Executive Summary

Introduction and scope

1. This document has been prepared with the support of the Societies listed above to provide guidance on prevention and treatment of osteoporosis. This guideline updates that previously developed by the Royal College of Physicians in the light of recent appraisals by the National Institute for Health and Clinical Excellence and the development of fracture risk assessment tools made available through the World Health Organization.

2. The scope of the guideline is to review the assessment and diagnosis of osteoporosis, the therapeutic agents available and the manner in which these can be used to develop management strategies for the prevention of osteoporotic fracture in postmenopausal women and in men aged over 50 years.

3. The guideline has been prepared by a writing group (see page 22) and have been sent out for wider consultation (see Appendix IV).

4. The conclusions and recommendations in the document are systematically graded, according to the quality of information available, to indicate the level of evidence on which recommendations are based. The grading methodology is summarised in the appendix. The recommendations in this report were agreed unanimously by the writing group.

5. This summary outlines:
   • introduction and scope
   • background
   • definition and diagnosis of osteoporosis
   • assessment of fracture risk
   • global strategies for the prevention of osteoporosis
   • supportive measures
   • high risk strategies
   • major pharmacological interventions
   • other pharmacological interventions
   • treatment of osteoporosis in men
   • treatment of fractures
   • case finding
   • recommendations for training
   • recommendations for health authorities and other commissioners of health care
   • recommendations to the Department of Health

6. The aim of the guidelines is not to provide a working document for clinical practice but rather to provide a framework from which local management protocols should be developed.

_The recommendations in the guideline should be used to aid management decisions but do not replace the need for clinical judgement in the care of individual patients in clinical practice._
Background

7. Osteoporosis is described by the World Health Organization as a ‘progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture’.

8. The clinical significance of osteoporosis lies in the fractures that arise. In the UK, osteoporosis results in over 200,000 fractures each year, causing severe pain and disability to individual sufferers at an annual cost to the National Health Service (NHS) of over £1.73 billion. More than one-third of adult women and one in five men will sustain one or more osteoporotic fractures in their lifetime.

9. Common sites of fracture include the vertebral bodies, distal radius, proximal femur and the proximal humerus. Hip fractures alone account for more than 20% of orthopaedic bed occupancy in the UK, and the majority of the direct health service cost of osteoporosis. Approximately 50% of patients suffering a hip fracture can no longer live independently and 20% die within 12 months of the fracture.

10. Fractures in patients over 60 years account for more than 2 million hospital bed days in England. This exceeds the bed occupancy attributable to diabetes, ischaemic heart disease, heart failure or chronic obstructive pulmonary disease.

In Europe, osteoporosis accounts for more disability-adjusted life years lost than many non-communicable diseases including rheumatoid arthritis, Parkinson’s disease, breast cancer and prostate cancer.

11. The ageing of the UK population will give rise to a doubling of the number of osteoporotic fractures over the next 50 years if changes are not made in present practice. The admission rate for hip fractures has increased in England by 2.1% per year since 1999, whilst hospital bed days have increased by 5.9% per year.

12. Fall-related risk factors add significantly to the risk of fracture and often overlap with risk factors for osteoporosis. Identification of elderly subjects at risk of fracture should therefore involve an integrated approach.

Definition and diagnosis of osteoporosis

13. Prospective studies have shown that the risk of fracture increases progressively with decreasing BMD. Systematic review and meta-analysis of observational population-based studies with the use of absorptiometric techniques indicate that the risk of fracture increases approximately twofold for each standard deviation decrease in BMD (evidence level Ia). The predictive value of BMD for hip fracture is at least as good as that of blood pressure for stroke.

14. Osteoporosis is defined operationally on the level of bone mass, measured as BMD. Two thresholds of BMD have been defined by the World Health Organization, on the basis of the relationship of fracture risk to BMD. ‘Osteoporosis’ denotes a value for BMD that is 2.5 standard deviations (SDs) or more below the young adult mean value for women (T-score equal to or less than −2.5 SD). A second, higher threshold more appropriate for epidemiological studies describes ‘low bone mass’ as a T-score that lies between −1 and −2.5 SD. ‘Severe’ or ‘established’ osteoporosis denotes osteoporosis as defined above in the presence of one or more documented fragility fractures.
15. The World Health Organization and the International Osteoporosis Foundation recommend that the reference technology for the diagnosis of osteoporosis is dual energy X-ray absorptiometry (DXA) applied to the femoral neck. The normal reference range in men and women is that derived from the NHANES survey for Caucasian women aged 20-29 years. The writing group endorses these recommendations (Grade C recommendation).

Other sites and validated technologies may be used in clinical practice but it should be recognised that the significance of a given T-score differs between sites and technologies.

16. The same diagnostic cut-off values for BMD can be applied to men since observational studies indicate (evidence level 1a) that the absolute risk of fracture for any given BMD and age is similar in men to that in women (Grade A recommendation).

17. Some guidelines favour the concurrent use of BMD at the proximal femur and at the lumbar spine for patient assessment. Patients are defined as having osteoporosis on the basis of the lower of two T-scores. The prediction of fracture is, however, not improved by the use of multiple sites (evidence level 1a) and selection of patients on the basis of a minimum value from 2 or more tests will increase the number of patients selected. The same result can be achieved by less stringent criteria for the definition of osteoporosis but this would undermine the value of a single diagnostic threshold and the use of multiple sites for diagnosis is not recommended (Grade B recommendation). However, where hip measurement is not possible for technical reasons or in younger postmenopausal women and men in whom the spine is differentially affected, spine BMD measurements may be used.

