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SIGN 142 • Management of osteoporosis and the prevention of fragility fractures

A national clinical guideline

March 2015

Evidence

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

RECOMMENDATIONS

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland, applicability of published evidence to the target population, consistency of the body of evidence, and the balance of benefits and harms of the options.

R For **'strong'** recommendations on interventions that 'should' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm.

R For **'conditional'** recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

GOOD PRACTICE POINTS

✓ Recommended best practice based on the clinical experience of the guideline development group

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Scottish Intercollegiate Guidelines Network

Management of osteoporosis and the prevention of fragility fractures

A national clinical guideline

March 2015

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Osteoporosis is a common bone disease characterised by reduced bone mass which is associated with an increased risk of low-trauma fractures. In 2012, fractures occurred in 19.8 out of 1,000 women and 8.4 out of 1,000 men over the age of 50 in Scotland. The majority of fractures occur in people over the age of 65 and a large proportion of these patients have osteoporosis. Fractures are an important cause of morbidity, and patients who suffer hip fractures and vertebral fractures have a decreased life expectancy compared with population-based controls. A wide range of treatments that can reduce the risk of fractures occurring in patients with osteoporosis is now available. These have the potential to improve clinical outcomes for patients with osteoporosis and to reduce societal costs of medical care associated with fractures.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the management of osteoporosis and prevention of fractures. It addresses risk factors for fracture, commonly-used tools for assessment of fracture risk, approaches to targeting therapy, pharmacological, and non-pharmacological treatments to reduce fracture risk, treatment of painful vertebral fractures and systems of care. The assessment and prevention of falls is excluded as it was covered by a national resource published by NHS Quality Improvement Scotland in 2010, which aimed to prevent fractures in older people by raising the profile of falls,[1] and also a clinical guideline published by the National Institute for Health and Care Excellence (NICE) in 2013.[2] The guideline also excludes issues surrounding the surgical management of fractures and postoperative care of patients with fractures.

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to rheumatologists, endocrinologists, general practitioners (GPs), physicians involved in care of the elderly, orthopaedic surgeons, gynaecologists, specialist nurses involved in the care of patients with osteoporosis and pharmacists. It will also be of interest to physiotherapists, occupational therapists and those involved in exercise sciences and nutritional management of people with osteoporosis. Patients affected by fractures and osteoporosis and their carers may also find the guideline to be of interest.

1.2.3 DEFINITIONS

Osteoporosis is defined as a syndrome associated with low bone mass and microarchitectural deterioration of bone tissue which lead to an increased risk of fractures.[3] The World Health Organization (WHO) has defined osteoporosis to exist in postmenopausal women or men when axial bone density T-score (measured by dual-energy X-ray absorptiometry (DXA)) at the femoral neck falls 2.5 standard deviations (SD) or more below the average value in young healthy women (T-score ≤ -2.5 SD).[4,5] The International Society for Clinical Densitometry has published an Official Position which states that osteoporosis may be diagnosed in postmenopausal women and in men aged 50 and older if the T-score of the lumbar spine, total hip, or femoral neck is -2.5 or less.[6]

Although the risk of fractures is substantially increased in people with osteoporosis, about two thirds of non-vertebral fractures occur in patients who do not have osteoporosis as defined by DXA.[7] In contrast, vertebral fractures almost always signify the presence of osteoporosis. Reflecting this fact, the presence of vertebral fractures has commonly been used as an entry criterion for enrolment into clinical trials of osteoporosis treatment.

Severe osteoporosis (established osteoporosis) is defined by bone mineral density (BMD) that is 2.5 SD or more below the young female adult mean in the presence of one or more fragility fractures.[4, 5]

Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level trauma.[8] Major fracture is taken to mean any of clinical vertebral fracture, forearm, hip or shoulder fracture.

Compliance refers to the extent to which a patient takes medication according to dosing instructions. Persistence refers to continuing the treatment for the prescribed duration. Adherence to medication is defined as the extent to which the patient takes medication as prescribed by their healthcare provider. Concordance is defined as "agreement between the patient and healthcare professional, reached after negotiation, that respects the beliefs and wishes of the patient in determining whether, when and how their medicine is taken, and (in which) the primacy of the patient's decision (is recognised)".[9] As such, adherence can be construed as encompassing the concepts of both compliance and persistence.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.3.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation, also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have marketing authorisation for medicinal use in humans.

Generally 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[10]

"Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability."[10]

The General Medical Council (GMC) recommends that when prescribing a medicine 'off label', doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to prescribing, the licensing status of a medication should be checked in the summary of product characteristics (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[11]

1.3.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

Healthcare Improvement Scotland processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Care Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to National Health Service (NHS) boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice relevant to this guideline is summarised in section 10.4.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

2.1 RISK FACTORS

R **People with a history of fragility fractures over the age of 50 should be offered DXA scanning to evaluate the need for antiosteoporosis therapy.**

2.2 QUANTIFYING THE RISK OF FRACTURE

R **Fracture-risk assessment should be carried out, preferably using QFracture, prior to DXA in patients with clinical risk factors for osteoporosis and in whom antiosteoporosis treatment is being considered.**

R **Measurement of bone mineral density by DXA at the spine and hip should be carried out following fracture-risk assessment in patients in whom antiosteoporosis treatment is being considered.**

2.3 MANAGEMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

R **Repeat BMD measurements by DXA after an interval of three years may be considered to assess response to treatment in postmenopausal women on alendronic acid, ibandronic acid, zolendronic acid or denosumab therapy.**

2.4 SYSTEMS OF CARE

R **Patients over the age of 50 who have experienced a fragility fracture should be managed within a formal integrated system of care that incorporates a fracture liaison service.**

3 Risk factors

3.1 RISK IN THE CONTEXT OF OSTEOPOROSIS

In the context of osteoporosis the risk that is of concern is risk of fracture. Fracture risk is usually considered in terms of vertebral fracture risk, non-vertebral fracture risk and hip fracture risk. The development of fracture- risk tools *(see section 4.2)* has made it possible for clinicians and their patients to make an estimate of the risk of fracture based on clinical risk factors over five- and 10-year timeframes.

3.1.1 DESCRIPTORS OF RISK

Relative risk (RR) is a ratio of the probability of an event (in the context of osteoporosis, a fracture) occurring in an exposed group versus a non-exposed group. Generally, a relative risk will remain constant for any given intervention or variable but the significance of the relative risk is completely dependent on the event absolute risk. The limitation of relative risk in the context of osteoporosis is the inability to make a quantification of overall risk of fracture.

Absolute risk is the chance of an event (in the context of osteoporosis, a fracture) occurring over a specified time interval. Lifetime risk is a way of expressing absolute risk over a lifetime timeframe. In the context of fracture risk, risk is usually expressed over five- or 10-year intervals.

Absolute risk can be described using widely available fracture-risk calculators *(see section 4.2)*. Treatment interventions are most effective when the absolute event risk is highest. Knowledge of absolute fracture risk makes it easier to assess the absolute benefit of a treatment intervention. This is particularly important when considering the benefits and harms of a treatment and when considering the cost effectiveness of an intervention.

3.1.2 MODIFIABLE RISK

Modifiable risk factors are those that can be treated or modified by an appropriate intervention. In the context of osteoporosis some risk factors such as alcohol intake, diet, smoking and BMD might be considered modifiable, whereas others such as age, gender and ethnicity are non-modifiable. The evidence for efficacy of treatment interventions is often limited to a defined group of modifiable risk factors. While risk factors have been categorised as modifiable or non-modifiable in the following section, it is recognised that both characteristics may apply to some risk factors. For example, while BMD can be modified by diet, exercise and drug treatments, it is believed that up to 90% of the variation in BMD is genetically determined and therefore non-modifiable.[12]

This concept of modifiable risk factors is important in the context of pharmacological interventions which act by regulating bone remodelling and increasing BMD. The available data show that the beneficial effects on fracture risk for most of these interventions is restricted to patients with osteoporosis as defined by the presence of pre-existing vertebral fractures and or those with BMD values that lie within or close to the osteoporotic range (T-score ≤ -2.5)[13] *(see section 6.4)*. 1^{++}

It is important to consider modifiable risk with any intervention otherwise a treatment might be used without evidence of benefit, exposing the patient to treatment-related harms while incurring unnecessary cost.

3.1.3 SINGLE AND MULTIPLE RISK FACTORS

A number of the most important modifiable and non-modifiable single risk factors are considered in detail in sections 3.2–3.6. The specific factors included were suggested by the guideline development group and those which were associated with a robust evidence base identified by a scoping search were retained. This list should not be considered comprehensive, however, as the evidence which supports the association between some medications, diseases and other factors with fracture risk is variable and constantly evolving.

There are some clinical measurements that can be made to further assess fracture risk. These measurements include assessment of bone density, for example, with DXA, measurement of bone quality, for example, with ultrasound densitometry, or measurement of bone turnover, for example, using biochemical markers.

3.2 NON-MODIFIABLE RISK FACTORS

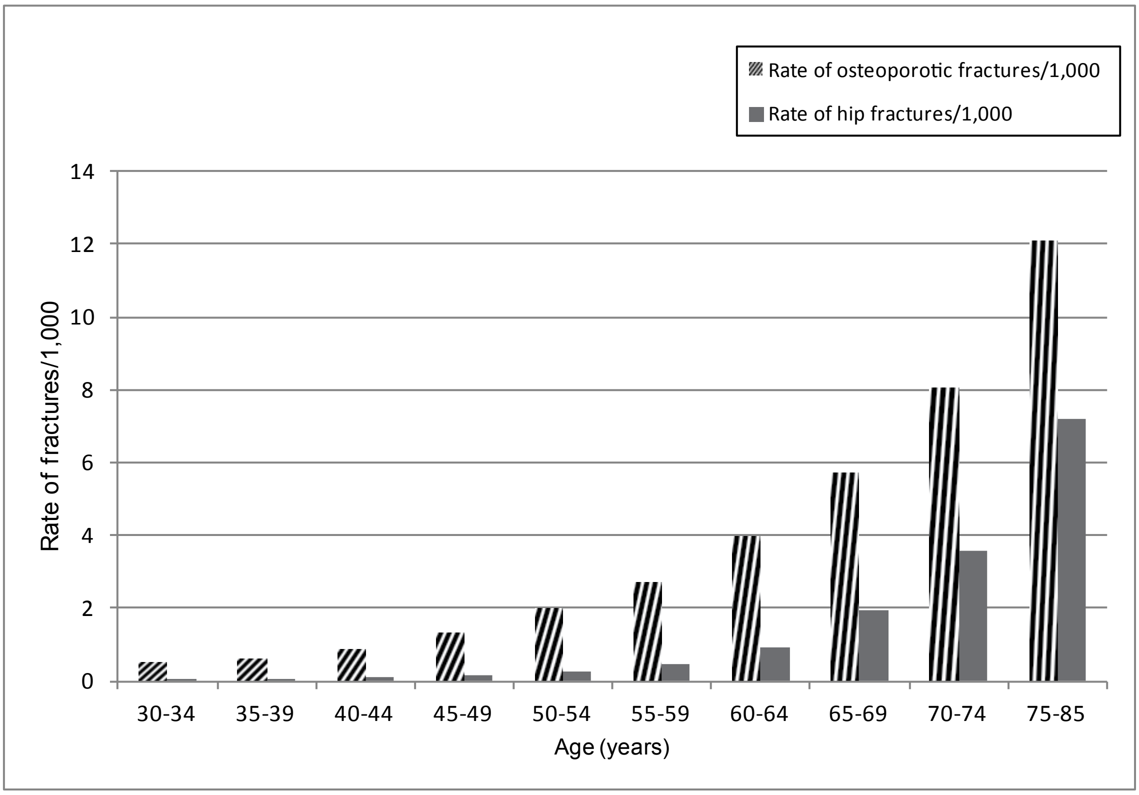
3.2.1 AGE

A large open cohort study drawn from 357 general practices in England and Wales which included 1,183,663 women and 1,174,232 men aged 30–85 who had not suffered a previous fracture demonstrated that risk of osteoporotic and hip fractures rose steadily with age, and more steeply after the age of 65 in women and 75 in men *(see Figures 1 and 2)*.[14] People below the age of 50 are likely to be at low risk of fracture in the absence of other risk factors. 2^{++}

3.2.2 GENDER

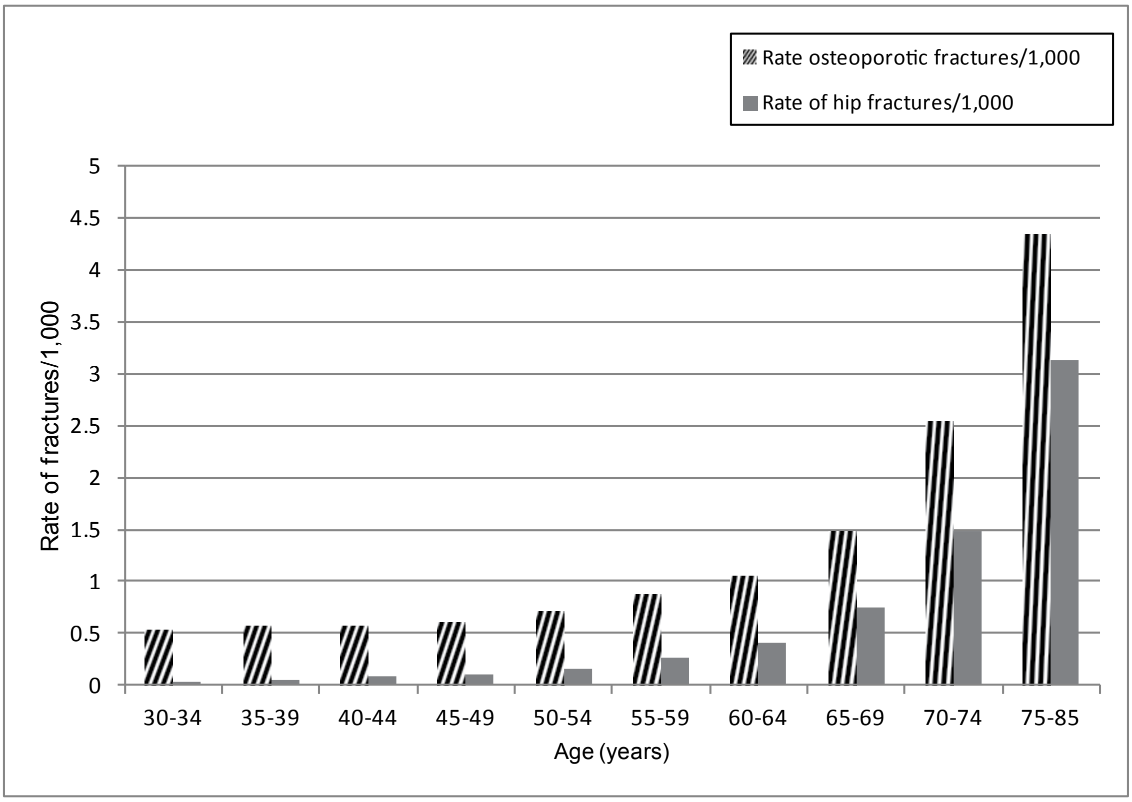
Women are at increased risk of osteoporotic (distal radius, hip or vertebral) and hip fractures compared with men. Pooling data for all patients in a cohort study *(see section 3.2.1)*, the overall incidence of osteoporotic fracture in women was 3.08 per 1,000 person-years (95% confidence interval (CI) 3.04 to 3.12) and 0.99 (95% CI 0.96 to 1.01) per 1,000 person-years in men. Hip fracture incidence was lower in both women and men at 1.15 (95% CI 1.13 to 1.17) and 0.38 (95% CI 0.36 to 0.39) per 1,000 person-years respectively.[14] 2^{++}

Figure 1: Incidence rates of osteoporotic and hip fractures per 1,000 person-years in women



Data adapted from Hippisley-Cox et al, 2009[14]

Figure 2: Incidence rates of osteoporotic and hip fractures per 1,000 person-years in men



Data adapted from Hippisley-Cox et al, 2009[14]

3.2.3 ETHNICITY

Analysis of ethnicity in Census data indicates that the proportion of the Scottish population constituted from ethnic minorities rose from 2% in 2001 to 4% in 2011.[15, 16] Projections of rates of fertility and mortality, internal and international migration among different ethnic groupings predict sustained increases in the overall proportion of minority ethnic groups to around 7% of the Scottish population and up to 20% of the UK population by 2050.[17, 18]

A cohort study of 23 million patient-years showed independent associations of ethnicity with overall fracture risk. Caucasian men and women are at increased risk of fragility fractures at all sites compared with other ethnic groups. Black Caribbean women are at the lowest risk of any osteoporotic fracture with a hazard ratio (HR) of 0.23 (95% CI 0.15 to 0.33) and for hip fracture of 0.27 (95% CI 0.15 to 0.47). In men, Bangladeshi men are at lowest risk with an HR of 0.29 (95% CI 0.15 to 0.53) for any osteoporotic fracture and an HR of 0.13 (95% CI 0.02 to 0.92) for hip fracture.[19] 2^{++}

Prospective data on ethnicity and fractures were gathered from 2,302 women and 1,810 men aged over 50 in Hong Kong. Women were followed up for an average of four years (range 1–14 years) and the cohort comprised 14,733 person-years. The incidence rate for vertebral fracture was 194/100,000 person-years in men and 508/100,000 person-years in women. At the age of 65–69, the hip fracture rates for Asian (Hong Kong Chinese and Japanese) men and women were less than half of those in Caucasians (49% and 33% respectively), but the vertebral fracture rate was higher in Asian women, resulting in a high vertebral-to-hip fracture ratio.[20] 2^{+}

3.2.4 PREVIOUS FRACTURE

A meta-analysis of 11 cohort studies (n=60,161 men and women), included in the NICE guideline on osteoporosis: assessing the risk of fragility fracture,[8] reported that a history of previous fracture was associated with an increased risk of any fracture (adjusted RR 1.77, 95% CI 1.64 to 1.91), osteoporotic fractures (adjusted RR 1.76, 95% CI 1.60 to 1.93) and hip fractures (adjusted RR 1.62, 95% CI 1.30 to 2.01). Considering history of previous fracture as a prognostic factor for risk of future fracture, there was no significant difference between men and women. 2^{++}

A large study from Taiwan assessed the risk of subsequent fracture in 9,986 patients with distal radius fracture and 81,227 controls without fracture. The incidence of hip fracture within one year increased with age in both cohorts. The risk was 5.7 times (84.6 *v* 14.9 per 10,000 person-years) greater in the distal radius fracture cohort than in the comparison cohort. Regression analyses showed the hazard ratios of hip fracture in relation to distal radius fracture was 3.45 (95% CI 2.59 to 4.61). The highest incidence was within the first month after distal radius fracture, 17-fold higher than the comparison cohort (17.9 *v* 1.05 per 10,000 person-years).[21] Incidence of subsequent hip fractures is significantly increased within the first month after distal radius fracture in patients older than 60 years. 2^{+}

The National Osteoporosis Risk Assessment (NORA) study assessed rate of fracture after incident rib fracture in postmenopausal women in the United States of America (USA) aged over 50, with no diagnosis of osteoporosis, on no bone medications, and with no BMD measurement in the previous 12 months. At baseline, 4,758 (3.07%) women reported a rib-fracture history without other fractures; 6,300 women reported 6,830 new clinical fractures, including wrist (2,271), rib (1,891), spine (1,136), hip (941) and forearm (591). Adjusted relative risk values for future fractures in women with history of rib fracture compared to women with no fracture history were 5.4 (95% CI 4.8 to 6.1) at the rib, 2.1 (95% CI 1.7 to 2.6) at the spine, and 1.4 (95% CI 1.1 to 1.7) at the wrist, and not significant for forearm or hip fractures. Future fracture risk was at least doubled in women with a history of rib fracture at all ages: RR 3.4 (95% CI 2.8 to 4.0) for those aged 50–59, 2.5 (95% CI 2.1 to 3.0) for those aged 60–69, 2.0 (95% CI 1.7 to 2.3) for those aged 70–79, and 2.0 (95% CI 1.6 to 2.6) for those aged over 80.[7] 2^{+}

In the Global Longitudinal Study of Osteoporosis in Women (GLOW) over the age of 55, further fractures were assessed following any incident fracture. Of 60,393 women enrolled across 10 countries in North America, Europe and Australia, follow-up data were available for 51,762. Of these, 17.6% had suffered one fracture, 4.0% had suffered two fractures, and 1.6% had suffered three or more fractures since age 45. After two years of follow up, 3,149 women suffered 3,683 incident fractures. Compared with women with no previous fractures, women with one, two, or three or more prior fractures were 1.8-, 3.0-, and 4.8-fold more likely to have any incident fracture. Those with three or more prior fractures were 9.1-fold more likely to sustain a new vertebral fracture. Nine out of 10 prior fracture locations were associated with an incident fracture. The strongest predictors of incident vertebral and hip fractures were prior vertebral fracture (HR 7.3) and hip fracture (HR 3.5). Prior rib fractures were associated with a 2.3-fold risk of subsequent vertebral fracture, and previous upper-leg fracture predicted a 2.2-fold increased risk of hip fracture. Women with a history of ankle fracture were at 1.8-fold risk of future fracture of a weight-bearing bone.[22] 2^{+}

R **People with a history of fragility fractures over the age of 50 should be offered DXA scanning to evaluate the need for antiosteoporosis therapy.**

3.2.5 FAMILY HISTORY

A large cohort study of 1,183,663 UK women found that parental history of osteoporosis was significantly associated with risk of any osteoporotic fracture (HR 1.63, 95% CI 1.38 to 1.92) but not hip fracture (HR 1.09, 95% CI 0.69 to 1.71). Parental history of osteoporosis was not significantly associated with incidence of fracture in men.[14] An extension and update of this cohort study which included 1,598,294 women found a stronger association between parental history of osteoporosis and risk of any osteoporotic fracture in women (HR 1.74, 95% CI 1.47 to 2.05) although risks of hip fracture or any fracture in men were not significantly associated.[19] 2^{++}

A non-systematic review and meta-analysis of seven pooled prospective cohort studies showed that a parental history of fracture was associated with a modest, but significantly increased, risk of any fracture, osteoporotic fracture and hip fracture in men and women combined. The risk ratio for any fracture was 1.17 (95% CI 1.07 to 1.28), for any osteoporotic fracture was 1.18 (95% CI 1.06 to 1.31), and for hip fracture was 1.49 (95% CI 1.17 to 1.89). A family history of hip fracture in parents was associated with a significant risk both of all osteoporotic fracture (RR 1.54, 95% CI 1.25 to 1.88) and of hip fracture (RR 2.27, 95% CI 1.47 to 3.49).[23] 2^{+}

A retrospective analysis of a single-cohort study from Finland investigated the effects of first degree relatives' fractures on fracture incidence in women following the menopause. Wrist and hip fractures sustained by sisters, but not brothers, mothers or fathers, were associated with a significantly lowered 10-year fragility fracture-free survival rate (HR 0.56, 95% CI 0.37 to 0.84).[24] 3

R **People with a parental history of osteoporosis, particularly those over the age of 50, should be considered for fracture-risk assessment.**

3.2.6 REPRODUCTIVE FACTORS

Observational studies have shown a significant relationship between reproductive factors and fragility fracture.

A survey which included 3,402 women aged 50–79 showed an age at menarche of 16 years or older was associated with an increased risk of vertebral fracture (RR 1.80, 95% CI 1.24 to 2.63).[25] 3

A prospective population study which included 6,936 women showed that age at menarche of 15 years or older was associated with a modest increase in risk of distal forearm (Colles') fracture (HR 1.5, 95% CI 1.1 to 2.0). The overall number of fractures in the cohort was low, however, and the effect of delayed menarche was no longer statistically significant on multivariate analysis (HR 1.3, 95% CI 0.8 to 2.1).[26] 2^{+}

A large cross-sectional population study showed that early menopause (natural cessation of menstruation before age of 45) was significantly associated with overall fracture rate (OR 1.5, 95% CI 1.2 to 1.8) and also with the specific outcomes of any lifetime fracture (OR 1.4, 95% CI 1.1 to 1.7), any fracture after age of 50 (OR 1.4, 95% CI 1.0 to 1.8) and any fracture after menopause (OR 2.1, 95% CI 1.6 to 2.7).[27] 2^{+}

A prospective observational study looked at the long-term effects of early menopause on risk of osteoporosis and fragility fractures. Women with early menopause (before the age of 47) had a risk ratio of 1.83 (95% CI 1.22 to 2.74) for osteoporosis at age of 77 and a risk ratio of 1.68 (95% CI 1.05 to 2.57) for fragility fracture compared to women with menopause occurring at age of 47 or later.[28] 2^{-}

In contrast to earlier studies, a cohort study of white females aged over 65 in the USA showed that a history of postmenopausal oophorectomy was not associated with an increased risk of hip (HR 1.1, 95% CI 0.9 to 1.5) or vertebral fracture (HR 0.7, 95% CI 0.5 to 1.2). There was the potential for bias in this study with poor reporting of loss to follow up.[29] 2^{+}

Hormone replacement therapy (HRT) which is often used to control menopausal symptoms is associated with fracture risk reduction *(see section 6.4.11)*, therefore women with a history of early menopause who were treated with HRT are less likely to be at increased risk of fracture linked to early menopause.

R **Women over the age of 50 with a history of previously untreated early menopause should be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.3 MODIFIABLE RISK FACTORS

3.3.1 BONE MINERAL DENSITY

Low bone mineral density is a strong risk factor for fracture which is influenced by both genetic and environmental factors as well as coexisting diseases and various drug treatments. In women and men BMD assessment using axial DXA (at femoral neck, total hip and/or lumbar spine) or peripheral DXA (including calcaneal BMD) are predictive of future fracture risk (including risk of hip fractures and non-vertebral fractures).[30]

While most studies have reported femoral neck BMD, studies reporting total hip BMD and lumbar spine BMD suggest that measurement at these sites perform similarly in terms of overall fracture risk prediction.[30] At axial sites, hip BMD is more predictive of osteoporotic fractures than spine BMD and may be more strongly 2^{+}
predictive of non-vertebral fractures in men (RR 1.6, 95% CI 1.5 to 1.8) than in women (p=0.01 for interaction).[31] Peripheral DXA predicts risk of future hip fracture but is less predictive than history of previous fracture.

In isolation, BMD as assessed by DXA accounts for only a small proportion of the increase in fracture risk that occurs with ageing, and performance of axial BMD in predicting future fracture risk is increased when 3
combined with clinical risk factors such as age and gender.[32]

R **Women and men with low BMD on DXA scanning should undergo further fracture-risk assessment to evaluate the need for antiosteoporosis therapy.**

3.3.2 ALCOHOL INTAKE

Although alcohol appears to have an effect on bone-forming cells (osteoblasts), slowing bone turnover, the specific mechanisms by which alcohol affects bone are poorly understood. Evidence for an association between alcohol consumption and fracture risk comes from two large meta-analyses.

A meta-analysis of eight prospective cohort studies and five case-control studies which included premenopausal and postmenopausal women and men showed that hip fracture risk was modified according to the level of alcohol consumption.[33] The authors converted the different measures of alcohol consumption reported in studies to a standard 'drink' of 14 g of pure alcohol (1.75 units). People consuming less than 0.5 drinks per day (0.88 units) had a non-significantly lower risk of hip fracture compared with abstainers (RR 0.84, 95% CI 0.70 to 1.01). People consuming from 0.5 to 1 drink per day (0.88 to 1.75 units) had a significantly lower risk of hip fracture compared to abstainers (RR 0.80, 95% CI 0.71 to 0.91). Those consuming one to 2^{++}
two drinks per day (1.75 to 3.5 units) did not differ from abstainers (RR 0.91, 95% CI 0.76 to 1.09). People consuming more than two drinks per day (3.5 units) had a higher risk of hip fracture compared to those abstaining from alcohol (RR 1.39, 95% CI 1.08 to 1.79).

There was conflicting evidence around the link between alcohol consumption and risk of wrist/forearm fracture. Two studies in the meta-analysis found no association while one found that women consuming 1.8 drinks or more per day (3.15 units) had a higher risk of wrist fracture than abstainers (RR 1.38, 95% CI 1.09 to 1.74). Two studies evaluated the effect of alcohol on vertebral fracture risk. One revealed no association and the other showed that men consuming more than 0.3 drinks per day (0.525 units) had increased odds of fracture, although confidence intervals were extremely wide (adjusted odds ratio (OR) 4.61, 95% CI 1.19 to 17.90).[34]

Alcohol consumption is estimated to be responsible for approximately 22% of falls in men and 14% of falls 4
in women below the age of 65 in Scotland, dropping to 12% and 4% respectively in people aged over 65.[35]

R **People over the age of 50 who consume more than 3.5 units of alcohol per day should be considered for fracture-risk assessment.**

R **People who consume more than 3.5 units of alcohol per day should be advised to reduce their alcohol intake to nationally recommended levels** (<21 units/week in men, <14 units per week in women).

3.3.3 WEIGHT

One non-systematic review and meta-analysis examined the effect of body mass index (BMI) on fracture risk. It included 12 large cohort studies comprising 59,644 people (44,757 female and 252,034 person-years with 1,141 incident hip fractures). The mean age of the cohorts in each contributing study was >50. The BMI level at the time of fracture was not recorded in most studies. The age-adjusted risk for any type of fracture increased significantly with lower BMI. Overall the RR per unit increase in BMI was 0.98 for any fracture, 0.97 for osteoporotic fracture and 0.93 for hip fracture (all p<0.001). Compared with a BMI of 25, a BMI of 20 was associated with a nearly twofold increase in relative risk for hip fracture (RR 1.95, 95% CI 1.71 to 2.22). A BMI of 30 was only associated with a 17% relative risk reduction compared with a BMI of 25 (RR 0.83, 95% CI 0.69 to 0.99).[36] 2^+

R **Adults with a low BMI** (<20 kg/m^2) **are at increased risk of fracture and should be encouraged to achieve and maintain a BMI level of 20–25 kg/m^2.**

R **People over the age of 50 with a low BMI** (<20 kg/m^2) **may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.3.4 SMOKING

Smoking is a well-established risk factor for fracture.[37] Evidence for the association between smoking and risk of future fractures, and the dependence of this risk on age, sex, BMI and BMD were described in a meta-analysis of cohort studies. 2^+

One non-systematic review and meta-analysis of 10 large prospective cohort studies (random population samples) from USA, Canada, Japan and Europe included 59,232 men and women (74% female) and 250,000 patient-years of follow up. It found that current smoking was associated with a significantly increased risk of any kind of fracture.[38] This risk was greater in men than women. Adjustments for BMD and BMI slightly reduced the risk ratio as smokers tend to be lighter than non-smokers. For all fractures, the unadjusted relative risk associated with current smoking was 1.25 (95% CI 1.15 to 1.36). The relative risk adjusted for BMD was 1.13 (95% CI, 1.01 to 1.25). For osteoporotic fractures, unadjusted relative risk was 1.29 (95% CI 1.17 to 1.43) and adjusted for BMD was 1.13 (95% CI 1.00 to 1.28). The highest risk was observed for hip fracture (RR 1.84, 95% CI 1.53 to 3.33) with slightly lower risk after adjustment for BMD (RR 1.6, 95% CI 1.27 to 2.02). 2^+

Adjustment for BMI had a downward influence on risk for all fracture outcomes. Ex-smokers were also at significantly increased risk of fracture compared with non-smokers though this was lower than for current smokers.

R **Smokers over the age of 50 should be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

R **Smokers should be advised to stop smoking to reduce their risk of fragility fracture.**

3.3.5 PHYSICAL INACTIVITY

Inactivity is often cited as a modifiable risk factor for fracture, based on associations in observational studies between lack of physical activity and bone health, measured by fractures, risk of falls, and BMD.[39, 40] Health status is the most powerful confounder for the association between physical activity and osteoporotic fractures.

Healthier individuals may choose to be active, while less healthy people may exercise less because of their illness. Therefore the causal link may be between illness and fracture, and illness and lack of exercise, not the fracture and lack of exercise. Conversely, people with greater muscular strength and function usually perform better in sports and may be more likely to choose a physically active lifestyle. Their genetically-inherited larger muscle mass and bone strength may confer a lower fracture risk, rather than the higher activity level. Without access to RCTs which can eliminate these potential confounding factors, it is not possible to draw definitive conclusions from observational data on the association between physical activity and fracture risk.

One barrier to publication of such trials may be the large sample size required. It has been estimated that to design an adequately-powered RCT to show the relationship between exercise and fracture, even among high-risk individuals, over 5,500 women would need to be recruited to each sample (assuming a rate ratio of 0.80).[41]

2^{-}

The relationship between bone health and exercise as a treatment strategy is covered in sections 6.2, 7.2.1 and 7.4.

3.4 COEXISTING DISEASES

Many diseases and drug treatments have been associated with osteoporosis and an increased risk of fragility fracture. The following section presents the evidence for associations between common diseases and an increased risk of fracture. It is important to emphasise that this is not an exhaustive list of all conditions that can be associated with osteoporosis since the literature search was limited to published data where an association between the disease and fracture was sought. Management of conditions associated with osteoporosis is outside of the remit of this guideline and specialist advice should be sought as appropriate.

3.4.1 DIABETES

Several systematic reviews and meta-analyses have reported an association between diabetes mellitus and fracture risk, although there is considerable variation in the populations studied.

One meta-analysis which included 80 studies calculated fracture risk and BMD changes across several skeletal sites.[42] Heterogeneity existed between the studies in terms of duration of diabetes, gender, definition of diabetes, age and complications. The large numbers of participants included in the meta-analysis of eight suitable studies, however, enabled significance to be shown for an increase in hip fracture rate in patients with type 2 diabetes with an RR of 1.38 (95% CI 1.25 to 1.53). Sensitivity analyses which eliminate heterogeneity yielded an overall RR of 8.65 for hip fracture in people with type 1 diabetes (95% CI 7.26 to 10.3) and 1.19 (95% CI 1.11 to 1.27) for any fracture in patients with type 2 diabetes. There was a borderline significance for wrist fracture but a dichotomy of results made this less convincing. BMD was reduced in people with type 1 diabetes at hip and spine, and increased at both sites in people with type 2 diabetes. Body mass index was a major determinant for BMD in both the spine and hip, reflecting the tendency for people with type 2 diabetes to be larger and heavier than people with type 1 diabetes.

2^{+}

Another systematic review included 16 observational studies involving 836,941 participants with 139,531 fractures.[43] Type 2 diabetes was associated with an increased risk of hip fracture in both men (summary RR 2.8, 95% CI 1.2 to 6.6) and women (summary RR 2.1, 95% CI 1.6 to 2.7). The association between type of diabetes and hip fracture incidence was stronger for type 1 diabetes (summary RR 6.3, 95% CI 2.6 to 15.1) than for type 2 diabetes (summary RR 1.7, 95% CI 1.3 to 2.2). Type 2 diabetes was weakly associated with fractures at other individual sites, but most effect estimates were not statistically significant. When combined, the overall relative risk for other non-vertebral fractures (excluding hip) for people with type 2 diabetes was 1.3, (95% CI 1.1 to 1.5). The duration of diabetes was unknown and no effect of long-term disease could be ascertained from this study.

2^{+}

A very large open cohort study drawn from primary-care populations in England and Wales which included 1,183,663 women and 1,174,232 men aged between 30 and 85 who had not suffered a previous fracture demonstrated that people with diabetes were at increased risk of both hip and osteoporotic fractures. In men with type 2 diabetes, the relative risks of hip and other osteoporotic fractures were 1.42 (95% CI 1.15 to 1.74) and 1.18 (95% CI 1.02 to 1.37) respectively. In women with type 2 diabetes the relative risks of hip and other osteoporotic fractures were 1.79 (95% CI 1.59 to 2.02) and 1.27 (95% CI 1.17 to 1.39) respectively.[14]

2^{++}

A case-control study included participants who had sustained a fracture during one calendar year in Denmark as cases (n=124,655), and control subjects of the same age and sex randomly selected from the general population (n=373,962). Exposure was a diagnosis of type 1 or 2 diabetes and use of antidiabetic medications (*see section 3.5.14*). A diagnosis of type 1 or type 2 diabetes was associated with an increased risk of any fracture (odds ratio (OR) 1.3, 95% CI 1.2 to 1.5 for type 1 diabetes and OR 1.2, 95% CI 1.1 to 1.3 for type 2 diabetes after adjustment for confounders) and of hip fractures (OR 1.7, 95% CI 1.3 to 2.2 for type 1

2^{+}

diabetes, and OR 1.4, 95% CI 1.2 to 1.6 for type 2 diabetes). No adjustment was made for BMI, smoking or glycaemic control.[44] 2^{+}

The effect of both type 1 and type 2 diabetes on fractures was evaluated in a subsequent analysis with multiple adjustments for comorbidities, durations and complications of diabetes, and medications. Risk of fracture was greater in the first 2.5 years of disease duration in people with type 2 diabetes with no specific additional effect of complications of diabetes or age. The lack of clarity about several aspects of the methodology of this study raises concerns about the reliability of the results.[45] 2^{-}

R **People over the age of 50 with diabetes may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.4.2 INFLAMMATORY RHEUMATIC DISEASES

A large prospective open cohort study used data from 420 UK general practices to develop scores for the Qfracture risk assessment tool *(see section 4.2.2)*.[19] A total of 3,142,673 people were in the derivation cohort and a further 1,583,373 in the subsequent validation cohort. A total of 59,772 incident diagnoses of osteoporotic fracture were identified in the derivation cohort and 28,685 in the validation cohort. There were 21,308 and 9,350 people with rheumatoid arthritis (RA) in these cohorts respectively with 1,627 and 827 patients with systemic lupus erythematosus (SLE). Adjusted hazard ratios for fracture in people with either RA or SLE were 1.33 (95% CI 1.25 to 1.43) for any major fracture and 1.69 (95% CI 1.53 to 1.86) for hip fracture in women. Hazard ratios for men were 1.55 (95% CI 1.33 to1.82) for any major fracture and 1.90 (95% CI 1.53 to 2.37) for hip fracture. 2^{++}

A cohort study of people with RA aged ≥40 in the UK General Practice Research Database (GPRD) reported that individuals with RA had an increased risk of fracture compared with controls, which was largest at the hip (RR 2.0, 95% CI 1.8 to 2.3) and spine (RR 2.4, 95% CI 2.0 to 2.8).[46] 2^{+}

R **People over the age of 50 with rheumatoid arthritis or systemic lupus erythematosus may be considered for fracture-risk assessment particularly in the presence of other risk factors.**

3.4.3 GASTROINTESTINAL DISEASES

A systematic review with meta-analysis of people with coeliac disease (CD) included eight suitable studies. The review evaluated 20,955 people with CD who suffered 1,819 (8.7%) fractures and 96,777 controls who suffered 5,955 (6.1%) fractures. There was a significant association between CD and fracture (pooled OR for all fractures 1.43, 95% CI 1.15 to 1.78). The studies included were very heterogeneous with wide variability in settings of care and between patients with well-established disease and recent diagnosis. There were differences in how fractures were ascertained, size of population, and duration of CD.[47] 2^{+}

A small cohort study of 265 patients with a diagnosis of CD was compared to 530 age- and sex-matched controls. Compared with the control group, the CD cohort showed significantly higher incidence rate and risk of first peripheral fracture before diagnosis (adjusted HR 1.78, 95% CI 1.23 to 2.56, p<0.002). Fracture risk was significantly associated with CD presentation with gastrointestinal (GI) symptoms (p<0.003). In the time period after diagnosis the risk of fractures was comparable between the CD cohort and controls in both sexes.[48] 2^{+}

Analysis of a large general practice-based cohort study in the UK involving 1,183,663 women and 1,174,234 men showed that people with a history of GI conditions including Crohn's disease, ulcerative colitis, coeliac disease, steatorrhoea and blind loop syndrome, were at increased risk of fracture. The adjusted hazard ratio was 1.23 (95% CI 1.06 to 1.43) for any fracture and 1.10 (95% CI 0.85 to 1.42) for hip fracture in women.[14] 2^{++}

R **People over the age of 50 with inflammatory bowel disease or malabsorption may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.4.4 CYSTIC FIBROSIS

One systematic review of patients with cystic fibrosis included 12 studies reporting prevalence of fracture, all of which were cross sectional.[49] A total of 1,055 patients were studied but no control data were reported. Pooled prevalence of vertebral fractures was 14.0% (95% CI 7.8 to 21.7%, six studies). Pooled prevalence for non-vertebral fractures was 19.7% (95% CI 6.8 to 38.8%, four studies) but increased to 30.6–35.7% on removal of individual studies during sensitivity analysis to limit heterogeneity. Actual numbers of fractures were not reported. Prevalence decreased with increasing BMI and age. Rib fractures were included in the estimation of non-vertebral fractures and, as these are usually not verified on X-ray, may result in an overestimate of risk. 2^{+}

Insufficient data were identified to make a recommendation with regard to fracture-risk assessment in patients with cystic fibrosis, however vertebral and non-vertebral fractures are common in this condition.

✓ The assessment and management of osteoporosis in patients with cystic fibrosis is complex and should be undertaken by a specialist team.

