



Contents lists available at [SciVerse ScienceDirect](#)

Maturitas

journal homepage: www.elsevier.com/locate/maturitas



Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013

J. Compston^{i,*}, C. Bowring^j, A. Cooper^c, C. Cooper^{e,f,g}, C. Davies^j, R. Francis^a, J.A. Kanis^h, D. Marsh^k, E.V. McCloskey^d, D.M. Reid^b, P. Selby^l

^a Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

^b School of Medicine and Dentistry, University of Aberdeen, UK

^c Bridge Medical Centre, Crawley, West Sussex, UK

^d Academic Unit of Bone Metabolism and Mellanby Centre for Bone Research, University of Sheffield, UK

^e MRC Lifecourse Epidemiology Unit, University of Southampton, UK

^f NIHR Nutrition Biomedical Research Centre, University Hospitals, Southampton, UK

^g NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, UK

^h WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK

ⁱ University of Cambridge School of Clinical Medicine, UK

^j National Osteoporosis Society, UK

^k Department of Clinical Orthopaedics, University College London, Royal National Orthopaedic Hospital, Stanmore, UK

^l Department of Medicine, Manchester Royal Infirmary, UK

ARTICLE INFO

Article history:

Received 14 May 2013

Received in revised form 22 May 2013

Accepted 24 May 2013

Available online xxx

Keywords:

Osteoporosis

Fracture

FRAX

Guideline

ABSTRACT

Since the launch in 2008 by the National Osteoporosis Guideline Group (NOGG), of guidance for the diagnosis and management of osteoporosis in postmenopausal women and older men in the UK there have been significant advances in risk assessment and treatment. These have been incorporated into an updated version of the guideline, with an additional focus on the management of glucocorticoid-induced osteoporosis, the role of calcium and vitamin D therapy and the benefits and risks of long-term bisphosphonate therapy. The updated guideline is summarised below. The recommendations in the guideline are intended to aid management decisions but do not replace the need for clinical judgement in the care of individuals in clinical practice.

© 2013 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

In 2008 the National Osteoporosis Guideline Group (NOGG), in collaboration with many Societies in the UK, produced guidance for the diagnosis and management of osteoporosis in postmenopausal women and older men in the UK [1,2]. Since that time there has been a number of advances in the field, particularly with respect to glucocorticoid-induced osteoporosis, the role of calcium and vitamin D therapy, and the benefits and risks of long-term bisphosphonate therapy. In addition new pharmacological interventions have been approved for the prevention of glucocorticoid-induced osteoporosis and the management of osteoporosis in postmenopausal women and men at increased risk

of fracture. These advances have been incorporated into an updated version of the guideline, detailed below.

2. Diagnosis of osteoporosis

The diagnosis of osteoporosis relies on the quantitative assessment of bone mineral density (BMD), usually by central dual energy X-ray absorptiometry (DXA). BMD at the femoral neck provides the reference site. It is defined as a value for BMD 2.5 SD or more below the young female adult mean (*T*-score less than or equal to -2.5 SD). Severe osteoporosis (established osteoporosis) describes osteoporosis in the presence of one or more fragility fractures [3].

Diagnostic thresholds differ from intervention thresholds for several reasons. Firstly, the fracture risk varies at different ages, even with the same *T*-score. In addition, other factors determine intervention thresholds including the presence of clinical risk factors (CRFs) and the cost and benefits of treatment.

* Corresponding author. Tel.: +44 1223336840.

E-mail addresses: jec1001@hermes.cam.ac.uk, jec1001@cam.ac.uk (J. Compston).

¹ On behalf of the National Osteoporosis Guideline Group (NOGG).

Table 1
Investigation of osteoporosis.**Routine**

History and physical examination
Blood cell count, sedimentation rate or C-reactive protein, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
Thyroid function tests
Bone densitometry (DXA)

Other procedures, if indicated

Lateral radiographs of lumbar and thoracic spine/DXA-based vertebral imaging
Protein immunoelectrophoresis and urinary Bence-Jones proteins
Serum 25-hydroxyvitamin D and PTH
Serum testosterone, SHBG, FSH, LH (in men)
Serum prolactin
24 h urinary cortisol/dexamethasone suppression test
Endomysial and/or tissue transglutaminase antibodies (coeliac disease)
Isotope bone scan
Markers of bone turnover, when available
Urinary calcium excretion

PTH – parathyroid hormone; SHBG – sex-hormone binding globulin; FSH – follicle stimulating hormone; LH – luteinising hormone.

