand. Setting: not stated. Funding:No details of funding	Inclusion criteria: Participants over 55 years, not receiving therapy for osteoporosis or taking calcium supplements, and free of ongoing disease. Exclusion criteria: not stated. Patient type: age: Mean 74 years (SD 4), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Some patients. Details: 28-29% had prevalent fracture at baseline. Years postmeopausal: mean of 25 years. BMD and Fracture assessment: BMD assessed with DXA scan; fractures assessed radiographically. Comorbidities: none. Vitamin D and calcium details: Supplements not given. Dietary calcium intake 861 mg/day (Ca) and 853 mg/day (p). Serum vitamin-D 20.6 µg/L/day (Ca) and 20.8 µg/L/day (p). Other study comments: Not licensed dose, but still included Some patients had osteoporotic medication during the trial (excluded from per protocol analysis).	1) Calcium as citrate; duration: 5 years; frequency per day: twice; amount 1g (2 x 500mg) elemental calcium (n=739). 2) placebo; duration: 5 years; frequency per day: twice; amount 732. Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Tablet counting. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Calcium

Calcium review

Study	*Participants*	*Interventions*
Riggs 1998 RCT (fracture) trial held in USA. Setting: not stated. Funding:Grant from National Institute of Health	Inclusion criteria: No details. Exclusion criteria: History of renal lithiasis, impaired renal function, hypercalciuria. Receiving oestrogen, large doses of vitamin D or Ca; or drugs affecting bone or bisphosphonates. Patient type: age: 61-70 years, Unclear, Postmenopausal women only. Not higher risk . No patients with history of fracture. Smoking: Not stated. Details: . Years postmeopausal: 10 years or more. BMD and Fracture assessment: BMD assessed at lumbar spine with DXA scan but no baseline values reported ; fracture assessed by X-ray. Comorbidities: not stated. Vitamin D and calcium details: No supplements given. Baseline dietary calcium 711 mg day (Ca) 717 mg/day (p). All had normal serum and urinary levels of calcium. None received large doses of vitamin-D or calcium prior to study. Other study comments: Higher than licensed dose, but still included.	1) Calcium citrate salt; duration: 4 years; frequency per day: 4 times; amount 1.6g (0.4g x 4) decreased if calcium levels too high (n=119). 2) Placebo (matching placebo); duration: 4 years; frequency per day: 4 times; amount decreased if calcium levels too high 117. Intervention concurrent medications: none. Control concurrent medications: None. Concordance: Pill counting at each visit. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Cross Review

Cross review

Study	*Participants*	*Interventions*
Black 2003 RCT (fracture) trial held in USA. Setting: secondary care. Funding:National Institute of Arthritis and muskuloskeletal and skin disorders, Merck, SmithKlineBeecham, NPS	Inclusion criteria: postmenopausal women 55-85yr with T score <-2.5 or <-2.0 plus at least 1 of: age 65+, prior fracture, maternal history hip fracture. Exclusion criteria: bisphosphonate>12 months total, or >4 weeks in previous 12 months; disease/drug affecting bone metabolism. Patient type: age: mean around 70 yr (55-85yr), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: 47% with a fracture. Years postmeopausal: mean 23 years. BMD and Fracture assessment: BMD assessed by DXA (spine, hip) & how fracture assessed. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Calcium carbonate 500mg; 400IU vitamin D. Other study comments: mean BMI around 26; 5% non-white.	1) alendronic acid; duration: 1 year; frequency per day: once; amount 10mg (n=60). 2) parathyroid hormone 1-84; duration: 1 year; frequency per day: once; amount 100µg (n=119). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: assessed by pill/cartridge count.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Cross Review

Cross review

Study	*Participants*	*Interventions*
Eviö 2004 RCT (fracture) trial held in Finland. Setting: secondary care. Funding:Merck and other non-pharmaceutical	Inclusion criteria: Elderly postmenopausal women. Exclusion criteria: Other metabolic bone disease, contraindications to HRT, use of bone-active agents, disease affecting bone turnover, GI mucosal disorders, history of thromboembolism, liver/kidney disease, diabetes, uterine/breast cancer, uncontrolled hypertension. Patient type: age: 71 years (65-80), Osteoporosis, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Some patients. Details: F; proportion of patients with a fracture not stated. Years postmeopausal: around 22 years. BMD and Fracture assessment: BMD assessed by DXA at spine, femoral neck & total hip fracture not assessed. Comorbidities: none stated. Calcium and Vitamin D regimens: All patients received Ca. Dietary calcium assessed at intake, then advised to take calcium supplements (500-1000mg daily) to increase intake to 1g daily and vitamin D from October to April (but not provided by study authors). Other study comments: 10% smokers; mean 12g alcohol per week; mean BMI 25.	1) alendronic acid; duration: 2 years; frequency per day: once; amount 10mg (n=30). 2) oestradiol plus norethisterone acetate; duration: 2 years; frequency per day: once; amount 2mg + 1mg (n=30). Concordance: Pill count.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Cross Review

Cross review

Study	*Participants*	*Interventions*
Luckey 2004 RCT (fracture) trial held in USA. Setting: secondary care. Funding:Merck	Inclusion criteria: women over 40 at least 18 months postmenopausal (or >25 if surgically postmenopausal) with T score -2SD or more at spine or hip. Exclusion criteria: illness/abnormality that cd compromise safety or study results (breast/uterine ca;DVT/PE;hepatic dysfunction; delayed oesoph emptying; metab bone dis; oestrogen/SERMS/ anabolic steroids/ bisphos/PTH<1 yr; fluoride>1mg/d or glucocort<6mo; drugs affect bone. Patient type: age: mean 64 years, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Some patients. Details: F; proportion of patients with a fracture not stated. Years postmeopausal: min 18 months; mean 17.5yr. BMD and Fracture assessment: BMD assessed by DXA (lumbar spine, total hip, trochanter); fracture reported as adverse events but not divided by trauma or no trauma. Comorbidities: 21% hypertension; 17% OA; 16% hypercholesterolaemia; 16% hysterectomy; 14% headache; 13% hypothyroidism. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Based on intake, patients took 1 or 2 caplets Os-Cal 500+ D daily (calcium 500mg, vit D 200IU) with noon and/or evening meal. Other study comments: 92% white; mean BMI 25.3; 27.4% current smokers.	1) alendronic acid; duration: 1 year; frequency per day: once weekly; amount 70mg weekly (n=223). 2) raloxifene; duration: 1 year; frequency per day: once; amount 60mg (n=233). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: diary of medication use validated with tablet counts.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Cross Review

Cross review

Study	*Participants*	*Interventions*
McClung 2005 RCT (fracture) trial held in Multinational. Setting: secondary care. Funding:Eli Lilly	Inclusion criteria: No: cervical cancer in situ within 1 yr; nephro/urolithiasis 2 yr; uncorrected abnormal thyroid function; liver disease/jaundice; impaired renal function; alc/drug abuse; poor medical/psychiatric risk. Exclusion criteria: Prior PTH; bisphosphonate within 12 mo; anabolic steroid/calcitriol/vit D within 6 mo; HRT/SERM within 3 mo; calcitonin within 2 mo; fluoride; steroid within 1 mo or >1mo in last yr; anticoag within 1mo; dis affecting bone metab; malignancy within 5 yr;. Patient type: age: mean 66 years (45-84), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: All women; prior fracture not stated. Years postmeopausal: at least 5 years (mean 19+yr). BMD and Fracture assessment: BMD assessed at lumbar spine & total hip; DXA. Clinical fracture only. Comorbidities: none stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. Supplemental calcium carbonate (1g Ca daily) and Vitamin D 800IU. Other study comments: Mean BMI around 25.5; 62% white.	1) alendronic acid; duration: 18 months; frequency per day: once; amount 10mg (n=101). 2) Teriparatide; duration: 18 months; frequency per day: once; amount 20μg (n=102). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: not stated. Washout period: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Cross Review

Cross review

Study	*Participants*	*Interventions*
Michalska 2006 RCT (fracture) trial held in Czech republic. Setting: secondary care. Funding:Eli Lilly	Inclusion criteria: ambulatory postmenopausal women 50-80 yr treated with alendronate 10mg/day for at least 3 yr (a mean of 43 months). Exclusion criteria: bone disease, endocrine/malignant disease, uterine/ovarian abn, postmeno symptoms requiring HRT, thromboembolism, severe chronic disease, drugs affecting bone turnover. Patient type: age: mean 65 years (50-80), Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: proportion of patients with a nonvertebral fracture 27.3% on alendronate & 48.5% on raloxifene. Years postmeopausal: mean around 18 years. BMD and Fracture assessment: BMD assessed by DXA (lumbar spine & proximal femur) incident non-vertebral fractures reported but not whether trauma-related. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. 500mg/day calcium + 800IU/day vit D. Other study comments: core part of trial: 12 months of double-blind raloxifene or placebo or open-label alendronate; extension 12 months same treatment but all open label.	1) alendronic acid; duration: 2 years (both open label); frequency per day: not stated; amount 10mg (n=33). 2) raloxifene; duration: 2 years (1st year blinded); frequency per day: not stated; amount 60mg (n=33). Other interventions: 3) placebo 2 years (n=33). Concordance: not stated. Washout period: none: all had at least 3 y alendronic acid before.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Cross Review

Cross review

Study	*Participants*	*Interventions*
Muscoso 2004 RCT (fracture) trial held in Italy. Setting: secondary care. Funding:not stated	Inclusion criteria: Women over 50 yr with osteoporosis. Exclusion criteria: not stated. Patient type: age: mean 68 years, Osteoporosis, Postmenopausal women only. Not higher risk . History of fracture unclear or not stated. Smoking: Not stated. Details: proportion of patients with a fracture not stated. Years postmeopausal: not stated. BMD and Fracture assessment: BMD assessed by DXA (lumbar spine) & how fracture assessed not reported. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. 1g calcium+800IU vit D daily. .	1) alendronic acid; duration: 2 years; frequency per day: once; amount 10mg (n=1000). 2) raloxifene; duration: 2 years; frequency per day: once; amount 60mg (n=100). Other interventions: 3) clodronate im 2 years (n=800) 4) risedronate 5 g/day for 2 years (n=100). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Cross Review

Cross review

Study	*Participants*	*Interventions*
Palomba 2005 RCT (fracture) trial held in Italy. Setting: secondary care. Funding:Research grant (not industry)	Inclusion criteria: natural postmenopause, T score <-2.5. No drug causing GI irritation or inhibiting gastric acid secretion; not smoking>20/day; not drinking >3 alcoholic drinks/day; no T score <-4.0. Exclusion criteria: active RA, GI/liver disease; metabolic,/neoplastic/endocrine disease, acute/recurrent thrombosis, 2ry causes of osteo, drug affecting bone metab, serum creatinine >133 micromol/L, GI side effects, BMI<18 or >30, vit D < 25nmol/L, abnormal ca/phosphate/PTH. Patient type: age: mean around 65 years, Osteoporosis, Postmenopausal women only. Not higher risk . No patients with history of fracture. Smoking: Some patients. Details: no patients with a fracture. Years postmeopausal: around 12 years. BMD and Fracture assessment: BMD assessed by DXA (lumbar spine); fracture assessed by x-ray. Comorbidities: not stated. Calcium and Vitamin D regimens: Some patients received Ca only. Patients with Ca intake <1000mg/day took Ca 500mg/day. No vitamin D supplement. Other study comments: All Caucasian or European; BMI around 26.	1) alendronic acid; duration: 1 year; frequency per day: once; amount 10mg (n=220). 2) raloxifene; duration: 1 year; frequency per day: once; amount 60mg (n=219). Other interventions: 3) alendronate + raloxifene (n=222) 4) HRT not licensed dose (n=219) 5) Alendronate + HRT (n=220). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: not stated.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Cross Review

Cross review

Study	*Participants*	*Interventions*
Recker 2007 RCT (fracture) trial held in USA/Canada. Setting: secondary care. Funding:Eli Lilly	Inclusion criteria: ambulatory postmenopausal women 50-80 yr, at least 2 yr postmenopause. Exclusion criteria: dis of calcium/bone metab; breast/oestrogen dependent cancer; vaginal bleeding; thromboembolism (or risk of); oesophageal abn; abn thyroid, hepatic or renal function; bone-active drug. Patient type: age: mean 65 yr, Osteoporosis, Postmenopausal women only. Not higher risk . No patients with history of fracture. Smoking: Not stated. Details: F; no patients with a fracture. Years postmeopausal: mean 19yr. BMD and Fracture assessment: BMD assessed by DXA (lumbar spine & femoral neck; Hologic, Lunar or Prodigy) & fracture assessed >20% loss in height. Comorbidities: not stated. Calcium and Vitamin D regimens: All patients received Ca and Vit D. 500mg calcium + 400IU vitamin D daily. Other study comments: study designed for non-inferiority of raloxifene (on fracture outcome) but terminated early so underpowered for this; 87% caucasian; BMI around 25. Treatment <1 yr so include tentatively.	1) alendronic acid; duration: mean 312 days (i.e. less than 1 year); frequency per day: once; amount 10mg (n=716). 2) raloxifene; duration: mean 312 days (i.e. less than 1 year); frequency per day: once; amount 60mg (n=707). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: pill count.

APPENDIX III
CHARACTERISTICS OF INCLUDED STUDIES

Class: Cross Review

Cross review

Study	*Participants*	*Interventions*
Sambrook 2004 RCT (fracture) trial held in Europe, South America and Asia-Pacific. Setting: secondary care. Funding:Merck	Inclusion criteria: at least 6 mo postmeno; T score <-2. Exclusion criteria: bilateral hip replacement, thromboembolism, hypertriglyceridaemia, oesophageal stricture/achalasia, bone active drug within 1 yr, drug/medical condition affecting bone metab. Patient type: age: mean 62 yr, Mixed osteoporosis/osteopenia, Postmenopausal women only. Not higher risk . Some patients with history of fracture. Smoking: Not stated. Details: F; 26% of patients with a fracture. Years postmeopausal: at least 6 mo; mean 15 yr. BMD and Fracture assessment: BMD assessed by DXA (spine, hip, femoral neck); fracture not assessed. Comorbidities: hypertension (30%), OA 13%, varicose veins (12%). Calcium and Vitamin D regimens: --- 'Calcium and vitamin D supplements were given in accordance with the standard care in the local community'. Other study comments: mean BMI around 25; 79% white.	1) alendronic acid; duration: 12 months; frequency per day: weekly; amount 70mg weekly (n=246). 2) raloxifene; duration: 12 months; frequency per day: daily; amount 60mg (n=241). Intervention concurrent medications: none. Control concurrent medications: none. Concordance: Not assessed.

APPENDIX IV
EXCLUDED STUDIES

Biphosphonates: Alendronic acid review

Study	*Reason for exclusion*
Adami 1995	BMD only
Aris 2003	Other high risk groups: alendronic acid for the treatment of low bone density in patients with cystic fibrosis
Bone 2000	BMD only: most as a result of trauma
Chesnut 1995	BMD only
de Nijs 2006	Comparator not in BNF
El-Agroudy 2005	Other high risk groups: alfacalcidol, alendronic acid and calcitonin on osteopenia and osteoporosis for the prevention of bone loss in patients with postrenal transplantation
El-Husseini 2004	Other high risk groups: the effect of alfacalcidol, alendronic acid and calcitonin on osteopenia and osteoporosis in renal transplant children and adolescents
Golden 2005	Other high risk groups: for the treatment of osteopenia in anorexia nervosa
Greenspan 2007	Other high risk groups: on the effect of bone loss in men receiving andogen deprivation therapy for prostate cancer
Guaraldi 2004	Other high risk groups: reduction of bone resorption in HIV associated osteopenia and osteoporosis
Guo-ping 2005	BMD only
Higashiyama	Other high risk groups: effect on bone loss in patients with cirrhosis of the liver
Hiskins 1998	BMD only
Ho 2005	BMD only
Ikeda 2004	Other high risk groups: on early changes in biochemical marker of resorption and BMD in postmenopausal women with type 2 diabetes mellitus
Kasayama 2005	BMD only
Keegan 2004	Other high risk groups: on the treatment of BMD and biochemical markers of bone turnover in type 2 diabetic women

APPENDIX IV
EXCLUDED STUDIES

Biphosphonates: Alendronic acid review

Study	*Reason for exclusion*
Kushida 2002	Comparator not in BNF
Kushida 2004	Comparator not in BNF
McClung 1998	BMD only
McClung 2004	BMD only
McClung 2005	BMD only
Mondy 2005	Other high risk groups: alendronic acid and calcium and vitamin D for the treatment of osteopenia associated with HIV infection
Moran de Brito 2005	Other high risk groups: on NMD in spinal cord injury patients
Negredo 2005	Other high risk groups: effect of alendronic acid on `reversal of HIV associated osteoporosis
Ringe 2001	Comparator not in BNF
Ringe 2004	Comparator not in BNF
Rossini 1994	BMD only
Sambrook 2004	BMD only
Sato 2006	Other high risk groups: alendronic acid and vitamin D for prevention of hip fracture in Parkinson's Disease
Shane 2004	Other high risk groups: on the prevention of bone loss after cardiac transplantation
Shilbayeh 2004	BMD only
Smith 2004	BMD only
Tascioglu 2005	Other high risk groups: alendronic acid and intranasal salmon calcitonin treatments on BMD in patients with rheumatoid arthritis receiving glucocorticoids

APPENDIX IV
EXCLUDED STUDIES

Biphosphonates: Alendronic acid review

Study	*Reason for exclusion*
Uchida 2005	BMD only
Wasnich 2004	BMD only
Wenstrup 2004	Other high risk groups: improvement on BMD in patients with Gaucher disease receiving enzyme therapy
Zein 2005	Other high risk groups: improvement of BMD in primary biliary cirrhosis