3.4.5 EPILEPSY

One meta-analysis was identified which included 11 studies that evaluated fracture risk in people with epilepsy (n=15,663).[50] There was an increase in the risk of fracture in people with epilepsy compared to controls. Relative risk of any fracture was 2.2 (95% CI 1.9 to 2.5, five studies); hip fracture (RR 5.3, 95% CI 3.2 to 8.8, six studies); forearm fracture (RR 1.7, 95% CI 1.2 to 2.3, six studies) and vertebral fracture (RR 6.2, 95% CI 2.5 to 15.5, three studies). One third of fractures were linked to seizures. Tonic-clonic seizures resulted in a higher rate of fracture than other types. Rate of fracture was higher in institutionalised patients compared to outpatients. The effects of epilepsy therapy could not be adequately assessed because very few studies specifically addressed this. Overall it is difficult to quantify the contribution other factors make to the excess of fractures in people with epilepsy and it is likely to be a combination of the seizures themselves, their treatment and other comorbidities. This study was unable to clarify this due to the heterogeneity of the study populations and the large number of confounders. 2^{+}

Although the relative risk of any fracture was found to be approximately doubled in people with epilepsy compared with controls, the author refers to another study where adjusted risk drops to 1.2, suggesting the multiple confounders in this population, which are not taken into account in this meta-analysis, may hold significant influence over the outcome.[51] Epilepsy may be linked to cerebral palsy, post stroke conditions, learning difficulties, intracranial neoplasms, and all of these conditions may contribute to the increase in fracture risk.

R **Institutionalised patients with epilepsy over the age of 50 are at an increased risk of fracture and may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.4.6 HUMAN IMMUNODEFICIENCY VIRUS

Two cohort studies assessed risk of fragility fracture in people with human immunodeficiency virus (HIV) infection.

The first study analysed fracture incidence in 119,318 men of whom 33% were infected. Fifty per cent of these were over the age of 50 and 55% were black or Hispanic. There was no analysis with ethnicity as a variable. Fracture rate was increased in infected individuals but this was reduced to a non-significant RR of 1.10 (95% CI 0.97 to 1.25) after adjustment for confounding factors.[52] 2^{++}

A second cohort study analysed the rate of fracture in 5,826 HIV-infected men and women, annualised it and then compared it with the annualised background rate of fracture in the United States (US) population derived from the National Hospital Ambulatory Medical Care Survey-Outpatient Departments (NHAMCS-OPD) database. An increase was shown in the annualised rate of fracture compared to the background US rate. Data were not adjusted for confounders due to the lack of available data from the indirect control database. Methodological quality in this study is therefore weak.[53] 2^{-}

A linked database study from Denmark showed that HIV-infected people had an increased risk of fracture (incidence rate ratio (IRR) 1.5, 95% CI 1.4 to 1.7) compared with population controls. The relative risk was 2^{-}

lower in HIV-monoinfected patients (IRR 1.3, 95% CI 1.2 to 1.4) than in HIV/hepatitis C virus (HCV)-coinfected patients (IRR 2.9, 95% CI 2.5 to 3.4). Both HIV-monoinfected and HIV/HCV-coinfected patients had increased risk of low-energy fracture, (IRR 1.6, 95% CI 1.4 to 1.8; and 3.8, 95% CI 3.0 to 4.9, respectively). However, only HIV/HCV-coinfected patients had increased risk of high-energy fracture (IRR 2.4, 95% CI 2.0 to 2.9). Among HIV-monoinfected patients the risk of low-energy fracture was only significantly increased after highly active antiretroviral therapy (HAART) exposure, (IRR 1.8, 95% CI 1.5 to 2.1). The increased risk in HAART-exposed patients was not associated with CD4 cell count, prior acquired immunodeficiency syndrome (AIDS), tenofovir or efavirenz exposure, but with comorbidity and smoking. This study was limited by failure to adequately adjust for known confounders and for treatment other than HAART.[54]

2^{-}

There is insufficient evidence to determine whether HIV infection itself predisposes to fractures independently of drug treatments and other confounding factors.

3.4.7 PRIMARY HYPERPARATHYROIDISM AND OTHER ENDOCRINE DISEASES

Analysis of a large general practice-based cohort study in the UK involving 1,183,663 women and 1,174,234 men showed that people with a history of endocrine diseases including primary hyperparathyroidism (HPT), secondary HPT, thyrotoxicosis and Cushing's disease were at increased risk of fracture. The adjusted hazard ratio was 1.11 (95% CI 1.00 to 1.25) for any fracture and 1.19 (95% CI 1.01 to 1.40) for hip fracture in women.[14]

2^{++}

A retrospective cohort study of the Danish national database of patients diagnosed with primary HPT (n=1,201, controls n=3,601) evaluated the effects of primary HPT on fractures.[55] It compared those who underwent surveillance, those who had surgery and controls. There was an increased incidence of fractures both before and after diagnosis compared to matched controls. The hazard ratio was not clearly defined for the comparison between patients and controls. There was no difference in fracture rate between those who had surgery and those who did not, which is at variance from other studies.[56-58] Survival was significantly greater in those who had surgery. There were some methodological concerns with this study, in that there was no adjustment for confounders when comparing fracture rate in HPT with controls and the criteria for diagnosis of primary HPT was not specified.

2^{-}

The effect of parathyroidectomy on fracture risk in patients with primary HPT was examined in a cohort study of 159 patients receiving surgery compared to 374 controls.[59] The 10-year fracture-free survival was 94% in those who had parathryoidectomy compared to 81% in those without surgery (HR 0.35, 95% CI 0.17 to 0.74, p=0.006). Those receiving surgery were more likely to have high calcium and parathyroid hormone levels but the outcome after surgery remained significant after adjusting for confounders.

2^{-}

Based on a consensus decision, the NICE guideline on assessing the risk of fragility fracture recommends that women under the age of 65 and men under the age of 75 with the following secondary causes of osteoporosis should be considered for fracture-risk assessment: hypogonadism in either sex including untreated premature menopause and treatment with aromatase inhibitors or androgen deprivation therapy; hyperthyroidism; hyperparathyroidism; hyperprolactinaemia; Cushing's disease; diabetes.[8]

4

R **People over the age of 50 with hyperparathyroidism or other endocrine diseases may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.4.8 CHRONIC LIVER DISEASE

A large open cohort study drawn from primary-care populations in England and Wales which included 1,183,663 women and 1,174,232 men aged between 30 and 85 who had not suffered a previous fracture demonstrated that people with chronic liver disease were at increased risk of fractures. The hazard ratios for hip and osteoporotic fractures in men with chronic liver disease were 3.75, (95% CI 2.01 to 6.99) and 3.59 (95% CI 2.54 to 5.24) respectively. The hazard ratios for hip and osteoporotic fractures in women with chronic liver disease were 1.75 (95% CI 1.02 to 3.02) and 1.79 (95% CI 1.30 to 2.06).[14]

2^{++}

A GPRD cohort study examining the effect of primary biliary cirrhosis (PBC) identified 930 people with PBC and 9,202 age- and sex-matched controls.[60] There was an approximate doubling of risk of any fracture (HR 2.03, 95% CI 1.7 to 2.44), hip fracture (HR 2.14, 95% CI 1.4 to 3.28) and ulna/radius fracture (1.96, 95% CI 1.42

2^{+}

to 2.71) in people with PBC. The absolute excess in fracture rates were 12.5 per 1,000 person-years (95% CI 8.1 to 16.9) for any fracture, 1.9 per 1,000 person-years (95% CI 0.3 to 3.5) for hip fracture, and 3.4 per 1,000 person-years (95% CI 1.2 to 5.7) for ulna/radius fracture. 2^{+}

R **People over the age of 50 with chronic liver disease may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.4.9 NEUROLOGICAL DISORDERS

Alzheimer's disease

One retrospective cohort study from the GPRD compared hip fracture rate in people with Alzheimer's disease (AD) with those who did not have the diagnosis. A total of 10,052 people with AD were compared to 10,052 people without AD from 391 general practices. Follow up was over an average of 2.2 years for those with AD. Hip fracture rate incidence was 17.4 per 1,000 patient-years (95% CI, 15.7 to 19.2) for patients with AD compared to 6.6 (95% CI 5.8 to 7.6) for people without AD. After adjusting for potential confounders, AD remained a significant risk for hip fracture in both men and women: HR for women 3.3 (95% CI 2.4 to 4.2) and men 3.2 (95% CI 1.4 to 7.1). At nine years 14.5% of people with AD had had a hip fracture compared to 5.9% of people without AD.[61] 2^{+}

A second retrospective cohort study compared 5,396 community-dwelling individuals with AD with 5,396 age- and sex-matched controls drawn from the combined databases of US managed care plans. Of the AD cohort, 17.7% suffered any fracture compared with 7.9% of the cohort without AD. Multiple adjustments were made for confounders. The adjusted OR for any fracture was 1.9 (95% CI 1.6 to 2.1). Higher odds ratios were associated with being female, being older, a prior diagnosis of osteoporosis, congestive heart failure, cerebrovascular disease, liver disease, and use of narcotic or antidepressant medication.[62] 2^{-}

Multiple sclerosis

One population-based cohort study using the GPRD matched 5,565 patients with multiple sclerosis (MS) with 33,360 people without MS and compared rates of fracture over an 11-year period. Risk of osteoporotic fracture was increased (HR 1.35, 95% CI 1.13 to 1.62) and hazard ratio for hip fracture was 2.79 (95% CI 1.83 to 4.26) after adjustment for confounders. Recent use of prednisolone increased the risk of fracture and absolute fracture rates increased with age. In people who had never received treatment for osteoporosis, the risk of hip fracture was greater (HR 3.05, 95% CI 1.97 to 4.73).[63] 2^{++}

Similar results were obtained in a large cohort study which used data from the English Hospital Episode Statistics with a total MS population of 8,783 patients. Significantly elevated risk for all fractures was found in patients with MS (rate ratio 1.99, 95% CI 1.93 to 2.05). Risks were particularly high for femoral fractures (rate ratio 2.79, 95% CI 2.65 to 2.93), femoral shaft fracture (rate ratio 6.69, 95% CI 6.12 to 7.29), and fractures of the tibia or ankle (rate ratio 2.81, 95% CI 2.66 to 2.96).[64] 2^{+}

A study conducted in Denmark compared a cohort of 2,963 patients with MS to a reference population of 15,436. Compared with controls, patients with MS had no overall increased risk of fracture (adjusted HR 1.0, 95% CI 0.9 to 1.2). The risk of femur/hip fracture (adjusted HR 1.9, 95% CI 1.1 to 3.4) was significantly increased compared to controls. As compared with unexposed individuals, patients with MS who had been exposed to a short course of methylprednisolone in the prior year had no significantly increased risk of osteoporotic fracture (adjusted HR 1.2, 95% CI 0.5 to 2.9). Disabled patients with MS who had Expanded Disability Status Scale (EDSS) scores between 6 and 10, had a 2.6-fold increased risk of osteoporotic fracture (adjusted OR 2.6, 95% CI 1.0 to 6.6) compared with patients with an EDSS score between 0 and 3.[65] 2^{+}

Another registry study from the Netherlands found that during follow up, there were 59 fractures among patients with MS (2.4%) and 227 fractures among controls (1.8%). Patients with MS had a 1.7-fold increased risk of osteoporotic fracture (HR 1.73, 95% CI 1.18 to 2.53) and a four-fold increased risk of hip fracture (HR 4.08, 95% CI 2.21 to 7.56). The risk of osteoporotic fracture was significantly greater for patients with MS who had been prescribed antidepressants (HR 3.25, 95% CI 1.77 to 5.97) or hypnotics/anxiolytics (HR 3.40, 95% CI 2.06 to 5.63) in the previous six months, compared with controls.[66] 2^{+}

Parkinson's disease

A study of 394 patients with Parkinson's disease (PD) and a reference population of 3,940 people in Taiwan found hip fractures in 10.4% of patients with PD and 4.1% of people in the comparison cohort during the follow-up period. The adjusted HR for hip fracture during the eight year follow-up period for patients with PD was 2.71 (95% CI 1.92 to 3.83) compared to people in the comparison cohort.[67] 2^+

A large multicentre cohort study from primary-care databases used data on incident fractures over a two-year period and comorbidities assessed by self report. Modelling was used to see which comorbidities added to the predictive value of the risk-assessment tool FRAX *(see section 4.2.1)* and whether combinations of comorbidities were significant. Of 52,960 women with follow-up data, 3,224 (6.1%) sustained an incident fracture over two years. All recorded comorbidities were significantly associated with fracture, except for high cholesterol, hypertension, coeliac disease, and cancer. The strongest association was seen with PD (age-adjusted HR 2.2, 95% CI 1.6 to 3.1). Comorbidities that contributed most to fracture prediction in a Cox regression model with FRAX risk factors as additional predictors were PD, MS, chronic obstructive pulmonary disease (COPD), osteoarthritis, and heart disease.[68] A GPRD records study included 4,687 patients with PD and a matched reference population. A statistically significant increased risk was observed for any fracture (adjusted HR 1.89, 95% CI 1.67 to 2.14), osteoporotic fracture (adjusted HR 1.99, 95% CI 1.72 to 2.30) and hip fracture (adjusted HR 3.08, 95% CI 2.43 to 3.89). Fracture risk further increased with history of fracture, falls, low BMI, renal disease, antidepressant use and use of high-dose antipsychotics.[69] 2^+

Stroke

A Dutch case-control study compared all patients aged over 18 with a hip or femur fracture with matched controls in a 1:4 ratio. Logistic regression adjusted for multiple confounders. Six thousand seven hundred and sixty three patients with a hip or femur fracture were compared to 26,341 controls. The mean age of cases and controls was 75. Patients with a stroke were more likely to have a hip or femur fracture (adjusted OR 1.96, 95% CI 1.65 to 2.33). The risk of fracture was highest in the first three months after a stroke (OR 3.35, 95% CI 1.87 to 5.97). Hip/femur fracture risk after stroke declined with increasing age.[70] 2^+

R **People over the age of 50 with neurological disease** (including Alzheimer's disease, Parkinson's disease, multiple sclerosis and stroke) **may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.4.10 DEPRESSION

A meta-analysis of ten cohort studies which investigated the association between depression and fracture showed that for studies that reported hazard ratios, depression was associated with a 17% increase in risk of fractures of all types (six studies, n=108,157; HR 1.17, 95% CI 1.00 to 1.36, p=0.05).[71] For studies that reported relative risk, depression was associated with a 52% increase in risk of fractures of all types (four studies, n=33,409; RR 1.52, 95% CI 1.26 to 1.85, p<0.001). Adjustment for antidepressant medication rendered the association between depression and fracture risk non-significant (three studies with no adjustment, n=14,777; HR 1.30, 95% CI 1.11 to 1.52, p=0.001 versus three studies with adjustment, n=93,380; HR 1.05, 95% CI 0.86 to 1.29, p=0.6). The authors suggest that much of the apparent association between depression and bone health may be mediated by the medications used to treat it (*see section 3.5.2*). Considerable heterogeneity was noted in the studies included in this review in relation to effect size, ethnicity/race of participants, sex, age, and duration or severity of depression, as well as other important covariables. 2^+

There is insufficient evidence to determine if depression is associated with an increased risk of fracture independently of drug treatments and other confounding factors.

3.4.11 CHRONIC KIDNEY DISEASE

Four studies of the association between chronic kidney disease (CKD), as characterised by estimated glomerular filtration rate (eGFR), and fracture were identified.

In a retrospective cohort study of 33,091 male veterans in the USA, 176 hip fractures were identified over 80 months. After adjustment for age, BMI, diabetes, and use of selected medications, relative risks of hip 3 fracture for men with an eGFR of 30 to 59 ml/min/1.73 m^2 and 15 to 29 ml/min/1.73 m^2 were 1.28 (95% CI 0.88 to 1.66) and 3.98 (95% CI 2.25 to 7.74), respectively. All data were obtained from medical records with use of estimated GFR based on two serum creatinine measurements during a six-month period. The control group had only one creatinine measurement.[72]

3

In a case-cohort study of women aged 65 or older, eGFR was correlated with risk of hip and vertebral fracture. A random sample of 149 women with incident hip fractures and 150 women with incident vertebral fractures from a cohort of 9,704 was compared to 396 randomly-selected controls from the same cohort. In models adjusted for age, weight, and calcaneal bone density, decreasing eGFR was associated with increased risk of hip fracture. Compared with women with an eGFR of 60 ml/min/1.73 m^2 or greater, the hazard ratio for hip fracture was 1.57 (95% CI 0.89 to 2.76) in those with an eGFR of 45–59 ml/min/1.73 m^2 and 2.32 (95% CI 1.15 to 4.68) in those with an eGFR of <45 ml/min/1.73 m^2 (p for trend 0.02). When, however, further factors were adjusted for (health status, smoking status, walking for exercise, history of falls, the presence of diabetes mellitus, previous fracture since age 50, inability to rise from a chair) the association was weaker and did not reach statistical significance (p for trend 0.09). Women with a reduced eGFR were at increased risk of trochanteric hip fracture. The fully-adjusted hazard ratio was 3.69 (95% CI 1.21 to 11.94) in women with an eGFR of 45–59 ml/min/1.73 m^2 and 5.04 (95% CI 1.38 to 18.45) in women with an eGFR of 45 ml/min/1.73 m^2 (p for trend 0.02).

2^{+}

Although decreasing eGFR was associated with increasing age-adjusted risk of new vertebral fracture, the association seemed to be due to lower body weight and lower BMD in women with impaired renal function and was removed by adjusting for these variables. The odds ratio adjusted for age, weight, and calcaneal BMD was 1.33 (95% CI 0.63 to 2.80) in women with an eGFR less than 45 ml/min/1.73 m^2 and 1.08 (95% CI 0.61 to 1.92) in women with an eGFR 45–59 ml/min/1.73 m^2 compared with women with an eGFR 60 ml/min/1.73 m^2 or greater (p for trend 0.47).[73]

In the Women's Health Initiative (WHI) Observational Study, 93,676 women aged 50–79 were followed for an average of seven years. Of these, 397 women with hip fracture were matched with 397 controls. The odds ratio for hip fracture was 2.50 (95% CI 1.32 to 4.72) for eGFR less than 60 ml/min/1.73 m^2 compared with stages 0 to 1, after adjustment for body mass, parental hip fracture, smoking, alcohol consumption, and physical function. No association was observed for an eGFR of 60–90 ml/min/1.73 m^2 (OR 1.04, 95% CI 0.66 to 1.64). Additional adjustment for poor health status, haemoglobin, serum 25-hydroxy vitamin D, and bone metabolism markers did not affect these associations.[74]

2^{+}

A cross-sectional study of the US population that was conducted over six years involved 6,270 individuals older than 50 who were assessed for eGFR, including 159 participants with a history of hip fracture. Chronic kidney disease, as defined by an eGFR of 15–60 ml/min/1.73 m^2, was present in 875 (14.0%) of the participants. There was a significantly increased likelihood of reporting a hip fracture in participants with an eGFR <60 ml/min/1.73 m^2 (OR 2.12, 95% CI 1.18 to 3.80). In younger participants (aged 50–74), the prevalence of CKD was approximately threefold higher in those with a history of hip fracture compared with those without a history of hip fracture (19.0 *v* 6.2% respectively, p=0.04). In regression analyses, only the presence of CKD (OR 2.32, 95% CI 1.13 to 4.74), a reported history of osteoporosis (OR 2.52, 95% CI 1.08 to 5.91), and low physical activity levels (OR 2.10, 95% CI 1.03 to 4.27) were associated with a history of hip fracture.[75]

3

A large general practice-based cohort study in the UK involving 1,598,294 women and 1,544,379 men showed that patients with chronic renal disease (not further defined) had an increased risk of fracture. In women, the adjusted hazard ratio was 1.27 (95% CI 1.07 to 1.51) for any fracture and 1.51 (1.17 to 1.96) for hip fracture, in men the adjusted hazard ratio was 1.58 (95% CI 1.20 to 2.08) for any fracture and 1.81 (95% CI 1.27 to 2.58) for hip fracture.[19]

2^{++}

R **People over the age of 50 with moderate to severe chronic kidney disease** (eGFR <60 ml/min/1.73 m^2) **may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

✓ The assessment and management of osteoporosis in patients with CKD who have an eGFR <30 ml/min/1.73 m^2 is complex and should be undertaken by specialists with experience in the area.

3.4.12 ASTHMA

A large general practice-based cohort study in the UK involving 1,183,663 women and 1,174,234 men showed that people with a history of asthma had an increased risk of fracture. The adjusted hazard ratio was 1.29 (95% CI 1.22 to 1.36) for any fracture and 1.32 (1.21 to 1.44) for hip fracture in women and similar in men.[14] 2^{++}

R **People over the age of 50 with asthma may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.5 PHARMACOLOGICAL RISK FACTORS

It is recognised that medications can induce liver enzymes and interfere with vitamin D metabolism and further influence bone metabolism through other mechanisms. The following section presents the evidence for associations between common medications and an increased risk of fracture. It is important to emphasise that this is not an exhaustive list of all drugs that can be associated with osteoporosis since the literature search was limited to published data where an association between the drug class and fracture was sought. Management of conditions associated with osteoporosis is outside of the remit of this guideline and specialist advice should be sought as appropriate.

3.5.1 ANTICOAGULANTS

Warfarin and other vitamin K antagonists (VKA) are prescribed to decrease the risk of blood clotting. Because γ-carboxylation of specific glutamic acid residues, which is the key mechanism of protection against clotting, is also required for activation of osteocalcin and other bone matrix proteins, use of VKA might increase the risk of osteoporotic fractures.[76]

A retrospective cohort study of patients (mean age 79–80) hospitalised for atrial fibrillation showed that the adjusted odds ratio of fracture in 4,461 patients prescribed long-term warfarin therapy for at least one year was 1.25 (95% CI, 1.06 to 1.48) compared with 7,587 patients who were not prescribed warfarin. The association between osteoporotic fracture and long-term warfarin use was significant in men (OR 1.63, 95% CI 1.26 to 2.10) but non-significant in women (OR 1.05, 95% CI 0.88 to 1.26).[76] There was a lack of clarity in this study about the exclusion of previous fractures from the analyses. 2^{+}

A case-control study of Canadian patients aged over 70 showed VKA oral anticoagulants were not significantly associated with osteoporotic fractures. There was no significant difference in the exposure to anticoagulants between participants who suffered a fracture (3.2%) and participants who did not (3.0%); (crude odds ratio 1.0, 95% CI 0.7 to 1.5).[77] Many participants had been using anticoagulants for less than 90 days. 2^{+}

A large Danish national registry was used to compare 124,655 people who had sustained a fracture during one calendar year with 373,962 age- and gender-matched controls. After adjustment for confounders, current use of VKA was associated with an increased risk of any fracture (OR 1.10, 95% CI 1.03 to 1.18). Fracture risk was not increased in former users. In dose-effect subanalyses, only those who had used a relatively low accumulated dose of VKA (less than 100 defined daily dosages) had an increased risk of any fracture (OR 1.49, 95% CI 1.31 to 1.69), as well as an increased risk of fractures at the hip (OR 1.43, 95% CI 1.09 to 1.87) and forearm (OR 1.42, 95% CI 1.02 to 1.97).[78] 2^{+}

The association between low molecular weight heparin use and fracture rate has not been adequately addressed by research.

The evidence regarding the association between anticoagulant use and risk of fracture is conflicting and it is not possible to form a recommendation.

3.5.2 ANTIDEPRESSANTS

A large prospective cohort study which included 1,598,294 women and 1,544,379 men from the UK showed that all types of antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, and others) were associated with increased fracture risks in both men and women, which were similar in magnitude for each type of antidepressant. In women, antidepressants were associated with increased risks of osteoporotic 2^{++}

fracture (adjusted HR 1.37, 95% CI 1.33 to 1.42) and hip fracture (HR 1.39, 95% CI 1.33 to 1.46). The hazard ratios were marginally higher in men than in women (adjusted HR 1.60, 95% CI 1.50 to 1.70 for osteoporotic fracture and 1.69, 95% CI 1.53 to 1.86 for hip fracture).[19] 2^{++}

A Canadian case-control study showed that in people over the age of 50 who have suffered a fracture, selective serotonin reuptake inhibitors (SSRIs) were associated with the highest adjusted odds of osteoporotic fractures (OR 1.45, 95% CI 1.32 to 1.59).[79] Monoamine oxidase inhibitors (OR 1.15, 95% CI, 1.07 to 1.24) and benzodiazepines (OR 1.10, 95% CI, 1.04 to 1.16) were associated with a smaller excess fracture risk compared with SSRIs. Lithium appeared to have a protective effect (OR 0.63, 95% CI 0.43 to 0.93), whereas the relationship between antipsychotics and fracture was not significant *(see section 3.5.4)*. 2^{+}

A further case-control study of patients from the GPRD compared current, previous and never use of lithium in 231,778 people who had sustained a fracture and 231,778 people without fractures. Current use of lithium was linked to a lower risk of fractures (adjusted OR 0.75, 95% CI 0.64 to 0.88) which did not vary with cumulative duration of use. Past use of lithium was associated with an increased risk of fractures (adjusted OR 1.35, 95% CI 1.01 to 1.79) which increased with time since discontinuation. The authors suggest a stronger link between the results of this study and the underlying mood disorders than to the pharmacological effect of lithium due to the lack of association with cumulative duration of therapy.[80] 2^{++}

Another case-control study of the Danish national registry *(see section 3.5.1)* studied the association between fracture risk and use and dosage of antidepressants. A dose-response relationship was observed for fracture risk (OR increasing from 1.15, 95% CI 1.11 to 1.19 at <0.15 defined daily dose/day to 1.40, 95% CI 1.35 to 1.46 for ≥0.75 defined daily dose/day). The risk of fracture was higher with SSRIs than with tricyclic antidepressants.[81] The study showed an increased risk of fractures at most sites except the forearm in those aged 60 or over for most types of psychotropic drugs and, in particular, for antidepressants. 2^{+}

Fracture risks appear to be increased in people taking antidepressant medications, particularly SSRIs. It is unknown whether these risks are due to changes in bone mass or due to an increased risk of falls.

R **People over the age of 50 on long-term antidepressant therapy** (in particular SSRIs) **may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.5.3 ANTICONVULSANTS

It is estimated that around 54,000 people in Scotland have a diagnosis of epilepsy and are treated with antiepileptic drugs (AEDs).[82] These medications may be associated with vitamin D deficiency and/or with increased rates of falls, both of which are linked with fracture rates.

In a large prospective cohort study of women aged 50–79 enrolled in the WHI, antiepileptic drugs were associated with a significantly-increased risk of total (HR 1.44, 95% CI 1.30 to 1.61) and site-specific fractures, including hip (HR 1.51, 95% CI 1.05 to 2.17), clinical vertebral fractures (HR 1.60, 95% CI 1.20 to 2.12) and lower arm or wrist fractures (HR 1.40, 95% CI 1.11 to 1.76).[83] The risk of fractures was a function of the number and type of AEDs used, with women who used more than one AED as opposed to single AED use (HR 1.55, 95% CI 1.15 to 2.09) and those who used enzyme-inducing AEDs as opposed to the more recently introduced non-enzyme-inducing AEDs (HR 1.36, 95% CI 1.09 to 1.69) more likely to have a fracture. There was a significant association of AED use with falls (>2 falls: HR 1.62, 95% CI 1.50 to 1.74). 2^{+}

A prospective cohort study assessed the longitudinal relationship between anticonvulsant medication use and fracture over a 4.5-year period among adults aged 50 and older, including a large sample of patients with bipolar disorder. Individuals with osteoporosis or epilepsy were excluded. Use of anticonvulsant medications was associated with more than a twofold increased risk of fracture over the study period for the entire sample (HR 2.42, 95% CI 2.23 to 2.63). Patients with bipolar disorder had a 21% increased risk of fracture independent of anticonvulsant use (HR 1.21, 95% CI 1.10 to 1.33) but no additional fracture risk compared to anticonvulsant users without serious mental illness. The authors note that patients with bipolar disorder are far more likely to be prescribed anticonvulsant medications than those without mental illness, so although the relative risk of fracture is not higher for this group, the absolute burden of disability and morbidity associated with fractures is greater.[84] 2^{+}

Individuals with epilepsy are at higher risk of fracture, partly due to seizures and increased risk of falls, however enzyme-inducing antiepileptic agents also increase fracture risk.

R **People with epilepsy over the age of 50 who are taking antiepileptic medication, in particular enzyme-inducing antiepileptic agents, may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.5.4 ANTIPSYCHOTICS

A meta-analysis of 12 observational studies calculated the pooled relative risk for any fracture in patients taking antipsychotic medications as 1.59 (95% CI, 1.27 to 1.98). Heterogeneity was noted to be large and there was evidence of publication bias. The study quality is limited by the pooling of all fracture types and antipsychotic drugs into a single risk statistic.[85] 2^{++}

A nested case-control study using data from a medical claims database identified 851 fracture cases and 4,220 controls with PD who had used atypical antipsychotics within 60 days of the analysis. After adjustment for potential confounders, use of any atypical antipsychotic was associated with a 60% increase in the relative risk of fracture (OR 1.6, 95% CI 1.2 to 2.0). For example, use of quetiapine (OR 2.3, 95% CI 1.5 to 3.7), risperidone (OR 1.2, 95% CI 0.9 to 1.7), or olanzapine (OR 1.7, 95% CI 1.2 to 2.5) was associated with a higher rate of fracture compared with non-use.[86] The use of a prescription database means that compliance with therapy could not be adequately monitored; also it is unclear to what extent the results of this study can be extrapolated to a non-Parkinsonian population. 2^{+}

Antipsychotic medication may be associated with an increased rate of fracture in people with Parkinson's disease, but further research is required to evaluate this further and determine if the risk applies to other disease groups taking these agents.

3.5.5 AROMATASE INHIBITORS AND TAMOXIFEN

One population-based cohort of 2,748 postmenopausal women with breast cancer aged 65 or older showed an increased relative risk of hip fracture for users of aromatase inhibitors (AI) compared with users of tamoxifen (HR 3.24, 95% CI 1.05 to 9.98), with an absolute risk increase of 1.1% over 36 months.[87] Hip fracture risk among women not taking any hormone therapy was also elevated compared to users of tamoxifen (HR 3.32, 95% CI 1.14 to 9.65). Confidence intervals for these estimates were wide indicating that it may be difficult to predict the true size of this effect. There was no significant difference between the adjusted risk of total non-vertebral fracture between AI users (HR 1.34, 95% CI 0.92 to 1.94) or patients not taking any hormone therapy (HR 1.07, 95% CI 0.75 to 1.54) compared with users of tamoxifen. 2^{+}

A large Danish case-control study identified 64,548 participants who had suffered a fracture and 193,641 age-matched controls. Ever use of tamoxifen was not associated with risk of any fracture (OR 1.06, 95% CI 0.88 to 1.27) or vertebral fracture (OR 0.49, 95% CI 0.19 to 1.29). There was an increased risk of hip fracture (OR 1.51, 95% CI 1.06 to 2.14) but this was only in past users (one year prior to fracture) and in low doses. The authors of the study suggest that as the increase in risk of hip fracture was seen with low doses and in prior, rather than current, users of tamoxifen, it was probably not linked to the pharmacological properties of the drug but rather to factors determining its discontinuation such as development of bone metastases, which increase the risk of fractures, or with changes to more aggressive therapy linked to disease progression which may increase use of AIs and chemotherapy associated with more pronounced bone loss and risk of fractures. Ever use of AIs was associated with an increased risk of hip fracture (OR 4.24, 95% CI 1.03 to 2.09) and any fracture (OR 2.03, 95% CI 1.05 to 3.93).[88] 2^{++}

Consensus guidelines recommend a DXA scan at commencement of AI treatment.[89]

R **Women over the age of 50 taking aromatase inhibitors may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.5.6 BETA BLOCKERS

Only one report of sufficient quality was identified that examined the relationship between use of beta blockers and risk of fracture.

This analysed two case-control studies, carried out in patients drawn from the UK GPRD and Dutch records linkage systems (RLS).[90] The study population in the GPRD comprised 22,247 cases and 22,247 controls, whereas in the Dutch RLS 6,763 cases and 26,341 controls were included. Current use of beta blockers was associated with a significantly decreased risk of hip/femur fracture in both studies (adjusted OR 0.83, 95% CI 0.75 to 0.92 in GPRD and 0.87, 95% CI 0.80 to 0.95 in Dutch RLS), whereas recent and past use was not. The protective effect of beta blockers was only present among patients who had been treated with other antihypertensive agents either concurrently or in the past. This finding was consistent in both the GPRD (adjusted OR 0.73, 95% CI 0.64 to 0.83) and Dutch RLS (adjusted OR 0.76, 95% CI 0.67 to 0.86). 2^{+}

No evidence was identified that suggested beta blockers increase fracture risk.

3.5.7 BENZODIAZEPINES

A case-control study of the Danish national registry *(see section 3.5.1)* investigated the association between fracture risk and the use of anxiolytics and sedatives (including benzodiazepines), neuroleptics and antidepressants. Thirty five thousand eight hundred and forty participants (28.8%) and 82,766 controls (22.1%) were recorded to have used sedatives, anxiolytics, and/or hypnotics but there was no subdivision that analysed benzodiazepines alone. Use of anxiolytics and/or sedatives increased fracture risk by around 10% but a dose-response relationship was only evident with hip fractures. There was an increased risk of fractures at most sites in the age group ≥60 for most types of psychotropic drugs and, in particular, for antidepressants. In the age group below 40 the overall fracture risk increased with the use of anxiolytics and sedatives.[81] 2^{+}

The role of benzodiazepines as a risk factor for fracture is unclear at present.

3.5.8 HORMONAL CONTRACEPTION

A systematic review investigated the association between the use of progestogen-only contraception and fracture risk or BMD change. Only one RCT was identified which included fracture as an outcome, and this did not show a significant association between depot medroxyprogesterone acetate (DMPA) and fracture risk in female military recruits after adjusting for baseline BMD.[91]

In observational studies current DMPA users had lower mean BMD than non-users and greater declines in BMD over time. The presence and magnitude of the deficit varied among studies; some found statistically significant differences in BMD between DMPA users and non-users and others did not. Among the cross-sectional studies, the deficits in BMD among DMPA users were generally within 1 SD of the mean BMD for the non-users. In the longitudinal studies of adult women, rates of change in BMD over time differed; most of the studies enrolled continuing DMPA users and reported decreases of less than 1% per year. However, the two studies that enrolled women initiating DMPA use found larger decreases of about 2–3% per year. Limited evidence suggests that women who discontinue DMPA use before menopause can regain lost bone mass, that women who discontinue DMPA when they reach menopause do not experience the rapid period of bone loss that non-DMPA users experience and that postmenopausal women who previously used DMPA have BMD levels similar to those of women who have never used DMPA.[91] 2^{+}

A Cochrane review identified 16 RCTs reporting bone outcomes in women using hormonal contraception. No trials reported fracture outcomes. Four studies included the injectable progestogen-only contraceptive DMPA of which two were placebo controlled. Since the oestrogen preparations and routes of administration differed for the trials, no meta-analysis was conducted. The two trials showed BMD increases for the women who received DMPA plus oestrogen supplement and decreases for those who had DMPA plus placebo. The methodological quality of studies was generally low with concerns about allocation concealment, blinding and drop-out rates. In addition, one of the placebo-controlled trials was conducted in a population of adolescent girls only.[92] 1^{++}

A UK case-control study drawn from GPRD identified 17,527 participants with incident fractures and 70,130 controls with exposure to either DMPA or oral contraceptives (DMPA exposure: 11 and 8%, respectively). Participants were aged 20–44. Compared with non-use, current use of one to two, three to nine, or 10 or more DMPA prescriptions yielded adjusted odds ratios for fractures of 1.18 (95% CI, 0.93 to 1.49), 1.36 (95% CI, 1.15 to 1.60), and 1.54 (95% CI, 1.33 to 1.78), respectively. The relative fracture risk was mainly increased for women with current exposure of more than two to three years but also with past exposure at a time over six months before the study index date. When a longer retrospective threshold was used (over two years before study index date) the increased risk for past exposure to DMPA largely disappeared, which may suggest the effect is reversible with discontinuation.[93]

2^{++}

A prospective nested case-control study was carried out in Scotland for the Royal College of General Practitioners (RCGP) Oral Contraception Study. Participants who had suffered a first fracture (n=651) were matched to controls (n=1,302) and adjusted for age, smoking, social class and parity. No significant association was identified between ever use of oral contraception and fracture (adjusted OR 1.05, 95% CI 0.86 to 1.29) compared with never users.[94]

2^{++}

Although the evidence from observational studies suggests that the relative risk of fracture is increased in users of DMPA versus non-users, the absolute risk is low given that these agents are used in premenopausal women. For example, using the QFracture calculator on the average demographic characteristics of the DMPA users in one UK study (age 35, non-smoker, BMI 22.5) yields a 10-year osteoporotic-fracture risk of only 0.6%, well below the proposed threshold for DXA of 10% (*see section 5.6*). Even for the oldest women in the study (age 44) with the above characteristics the 10-year risk of osteoporotic fractures remains low (1.2%).

Further research is required to determine whether long-term use of DMPA in younger women is associated with later fracture risk.

R **Women using long-term** (for at least two years) **depot medroxyprogesterone acetate should be advised that treatment can reduce bone density but that the effects reverse when treatment is stopped and the overall risk of fracture is low.**

3.5.9 GONADOTROPIN-RELEASING HORMONE AGONISTS

Gonadotropin-releasing hormone (GnRH) agonists yield a hypogonadal state by downregulating pituitary hormones receptors. They are used in the management of hormonally-sensitive cancers, fibroids and to reduce symptoms of endometriosis.

A composite Danish registry study included 15,716 men aged over 50 presenting with a fracture and 47,149 age-matched control men. Prostate cancer was associated with an increased odds ratio for all fractures of 1.8 (95% CI 1.6 to 2.1), for hip fractures of 3.7 (95% CI, 3.1 to 4.4), but no increased risk of vertebral fractures (OR 1.0, 95% CI 0.7 to 1.5). Of the 1,018 men with prostate cancer in this cohort, 9% were treated with androgen deprivation therapy (ADT). When adjusted for prostate cancer, age and previous fracture, ADT added to overall fracture risk with an OR of 1.7 (95% CI 1.2 to 2.5, p<0.01), and also to the risk of hip fracture (OR 1.9, 95% CI 1.2 to 3.0; p<0.05).[95] The odds of fracture associated with ADT in this study are likely underestimated due to the difficulty in recording GnRH prescription in this population.

2^{+}

A composite study of patient databases in Canada matched 19,079 men aged 66 or older who had prostate cancer with at least six months of continuous ADT or bilateral orchidectomy with men with prostate cancer who had never received ADT. At mean follow up of 6.5 years, ADT was associated with an increased risk of fragility fracture (HR 1.65, 95% CI 1.53 to 1.78) and any fracture (HR 1.46, 95% CI 1.39 to 1.54). A history of fragility fracture, increasing age and a diagnosis of dementia independently increased the fracture risk.[96]

2^{++}

A similar study was completed with 50,613 patients with a diagnosis of prostate cancer aged 66 or above in the USA. There was a small but statistically significant increase in the proportion of patients with any fracture during the 12 months before diagnosis in the group that received ADT as compared with the group that did not receive ADT. Of those in the ADT group, 19.4% had a fracture compared with 12.6% of those not receiving the study treatment (p<0.001). The relative risk of any fracture was 1.45 (95% CI, 1.36 to 1.56) among those receiving nine or more doses of GnRH agonist in the first 12 months after diagnosis.[97]

2^{+}

A cohort of men with non-metastatic prostate cancer who initiated GnRH agonist treatment (n=3,887) was compared with a group of men who did not receive GnRH agonist treatment but were matched for age, race, geographic location, and comorbidity (n=7,774). Gonadotropin-releasing hormone agonists significantly increased relative risk of any fracture (RR 1.21, 95% CI 1.14 to 1.29, p<0.001), vertebral fracture (RR 1.45, 95% CI 1.19 to 1.75, p<0.001) and hip/femur fractures (RR 1.30, 95% CI 1.10 to 1.53, p=0.002). Longer duration of treatment conferred greater fracture risk.[98] 2^{+}

No studies were identified which linked GnRH agonist use to fracture risk in women.

R **Men over the age of 50 with prostate cancer, who are taking GnRH agonists may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.5.10 LOOP DIURETICS

A large prospective cohort study of female patients aged 50–79 enrolled in the WHI found that, in fully-adjusted models, the association between ever use of loop diuretics and total fractures (HR, 1.09, 95% CI 1.00 to 1.19, p=0.052), hip fractures (HR 1.21, 95% CI 0.91 to 1.60), clinical vertebral fractures (HR 1.17, 95% CI 0.92 to 1.48, p=0.20), and falls (HR 1.01, 95% CI 0.96 to 1.08, p=0.62) was not statistically significant.[99] There was a modest increased risk for other clinical fractures (HR 1.16, 95% CI 1.01 to 1.33) and total fractures (HR 1.16, 95% CI 1.03 to 1.31) in women who had used loop diuretics for more than three years. Users and non-users of loop diuretics differed significantly in some factors which affect their baseline risk of fracture. Compared with non-users, loop diuretic users were older, more likely to have had a fracture on or before the age of 55, more likely to have lower physical function and more likely to have chronic heart failure or coronary heart disease (CHD). Further significant differences were found between the loop diuretic users and non-users with respect to ethnicity, smoking status, self reported health, number of chronic health conditions, and alcohol use. Loop diuretic users were shorter and heavier on average and had a higher BMI, a younger age at menopause, a higher unadjusted BMD of the lumbar spine and total hip, lower levels of physical activity, and lower intakes of vitamin D and calcium than did non-users. **2^{+}**

The evidence for an association between use of loop diuretics and fracture risk is unclear.