18. Additional techniques for assessing skeletal status have been less well validated than absorptiometric techniques. The writing group does not recommend the use of other techniques, including quantitative ultrasound and computed tomography for the diagnosis of osteoporosis. This does not preclude the use of these or other validated techniques in risk assessment.

Assessment of fracture risk

19. In addition to its diagnostic use, the assessment of BMD provides information on prognosis i.e. the likelihood of future fractures. The risk of fracture increases approximately twofold for each SD decrease in BMD, but the gradient of risk (RR/SD) varies according to the site and technique used, age and the fracture outcome (evidence level Ia).

20. Techniques of clinical value include single-energy absorptiometry at appendicular sites and DXA at central and appendicular sites. There has been considerable interest in the use of other non-invasive techniques, including quantitative ultrasound methods and computed axial tomography. No one technique subserves all the functions of skeletal assessment (diagnosis, prognosis and monitoring of treatment). For diagnostic purposes alone, DXA at the femoral neck is the preferred site, particularly in elderly individuals, because of its higher predictive value for fracture risk (evidence level Ia). The spine is not a suitable site for diagnosis in the elderly because of the high prevalence of arthrosis and arthritis, but it is the preferred site for assessing response to treatment (Grade B recommendation).

21. The use of BMD alone to assess risk has a high specificity but low sensitivity. The low sensitivity over most assumptions means that most osteoporotic fractures will occur in women who do not have osteoporosis as defined by a T-score ≤-2.5 (evidence level Ia). The working group recommends the use of BMD testing in the context of a case-finding strategy rather than for population screening (Grade B recommendation).
22. The performance characteristics of assessment can, however, be improved by the concurrent consideration of risk factors that operate independently of BMD. Of particular importance is age, which contributes to risk independently of BMD (evidence level Ia).

23. Several additional clinical risk factors have been identified that provide information on fracture risk independently of both age and BMD (evidence level Ia).

(a) Low body mass index (BMI). A low BMI is a significant risk factor for hip fracture, but the value of BMI in predicting other fractures is very much diminished when adjusted for BMD (Grade A recommendation).

(b) A history of a prior fracture at a site characteristic for osteoporosis is an important risk factor for further fracture. Fracture risk is approximately doubled in the presence of a prior fracture, including morphometric vertebral fractures. The increase in risk is even more marked for a vertebral fracture following a previous spine fracture. The risks are in part independent of BMD (Grade A recommendation).

(c) A parental history of hip fracture is a significant risk factor that is largely independent of BMD. (Grade A recommendation).

(d) Smoking is a risk factor that is in part dependent on BMD (Grade A recommendation).

(e) Glucocorticoids are an important cause of osteoporosis and fractures. The fracture risk conferred by the use of glucocorticoids is, however, not solely dependent upon bone loss and BMD independent risks have been identified (Grade A recommendation).

(f) Alcohol. The relationship between alcohol intake and fracture risk is dose-dependent. Where alcohol intake is on average two units or less daily there is no increase in risk. Indeed, some studies suggest that this level of intake may have beneficial effects on BMD. Intakes of 3 or more units daily are associated with a dose-dependent increase in fracture risk (Grade A recommendation).

(g) Rheumatoid arthritis. There are many secondary causes of osteoporosis (e.g. inflammatory bowel disease, endocrine disorders), but in most instances it is uncertain to what extent this is dependent on low BMD or other risk factors such as the use of glucocorticoids. By contrast, rheumatoid arthritis increases fracture risk independently of BMD and the use of glucocorticoids (Grade A recommendation).

24. The consideration of these risk factors improves the sensitivity of testing without sacrificing specificity, and the writing group recommend their inclusion in case finding algorithms (Grade B recommendation). There are many additional risk factors for fracture that act solely by reducing BMD and others that have been less well validated or identify a risk that may not be amenable to particular treatments. Liability to falls is an appropriate example where the risk of fracture is high, but treatment with agents affecting bone metabolism have an uncertain effect on risk. The writing group recommend the identification and validation of additional clinical risk factors as an important area for further research.

25. Biochemical indices of skeletal turnover have the potential of aiding in risk assessment as well as for monitoring of treatment (evidence level Ib). Further research in this field is recommended so that their utility in clinical practice can be evaluated for use in diagnosis, prognosis and monitoring of treatment.

26. The International Osteoporosis Foundation and the World Health Organization recommend that risk of fracture should be expressed as a short-term absolute risk, i.e. probability over a ten year interval. The absolute risk of fracture depends upon age and life expectancy as well as the current relative risk. The period of 10 years covers the likely duration of treatment and the benefits that may continue once treatment is stopped. The writing group endorses these recommendations (Grade C recommendation).
27. Algorithms that integrate the weight of clinical risk factors for fracture risk, with or without information on BMD, have been developed by the WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield using the risk factors given above (section 23). The FRAX® tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture. A major osteoporotic fracture is a clinical spine, hip, forearm or humerus fracture. The tool has been externally validated in independent cohorts (evidence level Ia).