APPENDIX IV
EXCLUDED STUDIES

Biphosphonates: Etidronate review

Study	*Reason for exclusion*
Adachi 1994	Not randomised
Fujita 2001	Dose not in BNF
Hasegawa 2003	BMD only
Ishida 2004	Dose not in BNF: 200 mg/day for 2 weeks then 10 week medication free period
Iwamoto 2001	Dose not in BNF: 200 mg/day for 14 days per 3 months
Jinnouchi 2000	Dose not in BNF: 200 mg/day for 14 days per 3 months
Lindor 2000	Other high risk groups
Nakahara 2006	Other high risk groups: effects of etidronate and calcium and vitamin D on bone therapy -tibial bone loss- in young women with anorexia nervosa
Nakayamada 2004	Dose not in BNF: 200 mg/day for 14 days per 3 months; comparator alfacalcidol
Pacifici 1988	Dose not in BNF: K-phosphate + 1g Ca/day for 3 days followed by etidronate 400 mg/day + 1g Ca/day for 2 weeks, then 8 weeks 1g Ca/day
Pitt 1998	Dose not in BNF: 400 mg/day etidronate for 14 days then 97mg/day Calcium plus 400 IU vitamin D for 76 days. Calcium dose too low.
Sato 2000	Other high risk groups
Sato 2003	Dose not in BNF
Sato 2006	Other high risk groups: fracture prevention in amyotrophic lateral sclerosis
Shiomi 2002	Dose not in BNF
Siffledeen 2005	Other high risk groups: Etidronate plus calcium and vitamin D for low bone mineral density in Crohn's Disease
Skingle 1997	Intervention not in BNF: 400mg/day etidronate for 2 weeks plus calcium 1g/day then calcium 1g/day for further 13 weeks. Too high dose of calcium

APPENDIX IV
EXCLUDED STUDIES

Biphosphonates: Etidronate review

Study	*Reason for exclusion*
Storm 1990	Dose not in BNF: 400 mg/day etidronate + 500mg/day Ca for 14 days then 500mg/day Ca for 13 weeks
Wimalawansa 1998	Intervention not in BNF: 400mg/day etidronate for 2 weeks plus calcium 1g/day then calcium 1g/day for further 10 weeks. Too high dose of calcium
Worth 1994	Dose not in BNF: continuous etidronate 7.5 mg/kg body weight (i.e. about 400 mg)
Yamaguchi 2003	BMD only

APPENDIX IV
EXCLUDED STUDIES

Biphosphonates: Risedronate review

Study	*Reason for exclusion*
Clemmensen 1997	Dose not in BNF
Durchsclag 2006	BMD only
Greenspan 2007	Other high risk groups: prevention of bone loss in survivors of breast cancer
Henderson 2006	Other high risk groups: in patients affected by inflammatory bowel disease
Kanaji 2006	Other high risk groups: effects of risedronate on lumbar BMD, bone resorption and incidence of vertebral fracture in elderly male patients with leprosy
Leung 2005	BMD only
Majima 2006	BMD only
Palomba 2005	Other high risk groups: in patients affected by inflammatory bowel disease
Poznak 2007	Other high risk groups: effects on BMD and bone metabolism in postmenopausal women with early breast cancer
Sato 2005	Other high risk groups: on the prevention of hip fracture after stroke in elderly women

APPENDIX IV
EXCLUDED STUDIES

Biphosphonates: Ibandronic Acid review

Study	*Reason for exclusion*
Adami 2004	BMD only
Body 2004	Other high risk groups: effect of ibandronic acid on the reduction of risk of skeletal complications in patients with breast cancer with metastatic bone disease
Lester 2007	Other high risk groups: effect of oral ibandronic acid on anastrozole-induced bone loss during adjuvant treatment for breast cancer
McClung 2004	BMD only
Recker 2004	Dose not in BNF: doses of ibandronic acid not in BNF (0.5 mg or 1 mg iv injections every 3 months)
Stakkestad 2003	BMD only
Thiébaud 1997	BMD only

APPENDIX IV
EXCLUDED STUDIES

Biphosphonates: Zoledronic acid review

Study	*Reason for exclusion*
Aapro 2006	Other high risk groups: adding effect of zoledronic acid to letrozole to improve bone health in patients with early breast cancer
Brufsky 2007	Other high risk groups: effects of zoledronic acid on the inhibition of adjuvant letrozole-induced bone loss in patients with early breast cancer
Crawford 2006	Other high risk groups: prevention of bone loss after liver transplantation
Gilfillan 2006	Other high risk groups: in patients with B-thalassemia associated osteopenia
Gnant 2007	Other high risk groups: on cancer treatment induced-bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer
Michaelson 2007	Other high risk groups: on the prevention of gonadotopin-releasing hormone agonist-induced bone loss in men with prostate cancer
Otrock 2006	Other high risk groups: in patients with B-thalassemia induced osteoporosis
Rodrigues 2006	Other high risk groups: effect of zoledronic acid or clodronate on BMD in patients submitted to radical prostatectomy undergoing androgen deprivation therapy
Ryan 2007	Other high risk groups: on the supression of bone density loss and bone turnover in patients with hormone-sensitive prostate cancer
Voskaridou 2006	Other high risk groups: in patients with B-thalassemia

APPENDIX IV
EXCLUDED STUDIES

Biphosphonates: Cross biphosphonates review

Study	*Reason for exclusion*
Atmaca 2006	BMD only
Iwamoto 2005	Dose not in BNF
Kushida 2004	Dose not in BNF
Yildirim 2005	BMD only

APPENDIX IV
EXCLUDED STUDIES

Parathyroid hormone: Teriparatide review

Study	*Reason for exclusion*
Body 2002	Dose not in BNF: 40 mcg and for cross review
Finkelstein 1998	Dose not in BNF: 40 mcg and for cross review and BMD only
Finkelstein 2003	Dose not in BNF: intended 40mcg but applied 37 mcg initially and this was lowered to 28 mcg and 18 mcg
Fujita 1999	Dose not in BNF: comparison of PTH subcutaneous injection doses: 15 mcg versus 30 mcg versus 60 mcg
Gonelli 2006	Comparison not of interest: teriparatide versus antiresorptive treatment which included: tibolone, salmon calcitonin, clorodronate, alendronic acid, and risedronate
Hesp 1981	Dose not in BNF: 50 mcg
Hodsman 1997	Dose not in BNF: 50 mcg (i.e. 800 IU) in 28 day courses at three months intervals; i.e. less than 12 months continous treatment
Matsumoto 2006	Dose not in BNF: comparison of hPTH nasal spray doses: 1,000 mcg (similar to subcutaneous injection of 20 mcg) with 500 mcg and 250 mcg
Nordin 1980	Not relevant outcome
Reeve 1976	Dose not in BNF: 100 mcg
Reeve 1976 b	Dose not in BNF: 100 mcg
Reeve 1976 c	Dose not in BNF: 100 mcg, 200 mcg and 400 mcg
Reeve 1980	Not randomised: and used 100 mcg which is a dose not in BNF
Reeve 1990	Dose not in BNF: initial subcutaneous injection of 100 mcg daily which was lowered during study and reached 50 mcg by the end of the trial
Reeve 1991	Dose not in BNF: 31.2 mcg (i.e. 500 IU)
Slovik 1986	Dose not in BNF: a range of 25 mcg to 31.25 mcg (i.e. 400-500 IU)
Sone 1995	Dose not in BNF: 6 mcg; not said to be randomised

APPENDIX IV
EXCLUDED STUDIES

Parathyroid hormone: Teriparatide review

Study	*Reason for exclusion*
Ste-Marie 2006	BMD only

APPENDIX IV
EXCLUDED STUDIES

Parathyroid hormone: PTH (1-84) review

Study	*Reason for exclusion*
Bauer 2006	Not comparison: partial report of information and data for only two thirds of groups included in the first 12 months of trial

APPENDIX IV
EXCLUDED STUDIES

Calcitonin review

Study	*Reason for exclusion*
Abellen Perez 1995	Non-English
Adami 1995	BMD only
Agrawal 1980	Dose not in BNF: subcutaneous MRC 100 units per day; sample size too small
Cristallini 1993	Non-English
Dursun 2001	Dose not in BNF: calcitonin spray 100 IU per day
Eileen Hay 2001	Duration less than 12 months: 6 months
Ellerington 1996	BMD only
Fujita 1992	Dose not in BNF: 10 U intramuscular injection twice a week
Gennari 1985	Dose not in BNF: subcutaneous or intramuscular MRC 100 U
Grøvle 1996	Dose not in BNF: Calcitonin dose not stated in the BNF: 200 IU/day for 1 month then 100 IU intranasal spray per day for 11 months
Hay 2001	Duration less than 12 months: 6 months
Hizmetli 1998	Dose not in BNF: 100 IU intranasal per day
Hodsman 1992	Dose not in BNF: subcutaneous injection 75 U per day
Ishida 2004	Dose not in BNF: 20 IU per week
Ishida 2004	Dose not in BNF: 20 IU per week
Karachalios 2004	Duration less than 12 months: 3 months
Kaskani 2005	BMD only

APPENDIX IV
EXCLUDED STUDIES

Calcitonin review

Study	*Reason for exclusion*
Peichl 2005	Not RCT
Pontiroli 1991	Dose not in BNF: fewer than 10 people in each arm; and less than 12 months duration of treatment: 6 months; Intramuscular injection of 100 U every other day
Rico 1995	Dose not in BNF: intramuscular injection of 100 IU per day
Ringe 1987	Duration less than 12 months: 6 months and evaluated a low dose of calcitonin -subcutaneous 100 IU every other day
Ringe 1990	Non-English
Sambrook 1993	Dose not in BNF: Calcitonin dose not stated in the BNF: 400 IU per day nasal spray
Tekeoğlu 2005	BMD only
Ushiroyama 2001	Dose not in BNF: 10 IU twice per month; calcitonin vs vitamin D
Välimäki 1999a	Other high risk groups: High risk population; bone marrow transplantation for malignant blood diseases
Välimäki 1999b	Other high risk groups: High risk population; cardiac transplantation

APPENDIX IV
EXCLUDED STUDIES

Hormone Replacement Therapy review

Study	*Reason for exclusion*
Ahlborg 2004	Not RCT
Aitken 1973	Dose not in BNF
Al-Azzawi 2005	BMD only
Alexandersen 1999	Dose not in BNF
Bhattoa 2004	Other high risk groups: osteopenic postmenopausal systemic lupus erythematosus patients
Boone 2006	Other high risk groups: efficacy and feasibility of estrogen and progestin in osteoporosis in primary biliary cirrhosis
Cauley 2001	Not RCT
Cauley 2001	Dose not in BNF
Cauley 2003	Dose not in BNF
Cheng 2005	BMD only
Christiansen 2005	BMD only
Davis 2005	Not RCT
Delmas 2004	Not RCT
Dören 2003	Not RCT
Eiken 1997	BMD only
Greenwald 2005	BMD only
Grey 1996	Other high risk groups: In women with hyperparathyroidism

APPENDIX IV
EXCLUDED STUDIES

Hormone Replacement Therapy review

Study	*Reason for exclusion*
Ishida 2001	Dose not in BNF
Ishida 2004	Dose not in BNF: HRT vs etidronate vs calcitonin vs alfacalcidol vs vitamin K
Kananen 2005	Other high risk groups: prevention of bone loss associated with stem cell transplantation by additional pamidronate with combination of HRT, Vitamin D or calcium
Komulainen 1998	Dose not in BNF
Liu 2005	BMD only
Nachtigall 1979	Dose not in BNF
Nielsen 2004	BMD only
Ormarsdottir 2004	Other high risk groups: effect on bone loss in primary biliary cirrhosis
Orr Walker 2000	Other high risk groups: In women with hyperparathyroidism
Pereira 2004	Other high risk groups: effect on bone density in patients with primary biliary cirrhosis
Popp 2006	BMD only
Practice Committee ASRM 2006	Not RCT
Recker 1999	Dose not in BNF
Sicat 2004	Not RCT
Strokosch 2006	Other high risk groups: effects of oral contraceptive on BMD in adolescent females with anorexia nervosa
Tauchmanova 2006	Other high risk groups: effect of HRT, zoledronic acid, risedronate and vitamin D and calcium on BMD in hypgonadal young women after allogeneic stem cell transplantation
Vickers 2007	Duration less than 12 months: trial closed prematurely during recruitment

APPENDIX IV
EXCLUDED STUDIES

Hormone Replacement Therapy review

Study	*Reason for exclusion*
Voss 2002	Cross review: HRT versus SERM not placebo or other type of HRT
Warming 2004	BMD only
Warming 2005	BMD only
Warren 2005	Not RCT
Zarcone 1997	Non-English

APPENDIX IV
EXCLUDED STUDIES

SERMs: Raloxifene review

Study	*Reason for exclusion*
Chiu Mok 2005	Other high risk groups: postmenopausal women with systemic lupus erythematosus
McClung 2006	BMD only
Smith 2004	BMD only

APPENDIX IV
EXCLUDED STUDIES

Sex hormones: Nandrolone review

Study	*Reason for exclusion*
Birkenhäger 1992	Dose not in BNF: nandrolone 50mg given once every 4 weeks (not 3 weekly)
Erdtsieck 1994	Dose not in BNF: nandrolone 50mg given once every 4 weeks (not 3 weekly)
Leidig-Bruckner 1997	Dose not in BNF: nandrolone 50mg given once every 4 weeks (not 3 weekly)
Szücs 1992	Dose not in BNF: nandrolone 50mg given once every 4 weeks (not 3 weekly)

APPENDIX IV
EXCLUDED STUDIES

Vitamin D review

Study	*Reason for exclusion*
Aloia 1988	Dose not in BNF: dose calcitriol 0.25 microg /day ro 2 microg / day(titrated)
Arthur 1990	Sample size too small
Baeksgaard 1998	BMD only
Barone 2007	BMD only
Bauman 2005	Other high risk groups: only BMD in patients with chronic spinal cord injury
Bernstein 1996	BMD only
Buckley1996	BMD only
Caniggia 1984	Sample size too small
Di Munno 1989	Intervention not in BNF: 25-hydroxycholecalciferol
Dukas 2004	Intervention not in BNF: alfacalcidol
Dukas 2005	Not fracture or BMD data
Dykman 1984	Dose not in BNF
El-Husseini 2004	Other high risk groups: treatment of bone loss during kidney transplantation in children and adolescents
Fujita 1992	Sample size too small: less than10 people in each arm
Gallagher 1990	Dose not in BNF: dose calcitriol 0.25 microg /day ro 2 microg / day(titrated)
Garay Lillo 1997	Intervention not in BNF: 25-hydroxy vitamin D
Geusens 1986	Dose not in BNF

APPENDIX IV
EXCLUDED STUDIES

Vitamin D review

Study	*Reason for exclusion*
Gorai 1999	Intervention not in BNF: alfacalcidol
Graafmans 1996	Not fracture or BMD data
Inkovaara 1983	Duration less than 12 months
Ishida 2004	Dose not in BNF
Komulainen 1999	Dose not in BNF
Lakatos 2000;	Intervention not in BNF: alfacalcidol
Lambrinoudaki 2000	BMD only
Law 2006	Duration less than 12 months: Mean duration only 10 months
Matsumoto 2005	Intervention not in BNF: ED-71 (1α-hydroxy-2β-(3-hydroxypropoxy) vitamin D3)
McDonald 2006	BMD only
Menczel 1994	Intervention not in BNF: alfacalcidol
Mikati 2006	BMD only
Mikati 2006	BMD only
Mizunuma 2006	Intervention not in BNF: alfacalcidol
Nuti 2006	Intervention not in BNF: alfacalcidol
Orimo 1987	Intervention not in BNF: alfacalcidol
Orimo 1994	Intervention not in BNF: alfacalcidol

APPENDIX IV
EXCLUDED STUDIES

Vitamin D review

Study	*Reason for exclusion*
Orwoll 1989	Intervention not in BNF: 25-hydroxycholecalciferol
Ott 1989	Dose not in BNF: dose calcitriol 0.25 microg /day ro 2 microg / day(titrated)
Peacock 2000	Dose not in BNF
Reginster 1999	Intervention not in BNF: alfacalcidol
Ringe 1999	Intervention not in BNF: alfacalcidol
Sambrook 1993	Dose not in BNF
Sambrook 2000	Dose not in BNF
Sato 1997	Intervention not in BNF: alfacalcidol
Sato 1999	Intervention not in BNF: alfacalcidol
Sato 2005	Other high risk groups: vitamin D with calcium and menatetrenone as supplements in the prevention of nonvertebral fractures in elderly people with Alzheimer's Disease
Shiraki 1996	Intervention not in BNF: alfacalcidol
Shiraki 2004	Intervention not in BNF: 25-hydroxycholecalciferol
Sosa 2000	Intervention not in BNF: 25-hydroxycholecalciferol
Stempfle 1999	Dose not in BNF
Stempfle 2002	Dose not in BNF
Talalaj 1996	Intervention not in BNF: 25-hydroxycholecalciferol
Torres 2004	Other high risk groups

APPENDIX IV
EXCLUDED STUDIES

Vitamin D review

Study	*Reason for exclusion*
Ushiroyama 2001	Intervention not in BNF: alfacalcidol
van Cleemput 1996	Other high risk groups: cardiac transplant patients
Vieth 2005	---: Review
Wissing 2005	Other high risk groups: renal transplantation
Yamada 1989	Intervention not in BNF: 25-hydroxycholecalciferol
Zhang 2005	Intervention not in BNF: 25-hydroxycholecalciferol

APPENDIX IV
EXCLUDED STUDIES

Calcium review

Study	*Reason for exclusion*
Frost 2007	Other high risk groups: on bone loss and fractures in congestive heart failure
Lovell 2006	Other high risk groups: BMD in patients with juvenile rheumatoid arthritis not treated with corticosteroids
Stellon 1985	Dose not in BNF