3.5.11 ACID-SUPPRESSIVE DRUGS

Three meta-analyses of a similar group of observational studies provide evidence on the association between use of acid-suppressive drugs and risk of fracture. Proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H_2RAs) are the most popular acid-suppressive drugs available and are indicated for a wide range of conditions, including dyspepsia, peptic ulcer and gastro-oesophageal reflux disease.

One meta-analysis of 11 observational studies showed that the overall use of PPIs was associated with a significantly increased risk of any fracture (pooled adjusted OR 1.29, 95% CI 1.18 to 1.41; 10 studies). Use of H_2RAs was not associated with an increased fracture risk, (pooled adjusted OR 1.10, 95% CI 0.99 to 1.23; seven studies).[100] 2^{+}

A second meta-analysis showed similar risks of fracture associated with PPIs but not H_2RAs. Analysis of fractures overall yielded an OR of 1.20 (95% CI 1.11 to 1.30, p<0.001) for PPIs, and OR of 1.08 (95% CI 1.00 to 1.18, p=0.06) for H_2RAs. Pooled analysis of PPI use showed significant risk for spine fractures (four studies, OR 1.50, 95% CI 1.32 to 1.72, p<0.001) but this was not significant for H_2RAs (three studies, OR 1.05, 95% CI 0.92 to 1.19, p=0.50). Similarly for hip fractures, there was a significant risk of fractures with PPIs (10 studies, OR 1.23, 95% CI 1.11 to 1.36, p<0.001), but not for H_2RAs (nine studies, OR 1.12, 95% CI 0.99 to 1.27, p=0.06).[101] 2^{+}

Another meta-analysis of the same studies reported the OR for hip fracture in PPI users compared with past or non-users was 1.25 (95% CI 1.14 to 1.37; nine studies). The OR for vertebral fracture was 1.50 (95% CI 1.32 to 1.72; four studies). The authors noted that the results should be interpreted with caution, due to the significant statistical and clinical heterogeneity among studies.[102] 2^{++}

R **People over the age of 50 taking PPIs may be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.5.12 STATINS

Evidence concerning the effect of statins on bone health is conflicting with observational studies often showing a reduction in fracture risk in statin users,[103] but RCTs showing no effect.[104] Meta-analyses have attempted to combine these studies to give an overall conclusion. 1^{++} 2^{+}

A meta-analysis identified six trials (n=3,022) which reported data on the association between statin use and BMD or fracture risk. There was no significant difference in fracture rates in the groups treated with statins or placebo in two RCTs. Data could not be combined due to pharmacokinetic differences in the statin used in these two trials. Four RCTs reported data on bone turnover markers but there was no significant effect on osteocalcin, bone-specific alkaline phosphates, c-telopeptide of type I collagen (CTX) or n-telopeptide of type I collagen (NTX). There was no significant difference in the reduction in lumbar spine or total hip BMD.[105] 1^{++}

The association between statin use and fracture risk was analysed using Bayesian empirical and random-effects models. Empirical Bayesian analysis showed that statin use was associated with a reduction in hip fracture risk (OR 0.57, 95% credible interval (CrI) 0.46 to 0.71) and non-vertebral fracture risk (OR 0.69, 95% CrI, 0.63 to 0.74). These results were comparable with results from the fully Bayesian random-effects meta-analysis only for hip fracture (OR 0.56, 95% CrI 0.42 to 0.73), but not for non-vertebral fracture (OR 0.77, 95% CrI 0.58 to 1.03). The probability that statin use reduces hip fracture risk by at least 20% was 0.97, however the effect on non-vertebral fracture was much less robust with a probability of 0.27.[106] 1^{++}

A meta-analysis of 24 observational studies and seven RCTs (n=510,646) showed that, overall, statin use was associated with fewer hip fractures (OR 0.60, 95% CI 0.45 to 0.78; n=15) and improved hip BMD (Z-score 0.12, 95% CI 0.05 to 0.19; n=13), with a non-significant reduction in vertebral fractures and no effect on vertebral BMD. There was evidence of heterogeneity in 12 of 14 analyses conducted with case-control studies showing consistently greater effects than cohort studies or RCTs.[107] 2^{+}

R **Patients may be reassured that statins do not increase risk of fractures.**

3.5.13 GLUCOCORTICOIDS

Inhaled glucocorticoids

Sixteen RCTs (n=17,513) comparing inhaled glucocorticoids with placebo and seven observational studies (n=69,000) examining the effect of exposure to glucocorticoids were combined in a meta-analysis of studies of treatments for COPD. Inhaled glucocorticoids were associated with a significantly increased risk of fractures (Peto OR 1.27, 95% CI 1.01 to 1.58; p=0.04) in the RCTs. In the observational studies, inhaled glucocorticoid exposure was associated with a significantly increased risk of fractures (OR 1.21, 95% CI 1.12 to 1.32; p<0.001), with each 500 microgram increase in beclomethasone dose equivalents associated with a 9% increased risk of fractures (OR 1.09, 95% CI 1.06 to 1.12; p<0.001).[108] 1^{++}

A further meta-analysis of 13 studies, including four RCTs did not show an association between use of inhaled glucocorticoids and increased risk of any fracture (pooled RR 1.02, 95% CI 0.96 to 1.08) or hip fracture (RR 0.91, 95% CI 0.87 to 0.96). A slight increase in risk of any fracture was noted among users of high-dose inhaled glucocorticoids (RR 1.30, 95% CI 1.07 to 1.58).[109] 2^{+}

The evidence on inhaled glucocorticoids is inconsistent and it is not possible to form a recommendation.

Oral glucocorticoids

Data from seven prospective cohort studies were combined in a meta-analysis comparing the association between risk of fracture and exposure to oral glucocorticoids (n=42,542). The ever use of glucocorticoids was associated with a significantly increased risk of any fracture at all ages (range 21–106 years) compared with those with no history of glucocorticoid use (risk ratio 1.57, 95% CI 1.37 to 1.80). This increase in relative risk was not explained by differences in BMD. The relative risk ranged from 1.98 at the age of 50 to 1.66 at the age of 85, and the increase in relative risk was most marked at ages younger than 65. There was no significant difference in relative risk by age or between men and women. For osteoporotic fractures, risk ratios were higher than those for all fractures combined (RR 1.66, 95% CI 1.42 to 1.92). Risk of hip fracture was associated with the largest effect size (RR 2.25, 95% CI 1.60 to 3.15) with risk ratios ranging between 2.13 and 4.42, depending on age (though this effect was not statistically significant).[110] 2+

The additional risk of fracture associated with glucocorticoids shown in this study may be a feature of the underlying disease for which glucocorticoids were initially prescribed. In the cohorts in which this could be analysed, RA was associated with an independent risk of fracture that persisted when adjusted for glucocorticoid use.

A retrospective cohort study of the adult population of Tayside (n=280,645) compared those who redeemed one or more prescription for oral glucocorticoids compared with those not prescribed glucocorticoids (oral or inhaled) in the population. There was a significantly higher risk of fracture in the oral glucocorticoid cohort when exposed to drugs compared with the general population (RR 1.90, 95% CI 1.68 to 2.16) after adjustment. Women were at higher risk than men, especially for vertebral fractures (RR 5.19, 95% CI 2.95 to 9.16).[111] 2+

R **Patients taking oral glucocorticoids should be considered for fracture-risk assessment.**

3.5.14 ANTIDIABETIC AGENTS

A meta-analysis included 10 RCTs (n=13,715) and two observational studies (n=31,679) involving patients with type 2 diabetes which reported on the risk of fractures associated with thiazolidinedione (TZD) use. Rosiglitazone and pioglitazone were associated with a significantly increased overall risk of fractures in the RCTs (OR 1.45, 95% CI 1.18 to 1.79; p<0.001). Five RCTs showed a significantly increased risk of fractures among women (OR 2.23, 95% CI 1.65 to 3.01; p<0.001) but not among men (OR 1.00, 95% CI 0.73 to 1.39; p=0.98). No significant association between TZD exposure and fractures among men was found in either observational study, but, in one study, rosiglitazone was significantly associated with fractures when compared with women taking metformin but not sulfonylurea, and a significant association was shown between TZD use and fractures among women in the other observational study.[112] 1++

A systematic review identified RCTs and observational studies which compared the benefits and harms of metformin, second-generation sulphonylureas, TZDs, meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 receptor agonists, as monotherapy and in combination, to treat adults with type 2 diabetes. Thiazolidinediones, either in combination with another medication or as monotherapy, were associated with a higher risk for bone fractures than metformin alone or combined with a sulphonylurea. Fractures were mainly in the limbs and not the hips.[113] 1+

One prospective population-based cohort study confirmed TZD use compared with sulphonylurea use was associated with a 28% increased risk of peripheral fracture in both men and women (HR 1.28, 95% CI 1.10 to 1.48).[114] 2+

One registry-based case-control study analysed the effects of a diagnosis of type 1 or 2 diabetes on fracture risk *(see section 3.4.1)* and on the effects of various antidiabetic medications. Use of metformin and sulphonylureas was associated with a decreased risk of fractures after adjustment for total number of defined daily doses used and confounders. Use of insulin had borderline association with reduced fracture risk at moderate dose levels. The authors conclude that the apparent protective effect of certain antidiabetic drugs on fracture risk may not be the result of a direct pharmacological antifracture effect, as it was only seen with oral agents at fractures sites where a diagnosis of diabetes itself was associated with an increased risk, for example, at the hip. In contrast, there was no increase in risk of forearm fracture in people with type 1 diabetes, and no fracture 2+

reducing effect of insulin at this site.[44] No adjustment for BMI was possible with this study, and there is the possibility that ascertainment of people with type 2 diabetes was incomplete, leading to an underestimate of the risk of fracture associated with this diagnosis. 2+

A matched case-control study was carried out using data from a multicentre prospective observational study of people with diabetes in managed care, to assess the odds of TZD exposure in patients with type 2 diabetes with and without fractures. A total of 747 cases with fracture and 2,657 age-, sex- and BMI-matched controls who had not experienced a fracture were identified. Among women aged 50 and older, those with fractures were significantly more likely ($p<0.05$) to be exposed to TZDs (OR 1.71; 95% CI 1.13 to 2.58), glucocorticoids (OR 1.90; 95% CI 1.36 to 2.65), and loop diuretics (OR 1.49; 95% CI 1.08 to 2.06) and to have limited mobility (OR 1.51; 95% CI 1.20 to 1.90). Thiazolidinediones were not significantly associated with fractures in women aged below 50, although there were only five fracture cases in TZD users in this age group. In men, fractures were significantly associated with concurrent use of loop diuretics and TZDs (OR 3.46; 95% CI 1.06 to 11.28), exposure to glucocorticoids (OR 1.79; 95% CI 1.11 to 2.87), and insulin (OR 1.59; 95% CI 1.11 to 2.29), as well as limited mobility (OR 1.96; 95% CI 1.45 to 2.65) and lower-extremity amputation (OR 2.29; 95% CI 1.21 to 4.32). High TZD doses were associated with significantly greater odds of fracture for women aged 50 and older (OR 1.42; 95% CI 1.12 to 1.79) but not for men or women aged below 50.[115] 2+

R **People aged over 50 using TZDs are at higher fracture risk than people with diabetes who are treated with other agents and should be considered for fracture-risk assessment, particularly in the presence of other risk factors.**

3.6 SUMMARY OF RISK FACTORS

Table 1 summarises recommendations relating to modifiable risk factors which, if implemented, may alter the individual's underlying risk of fragility fracture.

Table 1: Recommendations associated with modifiable risk factors for fragility fractures

Risk category	Affected group	Recommendation
ALCOHOL	people who consume more than 3.5 units per day of alcohol	reduce alcohol intake to nationally recommended levels (<21 units per week in men, <14 units per week in women).
SMOKING	all smokers	stop smoking
WEIGHT	people with low BMI (<20 kg/m^2)	achieve and maintain a BMI level of 20–25 kg/m^2

As fracture rates increase with age, particularly in those with osteoporosis, the risk of fractures in younger women (<50) who do not have clinical risk factors is likely to be very low *(see Figure 1)*. While the evidence for risk assessment and intervention in people below the age of 50 has not been sought, NICE recommends assessment of fracture risk in this group in the presence of major risk factors (previous fracture, oral or systemic glucocorticoid use, hazardous alcohol intake, family history of fracture, low BMI, history of falls and causes of secondary osteoporosis).[8]

Presence of any of the non-modifiable factors, diseases or use of any of the drugs listed in Table 2 is associated with an increased risk of fragility fracture and individuals over the age of 50 should be considered for fracture-risk assessment.

Table 2: Risk factors associated with fragility fracture which should prompt consideration of fracture-risk assessment

Risk category	Causative factor
NON-MODIFIABLE RISK FACTORS	previous fracture
	parental history of osteoporosis
	history of early menopause (below age of 45)
MODIFIABLE RISK FACTORS	low BMI (<20 kg/m^2)
	smoking
	low bone mineral density
	alcohol intake
COEXISTING DISEASES	diabetes
	inflammatory rheumatic diseases (RA or SLE)
	inflammatory bowel disease and malabsorption
	institutionalised patients with epilepsy
	primary hyperparathyroidism and endocrine diseases
	chronic liver disease
	neurological diseases (including Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke)
	moderate to severe chronic kidney disease
	asthma
DRUG THERAPY	long-term antidepressants
	antiepileptics
	aromatase inhibitors
	long-term DMPA
	GnRH agonists (in men with prostate cancer)
	PPIs
	oral glucocorticoids
	TZDs

4 Quantifying the risk of fracture

4.1 INTRODUCTION

Various techniques have been used to quantify the risk of fracture. The risk of fracture increases markedly with increasing age in both men and women *(see Figures 1 and 2)*. However, other clinical risk factors such as drug therapy, coexisting diseases, lifestyle factors such as smoking and alcohol intake, and family history of hip fracture act in a cumulative manner to modulate fracture risk. This has led to the development of assessment tools which can be used to estimate fracture risk in the individual patient based on clinical variables. The most widely used of these is FRAX, but others have been developed including QFracture and the Garvan risk calculator. In this section the role of these tools in quantifying the risk of fracture is reviewed along with other methods of fracture-risk assessment including BMD measurements, quantitative ultrasound and biochemical markers of bone remodelling.

4.2 RISK-ASSESSMENT TOOLS

4.2.1 FRAX

The FRAX algorithm was developed by analysis of several prospective population-based cohort studies in the UK, other countries in Europe, Canada, the USA and Japan.[116]

The FRAX risk-assessment tool, which is freely available through a web-based portal, allows calculation of the 10-year absolute risk of hip fracture and of other major osteoporotic fractures (defined as clinical vertebral fractures, forearm, hip and shoulder fractures), based on age, gender, BMI and on the presence or absence of previous fracture, parental hip fracture, current smoking, current use of glucocorticoids, RA, secondary osteoporosis and consumption of three or more units of alcohol per day. The FRAX website (www.shef.ac.uk/FRAX/index.aspx) defines previous fracture as "a fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture". Secondary causes of osteoporosis listed in FRAX include diabetes, osteogenesis imperfecta in adults, untreated longstanding hyperthyroidism, hypogonadism or premature menopause (age <45), chronic malnutrition, or malabsorption and chronic liver disease.

A strength of FRAX is that femoral neck BMD measurements can be included in the assessment whereas this is not possible for the QFracture algorithm *(see section 4.2.2)*. When femoral neck BMD measurements are included in FRAX this renders the data from secondary causes of osteoporosis redundant since the algorithm assumes that secondary causes of osteoporosis predispose the individual to fractures by reducing femoral neck BMD. Like other calculators FRAX most likely underestimates the risk of vertebral fracture. This is because many vertebral fractures are not detected clinically and may have been under-reported in the population-based studies upon which FRAX was based.

Diseases associated with osteoporosis (secondary causes of osteoporosis in the algorithm) are assigned an identical risk in FRAX, whereas, in practice, the strength of association with fracture has been shown to vary depending on the underlying conditions.[14] There is a lack of clarity about which secondary causes of osteoporosis listed in FRAX were validated as predictors of fracture in the original cohorts which underpinned the development of FRAX. Most of the risk factors in FRAX are scored in a dichotomous fashion. For example, fracture history has the same impact on score irrespective of whether the patient has experienced one or multiple fractures. The same applies to smoking and alcohol intake which are both entered as dichotomised variables. Although glucocorticoid use is also entered as a dichotomous variable, a recent version of FRAX provides different fracture risks for high and low doses of these drugs.[117] 4

The algorithm underlying the FRAX calculator has not been published in the public domain which has impaired attempts to independently validate it. A comparison of FRAX with the QFracture algorithm was carried out in 2009.[14] This was achieved by the development of a semiautomated method to calculate FRAX 2++
scores on an individual basis from the FRAX website. This showed that FRAX overestimated hip fracture risk in the UK population compared with QFracture, particularly in those at low risk (<4%).

A further attempt at validating FRAX against QFracture in 2011 was not possible due to changes in the tool, nonetheless, it was noted that discrepancies existed between the results returned by the FRAX calculator in 2008 and those returned by entering the same data in 2011.[118] The reasons for this are currently unclear.

The FRAX algorithm underestimates the 10-year fracture risk in older people compared with both Qfracture and the Garvan calculator. This has been attributed to the fact that FRAX takes the mortality rate of the general population into account when making the fracture calculation whereas the other calculators do 3
not.[119] Whilst the QFracture algorithm does not take mortality into account it has been shown to accurately 4
predict fracture risk in older people up to the age of 85.[120] This suggests that FRAX underestimates fracture risk, rather than QFracture and Garvan overestimating fracture risk.

Treatment thresholds are covered in section 5.6.

4.2.2 QFRACTURE

QFracture is an online fracture risk scoring tool, developed in the UK, which can be used to predict the absolute risk of hip fracture and of major osteoporotic fractures (spine, wrist, hip or shoulder) over timeframes of one to ten years.

The original algorithm was developed in 2009 using data from general practices in England and Wales and involving around 2.2 million men and women.[14] A refinement was published in 2012 involving over three million individuals in the derivation cohort and 1.5 million in the validation cohort.[19] An independent validation was carried out in 2011 involving 2.2 million individuals from general practices in the UK which were distinct from those involved in the development of QFracture.[120] More variables are included in QFracture than in FRAX. Information can be entered on age, gender, ethnicity, BMI, quantity of cigarettes smoked, quantity of alcohol consumed and on the presence or absence of previous fracture (at hip, spine, wrist or shoulder), parental hip fracture or osteoporosis, and of a number of other conditions such as diabetes, dementia, cancer, asthma or COPD, angina, myocardial infarction (MI), stroke or transient ischaemic attack (TIA), chronic liver disease, CKD, RA or systemic lupus erythematosus, malabsorption, Crohn's disease, ulcerative colitis, CD, steatorrhea or blind loop syndrome, endocrine problems (such as thyrotoxicosis, hyperparathyroidism, Cushing's syndrome), epilepsy or taking anticonvulsants, taking steroids regularly, taking antidepressants, taking oestrogen-only HRT, history of PD and history of falls. Care home or nursing home residence is also included as a binary variable.

The main strength of QFracture over other calculators is that it has been extensively validated in the UK population and has been shown to be more accurate at predicting fractures in the UK population than FRAX.[14] Calculations can be carried out over a wider age range than FRAX (30–99 years), for different ethnic groups, and for intervals of between one and 10 years *(see Table 3)*. Although it does not take mortality into account QFracture has been proven to provide an accurate prediction of fracture risk in elderly people up to the age of 85.[14,118,120] The algorithm underlying QFracture has been published and is freely available. A web-based interface and software are also available to allow automatic calculations from primary-care computer systems in the UK.

A weakness of QFracture is that fracture risk cannot be recalculated taking BMD measurements into account. However, since the main application of QFracture is to estimate fracture risk prior to carrying out a DXA scan, this may be less important clinically.

4.2.3 OTHER RISK SCORING TOOLS

A number of other risk scoring tools have been developed in other countries including the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool,[121] the Garvan Institute tool,[122] the Fracture Risk tool (FRISK),[123] and the WHI tool.[124] All use different combinations of risk factors in different national settings.

CAROC and FRISK performed similarly to FRAX when these tools have been compared,[121, 125] but FRAX yielded a lower fracture risk in older people when compared with the Garvan tool and QFracture *(see section 4.2.1)*.[119] 2^{++} 4

4.2.4 SUMMARY

The NICE guideline on assessing the risk of fragility fracture recommended that BMD measurements should not be done without prior calculation of fracture risk using FRAX or QFracture, although the guideline did not suggest a threshold of fracture risk above which BMD measurements should be considered.[8] While agreeing with the recommendation, the SIGN guideline group suggested a fracture risk threshold of 10% to indicate the need for DXA. The reasons for this are discussed in section 5.6.

In comparing the performance and characteristics of different calculators, the guideline development group felt that QFracture was the preferred method for calculating fracture risk in the UK. Reasons included the extensive validation of QFracture in the UK population, the ability to predict fracture risk over a wider age range than some other calculators, the ability to calculate risk in different ethnic groups, the more accurate prediction in different groups including the elderly, the ability to calculate risk over varying timeframes and the transparency of the methodology.

R **Fracture-risk assessment should be carried out, preferably using QFracture, prior to DXA in patients with clinical risk factors for osteoporosis and in whom antiosteoporosis treatment is being considered.**

Table 3: Risk factors included in FRAX and QFracture algorithms

Risk factor	FRAX	QFracture
Age	40–90 years	30–99 years
Sex	✓	✓
Weight	✓	✓
Height	✓	✓
Ethnicity	×	✓
Previous fracture	✓	✓
Parental history of hip fracture	✓	✓
Smoking	✓	✓
Alcohol	✓	✓
Menopausal symptoms	×	✓
Epilepsy (or use of anticonvulsants)	×	✓
Cardiovascular disease	×	✓
History of falls	×	✓
Use of glucocorticoids	✓	✓
Use of antidepressants	×	✓
Bone mineral density (femoral neck T-score/ absolute value)	✓ (option)	×
Secondary osteoporosis	Binary yes/no choice	*Endocrine*
		hyperparathyroidism, thyrotoxicosis, Cushing's disease, type 1 or 2 diabetes, use of HRT
		Gastrointestinal
		Crohn's disease, ulcerative colitis, coeliac disease, steatorrhoea, blind loop syndrome
		Metabolic
		chronic renal disease, chronic liver disease, immobility
		Neurological
		Alzheimer's disease, Parkinson's disease
		Oncological
		cancer
		Respiratory
		COPD, asthma
		Rheumatological
		rheumatoid arthritis, systemic lupus erythematosus
		Other
		care or nursing home residence

4.3 BONE MINERAL DENSITY MEASUREMENT

Measurements of BMD at the lumbar spine, femoral neck, total hip and wrist have been shown to predict future fracture occurrence. A meta-analysis of data from eleven prospective cohort studies which included 90,000 patient-years of follow up showed that BMD measurements at all sites had a similar ability to predict fractures with a relative risk of 1.5 (95% CI 1.4 to 1.6) for each standard deviation reduction in BMD. In the same study it was found that spine BMD was superior at predicting vertebral fractures (RR 2.3, 95% CI 1.9 to 2.8) and hip BMD was superior at predicting hip fractures (RR 2.6, 95% 2.0 to 3.5).[126] 2^{+}

There is variation in the utility of BMD at different sites with hip BMD performing better than spine BMD in predicting osteoporotic fractures. Combining results of spine BMD with clinical risk factors improves the prediction of future fractures *(see section 3.3.1)*.

In most clinical trials of drugs licensed for the treatment of osteoporosis the entry criteria have stipulated that patients had low BMD assessed by DXA of the spine or hip and/or vertebral fractures. Whilst the BMD cut-off varied between studies, the threshold in most studies was around a T-score ≤ -2.5.

Post hoc analysis of the Fracture Intervention Trial (FIT) of alendronic acid (which was targeted based on low BMD at the femoral neck, without vertebral fracture at baseline), suggests that significant fracture risk reduction is achieved only at femoral neck T-scores of -2.5 or lower.[127] 1^{+}

R **Measurement of bone mineral density by DXA at the spine and hip should be carried out following fracture-risk assessment in patients in whom antiosteoporosis treatment is being considered.**

4.4 PERIPHERAL BMD MEASUREMENT

Peripheral DXA predicts the risk of non-vertebral fractures but is less predictive than hip BMD for the prediction of hip fracture and spine BMD for the prediction of spine fracture.[126] No clinical trials have been undertaken in which peripheral BMD measurements have been used as a means of targeting antiosteoporosis therapy.

4.5 ULTRASOUND DENSITOMETRY

Quantitative ultrasound (QUS) parameters at the heel have been shown to be associated with risk of hip and vertebral fractures,[128] but tend to identify different patients from those deemed to be at greater fracture risk using DXA. There is some evidence to support a role for these parameters in combination with risk calculation tools to predict fracture risk,[128] however, the models are unwieldy and difficult to use in practice. Ultrasound assessment at other sites is not useful in clinical practice. 2^{++}

No clinical trials have been undertaken in which ultrasound densitometry has been used as a means of targeting antiosteoporosis therapy.

4.6 BIOCHEMICAL BONE TURNOVER MARKERS

Studies of biochemical markers to predict fractures have shown inconsistent results and, in studies where it has been observed, the relationship was lost after correction for baseline BMD.[126,127] 1^{++} 2^{++}

R **Biochemical markers should not be used in the evaluation of fracture risk.**

5 Targeting treatment

5.1 INTRODUCTION

Many drug treatments that reduce the risk of fractures have been identified and these are discussed in sections 6 and 7. This section covers the role of clinical risk factor analysis and bone mineral density measurements in targeting osteoporosis treatments.

The number of morbidities per individual and the proportion of people with multimorbidity increases substantially with age. A cross-sectional study of 1.75 million people in Scotland showed that by age 50, half of the population had at least one morbidity, and by age 65 most were multimorbid.[130] Osteoporosis is known to become more prevalent both with age and with significant comorbid medical conditions, and, when recommending assessment and treatment, patients' life expectancy and duration of treatment should be considered. Drug therapy should only be offered to patients who are likely to benefit from any intervention.

5.2 TARGETING TREATMENT ON THE BASIS OF FRACTURE RISK

People who are found to be at high risk of fracture using a risk analysis tool such as QFracture or FRAX potentially have the most to gain from effective treatment *(see section 4)*. There is limited information, however, on the effects of antiosteoporosis medications in patients who have high fracture risk in the absence of BMD measurements.

When FRAX was applied retrospectively to the FIT cohort no significant association was seen between FRAX score and the efficacy of alendronic acid in preventing non-vertebral, clinical or major osteoporotic fractures, or radiographic vertebral fractures.[127] 1^{+}

In a study of risedronate involving more than 9,000 participants, about 50% of the study population was enrolled either because of low BMD values (femoral neck T-score <-4.0 or <-3.0 and hip axis length of 11.1 cm or greater) or because they were elderly (≥80) and had clinical risk factors for hip fracture. Subgroup analysis showed that patients enrolled because of low BMD had a significant reduction in hip fracture risk (RR 0.60, 95% CI 0.40 to 0.90) whereas those with clinical risk factors had no significant reduction in fracture risk (RR 0.80, 95% CI 0.60 to 1.20).[131] 1^{+}

In another study, post hoc analysis of patients treated with alendronic acid showed no significant fracture risk reduction in osteopenic women but a significant reduction in osteoporotic women.[132] 1^{++}

In summary there is limited evidence to suggest that targeting treatment on the basis of high fracture risk in the absence of osteoporosis as defined by DXA is an effective means of reducing the risk of fracture.

✓ In the absence of BMD measurements, clinical risk factors analysis is not recommended as a means of selecting patients for drug treatment to prevent future fractures.

5.3 TARGETING TREATMENT ON THE BASIS OF AGE AND PREVIOUS NON-HIP FRACTURE OR NON-VERTEBRAL FRACTURE

In 2011, NICE recommended that postmenopausal women over the age of 75 who have two or more independent clinical risk factors for fracture (such as parental history of hip fracture, alcohol intake of four or more units per day, and rheumatoid arthritis) or indicators of low BMD (such as ankylosing spondylitis, Crohn's disease, conditions that result in prolonged immobility, or untreated premature menopause) should be commenced on bone-sparing therapy without BMD measurements if these are felt to be clinically inappropriate or unfeasible.[133,134] No studies were identified, however, demonstrating that targeting treatment in this way was effective at reducing fractures. Observational studies in which axial DXA examination had been conducted in postmenopausal women aged 75 and above with recent low-trauma fractures indicated that about half had osteoporosis on DXA, 35% had osteopenia and 15% had normal BMD.[135] 4

As discussed in section 5.2, the benefits of most antiosteoporosis drug treatment in patients with T-scores >-2.5 are uncertain.

✓ Postmenopausal women aged 75 and above who have suffered a previous non-hip or non-vertebral fragility fracture should not be initiated on bone-sparing drug treatments unless they are shown to have osteoporosis on DXA examination.

5.4 TARGETING TREATMENT ON THE BASIS OF VERTEBRAL FRACTURES

Patients with prevalent vertebral fractures are at increased risk of both vertebral and non-vertebral fractures. Randomised controlled trials of alendronic acid, risedronate and parathyroid hormone in male and female patients with prevalent vertebral fractures have shown that these agents are effective at preventing further vertebral and non-vertebral fractures in this patient group *(see sections 6.4.1, 6.4.2, 6.4.8)*. Most patients with vertebral fractures in these studies also had low BMD values on DXA analysis.[136, 137] 1^{++}

People who have suffered a vertebral fracture are considered to have osteoporosis, even in the absence of a BMD value in the diagnostic range and are eligible for pharmacological therapy to reduce risk of further fracture.

✓ Measurements of BMD by DXA should normally be performed prior to starting osteoporosis drug treatment, but therapy can be commenced in patients with prevalent vertebral fractures without undertaking BMD measurements if these are felt to be inappropriate or impractical.

5.5 TARGETING TREATMENT ON THE BASIS OF HIP FRACTURE

Patients with hip fracture are at high risk of future fracture and have a high mortality. Only one trial has investigated the effects of drug treatment in this patient group.[138] In this study around 2,000 patients who had recently suffered a hip fracture were randomised to receive either 5 mg of zoledronic acid intravenously or placebo. Patients were enrolled into the trial on the basis that they were unable or unwilling to take oral therapies for osteoporosis. The study showed that zoledronic acid reduced the risk of further fracture significantly and also reduced mortality *(see section 6.4.3)*. 1^{++}

In the absence of a submission from the holder of the marketing authorisation, zoledronic acid 5 mg is not recommended for use within NHSScotland for the treatment of osteoporosis in men at increased risk of fracture, including those with a recent low-trauma hip fracture *(see sections 7.3.3 and 10.4)*.

R **Zoledronic acid is recommended to prevent further fractures in postmenopausal women with hip fracture who are unable or unwilling to take oral osteoporosis treatments, without undertaking BMD measurements if these are felt to be inappropriate or impractical.**

5.6 DEVELOPING AN ALGORITHM FOR THE DETECTION AND MANAGEMENT OF OSTEOPOROSIS

One of the challenges in managing patients suspected to have osteoporosis and at increased risk of fracture is understanding how fracture-risk assessment tools, bone densitometry and the use of antiosteoporosis therapies can fit together to benefit patients.

In Figure 3 an algorithm is presented that clinicians may find helpful for this purpose. Two different groups of patients are considered in the upper section. Those who have already sustained a fracture (secondary fracture prevention) are represented on the left side of the algorithm. Those who have known risk factors for fracture but have not yet suffered a fracture (primary fracture prevention) are represented on the right side of the algorithm.

Intervention thresholds are based upon cost-effectiveness modelling and vary from country to country depending upon health priorities and the costs of treatment.

In the USA, the National Osteoporosis Foundation (NOF) recommend that treatment should be initiated for any patient with DXA-proven osteoporosis or for patients with osteopenia (T-score between -1.0 and -2.5) with a 10-year fracture risk of 20% or greater.[139]

In the UK, no accepted thresholds have been defined for progressing from fracture-risk assessment to DXA. The treatment thresholds previously suggested by NICE, which were based on T-scores, clinical risk factors and the acquisition cost of treatments that were available in 2008, may not be relevant for current clinical practice.[133,134] In considering this issue the guideline development group sought to identify an evidence-based treatment threshold based on a combination of absolute fracture risk and information from DXA.

Almost all of the RCTs of antiosteoporosis treatment have selected patients for inclusion based on low BMD values and/or the presence of vertebral fractures, rather than on fracture risk. However, information on fracture risk is available for two large-scale treatment trials; one with alendronic acid and one with denosumab.

In FIT, which compared the effects of oral alendronic acid with placebo, the average 10-year major osteoporotic fracture risk as assessed by FRAX was 30% with a standard deviation of 13.6%. In this study, which showed a significant benefit of alendronic acid in reducing fractures, 90% of patients had a 10-year fracture risk of >14% and virtually all patients had a fracture risk of >10%.[127] In a preplanned, but post hoc analysis of the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial which showed a benefit of denosumab in reducing fractures, the median fracture risk assessed by FRAX was 15% with an interquartile range of 10.4–21.4%. Denosumab significantly reduced fracture incidence in participants with a baseline 10-year fracture risk score of 12% or above.[140] 1^{+}

While neither of these trials were designed to identify the thresholds at which treatment starts to become effective, they both indicate that treatment significantly reduces the risk of fracture in patients with a fracture risk of >10% and low BMD.

A systematic review and economic evaluation of several antiosteoporosis treatments performed in 2005 provided estimates of the clinical and cost effectiveness of different agents for the prevention and treatment of postmenopausal osteoporosis.[13] Further details on the clinical effectiveness of antiosteoporosis treatments are presented in sections 6.4 and 6.5. No drugs yielded incremental cost-effectiveness ratios below £30,000 at ages 50 or 60 in the base case. Alendronic acid and risedronate produced cost-effective results in women at the age of 70 and 80 (average cost per quality-adjusted life year (QALY) £16,934 and £20,001 respectively). Etidronate was only likely to be considered cost effective at the age of 70, when observational data were excluded. Raloxifene was cost effective at age 60 and above, however, the authors note that great caution must be exercised when interpreting this result as the main constituent of the health gain was through reduction in breast cancer incidence rather than fracture reductions *(see section 6.4.13)*. Teriparatide could only be considered cost effective in women aged 70 and 80 with approximately a fourfold baseline risk of fracture compared with a woman with T-score of -2.5 SD and a previous fracture. 1^{++}

The default cost-effectiveness analyses assumed that a woman was at the diagnostic threshold of osteoporosis (T-score of -2.5 SD), however, in reality, most osteoporotic women will be at a relatively higher risk of fracture than this state due to lower BMD or the presence of risk factors. Further analyses which assumed that a woman was at double the relative risk of fracture compared with the default analysis (equivalent to a T-score of -3.22 SD) indicated that alendronic acid and risedronate were the most cost-effective drugs at all ages. It should be noted that the relevance of this evaluation to treatment of osteoporosis in the present day is limited given the reduction in acquisition costs of many of the drugs that were evaluated.

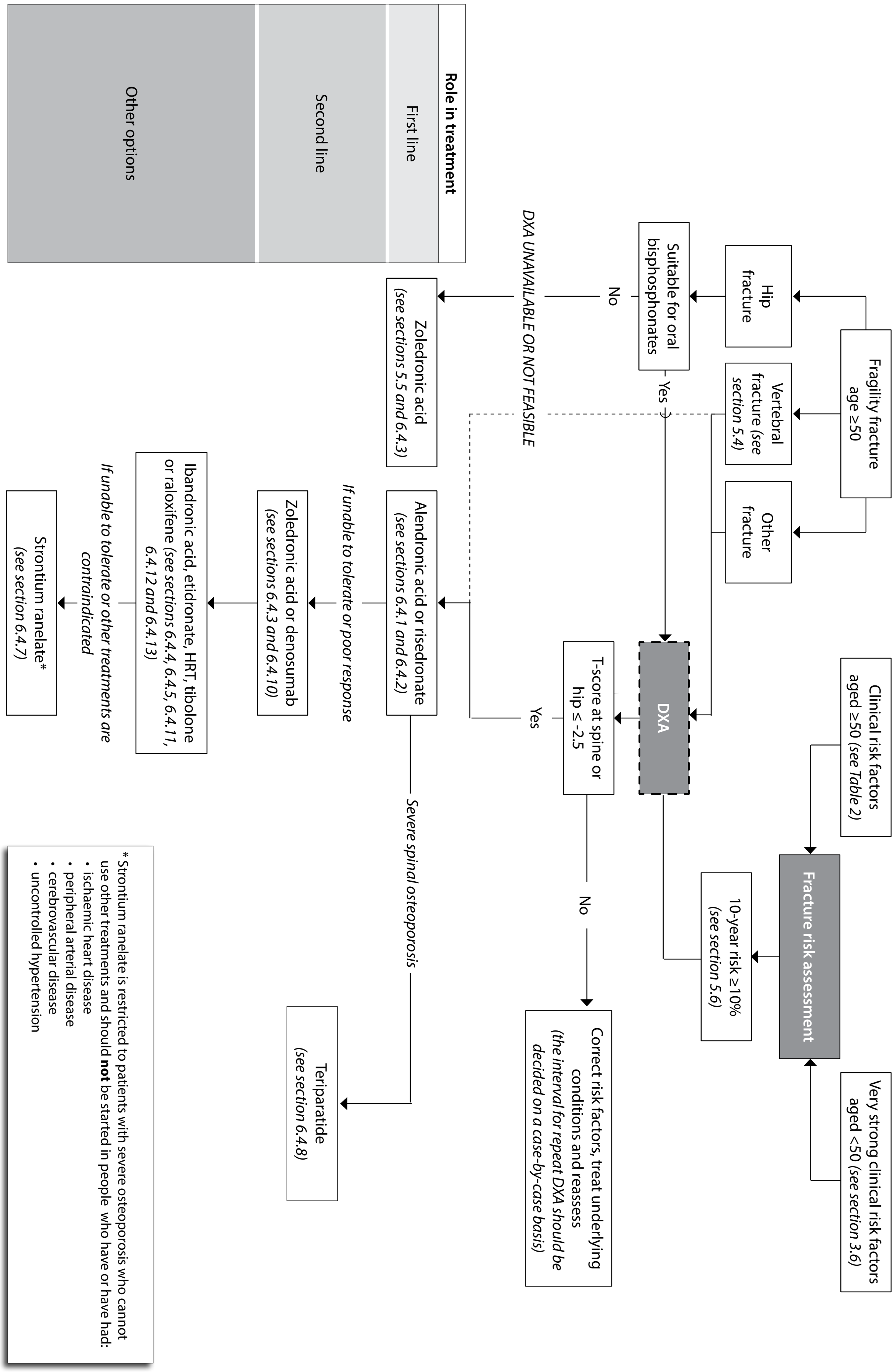
A more recent cost-effectiveness analysis in Sweden used computer simulations to estimate the costs, utilities and events of first-line treatment with teriparatide in a theoretical cohort of 1,000 postmenopausal women aged 69 with a T-score of -3.0 SD and either an incident vertebral fracture only, or an incident fracture and an additional historical vertebral fracture. The incremental cost-effectiveness ratio (ICER) for first-line treatment with teriparatide compared with bisphosphonates was greater than £30,000/QALY in the cohort with incident fracture only suggesting this treatment would not be cost effective at this willingness-to-pay threshold. However, the ICER in the cohort with both historical and incident fractures was £15,636/QALY (95% CI £14,863–£16,486) and probabilistic sensitivity analysis suggested that teriparatide was cost effective at a £30,000/QALY threshold in approximately 64% of replications of the simulation.[141]

A study from Switzerland indicated that patients with a 10-year risk of fracture of 20% or above could be treated cost effectively with branded alendronic acid at an ICER of around £34,000.[142] In this study the intervention threshold (that is, the fracture probability at which treatment became cost effective) was relatively stable across all ages and similar in both sexes. Treatment was cost effective in patients with a fracture probability equivalent to that of a woman with a prior fragility fracture and no other clinical risk factors in women and men from the age of 60 and 55, respectively. Economic analyses in this study were based on costs of branded alendronic acid in 2008 and a higher willingness-to-pay threshold than is generally used in the UK. As alendronic acid is now available in much cheaper generic formulations, the results of this study should be interpreted with caution. 1+

Based on these and other considerations, the guideline development group considered that BMD measurements should be used to define patients who will benefit from drug therapy *(see section 4.3)*. The guideline development group considered that a pragmatic approach was necessary which allows selection of patients at increased fracture risk for DXA assessment at a level appropriate for local resources. This algorithm proposes a 10-year fracture risk of 10% as the level at which DXA becomes appropriate. If the patient is confirmed to have osteoporosis by DXA then antiosteoporosis drug treatment should be offered.