28. The assessment takes no account of prior treatment or of dose-responses for several risk factors. For example, two prior fractures carry a much higher risk than a single prior fracture. Dose-responses are also evident for glucocorticoid use. A prior clinical vertebral fracture carries an approximately two-fold higher risk than other prior fractures. Since it is not possible to model all such scenarios with the FRAX® algorithm, these limitations should temper clinical judgement.

29. Diagnostic assessment of individuals with osteoporosis should include not only the assessment of BMD where indicated (see paras 48–53 below) but also the exclusion of diseases that mimic osteoporosis, elucidation of the cause of the osteoporosis and the management of any associated morbidity. Recommendations (Grade C recommendation) for the routine investigation of patients with osteoporosis are given in the Royal College of Physicians Clinical Guidelines for prevention and treatment of osteoporosis July 2000 and are included in the summary document.

Global strategies for the prevention of osteoporosis

30. Strategies for the prevention or treatment of osteoporosis include population-based strategies and those targeted to people at high risk (‘high-risk strategy’). Potential approaches to decreasing fracture risk for the population include increasing the level of physical activity at all ages, reducing the prevalence of smoking, and increasing dietary calcium intake. These risk factors are associated with osteoporosis and some are also important causes of morbidity and mortality through their effects on other body systems, but there is little evidence (positive or negative) about the effect on fracture risk of interventions aimed at changing these behaviours. The grades of these recommendations are summarised in the following table, which is based on a systematic literature review.

<table>
<thead>
<tr>
<th>Global strategies</th>
<th>Intervention</th>
<th>Effect on outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMD</td>
<td>Spine fracture</td>
</tr>
<tr>
<td>Exercise</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Calcium (± vitamin D) supplements</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Dietary calcium</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Reduced alcohol consumption</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Fall prevention programmes</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Hip protectors</td>
<td></td>
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</tbody>
</table>

31. The writing group makes no recommendations concerning such population-based strategies, for two reasons. First, not all the factors are necessarily causally related to osteoporosis. Second, the uptake and compliance of such strategies have not been adequately assessed, so the value and feasibility of population programmes in osteoporosis prevention or treatment cannot be evaluated. It is recommended that further research be undertaken on the feasibility and impact of population-based strategies.
Supportive measures

32. For high-risk strategies, there is some evidence that bone mass can be modulated by calcium intake or changes in other lifestyle habits before the attainment of skeletal maturity. There is, however, no evidence that attention to such risk factors would have any sustained effect on either peak bone mass or the subsequent risk of fracture. For these reasons, it is recommended that the major thrust of prevention of osteoporosis should be directed towards selective case finding (see sections 48–53 below).

33. Immobilisation is an important cause of bone loss and should wherever possible be avoided. The amount of exercise that is optimal for skeletal health in patients with osteoporosis is not known, but regular weight-bearing exercise forms an integral component of management and should be tailored according to the needs and fitness of the individual patient. Physiotherapy is an important component of rehabilitation after fracture. Increased strength may prevent falls by improving confidence and coordination as well as maintaining bone mass.

34. Modification of factors such as decreased visual acuity, consumption of medication that alters alertness and balance, and home environmental hazards (slippery floors, obstacles, insufficient lighting, and handrails) is important in preventing falls. Although large trials have shown that it is possible to reduce falls, randomised studies have not shown any significant decrease in fracture risk. Some randomised trials have shown that wearing hip protectors can markedly reduce hip fracture risk, particularly in the elderly living in nursing homes. A recent meta-analysis of well conducted randomised controlled trials has, however cast some doubt about the anti-fracture efficacy of this preventive measure.

35. There is a high prevalence of calcium, protein and vitamin D insufficiency in the elderly. Vitamin D supplements can reduce the risk of falling (evidence level Ib). Calcium and vitamin D supplements decrease secondary hyperparathyroidism and reduce the risk of proximal femur fracture in the elderly living in residential care homes (evidence level Ia) and it is recommended that this group, as well as the housebound elderly and those in nursing homes should be supplemented with 800 IU vitamin D and 1.0-1.2 g calcium daily. Daily intakes of 500-1000 mg/day of calcium and 800 IU of vitamin D can be recommended as adjuncts to other treatments in patients with osteoporosis.

36. Sufficient protein intakes are necessary to maintain the function of the musculoskeletal system and they also decrease the complications that occur after an osteoporotic fracture. Correction of poor protein nutrition in patients with a recent hip fracture has been shown to improve the subsequent clinical course by significantly lowering the rate of complications, such as bedsores, severe anaemia, and intercurrent lung or renal infection. The duration of hospital stay of elderly patients with hip fracture can thus be shortened (evidence level Ib).