APPENDIX IV
EXCLUDED STUDIES

Cross review

Study	*Reason for exclusion*
Adami 1995	BMD only: alendronic acid vs calcitonin
Arapova 1999	Sample size too small: less than 10 patients; alfacalcidol vs mono fluorophosphate
Arlot 2005	BMD only: teriparatide vs alendronic acid
Bergstrom 2005	BMD only: HRT vs physical training
Bianda 2000	Other high risk groups: heart transplant recipients; calcitonin vs pamidronate
Body 2001	Dose not in BNF: not BNF dose for teriparatide; teriparatide vs alendronic acid
Deng 2004	BMD only: therapeutic effectiveness of bushen zhuanggu medicament and calcitonin
Diamond 1997	BMD only: calcitrol vs etidronate
Finkelstein 2003	BMD only: PTH vs alendronic acid
Fujita 2007	Dose not in BNF: Comparator not included in BNF; etidronate versus alfacalcidol
Garcia-Delgado 1997	BMD only: calcitonin vs etidronate vs calcidiol
Geusens 1986	Comparator not in BNF: Comparator not included in BNF; nandrolone vs alfacalcidol
Greenspan 2005a	BMD only: alendronic acid vs HRT
Greenspan 2005b	BMD only: alendronic acid vs HRT
Henderson 2001	BMD only
Henderson 2001	BMD only: calcium vs etidronate
Hwang 2006	BMD only: calcitonin vs teriparatide

APPENDIX IV
EXCLUDED STUDIES

Cross review

Study	*Reason for exclusion*
Ishida 2004	Dose not in BNF: HRT vs etidronate vs calcitonin vs alfacalcidol vs vitamin K
Iwamoto 2001	Dose not in BNF: etidronate vs vitamin K vs calcium
Khung 2006	BMD only: teriparatide vs calcitonin
Kung 1999	BMD only: Calcitriol vs HRT
Kung 2006	BMD only: PTH (teriparatide) vs Calcitonin
Lydeking-Olsen 2004	BMD only: progesterone vs soymilk
Rhee 2006	BMD only: alendronic acid plus vitamin D (calcitrol) vs vitamin D (calcitrol)
Rozhinskaya 1999	BMD only
Sambrook 1993	Dose not in BNF: calcitonin vs calcitriol
Ushiroyama 2001	Dose not in BNF: 10 IU twice per month; calcitonin vs vitamin D
Voss 2002	Not fracture or BMD data: not BMD or fracture outcome: raloxifene vs HRT

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Adachi 2001	Unclear.	Unclear.	Patient: yes, single blind. Outcome assessor: Yes; double-blind; radiographers blinded.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) 166/208 (80%) completed 2 years. ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Yes, but limited data; comparable on age, sex/menopausal status, duration of prior glucocorticoid use, daily baseline glucocorticoid dose, and underlying glucocorticoid-ill.
Black 1996	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes; investigator unaware of treat assign. Participants and clinicians not told BMD during follow up.	Power calculation: Yes. 99% to detect a 40% reduction in risk of vertebral fractures and a power of 90% to detect a 32% reduction , assuming a 6.5% annual incidence. Attrition: No (≤ 20% loss to follow up) Follow-up radiographs obtained from 1946 atients (981 AL and 965 Placebo) (96%).96 PLB and 78 ALN discontinued med owing to adverse exposure. ITT: Yes (all included in analysis, no details).	Radiographic 20-25% reduction height.	Yes; comparable on age, BMI, height, Femoral neck BMD, Vert fractures, Calcium intake and Smoking.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Black 2003	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Based on SD from results at 24 months in previous trial, with a power of 0.9 and significance level of 0.05, to detect a difference between any two treatment groups in area BMD of 4% at the spine and 2.5% at total hip. Attrition: No (≤ 20% loss to follow up) 15/238 (6%) did not complete 24 month follow up. ITT: No (available case analysis).	Not applicable.	Yes; comparable on age, height, age at menopause, race, bmi, clinical fractures since 45.
Black 2005	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Based on SD from results at 24 months in previous trial, with a power of 0.9 and significance level of 0.05, to detect a difference between any two treatment groups in area BMD of 4% at the spine and 2.5% at total hip. Attrition: No (≤ 20% loss to follow up) 15/238 (6%) did not complete 24 month follow up. ITT: No (available case analysis).	Not applicable.	Yes; comparable on age, height, age at menopause, race, bmi, clinical fractures since 45.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Black 2006 (FLEX)	Partial; permuted block design.	Unclear.	Patient: yes, single blind. Outcome assessor: Yes; study staff and investigators blinded except for a senior statistician.	Power calculation: No. Partial: no a priori calculation reported, although based on 20% incidence of fracture, the trial had 80% power to detect a risk reduction of 33% to 13.5%. Attrition: No (≤ 20% loss to follow up) 38/333 (11%) in 10 mg group, 30/329 (9%) in 5 mg group and 36/427 (8%) did not complete follow-up. ITT: Yes (all included in analysis, no details).	Radiographic 20-25% reduction height.	Yes; comparable on age, BMI, ethnicity, general health, exercise, falls, vertebral fracture, clinical fracture, smoking, duration of alendronate use, BMD.
Bone 1997	Unclear.	Unclear.	Patient: yes, single blind. Outcome assessor: Yes; double-blind.	Power calculation: Yes. A sample of 60 per group was expected to provide 80% power to detect a 1.8% between-group difference in the mean % change from baseline in lumbar BMD. Attrition: No (≤ 20% loss to follow up) 1/91 was missing in the placebo group, and 8/92 were missing in ALN group for BMD (the numbers available for fractures were not presented). ITT: Yes (all included in analysis, no details).	Radiographic 20-25% reduction height.	Yes; comparable on age, weight, height, years since menopause, lumbar spine BMD, Ca intake, family history of osteoporosis, ethnicity, prevalent vertebral.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Carfora 1998	Unclear.	Unclear.	Patient: not stated. Outcome assessor: Unclear.	Power calculation: No. Attrition: Unclear or Not stated . ITT: Yes (all included in analysis, no details).	Not stated.	Not stated.
Cummings 1998	Adequate; computer generated codes.	Adequate; Generators of alloc seq not to comm with anyone else.	Patient: double blind. Outcome assessor: Yes; medically labelled with nonrepeating allocation no. Collect and review of data were blinded to treat assign.	Power calculation: Yes. Assuming 4% annual incidence of clinical fractures in placebo group, trial required 4000 women for 25% decrease in risk with 90% power, a level .05.8 Recruited 4432: 3.5% annual incidenceof fracture: 88% power to detect 25% reduction in risk. Attrition: No (≤ 20% loss to follow up) Permanent discontinuation: No. (%) ALN: 221(9.9), Placebo: 227(10.2); Follow-up radiographs for 2057/2214 in ALN group, and 2077/2218 in placebo group.	Radiographic 20-25% reduction height.	Yes mainly; comparable on age, BMI, height, years since menopause, smoking, hist of fractures since 45 years.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Dursun 2001	Unclear.	Unclear.	Patient: not blinded. Outcome assessor: No; ALN; tablet and Calc, Calcitonin; intranasal and Calc, Calc in tablet form. Different treatments.	Power calculation: No. Attrition: Unclear or Not stated Not Clear; Data on vertebral fracture available for 38/51 in AL group, and 40/50 in the calcitonin group. ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Yes; comparable on age, weight, height, BMI, years since meno, age at menopause.
Greenspan 2002	Adequate; computer generated schedule.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Not stated. Attrition: Unclear or Not stated . ITT: Unclear/not stated.	Clinical.	Yes, but limited data; Characteristics were said to be similar across groups.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Greenspan 2003	Adequate; computer generated randomisation list.	Adequate; research pharmacy involved; retained code.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. 92 participants per group needed for 80% power to detect of 3% (or 90% power to detect 4%) difference in BMD between each group and placebo. Attrition: No (≤ 20% loss to follow up) Missing data: ALN 8/93 (9%): placebo 8/93 (9%). ITT: Yes (all included in analysis, no details).	Not applicable.	Yes; comparable on age, weight, height, BMI, dietary Calcium and vitamin D, drugs, BMD.
Liberman 1995	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes; reported as double-blind.	Power calculation: No. Attrition: No (≤ 20% loss to follow up) 113/994 not included in fractures analysis, 909/994 included in year 1 evaluation. 16.3% (162) discontinued therapy. ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Yes, but limited data; comparable on age (year), years since menopause, BMI, vert fract, vert deformities, Mean BMD (g/cm2).

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Lindsay 1999	Unclear.	Unclear; blinded allocation number.	Patient: not stated. Outcome assessor: Unclear; but placebo used.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) 11/214 (ALN+HRT) and 23/214 (HRT) did not complete trial. ITT: Yes (all included in analysis, no details).	Not stated.	Some comparable; comparable on age, BMI, ethnicity, years since menopause, duration of HRT; not comparable for: family history and smoking (sig. more in ALN group).
Miller 2004	Adequate; computer-generated.	Partial; blinded allocation schedule (no other information reported).	Patient: yes, single blind. Outcome assessor: Yes; study was double-blinded.	Power calculation: Yes. 80 participants in treatment group and 40 in placebo group were estimated to detect a 3% change in spine BMD, with a power of 97% at a 5% significance level. Attrition: No (>20% loss to follow up; greater in 1 group) 85.6% completed the study (21% in placebo group and 11% in treatment group). ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Yes; comparable on age, weight, height, BMI.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Alendronic acid review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Orwoll 2000	Unclear.	Unclear.	Patient: yes, single blind. Outcome assessor: Yes; x-rays were assessed at a central site by personnel unaware of treatment assignment.	Power calculation: Not stated. Attrition: No (>20% loss to follow up; same each group) 86% completed study in treatment group and 83% in placebo group. ITT: Unclear/not stated.	Semi-quantitative.	Yes; comparable on age, race, serum free testosterone, smoking history, consumption of alcohol, BMI, BMD, vertebral fractures, biochemical markers.
Pols 1999	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes; matching image placebo tablets used.	Power calculation: Yes. 99% or more power to detect a 3.5% diff between ALN and PLB in mean % change from baseline in BMD of lumbar spine, assuming SD of 4.5%. Attrition: No (≤ 20% loss to follow up) 1697 (89%) completed study: 832 (88%) in the ALN groups and 865 (90%) in the PLB Group. ITT: No (available case analysis).	Not stated.	Yes; comparable on age in years, years post meno, weight, height, BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Adachi 1997	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) 10/67 (15%) etidronate; 9/74 (12%) placebo. ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Yes, but limited data; comparable on age, gender.
Campbell 2004	Partial; permuted blocks.	Unclear.	Patient: not stated. Outcome assessor: Yes.	Power calculation: Yes. Powered for new clinical fracturess (vertebral and non vertebral), at 5% level and 80% power would require 750 patients; only 349 recruited. Attrition: No (>20% loss to follow up; greater in 1 group) Deaths and loss to follow up: Et+Ca 29/88 (33%) no treatment 27/95 (28%). ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Yes; comparable on age, weight, gender, physical activity, fractures and BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Cortet 1999	Unclear.	Unclear.	Patient: not stated. Outcome assessor: Unclear.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) 1/44 (2%) etidronate and 3/39 (8%) placebo did not complete study. ITT: Unclear/not stated.	Radiographic no details.	Yes.
Geusens 1998	Unclear; randomly assigned in blocks of two within each centre.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (>20% loss to follow up overall) 5/18 (28%) etidronate; 6/19 (32%) patients withdrawn. ITT: Yes (all included in analysis, no details).	Radiographic no details.	Yes; comparable on age, weight, height, years since menopause, mean prednisolone dose, duration of corticosteroid treatment, bone density of spine and hip.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Herd 1997	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) 11/75 (15%) etidronate and 6/77 (8%) placebo withdrew; ie differential withdrawal. ITT: Yes (all followed).	Radiographic no details.	Yes; comparable on age, weight, height, years since menopause.
Jenkins 1999	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Not stated. Attrition: No (>20% loss to follow up; greater in 1 group) radiographs not available for 9/15 (60%) etidronate and 6/13 (46%) placebo. ITT: No (available case analysis).	Radiographic no details.	Yes mainly; comparable on age, weight, steroid use; Sig greater height and lumbar spine in placebo group which contained a greater proportion of men.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Meunier 1997	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) 2/27(7%) etidronate and 3/27 (11%) placebo withdrew. ITT: Yes (all included in analysis, no details).	Not stated.	Yes; comparable on age, weight,height, years since menopause.
Montessori 1997	Adequate; by computer in blocks of 4.	Unclear; no further details of allocation concealment given.	Patient: not blinded. Outcome assessor: Yes; to assessors of spinal X rays; open trial.	Power calculation: No. Attrition: No (≤ 20% loss to follow up) Missing data in each group. 3/40 (8%) etidronate and 5/40 (13%) calcium had missing data at 2 years, 64/80 (80%) completed third extension year. ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Yes; No differences in age ,height ,weight, time since menopause, BMD at baseline and prevalent vertebral fractures.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Pouilles 1997	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) 9/54 (17%) : 9/55 (16%) patients withdrew. ITT: Yes (all included in analysis, no details).	Not stated.	Yes mainly; comparable on age, weight,height, years since menopause; slight difference in mean lumbar spine BMD (etidronate lower).
Roux 1998	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Powered for % change in lumbar spine BMD, 90% power to detect a diff, req 42 pts, if 20% dropout 53 pts recruited in each arm. Attrition: No (≤ 20% loss to follow up) 7/58 (12%) etidronate and 3/58 (5%) placebo withdrew; ie differential loss to follow up. ITT: Unclear/not stated.	Radiographic no details.	Yes; comparable on age, weight, height, years since menopause.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Etidronate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Watts 1990	Adequate; computer generated.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) 13/105 (12%) etidronate and 15/104 (14%) placebo dropped out. Radiographs (vert fracture) not available for 7/105 etidronate and 13/104 placebo. ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Yes; comparable on age, weight, height, time since menopause, dietary calcium intake, BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Cohen 1999	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear; part blinding (confirmed by blinded radiologist).	Power calculation: Not stated. Attrition: No (>20% loss to follow up; greater in 1 group) 13/76 (17%) RSD and 19/77 (25%) place. ITT: Yes (all included in analysis, no details).	Radiographic 15% reduction height.	Yes mainly; comparable for gender, prior fractures, T-score, underlying conditions. Not comparable for age (RSD group older by 4.7 years (mean)).
Fogelman 2000	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. 180 patients per group to detect a 6% difference between placebo and risedronate in change in BMD at 24 months. Attrition: No (>20% loss to follow up; same each group) 40/179 (22%) dropped out from risedronate 5 mg group, and 37/180 (21%) from the placebo group. ITT: Yes (all followed).	Radiographic no details.	Yes; comparable on age, weight, height, smoking, lumbar spine T score.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Harris 1999	Adequate; randomisation generated by Quintiles Inc using SAS.	Partial; randomisation schedule generated by quintiles Inc.	Patient: double blind. Outcome assessor: Yes; investigators and other staff remained blind to treatment assignments.	Power calculation: Yes. Calculated to have a 90% power to detect a 40% reduction in vertebral fracture risk, with a 2 sided significance level of p = 0.5. Attrition: No (>20% loss to follow up; same each group) Risedronate drop out rate 324/821 (39%); placebo drop out rate 365/820 (44%). ITT: Yes (all followed).	Radiographic 15% reduction height.	Yes; comparable on age, weight, height, years since menopause, smoking history; lumbar spine T score.
Hooper 2005	Adequate; computer generated randomisation schedule.	Unclear.	Patient: not stated. Outcome assessor: Unclear.	Power calculation: Yes. Sample of 96 per group to provide a 90% power to detect a between group difference of 3% in mean % change in lumbar BMD at 24 months, assuming a 2 sided 5% significance. Attrition: No (>20% loss to follow up; greater in 1 group) risedronate drop outs = 26 (20%); placebo drop outs = 33 (26%). ITT: Unclear/not stated.	Radiographic 15% reduction height.	Yes; comparable on age, years since menopause, BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
McClung 2001	Unclear.	Partial.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Not stated. Not stated. Attrition: No (>20% loss to follow up; same each group) Risedronate 2197/6197 (35%) dropped out, and 1127/3134 (36%) dropped out of placebo. ITT: No (available case analysis).	Radiographic no details.	Yes mainly; comparable on age, weight, height, years since menopause, Tscore women aged between 70-79 years.
Mortensen 1998	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Not stated. Not stated. Attrition: Yes 5 dropped out of risedronate and 4 dropped out of placebo by 1 year, then remainder given choice to continue for either an extra 12 or 24 months. ITT: Yes (all followed).	Radiographic no details.	Yes, but limited data; comparable on age, BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Risedronate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Reginster 2000	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear; patient and clinic personnel maintained blinding throughout the study, no further details.	Power calculation: Yes. Sample based on an expected annual 17% vertebral fracture incidence in the placebo group; assuming a 50% drop out over 3 years the study had a 90% power to detect a 40% reduction in fracture risk. Attrition: Yes 156 dropped out of risedronate and 186 dropped out of placebo at 3 years. ITT: Yes (all followed).	Radiographic 15% reduction height.	Yes; comparable on age, height, BMD, time since menopause.
Reid 2000	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Study had at least 90% power to detect a between group difference of =/>3% in % change from lumbar baseline BMD at 12 months with a 2 sided 0.05 significance level. Attrition: No (>20% loss to follow up overall) No further details. ITT: Yes (fracture incidence carried forward).	Radiographic 15% reduction height.	Yes; comparable on age, ratios of male to female and pre-and-postmenopausal and corticosteroid use, and lumbar spine T score.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Ibandronic Acid review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Chesnut 2004	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes; qualitative confirmation by independent central reading facility.	Power calculation: Yes. Based on a clinically relevant difference of 40% in the incidence of new vertebral fractures, >2040 patients required to achieve a power of at least 80%. Attrition: No (>20% loss to follow up; same each group) 334/982 (34%) Ibandronate and 354/982 (36%) did not complete treatment; analysed population (99%) consisted of patients who received at least one dose of study medication and who attended at least one follow-up visit.	Radiographic 20-25% reduction height.	Yes; comparable on age, weight, height, BMI, years since menopause, mean LS BMD and prevalent vertebral fractures.
Eisman 2008	Unclear.	Adequate; centralised call-in system.	Patient: double blind. Outcome assessor: Unclear; double-blind, although some unblinding when placebo groups were combined for the analysis.	Power calculation: Yes. Using a margin of clinical equivalence of >1%, and an assumed SD of 4.5%, a one-sided 2.5% significance level noninferiority test, and a power of 80%, a sample size of 318 per group was estimated. Attrition: No (>20% loss to follow up; greater in 1 group) 99/471 (21%) 3 mg group and 86/470 (17%) in 2.5 mg daily group did not complete 2 years of study; analysis included all but 1%. ITT: No (per protocol analysis).	Clinical.	Yes; comparable on age, weight, height, BMI, years since menopause, Lumbar spine BMD T-score, hip BMD T-score, prevalent fracture, biochemical indices.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Ibandronic Acid review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Reginster 2006	Adequate; minimisation method.	Adequate; centralised call-in system.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Using a margin of clinical equivalence of >1%, and an assumed SD of 4.5%, a one-sided 2.5% significance level noninferiority test, and a power of 80%, a sample size of 318 per group was estimated. Attrition: No (≤ 20% loss to follow up) 79/401 (20%) did not complete 2 years treatment in 150 mg group; 77/402 [19%) in 2.5 mg daily group; analysis included all participants who received at least one dose of study drug, and had at least one follow-up (1-2% missing data).	Clinical.	Yes; comparable on age, weight, height, BMI, years since menopause, history of previous fracture, lumbar spine BMD and biochemical indices.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Zoledronic acid review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Black 2007	Partial; random permuted blocks.	Unclear.	Patient: double blind. Outcome assessor: Yes; investigators stated to be unaware of assignments.	Power calculation: Yes. 90% power (with a two sided alpha of 0.05) to detect a 50% reduction in morphometric vertebral fractures in the zoledronic acid group assuming an annual incidence of 1.9% in the placebo group, with 2252 in stratum 1. Attrition: No (≤ 20% loss to follow up) 627/3889 (16%) did not complete follow up in zoledronic group and 592/3876 (15%) in placebo group. ITT: No (per protocol analysis).	Radiographic 20-25% reduction height.	Yes; comparable on T scores at femoral neck, age, bone mineral density, BMI, previous hormone therapy, bisphosphonates, calcitonin, SERMs.
Lyles 2007	Adequate; interactive voice-response system created randomised permuted blocks.	Adequate.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. event driven and required 211 clinical fractures to have power of 90% to detect 35% reduction in rate of fracture Attrition: No (>20% loss to follow up; same each group) 295/1065 (28%) zoledronic acid and 316/1062 (30%) did not complete follow up. Trial stopped when 185 had fracture.. ITT: Yes (all included in analysis, no details).	Radiographic 20-25% reduction height.	Yes; comparable on age, gender, ethnicity, BMI, BMD, pts receiving concomitant treatment (p=0.07).