3. Investigation of osteoporosis

The range of tests will depend on the severity of the disease, age at presentation and the presence or absence of fractures. The aims of the clinical history, physical examination and clinical tests are to:

- exclude diseases that mimic osteoporosis (e.g. osteomalacia, myeloma);
- identify the cause of osteoporosis and contributory factors;
- assess the risk of subsequent fractures;
- select the most appropriate form of treatment;

The procedures that may be relevant to the investigation of osteoporosis are shown in Table 1. Other investigations, for example bone biopsy and genetic testing for osteogenesis imperfecta, are restricted to specialist centres.

4. Clinical risk factors

At present there is no universally accepted policy for population screening in the UK to identify individuals with osteoporosis or those at high risk of fracture. Patients are identified opportunistically using a case finding strategy on the finding of a previous fragility fracture or the presence of significant CRFs [4,5]. Some of these risk factors act independently of BMD to increase fracture risk whereas others increase fracture risk through their association with low BMD (e.g. some of the secondary causes of osteoporosis in Table 2).

Algorithms that integrate the weight of CRFs for fracture risk with or without information on BMD have been developed. The FRAX[®] tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture (clinical spine, hip, forearm or humerus) [4,5]. Probabilities can be computed for several European countries, including the UK.

5. Case finding

5.1. Postmenopausal women and men aged ≥ 50 years

Fracture probability should be assessed in postmenopausal women and in men aged 50 years or more using FRAX, where assessment would influence management.

Table 2
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 three months or more)
Current smoking
Alcohol intake of three 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
Falls^a

^a Not accommodated in the FRAX algorithm.

- Women with a prior fragility fracture should be considered for treatment without the need for further risk assessment although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women.
- In the presence of other CRFs, the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm or humerus) should be determined using FRAX (www.shef.ac.uk/FRAX), using BMD if indicated (see Section 6).

5.2. Individuals treated with oral glucocorticoids

FRAX assumes an average dose of prednisolone (2.5–7.5 mg/day or its equivalent) and may underestimate fracture risk in patients taking higher doses and overestimate risk in those taking lower doses. Using UK data, average adjustments (multiples of FRAX probabilities) over all ages in postmenopausal women and men aged ≥ 50 years have been estimated for doses less than 2.5 mg/day, 2.5–7.5 mg/day and >7.5 mg/day prednisolone or its equivalent [6,7].

When the UK FRAX model is used and the glucocorticoid box is filled, 3 points appear on the NOGG graphs, one for low dose, one for medium dose and one for high dose (as defined above). The assessment thresholds and intervention thresholds are then used in the same way as described below for postmenopausal osteoporosis.

6. Intervention thresholds

The intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture and, therefore rises with age. The proportion of women in the UK potentially eligible for treatment rises from 20% to 40% with age [5].

Probabilities of a major osteoporotic fracture (as well as hip fracture probabilities) can be plotted at the NOGG web site (www.shef.ac.uk/NOGG) available through FRAX (Fig. 1).

The chart is 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, so that treatment can be strongly recommended in most cases. Those with fracture probabilities in the intermediate category (orange) should be considered for BMD assessment using DXA and fracture probability should then be recomputed using FRAX.