High risk strategies

37. In the context of high-risk strategies, no distinction is made between prevention and treatment. Recommendations concerning the major interventions for osteoporosis are based on high levels of evidence (evidence level 1a and Ib), and the grade of these recommendations, are summarised in the following table which are based on systematic literature reviews or, where not available, on randomised controlled trials.
### Anti-fracture efficacy of approved treatments for postmenopausal women with osteoporosis when given with calcium and vitamin D

<table>
<thead>
<tr>
<th></th>
<th>Vertebral fracture</th>
<th>Non-vertebral fracture</th>
<th>Hip fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Etidronate</td>
<td>A</td>
<td>B</td>
<td>nae</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>A</td>
<td>A#</td>
<td>nae</td>
</tr>
<tr>
<td>Risedronate</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>A</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>A</td>
<td>B</td>
<td>nae</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>A</td>
<td>nae</td>
<td>nae</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>A</td>
<td>A</td>
<td>A#</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>A</td>
<td>A</td>
<td>nae</td>
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<tr>
<td>Recombinant human PTH (1-84)</td>
<td>A</td>
<td>nae</td>
<td>nae</td>
</tr>
<tr>
<td>HRT</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

nae: not adequately evaluated  
# in subsets of patients only (post-hoc analysis)

**Major pharmacological interventions**

38. Details of the major pharmacological treatments are summarised below:

**Bisphosphonates**  
The bisphosphonates are analogues of inorganic pyrophosphate and inhibit bone resorption.

*Alendronate* is approved for the treatment of postmenopausal osteoporosis (10 mg daily or 70 mg once weekly by mouth) and osteoporosis in men (10 mg daily). It is also approved for the prevention of postmenopausal osteoporosis (5 mg daily) and for prevention and treatment of glucocorticoid-induced osteoporosis (5 mg daily or, in postmenopausal women not receiving hormone replacement therapy 10 mg daily).

In postmenopausal women with osteoporosis alendronate 10 mg daily has been shown to reduce vertebral, non-vertebral and hip fractures. Approval for the 70 mg once weekly formulation was granted on the basis of a bone mineral density bridging study.

Alendronate is contraindicated in the presence of abnormalities of the oesophagus which delay emptying, inability to stand or sit upright for at least 30 minutes and hypocalcaemia. It should be used with caution in patients with other upper gastrointestinal disorders and is not recommended in patients with renal impairment (creatinine clearance <35 ml/min). Side-effects include upper gastrointestinal symptoms, bowel disturbance, headaches and musculoskeletal pain.

Alendronate should be taken after an overnight fast and at least 30 minutes before the first food or drink (other than water) of the day or any other oral medicinal products or supplementation (including calcium). Tablets should be swallowed whole with a glass of plain water (~ 200 ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 30 minutes after taking the tablet.
Ibandronate 150 mg once monthly by mouth or 3 mg as an intravenous injection every 3 months is approved for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. In a dose of 2.5 mg daily by mouth a significant reduction in vertebral fractures was demonstrated. In a post hoc analysis of high risk women (femoral neck BMD T-score below -3.0 SD), a significant reduction in non-vertebral fractures was shown. No data are available for hip fracture. Approval for the oral 150 mg once monthly and 3 mg intravenously every 3 months formulations was granted on the basis of BMD bridging studies.

Ibandronate is contra-indicated in patients with hypocalcaemia. Oral ibandronate should be used with caution with patients with upper gastrointestinal disease. Both oral and intravenous formulations should be used with caution in patients with renal impairment (serum creatinine above 200 µmol/l or a creatinine clearance below 30 ml/min). Side-effects with the oral preparation include upper gastrointestinal side-effects and bowel disturbance. Intravenous administration may be associated with an acute phase reaction, characterised by an influenza-like illness; this generally is short-lived and typically occurs only after the first injection.

Oral ibandronate should be taken after an overnight fast and 1 hour before the first food or drink (other than water) of the day or any other oral medicinal products or supplementation (including calcium). Tablets should be swallowed whole with a glass of plain water (180 to 240 ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 1 hour after taking the tablet.

Risedronate 5 mg daily or 35 mg once weekly by mouth is approved for the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fracture and for the treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. It is also indicated for the treatment of osteoporosis in men at high risk of fractures. Risedronate 5 mg daily is approved for the prevention of glucocorticoid-induced osteoporosis in postmenopausal women.

In postmenopausal women with osteoporosis risedronate 5 mg daily has been shown to reduce vertebral and non-vertebral fractures. In a large population of elderly women, risedronate significantly decreased the risk of hip fractures, an effect that was greater in osteoporotic women. Approval for the 35 mg once weekly formulation was granted on the basis of a BMD bridging study.

Risedronate is contraindicated in the presence of hypocalcaemia, pregnancy and lactation, and severe renal impairment (creatinine clearance <30ml.min). It should be used with caution in patients with upper gastrointestinal disease. Side-effects include upper gastrointestinal symptoms, bowel disturbance, headache and musculoskeletal pain.

Risedronate should be taken after an overnight fast and at least 30 minutes before the first food or drink (other than water) of the day or any other oral medicinal products or supplementation (including calcium). Tablets should be swallowed whole with a glass of plain water (~120 ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 30 minutes after taking the tablet.

Zoledronate 5 mg intravenously once yearly is approved for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. It has been shown to reduce the incidence of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis and to reduce the risk of clinical fracture and attendant mortality when given to patients shortly after their first hip fracture.