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Cross biphosphonates review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Miller 2008 (MOTION)	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Non-inferiority calculations on the basis of change from baseline of mean BMD. Attrition: No (>20% loss to follow up; same each group) Study not completed by 21.7% alendronic acid and 22.6% ibandronic acid. ITT: No (available case analysis).	Clinical.	Yes; comparable on age, weight, height, years since menopause, previous fracture, lumbar spine BMD.
Muscoso 2004	Unclear.	Unclear.	Patient: not blinded. Outcome assessor: Unclear; stated to be an open study.	Power calculation: No. Attrition: Unclear or Not stated . ITT: Unclear/not stated.	Clinical.	Yes, but limited data; comparable on age.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Cross biphosphonates review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Reid 2006b (FACTS)	Adequate; computer generated.	Partial; sequentially numbered containers; schedule generated by statistician.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Powered at 90% at 0.05 level to detect a difference of 1.2% in percentage change from baseline; estimated at least 732 patients needed. Attrition: No (≤ 20% loss to follow up) 8.1% alendronic acid and 9.4% risedronate did not complete the study. ITT: No (per protocol analysis).	Clinical.	Yes; comparable on age, weight, height, years since menopause, BMI.
Rosen 2005 (FACT)	Adequate; computer-generated.	Unclear.	Patient: double blind. Outcome assessor: Yes; outcome assessors (BMD) blinded to treatment assignment.	Power calculation: Yes. Sample size of 366 patients / group needed to detect a difference in the change from baseline in hip trochanter BMD of 1.2% points. Attrition: No (≤ 20% loss to follow up) discontinued study: 15.8% alendronic acid and 14.8% risedronate. Safety analysis included all who had at least 1 dose medication. ITT: No (per protocol analysis).	Clinical.	Yes; comparable on age, years since menopause, BMI, Tscore, age at menopause.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Bisphosphonate

Cross biphosphonates review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Sarioglu 2006	Unclear.	Unclear.	Patient: single blind. Outcome assessor: Unclear.	Power calculation: Not stated. Attrition: Unclear or Not stated States: some patients did not complete the 12month treatment period. ITT: Unclear/not stated.	Radiographic no details.	Yes; comparable on age, BMI, years since menopause, daily calcium intake; BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Strontium ranelate

Strontium ranelate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Adami 2006 (TROPOS)	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear; not reported.	Power calculation: No. No, because the original power calculation was rendered obsolete due to change in statistical methods. Attrition: No (>20% loss to follow up; same each group) By three years SR had 867 drop outs (34%) and placebo had 904 drop outs (35%); but time-to-event data analyses. ITT: Yes (all followed).	Radiographic 20-25% reduction height.	Yes; comparable on age, time since menopause, prevalent fractures, BMD T scores.
Meunier 2002 (STRATOS)	Partial; randomised by block; consecutive therapeutic unit numbers were allocated to patients in	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Planned to include 65 patients per group, to ensure 90% power to detect lumbar BMD slope of 4% with an SD of 6% between placebo and SR; this presupposed a treatment withdrawal rate of 20% in the first year. Attrition: Yes 77.1% completed study. ITT: Yes (all followed).	Radiographic 20-25% reduction height.	Yes; comparable on age, BMI, years since menopause, number of vertebral fractures, Lumbar T scores.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Strontium ranelate

Strontium ranelate review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Meunier 2004 (SOTI)	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes; radiologists were unaware of the treatment assignment.	Power calculation: No. Did not have sufficient power for adequate statistical comparison of the two groups. Attrition: Yes SR had 200 (24%) drop outs and placebo had 189 (32%) drop outs by 3 years; but time-to-event analyses. ITT: Yes (all followed).	Radiographic 20-25% reduction height.	Yes; comparable on age, cigarette smoking, years since menopause, previous vertebral fractures, BMI.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Parathyroid hormone

Teriparatide review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Cosman 2001	Adequate; randomly by computer program.	Partial; assignment was done by one of authors who did not have contact with patients.	Patient: not blinded. Outcome assessor: Yes; assessors of BMD, X-ray and biochemistry and radiographs were blinded; not possible to blind patients (no placebo).	Power calculation: Not stated. Attrition: No (>20% loss to follow up; greater in 1 group) missing data: PTH+HRT 6/27 (22%); in HRT alone: 0/25. ITT: Unclear/not stated.	Radiographic 20-25% reduction height.	Some comparable; comparable on weight, height, time since menopause; oestrogen therapy duration, calcium intake, prevalent VF (BMD spine and hip), bone mass at all sites; Not comparable for age (PTH group younger).
Cosman 2005	Adequate; computer generated.	Unclear.	Patient: not blinded. Outcome assessor: Yes; radiographs reviewed with group assignment and patient identifiers removed; no placebo: not possible to blind patients.	Power calculation: Yes. 108/126 completed 15 months FUP; 90% to detect absolute difference or 3% in spinal BMD increment between the 2 PTH groups given enrolment of 33 women in each group; greater power to identify differences between either PTH group and alendronate. Attrition: No (≤ 20% loss to follow up) Missing data; daily PTH 5/43 (11%); Cyclic PTH+alendronate 6/40 (15%); Alendronate 7/43 (16%). ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Some comparable; comparable on age, height. Not comparable for no. of prior non-spinal clinical fractures (2x higher for both PTH groups).

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Parathyroid hormone

Teriparatide review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Kurland 2000	Adequate; computer-generated randomly permuted blocks of 4.	Unclear.	Patient: double blind. Outcome assessor: Yes; radiologist blinded to treatment assignment.	Power calculation: Yes. In order to have 80% power at a 5% significance level to detect 20-25% reduction in vertebral height, 50 participants in each group would be required. Attrition: No (≤ 20% loss to follow up) 1/10 teriparatide group withdrew but included in ITT analysis; only 18 sets of radiographs could be properly evaluated; vertebral fracture data based on this 78% (18/23). ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Some comparable; comparable on age, weight, height, BMI, cigarette use, physical activity, use and duration of prior osteoporosis medication, fracture history. Not comparable for calcium intake (PTH 1400mg/day vs
Lane 1998	Adequate; randomly by computer generated table.	Unclear.	Patient: not blinded. Outcome assessor: Unclear; not possible to blind patients: placebo injections not used.	Power calculation: Not stated. Not stated. Attrition: No (>20% loss to follow up; greater in 1 group) Missing data: PTH 7% (2/28); oestrogen 22% (5/23). ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Yes; comparable on age, weight, height, years since menopause, duration of oestrogen therapy and corticosteroids, BMI, no. VF; no significant differences in BMD of total hip, femoral neck, trochanter, 1/3 distal radius at 6-12 mo.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Parathyroid hormone

Teriparatide review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Neer 2001 (FPT)	Unclear.	Unclear.	Patient: not stated. Outcome assessor: Yes; radiologist blinded to treatment; patient blinding assumed because placebo.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) Missing data: placebo: 96/544 (18%); 20mcg PTH 97/541 (18%). ITT: Yes (all included in analysis, no details).	Radiographic 20-25% reduction height.	Yes; age, prev fractures, BMI, BMD, current smoking, years since menopause.
Orwoll 2003	Adequate; random number table stratified based on initial morning testosterone measurement (normal vs low	Partial; centralised randomisation.	Patient: double blind. Outcome assessor: Yes; Investigators and patients were blinded to treatment assignment.	Power calculation: Not stated. Not stated. Attrition: No (>20% loss to follow up; greater in 1 group) Missing data: 28% in TPTD vs 17% placebo. ITT: Yes (fracture incidence carried forward).	Not stated.	Yes; comparable on age, ethnicity, BMI, Ca intake, smoking and alcohol status, previous osteo therapy, % with low serum free testosterone, vertebral BMD, T-scores.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Parathyroid hormone

Parathyroid hormone (1-84) review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Black 2003	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Based on SD from results at 24 months in previous trial, with a power of 0.9 and significance level of 0.05, to detect a difference between any two treatment groups in area BMD of 4% at the spine and 2.5% at total hip. Attrition: No (≤ 20% loss to follow up) 15/238 (6%) did not complete 24 month follow up. ITT: No (available case analysis).	Not applicable.	Yes; comparable on age, height, age at menopause, race, bmi, clinical fractures since 45.
Greenspan 2007 (TOP)	Adequate; computer-generated.	Adequate; women at each site were assigned treatments by telephone.	Patient: double blind. Outcome assessor: Yes; radiologists blinded and double blind for patients.	Power calculation: Yes. Sample size 1300 per group needed to detect 60% or greater reduction in fracture incidence at 90% power. Attrition: No (>20% loss to follow up; same each group) Missing data: PTH 462/1286 (35%); Placebo 369/1246 (30%). ITT: Imputed (authors assumed no fracture).	Semi-quantitative.	Yes mainly; comparable on age, ethnicity, years since menopause, BMI, prevalent vertebral fractures, BMD; previous osteoporosis treatment.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Calcitonin

Calcitonin review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Chesnut 2000	Adequate; computer-generated randomisation list.	Partial; nasal containers looked identical and had similar labels.	Patient: yes, single blind. Outcome assessor: Yes; double-blind.	Power calculation: Not stated. Attrition: Yes 783/1,255 (62%) completed 3 years of treatment, and 511 (41%) completed 5 years; radiographs obtained for 1,108 patients. ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Yes; comparable on age, years since menopause, BMI, number of prevalent fractures, lumbar spine BMD, Ca intake, history of smoking, and biochemical markers.
Luengo 1994	Unclear.	Unclear.	Patient: not blinded. Outcome assessor: Yes; radiologist blinded.	Power calculation: Not stated. Attrition: No (>20% loss to follow up; greater in 1 group) 5/22 (23%) dropouts in each group. ITT: Unclear/not stated.	Radiographic 20-25% reduction height.	Yes, but limited data; comparable on age, gender, glucocorticoid dose and duration.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Calcitonin

Calcitonin review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Overgaard 1992	Partial; random sampling numbers in blocks of four.	Unclear.	Patient: yes, single blind. Outcome assessor: Yes; radiographs blindly assessed - double-blind.	Power calculation: Yes. 52 patients were needed in each group to detect a difference of 2% between the groups, assuming a precision of 3% of the bone mineral content of the lumbar spine. Attrition: Yes 45/52 (87%) in 200 IU group completed the study; 44/52 (85%) in placebo group; 41/52 (79%) in 50 IU group; 46/52 (88%) in 100 IU completed the study. ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Yes; comparable on age, weight, height, years since menopause, bone mineral content of distal forearm, and lumbar spine, % vertebral fractures.
Toth 2005	Unclear.	Unclear.	Patient: not blinded. Outcome assessor: No.	Power calculation: Yes. Based on a SD of 3% for changes in spine BMD, 80% power to detect a significant difference of at least 2% between the groups with the recruited sample. Attrition: No (≤ 20% loss to follow up) No missing data in each group. ITT: Yes (all included in analysis, no details).	Radiographic 20-25% reduction height.	Yes, but limited data; comparable on age, weight, height, serum indices, alcohol consumption and smoking (although data not shown for these latter variables).

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Anderson 2004	Adequate; computerised.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. 12,375 women required for power of 81% to detect reduction of 21%in CHD rates over 9 year and this sample size would give 65% power to detect 20% reduction in hip fractures rates. Actual sample size had 55% power for hip fractures. Attrition: No (≤ 20% loss to follow up) 94.8% followed up; 95% on HRT + 94% on placebo. ITT: Yes (all included in analysis, no details).	Not stated.	Yes; comparable on age, ethnicity, prior hormone use, BMI, BP, smoking, parity, DM, high cholesterol, statin/aspirin use, MI, angina, stroke, DVT, PE, prior fractures.
Bone 2000	Adequate; computer generated.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (>20% loss to follow up; greater in 1 group) Missing data in each group: 21% combined; 24% HRT; 26% alendronate; 32% placebo. ITT: Yes (all included in analysis, no details).	Not applicable.	Yes; comparable on age, ethnicity, Ca intake, years since menopause, BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Bush 1996 [Mebane 1996]	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) Missing data in each group: 28/696 (4%) on HRT; 11/174 (6%) on placebo for BMD outcome. ITT: Unclear/not stated.	Not stated.	Yes; comparable on age, race, smoking, alcohol, Ca intake, physical activity, BMI, BMD, HRT.
Herrington 2000	Partial; permuted block randomisation.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. 80% power to detect a difference of 0.054mm in degree of change in minimal luminal diameter between active treatment and placebo groups. Attrition: No (≤ 20% loss to follow up) Missing data in each group: 17/309 died. ITT: Unclear/not stated.	Not applicable.	Yes; comparable on age, race, coronary disease, DM, HT, smoking, BMI, physical activity, years since menopause, medication.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Lufkin 1992	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) 11% overall: 2/36 (6%) on oestrogen + 5/39 (13%) on placebo. ITT: No (available case analysis).	Radiographic 15% reduction height.	Yes; comparable on age, weight,height, years since menopause, pregnancies, hysterectomy, prior HRT, smoking, alcohol, caffeinated drinks, prior frac, BMD.
Mosekilde 2000	Unclear.	Unclear; envelope method.	Patient: not blinded. Outcome assessor: Yes; blinded observer assessed fractures.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) Overall loss 11%; equal in 2 groups. ITT: Yes (all included in analysis, no details).	Radiographic 20-25% reduction height.	Yes; comparable on age, weight,height, BMI, prior frac, maternal fractures history, Ca/vit D intake, years since menopause, smoking, hysterectomy, activity, BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Pacifici 1988	Unclear.	Unclear.	Patient: not stated. Outcome assessor: Unclear.	Power calculation: Not stated. Attrition: No (>20% loss to follow up overall) 78/128 (61%) missing data overall. ITT: No (available case analysis).	Radiographic 15% reduction height.	Yes; only given for subset completing fracturest year.
Ravn 1999	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear; said to be randomised in a double blinded way, even though open label HRT.	Power calculation: Not stated. Attrition: Yes No missing data reported. ITT: Yes (all followed).	Not stated.	Yes; comparable on age, BMI, years since menopause, BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Hormone Replacement Therapy

Hormone Replacement Therapy review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Weiss 1999	Adequate; computer generated.	Partial; central randomisation, no details.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. Sample size of 176 patients based on detecting a difference of 4% in the change in BMD, corresponding to alpha 0.0022 and power of 60%. Attrition: No (>20% loss to follow up overall) 78/175 (45%) missing data overall. ITT: Yes (fracture incidence carried forward).	Not applicable.	Yes, but limited data; comparable on age, weight and ethnicity.
Wimalawansa 1998	Adequate; computer generated.	Unclear.	Patient: not blinded. Outcome assessor: Yes; not possible to blind patients.	Power calculation: Not stated. Attrition: No (>20% loss to follow up; greater in 1 group) Missing data in each group: 3/18 (17%) HRT; 3/17 (18%) etidronate group; 4/19 (21%) HRT+etidronate group; 4/18 (22%) placebo. ITT: Unclear/not stated.	Radiographic 15% reduction height.	Yes; comparable on age, BMI, years since menopause, Ca intake, BMD, prior fracture.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Selective Estrogen Receptor Modulators