Glucocorticoid therapy results in a rapid loss of BMD and patients treated with long-term glucocorticoids for chronic diseases such as asthma or inflammatory bowel disease are at increased risk of fracture compared with those who do not use these medications *(see section 3.5.13)*. As glucocorticoids contribute to the increase in fracture risk over and above the effect of low BMD, for any given level of BMD, the risk of fracture is higher in glucocorticoid-induced osteoporosis (GIOP) than in postmenopausal osteoporosis.[143] As certain underlying conditions which involve glucocorticoid treatment may also confer increased risks of fracture, (eg RA) conventional risk assessment tools may underestimate the absolute risk of fracture in these patients. Those with GIOP are excluded from the algorithm, but further guidance for evaluation and management is provided in the Royal College of Physicians guideline on glucocorticoid-induced osteoporosis[143] and section 7.5 of this guideline.

Figure 3: Pathway from risk factors to pharmacological treatment selection in postmenopausal women



6 Management of osteoporosis in postmenopausal women

6.1 INTRODUCTION

Strategies for the management of osteoporosis in postmenopausal women focus on the prevention of fragility fractures by pharmacological and non-pharmacological interventions and the primary outcome measure used in the formation of recommendations was the prevention of fractures. In some areas where this was not available, however, the evidence for effects of interventions on BMD is described. It should be noted that while there is an inverse relationship between BMD and fracture risk, in individuals the predictive power of BMD for fracture is mediated by age, the quality and shape of the bone, tendency to fall and other risk factors, such as previous fracture.

6.2 EXERCISE INTERVENTIONS

Low bone mass and low BMD are recognised risk factors for osteoporotic fractures (*see section 3.3.1*). Lack of physical activity is associated with reduced bone mass whereas exercise involving bone loading promotes increase in bone mass. Examples of exercise types include those which stress or mechanically load bones (either when bones support the weight of the body, for example walking or running, or when movement is resisted, for example when using weights).

Many types of exercise programmes have been evaluated for effectiveness in postmenopausal women. Eight systematic reviews have provided evidence on the effects of exercise on bone density and fractures.

6.2.1 STATIC WEIGHT-BEARING EXERCISE

A meta-analysis reported a statistically significant reduction in BMD decline from one small study of single leg standing (mean difference in hip BMD between exercise and control groups 2.42%, 95% CI 0.73 to 4.10). No risk of fracture/falls, or quality of life (QOL) outcomes were reported.[144]

1^{++}

6.2.2 DYNAMIC WEIGHT-BEARING EXERCISE (LOW FORCE)

Dynamic weight-bearing exercise with low force is performed in a standing position such as walking and tai chi. Studies of this type of exercise showed no effect on fractures.[144] Reduction in spine BMD decline is reported in a meta-analysis of seven studies (mean difference in spine BMD between exercise and control groups 0.84%, 95% CI 0.26 to 1.48), however no effect was observed for hip BMD.[144] Bone mineral density data at the femoral neck were inconsistent in showing a positive effect from walking.[145] However another systematic review demonstrated reduction in BMD decline associated with walking in two studies.[146] No data are available on the effect of low force dynamic weight-bearing exercise on the risks of falls or QOL.

1^{++}

6.2.3 DYNAMIC WEIGHT-BEARING EXERCISE (HIGH FORCE)

Dynamic weight-bearing exercise with high force is also performed in a standing position. Examples of these forms of exercise include jogging, jumping, running, dancing and use of vibration platforms. There was no effect on change in BMD of the spine reported in a meta-analysis of four studies involving dynamic weight-bearing exercise with high force.[144] Furthermore, high-impact only and odd-impact only protocols were ineffective in increasing BMD at any site.[147] No data were available on the effects of high-force dynamic weight-bearing exercise on the risks of fracture, falls, or QOL.

1^{++}

6.2.4 NON-WEIGHT-BEARING EXERCISE (LOW FORCE)

High-repetition strength training using low loads is an example of non-weight-bearing exercise with low force. No significant differences were observed for any BMD outcomes with low-force non-weight-bearing exercise, for example seated low-load, high-repetition strength training.[144] No data were available on the effects of non-weight-bearing exercise on the risks of fracture, falls, or QOL.

1^{++}

6.2.5 NON-WEIGHT-BEARING EXERCISE (HIGH FORCE)

Progressive resistance strength training using high loads is an example of non-weight-bearing exercise with high force. Meta-analyses have shown a reduction in BMD decline at the spine (mean difference in spine BMD between exercise and control groups 0.86%, 95% CI 0.58 to 1.13, eight studies) and neck of femur 1^- (mean difference in femoral neck BMD between exercise and control groups 1.03%, 95% CI 0.24 to 1.82, eight studies).[144] Following high-intensity resistance training an increase in spine BMD only was shown (increase in spine BMD of 0.006 g/cm^2 (95% CI 0.002 to 0.011, p=0.006, 14 studies)).[148] No data were available on the effects of non-weight-bearing high-force exercise on the risks of fracture, falls, or QOL.

6.2.6 COMBINATION OF EXERCISE TYPES

Risk of fractures in groups performing combinations of any two of the exercise types covered in sections 6.2.1 to 6.2.5 was significantly lower than that in controls (OR 0.33, 95% CI 0.13 to 0.85, two studies).[144] A reduction in BMD decline at the spine was reported (mean difference in spine BMD between exercise and control groups immediately following intervention 3.22%, 95% CI 1.80 to 4.64, four studies) although total hip BMD was reduced compared with controls (mean difference in total hip BMD between exercise and 1^- control groups -1.07%, 95% CI -1.58 to -0.56, four studies).[144] Impact protocols that included jogging mixed 1^+ with walking and stair climbing, and protocols that incorporated impact exercise with high-magnitude loading (resistance exercises), were effective at reducing bone density loss at the lumbar spine and femoral neck.[147] Combined aerobics and high-intensity resistance exercises had a positive effect on BMD decline.[146] Intervention with combined exercise programmes had better effects on physical function, pain and vitality domains than controls ($p<0.05$).[149] No data were available on the effects of these interventions on the risks of falls.

A systematic review and meta-analysis of moderate to high-quality RCTs which looked at the effect of falls-prevention exercise programmes on fracture rates, reported a significant reduction in the rate of falls resulting in fracture, with a pooled estimated rate ratio of 0.39 (0.23 to 0.66, six studies, I^2=0%). Whilst mixed populations 1^+ were included, 77% of participants were postmenopausal women, and no subgroup analysis for men was performed. The studies which decreased falls resulting in fractures included balance training, and most were multicomponent, including other exercise types such as strengthening, flexibility and endurance exercise.[150]

Another meta-analysis reported an overall fracture reduction in the exercise group compared with controls (RR 0.49; 95% CI 0.31 to 0.76).[151] The findings of this study are limited by methodological flaws of individual 1^+ studies, and potential for publication bias was noted by the authors.

6.2.7 SUMMARY

Eight systematic reviews indicate that there is a small but positive effect of exercise on BMD in postmenopausal women that is exercise type and site specific. There is evidence that exercise influences fracture risk where the exercise is multifactorial and part of a falls prevention programme. Exercise is assumed to be a safe intervention as no adverse events are reported. Exercise is a low-cost, accessible intervention which could be implemented with minimal resources. Consideration must be given to the perceived risks or concerns, such as fracture or other injury, which some individuals may have when starting or resuming exercise in later life. Conclusions must be interpreted with some caution as the original studies suffered from diverse methodological and reporting discrepancies and therefore were of predominantly low quality.

R **Combinations of exercise types including balance training, flexibility or stretching exercises, endurance exercise and progressive strengthening exercises should be considered to reduce risk of fractures caused by falls.**

R **Static weight-bearing exercise, for example, single-leg standing should be considered to slow decline of hip BMD.**

R **Progressive resistance strength training exercise** (such as weight training) **should be considered to slow decline of femoral neck BMD, either alone or in combination with impact exercise training** (such as jogging, walking or aerobics)**.**

R **Walking, tai chi, progressive resistance strength training** (such as weight training) **and different combinations of exercise types should be considered to slow decline of lumbar spine BMD.**

6.3 THE ROLE OF DIET

6.3.1 INTRODUCTION

The evidence for nutritional influences on fracture risk is not strong as there are few long-term intervention studies. Much of the evidence comes from observational studies, which do not prove causality and may be subject to confounding. Where evidence is lacking, good practice reflects current Government dietary recommendations.[152-154]

6.3.2 DIETARY-DERIVED CALCIUM

Calcium is the major mineral found in bone. Evidence from meta-analyses and prospective studies does not support increasing dairy or dietary calcium intakes in adults in order to reduce fracture burden. However, much of the evidence is confounded by the inclusion of ad hoc dietary supplements containing calcium. There are also issues concerning differences between studies in the size of food portions used to estimate dietary calcium; the different methods of assessing dietary intakes of calcium, which all rely on self reporting; and that those who may feel more at risk of osteoporosis may make changes to their diet, may tend to over-report dietary calcium, or may be more likely to take calcium supplements.

Nonetheless adequate dietary calcium is required to meet existing guidelines for recommended intakes and the dietary route is considered preferable to calcium supplements, as the latter have known side effects (constipation and, more seriously, renal calculi). Nearly all studies investigating treatments for osteoporosis have included calcium and vitamin D as adjuncts. Calcium is required for bone mineralisation. The reference nutrient intake for adults is 700 mg/day and although it is suggested that more calcium may be required for those with osteoporosis, this is usually met by supplements in order to comply with treatment regimens.[153,155]

Benefits

Four meta-analyses concluded that dietary calcium has no effect on fracture risk.

One meta-analysis included seven prospective cohort studies (n=170,991 women) and five RCTs (n=5,666 women).[156] Populations in the studies were of mixed age, but mostly postmenopausal. For the RCTs there was no statistically significant advantage of calcium supplementation over placebo in reducing the risk of non-vertebral fracture (pooled RR 0.92, 95% CI 0.81 to 1.05). The prospective cohort studies included total calcium intake from dietary sources and/or supplementation. There was no statistically significant association between total calcium intake and risk of hip fracture (pooled RR 1.01 per additional 300 mg calcium/day intake, 95% CI 0.97 to 1.05). It is not clear to what extent it is appropriate to combine studies which use different methods of assessing dietary calcium consumption, as it is known that food diaries tend to report lower calcium intake than food-frequency questionnaires and the 300 mg increment of dietary calcium intake used in the analyses may not be clinically significant. Study quality was not taken into account. 2^+

Another meta-analysis showed that in women (six cohort studies, 195,102 women, 3,574 hip fractures), there was no overall association between total milk intake and hip fracture risk (pooled RR per glass of milk per day 0.99; 95% CI 0.96 to 1.02). Study quality was not taken into account.[157] 2^+

An earlier meta-analysis of observational studies showed no association between dietary calcium intake and risk of hip fracture (risk ratio 1.01, 95% CI 0.96 to 1.07) for each daily increment of 300 mg dietary calcium intake). There is a suggestion that extremely low calcium intake may increase fracture risk, although as the single study which showed this result included only East Asian patients with significant soybean component to their diet, it is not possible to confidently distinguish the effects of ethnicity from calcium or soya intake. The literature search in this study was limited and may not have identified all relevant evidence. It is not clear if the studies included personal supplement use in their dietary calcium intake.[158] 2^-

A meta-analysis of six cohort studies showed that a low intake of calcium (less than one glass of milk daily) was not associated with a significantly increased risk of any fracture, osteoporotic fracture or hip fracture. There was no difference in risk ratio between men and women. There were some methodological concerns with this study. No literature search was carried out to inform the meta-analysis and the size of glasses of milk were not standardised in some included studies.[159] 2^+

Harms

No harm was reported for dietary calcium intake.

In general, studies assessing effects of calcium on fracture risk have been poorly designed, suffer from significant imprecision and were of insufficient duration to draw robust conclusions. Meta-analyses have reported considerable heterogeneity. Considering the body of evidence and its quality it appears that there is no significant benefit of increases in dietary calcium (by increments of 300 mg/day) on fracture risk. Calcium supplementation as a primary treatment for osteoporosis is covered in section 6.4.14.

✓ Adequate dietary calcium consumption is recommended to meet reference intake levels of 700 mg/day in adults.

6.3.3 VITAMIN D

Dietary intake of vitamin D in the population is usually very low since few foods naturally contain vitamin D. Most dietary vitamin D is in the form of cholecalciferol (vitamin D_3). Vitamin D status for most healthy adults in the UK is determined by sunlight exposure. A consensus statement representing the unified views of the British Association of Dermatologists, Cancer Research UK, Diabetes UK, the Multiple Sclerosis Society, the National Heart Forum, the National Osteoporosis Society and the Primary Care Dermatology Society recommends short periods of sunlight exposure in summer for vitamin D synthesis, taking care not to burn.[160] 4

The Committee on Medical Aspects of Food and Nutrition Policy recommended supplementation with 10 micrograms/day (400 international units (IU)) vitamin D for those at increased risk of deficiency. This included women whose clothing conceals them fully, those who are confined indoors, infants and children up to the age of three years, the elderly and black and ethnic minority groups.[161] This advice was reinforced in a joint letter distributed to relevant healthcare professionals from the Chief Medical Officers of all UK countries.[162] 4

There is not enough evidence to support a recommendation for food fortification or widespread vitamin D supplementation for the general population. Unlike vitamin D produced in the skin, there is the potential that vitamin D from supplements and fortificants could build up to toxic levels and there is insufficient evidence about the possible risks of raised vitamin D blood levels in the general population over a long period of time.

No meta-analyses on sunlight exposure and fracture risk were identified. Vitamin D supplementation as a treatment is covered in section 6.4.14.

✓ In Scotland, dietary vitamin D intakes are insufficient to meet the needs of people with inadequate sunlight exposure. Supplementation with 10 micrograms/day of vitamin D (400 IU) should be considered to avoid deficiency.

6.3.4 VITAMIN A

Vitamin A comes from two sources. One group, known as retinoids, comes from animal sources and includes retinol. The other group, known as carotenoids, comes from plants and includes beta carotene. The body converts carotenoids to vitamin A. Based on observational evidence linking vitamin A and retinol to fractures, the Scientific Advisory Committee on Nutrition (SACN) made recommendations in 2005 for reducing dietary vitamin A as preformed retinol and avoiding supplements containing retinol in those at risk of osteoporosis.[163] The recent evidence is inconsistent and does not support an adverse effect on fractures but it is considered prudent to follow current government guidelines to limit excessive intakes. 4

Benefits

One case-control study of British women aged over 75 found that serum retinol, retinyl palmitate, and beta carotene were not significant predictors of either hip fracture or any fracture (all p>0.05; Cox proportional hazards regression).[164] For all osteoporotic fractures, the HR was 0.92 (95% CI, 0.81 to 1.05) per 1 standard deviation increase in serum retinol. There was a tendency for increased serum retinol to predict benefit rather than harm in terms of BMD (r=0.09, p=0.002). Multivitamin or cod liver oil supplementation was associated with a significantly lower risk of any fracture (HR, 0.76, 95% CI 0.60 to 0.96, p=0.02). In multivariate analysis, only age, total hip BMD, and weight were associated with fracture risk (p<0.05). As this study was a retrospective case-control cross-sectional design nested in the placebo arm of a pharmacological treatment study it was not designed in advance to examine retinol intake, so the exact composition of multivitamins taken by participants was not recorded. 2^{+}

Harms

Four cohort studies which included over 90,000 participants showed mixed results for the association between vitamin A intake and fractures or BMD. One study reported that women who used vitamin A supplements had increased rates of hip (multivariate HR 1.07 10,000 IU per day, 95% CI 1.00 to 1.15) and wrist fracture (multivariate HR 1.15 10,000 IU per day, 95% CI 1.07 to 1.23),[165] however there was no clear association shown by other studies.[166,167,168] 2^{+}

✓ Avoid excessive intake of preformed retinol by restricting consumption of liver or liver products to once a week and avoiding or limiting dietary supplements containing preformed retinol to ensure total retinol consumption is no more than 1,500 micrograms/day.

6.3.5 VITAMIN B

The B vitamins are required for healthy metabolism. Diets composed of mostly processed foods tend to be lower in B vitamins compared to those which contain non-processed foods. There is evidence showing associations between dietary intakes of B vitamins (reflected by low circulating homocysteine or indicated by high dietary vitamin B_{12} or folate intake) and reduced fracture risk.[169] As RCT data in Caucasian populations are lacking it is uncertain whether the relationship is causal or if it is a marker for an overall healthy diet.

Evidence for the benefit of B vitamins on bone health from two RCTs is mixed; but three cohort studies are consistent in suggesting that B vitamins may be beneficial for bone health.

Benefits

One large RCT which included individuals aged 55 or older, at high risk for cardiovascular disease, analysed response to daily homocysteine-lowering therapy with combined folic acid, pyridoxine (vitamin B_6), and cyanocobalamin (vitamin B_{12}), or matching placebo. Fracture incidence was a secondary outcome and equal numbers of clinical fractures were observed in each group (HR 1.01, 95% CI 0.82 to 1.24, p=0.97). Use of osteoporosis medications or glucocorticoids was not recorded in this trial.[170] 1^{+}

An RCT of male and female Japanese patients one year after ischaemic stroke showed high levels of plasma homocysteine and low levels of serum cobalamin and serum folate. After two years of daily oral treatment with 5 mg of folate and 1,500 micrograms of mecobalamin (vitamin B_{12}), or placebo, plasma homocysteine levels decreased by 38% in the treatment group and increased by 31% in the placebo group (p=0.001). The number of hip fractures per 1,000 patient-years was 10 and 43 for the treatment and placebo groups, respectively (p=0.001). The adjusted relative risk and absolute risk reduction for hip fractures in the treatment versus placebo groups were 0.20 (95% CI, 0.08 to 0.50) and 7.1% (95% CI, 3.6% to 10.8%), respectively.[171] As this was a Japanese population that had suffered a stroke, it is not certain how relevant the findings are to a Scottish population. 1^{++}

Three cohort studies consistently reported that participants with higher homocysteine levels (and/or lower vitamin B levels) were at approximately double the risk of fractures compared with participants with normal homocysteine and vitamin B concentrations.[172,173,174] 2^{+}

Harms

No harms were reported.

✓ An adequate intake of dietary B vitamins can be met by consuming a healthy balanced diet and may help prevent fractures.

6.3.6 VITAMIN K

There are two forms of vitamin K. Vitamin K_1 (phylloquinone) is found in dark green leafy vegetables whereas fermented products such as 'natto' are rich sources of vitamin K_2 (menaquinone). Relevant evidence for vitamin K is lacking.

A subgroup of the Committee on Medical Aspects of Food and Nutrition Policy which focused on nutrition and bone health assessed dietary intake and the nutritional status of the population with regard to calcium and vitamin D. It concluded that 1 microgram of vitamin K per kg body weight was both safe and adequate daily dietary intake in adults.[153] 4

Two meta-analyses and five RCTs which provided data on the association between vitamin K and fracture were identified. Meta-analyses have included studies which involve intake levels that are a thousand-fold higher than would be found in a Western diet and have focussed on vitamin K_2. Randomised controlled trials of vitamin K_1 consistently show no effect on BMD.

Benefits

One meta-analysis identified thirteen trials with data on bone loss, and seven with reported fracture data (all in Japanese participants using menaquinone (vitamin K_2)). All studies but one showed an advantage of phytonadione and menaquinone in reducing bone loss. Pooled fracture data gave an OR favouring menaquinone of 0.40 (95% CI 0.25 to 0.65) for vertebral fractures, an OR of 0.23 (95% CI, 0.12 to 0.47) for hip fractures, and an OR of 0.19 (95% CI, 0.11 to 0.35) for all non-vertebral fractures. The author recommended viewing results with caution due to the high doses of vitamin K used which were not representative of dietary intakes.[175] 1^+

In a further meta-analysis, five trials compared either 5 mg of phylloquinone (vitamin K_1) or 45 mg of menatetrenone (vitamin K_2) with a relevant comparator in postmenopausal women with osteoporosis or osteopenia.[176] Phylloquinone was associated with a statistically significant reduction in the risk of clinical fractures relative to placebo (RR 0.46, 95% CI 0.22 to 0.99), but this trial was not designed to measure fractures and there was a considerable number of drop outs. The smaller menatetrenone trials found that menatetrenone was associated with a reduced risk of morphometric vertebral fractures relative to no treatment or calcium, however, the larger Study of Osteoporosis Fractures study found no evidence of a reduction in vertebral fracture risk. The three smaller trials found no significant difference between treatment groups in non-vertebral fracture incidence. 1^{++}

Of the five RCTs, three found no difference in BMD with vitamin K treatment,[177-179] one of which found reduced bone loss at the forearm with both vitamin K and D.[177] 1^+ 1^{++}

Harms

One meta-analysis concluded that adverse event reporting was generally poor; however, in the Study of Osteoporosis Fractures study, menatetrenone was associated with a significantly higher incidence of skin and skin appendage lesions (0.5 per 100 patient-years compared with 0.1 in the control group, $p<0.001$). Phylloquinone was not associated with an increase in adverse events.[176] 1^{++}

There is insufficient robust evidence available to form a recommendation on the use of vitamin K_1 supplementation.

R **High-dose vitamin K_2 supplements are not recommended for the treatment of osteoporosis or prevention of fragility fractures.**

✓ Adequate dietary vitamin K consumption (1 microgram/kg/day) is recommended to meet reference intake levels.

6.3.7 ANTIOXIDANT VITAMINS

One RCT and one retrospective case-control study were identified which provided data on the association between antioxidant vitamin intake and fracture. Limited evidence suggests a benefit of vitamin C on BMD and vitamin E in reducing fracture.

Benefits

The RCT found that 1,000 mg of ascorbic acid (vitamin C) with 400 IU of alpha-tocopherol (vitamin E) taken for one year increased hip BMD by 1% compared to 0.7% loss in a placebo group. There was also an association between enzyme markers of antioxidant activity and hip BMD.[180] 1^-

A case-control study in 1,215 men and women aged 50 or older who had suffered a hip fracture and 1,349 age- and sex-matched controls examined the relationship between antioxidant intake and risk of hip fracture as modified by smoking. Among ever smokers, those in the highest quintile of vitamin E intake (compared with the lowest) had a lower risk of hip fracture after adjustment for confounders (OR 0.29, 95% CI 0.16 to 0.52, p trend <0.0001). There was no significant association between vitamin C intake and risk of hip fracture in smokers or non-smokers.[181] 2^+

Harms

No harms were reported.

✓ Antioxidant consumption from dietary sources (fruit and vegetables) may promote bone health as part of a healthy balanced diet.

6.3.8 DIETARY OR SUPPLEMENTED PROTEIN

Dietary protein is required as part of a healthy balanced diet. There has been concern about the potential adverse effect of high protein diets as these produce acidic metabolites which are hypothesised to be detrimental to bone (*see section 6.3.14 on acid-balancing diets*).

One meta-analysis and one RCT provide inconsistent evidence for the benefit of protein supplementation on BMD. The evidence supporting the effect of protein supplementation on BMD is conflicting, with variations between the populations studied and the type and degree of supplementation. The effect of protein supplementation in populations with low dietary protein intake requires further research.

Benefits

A meta-analysis of RCTs indicated a significant positive influence of all protein supplementation on lumbar spine BMD (weighted mean difference WMD 0.02, 95% CI 0.00 to 0.04, p=0.04) but showed no association with relative risk of hip fractures (RR 0.75, 95% CI 0.47 to 1.21, p=0.24). Overall in observational studies, there was either no influence or a positive influence of protein intake on BMD. Fifteen cross-sectional surveys found a statistically significant positive relation between protein intake and at least one BMD site but 18 studies found no significant correlation between protein intake and at least one BMD site. When all correlation coefficients are pooled, the results suggested that protein intake explained 1–2% of BMD variability.[182] 1^{++}

An RCT of protein-enriched meals as a method of weight loss in 100 obese men and women showed no difference in BMD after one year in either standard- or high-protein meal groups.[183] 1^+

Harms

No harms were reported.

Insufficient evidence was identified to form a recommendation regarding the association between dietary protein and risk of fragility fracture.

6.3.9 FATTY ACIDS

There is limited information about the role of dietary fatty acids and fracture risk. Total fatty acid intake might reflect a poor quality diet *(see section 6.3.14)*. However, individual fatty acids, and in particularly the essential fatty acids, which cannot be made in the body, might have different effects.

A systematic review was not conclusive about the role of n-3 fatty acids on bone health.[184] 1^{-}

A large observational study of 137,486 postmenopausal women, which compared quartiles of dietary intakes, found that dietary saturated fatty acids were associated with increased hip fracture risk (HR 1.31, 95% CI 1.11 to 1.55; p=0.001); and dietary monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) were associated with reduced hip fracture risk (MUFA HR 0.94, 95% CI 0.89 to 0.98, p=0.05; PUFA HR 0.95, 95% CI 0.90 to 0.99, p=0.019). When types of PUFA were considered separately, it was found that n-6 fatty acids were associated with reduced number of total fracture (HR 0.94, 95% CI 0.89 to 0.98, p=0.009) whereas n-3 fatty acids from oily fish were associated with increased number of fractures (HR 1.07, 95% CI 1.02 to 1.12, p= 0.010).[185] 2^{+}

Insufficient evidence was identified to form a recommendation regarding the association between dietary fatty acids and risk of fragility fracture.

6.3.10 DIETARY SALT

Dietary salt (sodium chloride) can increase excretion of calcium particularly in Caucasians and, unless sufficient calcium is absorbed to compensate for this, it is suggested that high salt diets may be detrimental to bone health. The evidence to support this is inconsistent but overall the observational evidence suggests that high dietary salt intake is associated with lower BMD. There is no evidence that reducing salt intake would prevent fractures. However, the Government is committed to reducing salt intakes in the UK population to help reduce other disease outcomes which are linked to high blood pressure.[186]

Benefits

A study in which some participants halved their intake of dietary sodium and control group participants retained their current sodium intakes (3,000 mg a day) for three years showed that those with higher sodium intake had higher BMD in the forearm and spine at baseline and all subsequent time points (p<0.01). However the analysis was not carried out according to treatment groups, but as a continuum of intakes.[187] 2^{+}

Harms

A cohort study involving healthy premenopausal women found that dietary sodium intake correlated with 24 hour urinary calcium loss. Also, urinary sodium was inversely associated with hip BMD for all participants (r=-0.21, p=0.04) and among women with lower (r=-0.36, p<0.01) but not higher (r=-0.05, p=0.71) calcium intakes.[188] 2^{+}

✓ Reducing salt intakes in line with Government targets has no detrimental effect on bone health but is recommended for other health outcomes.

6.3.11 MINERALS

Although the major mineral in bone is calcium, there are a number of other mineral components for which there are plausible reasons for their involvement in bone biochemistry.[161]

Observational studies have reported associations between dietary mineral intake and BMD[189], however, such studies are subject to confounding due to common food sources. For example, fluoride is added to drinking water in some parts of the UK[190] and cadmium is a heavy metal contaminant that is found in the diet, and in tobacco smoking.

Benefits

A meta-analysis of 25 studies concluded that fluoride treatment increases spine and hip BMD dependent on duration.[191] Spine BMD increased by 7.9% (95% CI 5.4% to 10.5%, p<0.001, n=1,774) and hip BMD by 2.1% (95% CI 0.9% to 3.4%, p<0.01, n=1,434) after treatment with fluoride, but with evidence of significant heterogeneity (p<0.01). Meta regression analysis showed an increase in spine BMD with increasing duration of treatment (5.04% ±2.16% per year of treatment). There were no statistically significant effects of fluoride treatment on the risk of vertebral or non-vertebral fracture risk, but with evidence of significant heterogeneity. 1- Meta-regression analysis for non-vertebral fracture risk showed an increase of fracture risk with increasing fluoride dose (OR 0.14 per mg, p<0.01). There was no effect of treatment duration. Subgroup analysis showed that with a daily dose of 20 mg or less of fluoride equivalents there was a statistically significant reduction for both vertebral fracture risk (OR 0.28, 95% CI 0.09 to 0.87, six studies, n=593) and for non-vertebral fracture risk (OR 0.52, 95% CI 0.28 to 0.76, six studies, n=768). A daily dose of 20 mg or more of fluoride equivalents showed a non-statistically significant increase in the risk of both vertebral fractures (OR 1.26, 95% CI 0.78 to 2.04, 11 studies) and non-vertebral fracture (OR 1.46, 95% CI 0.77 to 2.76, seven studies).

One small RCT suggested that dietary silicon may improve bone formation with a small gain in femoral neck BMD seen when choline-stabilised orthosilicic acid was given daily for 12 months as a 6 mg dose (mean 0.78 (SD ±3%)) compared to a BMD loss of -1.22 ±3% for the placebo and -1.58 ±3% for the lower 3 mg dose.[192] 1- However, increasing to 12 mg daily dose caused a mean BMD loss of 0.84% ±2%. There was no change in BMD at the lumbar spine. Calcium and vitamin D supplements were given throughout.

The National Health and Nutrition Examination Survey (NHANES) did not find any association between dietary potassium, magnesium or zinc and femoral neck (FN) BMD.[193] However, an observational study showed that 3 dietary potassium was associated with higher BMD which was stronger in premenopausal women with a difference of 8% in FN BMD observed between the highest and lowest quartiles of potassium intake.[194]

Harms

The meta-analysis of fluoride treatment showed no significant differences in the frequency of GI symptoms in the fluoride treatment and control groups (14 studies). There was a significantly higher risk of pain for 1- fluoride-treated groups compared to controls (OR 2.76, 95% CI 1.35 to 5.65). There were similar increases in pain with doses of 20 mg fluoride or less and doses of 20 mg or more.[191]

One RCT suggested that increased dietary copper and zinc intakes might worsen bone loss. Bone mineral density decreased from baseline values to year two with the greatest decrease observed with copper and zinc supplementation. Based on five-day food diaries, the negative effect was caused by zinc and mainly occurred 1- with zinc intakes ≥8.0 mg/day With zinc intakes <8.0 mg/day, zinc supplementation apparently prevented a significant decrease in whole body BMD. Food diaries also indicated that magnesium intakes <237 mg/day, copper intakes <0.9 mg/day and zinc intakes <8.0 mg/day were associated with poorer bone health.[195]

A cohort study conducted in Swedish men found that multivariable-adjusted dietary cadmium intake was associated with a statistically significant 19% (HR 1.19, 95% CI 1.06 to 1.34) higher rate of any fracture comparing highest tertile with lowest.[196] Men in the highest tertile of dietary cadmium and lowest tertile of 2- fruit and vegetable consumption had a 41% higher rate of any fracture compared with contrasting tertiles. Hip fracture rates also were higher in the highest tertile of cadmium intake but only statistically significant among never smokers (HR 1.70, 95% CI 1.04 to 2.77).

Insufficient robust evidence was identified that consumption of dietary minerals such as potassium or magnesium, which may be markers of dietary fruit and vegetable intake, or other minerals may be associated with changes in BMD.

6.3.12 PHYTO-OESTROGENS (ISOFLAVONES)

Phyto-oestrogens are bioactive compounds found in the diet, with soya and pulses being the main sources. Their structural similarity to oestrogen means that they can exhibit weak oestrogenic or antioestrogenic effects.

Benefits

Several meta-analyses report either no association or a very weak beneficial effect on BMD at high doses of phyto-oestrogens, which are rarely found in the Western diet.[197-201] There is much heterogeneity regarding dose, type of phyto-oestrogen, whether soy protein or extract, site of benefit (spine or hip), treatment duration and population group (Asian versus Western). 1^{++} 1^{+}

Five out of six RCTs showed no effect on bone loss at recognised osteoporotic fracture sites.[202-206] Only one very small study suggested reduction in bone loss with two glasses of soy milk containing 76 mg isoflavone daily.[207] 1^{++} 1^{+} 1^{-}

Harms

No harms were reported.

R **Dietary phyto-oestrogens are not recommended as a means of preventing fractures or reducing bone loss in postmenopausal women.**

6.3.13 CAFFEINE-CONTAINING FOODS AND BEVERAGES

Caffeine-containing foods and beverages include tea, coffee, chocolate and cola drinks. In addition to the reported adverse effect of caffeine causing greater urinary calcium, there are suggested potential benefits from other bioactive compounds found in these foods such as flavonoids and anthocyanins. Caffeine-containing drinks showed opposing effects with tea being beneficial and coffee detrimental if dietary calcium was low. Cola drinks also contribute dietary acidity in addition to caffeine, but with any association there is likely to be a high degree of confounding.

Benefits

A prospective US cohort study reported that among 91,465 postmenopausal women, multivariate analyses suggested a positive trend towards increased total body BMD with tea drinking ($p<0.05$). However, results did not show any significant association between tea drinking and the risk of fractures at the hip and forearm/wrist. The results suggest that the effect of habitual tea drinking on bone density is small and does not significantly alter the risk of fractures.[208] 2^{+}

In one cross-sectional analysis, total hip BMD was 2.8% greater in tea drinkers (806 mg/cm^2, 95% CI 797 to 815 mg/cm^2) than in non-tea drinkers (784 mg/cm^2, 95% CI 764 to 803 mg/cm^2) ($p<0.05$). In the prospective analysis over four years, tea drinkers lost an average of 1.6% of their total hip BMD (-32 mg/cm^2, 95% CI -45 to -19 mg/cm^2), but non-tea drinkers lost 4.0% (-13 mg/cm^2, 95% CI -20 to -5 mg/cm^2) ($p<0.05$). Adjustment for covariates did not influence the interpretation of results.[209] 2^{-}

Harms

A large cohort study of over 30,000 women aged 40–76 identified through mammography screening invitations found 3,279 participants with osteoporotic fractures during mean follow up of 10.3 years. The highest quintile of caffeine intake (>330 mg/day) was associated with a modestly increased risk of fracture compared with the lowest (<200 mg/day) (HR 1.20, 95% CI 1.07 to 1.35). A high coffee consumption significantly increased the risk of fracture (p for trend 0.002), whereas tea drinking was not associated with greater risk. The increased risk of fracture with both a high caffeine intake and coffee consumption was confined to women with a low calcium intake (<700 mg/day) (HR 1.33, 95% CI 1.07 to 1.65) with ≥4 cups (600 ml)/day of coffee compared to <1 cup 2^{+}

(150 ml) per day. The same comparison but where risk was estimated for women with a high propensity for fractures (≥2 fracture types) revealed an HR of 1.88 (95% CI 1.17 to 3.00).[210] 2^{+}

A single-cohort study found that men consuming ≥4 cups of coffee per day had 4% lower BMD at the proximal femur (p=0.04) compared with low- or non-consumers of coffee. This difference was not observed in women. In high consumers of coffee, those with rapid metabolism of caffeine (C/C genotype) had lower BMD at the femoral neck (p=0.01) and at the trochanter (p=0.03) than slow metabolisers (T/T and C/T genotypes). Calcium intake did not modify the relation between coffee and BMD.[211] 2^{+}

A cross-sectional study found cola intake was associated with significantly lower BMD (p<0.001 to 0.05) at each hip site, but not the spine, in women but not in men. The mean BMD of those with daily cola intake was 3.7% lower at the femoral neck than of those who consumed one serving of cola/month. Similar results were seen for diet cola and, although weaker, for decaffeinated cola. No significant relations between non-cola carbonated beverage consumption and BMD were observed. Total phosphorus intake was not significantly higher in daily cola consumers than in non-consumers; however, the calcium-to-phosphorus ratios were lower.[212] 2^{+}

A further cross-sectional analysis of 1,001 women showed that higher frequency of chocolate consumption was linearly related to lower bone density and strength (p<0.05). Daily (or more frequent) consumption of chocolate, in comparison to <1 time/week, was associated with a 3.1% lower whole-body bone density; with similarly lower bone density of the total hip, femoral neck, tibia, and heel; and with lower bone strength in the tibia and the heel (p<0.05, for all). The assessment of chocolate intake was very crude with chocolate-covered products being included as chocolate. This study suggested that the strength of the relationship with bone density might be due to oxalate which inhibits calcium absorption, however, this does not concord with studies that drinking tea (which also contains oxalate) is beneficial to BMD.[213] 3

✓ The increased risk of fracture observed with high intakes of coffee may be subject to residual confounding, but it may be prudent to restrict intakes to no more than four cups per day, particularly if dietary calcium intakes are low.

6.3.14 WHOLE DIETS

The evidence for the role of diet (rather than individual nutrients) on bone outcomes is diverse and includes diets rich in fruit and vegetables, acid-balancing diets and diets aimed at reducing body weight. In addition, dietary patterns have been generated from food intake data of general populations, using statistical data reduction techniques such as principal components analysis or cluster analysis. An example of a healthy balanced diet is defined by the eatwell plate.[214]

Weight reduction diets

No studies of sufficient quality were identified to report on the use of weight reduction diets in the prevention of fractures. Dietary protein supplementation as a weight-loss strategy is covered in section 6.3.8.

Diets rich in fruit and vegetable intakes

There is conflicting evidence about the association between vegetarian diets and bone health. Whereas some data suggest that a raw vegetarian diet is associated with lower bone mass,[215] other studies have found no such association.[216, 217]

Benefits

A systematic review of eight randomised and non-randomised studies investigated the association of fruit and vegetable intake with bone health.[218] One cohort study reported cross-sectional as well as longitudinal data. There was significant between-study heterogeneity in design, definition, and amount of fruit and vegetable intake, outcomes, analyses, and reporting of results. Two cross-sectional analyses reported positive associations between fruit and vegetable intake and BMD of the forearm, lumbar spine, or total hip, whereas one RCT and two prospective cohort analyses reported no effects. 2^{++}

Harms

A meta-analysis of nine observational studies (five in Asian patients) showed that overall, BMD was approximately 4% lower in vegetarians than in omnivores (95% CI 2% to 7%) at both the femoral neck and the lumbar spine. Compared with omnivores, vegans had a significantly lower lumbar spine BMD (6% lower; 95% CI 2% to 9%). A Bayesian analysis showed that the probability that BMD was ≥5% lower in vegetarians than in omnivores (or approximately 0.3 SD) was 42% for the femoral neck and 32% for the lumbar spine suggesting that the observed BMD deficit in those following vegetarian diets may not be clinically significant.[219]

2^{+}

Acid-balancing diets

The hypothesis that a high protein diet produces excess non-carbonic acid, which, because the body has limited capacity to excrete, requires bone degradation to release buffering salts and in the long term results in osteoporosis, has not been convincingly proven. The interventions which aimed to balance excess dietary acidity and increase BMD have shown mixed results and there is no evidence of any antifracture benefit.

Benefits

A meta-analysis included 22 RCTs, two meta-analyses, and 11 prospective observational studies of bone health outcomes including: urine calcium excretion, calcium balance or retention, changes of BMD, or fractures, among healthy adults in which acid and/or alkaline intakes were manipulated or observed through foods or supplements. There were also 19 in vitro cell studies which examined the hypothesised biochemical mechanism of action. Urine calcium excretion rates were consistent with osteoporosis development, however calcium balance studies did not demonstrate loss of whole body calcium with higher net acid excretion. No intervention studies provided direct evidence of osteoporosis progression (fragility fractures, or bone strength as measured using biopsy). Prospective cohort studies which showed a positive association between acid imbalance and osteoporosis development were not adjusted for important confounders including weight loss during follow up, family history of osteoporosis, baseline BMD, and oestrogen status. No study revealed a biological mechanism functioning at physiological pH which was associated with fracture risk. Furthermore, RCTs failed to provide evidence for an adverse role of phosphate, milk, and grain foods in osteoporosis. A causal association between dietary acid load and osteoporotic bone disease was not supported by evidence and there is no evidence that an alkaline diet may be protective of bone health.[220]

1^{++}

Harms

An RCT of a Mediterranean diet with mixed nuts which had increased dietary acidity load compared to a control diet with one year follow up had no effect on BMD although there was an increase in parathyroid hormone.[221]

1^{-}

R **Acid-balancing diets are not recommended to reduce fracture risk.**

Dietary patterns

One twin study, two large population studies and one small study consistently showed that a nutrient-dense or healthy diet is associated with improved BMD and that diets of mainly processed foods are associated with a decline in BMD.