Zoledronate is contraindicated in the presence of hypocalcaemia, pregnancy and lactation. It should be used with caution in patients with severe renal impairment (creatinine clearance < 40 ml/min). Side-effects include an acute phase reaction (see above), usually only after the first infusion, and gastrointestinal symptoms. An increase in atrial fibrillation, reported as a serious adverse event, was also seen in the main phase III trial although this finding has not been replicated in other trials involving zoledronate. Zoledronate is given as an intravenous infusion over a minimum period of 15 minutes.
**Strontium ranelate**

Strontium ranelate contains two atoms of strontium linked to ranelic acid. Its mode of action is incompletely understood although it appears to have anti-resorptive properties whilst maintaining bone formation. It is approved for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures at a dose of 2 g daily. It has been shown to reduce the risk of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis over a broad age range, including in women aged over 80 years. In a post hoc analysis of women aged 74 years or older with a femoral neck BMD T-score below -2.4 SD a significant reduction in hip fracture was also shown.

Strontium ranelate should be used with caution in patients with a creatinine clearance below 30 ml/min and in patients with risk factors for venous thromboembolism. Side-effects include diarrhoea, headache, nausea and dermatitis. A small increase in the risk of venous thromboembolism was seen in the phase III trials and, very rarely, hypersensitivity reactions may occur. Strontium ranelate should be taken between meals and at least 2 hours after the last meal. It is usually taken at bedtime.

**Raloxifene**

Raloxifene is a selective oestrogen receptor modulator and inhibits bone resorption. It is approved for the treatment and prevention of osteoporosis in postmenopausal women, at a dose of 60 mg daily. It has been shown to reduce vertebral fracture risk but reduction in non-vertebral and hip fractures has not been demonstrated.

Raloxifene is contraindicated in women with child-bearing potential, a history of venous thromboembolism or unexplained uterine bleeding. Hepatic impairment and severe renal impairment are also contraindications. It should be used with caution in women with a history of stroke or with risk factors for stroke. Side-effects include leg cramps, oedema and vasomotor symptoms. There is a small increase in the risk of venous thromboembolism, mostly within the first few months of treatment and a small increase in the risk of stroke has been reported. In the phase III trials, women treated with raloxifene had a significantly decreased risk of developing breast cancer.

Raloxifene is taken as a single daily dose (60 mg) and may be taken at any time without regard to meals.

**Parathyroid hormone peptides**

Parathyroid hormone (PTH) peptides, when administered intermittently, have anabolic skeletal effects with an increase in bone formation. The effects are most marked in cancellous bone and may differ between cortical sites.

**Teriparatide** (recombinant human PTH 1-34) is approved for treatment of osteoporosis in postmenopausal women and in men at high risk of fracture and is given as a subcutaneous injection in a dose of 20 µg/day. Teriparatide is also approved for the treatment of osteoporosis associated with systemic glucocorticoid therapy in women and men at increased risk of fracture. The duration of treatment is limited to 18 months. It has been shown to reduce vertebral and non-vertebral fractures in postmenopausal women with osteoporosis but no data are available for hip fractures.

Teriparatide is contraindicated in patients with hypercalcaemia, metabolic bone diseases other than osteoporosis, severe renal impairment, prior radiation to the skeleton and malignant disease affecting the skeleton. It should be used with caution in patients with moderate renal impairment. Side effects include headache, nausea, dizziness and postural hypotension.

Teriparatide is given as a subcutaneous injection in a dose of 20 µg/day. The duration of treatment is limited to 18 months.
**Recombinant human PTH (1-84)** is approved for the treatment of osteoporosis in postmenopausal women at high risk of fractures. It has been shown to reduce vertebral fractures in postmenopausal women with osteoporosis but no data are available for non-vertebral and hip fractures.

Recombinant human PTH (1-84) is contraindicated in patients with hypercalcaemia, metabolic bone diseases other than osteoporosis, severe renal or hepatic impairment, prior radiation to the skeleton and malignant disease affecting the skeleton. PTH should be used with caution in patients with previous or active urolithiasis. Hypercalcaemia and/or hypercalciuria develop in approximately 25% of treated patients and serum and urine calcium should be monitored at 1, 3 and 6 months after starting treatment, with adjustment of calcium and vitamin D supplementation ± frequency of PTH administration if required. Other side-effects include nausea and headache.

Recombinant human PTH (1-84) is given as a subcutaneous injection in a dose of 100µg/day. The duration of treatment is limited to 24 months.

**Other pharmacological interventions**

**Calcitonin** is an endogenous polypeptide hormone that inhibits osteoclastic bone resorption. Salmon calcitonin, 200IU daily by intranasal administration, is approved for the treatment of established postmenopausal osteoporosis in order to reduce the risk of vertebral fracture. The approved dose has been shown to reduce vertebral fractures in postmenopausal women with osteoporosis but robust evidence for non-vertebral and hip fracture reduction is lacking. Calcitonin is contraindicated in patients with hypocalcaemia and should not be used in patients with nasal ulceration. The most frequently observed undesirable effects are local reactions such as rhinitis and nasal discomfort.

**Calcitriol** (1,25-dihydroxyvitamin D) is the active form of vitamin D and is approved for the treatment of established postmenopausal osteoporosis in a dose of 0.25µg twice daily. It acts mainly by inhibiting bone resorption. It has been shown to reduce vertebral fracture risk in postmenopausal women with osteoporosis but effects on non-vertebral and hip fractures have not been established. It is contraindicated in patients with hypercalcaemia and because it may cause hypercalcaemia and/or hypercalciuria, serum calcium and creatinine levels should be monitored at 1, 3 and 6 months after starting treatment and at 6 monthly intervals thereafter.