Raloxifene review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Ettinger 1999	Partial; randomisation performed by Eli Lilly clinical trials group who was not involved in patient monitoring.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Sample size provided a >90% power to detect a 40% reduction in vertebral fractures between pooled raloxifene doses and placebo. Attrition: No (≤ 20% loss to follow up) Withdrawals raloxifene 1152, placebo 652. ITT: Yes (fracture incidence carried forward).	Radiographic 20-25% reduction height.	Yes; comparable on age, BMI, smoking, BMD, previous oestrogen therapy.
Lufkin 1998	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Not stated. Not stated. Attrition: No (≤ 20% loss to follow up) 13 pts did not complete the study, no further details. ITT: Yes (fracture incidence carried forward).	Radiographic 15% reduction height.	Yes; comparable on age, years since menopause and Body Mass Index.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Selective Estrogen Receptor Modulators

Raloxifene review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Michalska 2006	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear; stated double blind, except for alendronate group who were open label.	Power calculation: Yes. Assuming a SD of 3.5, 33 patients in each group would be needed to detect a 2.4% difference in lumbar spine BMD between two groups with 80% power. Attrition: Yes One person in Raloxifene refused therapy after randomisation and was lost to follow up; two in alendronate group dropped out due to adverse events during the 12 months open label extension phase. ITT: Yes (all followed).	Not stated.	Yes; comparable on age, weight, years since menopause, BMD.
Reginster 2003	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear; stated as double blind.	Power calculation: Yes. 192 participants in each group provides ~ 90% power to detect % change in BMD of 1.5% after 18 months. Attrition: Yes Raloxifene group attrition N=89; Control group attrition N=76. ITT: No (available case analysis).	Radiographic no details.	Yes; comparable on age, weight, height, BMI, BMD at femoral neck.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Sex hormone therapies

Nandrolone review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Frisoli 2005	Unclear.	Adequate; randomised independently by the medical board of Organon/AKZO-Nobel; also principal investigator.	Patient: double blind. Outcome assessor: Yes; patients, principal investigator and assessors stated to be blinded.	Power calculation: Yes. Calculated on BMD outcome for a 7.5% increase of mean BMD of femoral neck in the intervention group by 2 years. Estimated sample needed was 25 in placebo and 25 in ND group. Attrition: No (>20% loss to follow up; greater in 1 group) in the ND group 4 dropped out (12.5%) and placebo had 12 (36%). ITT: Unclear/not stated.	Radiographic 20-25% reduction height.	Some comparable; comparable on, weight height, BMI, blood counts, BMD; not comparable on age (placebo group older).
Geusens 1986	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear; triple dummy interventions.	Power calculation: Not stated. Not applicable. Attrition: No (>20% loss to follow up; same each group) 34/60 (57%) dropouts, stated to be equal across groups. ITT: No (available case analysis).	Radiographic 20-25% reduction height.	Not stated; No baseline data reported, only for completers; but completers not comparable for age (nandrolone older).

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Sex hormone therapies

Nandrolone review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Passeri 1993	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Not stated. Attrition: No (>20% loss to follow up; same each group) ND= 12 (48%) dropped out, and placebo 9 dropped out (43%). ITT: No (available case analysis).	Radiographic no details.	Not stated; patient characteristics stated only for completers.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Vitamin D

Vitamin D review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Adachi 1996	Adequate; minimisation.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (>20% loss to follow up; same each group) Missing data in each group: 20/31 on placebo (64%) and 19/31 on treatment (61%). ITT: No (per protocol analysis).	Radiographic 15% reduction height.	Yes; comparable on age, gender, prednisone dose, BMD, disease.
Avenell 2004	Adequate; computer-generated.	Adequate.	Patient: not blinded. Outcome assessor: Yes.	Power calculation: Yes. 4200 pts to have 80% power (2p<0.05) to detect a decrease in incidence of fractures from 15% in controls to 12%. Attrition: No (≤ 20% loss to follow up) Loss to follow up: vit D + Ca 3/35 (9%); vit D 15/35 (43%); Ca 4/29 (14%); no tablets 6/35 (17%); ie differential loss to follow up. ITT: Yes (fracture incidence carried forward).	Clinical.	Yes; comparable on age, sex, race, type of fracture, time since fracture, weight, smoking, physical activity, thyearoxine, steroids, thiazide diuretics.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Vitamin D

Vitamin D review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Chapuy 1992	Unclear; randomly assigned in groups of 4.	Unclear.	Patient: yes, single blind. Outcome assessor: Unclear.	Power calculation: Yes. Reduction of 30% of annual hip fracture rate (estimated at 3.5%) could be detected but no figures given for sample size needed. Attrition: No (>20% loss to follow up; same each group) Missing data in each group: deaths: 16% vit D; 17% placebo; loss to F-U: 3% vit D; 4% placebo; total non-completers: 757/1624 (46%) vit D/Ca; 748/1636 (46%) Pl. Analysis excluded only death and loss to F-U. ITT: No (per protocol analysis).	Not applicable.	Yes; eg comparable on age, weight, height, dietary calcium, fallers.
Chapuy 2002	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (>20% loss to follow up; greater in 1 group) All missing data: vit D + Ca 27.2-29.1% placebo 36.1%. Most attrition due to death; 17% and 22%). ITT: No (per protocol analysis).	Radiographic no details.	Yes; comparable on age, weight, height, Ca and vit D intake, serum Ca and vit D, BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Vitamin D

Vitamin D review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Dawson-Hughes 1997	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) Missing data: overall 78/389 (20%). ITT: No (per protocol analysis).	Not applicable.	Yes mainly; comparable on age, weight, height, smoking, physical activity, BMD. Not comparable for dietary Ca in women (placebo group higher).
Ebeling 2001	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. 88% power to detect a difference of 3% in spinal BMD between groups at 2 years. Not power calculated for fractures. Attrition: No (≤ 20% loss to follow up) 15% of total participants did not complete the study. ITT: Yes (fracture incidence carried forward).	Radiographic 20-25% reduction height.	Yes; comparable on age, femoral neck BMD, number of fractures, calcium intake.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Vitamin D

Vitamin D review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Falch 1987	Unclear.	Unclear.	Patient: not stated. Outcome assessor: Yes; patient unlikely to be blinded because different frequency of dose.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) Missing data 17% on calcitrol and 5% on colecalciferol (ie, different between groups). ITT: No (available case analysis).	Radiographic 15% reduction height.	Yes; comparable on age, weight, height, years since menopause, BMC, previous fracture.
Gallagher 1989	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) Missing data: 4/38 (11%) calcitrol; 5/33 (15%) placebo. ITT: No (available case analysis).	Radiographic 15% reduction height.	Yes, but limited data; comparable on age, number of prior vertebral fractures.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Vitamin D

Vitamin D review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Gallagher 2001	Unclear.	Adequate; independent group performed the randomisation.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. Designed to have 90% power to detect 3year change in BMD of a 1% increase on HRT+calcitrol, no change on HRT alone or calcitrol alone, 1.5% decrease on placebo with $p<0.05$. Attrition: No (≤ 20% loss to follow up) Missing data in each group: 11/123 (9%) placebo; 22/123 (18%) calcitrol; 20/121 (17%) HRT; 20/122 (16%) HRT+calcitrol. ITT: Unclear/not stated.	Radiographic 20-25% reduction height.	Yes mainly; comparable on age, weight, height, Ca intake, BMD, T score. Not comparable for number with prior fractures (more in calcitrol group than placebo).
Harwood 2004	Adequate; computer generated random numbers.	Partial; sealed opaque envelopes.	Patient: not blinded. Outcome assessor: No; researcher not blinded to treatment allocation. Placebos not used.	Power calculation: Not stated. Attrition: No (>20% loss to follow up overall) Missing data: overall 50/150 (33%) of whom 23% died (14-31% between groups) and the rest withdrew from follow up (but not very clear). ITT: No (available case analysis).	Clinical.	Yes mainly; comparable on age, smoking, dietary Ca, alcohol, mobility, biochemistry, BMD; not comparable for number with no prior fracture (control 76%, interv 50%); vit D alone group had higher % with hypovitaminosis.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Vitamin D

Vitamin D review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Jackson 2006	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. 85% power to detect 18% reduction in hip fracture in 35,000 women at placebo rate of 33.6 per 10,000 person/year (=99% power for total fracture). Attrition: No (≤ 20% loss to follow up) 4.3% died; 2.7% withdrawn or lost to follow up; same each group. Unclear numbers analysed but seemed to be those alive and with outcomes data in last 18mo. ITT: No (per protocol analysis).	Radiographic no details.	Yes; comparable on age, race, family and personal history of fracture, falls, BMI, physical activity, calcium intake, vitamin D, sunlight, alcohol, smoke, HRT.
Komulainen 1998	Adequate; computer generated.	Partial; personnel involved were unaware of group allocation before randomisation.	Patient: not blinded. Outcome assessor: Yes; after randomisation study was open for all treatment groups.	Power calculation: Not stated. Powered for BMD not fracture outcomes but details not given. Attrition: No (≤ 20% loss to follow up) Missing data: calcium 3/116 (3%); vitamin D + Ca 3/116 (3%). ITT: Yes (fracture incidence carried forward).	Not applicable.	Yes; comparable on age, BMI, years since menopause, prior fracture, smoking, alcohol, physical activity, Ca intake, BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Vitamin D

Vitamin D review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Larsen 2004	Unclear.	Unclear.	Patient: not blinded. Outcome assessor: Yes; patients not blinded because of differences in interventions.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) Missing data in each group only 6 left the area during follow up out of 9605. ITT: Yes (all followed).	Clinical.	Yes; comparable on age, gender, marital status, prior fracture.
Lips 1996	Adequate; computer generated.	Adequate; sealed envelopes opened by hospital pharmacy.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) Missing data in each group: 258/1287 (20%) lost to F-U or dead on placebo; 230/1291 (18%) on vit D. Non completers 35% Vit D; 38% place. ITT: Yes (fracture incidence carried forward).	Not applicable.	Yes; comparable on age, sex, residence, amount of time outdoors/in sunshine, mobility, calcium intake.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Vitamin D

Vitamin D review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Lyons 2007	Adequate; computer generated.	Adequate; sequences generated by dispensing pharmacy.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. 4000 pts per group would give 82% power to detect fracture reduction from 20% to 17.5% after 3 year but only 3440 people recruited. Attrition: No (>20% loss to follow up; same each group) Missing data in each group: died/lost to follow up: vitamin D 805/1725 (47%); placebo 801/1715 (47%). ITT: Yes (fracture incidence carried forward).	Clinical.	Yes; comparable on age, sex, residence.
Meyer 2002	Unclear; days of month randomised to treatments and participant assigned to group according to their date of	Partial; nursing staff not aware of details in allocation process.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Based on 6% annual incidence of hip fractures in nursing home population, sample size of 1113 in each group would give 80% power to detect reduction in hip fractures of 30% at 80% power. Attrition: No (>20% loss to follow up; same each group) Deaths: 169/569 (30%) in vitamin D group, 163/575 (28%) in placebo. Rest appeared to be followed up. Only 32% and 35% completed treatment. ITT: Yes (all included in analysis, no	Not applicable.	Yes; comparable on age, gender, weight, height, BMI, dietary calcium intake; prior fracture; gait support.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Vitamin D

Vitamin D review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Pfeifer 2000	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. To prove a difference of 50% of the standard deviation in SHPT with a power of 80%, 74 subjects per group were needed. Attrition: No (≤ 20% loss to follow up) Missing data: 4/74 (5%) Vit D + Ca group; 7/74 (9%) calcium group. ITT: No (available case analysis).	Not applicable.	Yes; eg comparable on age, weight,height, years since menopause.
Porthouse 2005	Adequate; computer generated.	Adequate; randomisation by independent person with no knowledge of participants characteristics.	Patient: not blinded. Outcome assessor: Unclear.	Power calculation: Yes. To observe 34% reduction in fracture rate with 80% power would need 2855 participants in a 2:1 ratio in favour of control group. Attrition: No (≤ 20% loss to follow up) Missing data in each group: 109/1321 (8%) on intervention; 131/1993 (7%) placebo. ITT: Yes (all included in analysis, no details).	Not applicable.	Yes; comparable on age, weight, prior fracture, smoking, health, maternal hip fracture, falls, Ca intake.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Vitamin D

Vitamin D review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
RECORD 2005	Adequate; computer-generated.	Adequate; centralised.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. 4200 pts to have 80% power (2p<0.05) to detect a decrease in incidence of fractures from 15% in controls to 12%. Attrition: No (≤ 20% loss to follow up) data analysed 2 years after last person enrolled. Missing data in each group: vit D + Ca: deaths 221, withdrew 16 of 1306, ie. 18%; vit D: (217D+15W)/ 1343 (17%) ; Ca: (143D+22W) /1311 (13%); place (217D+14W)/1332 (17%). ITT: Yes (fracture incidence carried forward).	Clinical.	Yes; comparable on age, sex, race, type of fracture, time since fracture, weight, smoking, physical activity, thyearoxine, steroids, thiazide diuretics.
Smith 2007	Unclear.	Adequate; numbered identical ampoules prepared by 3rd party and distributed sequentially.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. 80% power to detect a difference in nonvertebral fractures of 30% at 5% significance with 5000 participants in each arm. Attrition: No (>20% loss to follow up; same each group) Missing data in each group: 1579/4727 (33%) in vitamin D group and 1638/4713 (35%) in placebo group failed to return fracture questionnaire. All pts randomised were included in ITT analysis. ITT: Yes (fracture incidence carried forward).	Not applicable.	Yes; comparable on age, gender, previous history of fracture, residential status, prevalence an frequency of falls.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Vitamin D

Vitamin D review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Tilyard 1992	Unclear.	Unclear; physicians: randomisation codes to assign women to treatment; assignment aware after randomisation.	Patient: not blinded. Outcome assessor: Yes.	Power calculation: Yes. 554 women were required to detect a 50% difference in fracture rates (2-tailed p<0.05) with 90% power. Attrition: No (>20% loss to follow up overall) Unclear, but missing data seemed to be 101/314 (32%) in vitamin D group and 90/318 (28%) in Ca group. Only 432/622 (69%) completed 3 years. ITT: No (available case analysis).	Radiographic 15% reduction height.	Yes; comparable on age, weight, height, years since menopause, dietary Ca, no of fractures.
Trivedi 2003	Unclear.	Adequate; pharmacy held the code.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) No loss to follow up in either group; but 17 and 18% deaths. 22.8% vitamin D and 24.2% place did not complete (includes deaths). ITT: Yes (all included in analysis, no details).	Not stated.	Yes; comparable on age, BMI, comorbidity, smoking, steroids, HRT, alcohol, physical activity.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Calcium

Calcium review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Avenell 2004	Adequate; computer-generated.	Adequate.	Patient: not blinded. Outcome assessor: Yes.	Power calculation: Yes. 4200 pts to have 80% power (2p<0.05) to detect a decrease in incidence of fractures from 15% in controls to 12%. Attrition: No (≤ 20% loss to follow up) Loss to follow up: vit D + Ca 3/35 (9%); vit D 15/35 (43%); Ca 4/29 (14%); no tablets 6/35 (17%); ie differential loss to follow up. ITT: Yes (fracture incidence carried forward).	Clinical.	Yes; comparable on age, sex, race, type of fracture, time since fracture, weight, smoking, physical activity, thyearoxine, steroids, thiazide diuretics.
Chevalley 1994	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Not stated. Not applicable. Attrition: No (≤ 20% loss to follow up) 13 (14%) dropped out. Numbers for each group were not reported. ITT: Unclear/not stated.	Radiographic 20-25% reduction height.	Yes, but limited data; comparable on age, BMI, years since menopause.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Calcium

Calcium review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Hansson 1987	Unclear.	Unclear.	Patient: not stated. Outcome assessor: Unclear.	Power calculation: Not stated. Attrition: No (>20% loss to follow up; greater in 1 group) 3/25 (12%) missing data for calcium and 6/25 (24%) for placebo. ITT: Unclear/not stated.	Not stated.	Yes, but limited data; comparable on age, bone mineral content.
Peacock 2000	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Not stated. Not applicable. Attrition: No (>20% loss to follow up; same each group) Calcium 71 (56%) dropped out; 69 (51%) in Vit-D and 61 (45%) from placebo. ITT: Unclear/not stated.	Radiographic 20-25% reduction height.	Yes; comparable on age, weight, height, total BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Calcium

Calcium review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Prince 2007	Adequate; random number generation and stratified according to previous non-traumatic fracture.	Adequate; pharmacy had randomisation list and assigned the medications.	Patient: double blind. Outcome assessor: Unclear.	Power calculation: Yes. Assuming fracture rate of 3.5% p.a. in placebo group and that calcium would reduce event rate by 35%. At 80% power 737 people per group required. Attrition: No (≤ 20% loss to follow up) Missing data: 113 (15%) participants for calcium and 119 (16%) for placebo. ITT: Yes (all included in analysis, no details).	Radiographic 20-25% reduction height.	Yes; comparable on age, weight, height, years since menopause, T-score, smoking, activity.
Recker 1996	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes; blind broken after assessments.	Power calculation: Not stated. Attrition: Unclear or Not stated 54/251 (22%) said to be excluded from the analysis, but all included in analysis. ITT: Yes (all included in analysis, no details).	Radiographic 20-25% reduction height.	Some comparable; comparable on age, BMC, Ca intake; not comparable on proportion fractures at baseline.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Calcium

Calcium review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
RECORD 2005	Adequate; computer-generated.	Adequate.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. 4200 pts to have 80% power (2p<0.05) to detect a decrease in incidence of fractures from 15% in controls to 12%. Attrition: No (≤ 20% loss to follow up) data analysed 2 years after last person enrolled. Missing data in each group: vit D + Ca: deaths 221, withdrew 16 of 1306, ie. 18%; vit D: (217D+15W)/ 1343 (17%) ; Ca: (143D+22W) /1311 (13%); place (217D+14W)/1332 (17%). ITT: Yes (fracture incidence carried forward).	Clinical.	Yes; comparable on age, sex, race, type of fracture, time since fracture, weight, smoking, physical activity, thyearoxine, steroids, thiazide diuretics.
Reid 1993	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes; outcome assessor blinding stated in text of Reid 1995.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) 11/135 (7%) missing data overall. ITT: Unclear/not stated.	Radiographic 20-25% reduction height.	Yes; age, years since menopause, weight, height, dietary calcium intake, alcohol intake.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Calcium