Benefits

Two dietary patterns were identified in a retrospective cohort study of postmenopausal women and men aged 50 or older. The first (nutrient-dense) was most strongly associated with intake of fruits, vegetables and whole grains. The second (energy-dense) was most strongly associated with intake of soft drinks, potato chips and French fries, certain meats (hamburger, hot dog, lunch meat, bacon, and sausage), and certain desserts (doughnuts, chocolate, ice cream). The nutrient-dense factor was associated with a reduced risk of fracture per 1 SD in men overall (HR 0.83, 95% CI 0.64 to 1.08) and in women overall (HR 0.86, 95% CI 0.76 to 0.98). An age trend (p=0.03) was observed in women, with a lower HR of 0.82 for older women (age ≥70) compared to HR of 0.97 for younger women (age <70).[222]

2^{+}

A single-cohort twin study observed a positive correlation between alcohol intake (from wine but not from beer or spirits) and spine BMD (Beta 0.050, 95% CI 0.017 to 0.083,

2^{+}

p=0.01) and an inverse correlation with a traditional English diet at the femoral neck (Beta -0.055, 95% CI -0.090 to -0.020, p=0.01). Both associations remained borderline significant after adjustment for mean twin-pair intakes (p=0.04 and p=0.055, respectively). Other dietary patterns and intakes of calcium, vitamin D, and protein were unrelated to BMD.[223] 2^+

A cross-sectional study identified five dietary patterns in over 3,000 postmenopausal women. The diet classified as healthy was positively associated with BMD at both sites (lumbar spine (LS) BMD r=0.054, p=0.002; FN BMD r=0.056, p=0.001).[224] 3

A smaller cross-sectional study (n=220 women) generated 10 dietary patterns from three-day food records and found that adherence to a dietary pattern close to the Mediterranean diet, that is, high consumption of fish and olive oil and low red meat intake was positively related to bone mass (standardised beta 0.185 (p=0.02) at the spine).[225] 3

Harms

Two studies showed that a diet rich in processed foods or snack foods, or an energy-dense diet was associated with lower BMD.[224, 226]

A retrospective single-cohort study showed that an energy-dense ('unhealthy') diet was associated with higher BMI independent of other demographic and lifestyle factors, and BMI was a strong independent predictor of BMD. However, a similar positive association between diet and BMD was not seen. In fact, when adjusted for BMI, each standard deviation increase in the energy-dense score was associated with a BMD decrease of 0.009 g/cm^2 (95% CI 0.002 to 0.016 g/cm^2) for men aged 50 or above and 0.004 g/cm^2 (95% CI 0.000 to 0.008 g/cm^2) for postmenopausal women. In contrast, for men 25–49, each standard deviation increase in the nutrient dense score, adjusted for BMI, was associated with a BMD increase of 0.012 g/cm^2 (95% CI 0.002 to 0.022 g/cm^2).[226] 2^+

A cross-sectional study showed that a diet classified as processed food was negatively associated with BMD at both sites (LS BMD r=-0.043, p=0.015; FN BMD r=-0.056, p=0.002), as was the diet classified as snack food (LS BMD r=-0.041, p=0.020; FN BMD r=-0.044, p=0.012).[224] 3

One RCT showed after a mean 8.1 years of follow up, 215 women in the intervention group (low fat diet with increased fruit vegetables and grains) and 285 women in the comparison group (annualised rate: 0.14% and 0.12%, respectively) experienced a hip fracture (HR 1.12, 95% CI 0.94 to 1.34; p=0.21). There was a significant interaction according to hormone therapy use; those in the comparison group receiving hormone therapy had the lowest incidence of hip fracture. In a subset of 3,951 women, hip BMD at years three, six, and nine was 0.4–0.5% lower in the intervention group than in the comparison group (p=0.003). The intervention group (n=5,423; annualised rate 3.44%) had a lower rate of reporting two or more falls than did the comparison group (n=8,695; annualised rate 3.67%) (HR 0.92, 95% CI 0.89 to 0.96; p=0.01). The intervention diet resulted in a slightly greater weight reduction than the comparison group (0.8 kg compared with 0.1 kg).The authors concluded that a low-fat and increased fruit, vegetable, and grain diet intervention modestly reduced the risk of multiple falls and slightly lowered hip BMD but did not change the risk of osteoporotic fractures.[227] 1^+

R **A balanced diet is recommended for bone health but there is no evidence that specific diets reduce fracture risk. Changes to the diet which result in an imbalance of food groups could affect overall nutrient intake and be detrimental to general health.**

6.4 PHARMACOLOGICAL MANAGEMENT

Therapies used in the management of osteoporosis are designed to reduce the risk of fracture. Their mechanism of action is either to reduce the rate of bone turnover (antiresorptives) or stimulate bone formation (anabolic therapies). Antiresorptive therapies include bisphosphonates, raloxifene, HRT and denosumab. Parathyroid hormones, such as teriparatide, have a purely anabolic or bone-forming action. Strontium ranelate has evidence for a dual role as antiresorptive and some bone-forming activity. Bisphosphonates vary in potency from the weakest, etidronate, to more potent oral therapies, risedronate, alendronate and ibandronate, through to the most potent, zoledronic acid.

6.4.1 ALENDRONIC ACID

Alendronic acid is a nitrogen-containing bisphosphonate which has potent inhibitory effects on osteoclastic bone resorption, a high affinity for binding bone mineral and a prolonged duration of action. It is widely used in the treatment of osteoporosis.[228-230] Treatment is almost always given in a dose of 70 mg once weekly which is bioequivalent in terms of BMD response to the oral dose of 5 mg or 10 mg daily which was used in the pivotal fracture prevention trials.

Benefits

Meta-analyses show the effectiveness of alendronic acid at 10 mg daily in preventing vertebral and non-vertebral fractures among postmenopausal women with osteoporosis.[228, 230]

Among 7,361 postmenopausal women, significantly fewer patients suffered vertebral fractures in the alendronic acid group compared with placebo/no treatment (RR 0.55, 95% CI 0.45 to 0.67; six studies). Among 9,625 postmenopausal women, alendronic acid reduced non-vertebral fractures compared with placebo/no treatment (RR 0.84, 95% CI 0.74 to 0.94; six studies). Similarly, hip fractures were reduced among 9,952 postmenopausal women treated with alendronic acid compared with placebo/no treatment (RR 0.61, 95% CI 0.40 to 0.92; seven studies). Alendronic acid is therefore effective in preventing fractures in postmenopausal women who have osteoporosis, or low BMD with baseline vertebral fracture.[228] 1++

The relationship between alendronic acid and fracture risk in other populations with higher T-scores or on the basis of FRAX scores has also been studied.

A post hoc analysis of FIT studied patients with baseline femoral neck T-scores between -1.6 to -2.5 in well-matched baseline populations of women with and without previous vertebral fracture. At three years alendronic acid significantly reduced the overall risk of clinical vertebral fractures by 60% compared with placebo (RR 0.40, 95% CI 0.19 to 0.76, p=0.005).[229] 1++

Another post hoc analysis of FIT looked at the effectiveness of alendronic acid to examine the relationship between FRAX score and fracture risk. There are some limitations to this study because paternal hip fracture was unknown and baseline radiographic vertebral fractures were not allocated as a previous fracture, which may underestimate FRAX risk.[127] Patients were divided according to deciles of FRAX risk (computed with FN BMD). The risk reduction associated with alendronic acid for non-vertebral fracture was similar for patients with low baseline FRAX risk (<20%) to those with higher baseline FRAX risk (>20%) and fracture risk reduction with alendronic acid did not correlate with increasing FRAX risk. The authors make the point however, that as FRAX risk increases there is still a greater absolute risk reduction with treatment because overall fracture risk is higher. 1+

There have been direct comparisons of alendronic acid and other drugs used to treat osteoporosis but these are underpowered to detect differences in fracture outcomes.[230] Indirect methodologically robust comparisons have been carried out which attempt to rank drugs using Bayesian analysis. The drugs with the greatest probability of preventing vertebral, hip and wrist fractures were teriparatide, zoledronic acid and denosumab. Alendronic acid and risedronate had the highest effect size in preventing non-vertebral, hip or wrist fractures which indicates that these drugs have the lowest odds for fractures compared with placebo and/or that the standard error is smallest.[231] 1++ 1+

Harms

Alendronic acid is generally a safe drug and evidence from RCTs shows that the rate of upper GI events or any treatment discontinuation due to adverse events did not differ between treatment and placebo groups.[228] 1++

However, clinical experience and postmarketing surveillance shows that alendronic acid can cause GI upset and oesophageal erosion and ulcers. A review by the Medicines and Healthcare Products Regulatory Agency (MHRA) highlights the use of alendronic acid with caution in patients who have upper GI problems and avoiding it in those with stricture or achalasia. They also investigated a possible link to oesophageal cancer but stated there was insufficient evidence to confirm such an association.[232] 4

Other suggested adverse effects of bisphosphonates include atrial fibrillation (AF), osteonecrosis of the jaw (ONJ) and atypical stress fractures, eg subtrochanteric fractures *(see section 6.4.6)*.[228] There was a trend towards increasing cases of AF with alendronic acid (OR 1.26, 95% CI 0.96 to 1.66) using data from FIT. However, there was no difference between alendronic acid and placebo in the rates of cardiac death or venous thromboembolism (in the trials which reported this). A meta-analysis showed an association with bisphosphonates (data from alendronic acid, risedronate and zoledronate combined) and risk of AF although a lack of data prevented a firm conclusion.[233] The rate of serious AF events with bisphosphonates compared with placebo was increased (RR 1.53, 95% CI 1.17 to 2.00). Similar conclusions were reached in another meta-analysis,[234] while a third meta-analysis showed there was a non-significant higher risk of overall (OR 1.18, 95% CI 0.84 to 1.67) and serious AF (OR 1.59, 95% CI 0.61 to 3.75) among bisphosphonate-treated patients.[235]

1^{++}
1^{+}

General harms associated with bisphosphonates are covered in section 6.4.6.

R **Alendronic acid is recommended to prevent vertebral fractures, non-vertebral fractures and hip fractures in postmenopausal women with pre-existing vertebral fractures and/or DXA-proven osteoporosis.**

6.4.2 RISEDRONATE

Risedronate is a nitrogen-containing bisphosphonate which has powerful inhibitory effects on osteoclastic bone resorption but a lower affinity for binding bone mineral than alendronic acid. At the doses used clinically it has less of an inhibitory effect on bone resorption than alendronic acid and a shorter duration of action. Evidence of the benefits of therapy comes from meta-analyses of RCTs comparing risedronate with placebo in combination with calcium and vitamin D supplements. In routine clinical practice risedronate is almost always given in a dose of 35 mg once weekly which is bioequivalent in terms of BMD response to the oral dose of 5 mg daily which was used in the pivotal fracture prevention trials.

Benefits

A meta-analysis of five RCTs which included 2,620 postmenopausal women with pre-existing vertebral fractures or low BMD by DXA, showed that risedronate significantly reduced the risk of vertebral fracture compared with placebo after three years treatment (RR 0.64, 95% CI 0.52 to 0.78).[230] Three trials were noted to be at risk of bias due to missing data, or for using a change of 15% of participants' height as a measurement threshold for vertebral fractures. 1^{++}

The effects of risedronate on non-vertebral fracture and hip fracture were also evaluated in a meta-analysis[230] and a further RCT designed to investigate the effects of risedronate on hip fracture.[131] This study enrolled 9,331 postmenopausal women; 5,445 were enrolled on the basis that they were aged 70–79 and had low hip BMD by DXA (femoral neck T-score <-4.0 or <-3.0 and a hip axis length of 11.1 cm or greater) whereas the remaining 3,886 patients were enrolled on the basis that they were aged over 80 with at least one clinical risk factor for hip fracture. This study showed a significant reduction in hip fracture risk overall (RR 0.70, 95% CI 0.60 to 0.90). Subgroup analysis showed that the reduction in risk of hip fracture was statistically significant in patients with low BMD (RR 0.60, 95% CI 0.40 to 0.90) but not significant in those with clinical risk factors alone (RR 0.80, 95% CI 0.60 to 1.20). Meta-analysis showed significantly fewer non-vertebral fractures in postmenopausal women treated with risedronate (RR 0.80, 95% CI 0.72 to 0.90; six studies) and significantly fewer hip fractures (RR 0.74, 95% CI 0.59 to 0.94; four studies).[230] 1^{++}

A Cochrane review of risedronate in postmenopausal women who had suffered a previous fracture showed that risedronate was effective in reducing the risk of subsequent vertebral and hip fractures. A total of 2,812 women from three studies of moderate quality were included in the meta-analysis which showed a significant reduction in vertebral fractures (RR 0.61, CI 0.5 to 0.76). For hip fractures, meta-analysis of data from 11,786 women in three studies showed that risedronate reduced fracture by 26% (RR 0.74, 0.59 to 0.94). In contrast, there were two studies which included 327 women without previous fracture and showed no significant reduction in vertebral fracture rates. However, these were of low methodological quality as they included populations at low risk of fracture and were underpowered to detect fracture outcomes.[236] 1^{++}

Harms

Using data from RCTs adverse events were generally similar compared with placebo, including GI events. Upper GI irritation and reactions are the most common serious adverse effect with oral bisphosphonates.[133, 134] Risedronate may be used with caution in patients with abnormalities of the oesophagus and/or other factors which delay oesophageal emptying such as stricture or achalasia (in contrast to alendronic acid and oral ibandronic acid which are contraindicated). 4

There are fewer reports of ONJ and atypical femoral fractures with risedronate than alendronic acid, but this may reflect the fact that it is less widely used. Risedronate has not been associated with AF.[237] 4

General harms associated with bisphosphonates are covered in section 6.4.6.

R **Risedronate is recommended to prevent vertebral fractures, non-vertebral fractures and hip fractures in postmenopausal women with pre-existing vertebral fractures and/or DXA-proven osteoporosis.**

6.4.3 ZOLEDRONIC ACID

Zoledronic acid is a nitrogen-containing bisphosphonate with potent inhibitory effects on osteoclastic bone resorption and high binding affinity for bone mineral. It has a long duration of action and is the most potent bisphosphonate currently licensed for the treatment of osteoporosis. Evidence on the effects of zoledronic acid in people with osteoporosis comes from RCTs in which zoledronic acid was administered intravenously in a dose of 5 mg annually in comparison with placebo infusions, with administration of calcium and vitamin D supplements to both treatment groups.

Benefits

The effects of zoledronic acid on the risk of fracture in postmenopausal women were studied in a large RCT of 3,889 women with osteoporosis (BMD T-score <-2.5 or vertebral fracture and a T-score of -1.5).[238] Women received either annual infusions of 5 mg zoledronic acid intravenously for three years or an equivalent placebo infusion. The relative risk of vertebral fractures with zoledronic acid was 0.30 (95% CI 0.24 to 0.38) when compared with placebo. The corresponding risk for hip fracture was 0.59 (95% CI 0.42 to 0.83) and for non-vertebral fractures was 0.75 (95% CI 0.74 to 0.87). 1^{+}

In a further RCT the effects of zoledronic acid or placebo on recurrent fractures were investigated in 2,127 patients over the age of 50 who had suffered a hip fracture.[138] Around three quarters of the patients in the trial were women. Patients were included in the study if they were unable or unwilling to take oral bisphosphonates. The hazard ratio for vertebral fractures in the zoledronic acid group was 0.54 (95% CI 0.32 to 0.92), and for non-vertebral fractures was 0.73 (95% CI 0.55 to 0.98). The risk of recurrent hip fracture was reduced but not significantly (HR 0.70, 95% CI 0.41 to 1.19). In addition, mortality was significantly reduced in the zoledronic acid group (HR 0.72, 95% CI 0.56 to 0.93). 1^{++}

Harms

Adverse effects were significantly more common in the zoledronic acid group than placebo group, most notably influenza-like symptoms which typically occurred within three days of the infusion. The frequency was 31.6% *v* 6.2% after the first infusion; 6.6% *v* 2.1% after the second infusion and 2.8% *v* 1.1% after the third infusion. In one trial, AF was more common overall in the zoledronic acid group (2.5% *v* 1.9%, not significant (NS)) but the difference was significant for patients with serious AF (50 patients (1.3%) versus 20 patients (0.5%)). The vast majority of events occurred more than 30 days after infusion, by which time zoledronic acid is undetectable in the circulation.[238] 1^{+}

General harms associated with bisphosphonates are covered in section 6.4.6.

R **Zoledronic acid is recommended to prevent vertebral, non-vertebral and hip fractures in postmenopausal women with pre-existing vertebral fractures or DXA-proven osteoporosis. It should be considered in those who are intolerant of oral therapy and those in whom adherence with oral therapy may be difficult.**

R **Zoledronic acid may be considered to prevent clinical fractures and reduce mortality in selected postmenopausal women who have suffered a hip fracture. It should be considered in those who are intolerant of oral therapy and those in whom adherence with oral therapy may be difficult.**

6.4.4 IBANDRONIC ACID

Ibandronic acid is a nitrogen-containing bisphosphonate with osteoclast-inhibitory effects and bone mineral binding properties intermediate between those of alendronic acid and risedronate. It may be given orally or intravenously in the treatment of osteoporosis.

Effectiveness in preventing fractures has mainly been demonstrated for oral ibandronic acid at 2.5 mg daily but this regimen is not licensed in the UK. The licensed doses (150 mg oral once monthly and 3 mg intravenous (IV) quarterly) have been compared to daily 2.5 mg in non-inferiority studies as well as being combined in pooled analyses.

Benefits

Meta-analyses and systematic reviews have shown that 2.5 mg daily ibandronic acid significantly reduced the relative risk of vertebral fractures compared with placebo/no treatment by 30–62%.[230, 239, 240] 1^{++} 1^{+}

While studies have shown that changing from daily to weekly dosing improves both compliance and persistence with bisphosphonates,[241] the evidence for equivalence of monthly compared with daily dosing is derived from a non-inferiority study comparing BMD responses to four different regimens. The trial employed a non-inferiority design in a population of 1,290 postmenopausal women with osteoporosis given ibandronic acid. The primary end point was change in lumbar spine BMD after one year. The results showed increases in BMD of 3.9%, 4.3%, 4.1% and 4.9% for daily 2.5 mg dosing, 50+50 mg single daily doses given on two consecutive days monthly, 100 mg monthly or 150 mg monthly, respectively.[242] 2^{+} 1^{++}

A pooled analysis of individual data from four trials included 8,710 postmenopausal women with osteoporosis in groups according to the dose levels.[243] The group on high-dose ibandronic acid (which included monthly 150 mg oral preparation or quarterly 3 mg IV preparation) showed a significant reduction in the risk of a non-vertebral fracture (34.4%, p=0.032) relative to those on placebo. The high-dose group also had a significantly longer time to fracture compared with placebo for non-vertebral fractures (p= 0.031). Not all studies were placebo controlled, there were a limited number of baseline characteristics available for multivariate analyses and there was no formal quality assessment of trials which limit the strength of these findings. 1^{+}

Meta-analysis of single studies has suggested that neither monthly oral (RR 1.12, 95% CI 0.66 to 1.91) nor quarterly IV (RR 0.79, 95% CI 0.46 to 1.34) preparations of ibandronic acid are more effective than daily oral 2.5 mg doses for reducing any clinical fracture.[230] 1^{++}

Harms

A pooled analysis of two RCTs found that participants taking ibandronic acid had fewer episodes of upper GI perforations, ulcerations or bleeding episodes than those taking placebo (absolute risk 0.4% in the treatment group versus 1.5% in the placebo group).[240] There is a low risk of serious adverse effects including ONJ and atypical femoral fractures. The SMC reported that the incidence of influenza-like symptoms was higher with 150 mg monthly ibandronic acid (8.3%) compared with the daily 2.5 mg dose (2.3%). 1^{++}

General harms associated with bisphosphonates are covered in section 6.4.6.

R **Oral ibandronic acid** (150 mg monthly) **may be considered to prevent vertebral fractures in postmenopausal women with DXA-proven osteoporosis.**

R **Intravenous ibandronic acid** (3 mg every three months) **may be considered to prevent vertebral fractures in postmenopausal women with DXA-proven osteoporosis who are intolerant of oral therapy or those in whom adherence to oral therapy may be difficult.**

6.4.5 CYCLICAL ETIDRONATE

Etidronate is a non-nitrogen-containing bisphosphonate for the treatment of osteoporosis. It is given in a cyclical regimen of 400 mg daily for 10 days every three months in combination with calcium supplements for the remainder of the treatment cycle.

Benefits

Two systematic reviews and meta-analyses provide evidence on the benefit of etidronate for fracture prevention. One meta-analysis which included eight RCTs (n=1,039) showed etidronate to be significantly more effective than placebo for reducing incidence of vertebral fracture (RR 0.51, 95% CI 0.31 to 0.83). Meta-analysis of four studies with 472 patients showed there was no significant difference between interventions for the reduction in non-vertebral fractures but there was considerable heterogeneity between studies (RR 0.72, 95% CI 0.29 to 1.80).[230] 1^{++}

A second systematic review of trials of primary and secondary prevention of fracture included 11 studies and a total of 1,248 patients.[244] A significant 41% relative risk reduction in vertebral fractures was found across eight studies (RR 0.59, 95% CI 0.36 to 0.96). The six secondary prevention trials demonstrated a significant reduction of 47% in relative risk of vertebral fractures (RR 0.53, 95% CI 0.32 to 0.87) and a 5% absolute risk reduction (ARR); compared with the pooled result for the two primary prevention trials (RR 3.03, 95% CI 0.32 to 28.44), which was not significant. There were no statistically significant risk reductions for non-vertebral (RR 0.98, 95% CI 0.68 to 1.42), hip (RR 1.20, 95% CI 0.37 to 3.88) or wrist fractures (RR 0.87, 95% CI: 0.32 to 2.36). 1^{++}

Harms

No statistically significant differences in adverse events were found in the included studies. However, observational data have led to concerns regarding potential risk for upper GI injury.[244] 1^{++}

General harms associated with bisphosphonates are covered in section 6.4.6.

R **Cyclical etidronate may be considered to prevent vertebral fractures in postmenopausal women when other drugs are poorly tolerated or contraindicated.**

6.4.6 GENERAL HARMS ASSOCIATED WITH BISPHOSPHONATES

Osteonecrosis of the jaw

Osteonecrosis of the jaw is a rare event caused by potent antiresorptive therapy used to treat osteoporosis including bisphosphonates and denosumab. The risk in patients with osteoporosis is much less than it is for patients with cancer who take bisphosphonates. Osteonecrosis of the jaw related to bisphosphonates is defined as a greater than eight-week history of exposed or necrotic bone in the maxillofacial region which is not due to irradiation of the jaw, among patients previously exposed to or currently taking bisphosphonates.[245] It is recommended that those with poor dental status are assessed by a dentist prior to commencing oral bisphosphonate therapy.[246] Good oral hygiene is recommended during bisphosphonate therapy and patients should report dental symptoms such as pain or swelling. 4

A systematic review of ONJ associated with use of either oral or IV bisphosphonates in patients with osteoporosis identified 18 studies. The number of identified cases was very small and the authors state that when used among patients at high risk of fracture, the balance of benefit to harm still favours bisphosphonates. There is insufficient evidence to conclude that, in the doses used to treat osteoporosis, oral or IV bisphosphonates lead to a significant risk of ONJ.[247]

✓ Patients starting bisphosphonates should be advised to have a dental check up as soon as possible.

Atypical femoral fractures

Atypical femoral fractures are an uncommon type of stress fracture that occurs with little or no trauma. They have been associated with long-term bisphosphonate and denosumab treatment. There may be preceding thigh pain which may involve both sides and be associated with poor fracture healing.

A large observational study demonstrated that atypical stress fractures, for example subtrochanteric and diaphyseal fractures, occurred at a rate of 13 per 10,000 patients in untreated women and 31 per 10,000 patients taking alendronic acid respectively.[248] This was a large cohort study using hospital discharge and prescription database figures including a mixed population of men and women. Populations were well matched except for comorbidities and previous fracture. There was no association between length of treatment and risk of subtrochanteric fracture, with a similar risk following only several months' treatment to longer duration (seven years), which did not suggest an exposure risk associated with alendronic acid. 2^+

Cases of atypical fractures of the femur associated with bisphosphonate therapy were identified in 196 patients in a systematic review of case reports.[249] Patients tended to have a higher rate of chronic disease and in more than 74% of cases patients had T-scores >-2.5. Glucocorticoids and PPIs were recognised as important risk factors and it was suggested that bisphosphonate treatment should be discontinued among patients with normal BMD in whom the benefits of treatment are less. 3

A case-control study demonstrated that bisphosphonate use was associated with atypical fracture in a Swiss population. Eighty-two per cent of the patients with atypical fracture had exposure to bisphosphonates compared with 6.4% in the classical fracture group. After adjustment for potential risk factors (vitamin D, glucocorticoids, PPI, sex, and age), use of bisphosphonates (any versus none) was associated with an OR of 69.1 (95% CI, 22.8 to 209.5) for an atypical fracture compared with the classic fracture group. There was an increase in frequency with duration of bisphosphonate use but overall atypical fracture was a very rare occurrence (32 cases per million).[250] 2^+

A further case-control study measured exposure to oral bisphosphonates prior to atypical fractures and compared this to five age-matched controls without history of fracture drawn randomly from the Spanish population aged over 65. Spontaneous fractures occurred in nine patients receiving long-term bisphosphonates within three to eight years. In multivariate analysis, the odds ratio of atypical fracture was 4.3 (95% CI 1.55 to 11.9) in ever versus never users of bisphosphonates, and this increased to 9.46 (95% CI 2.17 to 41.3) with exposure over three years. Efforts were made to blind assessors although no mention is made of the definition used for subtrochanteric atypical fracture. Cases were few so confidence intervals are wide and prescription data were used rather than actual drug consumption (which may underestimate the association).[251] 2^+

A Swedish registry-based cohort and case-control analysis of 12,777 women who suffered a hip fracture in 2008 identified those with oral bisphosphonate prescriptions for the preceding three years. There were 59 patients with subtrochanteric hip fracture type, of which 78% were being prescribed bisphosphonates. The age-adjusted relative risk for atypical fracture was 47 (95% CI 25.6 to 87) which equated to an absolute risk of five cases per 10,000 patient-years (95% CI 4 to 7). The risk increased annually between one to three years with duration of oral bisphosphonate. After stopping the drug the risk decreased by 70% per year since the last use (OR, 0.28, 95% CI 0.21 to 0.38). A case-control analysis was performed using 263 controls with a standard fragility hip fracture, ie non-atypical type. There were differences in age (controls were older), fracture history, glucocorticoids and antidepressants and significant concerns regarding confounders limit the strength of these data. This study showed that oral bisphosphonates (alendronic acid and risedronate) were associated with increased risk of atypical fractures.[252] 2^+

There seems to be a time-dependent association between bisphosphonates and atypical fractures. The risk appears to be a class effect and greatest with increasing potency of bisphosphonate. The potent antiresorptive denosumab has also been associated with atypical fracture. However, for users of bisphosphonates or denosumab the overall benefit in preventing hip fractures greatly exceeds the risks of causing atypical fracture. The MHRA recommends that bisphosphonate discontinuation should be considered among patients with suspected atypical fracture while they are being evaluated.[253]

Upper GI cancers

Oral bisphosphonates can cause oesophageal irritation and upper GI side effects are a common consequence of these therapies.

A retrospective observational study found an increased risk of upper GI cancer for postmenopausal women, but not men, prescribed bisphosphonates.[254] Data were derived from the UK GPRD (1995–2007). Each cancer case was given four age- and gender-matched controls from the general population. Baseline characteristics were adequately matched and confounders such as PPI use, *Heliobacter pylori* status, dyspepsia, smoking and BMI were adjusted for. An analysis was also performed to exclude bisphosphonates within six months of cancer diagnosis on the grounds that the time interval was too short for bisphosphonates to be causative. 2^- Only adjustment for smoking altered the results (not the other potential confounders). The risk of upper GI cancer adjusted for smoking status and excluding bisphosphonates within six months of cancer diagnosis was higher among women (OR 1.30, 95% CI 1.10 to 1.53) but not men (OR 0.77, 95% CI 0.58 to 1.04) taking bisphosphonates. There was a small increased risk of oesophageal cancer among women, but not men, taking bisphosphonates after adjusting for confounders (OR 1.43, 95% CI 1.16 to 1.75) and the effect was greatest for alendronic acid.

A systematic review showed an association between oral bisphosphonates and oesophageal cancer that increased with duration of exposure with an odds ratio of 1.74 (95% CI 1.19 to 2.55). Subgroup analysis showed etidronate was associated with an increased risk of oesophageal cancer (OR 1.58, 95% CI 1.12 to 2.24) but alendronic acid was not significantly associated with this risk. Only a small number of studies were included, although this involved 19,700 oesophageal cancer patients. There was significant heterogeneity 2^+ in the meta-analyses, due to an inability to differentiate between the two histologically different types of oesophageal cancer. Furthermore, different doses and durations of bisphosphonates may have added to heterogeneity. In conclusion the authors stated that exposure to bisphosphonates may increase the risk of oesophageal cancer but further studies are required to confirm this.[255]

A meta-analysis evaluating any association between bisphosphonates and risk of oesophageal cancer identified four cohort and three case-control studies. An overall analysis demonstrated no association between bisphosphonates and oesophageal cancer in cohort studies (pooled RR 1.23, 95% CI 0.79 to 1.92) and case-control studies (pooled OR 1.24, 95% CI 0.98 to 1.57). Significant heterogeneity was present in the cohort 2^+ studies but not in case-control studies. The studies covered different geographical areas with Denmark, UK, Taiwan and America represented. These studies are limited in measuring what has been prescribed but not what has been actually consumed by the patient and low compliance may lead to an underestimation of risk.[256]

There is currently no definitive evidence of an association between bisphosphonates causing oesophageal cancer. The MHRA has suggested that the apparent association in some studies may have been due to ascertainment bias because patients taking these therapies were more likely to have had investigations due to upper GI symptoms.[232]

Uveitis

A retrospective cohort study compared first time users of bisphosphonates in Canada who attended an ophthalmology clinic over a seven-year period with patients who did not use bisphosphonates. Differences were noted in these populations (bisphosphonate users were older and more of them suffered from ankylosing spondylitis, inflammatory bowel, RA, sarcoidosis and took sulfa-containing drugs). There was no mention of 2^+ some potential confounders such as glucocorticoid or anti-TNF therapy. Exposure to bisphosphonate was based on prescription data not actual intake. Cases were checked to make sure there was no previous diagnosis of uveitis or scleritis within the monitoring period. First-time users of bisphosphonates had an increased risk of uveitis (adjusted RR 1.45, 95% CI 1.25 to 1.68) and scleritis (adjusted RR 1.51, 95% CI 1.34 to 1.68).[257]

A retrospective study of 2,001 women with osteopenia found that, of the 1,001 patients who had zoledronic acid, there were eight cases of painful red eye diagnosed as acute anterior uveitis (AAU) by an ophthalmologist following the first infusion of zoledronic acid. These all occurred within one week of starting zoledronic acid. 2^- There were no cases of uveitis in the control population. The rate of AAU was estimated as 0.8%.[258]

✓ Bisphosphonate therapy should be evaluated every five years to determine if the benefits in continuing therapy outweigh potential risks.

6.4.7 STRONTIUM RANELATE

Strontium ranelate has been reported to have an inhibitory effect on osteoclast activity and to stimulate biochemical markers of bone formation as well as to substitute for calcium in hydroxyapatite. The data summarised here derive from a meta-analysis of RCTs of strontium ranelate, given in a dose of 2 g at night as compared with placebo, in which both groups received calcium and vitamin D supplements.

Benefits

A meta-analysis of three studies of 5,254 patients showed that strontium ranelate was significantly more effective at reducing vertebral fractures compared with placebo after three years (RR 0.62, 95% CI 0.55 to 0.71). This included five reports of three trials (spinal osteoporosis therapeutic intervention (SOTI), strontium ranelate for treatment of osteoporosis (STRATOS) and treatment of peripheral osteoporosis (TROPOS)). SOTI and STRATOS involved postmenopausal women with at least one baseline fragility fracture. TROPOS and STRATOS included only BMD-determined osteoporotic women while SOTI included osteopenic and osteoporotic women. A methodological concern about these trials was missing data with 34% and 35% dropping out of the strontium ranelate and placebo groups respectively. A meta-analysis of two studies consisting of 6,374 women showed that strontium ranelate was significantly more effective at reducing non-vertebral fractures compared with placebo after three years (RR 0.86, 95% CI 0.74 to 0.99). There was no significant reduction overall in the rates of hip fracture in one RCT (RR 0.85, 95% CI 0.61 to 1.19).[230] 1^{++}

The SMC conducted a cost-utility analysis of strontium ranelate which gave a point estimate of cost per QALY suggesting strontium is less cost effective than alendronic acid or risedronate. The case for strontium being at least as cost effective as commonly used bisphosphonates has not been made. An MTA published by NICE indicated some differences: the manufacturer's model suggested cost effectiveness at the maximum incremental cost-effectiveness ratio (ICER) of £30,000 per QALY gained. Although this was more favourable than the NICE Assessment Group's report, different assumption models were used. The Assessment Group's results were that risedronate, raloxifene and strontium ranelate were dominated by alendronic acid; that is, these three drugs had a higher acquisition cost than alendronic acid, but were not more efficacious.[133] 4

Harms

One RCT which reanalysed data from two large trials of postmenopausal women treated with strontium ranelate reported that in a subgroup of women aged above 80, headaches (3.3% *v* 1.7%), venous thromboembolic (VTE) events (4.5% *v* 2.5%) and seizure and seizure disorders (0.7% *v* 0%) were reported significantly more often in the strontium ranelate group than in the placebo group. Overall, 35% of each group reported serious adverse events over five years.[259] 1^{+}

A controlled clinical trial which followed up women treated with strontium ranelate for eight years concluded that although 88% of patients reported adverse events, the treatment-related adverse events were of low frequency with, for example, VTE recorded at 1.0% per year and headache at 0.7% per year.[260] 1^{+}

Strontium ranelate is the subject of MHRA warnings following RCT evidence of both increased risk of VTE and, more recently, an increased risk of cardiovascular events.[261,262] Following a review of the risks and benefits associated with the drug, the EMA has advised that:

- strontium ranelate is now restricted to the treatment of severe osteoporosis in postmenopausal women and adult men at high risk of fracture who cannot use other osteoporosis treatments due to, for example, contraindications or intolerance
- treatment should only be started by a physician with experience in the treatment of osteoporosis
- the risk of developing cardiovascular disease should be assessed before starting treatment. Treatment should not be started in people who have or have had: 4
  - ischaemic heart disease
  - peripheral arterial disease
  - cerebrovascular disease
  - uncontrolled hypertension
- cardiovascular risk should be monitored every 6–12 months
- treatment should be stopped if the individual develops ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease, or if hypertension is uncontrolled.[263]

R **Strontium ranelate may be considered for the treatment of severe postmenopausal osteoporosis to reduce the risk of vertebral and non-vertebral fractures in patients without established cardiovascular disease when other treatments are contraindicated.**

6.4.8 PARATHYROID HORMONE

Parathyroid hormone (PTH) 1-34 and PTH 1-84 are peptides of the parathyroid hormone family. They represent the intact molecule (1-84) or the 1-34 N-terminal fragment (teriparatide). Unlike endogenous PTH which leads to mobilisation of calcium from skeletal sites (loss of bone mineral) the intermittent exposure to once daily exogenous PTH increases bone formation more than bone resorption resulting in an anabolic effect and increased bone mass. The effects of parathyroid hormone are maximal at skeletal sites which are predominantly composed of trabecular bone such as the spine. The data summarised here derive from analysis of RCTs in which parathyroid hormone was compared with placebo in patients who also received calcium and vitamin D supplements.

While clinical studies have been conducted using both teriparatide and PTH 1-84 in the treatment of osteoporosis, the European Commission withdrew marketing authorisation for PTH 1-84 in May 2014 for commercial reasons following instruction from the marketing authorisation holder.[264] As this product is no longer available in UK and Europe, it will not be further discussed in this guideline.

Benefits

The effect of teriparatide on fractures was evaluated in a large RCT which involved 2,532 postmenopausal women with severe osteoporosis (mean T-score -2.6 and mean number of previous vertebral fractures 2.3). Two doses of teriparatide were used (20 micrograms daily and 40 micrograms daily given by subcutaneous injection for up to 18 months). Both had similar effects, but the data summarised here refer to the 20 micrograms dose which is currently licensed for clinical use. The relative risk of vertebral fractures was 0.35 (95% CI 0.22 to 0.55) in the 20 micrograms teriparatide group when compared with placebo and the relative risk of non-vertebral fractures was 0.47 (95% CI 0.25 to 0.99). There was no significant reduction in hip fractures, although the numbers of events were small (1/541 in the teriparatide group and 4/544 in the placebo group).[265] 1^{+}

Treatment with 20 micrograms of teriparatide daily was compared to standard care in an observational study of patients with severe osteoporosis (T-score ≤ -4.0) attending a specialist clinic in Scotland. All patients with T-scores below this threshold were included in the study (n=323). Patients were started on teriparatide unless they could not or did not want to self inject (n=64, 59.4%), they were already stabilised on another treatment (n=35, 33.0%), or they had a contraindication (n=8, 7.5%). The baseline characteristics of the teriparatide and standard care groups were similar except that teriparatide-treated patients were slightly 2^{-}

younger (68.8 *v* 72.7) and a greater proportion had previously failed to respond to other treatments (11.6% *v* 1.9%, p<0.001). There was no significant difference in calculated risk of major osteoporotic fracture between the groups assessed by FRAX at baseline (26.4% ±12.8 *v* 27.9% ±14.5, p=0.33). Patients in the teriparatide group (n=217) received 20 micrograms daily for 18–24 months with calcium and vitamin D supplements at which point patients were switched onto bisphosphonate therapy. Patients in the standard care group (n=106) were predominantly treated with oral bisphosphonates and calcium and vitamin D supplements. The proportion of patients with a new vertebral fracture during a follow-up period of approximately three years was significantly lower in the teriparatide group (1.4% *v* 6.6%, p=0.01). There was no difference between the groups in the incidence of non-vertebral fractures (11.1% *v* 8.5%, p=0.46). Logistic regression analysis corrected for baseline characteristics of the groups showed that the odds ratio of vertebral fracture with teriparatide was significantly reduced compared with standard care (OR 0.12, 95% CI 0.03 to 0.55, p=0.007). Adverse events rates were not significantly different in the two groups (10.6% *v* 8.5%, p=0.57). The authors concluded that teriparatide treatment is associated with an improved clinical outcome in patients with severe osteoporosis while acknowledging that the results of the study have to be interpreted with caution given that allocation to treatment was not randomised. 2^-

Harms

Adverse effects that were more common in teriparatide-treated patients than placebo-treated patients included nausea (18% *v* 8%); headache (13% *v* 8%); dizziness (9% *v* 6%) leg cramps (3% *v* 1%) and mild hypercalcaemia (11% *v* 2%).[265] 1^+

R **Teriparatide** (parathyroid hormone 1-34) **is recommended to prevent vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis and may be of particular value in patients at high risk of vertebral fracture.**

6.4.9 CALCITONIN

Following concerns about an increased risk of cancer with long-term therapy, marketing authorisation for calcitonin has been withdrawn for the treatment of osteoporosis in the UK and Europe. It is not discussed further in this guideline except for in the short-term treatment of painful vertebral fractures *(see section 7.6.2)*.

6.4.10 DENOSUMAB

Denosumab is a monoclonal antibody directed against receptor activator of nuclear factor kappa B ligand which is required for osteoclast differentiation and function. Denosumab has potent inhibitory effects on osteoclastic bone resorption and is administered as a subcutaneous injection of 60 mg every six months. Unlike bisphosphonates, the effects of denosumab on bone resorption do not persist after treatment is stopped. The data summarised in this section derive from analysis of RCTs in which denosumab was compared with placebo in patients who also received calcium and vitamin D supplements.

Benefits

The effects of denosumab on fracture were evaluated in a large RCT involving 7,868 postmenopausal women with a BMD T-score of less than -2.5 at the lumbar spine or femoral neck who were randomised to receive denosumab or placebo. Patients with severe osteoporosis (T-score <-4.0) were excluded from the study. Denosumab significantly reduced the relative risk of vertebral fracture (RR 0.32, 95% CI 0.26 to 0.41), non-vertebral fractures (RR 0.80, 95% CI 0.67 to 0.95) and hip fractures (RR 0.60, 95% CI 0.67 to 0.95) compared with placebo.[266] 1^+

A meta-analysis of phase II trials with denosumab which included the above phase III trial reported a reduction in overall fracture relative risk (RR 0.58, 95% CI 0.52 to 0.66) compared with placebo.[267] 1^{++}

A NICE single technology appraisal recommended denosumab for the treatment of postmenopausal osteoporosis in women who were unable to take oral therapies providing they have low BMD and independent risk factors for the disease.[268] 4

Harms

There was no overall difference in adverse effects, serious adverse effects or deaths between the groups receiving denosumab or placebo reported in RCTs.[266, 267] 1^{+} 1^{++}

Denosumab has been associated with risk of severe hypocalcaemia in a number of case reports, especially in patients with poor renal function. The MHRA has issued guidance regarding this risk and has recommended that serum calcium be monitored before each dose and within two weeks of the initial dose in patients with an eGFR <30 ml/min/1.73 m^2.[269]

The MHRA has also reported that ONJ is rare in patients taking the indicated 60 mg dosage for osteoporosis but more common at higher doses for cancer indications. It has advised that ONJ risk factors should be checked before starting denosumab (eg smoking, poor oral hygiene, invasive dental procedures, comorbidities or specific concomitant treatments) and a dental examination and appropriate preventive dentistry are recommended for patients with risk factors.[269]

Atypical femoral fractures are rarely associated with long-term denosumab treatment. The summary of product characteristics cites incidence rates similar to those associated with long-term bisphosphonate therapy (<10/10,000) *(see section 6.4.6)*.

R **Denosumab is recommended to prevent vertebral, non-vertebral and hip fractures in postmenopausal women with DXA-proven osteoporosis for whom oral bisphosphonates are unsuitable due to contraindication, intolerance or inability to comply with the special administration instructions.**

✓ Denosumab is contraindicated in patients with hypocalcaemia and should be used with caution in patients with renal impairment. Patients who are treated with denosumab should be given calcium and vitamin D supplementation unless their dietary intake is adequate.