**Etidronate** in the formulation Didronel PMO is approved for treatment of osteoporosis and for prevention in postmenopausal women considered to be at risk. Etidronate is also approved for the prevention and treatment of glucocorticoid-induced osteoporosis in postmenopausal women. Etidronate has been shown to reduce vertebral fractures in postmenopausal women with osteoporosis but no effect on non-vertebral or hip fractures has been shown in randomized controlled trials. Didronel PMO is a long-term cyclical regimen administered in 90-day cycles. Each cycle consists of etidronate 400mg tablets for the first 14 days, followed by Cacit (calcium) 500mg tablets for the remaining 76 days. Its use has largely been supplanted by the newer bisphosphonates.

**Hormone replacement therapy (HRT)** comprises a large number of formulations of oestrogen or oestrogen plus progestagen combinations, some of which are approved for the prevention of osteoporosis in postmenopausal women at high risk of fracture. Conjugated equine oestrogens 0.625 mg daily ±2.5 mg/day of medroxyprogesterone acetate have been shown to reduce vertebral, non-vertebral and hip fractures in postmenopausal women not selected on the basis of low bone density or high fracture risk. Because of the unfavourable risk/benefit balance in older postmenopausal women, the use of HRT for osteoporosis prevention is mostly restricted to younger postmenopausal women who are at high risk of fracture and also have menopausal symptoms.
No trials have been designed and powered to detect differences in the magnitude of fracture reduction between different treatments. Thus the choice of agent is determined by the spectrum of anti-fracture effects across skeletal sites, side effects and cost. The low cost of generic alendronate, which has a broad spectrum of anti-fracture efficacy, makes this the first line treatment in the majority of cases. In women who are intolerant of alendronate or in whom it is contraindicated, other bisphosphonates, strontium ranelate or raloxifene may provide appropriate and cost-effective treatment options. The high cost of parathyroid hormone peptides restricts their use to those at very high risk, particularly for vertebral fractures.

**Treatment of osteoporosis in men**

Treatments have been less extensively evaluated in men with osteoporosis than in women, though there is no evidence that skeletal metabolism in men differs fundamentally from that of women. Alendronate, risedronate and teriparatide are approved for the treatment of osteoporosis in men.

Secondary causes of osteoporosis are commonly found amongst men, so this population requires thorough investigation (**Grade C recommendation**).

Consideration should be given to referring men with osteoporosis to specialist centres, particularly younger men or those with severe disease (**Grade C recommendation**).

**Treatment of fractures**

Collaboration between geriatricians and orthopaedic surgeons, and between the medical and non-medical disciplines concerned, should be encouraged wherever possible (**Grade B recommendation**).

Surgeons and general practitioners should note the relevance of osteoporosis as an underlying condition, and where appropriate institute treatment.

All individuals with fracture should be fully assessed for fall risk factors and appropriate interventions to reduce falls should be undertaken (**Grade C recommendation**). An example of such an integrated care pathway is provided in The Care of Patients with Fragility Fracture, published by the British Orthopaedic Association and the British Geriatrics Society.

General practitioners should be encouraged to follow-up patients to monitor the use of medications that increase the risk of falls and/or fracture, to ensure co-prescription of calcium and vitamin D with bone protective interventions and to encourage adherence to therapy.

**Case finding**

At present there is no universally accepted policy for screening to identify patients with osteoporosis. With the recognition that factors in addition to BMD can improve fracture risk prediction, it is possible that screening strategies might be developed in the future and this is a **recommendation** for further research. In their absence, a case-finding strategy is recommended (**grade C recommendation**) where patients are identified because of a fragility fracture or by the presence of clinical risk factors. The use of risk factors that add information on fracture risk independently of BMD improves the predictive value of the assessment.

Fracture risk should be assessed in postmenopausal women and men aged 50 years or more with the risk factors outlined below where assessment would influence management (**grade C recommendation**).
Clinical risk factors used for the assessment of fracture probability*

- Age
- Sex
- Low body mass index (≤19 kg/m²)
- Previous fragility fracture, particularly of the hip, wrist and spine including morphometric vertebral fracture
- Parental history of hip fracture
- Current glucocorticoid treatment (any dose, by mouth for 3 months or more)
- Current smoking
- Alcohol intake 3 or more units daily
- Secondary causes of osteoporosis including:
  - Rheumatoid arthritis
  - Untreated hypogonadism in men and women
  - Prolonged immobility
  - Organ transplantation
  - Type I diabetes
  - Hyperthyroidism
  - Gastrointestinal disease
  - Chronic liver disease
  - Chronic obstructive pulmonary disease

*Probability based assessment using FRAX®

Falls are an important risk factor for fracture but are not presently accommodated in the FRAX® algorithm

49. The approach recommended for decision making is based on fracture probabilities derived from FRAX® and can be applied to men and women. This approach is underpinned by cost-effectiveness analysis with generic alendronate as the intervention. The assumptions used on cost-effectiveness are conservative and would permit the use of second line intervention in approximately 20% of patients.