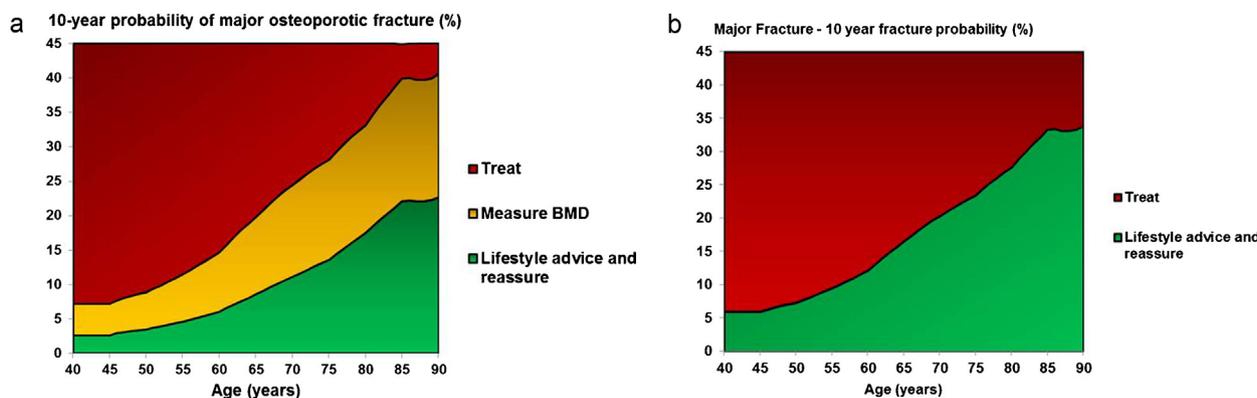


Fig. 1. Assessment and treatment thresholds in the absence of a BMD test (a) and with a BMD test to compute fracture probability (b) for men and women. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

7. Treatment of osteoporosis

General management includes assessment of the risk of falls and their prevention. Maintenance of mobility and correction of nutritional deficiencies, particularly of calcium, vitamin D and protein, should be advised.

7.1. Postmenopausal women and men aged ≥50 years

Major pharmacological interventions are the bisphosphonates, denosumab, parathyroid hormone peptides, raloxifene and strontium ranelate. All these interventions have been shown to reduce the risk of vertebral fracture and some have been shown to also reduce the risk of non-vertebral fractures, in some cases specifically at the hip (see Table 3).

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 individuals who are intolerant of alendronate or in whom it is contraindicated, ibandronate, risedronate, zoledronic acid, denosumab, raloxifene or strontium ranelate may provide appropriate treatment options. The high cost of parathyroid hormone peptides restricts their use to those at very high risk, particularly for vertebral fractures. Other approved pharmacological interventions for postmenopausal women include calcitriol, etidronate and hormone replacement therapy.

Alendronate, risedronate, zoledronic acid, strontium ranelate and teriparatide are approved for treatment of men at increased risk of fracture.

7.2. Individuals taking oral glucocorticoids

Alendronate, etidronate and risedronate are approved for the prevention and treatment of glucocorticoid-induced

osteoporosis in postmenopausal women. Teriparatide and zoledronic acid are approved for treatment of glucocorticoid-induced osteoporosis in men and women at increased risk of fracture. Bone-protective treatment should be started at the onset of glucocorticoid therapy in patients at increased risk of fracture. The low cost of generic formulations of alendronate makes them the first line option in the majority of cases. In individuals who are intolerant of these agents or in whom it is contraindicated, etidronate, risedronate and zoledronic acid are appropriate options. The high cost of teriparatide restricts its use to those at very high risk, particularly for vertebral fractures.

8. Calcium and vitamin D supplementation

Calcium and vitamin D supplementation is widely recommended in older people who are housebound or living in residential or nursing homes, where vitamin D deficiency and low dietary calcium intake are common. Supplementation is also often advocated as an adjunct to other treatments for osteoporosis, as the clinical trials of these agents were performed in patients who were calcium and vitamin D replete. It has been suggested that calcium supplementation may potentially be associated with adverse cardiovascular outcomes [8,9], but these studies have been widely criticised and the putative association requires further clarification [10]. Although a longitudinal cohort study also suggested an increased risk of cardiovascular events with calcium supplementation this was not seen with a high dietary intake of calcium [11]. It may therefore be prudent to increase dietary calcium intake and use vitamin D alone, where the use of calcium and vitamin D supplementation might otherwise be considered [12].

9. Duration and monitoring of therapy

In most patients at increased risk of fracture, treatment needs to be continued long-term. The beneficial effects of treatment with drugs other than bisphosphonates wear off soon after therapy is discontinued, but may be maintained for longer periods of time after cessation of bisphosphonate therapy. This, together with concerns over possible adverse effects of long-term bisphosphonate therapy, particularly osteonecrosis of the jaw and atypical femoral fractures [2], has raised questions over the optimal duration of bisphosphonate treatment and whether, in some individuals, treatment should be discontinued for a period of time (the so-called “drug holiday”).