Calcium review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Reid 2006	Adequate; computer generated.	Unclear.	Patient: not stated. Outcome assessor: Unclear.	Power calculation: Yes. Powered at 80% at 0.05 level to detect a 40% decrease in fracture rate. Attrition: No (≤ 20% loss to follow up) Missing data: placebo 104/739 (14%) calcium 112/732 (15%); some patients (unclear how many) eliminated from per protocol analysis because took osteoporosis medication. ITT: Yes (all included in analysis, no details).	Radiographic 20-25% reduction height.	Yes; comparable on age, weight, height, years since menopause, BMI.
Riggs 1998	Unclear.	Partial; study medications dispensed by research pharmacist.	Patient: double blind. Outcome assessor: Yes; assessors stated to be blinded.	Power calculation: Not stated. Attrition: No (>20% loss to follow up; same each group) 31 (26%) dropped out of calcium and 28 (24%) dropped out of placebo. ITT: Yes (all included in analysis, no details).	Radiographic 15% reduction height.	Yes, but limited data; comparable on age, years since menopause, dietary calcium.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Cross Review

Cross review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Black 2003	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. Apparently post-hoc: given the standard deviations in this trial, with a power of 90%, we could detect a difference in the area BMD of about 2.8% for the spine and 2.2% for the hip. Attrition: No (≤ 20% loss to follow up) 15/238 (6%) did not complete 24 month follow up. ITT: No (available case analysis).	Not stated.	Yes; comparable on age, race, years since menopause, BMI, clinical fracture, prior alendronate.
Eviö 2004	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (>20% loss to follow up; same each group) 8/30 (27%) discontinued alendronate; 7/30 (23%) discontinued HRT. ITT: No (available case analysis).	Not applicable.	Yes; comparable on age, weight, height, BMI, years since menopause, smokers, calcium intake, alcohol, BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Cross Review

Cross review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Luckey 2004	Adequate; computer generated.	Partial; described as concealed but no details.	Patient: double blind. Outcome assessor: Yes; central analysis facility blinded to treatment group.	Power calculation: Yes. 150 pts per group had 90% power to detect treatment diff in change from baseline in lumbar BMD of 1.5 percentage points between groups. Attrition: No (≤ 20% loss to follow up) 80.3% completed on alendronate and 82.8% on raloxifene; 89.2% and 88.4% available for last observation carried forward analysis. ITT: Yes (fracture incidence carried forward).	Not applicable.	Yes; comparable on age, race, BMI, years since menopause, family history of osteoporosis, T score.
McClung 2005	Unclear.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: No. Attrition: No (≤ 20% loss to follow up) Missing data 13% on alendronate vs. 18% on teriparatide. ITT: Yes (all included in analysis, no details).	Not applicable.	Yes; comparable on age, BMI, years since menopause, ethnicity, pre-existing back pain, BMD.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Cross Review

Cross review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Michalska 2006	Unclear.	Unclear.	Patient: not blinded. Outcome assessor: Unclear; alendronic acid patients had 2 years open label.	Power calculation: Yes. 33 pts per group needed to detect a 2.4% difference in lumbar spine BMD between 2 groups with 80% power. Attrition: Yes 1/100 (1%) missing data overall. All patients given at least 1 dose were analysed. ITT: No (per protocol analysis).	Not applicable.	Yes mainly; comparable on age, weight,height, years since menopause, duration of prior alendronate treatment; alendronate group fewer prior fractures: 27.3% vs 48.5%.
Muscoso 2004	Unclear.	Unclear.	Patient: not blinded. Outcome assessor: Unclear; stated to be an open study.	Power calculation: Not stated. Attrition: Unclear or Not stated Apparently no missing data reported for study of 2000 women over 2 years. ITT: Yes (all followed).	Not stated.	Yes, but limited data; comparable on age.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Cross Review

Cross review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Palomba 2005	Adequate; computer generated.	Unclear.	Patient: not blinded. Outcome assessor: Yes; radiologist blind to treatments; patients received different interventions.	Power calculation: Yes. Sample size of 40 per group to detect 2% difference in mean change from baseline in lumbar spine BMD. Attrition: No (≤ 20% loss to follow up) 17/220 (8%) ALN, 14/219 (6%) Raloxifene. ITT: No (available case analysis).	Radiographic no details.	Not stated.
Recker 2007	Adequate; random number table.	Adequate; computerised telephone system.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Yes. Power calc assumed 1750 pre arm giving 90% power to establish equivalence between alendronate and raloxifene; study stopped early and this number not reached. Attrition: No (≤ 20% loss to follow up) <1% lost; for vertebral fractures data only available for 255/716 (35%) of the randomised patients. ITT: Yes (fracture incidence carried forward).	Radiographic 20-25% reduction height.	Yes; comparable on age, BMI, years since menopause.

APPENDIX V
METHODOLOGICAL QUALITY OF STUDIES

Class: Cross Review

Cross review

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*Power Calculation, Attrition and ITT*	*Vertebral Fracture Method*	*Baseline Comparable*
Sambrook 2004	Adequate; computer generated.	Unclear.	Patient: double blind. Outcome assessor: Yes.	Power calculation: Not stated. Attrition: No (≤ 20% loss to follow up) 88% and 86% completed. ITT: Yes (fracture incidence carried forward).	Not applicable.	Yes; comparable on age, BMI, years since menopause, race, T score.

APPENDIX VI: EVIDENCE SUMMARY

Alendronic acid review: alendronic acid vs placebo/no treatment

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	9 trials; 8074 patients from meta analysis all populations	RR=0.55 (95%CI 0.46, 0.66)	p=0.59 I2 =0%	Highly significant; fewer patients with fracture in alendronic acid group; NNT 33	Good	Direct	Precise	Consistent	Poor - studies, industry	3/9 studies only gave percentages; 1/9 had too short duration. No effect of these in sensitivity analyses. 7/9 had industry funding; funnel plot symmetrical	High / moderate
Nonvertebral fracture	8 trials; 10429 patients from meta analysis all populations	RR=0.83 (95%CI 0.74, 0.93)	p=0.64 I2 =0%	Statistically significant; fewer patients with fracture in alendronic acid group; NNT 50	Good	Direct	Precise	Consistent	Poor - studies, industry	3/8 studies only gave percentages; 1/8 had too short duration; 2 more included trauma fractures. No effect of these in sensitivity analyses. All had industry funding; some asymmetry	High / moderate
Hip fracture	3 trials; 7453 patients from meta analysis all populations	RR=0.62 (95%CI 0.4, 0.96)	p=0.40 I2 =0%	Statistically significant; fewer patients with fracture in alendronic acid group; NNT 100	Good	Direct	Precise	Consistent	Poor - studies, industry	1/3 studies included trauma fractures. All had industry funding	High / moderate

APPENDIX VI: EVIDENCE SUMMARY

Alendronic acid review: alendronic acid vs placebo/no treatment

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Wrist fracture	3 trials; 7453 patients from meta analysis all populations	RR=0.85 (95%CI 0.67, 1.09)	p=0.002 I2 =84%	High heterogeneity. Not statistically significant (0.21)	Good	Direct	Precise	Major inconsistency	Poor - studies, industry	1/3 studies included trauma fractures. All had industry funding. Significant unexplained heterogeneity	Low / very low

APPENDIX VI: EVIDENCE SUMMARY

Alendronic acid review: alendronic acid + HRT vs HRT

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Nonvertebral fracture	1 trial; 428 patients from RCT (fracture) postmenopausal women	RR=1.67 (95%CI 0.75, 3.73)		Not statistically significant; fairly wide CI	Poor - baseline not comparable	Direct	Fairly wide CI	Consistent	Poor - studies, industry	Not comparable at baseline for history of fracture and smoking; adverse events reporting. Industry trial	Low / very low
Wrist fracture	1 trial; 428 patients from RCT (fracture) postmenopausal women	RR=1 (95%CI 0.06, 15.88)		Not statistically significant; wide CI	Poor - baseline not comparable	Direct	Wide CI	Consistent	Poor - studies, industry	Not comparable at baseline for history of fracture and smoking; adverse events reporting; industry trial	Very low

APPENDIX VI: EVIDENCE SUMMARY

Alendronic acid review: alendronic acid vs placebo following 5 years alendronic acid

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	1 trial; 1099 patients from RCT (fracture) postmenopausal women	RR=0.86 (95%CI 0.6, 1.24)		Not statistically significant	Good	Direct	Precise	Consistent	Poor - studies, industry	Morphometric fractures; industry funding	High / moderate
Nonvertebral fracture	1 trial; 1099 patients from RCT (fracture) postmenopausal women	RR=0.99 (95%CI 0.77, 1.28)		Not statistically significant	Good	Direct	Precise	Consistent	Poor - studies, industry	Industry funding	High / moderate
Hip fracture	1 trial; 1099 patients from RCT (fracture) postmenopausal women	RR=1.02 (95%CI 0.51, 2.02)		Not statistically significant; CI borderline acceptable width	Good	Direct	Precise	Consistent	Poor - studies, industry	Industry funding	Moderate

APPENDIX VI: EVIDENCE SUMMARY

Alendronic acid review: alendronic acid vs placebo following 5 years alendronic acid

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Forearm fracture	1 trial; 1099 patients from RCT (fracture) postmenopausal women	RR=1.08 (95%CI 0.62, 1.88)		Not statistically significant	Good	Direct	Precise	Consistent	Poor - studies, industry	Industry funding	High / moderate

APPENDIX VI: EVIDENCE SUMMARY

Etidronate review: etidronate vs placebo/no treatment

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	8 trials; 1039 patients from meta analysis all populations	RR=0.51 (95%CI 0.31, 0.83)	p=0.98 I2 =0%	Highly significant; NNT=25; funnel plot fairly symmetrical	Poor - incomplete follow up	Direct	Precise	Consistent	Adequate	3/8 industry funded; 2/8 (47% weight) had >20% missing data; largest (22.6% weight) had <20% missing data; 2/8 (28.6% weight) had no patient blinding	Moderate
Vertebral fracture sensitivity analysis	3 trials; 394 patients from meta analysis all populations	RR=0.53 (95%CI 0.27, 1.07)	p=0.90 I2 =0%	Not significant; CI borderline acceptable width	Good	Direct	Precise	Consistent	Poor - studies, industry	Second largest (45% weight) baseline comparability for age and gender only; smallest study had less than 10% missing data; two largest (95% weight) industry funded	Moderate
Nonvertebral fracture	4 trials; 472 patients from meta analysis all populations	RR=0.72 (95%CI 0.29, 1.8)	p=0.30 I2 =18%	Not significant	Poor - incomplete follow up	Direct	Fairly wide CI	Consistent	Adequate	Second largest (37.3% weight) had >20%missing data and largest (38.7%) had differential missing data; 1/4 was industry sponsored	Low

APPENDIX VI: EVIDENCE SUMMARY

Etidronate review: etidronate vs placebo/no treatment

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Hip fracture	2 trials; 246 patients from meta analysis all populations	RR=1.02 (95%CI 0.21, 4.94)	p=0.43 I2 =0%	Not significant	Poor - incomplete follow up	Direct	Wide CI	Consistent	Poor - studies, industry	Largest (66% weight) had >20%missing data	Very low
Wrist fracture	1 trial; 209 patients from RCT (fracture) postmenopausal women	RR=4.95 (95%CI 0.24, 101.93)	p=0.30 I2 =0%	Not significant; extremely wide CI	Good	Direct	Wide CI	Consistent	Adequate		Very low
All fractures	4 trials; 420 patients from RCT (fracture) postmenopausal women	RR=0.78 (95%CI 0.42, 1.44)	p=0.33 I2 =13%	Not significant	Poor - incomplete follow up	Direct	Precise	Consistent	Adequate	2/4 including largest (55% weight) had >20% missing data & had no patient blinding	Moderate

APPENDIX VI: EVIDENCE SUMMARY

Risedronate review: risedronate vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	7 trials; 2845 patients from meta analysis all populations	RR=0.61 (95%CI 0.5, 0.74)	p=0.64 I2 =0%	Highly significant; fewer patients with vertebral fractures in risedronate group; NNT 17	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	Missing data: 3/7 had >20%; 5/7 used 15% cut-off height; 1/7 included traumatic fractures; 1/7 used unlicensed dose for 50% pts; all industry funded; funnel plot mainly symmetrical	Moderate / low
Vertebral fracture sensitivity analysis	7 trials; 2845 patients from meta analysis all populations	RR=0.56 (95%CI 0.45, 0.69)	p=0.61 I2 =0%	Sensitivity analysis: highly significant; more efficacious when using adjusted Cox RR reported in 2/7 studies	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	Missing data: 3/7 had >20%; 5/7 used 15% cut-off height; 1/7 included traumatic fractures; 1/7 used unlicensed dose for 50% pts; all industry funded	Moderate / low
Nonvertebral fracture	7 trials; 12658 patients from meta analysis all populations	RR=0.81 (95%CI 0.72, 0.9)	p=0.68 I2 =0%	Highly significant (p=0.0002); fewer patients with non-vertebral fractures in risedronate group; NNT 50. Sensitivity analyses: no effect on summary statistics with Cox RR reported in 2/7	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	Missing data: largest study (78% weight) had >20% missing data; 1/7 included traumatic fractures; 1/7 used unlicensed dose for 50% pts; all industry funded; funnel plot symmetrical	Moderate / low

APPENDIX VI: EVIDENCE SUMMARY

Risedronate review: risedronate vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Hip fracture	4 trials; 11923 patients from meta analysis all populations	RR=0.73 (95%CI 0.58, 0.92)	p=0.73 I2 =0%	Significant; fewer patients with hip fractures in risedronate group; NNT 100	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	Largest study (78% weight) had >35% missing data intervention & >40% control; 1/4 included traumatic fractures; 1/4 unlicensed dose for 50% patients; funnel plot some asymmetry; all industry funded	Moderate / low
Wrist fracture	2 trials; 2439 patients from meta analysis all populations	RR=0.68 (95%CI 0.43, 1.07)	p=0.81 I2 =0%	Not significant	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	All with potential sources of bias; both had >20% missing data; 1/2 included traumatic fractures; industry studies	Moderate / low
Humerus fracture	2 trials; 2439 patients from meta analysis all populations	RR=0.46 (95%CI 0.23, 0.93)	p=0.77 I2 =0%	Significant; fewer patients with humerus fractures in risedronate group; NNT=100; borderline acceptable CI	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	All with potential sources of bias; both had >20% missing data; 1/2 included traumatic fractures; industry studies	Moderate / low

APPENDIX VI: EVIDENCE SUMMARY

Ibandronic acid review: ibandronic acid vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	1 trial; 1952 patients from RCT (fracture) postmenopausal women	RR=0.51 (95%CI 0.34, 0.74)		Highly significant; fewer patients with vertebral fractures in the ibandronic acid group; NNT 25	Poor - incomplete follow up	Indirect intervn - minor, different dose	Precise	Consistent	Poor - studies, industry	Non-vertebral fractures recorded as adverse events; more than 20% withdrawals; industry funded; dose not in BNF but included for comparative reasons	Low / very low
Nonvertebral fracture	1 trial; 1952 patients from RCT (fracture) postmenopausal women	RR=1.11 (95%CI 0.83, 1.48)		Not significant	Poor - incomplete follow up	Indirect intervn - minor, different dose	Precise	Consistent	Poor - studies, industry	Non-vertebral fractures recorded as adverse events; more than 20% withdrawals; industry funded; dose not in BNF but included for comparative reasons	Low / very low

APPENDIX VI: EVIDENCE SUMMARY

Ibandronic acid review: Ibandronic acid licensed dose vs ibandronic acid unlicensed dose

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture: clinical	2 trials; 1725 patients from meta analysis postmenopausal women	RR=0.94 (95%CI 0.65, 1.36)	p=0 I2 =0.35%	Not significant (p=0.74)	Poor - adverse events	Indirect intervn - minor, different dose	Precise	Consistent	Poor - studies, industry	Not powered to examine fracture outcomes; outcomes & fractures reported as adverse events; biggest study (55% weight) had 21% vs 17% withdrawals in the intervention and control groups	Low / very low
Nonvertebral fracture	0 trials; 0 patients			No evidence for this outcome	----	---	----	----	---	No evidence for nonvertebral fractures	----

APPENDIX VI: EVIDENCE SUMMARY

Zoledronic acid review: zoledronic acid vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	2 trials; 7802 patients from meta analysis all populations	RR=0.33 (95%CI 0.27, 0.4)	p=0.05 I2 =75%	Highly significant; fewer people with fractures in zoledronic acid group; heterogeneity	Good	Direct	Precise	Minor inconsistency	Poor - studies, industry	Smaller study (11%) had >20% missing data, only symptomatic fractures, 10% pts had osteoporosis medication and possibly unrepresentative population; both studies industry funded	Moderate / low
Vertebral fracture sensitivity analysis	1 trial; 5675 patients from RCT (fracture) postmenopausal women	RR=0.3 (95%CI 0.24, 0.38)		Highly significant; fewer patients with vertebral fractures in the zoledronic acid group; NNT 13	Good	Direct	Precise	Consistent	Poor - studies, industry	Morphometric; stratum1: people not taking osteoporosis medicines at baseline	High / moderate
Vertebral fracture: clinical	1 trial; 7736 patients from RCT (fracture) postmenopausal women	RR=0.23 (95%CI 0.14, 0.37)		Highly significant; fewer patients with vertebral fractures in the zoledronic acid group; NNT 50	Good	Direct	Precise	Consistent	Poor - studies, industry	Industry funding; all patients included; clinical fractures	High / moderate