50. Women with a prior fragility fracture should be considered for treatment without the need for further assessment, although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women. In men with or without a fragility fracture and in women without a previous fragility fracture, management strategy should be based on the assessment of the ten year probability of a major osteoporotic fracture (clinical spine, hip, forearm or humerus). Men and women with probabilities below the lower assessment threshold can be reassured. Men and women with probabilities above the upper assessment threshold can be considered for treatment. Men and women with probabilities between the upper and lower assessment threshold should be referred for bone mineral density measurements and their fracture probability reassessed. The thresholds are summarised on the next page.
51. The intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture, in line with current clinical practice, and therefore rises with age. The proportion of women potentially eligible for treatment rises from 20% to 40% with age. Fracture probabilities based on FRAX® can be input into the web site of the National Osteoporosis Guideline Group (www.shef.ac.uk/NOGG) to enhance management decisions. Simplified tables are provided in Appendix III of this report.

52. The use of BMD assessments using either strategy saves more resources than the undirected use of treatments. The strategy using the FRAX tool advantages more individuals at high risk, and can be applied to men.

53. The Guideline Group is aware of the view that treatment should not be undertaken in women without recourse to a BMD test except in women with prior fragility fractures. The view arises because of a post-hoc analysis showing reduced efficacy of alendronate in patients with T-scores that exceed -2.5 SD (evidence level 1b). However, several other studies have shown little or no interaction of BMD on effectiveness of several agents, including bisphosphonates, raloxifene and teriparatide (evidence level Ib). Moreover, the clinical risk factors are not totally independent of BMD and, when clinical risk factors alone are used in women aged 70 years or more to select patients at high risk, BMD is approximately 1 SD lower in the high-risk group compared with a low risk group (evidence level Ib). A recent analysis has shown that the efficacy of the bisphosphonate, clodronate, is greater in patients with the higher fracture probabilities identified on the basis of clinical risk factors alone (evidence level Ib).
Recommendations for training

54. Audit of the guidelines of the Royal College of Physicians suggests that implementation of its recommendations for BMD testing and treatment is suboptimal. It is recommended that locally developed guidelines include similar audits of the present guidelines as part of quality assurance.

55. It is recognised that osteoporosis is not subserved by any one specialty. The relevant specialties include rheumatology, orthopaedics, general practice, endocrinology, metabolic medicine, geriatrics, and obstetrics and gynaecology. The problem is compounded by the fact that few specialties dealing with osteoporosis recognise training in osteoporosis and metabolic bone diseases as a component of higher professional training. It is recommended that this be given consideration by the relevant Royal Medical Colleges.

56. The issues associated with osteoporosis are also relevant to several specialties in nursing and other professions allied to medicine. It is recommended that the management of osteoporosis should be a component of training in all the relevant disciplines.

Recommendations for health authorities and other commissioners of health care

57. We recommend that health authorities and other commissioners of healthcare should recognise that fractures due to osteoporosis are a significant public health issue, and ensure that they are dealt with explicitly in their local healthcare programme.

Prevention

58. They should ensure that the local healthcare programme addresses approaches to reducing the prevalence of avoidable risk factors for osteoporosis and fractures related to falls and poor bone health and, in so doing, makes explicit the roles of both the NHS and other agencies.

59. They should ensure that accurate up-to-date information about the effects of pharmacological interventions is widely available to postmenopausal women and their professional advisers so that patients may make an informed decision about their use.

60. They should put arrangements in place so that those at particularly high risk of osteoporotic fractures have the opportunity to receive appropriate investigation (e.g. fracture risk assessment, falls risk assessment, bone density measurement), life style advice (e.g. about diet, exercise, and smoking) and bone protective therapy.

Diagnosis and investigation

61. BMD measurements may be used to evaluate the degree of bone loss, to assess suitability for treatments such as parathyroid hormone peptides and to monitor the effects of treatment. Their optimal use in monitoring response to treatment or as an aid to compliance is uncertain and we recommend this as an area for further research. There is some evidence that consultation with a nurse practitioner 3 months after starting treatment may improve compliance and persistence.

62. They should NOT institute mass population screening of bone density in men or postmenopausal women.
Treatment

63. They should bring together local specialists, generalists and other stakeholders (including patient representatives) to agree local treatment and referral practices for the management of osteoporosis and prevention of fragility fractures. It may be helpful to identify a lead clinician. The recommendations of the group should take account of local resources and relevant cost-effectiveness data. Guidelines should also be consistent with the evidence presented in this document. Once local guidelines have been agreed, they should be widely disseminated to relevant professionals and potential patients, and the necessary service changes made to allow the guidelines to be implemented. Implementation should be audited and appropriate changes in practice should be instituted where standards are not met.

Recommendations to the Department of Health

64. As these guidelines will be adapted for local use, we recommend that criteria for monitoring compliance to the guidelines be developed.

Future policy

65. Several new treatment options are currently being developed. It is recommended that these guidelines are reviewed at an interval of not more than 5 years.