6.4.11 HORMONE REPLACEMENT THERAPY

Hormone replacement therapy (HRT) has been used to treat hot flushes and other menopausal symptoms for over 50 years and its effectiveness is well established.[270] Women take oestrogen-only or combined oestrogen and progestogen HRT depending on whether or not they have had a hysterectomy. 1^{++}

Benefits

A Cochrane review which included data from 19 trials (n=42,830) investigated the long-term effect of HRT on multiple outcomes, including the incidence of hip fractures, clinically diagnosed vertebral fractures and total clinically diagnosed fractures. The majority of the evidence was derived from two large RCTs conducted by the WHI. The fracture-related data were considered as outcomes of secondary harm, therefore no power calculations were provided.[271]

Both oestrogen-only and combined hormone therapy interventions were associated with a significantly reduced risk of hip fracture. There was a 36% reduction in the risk of hip fracture for women taking oestrogen-only therapy HRT at 7.1 years' mean follow up (RR 0.64, 95% CI 0.45 to 0.93). The benefit from HRT was not maintained during extended follow up (to 10.7 years). There was also a 32% reduction in risk of hip fracture associated with combined HRT at 5.6 years follow up, (RR 0.68, 95% CI 0.48 to 0.97) but not at one to four years' follow up. There was a reduction in vertebral fractures for women taking HRT in the form of oestrogen-only therapy (RR 0.62, 95% CI 0.42 to 0.93) and combined HRT (RR 0.68, 95% CI 0.48 to 0.97). There was a significant reduction in risk of any fracture with women taking oestrogen-only HRT (RR 0.73, 95% CI 0.65 to 0.80) and combined HRT (RR 0.78, 95% CI 0.71 to 0.85). 1^{++}

Harms

The Cochrane review evaluated the main cardiovascular and cancer risks associated with use of HRT.[271]

No statistically significant differences in total mortality or death from CHD or stroke, colorectal cancer or endometrial cancer were identified between populations receiving HRT or placebo. No statistically significant difference was found in death from breast cancer between groups who received HRT and placebo at one 1^{++}

or 5.6 years. At 11 years' follow up in one trial involving combined HRT there were more deaths from breast cancer in the HRT group than in the placebo group, however this was of borderline statistical significance (RR 1.98, 95% CI 1.00 to 3.95). The absolute risk of breast cancer increased from 1 per 1,000 in the control group to 3 per 1,000 (95% CI 1 to 6) in the HRT group.

No statistically significant difference in death from lung cancer was found between those receiving oestrogen-only HRT and placebo. However, in the combined HRT arm of one RCT, women in the intervention group were significantly more likely to die from lung cancer overall (RR 1.74, 95% CI 1.19 to 2.57) or from non-small cell lung cancer (RR 1.91, 95% CI 1.24 to 2.95) than women in the placebo arm. This finding was independent of smoking status. There were no statistically significant differences in mortality between groups in one trial of combined sequential HRT.

When followed up for the entire 10.7 years' period in one trial there was a significantly lower rate of breast cancer in the oestrogen-only HRT group (RR 0.78, 95% CI 0.63 to 0.96). The absolute risk of breast cancer decreased over 10.7 years' follow up from 37 per 1,000 in the control group to 29 per 1,000 (95% CI 23 to 35) in the HRT group. There was no statistically significant difference between groups taking combined HRT and placebo in the incidence of breast cancer during the first four years of follow up, but the HRT group was at a significantly higher risk of breast cancer after taking HRT for five or more years. When pooled in the Cochrane review, data from two RCTs indicated that those using combined HRT had a reduced risk of breast cancer at one year (RR 0.53, 95% CI 0.28 to 0.96). Cancer risk increased proportionately, however, as duration of follow up increased up to 11 years (RR 1.25, 95% CI 1.08 to 1.45). 1^{++}

There were no significant differences between HRT and placebo groups across all comparisons for incidence of colorectal, lung, endometrial and ovarian cancers, with the exception of women taking combined continuous HRT who had a significantly lower incidence of colorectal cancer at 5.6 years' follow up (RR 0.64, 95% CI 0.44 to 0.91).

Use of either oestrogen-only or combined HRT was associated with a statistically significant increase in risk of stroke or VTE. Pooled data from two trials indicated a large relative risk of VTE of 4.28 (95% CI 2.49 to 7.34) at one year. Risk of thromboembolism declined over time.

There is good evidence that HRT prevents fractures in postmenopausal women but the risk of adverse effects including cardiovascular disease and cancer is increased in older women and with longer term therapy. The available evidence does not allow strict age ranges to be defined for those who will derive the greatest benefit and the MHRA has recommended that the decision to prescribe HRT should be based on a thorough evaluation of the potential benefits and risks of treatment for each woman.[272] It also notes that evidence for the risks of HRT in women who had premature menopause is limited. However, the baseline risk of adverse events in these younger women is low, and the balance of benefits and risks may be more favourable than in older women.

R **Hormone replacement therapy may be considered for the prevention of vertebral, non-vertebral and hip fractures in younger postmenopausal women.**

✓ Before initiating HRT healthcare professionals should assess every woman's overall risk, including cardiovascular risk, particularly in those aged over 60 who have increased baseline risk of serious adverse events.

✓ For all women, the lowest effective dose of HRT should be used for the shortest time.

6.4.12 TIBOLONE

Tibolone acts as a partial oestrogen-, progestogen- and androgen-receptor agonist and is effective at improving menopausal symptoms.

Benefits

A dose of 1.25 mg of tibolone daily was compared with placebo in a randomised trial of 4,538 postmenopausal women between the age of 45–85 who had a T-score of -2.5 or less at the spine or hip or at least one vertebral fracture and a T-score of -2.0 or less at either site. All patients received calcium and vitamin D supplements. 1^{+}

When compared with placebo, tibolone reduced the risk of vertebral fractures (RR 0.55, 95% CI 0.41 to 0.74) and non-vertebral fractures (RR 0.74, 95% CI 0.58 to 0.93) over a three-year follow-up period. The risk of colon cancer (RR 0.31, 95% CI 0.12 to 0.96) and breast cancer (RR 0.32, 95% CI 0.13 to 0.80) were also reduced.[273] 1^{+}

Harms

A Cochrane review compared the short- and long-term effects of tibolone on menopausal symptoms with placebo, oestrogens or combined HRT. There were too few events to draw conclusive results regarding risk of VTE, however, a trend towards increased risk of endometrial cancer was observed. The pooled OR suggested a trend toward a harmful effect of tibolone (OR 1.98, 95% CI 0.73 to 5.32) based on 15 cases occurring in tibolone arms compared with five cases in placebo arms in four RCTs. Data on the risk of breast cancer were inconsistent between trials and varied according to previous experience of breast cancer. Meta-analysis of two trials showed that tibolone significantly increased breast cancer in high-risk women who had been surgically treated within a five-year period for breast cancer (for whom usual oestrogen and combined HRT are contraindicated) (OR 1.50, 95% CI 1.21 to 1.85).[274] In contrast, in another RCT, tibolone significantly reduced new onset breast cancer in patients at lower risk of disease (OR 0.32, 95% CI 0.13 to 0.79), although the absolute rates of cancer were very low.[273] In this trial, the risk of stroke was 4.3 per 1,000 person-years in the group taking 1.25 mg tibolone daily and 1.9 per 1,000 person-years in the control group (RR 2.19, 95% CI 1.14 to 4.23) for which the trial was stopped early. Other adverse effects that were significantly more common in the tibolone group included breast discomfort (9.0% *v* 2.9%); vaginal discharge (9.8% *v* 1.8%) vaginal bleeding (9.5% *v* 2.5%), vaginal infection (8.3% *v* 2.5%) and pelvic pain (2,4% *v* 1.3%).[273] 1^{++} 1^{+}

R **Tibolone may be considered to prevent vertebral and non-vertebral fractures in younger postmenopausal women, particularly those with menopausal symptoms.**

6.4.13 RALOXIFENE

Benefits

A meta-analysis included two RCTs of postmenopausal women who were treated with raloxifene compared with placebo. One trial was split into separate analyses for those with previous vertebral fractures and those with osteoporosis but no fracture. Of the three comparisons across 4,639 patients, raloxifene was significantly more effective than placebo in the prevention of vertebral fractures (RR 0.64, 95% CI 0.54 to 0.78). A meta-analysis of two studies with 7,793 patients showed that there was no significant difference between raloxifene and placebo in the prevention of non-vertebral fractures (RR 0.91, 95% CI 0.78 to 1.05), for a control group rate range of 7–9% or between raloxifene and placebo in the prevention of hip fractures (RR 1.12, 95% CI 0.64 to 1.94), for a control group rate of 0.7%.[230] 1^{++}

In an RCT of 10,101 postmenopausal women with CHD or multiple risk factors for CHD, raloxifene reduced the risk of oestrogen-receptor positive invasive breast cancer by almost half (HR 0.56, 95% CI 0.38 to 0.83; ARR 1.2 invasive breast cancers per 1,000 women treated for one year).[275] 1^{++}

Harms

A meta-analysis of nine trials including 24,523 postmenopausal women showed that therapy with raloxifene was associated with a 62% increase in odds of either deep vein thrombosis (DVT) or pulmonary embolism (PE) (OR 1.62, 95% CI 1.25 to 2.09, p<0.001). Similarly, raloxifene therapy was associated with a 54% increase in odds of DVT (OR 1.54, 95% CI 1.13 to 2.11, p =0.006) and 91% increase odds of PE alone (OR 1.91, 95% CI 1.05 to 3.47, p =0.03).[276] 1^{+}

Raloxifene has been shown to be associated with an increased fatal stroke risk compared with placebo in one RCT (HR 1.49, 95% CI 1.00 to 2.24).[275] 1^{++}

R **Raloxifene may be considered as a treatment option for the prevention of vertebral fractures in postmenopausal women when other treatments are contraindicated or unsuitable.**

6.4.14 CALCIUM AND VITAMIN D SUPPLEMENTATION

Nearly all studies investigating treatments for osteoporosis have included calcium and vitamin D as adjuncts, although it is uncertain that such supplementation is essential if dietary intakes are adequate.

Separately, supplementation with calcium and vitamin D has been suggested as a treatment of choice for the elderly, particularly the institutionalised elderly who are at risk of vitamin D deficiency.[277]

Vitamin D is usually given as the native form (with vitamin D_3 generally being preferred to vitamin D_2). Some studies have tested the more potent hydroxylated form, calcidiol (25-hydroxyvitamin D); the active form, calcitriol (1,25 dihydroxyvitamin D); or synthetic analogues of vitamin D, such as alfacalcidiol (1-hydroxyvitamin D).

There are differing guidelines on what vitamin D dose should be recommended.[278,279] The National Osteoporosis Society has issued guidelines for treatment in which it recommends vitamin treatment and maintenance regimens.[280] The Chief Medical Officers of the UK have issued advice that up to a quarter of people in the UK have low blood levels of vitamin D (defined as a plasma concentration of 25-hydroxyvitamin D ($25(OH)D_3$) <25 nmol/l).[281]

Benefits

Nine meta-analyses were identified that analysed data on fracture risk from studies of vitamin D supplementation with or without calcium.[282-290] There is considerable overlap in the RCTs included in these reviews, therefore only two are described below.

A Cochrane review and meta-analysis suggested that frail older people confined to institutions may sustain fewer hip fractures if given vitamin D with calcium, but vitamin D alone is unlikely to prevent fracture. For vitamin D only, there were nine trials on hip fracture (24,749 participants, RR 1.15, 95% CI 0.99 to 1.33), five trials on vertebral fracture, 9,138 participants, RR 0.90, 95% CI 0.42 to 1.92) and 10 trials on any new fracture (25,016 participants, RR 1.01, 95% CI 0.93 to 1.09). Vitamin D with calcium reduced hip fractures (eight trials, 46,658 participants, RR 0.84, 95% CI 0.73 to 0.96). Although subgroup analysis by residential status showed a significant reduction in hip fractures in people in institutional care, the difference between this and the community-dwelling subgroup was not significant (p=0.15).[282] 1^{++}

One meta-analysis considered other vitamin D metabolites and analogues. It included 16 RCTs (n=2,139, range 14 to 622) which compared treatment with calcitriol or alfacalcidol (with or without calcium) versus placebo or calcium. There was no statistically significant difference between the groups in the risk of new vertebral fractures (OR 0.89, 95% CI 0.57 to 1.39, 13 RCTs, n=1,396). The funnel plot for this outcome suggested significant publication bias (p=0.10). There were significantly fewer non-vertebral fractures (OR 0.51, 95% CI 0.30 to 0.88, six RCTs, n=1,014) in the intervention group. Subgroup and sensitivity analyses showed that alfacalcidol (with or without calcium) was associated with a significantly lower rate of vertebral fractures than placebo or calcium (OR 0.50, 95% CI 0.25 to 0.98, five RCTs, n=410), although calcitriol was not (eight RCTs, n=986). Other analyses did not change the statistical significance of the overall results. Statistical heterogeneity was generally low for all analyses.[291] 1^{++}

Harms

Many trials of calcium and vitamin D exclude patients with known history of hypercalcaemia or renal stones, so conclusions may not be generalisable to the overall population. There is concern that calcium supplements may reduce adherence to osteoporosis treatment (due to the side effects of calcium supplementation) and treatment efficacy (due to patients taking supplements too close to their antifracture treatment). Bisphosphonates are poorly absorbed from the GI tract and are tightly bound by calcium. Therefore, bisphosphonates should be taken on an empty stomach with a 30–60 minute post-dose fast. To ensure adequate absorption, it is essential to avoid taking calcium supplements around the dose of oral bisphosphonates.

A meta-analysis of trials of calcium supplementation analysed five RCTs with patient-level data (8,151 participants) and 11 with trial-level data (11,921 participants). In the patient-level analysis, the risk of incident MI in those allocated to calcium increased by 31% (HR 1.31, 95% CI 1.02 to 1.67, p=0.035). The risk of stroke 1^{++}

(HR 1.20, 95% CI 0.96 to 1.1.50, p=0.11) or death (HR 1.09, 95% CI 0.96 to 1.23, p=0.18) was not significantly increased in those who took calcium supplementation. Similar results were seen in the trial-level analysis. Allocation to calcium supplements was associated with an increased risk of MI (RR 1.27, 95% CI 1.01 to 1.59, p=0.038) but not stroke or death.[292] The applicability of these results may be limited by the fact that the authors 1^{++} excluded trials that compared coadministered calcium and vitamin D supplements with placebo. In other words, only studies that employed a vitamin D comparator were included. A limitation of this meta-analysis is that none of the trials had cardiovascular outcomes as the primary end points, and data on cardiovascular events were not gathered in a standardised manner.

The Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD) reported no adverse effect of calcium and vitamin D supplementation (1 g calcium and 400 IU vitamin D daily: 1 microgram of vitamin D is 40 IU) on any cardiovascular end point in their large (n=36,282), seven-year, randomised, placebo-controlled trial.[293, 294] However, 54% of the participants were taking personal (non-protocol) calcium supplements at randomisation and 47% were taking personal vitamin D supplements, effectively rendering 1^{+} this trial a comparison of higher-dose and lower-dose calcium and vitamin D for most of the participants. When the data from this trial were reanalysed to compare only women who were not taking personal supplements with the experimental group allocated to supplementation, studies have reported conflicting findings.

A meta-analysis of the effects of calcium and vitamin D supplementation on cardiovascular risk included six trials with patient-level data (24,869 participants) and nine trials with trial-level data (28,072 participants) and included a reanalysis of the WHI CaD trial compensating for the effects of personal supplementation. In the patient-level analysis calcium or calcium and vitamin D supplements increased the risk of MI (HR 1.26, 95% CI 1.07 to 1.47, p=0.005), stroke (HR 1.19, 95% CI 1.02 to 1.39, p=0.03), and the composite end point of MI or stroke (HR 1.17, 95% CI 1.05 to 1.31, p=0.005). There were similar results in the trial-level analysis with 1^{+} increased risks of MI (RR 1.24, 95% CI 1.07 to 1.45, p=0.004), and the composite end point of MI and stroke (RR 1.15, 95% CI, p=0.009). There was no significant increase in risk of death in either analysis.[295] This meta-analysis showed that there was a significant risk of cardiovascular harm associated with taking calcium and vitamin D in patients who were not previously taking supplementation. In women taking personal calcium supplements at randomisation, however, the addition of calcium and vitamin D did not increase cardiovascular risk, and the risk of cardiovascular events with calcium and vitamin D was also not affected by the dose of personal calcium supplements.

In contrast, a study which combined and contrasted data drawn from the WHI CaD trial and WHI observational study (93,676 postmenopausal women drawn from the same catchment areas as the trial) showed no 1^{-} significant effect of calcium and vitamin D supplementation on MI, CHD, total heart disease, stroke or total cardiovascular disease (CVD), either overall or in the subset not using supplements at baseline.[296]

Observational studies investigating the harms of calcium supplementation in men and women also have conflicting results in terms of CVD risk.[297-301]

It is suggested that calcium supplements may cause transient hypercalcaemia which is supported by observations of renal impairment. However, there is no dose response (that is, increased risk for baseline non-users but not for baseline users) and dietary calcium is not associated with increased risk *(see section 6.3.2)*. It is possible that there are other factors in the diet that are protective.

A Cochrane review concluded that there is a small but significant increase in GI symptoms and renal disease associated with taking vitamin D or its analogues.[282] Overall hypercalcaemia was significantly more common in people receiving vitamin D or an analogue, with or without calcium (18 trials, 11,346 participants, RR 2.35, 95% CI 1.59 to 3.47); this was especially true of calcitriol (four trials, 988 participants, RR 4.41, 95% CI 2.14 1^{++} to 9.09). There was a modest increase in GI symptoms (11 trials, 47,042 participants, RR 1.04, 95% CI 1.00 to 1.08, p=0.04) and a small but significant increase in renal disease (11 trials, 46,537 participants, RR 1.16, 95% CI 1.02 to 1.33).

Another meta-analysis suggested that participants in the intervention group (calcitriol or alfacalcidol) had a significantly higher risk of hypercalcaemia (OR 3.63, 95% CI 1.51 to 8.73, 10 RCTs) and a trend to increased risk of hypercalciuria (five RCTs, unsuitable for meta-analysis) compared with those taking either placebo or 1 g 1^{++} calcium daily. There was no statistically significant difference between the intervention and control groups in the risk of total or harm-related withdrawal, death, renal stones or GI side effects. There was a significantly higher risk of hypercalcaemia in the intervention group (OR 2.85, 95% CI 1.21 to 6.70, five RCTs, n=536).[291] 1++

A further meta-analysis of four RCTs (n=5,340) showed that calcium supplementation between 800 and 1,200 mg/day (but not dietary calcium intake) increased the risk of hip fracture by 64% (pooled RR 1.64, 95% CI 1.02 to 2.64).[156] 2+

There has been concern about potential adverse effects of calcium supplementation (such as increased risk of cardiovascular events), which do not apply to dietary calcium. The evidence investigating a possible association between calcium intake and cardiovascular outcomes has conflicting findings, although, if dietary calcium intakes are adequate, many clinicians prefer to supplement with vitamin D only because of patient concerns and other minor side effects attributable to calcium supplementation (such as constipation and renal calculi) as these may influence adherence.

The evidence from the large number of meta-analyses of calcium and vitamin D studies is also mixed, with results divided as to whether vitamin D alone is ineffective, and any antifracture benefit is driven by calcium supplementation; or whether it is the dose of vitamin D that is the key behind fracture prevention, with only doses greater than 800 IU daily showing benefit. There is some heterogeneity in studies between type of vitamin D, route of administration and the dose, whether daily or as a bolus, and the population (free living or institutionalised) and there have been different conclusions according to the fracture site.

The higher-quality trials conclude that calcium is required in addition to vitamin D for antifracture efficacy. However, it is impossible to separate whether it is calcium or high-dose vitamin D that is important, as the trials in the meta-analyses which gave the higher doses of vitamin D also included calcium.

R **Calcium and vitamin D supplements may be considered to reduce the risk of non-vertebral fractures in patients who are at risk of deficiency due to insufficient dietary intake or limited sunlight exposure.**

✓ People who have low or no exposure to the sun, for example those who cover their skin for cultural reasons, who are housebound or confined indoors for long periods should be considered at risk of vitamin D deficiency.

✓ Calcium supplements should not be taken within two hours of bisphosphonates.

✓ If dietary calcium intake is adequate (700 mg/day) vitamin D only may be preferred as the osteoporosis treatment adjunct.

6.4.15 COMPARISONS BETWEEN DIFFERENT DRUGS

The majority of trials of pharmacological treatments to prevent fracture have been placebo-controlled and demonstrate the efficacy of a single drug compared with no active comparator. This evidence base is considered in sections 6.4.1–6.4.14. A small number of studies have provided head-to-head comparisons between different drugs in an attempt to estimate the magnitude of benefit attributable to each medication. In addition, several meta-analyses using indirect comparison methods have been published, which attempt to provide a hierarchy of likelihood of effect across multiple drugs or doses. Such indirect comparisons are subject to greater bias (especially selection bias) than head-to-head randomised comparisons, as the benefit of randomisation does not hold across trials. Direct and indirect comparisons between different drugs used for the treatment of osteoporosis or prevention of fractures are discussed in this section.

Direct comparisons

A meta-analysis of RCTs reported on a range of comparisons between different drugs.[230] Meta-analysis of two trials in 1,978 patients compared alendronic acid with risedronate and showed no difference in the fracture rates after one year of therapy (RR 1.15, 95% CI 0.75 to 1.76). One study compared alendronic acid to ibandronic acid in 1,733 patients. There was no difference in fracture rates but wide confidence intervals. Alendronic acid was compared to raloxifene in a meta-analysis of three studies (2,304 patients) which showed no significant difference in the rate of all fractures (RR 0.99, 95% CI 0.62 to 1.60). Meta-analysis of two trials 1++

comparing the effects of teriparatide plus HRT with HRT alone showed that the relative risk for vertebral fracture was 0.11 (95% CI 0.01 to 0.91) in the combination treatment group compared with the HRT group alone. There was some potential for bias in both studies because of large differences between groups in missing data, which may have confounded the results, and because of the lack of blinding. 1^{++}

A meta-analysis compared the clinical effectiveness and safety of subcutaneous denosumab at 60 mg every six months to alendronic acid at 70 mg once weekly. Four suitable studies with vertebral fracture outcomes of at least one year duration were included. Two of these compared denosumab directly with alendronic acid while the other two also included a placebo group. Overall, the studies were of low methodological quality. There was a non-significant trend favouring denosumab in preventing vertebral fractures (OR 1.42, 95% CI 0.84 to 2.40). There was no significant heterogeneity between these studies. The safety data were derived from four studies graded as very low quality and showed similar rates of serious adverse effects between denosumab and alendronic acid (OR 0.91).[302] 1^{++}

An RCT compared the effects of 20 micrograms teriparatide daily with 35 mg of oral risedronate weekly in 710 women with postmenopausal osteoporosis and chronic back pain due to vertebral fractures. The primary outcome was reduction in back pain. The teriparatide group had significantly fewer new vertebral fractures over an 18 month treatment period (9.4% *v* 4.4%, p=0.01). There was no difference in the incidence of non-vertebral fractures (8.3% *v* 7.8%, p=0.89).[303] 1^{+}

A suggested pathway for treatment selection is provided in Figure 3.

Indirect comparisons

Indirect comparison has been carried out in an attempt to rank drugs by their effectiveness in preventing vertebral, non-vertebral and hip fractures. Studies have tended to combine effect size with the degree of standard error using pooled data for individual drugs in comparison with placebo for prevention of fractures. Zoledronic acid, denosumab and teriparatide were reported as having the highest probability of being effective compared to risedronate, alendronic acid and ibandronic acid. These studies are weakened by not taking into account factors which are important in routine clinical decision making, such as risk of harms, ability to tolerate the drug and cost.[231, 304, 305] 1^{+} 1^{-}

6.5 DURATION OF TREATMENT

All drugs that are used for the treatment of osteoporosis affect the bone remodelling process either directly or indirectly and are frequently given for prolonged periods of time. Because the bone remodelling process is important in maintaining a healthy skeleton by repairing microdamage, there is a theoretical concern that prolonged treatment could in some circumstances, have a detrimental effect on the skeleton. This is especially relevant for bisphosphonates which are the most widely used treatments for osteoporosis. Due to their chemical structure, bisphosphonates bind to bone mineral and exert inhibitory effects on osteoclastic bone resorption which can extend for months or years after treatment has been stopped. Furthermore, long-term bisphosphonate therapy has been linked to the development of skeletal adverse effects including atypical subtrochanteric fractures and ONJ *(see section 6.4.6)*. This has led to the suggestion that patients on bisphosphonates may benefit from a ‘drug holiday’. Defining the optimal duration of bisphosphonate treatment is therefore relevant to weigh up the risks and benefits of treatment. The same comments apply to other antiosteoporosis medications, although the effects of these wear off much more quickly when treatment is stopped.

6.5.1 DRUG HOLIDAYS

It has been suggested that patients on oral bisphosphonates may benefit from ‘drug holidays’ following a spell on treatment in the hope that this may reduce the risk of skeletal adverse effects.[306] No published evidence was identified from randomised trials to suggest that drug holidays were effective in reducing the risk of skeletal adverse effects. 4

6.5.2 ALENDRONIC ACID

Evidence on the optimal duration of alendronic acid is limited and comes principally from the Fracture Intervention Trial Long-term Extension (FLEX) study[307] which was an extension of the FIT study.[136] Patients were eligible for entry into the study if they had been treated with oral alendronic acid (5 mg or 10 mg daily) in the FIT study. Of 3,236 patients who were potentially eligible, 1,099 were randomised into the FLEX study. Eligible patients were required to have been on treatment for at least three years, but those with a femoral neck T-score of less than -3.5 and those whose BMD had fallen significantly during FIT were excluded. The average duration of alendronic acid therapy in those who took part in FLEX was five years. At baseline around 30% of patients had prevalent vertebral fractures; 30% had femoral neck T-scores below -2.5; 30% had T-scores between -2.0 and -2.5 and 40% had T-scores greater than -2.0. Of the 1,099 included participants, 437 were randomised to placebo, 329 to alendronic acid at 5 mg and 333 to alendronic acid at 10 mg. Treatment was continued for five years, at which point 553 (84%) patients in the alendronic acid groups were analysed compared with 361 (82%) in the placebo group. There was no significant difference between the groups in non-vertebral fractures or morphometric vertebral fractures but clinical vertebral fractures were fewer in the groups who had been randomised to alendronic acid. (16% *v* 25%, HR 0.45, 95% CI 0.24 to 0.85). There was no significant difference in adverse effects between the placebo and alendronic acid treatment groups. The authors concluded that 10 years' treatment with alendronic acid may be preferable to five years in patients at high risk of vertebral fractures, but were unable to identify any clinical or BMD characteristics that were associated with the risk of incident fractures. 1^{++}

R **Alendronic acid may be continued for up to 10 years in postmenopausal women with osteoporosis, especially those that are at high risk of vertebral fracture.**

6.5.3 RISEDRONATE

Evidence on the duration of risedronate treatment comes from a study which extended a previous three-year intervention trial for a further two years.[308] Patients were randomised to receive five years' risedronate at 5 mg daily or placebo. During the follow-up phase fewer patients in the risedronate group (n=15, 13.8%) had vertebral fractures than the placebo group (n=29, 28.2%) (RR 0.41, 95% 0.21 to 0.81). Non-vertebral fractures were also less common in the risedronate group (n=7, 5.2% *v* n=11, 8.5%) but the difference was not significant. The authors concluded that five years' therapy with risedronate was effective in the prevention of fractures in postmenopausal osteoporosis. 1^{+}

A further open-label extension of this study analysed fractures in patients in the risedronate group who continued treatment for a further two years, while those in the placebo group were switched onto risedronate. The incidence of new morphometric vertebral fractures during years six to seven in the risedronate group was 3.8% which was similar to the incidence reported during years zero to three (4.7%) and four to five (5.2%). The rate of new morphometric fractures in the patients that were formerly on placebo fell from 7.6% during years zero to three and 12.3% during years four and five to 3.6% during years six to seven.[309] 2^{+}

One trial analysed the effect of stopping risedronate on fracture risk in women who had participated in an earlier intervention study.[310] Patients in the risedronate 5 mg daily group and those in the placebo group were given the option of withdrawing from the study or continuing observation (with calcium and vitamin D supplementation but without active treatment or placebo) for a further year. Those in a third group (risedronate 2.5 mg daily) in the original trial were ineligible. During the fourth year, vertebral fractures occurred in 42/361 of patients in the former placebo group (11.6%) and 26/398 (6.5%) of patients who had received three years risedronate (RR 0.54, 0.34 to 0.86). Non-vertebral fractures were similar in the former placebo group (18/361, 5%) and the former risedronate group (19/398, 4.8%). The authors concluded that three years' risedronate therapy protects against vertebral fractures for one year after discontinuation. 1^{+}

R **Risedronate may be continued for up to seven years in postmenopausal women with osteoporosis.**

6.5.4 ZOLEDRONIC ACID

The effects of long-term zoledronic acid were studied in women with postmenopausal osteoporosis who had previously received three years' therapy as part of a placebo-controlled study.[311] Patients were eligible if they were aged less than 93 at baseline and had already received three infusions of zoledronic acid in the first study. Of 2,629 potentially eligible patients 1,223 (46%) were enrolled into the extension. They were randomised to receive three further infusions of zoledronic acid or placebo over three years. Both groups received calcium and vitamin D supplements. The average age of participants was 75.5; more than 50% had femoral neck T-scores <-2.5 SD and 60% had at least one vertebral fracture. There was no significant difference between the treatment groups in non-vertebral fractures (8.2% zoledronic acid *v* 7.6% placebo), hip fractures (1.4% *v* 1.3%), any fracture (HR 1.04, 95% CI 0.71 to 1.54), or clinical vertebral fractures (HR 1.81, 95% CI 0.53 to 6.2). Morphometric vertebral fractures were less common in the zoledronic acid group (3% *v* 6.2%), (HR 0.51, 95% CI 0.26 to 0.95). 1^{++}

Adverse effects that were more common in the zoledronic acid group included a rise in serum creatinine (2.94% *v* 0.65%, p=0.002), and stroke (3.1% *v* 1.5%, p=0.06). Myocardial infarction and stroke when combined were also more common in the zoledronic acid group (p=0.04). Hypertension (reported as an adverse event) was more common in the placebo group (15.1% *v* 7.8%, p=0.001).[311]

Given that no significant differences in clinical fractures were reported between those treated for three or six years and that significant cardiovascular harms were associated with six years continuous therapy, patients may discontinue treatment with zoledronic acid for up to three years following three years of treatment, during which time residual fracture protection appears to be conferred. In the absence of studies investigating further therapy for patients after a three year period without treatment, a review of fracture risk should be carried out to determine whether zoledronic acid should be restarted.

R **Zoledronic acid may be continued for three years in postmenopausal women with osteoporosis. After an interval of at least three years without treatment, fracture risk may be reassessed to determine the need for further therapy.**

6.5.5 STRONTIUM RANELATE

Evidence on the duration of therapy comes from one RCT of 1,649 postmenopausal osteoporotic women who were randomised to receive 2 g/day of strontium ranelate or placebo for four years and then switched so that strontium-treated patients were randomised to continue therapy or to receive placebo for one year, whereas placebo-treated patients all received 2 g/day of strontium for one year. Patients receiving four years' strontium had fewer vertebral fractures than those receiving placebo (RR 0.67, 95% CI 0.55 to 0.81). During the fifth year vertebral fracture rates were similar in patients receiving five years' strontium (6.9%, 14 patients) to those who received four years' therapy and were switched to placebo (8.9%, 19 patients). The authors conclude that four years of strontium therapy is effective in reducing vertebral fracture risk and that protection continues for one year after stopping therapy.[312] 1^{++}

An observational study extended the previous extension to combined populations from the TROPOS and SOTI trials *(see section 6.4.7)* resulting in a group of 237 women who had 10 years' exposure to strontium ranelate.[313] Baseline controls from TROPOS were matched to the extension (year six) treatment group using FRAX scores which took account of some confounding factors such as increasing age. Although FRAX does not account for the effects of therapy on future fracture risk, nor the multiplicative risk associated with more than one fracture, baseline characteristics were fairly similar. The study showed that ten-year treatment with strontium ranelate significantly reduced the risk of vertebral (RR 35%, p=0.016) and non-vertebral (RR 38%, p=0.023) fracture incidence for years five to ten compared with the case-control FRAX-matched population. The rates of VTE, diarrhoea and headache in the strontium group during years five to ten of the extension study were 0.4%, 4.6% and 1.3% respectively. 2^{-}

R **Strontium ranelate may be continued for up to 10 years in postmenopausal women with severe osteoporosis when other treatments are unsuitable.**

6.5.6 DENOSUMAB

The effects of denosumab on BMD, fractures and adverse events over a five-year period were reported in a two-year extension to the FREEDOM study.[314] During the extension, patients who had received denosumab during years one to three were continued on the same treatment during years four and five. Those who received placebo during years one to three were changed to denosumab during years four and five. The estimated rate of fractures in placebo-treated participants was derived from a simulation method developed for extension study design to estimate expected fracture rates in a hypothetical cohort of long-term placebo controls (so-called 'virtual twins'), with the baseline characteristics of the treated patients.[315] The incidence of new vertebral fractures in the denosumab group during years four and five was 1.4% compared with an estimated rate of 2.2% in simulated placebo-treated participants. For non-vertebral fractures the incidence was 1.4% during year four and 1.1% during year five, compared with an estimated rate of 2.6% in simulated placebo-treated patients. The type and numbers of adverse events in the extension study were similar to those in the original study. The authors concluded that denosumab is safe and effective for up to five years for the treatment of postmenopausal women with osteoporosis. There are methodological concerns with this study due to differences between the baseline characteristics in the crossover group and the long-term denosumab group. 2^-

6.6 MONITORING OF PHARMACOLOGICAL EFFECT

Monitoring has been proposed as a means of evaluating treatment efficacy. The principal methods that have been used are serial measurements of BMD, and of bone turnover markers (BTM). The evidence in this section is from studies in which various monitoring procedures have been evaluated with regard to their ability to predict the risk of fractures.

Epidemiological evidence demonstrates a strong relationship between decreases in baseline BMD and increases in fracture risk. At the study level, a robust relationship has been suggested. However, at the individual patient level, different changes in BMD can yield similar reductions in fracture risk, suggesting that BMD, although a strong predictor of fracture risk in untreated patients, may not be as strong a predictor for effects of osteoporosis treatments on fracture risk.

Biochemical markers of bone turnover may also be useful in monitoring the progression of disease in an individual because the response to therapy is earlier and more pronounced than changes in BMD.[316] Moreover, patient monitoring during the early stages of treatment has the potential to encourage continued treatment compliance and identify individuals who are not responding to treatment.

6.6.1 MONITORING TREATMENT RESPONSE BY DXA

A post hoc study using data from both the vertebral and clinical fracture arms of the FIT study investigated the relationship between vertebral fracture incidence among patients who lost BMD at either the spine or femoral neck sites when treated with alendronic acid 10 mg daily or placebo.[317] Treatment and placebo groups were controlled for possible confounders and analysis was restricted to patients who had adhered to at least 70% of pills. Patients who lost 0–4% BMD at either spine or hip were shown to have a reduced risk of vertebral fracture after one and two years when treated with alendronic acid compared with placebo (OR 0.43, 95% CI 0.26 to 0.73 at one year for a change of -4 to 0% total hip BMD and OR 0.40, 95% CI 0.16 to 0.99 for 4 to 0% loss in spine BMD). Patients who lost more than 4% in BMD did not have a significant reduction in fracture risk when treated with alendronic acid compared with placebo. Although this study was well conducted, it may underestimate the significance of reduced BMD in routine clinical practice because it purposely excluded non-adherent patients. 1^{++}

Increases in BMD following different doses of ibandronic acid were associated with greater fracture risk reduction compared with placebo in a post hoc analysis of two trials including 4,985 participants.[318] Percentage change from baseline in total-hip BMD at years 2 and 3 was significantly associated with vertebral fracture risk reduction at year 3 in one trial and changes at years 1, 2, and 3 were all significantly associated with fracture risk reduction at year 3 in the other RCT. The pooled proportion of fracture risk reduction explained by a 3% increase in total-hip and LS BMD was 37% and 27% respectively. The results must be interpreted 2^+

with caution, however, due to a high risk of bias owing to the retrospective study design and the fact that studies with different ibandronic acid doses and modes of administration were combined. 2^{+}

A post hoc analysis of three trials (VERT-NA, VERT-MN and HIP) examined the relationship between changes in BMD in response to risedronate therapy or placebo and the risk of non-vertebral fracture.[319] Women received risedronate at 2.5 mg or 5 mg (both arms combined n=2,561) or placebo (n=1,418) daily for three years. Change in LS and FN BMD was considered in deciles for those patients who had an incident non-vertebral fracture. No significant correlation between BMD and risk of non-vertebral fractures was shown. It was estimated that changes in LS BMD in response to risedronate compared with placebo only accounted for 12% (95% CI 2 to 21%, p=0.014) of non-vertebral fracture incidence. The authors noted that the magnitude of change in BMD associated with risedronate treatment did not in itself predict the size of the effect of osteoporosis treatment on non-vertebral fracture risk. 1^{+}

In a post hoc reanalysis of HORIZON-PFT 7,736 postmenopausal women were randomised to once-yearly zoledronic acid at 5 mg or placebo. Changes in both BMD and the bone turnover marker procollagen type 1 amino-terminal propeptide (PINP) were associated with significant reductions in both vertebral and non-vertebral fractures. Participants taking zoledronic acid had a 70% relative reduction in risk of new vertebral fracture compared with those taking placebo (OR 0.30, 95% CI 0.24 to 0.38) in the combined three-year analysis and total-hip BMD explained 40% (95% CI, 30% to 54%) of this fracture risk reduction. In the same analysis, participants taking zoledronic acid had a 21% relative reduction in risk of new non-vertebral fracture compared with those taking placebo (OR 0.79, 95% CI 0.66 to 0.95) and total-hip BMD explained 61% (95% CI, 24% to 156%) of this fracture risk reduction. Changes in PINP explained 58% (95% CI 15% to 222%) of the effect of zoledronic acid in reducing new vertebral fracture risk. PINP and BMD were not independent.[320] 1^{+}

An RCT studied the relationship between changes in hip BMD in response to denosumab compared with placebo and how this correlated with fracture risk. This study was a post hoc analysis of the FREEDOM trial which included 7,808 women randomised to either subcutaneous denosumab at 60 mg six-monthly or placebo. There was a strong association especially for non-vertebral fractures at three years with 87% (95% CI 35% to 100%) of the fracture risk reduction accounted for by this change in BMD. Changes in BMD accounted for 35% of the proportion of the effect of denosumab in reducing new or worsening vertebral fracture risk.[321] 1^{+}

Changes in BMD did not predict fracture reduction after treatment with calcium with or without vitamin D compared with placebo in a meta-analysis of 15 RCTs including 47,365 patients.[322] Although a significant association was found in hip BMD increase and fracture risk reduction, these results were not significant after excluding both of the largest studies (where BMD changes were only measured in a small subset of patients). 1^{+}

Further research is required to establish the predictive value of DXA monitoring on clinical decision making in individual patients and using a wider range of antiosteoporosis drug treatments.

R **Repeat BMD measurements by DXA after an interval of three years may be considered to assess response to treatment in postmenopausal women on alendronic acid, ibandronic acid, zolendronic acid or denosumab therapy.**

6.6.2 MONITORING TREATMENT RESPONSE BY BONE TURNOVER MARKERS

Post hoc analysis of the FIT trial data (n=6,186) studied three different BTMs at one year and their relationship with fracture rates among patients given alendronic acid compared with placebo followed over four years.[323] Within a population of postmenopausal women aged 55–80 each SD reduction in bone alkaline phosphatase (BALP) in one year was associated with fewer spine fractures (OR 0.74, 95% CI 0.63 to 0.87). Women treated with alendronic acid with at least a 30% reduction in BALP had a lower risk of hip fractures (relative hazard 0.26, 95% CI 0.08 to 0.83) than those with smaller BALP reductions. A 30% reduction in BALP was considered the least significant change and at this level the probability of suffering a non-vertebral fracture was 9.8% in women treated with placebo compared with 8.7% in alendronic acid-treated women. Levels of CTX did not correlate with fracture risk reduction. 1^{++}

A post hoc observational study using data from the active arms of SOTI and TROPOS included 2,373 postmenopausal women at high risk of fracture and studied the association between three-monthly BTM 2^{+}

measurement and fracture risk after three years.[324] Changes in biochemical markers C-terminal propeptide of type I procollagen (PICP), NTX, BALP and CTX between baseline and three months were not significantly associated with fracture incidence at three years. This study only included the women treated with strontium ranelate and had no comparator group. 2+

A well-conducted post hoc analysis of patients from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial taking raloxifene considered the relationship between changes in the BTM osteocalcin after one and two years and vertebral fractures after three years compared with placebo.[325] The results showed that the percentage change in osteocalcin after treatment was better than the percentage change in FN BMD at predicting reduction in vertebral fracture risk. A linear relationship was demonstrated whereby greater reductions in osteocalcin correlated with greater reductions in vertebral fracture risk. From logistic regression calculations, changes in osteocalcin were thought to explain 34% (95% CI -0.7 to 61%) of the overall vertebral fracture risk reduction of raloxifene. 1++

Large clinical studies show the potential of some BTMs to predict the extent of fracture risk reduction resulting from certain therapies such as alendronic acid, zolendronic acid and raloxifene but in clinical practice wide interperson variability limits their usefulness in monitoring.