APPENDIX VI: EVIDENCE SUMMARY

Zoledronic acid review: zoledronic acid vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Nonvertebral fracture	2 trials; 9863 patients from meta analysis all populations	RR=0.75 (95%CI 0.66, 0.85)	p=0.87 I2 =0%	Highly significant; fewer people with fractures in zoledronic acid group; NNT 50	Good	Direct	Precise	Consistent	Poor - studies, industry	Smaller study (22%) had >20% missing data, 10% pts had osteoporosis medication and possibly unrepresentative population; both studies industry funded	High / moderate
Hip fracture	2 trials; 9863 patients from meta analysis all populations	RR=0.62 (95%CI 0.47, 0.83)	p=0.62 I2 =0%	Highly significant; fewer people with fractures in zoledronic acid group; NNT 100	Good	Direct	Precise	Consistent	Poor - studies, industry	Smaller study (27%) had >20% missing data, 10% pts had osteoporosis medication and possibly unrepresentative population; both studies industry funded	High / moderate

APPENDIX VI: EVIDENCE SUMMARY

Cross biphosphonates review: alendronic acid vs risedronate

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
All fractures	2 trials; 1978 patients from meta analysis postmenopausal women	RR=1.15 (95%CI 0.75, 1.76)	p=0.44 I2 =0%	Not significant	Poor - adverse events	Direct	Precise	Consistent	Poor - studies, industry	Fractures recorded as adverse events; 1/2 (47.7% weight) did not include all randomised patients & reported % of people with fractures thus denominator used was the no. of randomised patients	Moderate / low

APPENDIX VI: EVIDENCE SUMMARY

Cross biphosphonates review: ibandronic acid vs alendronic acid

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	1 trial; 1733 patients from RCT (fracture) postmenopausal women	RR=0.98 (95%CI 0.29, 3.38)		Not significant	Poor - incomplete follow up	Direct	Wide CI	Consistent	Poor - studies, industry	More than 20% missing data, fractures recorded as adverse events	Very low
Nonvertebral fracture	1 trial; 1733 patients from RCT (fracture) postmenopausal women	RR=1.15 (95%CI 0.53, 2.46)		Not significant	Poor - incomplete follow up	Direct	Fairly wide CI	Consistent	Poor - studies, industry	More than 20% missing data	Low / very low

APPENDIX VI: EVIDENCE SUMMARY

Strontium ranelate review: strontium ranelate vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	3 trials; 5254 patients from meta analysis all populations	RR=0.62 (95%CI 0.55, 0.71)	p=0.43 I2 =0%	Highly significant; fewer patients with fracture in strontium ranelate group Reported Cox RR were used in analysis	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	2/3 had >30% missing data: largest study had >30% missing data in both arms & another had >30% missing data in one arm	Moderate / low
Nonvertebral fracture	2 trials; 6374 patients from meta analysis all populations	RR=0.86 (95%CI 0.74, 0.99)	p=0.67 I2 =0%	Significant; fewer patients with non-vertebral fracture in strontium ranelate	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	Both had >30% missing data: largest study had >30% missing data in both arms & the other had >30% missing data in one arm; this taken into account in the time-to-event analyses for one study	Moderate / low
Hip fracture	1 trial; 4932 patients from RCT (fracture) all populations	RR=0.85 (95%CI 0.61, 1.19)		Not statistically significant (0.34)	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	>30% missing data in this largest study in both arms which was partly taken into account in the time-to-event analyses for the study	Moderate / low

APPENDIX VI: EVIDENCE SUMMARY

Strontium ranelate review: strontium ranelate vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Wrist fracture	1 trial; 4932 patients from RCT (fracture) all populations	RR=1 (95%CI 0.74, 1.36)		Not statistically significant	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	>30% missing data in both arms	Moderate / low
Humerus fracture	1 trial; 4932 patients from RCT (fracture) all populations	RR=0.53 (95%CI 0.29, 0.94)		Statistically significant; fewer patients with fracture in the strontium ranelate group	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	>30% missing data in both arms	Moderate / low

APPENDIX VI: EVIDENCE SUMMARY

Teriparatide review: teriparatide vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	2 trials; 910 patients from meta analysis all populations	RR=0.36 (95%CI 0.23, 0.57)	p=0.35 I2 =0%	Highly significant; fewer patients with vertebral fractures in teriparatide group; NNT 11. Sensitivity analysis did not affect results	Poor - early stopping	Direct	Precise	Consistent	Poor - studies, industry	Biggest study (98% weight) was industry funded and used number of patients with adequate radiographs only; early stopping due to osteosarcomas in rats	Moderate
Nonvertebral fracture	2 trials; 1383 patients from meta analysis postmenopausal women	RR=0.49 (95%CI 0.27, 0.87)	p=0.74 I2 =0%	Significant; fewer patients with non-vertebral fractures in teriparatide group; NNT 50	Poor - early stopping	Direct	Precise	Consistent	Poor - studies, industry	Largest study (91% weight was industry funded. Early stopping due to osteosarcomas in rats	Moderate
Hip fracture	1 trial; 1085 patients from RCT (fracture) postmenopausal women	RR=0.25 (95%CI 0.03, 2.24)		Not significant	Poor - early stopping	Direct	Wide CI	Consistent	Poor - studies, industry	Industry funded, stopped study early due to osteosarcoma in rats	Very low

APPENDIX VI: EVIDENCE SUMMARY

Teriparatide review: teriparatide vs placebo

Outcome	Meta-analysis details	Summary statistics	Hetero p, I2	Comments	Study quality	Directness	Imprecision	Inconsistency	Reporting Bias	GRADE Comments	GRADE Evidence Rating
Wrist fracture	1 trial; 1085 patients from RCT (fracture) postmenopausal women	RR=0.29 (95%CI 0.06, 1.38)		Not significant	Poor - early stopping	Direct	Wide CI	Consistent	Poor - studies, industry	Industry funded; stopped study early due to osteosarcoma in rats	Very low
Humerus fracture	1 trial; 1085 patients from RCT (fracture) postmenopausal women	RR=1.01 (95%CI 0.14, 7.11)		Not significant	Poor - early stopping	Direct	Wide CI	Consistent	Poor - studies, industry	Industry funded; stopped study early due to osteosarcoma in rats	Very low
Other osteoporotic medication during follow up: at 18 months	1 trial; 850 patients from RCT (fracture) all populations	RR=0.84 (95%CI 0.73, 0.96)		Significant; fewer patients requiring other osteoporosis medications in the teriparatide group; NNT 12	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	Industry funding; 77% patients from original study in follow up study	Moderate / low

APPENDIX VI: EVIDENCE SUMMARY

Teriparatide review: teriparatide vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Other osteoporotic medication during follow up: at 30 months	2 trials; 1210 patients from meta analysis all populations	RR=0.86 (95%CI 0.77, 0.95)	p=0.14 I2 =53.2%	Significant; fewer patients requiring other osteoporosis medications in the teriparatide group; NNT 13	Poor - incomplete follow up	Direct	Precise	Minor inconsistency	Poor - studies, industry	Sample of 77% of initial patients to follow up; industry funded	Low / very low

APPENDIX VI: EVIDENCE SUMMARY

Teriparatide review: teriparatide + HRT vs HRT

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	2 trials; 90 patients from meta analysis postmenopausal women	RR=0.11 (95%CI 0.01, 0.91)	p=0.60 I2 =0%	Significant; fewer patients with fractures in the teriparatide group; NNT 6	Poor - incomplete follow up	Direct	Wide CI	Consistent	Poor - studies, pub bias	Large differences in missing data in the teriparatide and control groups: one had 22% vs 0% & other had 24% vs 12%; patients were not blinded	Very low
Nonvertebral fracture	1 trial; 44 patients from RCT (fracture) postmenopausal women	RR=0.69 (95%CI 0.11, 4.47)		Not significant	Poor - incomplete follow up	Direct	Wide CI	Consistent	Adequate	Large differences in missing data in the teriparatide and control groups 22% vs 0% and patients were not blinded	Very low

APPENDIX VI: EVIDENCE SUMMARY

Teriparatide review: teriparatide + alendronic acid vs alendronic acid

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	1 trial; 108 patients from RCT (fracture) postmenopausal women	RR=0.38 (95%CI 0.09, 1.6)	p=0.60 I2 =0%	Not significant; meta-analysis of 2 comparisons	Poor - not blinded	Direct	Wide CI	Consistent	Poor - studies, industry	Patients not blinded; significant difference in number of baseline spinal clinical fractures and differed in Ca intake. Industry funded	Very low
Nonvertebral fracture	1 trial; 108 patients from meta analysis postmenopausal women	RR=1.48 (95%CI 0.31, 7.03)	p=0.72 I2 =0%	Not significant; meta-analysis of 2 comparisons	Poor - not blinded	Direct	Wide CI	Consistent	Poor - studies, industry	Patients not blinded; significant difference in number of spinal clinical fractures and differed in Ca intake. Industry funded	Very low

APPENDIX VI: EVIDENCE SUMMARY

Parathyroid hormone (1-84) review: PTH (1-84) vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	1 trial; 2532 patients from RCT (fracture) all populations	RR=0.39 (95%CI 0.22, 0.69)		Highly significant; fewer patients with fractures in the PTH group; NNT 50	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	Missing data: 36% and 30% in the PTH and placebo groups. Industry funded	Moderate / low
Nonvertebral fracture	1 trial; 2532 patients from RCT (fracture) all populations	RR=0.97 (95%CI 0.71, 1.33)		Not significant	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	Missing data: 36% and 30% in the PTH and placebo groups. Industry funded. No distinction between traumatic and fragility non-vertebral fractures	Moderate / low
Hip fracture	1 trial; 2532 patients from RCT (fracture) all populations	RR=0.65 (95%CI 0.11, 3.86)		Not significant	Poor - incomplete follow up	Direct	Wide CI	Consistent	Poor - studies, industry	Missing data: 36% and 30% in the PTH and placebo groups. Industry funded. No distinction between traumatic and fragility non-vertebral fractures	Very low

APPENDIX VI: EVIDENCE SUMMARY

Calcitonin review: calcitonin vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	4 trials; 753 patients from meta analysis all populations	RR=0.65 (95%CI 0.48, 0.88)	p=0.58 I2 =0%	Highly significant; fewer patients with vertebral fractures in calcitonin group; NNT 13	Very poor	Direct	Precise	Consistent	Poor - studies, industry	Largest study (87%) had 58% and 59% missing data in intervention and control groups; largest was industry funded; other 2/4 were not blinded	Low / very low
Vertebral fracture sensitivity analysis	3 trials; 196 patients from meta analysis all populations	RR=0.41 (95%CI 0.14, 1.17)	p=0.51 I2 =0%	Not significant	Poor - not blinded	Direct	Fairly wide CI	Consistent	Adequate	2/3 were not blinded	Low
Nonvertebral fracture sensitivity analysis	2 trials; 152 patients from meta analysis all populations	RR=0.22 (95%CI 0.02, 1.96)	p=0.90 I2 =0%	Not significant	Poor - not blinded	Direct	Wide CI	Consistent	Adequate	Both studies were not blinded	Very low

APPENDIX VI: EVIDENCE SUMMARY

Calcitonin review: calcitonin vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Hip fracture	1 trial; 620 patients from RCT (fracture) all populations	RR=0.54 (95%CI 0.18, 1.59)		Not significant	Very poor	Direct	Fairly wide CI	Consistent	Poor - studies, industry	Largest study had 58% and 59% missing data in intervention and control groups	Very low
Arm: all fractures wrist, ulna, humerus, radius	1 trial; 620 patients from RCT (fracture) all populations	RR=0.79 (95%CI 0.38, 1.61)		Not significant	Very poor	Direct	Fairly wide CI	Consistent	Poor - studies, industry	Largest study had 58% and 59% missing data in intervention and control groups	Very low

APPENDIX VI: EVIDENCE SUMMARY

Hormone replacement therapy review: HRT vs placebo/no treatment

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	4 trials; 11842 patients from meta analysis all populations	RR=0.67 (95%CI 0.48, 0.93)	p=0.25 I2 =27%	Significant; fewer patients with fractures in the HRT group; NNT 100	Good	Direct	Precise	Consistent	Adequate	2/4 smaller studies did not blind patients; 2/4 used 15% reduction in height; 1/4 was industry funded	High / moderate
Vertebral fracture sensitivity analysis	4 trials; 11842 patients from meta analysis all populations	RR=0.62 (95%CI 0.43, 0.88)	p=0.88 I2 =0%	Sensitivity analysis: significant (p=0.08); fewer patients with fractures in the HRT group; NNT 100	Good	Direct	Precise	Consistent	Adequate	In the absence of 2 studies with most bias: 1/2 used 15% reduction in height and 1/2was industry funded	High
Nonvertebral fracture	3 trials; 11774 patients from meta analysis all populations	RR=0.73 (95%CI 0.65, 0.81)	p=0.65 I2 =0%	Highly significant; fewer patients with fractures in the HRT group; NNT 33. Sensitivity analysis did not differ much	Good	Direct	Precise	Consistent	Adequate	2/3 (3% weight) did not blind patients	High

APPENDIX VI: EVIDENCE SUMMARY

Hormone replacement therapy review: HRT vs placebo/no treatment

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Hip fracture	2 trials; 11745 patients from meta analysis all populations	RR=0.63 (95%CI 0.42, 0.93)	p=0.33 I2 =0%	Significant; fewer patients with fractures in the HRT group; NNT infinity	Good	Direct	Precise	Consistent	Adequate		High
All fractures	3 trials; 11556 patients from meta analysis all populations	RR=0.7 (95%CI 0.63, 0.78)	p=0.49 I2 =0%	Highly significant; fewer patients with fractures in the HRT group; NNT 25. Sensitivity analyses in the absence did not change findings	Good	Direct	Precise	Consistent	Adequate		High

APPENDIX VI: EVIDENCE SUMMARY

Hormone replacement therapy review: HRT + etidronate vs etidronate

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	1 trial; 29 patients from RCT (fracture) all populations	RR=0.31 (95%CI 0.04, 2.65)		Not significant but too wide CI	Poor - not blinded	Direct	Wide CI	Consistent	Adequate	Patients were not blinded and use of 15% reduction in height for vertebral fractures	Very low
Nonvertebral fracture	1 trial; 29 patients from RCT (fracture) all populations	RR=0.93 (95%CI 0.06, 13.54)		Not significant	Poor - not blinded	Direct	Wide CI	Consistent	Adequate	Patients were not blinded	Very low

APPENDIX VI: EVIDENCE SUMMARY

Raloxifene review: raloxifene vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	2 trials; 4639 patients from meta analysis all populations	RR=0.64 (95%CI 0.54, 0.78)	p=0.49 I2 =0%	Highly significant; fewer patients with vertebral fractures in raloxifene group; NNT=25	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	Largest study had 22% and 25% missing data in intervention and control groups; industry funded	Moderate / low
Nonvertebral fracture	2 trials; 7793 patients from meta analysis all populations	RR=0.91 (95%CI 0.78, 1.05)	p=0.23 I2 =32%	Not significant	Poor - incomplete follow up	Indirect intervn - minor, different dose	Precise	Consistent	Poor - studies, industry	60mg & 120mg combined; largest study (99%) unlicensed dose for 50% patients and 22% and 25% missing data in intervention and control groups; industry studies	Low
Hip fracture	2 trials; 7793 patients from RCT (fracture) all populations	RR=1.12 (95%CI 0.64, 1.94)		Not significant	Poor - incomplete follow up	Indirect intervn - minor, different dose	Precise	Consistent	Poor - studies, industry	60mg & 120mg combined; largest study (99%) unlicensed dose for 50% patients and 22% and 25% missing data in intervention and control groups; industry studies	Low

APPENDIX VI: EVIDENCE SUMMARY

Raloxifene review: raloxifene vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Wrist fracture	1 trial; 7705 patients from RCT (fracture) all populations	RR=0.88 (95%CI 0.68, 1.14)		Not significant (p=0.34)	Poor - incomplete follow up	Indirect intervn - minor, different dose	Fairly wide CI	Consistent	Poor - studies, industry	60mg & 120mg combined; largest study (99%) unlicensed dose for 50% patients and 22% and 25% missing data in intervention and control groups; Industry funding	Very low

APPENDIX VI: EVIDENCE SUMMARY

Raloxifene review: raloxifene + fluoride vs placebo + fluoride

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	1 trial; 466 patients from RCT (fracture) all populations	RR=0.78 (95%CI 0.29, 2.05)		Not significant (p=0.61)	Poor - incomplete follow up	Direct	Fairly wide CI	Consistent	Poor - studies, industry	Missing data: 30% in intervention & 26% in control; industry funded	Low / very low
Nonvertebral fracture	1 trial; 581 patients from RCT (fracture) all populations	RR=0.57 (95%CI 0.24, 1.34)		Not significant (p=0.20)	Poor - incomplete follow up	Direct	Fairly wide CI	Consistent	Poor - studies, industry	Missing data: 30% in intervention & 26% in control; Industry funding	Low / very low
Hip fracture	1 trial; 581 patients from RCT (fracture) all populations	RR=0.5 (95%CI 0.05, 5.46)		Not significant	Poor - incomplete follow up	Direct	Wide CI	Consistent	Poor - studies, industry	Missing data: 30% in intervention & 26% in control; Industry funding	Very low

APPENDIX VI: EVIDENCE SUMMARY

Raloxifene review: raloxifene + fluoride vs placebo + fluoride

Outcome	Meta-analysis details	Summary statistics	Hetero p, I2	Comments	Study quality	Directness	Imprecision	Inconsistency	Reporting Bias	GRADE Comments	GRADE Evidence Rating
Humerus fracture	1 trial; 581 patients from RCT (fracture) all populations	RR=0.28 (95%CI 0.06, 1.36)		Not significant	Poor - incomplete follow up	Direct	Wide CI	Consistent	Poor - studies, industry	Missing data: 30% in intervention & 26% in control; Industry funding	Very low