66. We recommend that osteoporotic fracture prevention should be included in the Quality Outcomes Framework.
Appendix I

Grading of recommendations and evidence levels

Levels of evidence for studies of intervention are defined as follows:
Ia from meta-analysis of randomised controlled trials (RCTs)
Ib from at least one RCT
IIa from at least one well designed controlled study without randomisation
IIb from at least one other type of well designed quasi-experimental study
III from well designed non-experimental descriptive studies, eg comparative studies, correlation studies, case-control studies
IV from expert committee reports or opinions and/or clinical experience of authorities

The validity of candidate risk factors is also assessed by an evidence-based approach:
Ia Systematic reviews or meta-analysis of level I studies with a high degree of homogeneity
Ib Systematic reviews or meta-analysis with moderate or poor homogeneity
Ic Level I studies (with appropriate populations and internal controls)
IIa Systematic reviews or meta-analysis of level II studies
IIb Level II studies (inappropriate population or lacking an internal control)
IIIa Systematic reviews or meta-analysis of level III studies
IIIb Case-control studies
IV Evidence from expert committees without explicit critical scientific analysis or that based on physiology, basic research or first principles.

The quality of the guideline recommendations is similarly graded to indicate the levels of evidence on which they are based:
grade A evidence levels Ia and Ib
grade B evidence levels IIa, IIb and III
grade C evidence level IV

Risk factors are also be categorised according to evidence for reversible risk:
grade A Validated by use as inclusion criteria in randomized controlled trials
grade B Do not adversely affect fracture outcomes in randomized controlled trials
grade C Untested or adversely affect intervention outcomes
Appendix II

Resource documents and additional references


British Orthopaedic Association Care of the patient with fragility fracture. September 2007 www.boa.ac.uk


Appendix III
Assessment charts

UK Charts v2
Assessment and treatment charts for the management of osteoporosis.
The most precise estimate of fracture probability is provided by the FRAX® computer model available at www.shef.ac.uk/FRAX. Charts of the FRAX® tool are also available from the same site. These give (a) the range of probabilities according to sex, age, body mass index (BMI) and the number of clinical risk factors (CRFs) and (b) the range of probabilities according to sex, age, BMD and the number of CRFs. The range arises because the weight of the different CRFs varies according their predictive strength. In general, smoking and alcohol are weak risk factors, glucocorticoids and secondary causes of osteoporosis are moderate risk factors, and a prior fracture (in men) and a parental history of hip fracture are strong risk factors. Thus individuals with strong risk factors lie towards the upper estimate of the probability estimate, and vice versa.

The following charts are derived from information on the average ten year probability of a major osteoporotic fracture (clinical spine, hip, forearm or proximal humerus fracture) for sex, age and the number of CRFs. It is assumed that women with a previous fragility fracture may be treated without recourse to a BMD test. It is also assumed that all men and women would not be assessed in the absence of a CRF.

The first set of charts is applicable for assessment without BMD to decide who should have a BMD test. In this instance BMI is used as a surrogate for BMD. The chart is colour coded. Green denotes that an individual’s risk lies below the assessment threshold i.e. neither treatment nor a BMD test is indicated. Red denotes that the fracture probability is consistently above the upper assessment threshold, irrespective of the mix of CRFs, so that treatment can be recommended where clinically appropriate. The intermediate category (orange) denotes that probabilities lie between these limits and that a BMD test can be recommended in order better to characterise risk.

The second set of charts is applicable for assessment with information on BMD (T-score at the femoral neck). The charts give information according to BMD and the number of CRFs. Note that the only secondary cause of osteoporosis that should be used with BMD is rheumatoid arthritis. The charts are derived from the average 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm or proximal humerus fracture).

The charts are colour coded. Green denotes that an individual’s risk lies below the intervention threshold i.e. treatment is not indicated. Red denotes that the fracture probability is consistently above the upper assessment threshold, irrespective of the mix of CRFs, so that treatment can ordinarily be strongly recommended. The intermediate category (orange) denotes that probabilities lie between these limits and that treatment can be recommended in those with the stronger risk factors.
## Assessment without BMD

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- **Green:** Reassure
- **Yellow:** Consider BMD
- **Red:** Consider treatment
## Assessment with BMD

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**Reassure**

**May consider treatment if strong risk factors are present**

**Consider treatment**
Appendix IV

This executive summary was sent to the following organisations as part of the consultation process:

Age Concern England
Arthritis and Musculoskeletal Alliance
Arthritis Research Campaign
Bone Research Society
British Geriatrics Society
British Orthopaedic Association
British Menopause Society
British Society of Gastroenterology
British Society of Rheumatology
British Thoracic Society
European Calcified Tissues Society
European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis
Help the Aged
International Osteoporosis Foundation
International Society of Bone and Mineral Research
Medical Women’s Federation
National Osteoporosis Society
National Rheumatoid Arthritis Society
Osteoporosis 2000
Osteoporosis Dorset
Primary Care Rheumatology Society
Research Institute for Care of the Elderly
Royal College of General Practitioners
Royal College of Nursing
Royal College of Obstetrics and Gynaecology
Royal College of Physicians
Royal Pharmaceutical Company
Society for Endocrinology
Womens’ Health Concern

Appendix V

Acknowledgements

The National Osteoporosis Guideline Group comprised

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Prof David Marsh, Dept of Clinical Orthopaedics, University College London and Royal National Orthopaedic Hospital, Stanmore
Dr EV McCloskey, WHO Collaborating Centre for Metabolic Bone Diseases and Academic Unit of Bone Metabolism, University of Sheffield
Prof DM Reid, Division of Applied Medicine, University of Aberdeen
Dr P Selby, Department of Medicine, Manchester Royal Infirmary
Ms Margery Wilkins, Patient Representative
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