Further research is required to establish the predictive value of BTM monitoring on clinical decision making in individual patients.

R **Measurement of BTMs may be considered to assess response to treatment in patients treated with selected antiosteoporosis drug therapies.**

6.7 ADHERENCE, COMPLIANCE AND CONCORDANCE

6.7.1 INTRODUCTION

It is well recognised that the benefits of treatment rely on a patient's ability and willingness to comply with that therapy (compliance, persistence, concordance and adherence are defined in section 1.2.3). The treatments that are used for osteoporosis do not typically result in a symptomatic improvement and patients seldom gain a tangible benefit from taking the medication. On the contrary, many treatments have complicated instructions for dosing to ensure adequate absorption and some can be associated with adverse effects. Accordingly ensuring that the patient adheres to medication represents a significant hurdle in the effective management of patients with osteoporosis.

6.7.2 REINFORCEMENT AND BIOMARKER FEEDBACK

A multicentre study including 2,382 postmenopausal women aged 65–80 compared the effect of reinforcement using BTM (RF+) with no reinforcement (RF-) over one year to improve persistence with risedronate.[326] Randomisation was by centre rather than by individual and a modified intention-to-treat analysis was performed. The overall study population had a very high rate of persistence (RF- 77% and RF+ 80% p=0.160) and at weeks 13 and 25 both groups were given information about the need to continue medication. A significant relationship was evident between the type of message and persistence. When patients were given reinforcement based on a positive change (NTX graphed feedback versus no feedback) there was a significant, albeit marginal improvement in persistence (HR 0.71, 95% CI 0.53 to 0.95). Furthermore, reinforcement was associated with a lower incidence of new radiological vertebral fractures (OR 0.4, 95% CI 0.2 to 1.0). Among the RF+ group the message had an important bearing on persistence with those with poor response (NTX increase >30%) being more than twice as likely to discontinue medication compared with RF- group (HR 2.22, 95% CI, 1.27 to 3.89, p =0.005). 1+

One trial randomised 240 women (T-score ≤ -2) into four groups to study the association between providing education and feedback about bone marker measurements and persistence with alendronic acid.[327] The groups were as follows: bone marker results at baseline, three and 12 months; educational materials every month plus membership to the National Osteoporosis Foundation; educational materials and bone marker results; control (usual care). Overall persistence was 54% at 12 months and there was no significant difference in the four groups. Therefore, interventions such as providing patients with education about osteoporosis or feedback regarding BTMs did not change rates of persistence. High levels of non-adherence in this study may have underpowered it. Standard scripts were given in relation to NTX results but there was no detail regarding rate of drop outs among patients given poor results as was shown in another study.[326] The most common reason for stopping medication was GI side effects. Fifty one per cent of the education group stated that this education affected their decision to remain on treatment. 1^{+}

An RCT evaluated the effects of biomarker feedback (BMF) on adherence and patient satisfaction to once-monthly ibandronic acid at 150 mg. Feedback on serum CTX provided at three months showed no effect on adherence rates compared with no feedback in ambulatory postmenopausal women (628 patients) (non-BMF 92.6% *v* BMF 96%, p=0.16). This Asian population from five countries had a high adherence rate which may not be generalisable to other countries.[328] 1^{+}

Simple medication review by a nurse at three, six and nine months improved adherence to raloxifene in one RCT.[329] It found that nurse intervention alone or positive reinforcement using BTMs increased adherence by 57% at one year (p=0.04). This study was very small (75 patients divided into three groups) and was underpowered for persistence but there was a trend towards better persistence in the monitored group (25% longer). 1^{++}

6.7.3 GENERAL AND MIXED INTERVENTIONS

A systematic review included studies which assessed interventions by physiotherapists, physicians, nurses, dieticians and multidisciplinary teams in affecting adherence to medications for osteoporosis.[330] Heterogeneity made comparison between studies difficult. Collectively the studies showed that interventions made by healthcare professionals improved the QOL, medication compliance and calcium intake of patients. Effect on BMD, medication persistence, knowledge and other lifestyle modifications were less conclusive. No data were reported on fracture rate. In general, the studies on compliance showed a benefit and those on persistence did not. The method and techniques used to assess compliance and persistence to medication, as well as the type of intervention provided have the potential to affect the results obtained. 1^{++}

A systematic review included four RCTs, two quasi-experimental trials and three descriptive longitudinal comparative studies.[331] Eight out of nine studies showed improvement in adherence with treatment recommendations for patients with osteoporosis or those at high risk of osteoporosis after the healthcare professional-led educational intervention. However, six studies were in women aged less than 65. A single intervention was shown to be effective in seven studies. Lifestyle and dietary changes were the most frequently analysed outcomes. There was no information on fracture rates. 1^{+}

A further systematic review of RCTs included postmenopausal women with vertebral and non-vertebral fractures who were on bisphosphonate treatment (n=4,648).[332] There was considerable heterogeneity in all aspects of quality, measurement of adherence, length of follow up and type of intervention. Combined results of biomarker feedback and motivational interventions led to a reduction in the proportion of women not persisting with antiresorptive medication compared with control groups (RR 0.78, 95% CI 0.65 to 0.95; four RCTs). When stratified by intervention type, the results were no longer significant for biomarker feedback compared with control (RR 0.86, 95% CI 0.74 to 1.01; two RCTs) or for motivational feedback (RR 0.76, 95% CI 0.50 to 1.15; three RCTs). 1^{+}

One RCT reported that the percentage change in bone turnover markers was significantly correlated with adherence to therapy (data not reported), while four RCTs reported no significant differences between groups.

R **Interventions by healthcare professionals, with or without feedback of biomarker results, aimed at improving adherence are recommended in patients who are being given drug treatment for osteoporosis.**

7 Management of osteoporosis in other groups

7.1 INTRODUCTION

While postmenopausal women are the patient group predominantly affected by osteoporosis the condition can also affect other groups such as premenopausal women and men. Glucocorticoid-induced osteoporosis (GIOP) is also discussed here since it represents a distinct management problem which can affect all patient groups. There is evidence that the pathophysiology of GIOP is distinct from other causes of osteoporosis in that it is predominantly mediated by a reduction in bone formation. There is also evidence to suggest that bone fragility is greater in GIOP than in postmenopausal osteoporosis for any given level of BMD. The evidence base for treatment in the patient groups discussed here is limited and relies on 'bridging' studies reporting on BMD rather than fracture as an outcome.

7.2 NON-PHARMACOLOGICAL MANAGEMENT OF OSTEOPOROSIS IN MEN

7.2.1 EXERCISE

One meta-analysis identified three studies which investigated the effects of exercise on BMD in men. These studies included diverse populations, with varied exercise types and used different measures of BMD. Study quality was unclear overall and two studies were unpublished dissertations. The primary outcome measures of change in lumbar spine or FN BMD were calculated as standardised effect sizes (g). The g statistic for each group from each study was calculated as the change score difference (absolute or relative) in the exercise group minus the change score difference in the control group, divided by the pooled standard deviation of the exercise and control groups. The relative magnitude of g may be described as trivial (<0.20), small (≥0.20 to <0.50), medium (≥0.50 to <0.80), or large (≥0.80). 1^+

Overall, a moderate and statistically significant benefit of exercise on FN BMD was observed (g=0.583, 95% CI 0.031 to 1.135). No significant effect was seen with exercise on lumbar spine BMD (g=0.190, 95% CI -0.036 to 0.416).[333]

Another systematic review considered the effect of resistance training (for example weight training) on its own, or in combination with impact-loading (weight-bearing) activities. This small review considered heterogeneous study designs of varying and limited quality which used different sites to measure BMD. The authors concluded that exercise may be a safe and effective means to reduce BMD loss in middle- and older-aged men.[334] 1^+

There is currently limited evidence on the role of exercise in reducing BMD loss in men. Further well-designed RCTs in men are needed before any recommendations can be made.

7.2.2 DIET

The advice for men with osteoporosis or at risk of fragility fracture is the same as for postmenopausal women. Men should aim to consume a healthy balanced diet which contains adequate intake of dietary calcium and vitamin D *(see section 6.3.14)*.

7.3 PHARMACOLOGICAL MANAGEMENT OF OSTEOPOROSIS IN MEN

Osteoporosis and fractures related to osteoporosis are less common in men than in women.[335] It has been estimated that up to 50% of osteoporosis in men is due to an underlying cause such as hypogonadism, glucocorticoid use, alcohol excess or other predisposing drugs and diseases. Many of the treatments that have been used in postmenopausal osteoporosis have also been investigated in men with osteoporosis. Most of the studies that have been carried out are so-called bridging studies in which the aim has been to demonstrate that the agent increases BMD in men with osteoporosis compared with placebo and to demonstrate that the increase in BMD is similar in men and women. Agents which are successful in meeting these criteria meet the regulatory requirements for marketing authorisation based on the assumption that bioequivalence in terms of BMD response would be reflected by therapeutic equivalence in fracture-reduction licensing. Few studies have been designed to investigate the effects of osteoporosis medications on fracture incidence in men. The results of these studies are discussed in this section.

The Scottish Medicines Consortium has not assessed the cost effectiveness of bisphosphonates in men as the manufacturers of branded products declined to make a submission. However, non-proprietary preparations have subsequently become available at lower cost.

For the purposes of this guideline, osteoporosis in men is defined by a T-score of -2.5 SD or less at the lumbar spine, total hip, or femoral neck in men aged 50 and older (*see section 1.2.3*).

7.3.1 ALENDRONIC ACID

Alendronic acid is licensed in the UK for use in men with osteoporosis only at a dose of 10 mg daily. In routine clinical practice the weekly 70 mg preparation is standard. This has become established from bridging studies *(see section 7.3)*.

An RCT compared the effects of 10 mg of alendronic acid daily with those of placebo in 241 men with osteoporosis over a two-year period. All patients received calcium and vitamin D supplements. Patients were eligible for inclusion if they had a T-score of ≤ -2.0 at the femoral neck and a spine T-score of ≤ -1.0, or a T-score of ≤ -1.0 and a prevalent vertebral fracture or osteoporotic fracture. Alendronic acid increased BMD at the spine by a mean value of 7.1% (standard error (SE) ±0.3%) compared with 1.8% (SE ±0.3%) in the placebo group, a difference that was significant ($p<0.001$). Corresponding values at the femoral neck were 2.5% (SE ±0.4%) versus -0.1% (SE ±0.5%, $p<0.001$). The changes in BMD in men with osteoporosis were similar to those previously reported for alendronic acid in postmenopausal women with osteoporosis. Quantitative morphometric analysis indicated significantly fewer vertebral fractures in the alendronic acid group than the placebo group (0.8% *v* 7.1%, $p=0.02$). There was no significant difference between the numbers of non-vertebral fractures observed in the alendronic acid and placebo groups (5.2% *v* 6.2% respectively).[336] 1^-

A meta-analysis identified only two studies describing the effect of alendronic acid on fractures in men, one of which is described above. There was significant heterogeneity between these studies ($I^2=74\%$). Vertebral fractures occurred in 7/223 (3%) patients treated with alendronic acid and 10/135 (7.4%) patients treated with placebo, a difference that was not statistically significant (RR 0.39, 95% CI 0.15 to 1.04). Corresponding figures for non-vertebral fractures were 7/255 (2.7%) and 6/152 (3.9%) respectively (RR 0.73, 95% CI 0.25 to 2.12).[230] 1^{++}

In summary, while alendronic acid increases BMD in men to a similar extent as in women, evidence that it reduces fracture risk in men with low BMD is either not methodologically robust or conflicting and it is not possible to form a recommendation for its use.

7.3.2 RISEDRONATE

The effects of risedronate in men with osteoporosis has been evaluated in one RCT.[337] Men age >30 with lumbar spine T-score ≤ -2.5 and femoral neck T-score ≤ -1 SD or lumbar spine T-score ≤ -1 and femoral neck T-score ≤ -2 SD were randomised to receive 35 mg of risedronate weekly combined with calcium and vitamin D supplements or calcium and vitamin D supplemented placebo over a two year period. Bone mineral density values at the lumbar spine increased by 6.0% after 24 months in the risedronate group and 1.4% in the placebo group, a difference that was significant ($p<0.001$). At the femoral neck, BMD increased by about 1.6% in the risedronate group compared with an increase of about 0.4% in the placebo group (data estimated from charts, exact percentage changes were not reported in the paper, nor were p-values, although the difference was reported as significant). Clinical fractures occurred in 9/191 (4.7%) patients in the risedronate group and 6/93 (6.5%) of the placebo group, a difference that was not significant. Morphometric vertebral fractures occurred in 2/191 of the risedronate group and 0/93 of the placebo group. 1^{++}

The increase in spine and FN BMD in this study at 24 months is very similar to that previously reported in postmenopausal women treated with 5 mg of risedronate daily for 24 months.[137]

In the absence of a submission from the holder of the marketing authorisation to SMC, risedronate sodium is not recommended for use within NHSScotland for the treatment of osteoporosis in men at high risk of fractures *(see section 10.4)*.

7.3.3 ZOLEDRONIC ACID

Zoledronic acid has been investigated in two studies of men with osteoporosis.

One study investigated the effects of zoledronic acid or placebo in 2,127 men and women who had suffered a hip fracture (*see section 6.4.3*).[138] About 25% of the study population were men. The study showed that zoledronic acid increased BMD and reduced the risk of vertebral and non-vertebral fractures compared with placebo. A subsequent subgroup analysis of this study demonstrated that the effects of zoledronic on femoral BMD in this study were similar in men and women. The analysis reported that zoledronic acid was associated with a non-significant reduction in fracture risk of 15% although the study was not powered for this outcome (HR 0.85, 95% CI 0.44 to 1.65, p=0.64).[338] 1^{++}

A subsequent study specifically evaluated the effects of zoledronic acid in men with osteoporosis. In this study 1,199 men aged 50–85 were randomised to receive annual infusions of either 5 mg of zoledronic acid intravenously or placebo along with calcium and vitamin D supplements.[339] Participants were eligible for inclusion if they had a T-score ≤ -2.5, or a BMD T-score at spine or hip of ≤ -1.5 plus one to three vertebral fractures. Zoledronic acid reduced the risk of morphometric vertebral fractures by 67% over a 24-month follow-up period (RR 0.33, 95% CI 0.16 to 0.70). There was no significant difference in the occurrence of non-vertebral fractures which occurred in 5/588 (0.9%) of the zoledronic acid group and 8/611 (1.3%) of the placebo group (RR 0.60, 95% CI 0.20 to 2.0). There were no significant differences in the rates of serious adverse effects, risk of death or AF and no cases of ONJ, but pyrexia, myalgia and influenza-like symptoms were more common in the zoledronic acid group. 1^{++}

While treatment with zoledronic acid substantially reduces the risk of vertebral fractures in men with DXA-proven osteoporosis, osteopenia and radiological evidence of vertebral fractures or following a hip fracture, in the absence of a submission from the holder of the marketing authorisation to SMC, zoledronic acid (5 mg) is not recommended for use within NHSScotland for the treatment of osteoporosis in men at increased risk of fracture, including those with a recent low-trauma hip fracture *(see section 10.4)*.

7.3.4 STRONTIUM RANELATE

Strontium ranelate is licensed in the UK for the treatment of severe osteoporosis in men at risk of fracture.

The effects of strontium ranelate were studied in an RCT of 261 white men aged 65 or above with osteoporosis. Patients were eligible if they had a lumbar spine T-score of ≤ -2.5 or femoral neck T-score of ≤ -2.4 and at least one clinical risk factor for osteoporosis. The intervention and placebo groups both received calcium and vitamin D supplements The primary end point was change in spine BMD with secondary end points of change in hip BMD, morphometric vertebral fracture rate and QOL. There was a significant relative increase in BMD in the strontium group at both spine (+9.8%) and hip (+3.3%) compared with placebo (p<0.001). There was no difference in the rates of vertebral fracture over two years (5.8% in the strontium group versus 7.8% with placebo). There was a significant improvement in QOL associated with strontium which reduced the rate of pain interfering with sleep (17% *v* 4%). More patients had adverse events with strontium (19% *v* 15%) and three developed VTE with active treatment. Furthermore, angina or coronary artery disease was reported more in patients taking strontium ranelate (8.7%) than placebo (4.6%), however, more patients with MI were randomly allocated to the strontium ranelate group than to the placebo group, which may account for this. In this study among men there seems to be a benefit in reducing pain interfering with sleep but this must be balanced against a higher rate of adverse events.[340] 1^{+}

In the absence of a submission from the holder of the marketing authorisation to SMC, strontium ranelate is not recommended for use within NHSScotland for treatment of osteoporosis in men at increased risk of fracture *(see section 10.4)*.

7.3.5 DENOSUMAB

The effects of denosumab on BMD and fracture risk in men were studied in an RCT of 1,468 men with prostate cancer undergoing androgen deprivation therapy. The intervention and placebo groups both received calcium and vitamin D supplements. At baseline, BMD values at the spine and hip were in the osteopenic range (lumbar spine T-score -0.5; femoral neck T-score -1.5). Bone mineral density at the spine, hip and wrist increased in the denosumab group as compared with placebo. At the spine the difference between denosumab and placebo was 6.7% and at the total hip 4.8% at 24 months. The increase in BMD was comparable to that observed in postmenopausal women treated with denosumab.[266] When compared with placebo the relative risk for vertebral fractures in men receiving denosumab was significantly reduced (RR 0.38, 95% CI 0.19 to 0.78). The RR for non-vertebral fractures was also lower in those taking denusomab but this was not significant (RR 0.72, 95% 0.48 to 1.17).[341] 1^{++}

While treatment with denosumab substantially reduces the risk of vertebral fractures in osteopenic men with prostate cancer undergoing androgen deprivation therapy, in the absence of a submission from the holder of the marketing authorisation to SMC, denosumab 60 mg solution for injection in pre-filled syringe is not recommended for use in NHSScotland for bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures or for use in men with osteoporosis at increased risk of fractures *(see section 10.4).* 1^{++}

7.3.6 PARATHYROID HORMONE

Limited data are available on the effects of parathyroid hormone in men with osteoporosis. One trial investigated the effects of teriparatide in 437 men with BMD T-score values of -2.0 or less. Treatment allocations were placebo (n=147), 20 micrograms of teriparatide daily (n=151) or 40 micrograms of teriparatide daily (n=139). All patients received calcium and vitamin D supplements. The trial was terminated prematurely because of preclinical studies which showed that lifelong teriparatide increased the risk of osteosarcoma in rats. However, subsequent clinical studies and preclinical primate studies have shown no evidence to suggest that this risk is observed in humans treated with teriparatide. Because the study was terminated prematurely the duration of treatment was highly variable ranging from two to 15 months with median treatment duration of 11 months. Bone mineral density increased to a significantly greater extent at the spine (mean 5.87%, SE ±4.50% *v* 0.5%, SE ±3.9%, p<0.001) and femoral neck (1.53%, SE ±3.95% *v* 0.31%, SE ±4.1%, p=0.029) in the 20 micrograms teriparatide group when compared with placebo. There were also significant increases in those receiving 40 micrograms teriparatide compared with 20 micrograms for lumbar spine BMD (9.03%, SE ±6.46% *v* 5.87%, SE ±4.50%) and FN BMD (2.93%, SE ±6.34% *v* 1.53%, SE ±3.95%). Non-vertebral fractures occurred in 3/147 of the placebo group, 2/151 of the 20 micrograms group and 0/139 of the 40 micrograms group, differences that were not significant.[342] 1^{+}

The changes in BMD were reported by the authors to be comparable to those previously observed after 12 months in women with postmenopausal osteoporosis treated with teriparatide,[265] although direct comparison is difficult due to the variable duration of treatment in the study of postmenopausal osteoporosis. Accordingly, in the study of postmenopausal women the average percentage increase in lumbar spine BMD in the teriparatide 20 micrograms group versus placebo was 8.6% over an average of 18 months treatment compared with 5.7% in men over 11 months. 1^{+}

While teriparatide may have positive effects on BMD in men with osteoporosis, the only RCT which investigated fracture prevention failed to show a significant effect, although the power to detect an effect was low. There is insufficient evidence to recommend the use of teriparatide for the prevention of fragility fractures in men with osteoporosis. The Scottish Medicines Consortium notes that the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

7.3.7 DURATION OF THERAPY

While there are no data available to form recommendations for duration of therapy in men, there are no clear reasons why the advice for men with osteoporosis aged 50 or over should differ from the advice for postmenopausal women (*see section 6.5*).

7.4 EXERCISE INTERVENTIONS IN PREMENOPAUSAL WOMEN

Several types of exercise programmes have been evaluated for effectiveness in premenopausal women with osteoporosis. Two systematic reviews have provided evidence on the effects of exercise on bone density. No reviews reported on QOL outcomes.

7.4.1 STATIC WEIGHT-BEARING EXERCISE

No systematic reviews have provided evidence on these forms of exercise intervention in premenopausal women.

7.4.2 DYNAMIC WEIGHT-BEARING EXERCISE (LOW FORCE)

No systematic reviews have provided evidence on these forms of exercise intervention in premenopausal women.

One meta-analysis of 10 RCTs on the effect of walking on BMD in postmenopausal and perimenopausal women reported only a single small trial which included perimenopausal women aged 40–60 (n=50). This study showed no effect of walking on BMD in this cohort.[343] 1^{+}

7.4.3 DYNAMIC WEIGHT-BEARING EXERCISE (HIGH FORCE)

High-impact only programmes were effective in reducing BMD decline only at the femoral neck (weighted mean difference, WMD 0.024 g/cm^2, 95% CI 0.002 to 0.027, p<0.00001).[344] 1^{++}

7.4.4 NON-WEIGHT-BEARING EXERCISE (LOW FORCE)

No systematic reviews have provided evidence on these forms of exercise intervention in premenopausal women.

7.4.5 NON-WEIGHT-BEARING EXERCISE (HIGH FORCE)

High-intensity progressive resistance training was shown to be effective in increasing absolute BMD at the lumbar spine (WMD 0.014 g/cm^2, 95% CI 0.009 to 0.019, p<0.00001) but not the femoral neck (WMD 0.001 g/cm^2, 95% CI -0.006 to 0.008, p=0.78) in premenopausal women.[345] 1^{++}

7.4.6 COMBINATION OF EXERCISE TYPES

Exercise programmes that combine odd- or high-impact activity with high-magnitude resistance training appear effective in increasing BMD in premenopausal women at the femoral neck (WMD 0.007 g/cm^2, 95% CI 0.001 to 0.013, p=0.02) and spine (WMD 0.009 g/cm^2, 95% CI 0.002 to 0.015, p=0.01).[344] 1^{++}

7.4.7 SUMMARY

No systematic reviews have reported on fracture/falls risk, adverse effects or QOL outcomes of exercise interventions for premenopausal women with osteoporosis. Although two systematic reviews reported a small but positive effect of exercise on BMD it was exercise-type and site specific. Surrogate measures such as BMD and physical function may not reflect changes in fracture risk which is the most important outcome to patients. The lack of head-to-head comparisons of interventions makes the choice between interventions difficult for clinicians and patients. Exercise is assumed to be a safe intervention, but consideration must be given to the perceived risks or concerns such as fracture or other injury that some individuals may have when starting or resuming exercise. High-impact exercise can reduce BMD decline at the femoral neck, progressive-resistance exercise can reduce BMD decline at the lumbar spine, and impact protocols combined with resistance can reduce BMD decline at both the femoral neck and lumbar spine. Conclusions must be interpreted with some caution as the original studies suffered from diverse methodological and reporting discrepancies and so were of predominantly low quality.

R **High-impact exercise** (such as jogging) **and combining impact exercise** (such as stair climbing) **with progressive-resistance strength training** (such as weight training) **should be considered to slow decline of femoral neck BMD.**

R **Progressive-resistance strength training** (such as weight training) **alone, or in combination with impact exercise** (such as stair climbing or jogging)**, should be considered to slow decline of lumbar spine BMD.**

7.5 GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Glucocorticoid therapy is strongly associated with the development of osteoporosis and fragility fractures in both men and women *(see section 3.5.13)*. The increased risk of fracture is dependent on glucocorticoid dose and duration of therapy. There is evidence to suggest that fractures occur at higher levels of BMD in patients on glucocorticoids as compared with non-glucocorticoid-treated patients suggesting that glucocorticoids might also affect bone quality and/or non-skeletal risk factors for fracture as well as reducing bone density.[346]

7.5.1 ALENDRONIC ACID

The effects of alendronic acid at doses of 5 mg and 10 mg daily were evaluated in 477 patients with GIOP (61% female, of whom 13.6% were premenopausal) between the ages of 17 and 85. Although recruited on the basis of having an underlying condition that required long-term glucocorticoid use (7.5 mg prednisolone or equivalent daily for at least one year), only 45% of patients had been treated for this period. A third of patients had been treated for less than four months.[347] Over 12 months' follow up, morphometric vertebral fractures occurred in 6/266 (2.3%) of the combined alendronic acid groups and 5/134 (3.7%) of the placebo group; a difference that was not significant (RR 0.60, 95% CI 0.10 to 4.40). The incidence of non-vertebral fractures was identical (4.4%) in the alendronic acid and placebo groups. In an extension of this study to 24 months involving 202 participants (42% of the original cohort) morphometric vertebral fractures occurred in 1/143 of the alendronic acid treated patients (0.7%) compared with 4/59 (6.8%) placebo-treated patients, a difference that was significant (p=0.026).[348] 1^+

Patients in the extension study were not representative of the initial study group in that they had fewer prior fractures and they were on a higher dose of steroids compared with the patients who did not enter the extension.

R **Alendronic acid may be considered to prevent vertebral fractures in men and women on prednisolone doses of 7.5 mg daily or greater** (or an equivalent dose of glucocorticoids) **for three months or more.**

7.5.2 RISEDRONATE

The effects of risedronate at doses of 2.5 mg daily and 5 mg daily were investigated in two parallel trials which included a total of 518 patients receiving glucocorticoid therapy (64% female of whom around 21% were premenopausal). In one study 7.5 mg prednisolone daily or more had been given for less than three months and in another, prednisolone had been given in a dose of 7.5 mg daily or more for at least six months. Analysis of pooled data from both trials showed that risedronate was effective in reducing vertebral fractures (RR 0.33, 95% CI 0.13 to 0.81) but there was no significant effect on non-vertebral fractures (RR 1.08, 95% CI 0.45 to 2.59).[230] 1^+

R **Risedronate should be considered to prevent vertebral fracture in men and women on prednisolone doses of 7.5 mg daily or greater** (or an equivalent dose of glucocorticoids) **for three months or more.**

7.5.3 IBANDRONIC ACID

There is very limited evidence from one small trial (n=35) that 2 mg of ibandronic acid given IV quarterly reduced the risk of vertebral fractures compared with placebo in a group of male cardiac transplant patients receiving triple immunosuppressive treatments and glucocorticoids.[349] In the treatment group 13% sustained a new morphometric fracture compared with 53% in the control group (RR 0.40, p=0.04). 1^+

7.5.4 ZOLEDRONIC ACID

The effects of zoledronic acid in GIOP were studied in a comparative trial with risedronate conducted over 12 months.[350] Patients were admitted to the study if they had been on ≥7.5 mg of prednisolone daily and were expected to remain on this treatment for 12 months. About 70% of the patients were female. New vertebral fractures occurred in 5% of the zoledronic acid group and 3% of the risedronate group, a difference that was not significant. Adverse effects were similar between the groups except fever and influenza-like illness which were more common in the zoledronic acid group. Zoledronic acid gave significantly greater increases in bone density at the spine and hip than risedronate. 1^{++}

R **Zoledronic acid should be considered to prevent vertebral fracture in men and women on prednisolone doses of 7.5 mg daily or greater** (or an equivalent dose of glucocorticoids) **for three months or more. The treatment should be considered in patients who are intolerant of oral bisphosphonates and those in whom adherence to oral therapy may be difficult.**

7.5.5 PARATHYROID HORMONE

One RCT compared teriparatide with alendronic acid in 428 women and men with osteoporosis aged 22–89 who had received glucocorticoids for at least three months (prednisolone equivalent, ≥5 mg daily). New vertebral fractures occurred in 1/171 of the teriparatide group (0.6%) compared with 10/165 (6.1%) of the alendronic acid group (p<0.001). Corresponding figures for non-vertebral fractures were 12/214 (5.6%) in the teriparatide group versus 8/214 (3.7%) of the alendronic acid group (p=0.36).[351] An extension of this study to 36 months showed similar results on vertebral (1.7% *v* 7.7%, p=0.007) and non-vertebral fractures (7.5% *v* 7.0%, p=0.843).[352] 1^{+} 1^{-}

While teriparatide substantially reduces the risk of vertebral fractures in men and women with GIOP with effects that are superior to those of alendronic acid, in the absence of a submission from the holder of the marketing authorsiation to SMC, teriparatide is not recommended for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture *(see section 10.4)*.

7.5.6 ETIDRONATE

A meta-analysis of four studies which included 420 patients receiving glucocorticoids reported that 400 mg of cyclical etidronate daily for 10 days in a three month period, when combined with calcium supplements did not reduce the risk of vertebral fractures when compared with calcium supplemented placebo (RR 0.59, 95% CI 0.26 to 1.31). Similarly, a meta-analysis of two studies involving 154 patients showed no effect of cyclical etidronate on non-vertebral fractures (RR 0.38, 95% CI 0.10 to 1.38) although power was limited.[230] 1^{++}

7.6 MANAGEMENT OF PAINFUL VERTEBRAL FRACTURES

7.6.1 SURGICAL INTERVENTIONS

The evidence base for kyphoplasty (KP), and vertebroplasty (VP) in patients with acute vertebral fractures has been evaluated in one systematic review which included two RCTs which compared VP with a sham procedure; two RCTs which compared VP with non-surgical care; one RCT which compared VP with KP and one which compared KP with non-surgical care.[353] Since the publication of this review two further trials have been conducted comparing VP with standard care and a meta-analysis has been performed in which a pooled analysis of VP compared with sham procedure was carried out. NICE has recently published an MTA on KP and VP.[354]

Vertebroplasty compared with sham treatment

A systematic review which included two RCTs comparing VP with sham showed no significant difference in pain or QOL between the interventions during a follow-up period of up to six months.[353] The conservatively-treated group had fewer vertebral fractures (but this was not significant) and had fewer complications. The results of these trials were also analysed in a meta-analysis which investigated if specific subgroups of patients might benefit from VP. This meta-analysis showed no benefit of VP as compared with the sham procedure for any end point in any subgroup of patients and revealed that patients who were randomised to VP were more likely to be using opiates at one month after the procedure.[355]

1++
1-

Vertebroplasty compared with usual care

Two small RCTs[356, 357] were reported in a systematic review of trials comparing VP with non-surgical usual care[353] and two relevant RCTs were published subsequent to this.[358, 359]

The systematic review reported that there were no significant differences between pain outcomes after one day for patients treated with VP compared with those receiving optimal medical treatment. One trial showed that improvement in pain was similar between the two groups at three months and was sustained to 12 months. The other small open RCT detected a significantly greater reduction in pain scores at one day after the intervention in the VP group compared with the conservative treatment group (mean difference between groups -2.4, 95% CI -3.7 to -1). At two weeks follow up, however, this difference was smaller and was not statistically significant (mean difference -1.5, 95% CI -3.2 to 0.2, not significant).[353]

1++
1+

In another RCT 80 patients were randomised to VP or non-surgical treatment. Pain reduction was significantly better at one week in the VP group (difference -3.1, 95% CI -3.72 to -2.28; p<0.001), but gradually the differences reduced and by 12 months and 36 months, the differences were not significant. Low back pain as assessed by the Oswestry score improved more in the VP group and the differences were significant for up to 36 months.[358]

1++

In the final RCT 202 patients were randomised to VP or standard medical care. Pain relief assessed by visual analogue score was better in the VP group at one month (mean difference between groups 2.6 (95% CI 1.74 to 3.37, p<0.0001)) and the difference remained significant at one year (mean difference between groups 2.0 (95% CI 1.13 to 2.80, p<0.0001)). Quality of life (QUALEFFO and Roland Morris Disability scores) improved more at one month and one year in the VP group. Complications and rates of new vertebral fractures were similar in both groups.[359]

1+

Vertebroplasty compared with kyphoplasty

The only RCT identified which directly compared VP with KP included 100 patients with recent vertebral fractures. Pain improved in both groups when compared with baseline but there was no difference in pain control between the allocated groups at baseline, at one week or six months or in adverse effects.[360]

1+

The pain response is in accordance with a meta-analysis which compared outcomes in non-randomised studies of VP and KP and found that the reduction in pain with both procedures was similar.[361] Another systematic review of complications of VP and KP concluded that medical complications such as non-cement embolism, temporary respiratory insufficiency, stroke, cardiovascular complications, pneumonia, and fever were significantly more likely with KP (1.6%) than with VP (0.4%) (p<0.001).[362] However, procedure-related complications which include cement embolism, neurologic deficit, fracture (rib, transverse process, and pedicle), discitis, dural tear, pain worse than before surgery, and subcutaneous haematoma were less common with KP compared with VP (3.8% *v* 0.6%, p<0.001). There was no difference between VP and KP in the likelihood of a new vertebral fracture occurring at another level (18% *v* 17%).

1-

Kyphoplasty compared with standard care

One RCT which compared KP with standard care showed that KP gave better pain relief than standard care for up to six months but the differences between groups diminished thereafter and by 12 months the difference between groups was not statistically significant. A similar response was seen for quality of life which improved to a greater extent in the KP group for up to 12 months, but with a diminishing difference between the groups with time. Adverse events were slightly more common in the KP group.[363] A longer term follow up of this study for 24 months showed similar results to those observed at 12 months, but with further attenuation of the differences between groups at this time point.[364] 1^{+}

Kyphoplasty and vertebroplasty both improve pain and quality of life compared with medical treatment in patients with painful vertebral fractures in the short term although the differences attenuate with time. However, evidence from RCTs where the effects of vertobroplasty have been compared with a sham procedure indicates that the symptomatic benefit cannot be attributed to the vertebral augmentation procedure but rather to a placebo response.

The NICE MTA on percutaneous vertebroplasty and percutaneous balloon kyphoplasty for treating osteoporotic vertebral compression fractures also notes that the only double-blinded trials conducted on these technologies showed no statistically significant differences in the change from baseline between vertebroplasty and operative placebo.[354] 1^{++}

There is insufficient evidence to recommend the use of kyphoplasty or vertebroplasty for the treatment of painful vertebral fractures.

7.6.2 PHARMACOLOGICAL INTERVENTIONS

A number of RCTs and meta-analyses have been conducted evaluating the effects of various pharmacological interventions on acute or chronic pain associated with fractures.

Intravenous pamidronate

Patients with acute vertebral fracture (n=32) who were seen within 21 days of a fracture were randomised to receive 30 mg of pamidronate intravenously for three days or a placebo infusion. Both groups received supportive treatment with 3 g of paracetamol daily and were given calcium and vitamin D. Pain recorded on a 100 mm visual analogue scale improved in both groups after one week and after one month but the response was significantly greater in the pamidronate group (difference in pain scores between groups: -23.25 mm (95% CI -42.3 to -4.2, p=0.018) at day 7 and -26 mm at day 30 (p=0.03), in favour of pamidronate). Analgesic use in both groups did not differ. Two patients in the pamidronate group (12.5%) experienced fever and muscle pain. There was no adjustment for baseline variables and the modest benefits observed may be accounted for, or enhanced by methodological weaknesses.[365] 1^{-}

Calcitonin

A meta-analysis of RCTs compared calcitonin with placebo in the treatment of acute or chronic pain associated with vertebral fractures.[366] Ten eligible trials were identified with a placebo arm, five of which studied the effects on pain from an acute vertebral fracture (<10 days) and five of which studied the effects on chronic pain (>3 months) associated with vertebral fracture. Various modes of calcitonin administration were used including nasal spray, injection and suppositories. There was a significant beneficial effect from calcitonin on pain at rest in patients with acute vertebral fracture with a standardised mean difference (SMD) of -2.83 points (95% CI -4.09 to -1.57) between groups. Similar effects were observed with regard to pain on walking (SMD -2.92, 95% CI 3.97 to -1.87). In contrast, calcitonin had no significant benefit on chronic pain associated with vertebral fracture (SMD -0.14, 95% CI -0.41 to +0.13). Side effects (mainly flushing and GI disturbances) were significantly more common in calcitonin-treated patients (RR 3.09, 95% CI 1.80 to 5.32, p<0.001). The trials were generally small, of poor quality and lacking information on methods of recruitment and randomisation. The meta-analysis showed significant heterogeneity. 1^{++}

Other agents

One RCT compared the effects of 35 mg risedronate weekly with 20 micrograms of teriparatide daily in 712 postmenopausal osteoporotic women with back pain thought to be due to vertebral fractures.[303] Treatment was continued for 18 months. Back pain improved in both treatment groups with time and, at 18 months, 69.3% of the risedronate group and 72.2% of the teriparatide group reported an improvement of 30% or more in worst or average back pain severity. There was no difference between the treatment groups at any time except that the proportion of patients who reported worsening of back pain between six and 12–18 months was slightly less in the teriparatide group (23.6% *v* 30.6%, p=0.04). 1^+

Both calcitonin and intravenous pamidronate seem to confer better pain relief than placebo in patients with recent vertebral fracture but both agents can cause adverse effects and there are concerns about the quality of the trials that have studied this issue. More research is needed before these procedures can be recommended for routine use. There is limited evidence that other osteoporosis treatments improve back pain associated with vertebral fractures.

There is insufficient evidence to recommend the use of calcitonin, pamidronate or teriparatide as treatments for painful vertebral fractures.

7.6.3 NON-PHARMACOLOGICAL INTERVENTIONS

An RCT investigated two types of transcutaneous electrical stimulation therapy in participants with low back pain, about two thirds of whom had osteoporotic vertebral fractures.[367] The therapies studied were interferential therapy (IFT; n=45), horizontal therapy (HT; n=45) and sham HT (n=30). In the sham HT group electrical pads identical to those used in HT were applied to the patient, but no electrical stimulation was given. Treatments were given five days per week for the first two weeks and patients were followed up for 14 weeks. All patients were also provided with an exercise programme five days per week for the first two weeks. Patients in both intervention groups experienced a greater functional improvement than the sham group at 14 weeks and had less pain at both 6 and 14 weeks. During the last week, analgesic use was less in the HT group, but there was no difference between the IFT group and sham HT group. A subgroup analysis was performed showing that the effects of these treatments were similar in subgroups of patients with vertebral fracture and degenerative disk disease but further details were not provided. 1^{++}

The same authors conducted a further trial of identical design in 105 patients with vertebral fracture (35 in each group).[368] In all three groups patients were also provided with an exercise programme five days per week for the first two weeks. This study showed improvements in functional score at six weeks and 14 weeks in the HT and IFT groups when compared with the sham HT group and improvements in pain in the HT and IFT groups at 6 and 14 weeks when compared with the sham HT group. Analgesic use was reported to lessen in the HT group over the 14 weeks of the study as compared with the sham HT group, but no difference was observed between the IFT and sham HT groups. It is unclear if there was any overlap between patients enrolled into this study and the earlier study performed by the same authors. 1^+

A further RCT investigated capacitive coupled electrical field therapy (CCEF) in patients with back pain due to vertebral fractures. The active treatment group (n=25) received a 7 volt peak-to-peak sine wave electric field through the CCEF device whereas the control group (n=26) received a 0.1 volt peak-to-peak sine wave from the same device representing the lowest electric field required to detect the actual contact of the electrodes with the skin and the cable connection. Patients were asked to wear the device for at least 10 hours daily for eight weeks. Patients were treated for eight weeks and followed up for a further four weeks after treatment. Pain score, and QUALEFFO score progressively improved in both groups with time. There was no significant difference between the groups at any point. Overall use of NSAIDs (measured by the number of patients taking these drugs) was lower in the intervention group compared with the control group at the end of treatment and at the end of the follow up period (p<0.001). Although high overall, there was no difference between groups in discontinuation rates due to skin reactions or problems with the device (19% control *v* 16% active group). Limitations of this study include the high withdrawal rate, and the fact that the analysis was not conducted on an intention-to-treat basis. There was insufficient detail on the amounts of analgesics taken in the two groups and inconsistencies in the description of outcomes measures.[369] 1^{++}

R **Electrical field therapy, with or without an exercise programme, may be considered to reduce pain and improve function in patients with painful vertebral fractures.**

7.6.4 PHYSIOTHERAPY INTERVENTIONS

An RCT of women above the age of 60 with osteoporosis and a previous history of vertebral fracture allocated participants to receive exercise therapy consisting of a one-hour group exercise session coupled to a three hour information session supervised by a physiotherapist (n=47) or to receive standard care (n=42). At three months, walking speed (p=0.001), timed up-and-go (p=0.026), general health measured by General Health Questionnaire-20 (GHQ-20) scale (p=0.009) and QUALLEFO-41 mental function scores (p=0.006) were significantly better in the intervention group. By 12 months the differences remained significant for walking speed (p=0.019), up-and-go (p=0.021), and QUALEFFO-41 mental function (p=0.04). In addition QUALEFFO-41 total score (p=0.019) and QUALEFFO-41 pain scores (p=0.005) were significantly better in the exercise group at 12 months. Limitations include the small sample size and possibility that some of the benefits observed in the exercise group may not have been due to the intervention but instead increased social contact with others in the group and with the therapist. It was also not possible to determine whether the information sessions had any effect.[370] 1^+

Another RCT investigated the relationship between exercise and quality of life, although did not include specific pain measures as primary outcomes.[371] Seventy four postmenopausal women with osteoporosis and at least one vertebral fracture were randomised to an exercise programme (n=37) or a control group (n=37). The exercise group received a short training session and then were instructed to perform a one-hour programme of exercise three days per week for 12 months. During this time an exercise therapist visited the participants on a monthly basis for six months. Patients in this group also received telephone calls to check on progress every two weeks for 12 months. The control group were instructed to continue normal activities and were contacted monthly by telephone. Osteoporosis Quality of Life Questionnaire (OQLQ) scores improved to a greater extent in the exercise group for the subdomains of symptoms, (p=0.003) emotion (p=0.01) and leisure/social activities (p=0.03) at six months. The differences were less pronounced at 12 months but remained significant for symptoms (p=0.02) and became significant for activities of daily living (p=0.04). A limitation of the study is that some participants had asymptomatic vertebral fractures. The exercise intervention may actually be most effective in those individuals with symptomatic fractures. It is also difficult to distinguish to what extent improvement in quality of life was attributed to the programme itself or the monthly visits and telephone calls. The authors report reductions in pain from standing (mean change 0.53), carrying (mean change 0.37) and walking (mean change 0.40) in the exercise group as a subdomain analysis of the symptom domain of the OQLQ. 1^+

Further studies are required to adequately explore the components of the exercise programme which may confer benefit, for example exercise type, frequency and intensity, and particularly to dissect out the relative role of the exercise and increased social and practitioner contact as mediators of the effects observed.