Raloxifene review: raloxifene vs placebo following 3 years alendronic acid

Outcome	Meta-analysis details	Summary statistics	Hetero p, I2	Comments	Study quality	Directness	Imprecision	Inconsistency	Reporting Bias	GRADE Comments	GRADE Evidence Rating
Nonvertebral fracture	1 trial; 66 patients from RCT (fracture) all populations	RR=0.5 (95%CI 0.05, 5.25)		Not significant (p=0.56)	Poor - not blinded	Direct	Wide CI	Consistent	Poor - studies, industry	First year double blind & second year open label interventions	Very low

APPENDIX VI: EVIDENCE SUMMARY

Nandrolone review: nandrolone vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	2 trials; 95 patients from meta analysis all populations	RR=0.89 (95%CI 0.61, 1.31)	p=0.43 I2 =0%	Not significant	Very poor	Direct	Precise	Consistent	Adequate	Missing data: largest study (91% weight) >30% in placebo group vs 12% in nandrolone group and had significantly older patients in placebo group	Low
Nonvertebral fracture	0 trials; 0 patients			No evidence for this outcome	----	---	----	----	---	No evidence on non-vertebral fractures	----

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: hydroxylated vitamin D vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	1 trial; 246 patients from RCT (fracture) postmenopausal women	RR=4 (95%CI 0.45, 35.28)		Not significant	Very poor	Direct	Wide CI	Consistent	Poor - studies, industry	Baseline differences: more women w/vertebral fractures in intervention than control group; differential loss to follow up higher in the intervention (18%) than in the control (9%) group; Industry funding	Very low
Nonvertebral fracture	1 trial; 246 patients from meta analysis postmenopausal women	RR=0.46 (95%CI 0.18, 1.18)		Not significant	Very poor	Direct	Fairly wide CI	Consistent	Poor - studies, industry	Baseline differences: more women w/vertebral fractures in intervention than control group; differential loss to follow up higher in the intervention (18%) than in the control (9%) group; Industry funding	Very low

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: hydroxylated vitamin D vs calcium

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	2 trials; 467 patients from meta analysis postmenopausal women	RR=0.4 (95%CI 0.23, 0.67)	p=0.007 I2 =87%	Very significant	Very poor	Direct	Precise	Major inconsistency	Poor - studies, industry	Largest (97.5%) study had lack of patient blinding, missing data of 32% in the vitamin D & 28% in the calcium groups (only 69% completed 3 years) & used a 15% cut off for vertebral fractures	Very low
Nonvertebral fracture	2 trials; 467 patients from meta analysis postmenopausal women	RR=0.65 (95%CI 0.34, 1.23)	p=0.10 I2 =63%	Not significant	Very poor	Direct	Precise	Minor inconsistency	Poor - studies, industry	Largest (97.5% weight) study had lack of patient blinding, missing data of 32% in the vitamin D & 28% in the calcium groups; Industry funding	Very low

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: native vitamin D vs placebo/no treatment

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	3 trials; 8801 patients from meta analysis all populations	RR=0.66 (95%CI 0.4, 1.08)	p=0.16 I2 =45%	Not significant	Poor - adverse events	Direct	Precise	Consistent	Adequate	2/3 (97.4% weight) non-industry; 1/3 (23.7% weight) had 47% missing data in each group; 2/3 (26% weight) reported clinical vertebral fracture data; largest (73.6% weight) had fracture data based on self-report/death certificate	Moderate
Vertebral fracture: clinical sensitivity analysis	2 trials; 5361 patients from meta analysis all populations	RR=0.76 (95%CI 0.44, 1.31)	p=0.11 I2 =60%	Not significant	Poor - adverse events	Direct	Precise	Minor inconsistency	Adequate	Largest non-industry & had fracture data based on self-report/death certificate; smallest study reported clinical vertebral fracture data	Moderate / low
Nonvertebral fracture	8 trials; 22098 patients from meta analysis all populations	RR=1.01 (95%CI 0.94, 1.1)	p=0.62 I2 =0%	Not significant (p=0.72)	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, pub bias	5/8 (>50% weight) had higher potential of bias due to methodological problems; funnel plot showed asymmetry	Moderate / low

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: native vitamin D vs placebo/no treatment

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Nonvertebral fracture sensitivity analysis	3 trials; 7939 patients from meta analysis all populations	RR=1.02 (95%CI 0.91, 1.14)	p=0.57 I2 =0%	Not significant	Good	Direct	Precise	Consistent	Adequate	1/3 (36% weight) had low concordance (42-53%)	High / moderate
Hip fracture	8 trials; 22098 patients from meta analysis all populations	RR=1.14 (95%CI 0.98, 1.32)	p=0.76 I2 =0%	Not significant; sensitivity analysis showed very similar summary statistics	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, pub bias	More than half of the studies (>50% weight) had missing data; funnel plot asymmetrical; <50% had industry funding	Moderate / low

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: native vitamin D + calcium vs calcium

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture: clinical	1 trial; 2617 patients from RCT (fracture) all populations	RR=0.14 (95%CI 0.01, 2.77)		Not significant	Good	Direct	Wide CI	Consistent	Adequate	Reported clinical vertebral fractures; had low concordance (42-53%); very wide CI	Low / very low
Nonvertebral fracture	4 trials; 3050 patients from meta analysis all populations	RR=0.92 (95%CI 0.76, 1.1)	p=0.20 I2 =36%	Not significant; sensitivity analysis showed similar results but with increased heterogeneity	Good	Direct	Precise	Consistent	Adequate	2/4 (10.4% weight) had no patient blinding; 1/4 had low concordance (42-53%)	High / moderate
Hip fracture	3 trials; 3103 patients from meta analysis all populations	RR=0.9 (95%CI 0.62, 1.33)	p=0.70 I2 =0%	Not significant (p=0.61); sensitivity analysis showed similar results	Good	Direct	Precise	Consistent	Adequate	2/3 (8% weight) had no patient blinding; one study had low concordance (42-53%)	High / moderate

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: native vitamin D + calcium vs calcium

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Arm: all fractures wrist, ulna, humerus, radius	2 trials; 2849 patients from meta analysis all populations	RR=0.98 (95%CI 0.63, 1.51)	p=0.79 I2 =0%	Not significant; sensitivity analysis showed similar results	Good	Direct	Precise	Consistent	Adequate	Smallest study (17.5% weight) had no patient blinding; 1/2 had low concordance (42-53%)	High / moderate

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: native vitamin D vs calcium

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	1 trial; 2654 patients from RCT (fracture) all populations	RR=1.3 (95%CI 0.29, 5.8)	p=0 I2 =0%	Not significant	Good	Direct	Wide CI	Consistent	Adequate	Low concordance (42-53%)	Low
Nonvertebral fracture	2 trials; 2718 patients from meta analysis all populations	RR=1.08 (95%CI 0.89, 1.31)	p=0.14 I2 =53%	Not significant (p=0.46)	Good	Direct	Precise	Minor inconsistency	Adequate	Largest study (96%) had low concordance (42-53%)	Moderate
Hip fracture	2 trials; 2718 patients from meta analysis all populations	RR=0.9 (95%CI 0.61, 1.32)	p=0.26 I2 =21%	Not significant	Good	Direct	Precise	Consistent	Adequate	Largest study (96%) had low concordance (42-53%)	High / moderate

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: native vitamin D vs calcium

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Distal forearm fracture	1 trial; 2654 patients from RCT (fracture) all populations	RR=0.98 (95%CI 0.61, 1.57)		Not significant (p=0.92)	Good	Direct	Precise	Consistent	Adequate	Low concordance (42-53%)	High / moderate

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: native vitamin D + calcium vs placebo/no treatment

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture sensitivity analysis	1 trial; 2638 patients from meta analysis all populations	RR=0.34 (95%CI 0.01, 8.34)		Not significant	Good	Direct	Wide CI	Consistent	Adequate	Low concordance (42-53%); very wide CI	Low / very low
Nonvertebral fracture sensitivity analysis	6 trials; 6559 patients from meta analysis all populations	RR=0.83 (95%CI 0.73, 0.94)	p=0.32 I2 =14%	Significant; fewer patients with nonvertebral fractures in the intervention group, NNT=50	Poor - incomplete follow up	Direct	Precise	Consistent	Adequate	Largest (45.3% weight) had 46% missing data in each group; another (37%) had low concordance (42-53%); funnel plot approximately symmetrical; <50% had industry funding	Moderate
Hip fracture: sensitivity analysis	7 trials; 9872 patients from meta analysis all populations	RR=0.79 (95%CI 0.65, 0.97)	p=0.50 I2 =0%	Significant, NNT=100	Poor - incomplete follow up	Direct	Precise	Consistent	Adequate	Largest (55.4% weight) had 46% missing data in each group; 2nd largest (20.6% weight) had low concordance; another (14% weight) had less missing data in intervention (28%) than control (36%) group	Moderate

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: native vitamin D + calcium vs placebo/no treatment

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Wrist and lower arm: sensitivity analysis	1 trial; 2638 patients from meta analysis all populations	RR=1.2 (95%CI 0.73, 1.98)		Not significant	Good	Direct	Precise	Consistent	Adequate	Low concordance (42-53%); wrist or lower arm	High / moderate
All clinical fractures	1 trial; 3314 patients from RCT (fracture) all populations	RR=0.96 (95%CI 0.7, 1.33)		Not significant	Poor - not blinded	Direct	Precise	Consistent	Poor - studies, industry	No patient blinding	Moderate / low
All clinical fractures	1 trial; 2638 patients from RCT (fracture) all populations	RR=0.94 (95%CI 0.77, 1.15)		Not significant	Good	Direct	Precise	Consistent	Adequate	Low concordance	High / moderate

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: native vitamin D + calcium vs placebo/no treatment

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
All clinical fractures	1 trial; 5063 patients from RCT (fracture) all populations	RR=0.96 (95%CI 0.78, 1.18)		Not significant	Poor - not blinded	Direct	Precise	Consistent	Poor - studies, industry	No patient blinding; did not take into account intra-cluster correlation but analysed data as individual participants; Industry funding	Moderate / low

APPENDIX VI: EVIDENCE SUMMARY

Vitamin D review: hydroxylated vitamin D vs native vitamin D

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	1 trial; 62 patients from RCT (fracture) all populations	RR=1.56 (95%CI 0.65, 3.77)		Not significant (p=0.32)	Very poor	Direct	Fairly wide CI	Consistent	Adequate	No patient blinding and a differential loss of follow up of 17% in the calcitrol compared to 5% in the colecalciferol group and had a 15% cut off for vertebral fractures	Very low
Nonvertebral fracture	1 trial; 62 patients from RCT (fracture) all populations	RR=1.31 (95%CI 0.47, 3.69)		Not significant	Very poor	Direct	Fairly wide CI	Consistent	Adequate	No patient blinding and a differential follow up of 17% in the calcitrol compared to 5% in the colecalciferol group	Very low

APPENDIX VI: EVIDENCE SUMMARY

Calcium review: calcium vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	7 trials; 6013 patients from meta analysis all populations	RR=0.84 (95%CI 0.66, 1.08)	p=0.80 I2 =0%	Not significant	Good	Indirect intervn - minor, different dose	Precise	Consistent	Adequate	1/7 baseline differences; other >50% weight had calcium above licensed dose; 1/7: patients had other osteoporosis drugs 3/7 industry; funnel plot was symmetrical; sensitivity analysis made little difference	Moderate
Vertebral fracture sensitivity analysis	7 trials; 4542 patients from meta analysis all populations	RR=0.9 (95%CI 0.67, 1.19)	p=0.78 I2 =0%	Not significant	Good	Indirect intervn - minor, different dose	Precise	Consistent	Adequate	In the absence of study in which patients with osteoporosis tx during trial were eliminated from protocol analysis; funnel plot symmetrical	Moderate
Nonvertebral fracture	5 trials; 5717 patients from meta analysis all populations	RR=0.92 (95%CI 0.79, 1.05)	p=0.86 I2 =0%	Not significant; sensitivity analysis was very similar	Good	Direct	Precise	Consistent	Adequate	2/5: Ca above licensed dose; 1/5 possibly confounded because patients took osteoporosis medications; funnel plot fairly symmetrical	High / moderate

APPENDIX VI: EVIDENCE SUMMARY

Calcium review: calcium vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Hip fracture: sensitivity analysis	2 trials; 4103 patients from meta analysis postmenopausal women	RR=1.29 (95%CI 0.89, 1.88)	p=0.45 I2 =0%	Not significant	Good	Direct	Precise	Consistent	Adequate	1/2 had calcium a little above licensed dose; 1/2 had about 50% concordance	High / moderate
Wrist fracture	1 trial; 1460 patients from RCT (fracture) postmenopausal women	RR=1.05 (95%CI 0.57, 1.92)		Not significant (p=0.87)	Good	Indirect intervn - minor, different dose	Precise	Consistent	Adequate	Had calcium a little above licensed dose	Moderate
Distal forearm fracture	1 trial; 1471 patients from RCT (fracture) postmenopausal women	RR=0.64 (95%CI 0.4, 1.02)		Not significant (p=0.06)	Poor - no comparable on other osteo treatment	Direct	Precise	Consistent	Adequate	Patients with osteoporosis tx during trial were eliminated from protocol analysis	Moderate

APPENDIX VI: EVIDENCE SUMMARY

Calcium review: calcium vs placebo

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Upper limb	2 trials; 4103 patients from meta analysis postmenopausal women	RR=1.06 (95%CI 0.75, 1.5)	p=0.49 I2 =0%	Not significant	Good	Direct	Precise	Consistent	Adequate	1/2 studies had calcium a little above licensed dose	High / moderate
All fractures	1 trial; 5574 patients from RCT (fracture) postmenopausal women	RR=0.9 (95%CI 0.79, 1.03)	p=0.85 I2 =0%	Not significant	Good	Direct	Precise	Consistent	Adequate	Calcium a little above licensed dose; potentially confounded by osteoporosis medications	Moderate

APPENDIX VI: EVIDENCE SUMMARY

Cross review: alendronic acid vs raloxifene

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Vertebral fracture	2 trials; 922 patients from meta analysis postmenopausal women	RR=1.35 (95%CI 0.57, 3.18)	p=0.60 I2 =0%	Not significant (p=0.48);	Poor - incomplete follow up	Direct	Fairly wide CI	Consistent	Poor - studies, industry	Largest (55% weight) had only 35% of patients providing results for the vertebral fracture outcome, terminated early w/mean duration ~10 months & was industry funded	Low / very low
Nonvertebral fracture	4 trials; 2370 patients from meta analysis postmenopausal women	RR=0.89 (95%CI 0.53, 1.5)	p=0.91 I2 =0%	Not significant	Poor - incomplete follow up	Direct	Precise	Consistent	Poor - studies, industry	2/4 including largest (52% weight) reported clinical fractures only; largest terminated early and >20% missing data; all industry funded; 1/5 did not blind patients	Moderate / low
Hip fracture	1 trial; 1412 patients from RCT (fracture) postmenopausal women	RR=0.49 (95%CI 0.04, 5.39)		Not significant	Very poor	Direct	Wide CI	Consistent	Poor - studies, industry	Largest study terminated early w/mean duration ~10 months; >20% missing data & was industry funded	Very low

APPENDIX VI: EVIDENCE SUMMARY

Cross review: alendronic acid vs raloxifene

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Wrist fracture	1 trial; 1412 patients from RCT (fracture) postmenopausal women	RR=0.74 (95%CI 0.26, 2.11)		Not significant	Very poor	Direct	Wide CI	Consistent	Poor - studies, industry	Largest study terminated early w/mean duration ~10 months; >20% missing data & was industry funded	Very low
All fractures	3 trials; 2304 patients from meta analysis postmenopausal women	RR=0.99 (95%CI 0.62, 1.6)	p=0.69 I2 =0%	Not significant	Poor - early stopping	Direct	Precise	Consistent	Poor - studies, industry	3/4 including largest (61% weight) industry funded; largest terminated early (mean duration ~10 months) and had >20% missing data	Moderate / low

APPENDIX VI: EVIDENCE SUMMARY

Cross review: alendronic acid vs teriparatide

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
All clinical fractures	1 trial; 203 patients from RCT (fracture) postmenopausal women	RR=0.9 (95%CI 0.36, 2.23)		Not significant	Poor - adverse events	Direct	Fairly wide CI	Consistent	Poor - studies, industry	Fractures reported as safety/adverse event data; Industry funding	Low / very low

APPENDIX VI: EVIDENCE SUMMARY

Cross review: alendronic acid vs HRT

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
Concordance	1 trial; 186 patients from RCT (fracture) postmenopausal women	RR=0.97 (95%CI 0.78, 1.2)		Not significant (p=0.76)	Good	Direct	Precise	Consistent	Adequate		High
Hip fracture	1 trial; 60 patients from RCT (fracture) postmenopausal women	RR=3 (95%CI 0.13, 70.83)		Not significant	Poor - incomplete follow up	Direct	Wide CI	Consistent	Poor - studies, industry	More than 20% missing data and industry funded	Very low
Wrist fracture	1 trial; 60 patients from RCT (fracture) postmenopausal women	RR=0.33 (95%CI 0.01, 7.87)		Not significant	Poor - incomplete follow up	Direct	Wide CI	Consistent	Poor - studies, industry	More than 20% missing data and industry funded	Very low

APPENDIX VI: EVIDENCE SUMMARY

Cross review: alendronic acid vs HRT

Outcome	*Meta-analysis details*	*Summary statistics*	*Hetero p, I2*	*Comments*	*Study quality*	*Directness*	*Imprecision*	*Inconsistency*	*Reporting Bias*	*GRADE Comments*	*GRADE Evidence Rating*
All clinical fractures	1 trial; 60 patients from meta analysis postmenopausal women	RR=1 (95%CI 0.07, 15.26)		Not significant	Poor - incomplete follow up	Direct	Wide CI	Consistent	Poor - studies, industry	More than 20% missing data and industry funded	Very low