R **Physiotherapist-supervised exercise programmes, with or without an information package, are recommended to reduce pain and improve quality of life in patients with painful vertebral fractures.**

8 Systems of care

8.1 INTRODUCTION

The care of patients who may be at risk of osteoporosis and fracture, or those who have already sustained a fracture, is complex as it requires identification, assessment and possibly treatment of individuals who may be unaware of this need. Furthermore, in many areas, no specific service has overall responsibility for the process and it relies on a high index of suspicion from all healthcare professionals to initiate appropriate investigation and interventions. Education of healthcare professionals and patients is therefore likely to be important. Multifaceted systems of care that integrate all aspects of bone health and falls leading to fracture are likely to deliver greater reductions in fracture than disparate and unco-ordinated efforts.

Interventions have been delivered in the primary-care setting, secondary-care setting and with a combined multisystem approach. Some interventions are aimed at primary prevention, some at secondary prevention and some provide elements of both. Interventions may be as simple as physician and patient education or may be multifaceted across all areas of care.

8.2 REMINDERS AND EDUCATIONAL STRATEGIES

Education can be aimed at the public, patients or at clinicians and other healthcare professionals in order to change behaviour and improve outcomes. Most research on systems of osteoporosis care has involved a multifactorial approach of which education was one aspect.

A systematic review of RCTs of men and women who were either at risk of osteoporosis (age ≥65, postmenopausal women, or more than three months, systematic use of glucocorticoids) had a confirmed diagnosis of osteoporosis or an existing fragility fracture included 13 RCTs which investigated disease management interventions.[372] Outcomes were vertebral and non-vertebral fracture, BMD investigations, initiation of any osteoporosis treatment and fracture-related complications, for example mortality, and reported study quality was generally poor. Heterogeneity of interventions, study design, controls and outcomes made it impossible to combine the data for meta-analysis. Follow up was generally short (ranging from ten weeks to 28 months).

Seventy-seven per cent of studies included a reminder on education as a component of their intervention. Six RCTs included a reminder plus education, of which three studies included reminders plus education intervention targeted at both physicians and patients. These showed an increase in BMD testing (RR range 1.43 to 8.67) and osteoporosis medication use (RR range 1.6 to 16.24). 1^{++}

Three studies within this review gave reminders and education to physicians and patients at risk of GIOP but there was no difference found in testing for BMD or for initiation of osteoporosis preventative therapy.

Two studies from the review combined a reminder and education with a risk assessment strategy, of which one (the osteoporosis population-based risk assessment (OPRA) trial) targeted reminders at both physicians and patients. More patients received osteoporosis therapies than controls across these two studies (RR 1.27, CI 1.03 to 1.56) but there was no difference in fracture rate between the two groups (RR 0.96, CI 0.69 to 1.34). The second study also showed increased rates of prescriptions for bisphosphonates.

Two studies within this systematic review evaluated education with exercise or risk assessment with improvements shown in quality of life scores in one study and no difference in calcium or vitamin D initiation in the other.

In conclusion, multifactorial approaches involving education for the identification of at-risk or high-risk patients and their subsequent assessment and management appear to be moderately successful in promoting initiation of osteoporosis therapies, increasing BMD testing but have mixed success in reducing fracture rates. The short duration of studies and the wide heterogeneity of the interventions make it difficult to form recommendations regarding who should provide the education and when and how it should be provided, although five of the six studies that showed significant improvement in outcomes were targeted to both physicians and patients.

8.3 MULTIFACETED INTERVENTIONS

The effectiveness of interventions aimed at detection and treatment of osteoporosis to prevent first fractures (or further fractures in high-risk groups) has been evaluated in a systematic review of 13 studies, all of which were based in primary care.[373] Most studies were multifaceted and involved patient education material (eight studies), physician notification and/or physician education. Absolute differences in the incidence of BMD testing ranged from 22–51% for high-risk patients and 4–18% in studies targeting both at-risk and high-risk patients. Absolute differences in osteoporosis treatment initiation ranged from 18–29% for high-risk patients 1^{++} and from 2–4% for both at-risk and high-risk groups. Pooling the results of four trials showed an increase in incidence of osteoporosis treatment initiation (risk difference 20%, range 7–33%) and of BMD testing and/or treatment initiation. Two studies had fracture as a primary outcome and showed no difference between the intervention group and controls in patients with a previous hip fracture who were not receiving osteoporosis treatment. In general, interventions with three or more facets were more effective than those with fewer.

Models of care for secondary fracture prevention have been assessed in a meta-analysis of 44 studies including cohort studies, before-and-after studies, cross-sectional designs and RCTs.[374] Six studies excluded men and 25 studies included both sexes although the percentage of each was not always reported. Mean female percentage was 70.8% (range 4–86%) with Caucasian percentage of 64–95% in the eight studies which reported ethnicity. All studies were conducted in populations over the age of 50. The interventions were divided into four types: type A was the highest level of care comprising a co-ordinated approach to secondary fracture prevention. These models of care identified patients following a fracture who were then fully assessed and treated as part of a co-ordinated package of care managed by a fracture liaison co-ordinator (FLC). Fourteen studies were included in the analysis, of which 11 services used an FLC. Type B models of care were similar to type A except that treatment was required to be initiated by the patients' primary-care physician. An FLC was also pivotal to the success of this model of care. An example of this type of care is the Glasgow Osteoporosis Service. Eighteen studies of type B models of care were incorporated into the study, 12 of these services used an FLC. Type C models of care were more varied and less intensive (10 studies). Patients generally received education about osteoporosis, the benefits of treatment and falls prevention along with lifestyle education. The patients' primary-care physician would then be alerted to the recent fracture and advised of the need for further investigation and treatment. In the two studies involving type D interventions patients received specific osteoporosis education only via letter, patient information 1^{++} sheet, video, telephone or in a face-to-face interaction. This model did not include physician education or intervention. Intervention effectiveness was assessed by meta-analysis in those studies with control groups and which reported BMD testing and treatment initiation rates (25 studies). It was not possible to undertake meta-analysis of adherence or refracture rates as insufficient studies reported these outcomes.

Almost all studies in models A to C showed a significant improvement in the rate of BMD testing with intervention: type A risk difference (RD) 0.56 (95% CI 0.39 to 0.72, p<0.001, eight studies); type B RD 0.50 (95% CI 0.23 to 0.76, p<0.001, five studies; type C RD 0.30 (95% CI 0.18 to 0.42, p<0.001, seven studies). Meta-regression analysis of risk difference between models A to C showed a non-significant trend towards better outcomes with the more intensive treatments (coefficient=0.13, 95% CI 0.00 to 0.25, p=0.06).[374]

Treatment initiation was assessed for all treatment groups. Risk differences were: type A 0.29 (95% CI 0.19 to 0.40, p<0.001, eight studies); type B 0.21 (95% CI 0.05 to 0.37, p<0.01, five studies); type C 0.16 (95% CI 0.07 to 0.25, p<0.001, seven studies); type D 0.03 (95% CI 0.00 to 0.07, p<0.06, one study). Meta regression of RD across groups showed a significant trend towards better outcomes with more intensive interventions, although the confidence limit approached zero, (coefficient=0.07, 95% CI 0.01 to 0.14).[374]

Self reported adherence data were insufficiently robust to submit to meta-analysis. Refracture rates were reported in six studies but only two of the studies, both type A models, included sufficient data for effectiveness at reducing fractures to be assessed. One study reported a significant improvement in refracture rate at four years from 19.7% in the control group to 4.1% in the intervention group. The second study reported an overall risk reduction of 37.2% for hip fractures over three years using historical data.[374]

In 2010 the Glasgow Osteoporosis Service reported a reduction in hip fracture rates in Glasgow of 7.3% compared to a 17% increase in England where there were few co-ordinated systems of care.[375] 4

Several studies demonstrated that services delivered in co-ordinated models were cost effective. A well-defined analysis of refracture rates found their type A service to be extremely cost effective with a cost per QALY of 20,000–30,000 Australian dollars.[376] It was estimated that USA $30.8 million were saved by the Healthy Bones Program (type A) in Southern California in 2006, when comparing hip fracture rates with historical data.[377] The Glasgow Osteoporosis Service (type B) showed that the cost per QALY gained was £5,740. Even when using the worst efficacy data, 15 fractures were averted at the expense of £84,076 per 1,000 individuals with fractures.[378]

Other factors influencing the effectiveness of the various programmes were also assessed. Efficacy tended to be greater if the intervention was within six months of the fracture rather than later. Men had lower rates of pretreatment diagnoses of osteoporosis and lower rates of treatment both pre- and postintervention.[374] 1^{++}

In summary, a meta-analysis has provided robust data on the effectiveness of integrated and co-ordinated systems that are centred around fracture liaison services and central co-ordination by a fracture liaison co-ordinator. Cost effectiveness has been demonstrated for both type A and type B programmes.

R **Patients over the age of 50 who have experienced a fragility fracture should be managed within a formal integrated system of care that incorporates a fracture liaison service.**

R **Systems of care should also incorporate strategies for education of patients and professionals and primary prevention in addition to secondary fracture prevention.**

9 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing osteoporosis with patients and carers and in guiding the production of locally produced information materials.

9.1 SOURCES OF FURTHER INFORMATION

9.1.1 NATIONAL ORGANISATIONS

National Osteoporosis Society
Camerton, Bath, BA2 0PJ
Helpline: 0808 800 0035
Helpline email: nurses@nos.org.uk
www.nos.org.uk

Mayrine Fraser
Development Manager for Scotland
National Osteoporosis Society
Tel: 01761 471771 • Email: m.fraser@nos.org.uk

The National Osteoporosis Society is a UK charity dedicated to improving the diagnosis, prevention and treatment of osteoporosis. It runs a dedicated helpline (by phone, email and post) on weekdays between 9am and 5pm to answer medical queries relating to osteoporosis. The website provides a large volume of information and advice regarding living with the condition, current news and support groups.

NHS Health Scotland
Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB
Tel: 0131 536 5500 • Fax: 0131 536 5501
www.healthscotland.com • E-mail: nhs.healthscotland-generalenquiries@nhs.net

NHS Health Scotland is the national agency for improving the health of the population. It provides access to a wide range of health information, including resources relating to falls and osteoporosis.

Age Scotland
Causewayside House,160 Causewayside, Edinburgh, EH9 1PR
Helpline: 0800 4 70 80 90 • Fax: 0845 833 0759
www.ageuk.org.uk/scotland • Email: info@agescotland.org.uk

Age Scotland is a charity which represents all older people in Scotland. It campaigns, commissions research and fundraises to support a better quality of life for everyone in later life. Age Scotland provides a wide range of confidential, impartial and simple information and promotes healthy living and active ageing. It also helps people to claim their entitlements and provides access to financial services targeted towards older people.

9.1.2 USEFUL PUBLICATIONS FOR PATIENTS AND CARERS

Understanding Osteoporosis.
Compston JE. BMA Family Doctor Publications (2008). ISBN 1903474507

Osteoporosis: The Facts.
Black AJ, Sandison R and Reid D. Oxford University Press (2009). ISBN 0199215898

All about osteoporosis: A guide to bone health, fragile bones and fractures.
National Osteoporosis Society. Available from www.nos.org.uk/page.aspx?pid=1024

9.2 CHECKLIST FOR PROVISION OF INFORMATION TO PATIENTS AT RISK OF FRACTURE

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Initial consultation with GP	• Ensure that patients presenting with risk factors for osteoporosis are informed about tests for fracture risk (for example, Qfracture or FRAX). • Patients referred for a DXA scan should be given clear reasons for their referral and how the outcome will affect them with regard to any treatment.
On diagnosis	• Provide written information to explain the diagnosis of osteoporosis including the possible causes and provide reassurance that treatment is available. • Provide contact details of a specialist nurse for support, if available, and the National Osteoporosis Society helpline number. • Self help strategies, where appropriate, should be discussed. • Risk factors for falling should be evaluated.
Treatment	• All treatment options should be discussed with the patient and consideration should be given to the patient's ability and motivation to adhere to treatment recommendations. • Possible benefits and adverse effects of any treatment should be discussed and reassurance given that other options are available if adverse effects prove too onerous. • The expected outcomes of any treatment should be discussed and the aim of reducing risk of fracture explained. • Information on a healthy balanced diet (for example, the eatwell plate) should be discussed with patients. • Advice on mineral and vitamin supplementation should be provided. • Occupation and lifestyle, including current diet, alcohol intake, exercise capacity and smoking status should be considered. • Advice on appropriate forms of exercise and support with smoking cessation should be offered. • Pain management should be discussed and a referral to a pain clinic given, if appropriate. • Aids to daily living should be discussed, as appropriate. • An outline of the care pathway that patients may expect should be given.
Follow up and review	• Reassure patients about how the effectiveness of their treatment will be reviewed, including the possibility of further DXA scans. • Remind patients that they can ask for help at any time if they are worried about adverse drug effects, further fractures or any other issues of importance to them. • Sources of further information (for example, helplines, video guides, written material and websites) should be made available.

10 Implementing the guideline

10.1 IMPLEMENTATION STRATEGY

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

Implementation of national clinical guidelines is the responsibility of each NHS board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

10.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations are considered likely to reach the £5 million threshold which warrants full cost impact analysis.

Key recommendations associated with significant material costs are as follows:

10.2.1 MANAGEMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

R **Repeat BMD measurements by DXA after an interval of three years may be considered to assess response to treatment in postmenopausal women on alendronic acid, ibandronic acid, zolendronic acid or denosumab therapy.**

The recommendation that repeat DXA should be considered to assess response to treatment is likely to have resource implications within NHSScotland. Clinical trials indicate that repeat DXA examinations performed at between one and three years after commencing therapy can identify groups of patient who are more or less likely to experience fractures on treatment. The value of this technique in the individual patient is less certain. Therefore the need for repeat DXA should be assessed on a case-by-case basis.

10.2.2 SYSTEMS OF CARE

R **Patients over the age of 50 who have experienced a fragility fracture should be managed within a formal integrated system of care that incorporates a fracture liaison service.**

The most recent national audit of fracture liaison services in Scotland which was conducted in 2009 showed that 77.6% of the Scottish population had access to routine postfracture assessment.[379] In 2011 the National Osteoporosis Society reported that 66% of Community Health and Care Partnerships provided fracture liaison services to people over the age of 50 in Scotland.[380] The audit reported that six NHS boards in Scotland had board-wide access to assessment following fracture, three NHS boards had limited access and five NHS boards had no formal arrangements. Costs of standardising assessment for secondary prevention of fractures for women and men over 50 in Scotland by means of providing access to a fracture liaison service were estimated in 2009 to be £913,000 recurring annually plus £140,000 non-recurring.[379]

An economic evaluation completed by the Department of Health in 2009 reported that the establishment of a fracture liaison service would be associated with savings of £290,708 over a five-year period in NHS acute and community services and local authority social care costs. This was offset against an additional £234,181 revenue cost (falling both in year one and covering drug therapy for five years spent by the NHS on this patient cohort). This is for an annual patient cohort of 797 hip, humerus, spine and forearm fractures, anticipated from a population of 320,000 people. Although there have been changes to staffing, DXA, and drug costs since 2009, the conclusion that co-ordinated service provision may lead to efficiencies is unlikely to be altered. While the economic analysis takes into account the then imminent availability of generic medicines, the cost reduction associated with the move to generic products is underestimated.[381]

10.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- the proportion of patients who are receiving drug treatment for fracture-risk reduction without evidence of a DXA result
- the proportion of patients presenting with risk factors for fragility fractures at primary care who receive formal fracture-risk assessment.

10.4 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

On 4 October 2005 SMC advised that:

alendronate/colecalciferol (Fosavance®) is accepted for use within NHSScotland for the treatment of postmenopausal osteoporosis in patients at risk of vitamin D insufficiency who require treatment with both alendronate and vitamin D and for whom once-weekly administration is appropriate. The combination preparation is cost saving compared to the two drugs administered separately.

Weekly administration of vitamin D represents a departure from routine clinical practice. In patients who also require calcium supplementation this will have to be administered separately, using a calcium preparation that does not also contain vitamin D.

On 22 October 2008 this SMC advice was superseded by NICE MTA 160 and 161.

On 13 December 2010 SMC advised that:

denosumab 60 mg solution for injection in a pre-filled syringe (Prolia®) is accepted for restricted use in NHSScotland for treatment of osteoporosis in postmenopausal women at increased risk of fractures. Denosumab significantly reduces the risk of vertebral, non vertebral and hip fractures.

SMC restriction: use only in patients with a BMD T-score <-2.5 and ≥ -4.0 for whom oral bisphosphonates are unsuitable due to contraindication, intolerance or inability to comply with the special administration instructions.

Treatment with denosumab for three years significantly reduced the incidence of new vertebral, non-vertebral and hip fractures compared with placebo in postmenopausal women at increased risk of fractures.

On 13 December 2010 SMC advised that:

in the absence of a submission from the holder of the marketing authorisation, denosumab 60 mg solution for injection in pre-filled syringe (Prolia®) is not recommended for use in NHSScotland for bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

On 10 October 2014 SMC advised that:

in the absence of a submission from the holder of the marketing authorisation, denosumab 60 mg solution for injection in pre-filled syringe (Prolia®) is not recommended for use in men with osteoporosis at increased risk of fractures. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

On 11 September 2006 SMC advised that:

intravenous ibandronic acid (Bonviva®) is accepted for restricted use within NHSScotland for the treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established.

Intravenous ibandronic acid is restricted to use in patients who are unsuitable for, or unable to tolerate oral treatment options for osteoporosis. Treatment initiation should be under specialist supervision.

On 13 February 2006 SMC advised that:

ibandronic acid (Bonviva®) is accepted for use within NHSScotland for the treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures.

Ibandronic acid 150 mg monthly is superior to daily ibandronic acid in terms of lumbar spine BMD at one year. Compared with placebo, daily administration of ibandronic acid results in a relative risk reduction for vertebral fractures of 62%. Unlike some other bisphosphonates, efficacy in reducing femoral neck fractures (and other non-vertebral fractures) has not been established.

On 9 May 2003 SMC advised that:

risedronate (Actonel®) is recommended for general use within NHSScotland. Risedronate sodium (Actonel®) is a once-weekly formulation which offers a convenient, cost-neutral alternative to once-daily medication for the prophylaxis and treatment of osteoporosis in postmenopausal women.

On 22 October 2008 this SMC advice was superseded by NICE MTA 160 and 161.

On 10 December 2007 SMC advised that:

in the absence of a submission from the holder of the marketing authorisation, risedronate sodium (Actonel®) is not recommended for use within NHSScotland for the treatment of osteoporosis in men at high risk of fractures. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

On 8 Aug 2005 SMC advised that:

Strontium ranelate (Protelos®) is accepted for restricted use within NHSScotland for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures when bisphosphonates are contraindicated or not tolerated and then only in women aged over 75 with a previous fracture and T-score <-2.4 or other women at equivalent high risk.

In the trial population of postmenopausal women, strontium ranelate reduced the risk of developing a vertebral fracture by 41%. In women ≥74 years with a femoral neck BMD T-score <-2.4 the risk of hip fractures was reduced by 36%. However equivalent cost effectiveness to bisphosphonate therapy has not been demonstrated.

On 22 October 2008 this SMC advice was superseded by NICE MTA 160 and 161.

On 8 October 2010 SMC advised that:

in the absence of a submission from the holder of the marketing authorisation, strontium ranelate (Protelos®) is not recommended for use within NHSScotland for treatment of osteoporosis in men at increased risk of fracture. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

On 8 December 2003 SMC advised that:

teriparatide (Forsteo®) is accepted for restricted use within NHSScotland for the treatment of established (severe) osteoporosis in postmenopausal women.

This medicine should be restricted to initiation by specialists experienced in the treatment of osteoporosis following assessment of fracture risk including measurement of BMD. It is the first product to be licensed specifically for established (severe) postmenopausal osteoporosis. It has shown efficacy in reducing vertebral and non-vertebral fractures in postmenopausal women with prior vertebral fractures, particularly in a subgroup with documented severe osteoporosis. At the recommended daily dose it is expensive but appears to be cost effective in women with proven osteoporosis who have developed fractures.

On 22 October 2008 this SMC advice was superseded by NICE MTA 160 and 161.

On 9 June 2008 SMC advised that:

in the absence of a submission from the holder of the marketing authorisation, teriparatide (Forsteo®) is not recommended for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

On 11 August 2008 SMC advised that:

teriparatide (Forsteo®) is not recommended for use within NHSScotland for the treatment of osteoporosis in men at increased risk of fracture. Teriparatide was associated with a greater increase in lumbar spine BMD than placebo. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

On 10 March 2008 SMC advised that:

zoledronic acid 5 mg solution for infusion (Aclasta®) is accepted for restricted use within NHSScotland for treatment of osteoporosis in postmenopausal women at increased risk of fractures.

Intravenous zoledronic acid is restricted to use in patients who are unsuitable for or unable to tolerate oral treatment options for osteoporosis. Treatment initiation should be under specialist supervision. This preparation is licensed for administration once a year and has been shown to reduce the incidence of vertebral and hip fractures over three years compared with placebo.

On 12 January 2009 SMC advised that:

in the absence of a submission from the holder of the marketing authorisation, zoledronic acid 5 mg (Aclasta®) is not recommended for use within NHSScotland for the treatment of osteoporosis in men at increased risk of fracture, including those with a recent low-trauma hip fracture. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

11 The evidence base

11.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2003–2013. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

11.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to management of patients with osteoporosis. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Officer and presented to the guideline development group.

11.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline *(see Annex)*. The following areas for further research have been identified:

- prospective controlled observational studies designed to demonstrate the association between:
  - cystic fibrosis and fracture risk
  - HIV infection and fracture risk
  - dietary calcium consumption and fracture risk
  - dietary fatty acids and fracture risk
  - anticoagulant use and fracture risk
  - antipsychotics use in a non-Parkinsonian population and fracture risk
  - loop diuretic use and fracture risk
  - inhaled glucocorticoid use and fracture risk
- studies designed to demonstrate the effect of protein supplementation or the association between dietary protein intake and fracture risk
- systematic reviews updated to incorporate all relevant evidence for the risk of ONJ and atypical femoral fractures associated with bisphosphonate use
- the optimal interval for repeat DXA measurement to monitor the effectiveness of osteoporosis treatments and the predictive value of these measurements in individual patients
- randomised trials to determine if targeting treatment on the basis of high fracture risk in the absence of DXA is an effective strategy for preventing fractures
- prospective controlled observational studies designed to demonstrate the association between long-term use of DMPA in younger women and later fracture risk
- randomised trials to evaluate the effects of osteoporosis treatments on non-vertebral fractures in patients with GIOP

- a budget impact analysis of the establishment of an integrated fracture liaison system in health boards within NHSScotland where different baseline services are currently being provided
- long-term studies designed to investigate the optimal duration of osteoporosis treatments taking risks and benefits into account
- comparative studies to investigate the efficacy of different osteoporosis treatments and reporting fracture outcomes
- randomised trials to evaluate the effects of osteoporosis treatments on fracture risk in men with osteoporosis.

11.3 REVIEW AND UPDATING

This guideline was issued in 2015 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

12 Development of the guideline

12.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at **www.sign.ac.uk**

12.2 THE GUIDELINE DEVELOPMENT GROUP

Professor Stuart Ralston *(Chair)*	*Arthritis Research UK Professor of Rheumatology, Centre for Genomic and Experimental Medicine, University of Edinburgh, Western General Hospital, Edinburgh*
Ms Moira Bankier	*Patient Representative, Dunblane*
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Dr Moray Nairn	*Programme Manager, SIGN*
Dr Andrew Pearson	*Consultant Radiologist, Borders General Hospital, Melrose*
Mr Craig Ross	*Clinical Specialist Physiotherapist, Physiotherapy Service for Osteoporosis, Glasgow*
Dr David Stephens	*General Practitioner, Loch Ness*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on the contacts page of the SIGN website **www.sign.ac.uk**

Mrs Lesley Forsyth	*Events Co-ordinator*
Mrs Karen Graham	*Patient Involvement Officer*
Ms Karen King	*Distribution and Office Co-ordinator*
Mr Stuart Neville	*Publications Designer*
Miss Gaynor Rattray	*Guideline Co-ordinator*

12.3 ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

Mr Euan Bremner	*Project Officer, SIGN*
Sister Wendy Feeney	*Lead Nurse Specialist in Fracture/Osteoporosis, Coathill Hospital, Coatbridge*
Professor Tracey Howe	*Professor of Rehabilitation Sciences, Glasgow Caledonian University*
Dr Tahir Mahmood CBE	*Consultant Obstetrician and Gynaecologist, Forth Park Hospital, Kirkcaldy*
Miss Jan Manson	*Evidence and Information Scientist, SIGN*

12.4 CONSULTATION AND PEER REVIEW

12.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 8 March 2013 and was attended by 134 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

12.4.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Professor Eamonn Brankin	*Honorary Clinical Associate Professor, University of Glasgow*
Dr Linda Buchanan	*Consultant Endocrinologist, Forth Valley Royal Hospital, Larbert*
Dr Lucy Caird	*Consultant Gynaecologist, Raigmore Hospital, Inverness*
Mr Edward Clifton	*Senior Health Economist, Healthcare Improvement Scotland, Glasgow*
Mr Gary Cook	*Principal Clinical Pharmacist, Ninewells Hospital, Dundee*
Professor Cyrus Cooper	*Director, MRC Lifecourse Epidemiology Unit, University of Southampton*
Dr Alastair Gordon	*Consultant Physician, Borders General Hospital, Melrose*
Dr John Harvie	*Consultant Rheumatologist, Raigmore Hospital, Inverness*
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Dr Robin Munro	*Consultant Rheumatologist, Wishaw General Hospital*
Professor Dawn Skelton	*Professor in Ageing and Health, Glasgow Caledonian University*
Mrs Janet Thomas	*Team Lead Physiotherapist, Queen Margaret Hospital, Dunfermline*
Ms Anne Thurston	*Health Sector Relations Manager, National Osteoporosis Society, Camerton, Bath*
Dr Kate Ward `	*Senior Investigator Scientist, MRC Human Nutrition Research, Cambridge*
Dr Ailsa Welch	*Reader in Nutritional Endocrinology, University of Norwich*

12.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council Membership page of the SIGN website **www.sign.ac.uk**

Mrs Noreen Downes	*Royal Pharmaceutical Society*
Dr Roberta James	*SIGN Programme Lead; co-Editor*
Professor John Kinsella	*Chair of SIGN; co-Editor*
Dr Rajan Madhok	*Royal College of Physicians and Surgeons of Glasgow*
Dr Sara Twaddle	*Director of SIGN; co-Editor*

Abbreviations

AAU	acute anterior uveitis
AD	Alzheimer's disease
ADT	androgen deprivation therapy
AED	antiepileptic drug
AF	atrial fibrillation
AI	aromatase inhibitor
AIDS	acquired immunodeficiency syndrome
ARR	absolute risk reduction
BALP	bone alkaline phosphatase
BMD	bone mineral density
BMF	biomarker feedback
BMI	body mass index
BNF	British National Formulary
BTM	bone turnover markers
CAROC	Canadian Association of Radiologists and Osteoporosis Canada
CCEF	capacitive coupled electrical field
CD	coeliac disease
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CrI	credible interval
CTX	c-telopeptide of type I collagen
CVD	cardiovascular disease
DMPA	depot medroxyprogesterone acetate
DPP-4	dipeptidyl peptidase-4
DVT	deep vein thrombosis
DXA	dual-energy X-ray absorptiometry
ECKO	evaluation of the clinical use of vitamin K supplementation in postmenopausal women with osteopenia trial
EDSS	Expanded Disability Status Scale
eGFR	estimated glomerular filtration rate
EMEA	European Medicines Agency
FIT	Fracture Intervention Trial
FLC	fracture liaison co-ordinator

FLEX	Fracture Intervention Trial Long-term Extension
FN	femoral neck
FREEDOM	Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months
FRISK	the Fracture Risk tool
GFR	glomerular filtration rate
GHQ	General Health Questionnaire
GI	gastrointestinal
GIOP	glucocorticoid-induced osteoporosis
GLOW	Global Longitudinal Study of Osteoporosis in Women
GnRH	gonadotropin-releasing hormone
GP	general practitioner
GPRD	General Practice Research Database
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAART	highly active antiretroviral therapy
HCV	hepatitis C virus
HIP	Hip Intervention Programme
HIV	human immunodeficiency virus
HORIZON-PFT	Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly–Pivotal Fracture Trial
HPT	hyperparathyroidism
HR	hazard ratio
HRT	hormone replacement therapy
HT	horizontal therapy
H_2RA	histamine 2 receptor antagonist
ICER	incremental cost-effectiveness ratio
IFT	interferential therapy
IRR	incidence rate ratio
IU	international unit
IV	intravenous
KP	kyphoplasty
LS	lumbar spine
MET	metformin
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
MORE	Multiple Outcomes of Raloxifene Evaluation
MS	multiple sclerosis
MTA	multiple technology appraisal
MUFA	monounsaturated fatty acid

NHAMCS-OPD	National Hospital Ambulatory Medical Care Survey - Outpatient Departments
NHANES	The National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NOF	National Osteoporosis Foundation
NORA	National Osteoporosis Risk Assessment
NS	not significant
NTX	n-telopeptide of type I collagen
ONJ	osteonecrosis of the jaw
OPRA	the osteoporosis population-based risk assessment trial
OR	odds ratio
OQLQ	Osteoporosis Quality of Life Questionnaire
PBC	primary biliary cirrhosis
PD	Parkinson's disease
PE	pulmonary embolism
PICP	C-terminal propeptide of type I procollagen
PINP	procollagen type 1 amino-terminal propeptide
PPI	proton pump inhibitor
PTH	parathyroid hormone
PUFA	polyunsaturated fatty acids
QALY	quality-adjusted life year
QOL	quality of life
QUALEFFO	Quality Of Life Questionnaire on the European Foundation for Osteoporosis
QUS	quantitative ultrasound
RA	rheumatoid arthritis
RCGP	Royal College of General Practitioners
RCT	randomised controlled trial
RD	risk difference
RLS	records linkage systems
RR	relative risk
SACN	The Scientific Advisory Committee on Nutrition
SIGN	Scottish Intercollegiate Guidelines Network
SD	standard deviation
SE	standard error
SLE	systemic lupus erythematosus
SMC	Scottish Medicines Consortium
SMD	standardised mean difference

SOTI	spinal osteoporosis therapeutic intervention
SSRI	selective serotonin reuptake inhibitor
STRATOS	strontium ranelate for treatment of osteoporosis
TIA	transient ischaemic attack
TROPOS	treatment of peripheral osteoporosis
TZD	thiazolidinedione
US	United States
USA	United States of America
VERT-MN	Vertebral Efficacy with Risedronate Therapy-Multinational
VERT-NA	Vertebral Efficacy with Risedronate Therapy-North America
VKA	vitamin K antagonist
VP	vertebroplasty
VTE	venous thromboembolism
WHI	Women's Health Initiative
WHI CaD	Women's Health Initiative Calcium/Vitamin D Supplementation Study
WHO	World Health Organization
WMD	weighted mean difference

Annex

Key questions used to develop the guideline

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Key question	See guideline section
1. What factors contribute to increased fracture risk/increased number of fractures? *Population:* Adults *Interventions:* • non-modifiable risk (age, gender, ethnicity, reproductive factors, family history) • modifiable risk (weight, smoking, alcohol, physical activity, diet and nutritional status) • comorbidities (anorexia nervosa, chronic liver disease, chronic kidney disease, coeliac disease, depression, diabetes, HIV, immobility, low body weight, neurological disorders, previous fracture, primary hyperparathyroidism, spinal injury) • medications (antipsychotics, aromatase inhibitors, beta blockers, gonadotrophin releasing hormone inhibitors, inhaled/oral glucocorticoids, long-acting progestogen-only contraceptives (DMPA), loop diuretics, proton pump inhibitors, statins, thiazolidinediones) *Comparisons:* reference population *Outcomes:* relative or absolute fracture risk	3.2–3.6
2. Which diagnostic measurements or tools are effective in identifying increased risk of fracture? *Population:* individuals being assessed *Interventions:* biomarkers, Dubbo nomogram, DXA (peripheral or axial), Foundation for Osteoporosis Research and Education 10-year fracture-risk calculator, FRAX, Garvin Institute fracture-risk calculator, Osteoporosis Index of Risk, Osteoporosis Risk Assessment Instrument, Osteoporosis Risk Estimation Score for Men, parathyroid hormone levels, radiographs, QFracture, quantified computed tomography, quantitative ultrasound, RhF levels, simple calculated risk estimation score, Woman's Health Initiative hip fracture-risk calculator *Comparisons:* DXA, age and gender *Outcomes:* diagnostic accuracy of fracture (sensitivity, specificity, positive or negative predictive value)	4.2–4.6

3. Which diagnostic methods or tools best predict response to pharmacological treatment? *Population:* individuals being assessed and subsequently treated *Interventions:* biomarkers, Dubbo nomogram, DXA (peripheral or axial), Foundation for Osteoporosis Research and Education 10-year fracture-risk calculator, FRAX, Garvin Institute fracture-risk calculator, Osteoporosis Index of Risk, Osteoporosis Risk Assessment Instrument, Osteoporosis Risk Estimation Score for Men, parathyroid hormone levels, radiographs, QFracture, quantified computed tomography, quantitative ultrasound, RhF levels, simple calculated risk estimation score, Woman's Health Initiative hip fracture -risk calculator *Comparisons:* DXA, age and gender *Outcomes:* reduction in fracture incidence	5.2–5.5
4. Which pharmacological interventions are effective in fracture prevention? (exclude phase I and II trials and studies of less than one year duration) *Population:* premenopausal women with/without a diagnosis of osteoporosis, postmenopausal women with/without a diagnosis of osteoporosis, all postmenopausal women (uncategorised), men with without a diagnosis of osteoporosis, men and women mixed over the age of 50, men and women on glucocorticoid medication *Interventions:* alendronic acid, calcitonin, calcium and/or vitamin D at pharmacological concentrations, cyclical etidronate, denosumab, HRT, ibandronic acid, parathyroid hormone (PTH 1-84), raloxifene, risedronate, strontium renelate, teriparatide, tibolone, zoledronic acid, other *Comparisons:* no intervention, placebo, calcium and/or vitamin D, other single medications, combinations of medications *Outcomes:* risk of vertebral/hip/other fracture at end of study/one year/three years/five years/10 years, adverse effects, quality of life (QUALEFFO-41, QUALIOST, EQ-SD/SF36), treatment adherence	6.4, 7.3, 7.5
5. For individuals prescribed pharmacological interventions, what is the optimal duration of treatment? *Population:* individuals prescribed medication for fracture prevention *Interventions:* duration of treatment (one year, five years, 10 years, indefinite) *Comparisons:* different duration of treatment *Outcomes:* risk of vertebral/hip/other fracture at end of study/one year/three years/five years/10 years, adverse effects, quality of life (QUALEFFO-41, QUALIOST, EQ-SD/SF36), treatment adherence	6.5, 7.3.7

6. What monitoring should be conducted in individuals taking pharmacological interventions? *Population:* individuals prescribed medication for fracture prevention *Interventions:* assessment/measurement techniques (DXA, biomarkers, other), time to/between monitoring tests *Comparisons:* alternative assessment technique, alternative time to monitoring *Outcomes:* indication of pharmacological efficacy (change in BMD, bone turnover), medication compliance	6.6
7. What interventions are effective in improving concordance with pharmacological interventions for fracture prevention? *Population:* individuals prescribed medication for fracture prevention *Interventions:* drug administration pattern, drug administration route (oral *v* parenteral), follow up (nurse-led clinics, regular review, support groups), patient information *Comparisons:* drug administration (daily *v* non-daily, oral *v* parenteral), no follow up, no patient information *v* written information *v* verbal information *v* teleinformation *Outcomes:* concordance, compliance, patient satisfaction	6.7
8. What exercise interventions are effective in reducing the risk of fracture or improving BMD levels? *Population:* premenopausal women with/without a diagnosis of osteoporosis, postmenopausal women with/without a diagnosis of osteoporosis, all postmenopausal women (uncategorised), men with/without a diagnosis of osteoporosis, men and women mixed over the age of 50, men and women on glucocorticoid medication *Interventions:* static weight-bearing exercise, including single leg standing; dynamic weight-bearing exercise (low force), eg walking and Tai Chi; dynamic weight-bearing exercise (high force), eg jogging, jumping, running, dancing and vibration platform; non-weight-bearing exercise (low force), eg low load, high repetition strength training; non-weight-bearing exercise (high force), eg progressive resisted strength training; combination, more than one of the above exercise types *Comparisons:* no exercise intervention, alternative exercise intervention, non-pharmacological non-exercise-based intervention (eg educational or social programmes) *Outcomes:* risk of vertebral/hip/other fracture at end of study/one year/three years/five years/10 years, percentage change in vertebral/hip/other BMD at end of study/one year/three years/five years/10 years, adverse effects, quality of life (QUALEFFO-41, QUALIOST, EQ-SD/SF36)	6.2, 7.2.1, 7.4

9. What dietary interventions are effective in reducing the risk of fracture or improving BMD levels? *Population:* premenopausal women with/without a diagnosis of osteoporosis, postmenopausal women with/without a diagnosis of osteoporosis, all postmenopausal women (uncategorised), men with/without a diagnosis of osteoporosis, men and women mixed over the age of 50, men and women on glucocorticoid medication *Interventions:* any dietary intervention including, but not limited to, protein including excess, fatty acids, dairy consumption, fruit and vegetable consumption, phytoestrogens, acid balance, alkaline salts (potassium bicarbonate, sodium bicarbonate, potassium citrate), mineral intake* (magnesium, boron, silicon), vitamin intake* (vitamin K_1, vitamin K_2, vitamin C, B vitamins inc folate/riboflavin, vitamin A), calcium and/or vitamin D intake*, salt, caffeine • At non-pharmacological concentration *Comparisons:* placebo, no intervention, comparison intervention *Outcomes:* risk of vertebral/hip/other fracture at end of study/one year/three years/five years/10 years, percentage change in vertebral/hip/other BMD at end of study/one year/three years/five years/10 years, adverse effects, quality of life (QUALEFFO-41, QUALIOST, EQ-SD/SF36)	6.3, 7.2.2
10. What is the clinical and cost effectiveness of integrated models of care (which include assessment, identification, treatment and follow up) compared with stand-alone elements for the primary and secondary prevention of fragility fracture? *Population:* individuals who have suffered a fragility fracture or identified as at increased risk of fracture *Interventions:* nurse-led clinics, structured service delivery models, fracture liaison service, educational materials (eg fracture/osteoporosis guidelines) *Comparisons:* individual osteoporosis services without integration (usual care) *Outcomes:* risk of vertebral/hip/other fracture at end of study/one year/three years/five years/10 years, proportion of patients assessed and treated, adverse effects, incremental cost-effectiveness ratios	8.1–8.3

11. In individuals with vertebral fracture, which interventions reduce pain, reduce deformity and improve outcome? *Population:* individuals with vertebral fracture *Interventions:* vertebroplasty, kyphoplasty, TENS, interventions carried out by physiotherapists, calcitonin, antidepressants, other pain medication *Comparisons:* usual care with no surgical intervention (for vertebroplasty and kyphoplasty), placebo (for pharmacological interventions), no alternative treatment (for physiotherapist interventions or TENS) *Outcomes:* risk of subsequent fracture, short-term pain levels, long-term pain levels, level of deformity (kyphosis, height), increased pain, adverse effects, quality of life (QUALEFFO-41, QUALIOST, EQ-SD/SF36)	7.6

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