Based on the data available, it is recommended that treatment review should be performed after 5 years for alendronate, risedronate or ibandronate and after 3 years for zoledronic acid.

Table 3

Effect of major pharmacological interventions on fracture risk when given with calcium and vitamin D in postmenopausal women with osteoporosis.

	Vertebral fracture	Non-vertebral fracture	Hip fracture
Alendronate	A	A	A
Ibandronate	A	A ^a	nae
Risedronate	A	A	A
Zoledronic acid	A	A	A
Denosumab	A	A	A
Raloxifene	A	nae	nae
Strontium ranelate	A	A	A ^a
Teriparatide	A	A	nae
PTH [1–84]	A	nae	nae

PTH – recombinant parathyroid hormone; nae – not adequately evaluated.

^a In subsets of patients (post hoc analysis).

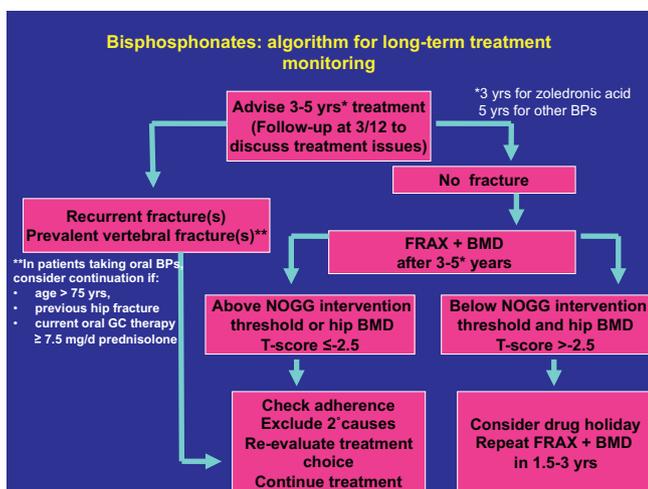


Fig. 2. Algorithm for long-term monitoring of therapy.

9.1. Alendronate, ibandronate and risedronate

Withdrawal of treatment with these bisphosphonates is associated with decreases in bone mineral density (BMD) and bone turnover after 2–3 years for alendronate and 1–2 years for ibandronate and risedronate [13–15]. Continuation of treatment without the need for further assessment can generally be recommended in the following groups:

- High-risk individuals, for example:
 - those aged 75 years or more;
 - those who have previously sustained a hip or vertebral fracture;
 - those who are taking continuous oral glucocorticoids in a dose of ≥ 7.5 mg/d prednisolone or equivalent.
- Individuals who sustain one or more low trauma fractures during treatment, after exclusion of poor adherence to treatment (for example less than 80% of treatment has been taken) and after causes of secondary osteoporosis have been excluded. In such cases the treatment option should be re-evaluated.
- If the total hip or femoral neck BMD T-score is ≤ -2.5 SD, continuation of treatment should generally be advised.

In the above individuals in whom treatment is continued, treatment review should be performed every 5 years, including assessment of renal function.

If treatment is discontinued, fracture risk should be reassessed:

- after a new fracture regardless of when this occurs;
- if no new fracture occurs, after two years.

9.2. Zoledronic acid

When treatment is discontinued after three years of zoledronic acid therapy, the beneficial effects on BMD persist for at least another three years [16]. For the majority of treated individuals, treatment should be stopped after three years and the case for continuation of therapy reviewed three years later. Individuals with a previous vertebral fracture or a pre-treatment hip BMD T-score ≤ -2.5 SD may be at increased risk of vertebral fracture if treatment is stopped.

9.3. Assessment of fracture risk in treated individuals

- Reassessment of fracture risk in treated individuals can be performed using FRAX with femoral neck BMD [17]. The NOGG

intervention thresholds can then be used to guide the decision as to whether treatment can be stopped for a period of time (Fig. 2).

- If biochemical markers of bone turnover indicate relapse from suppressed bone turnover and BMD has decreased following withdrawal, resumption of treatment should be considered.

Contributors

All authors contributed to the revision of the guideline. The paper was drafted by JEC and reviewed by all contributing authors.

Competing interest

All members of NOGG have provided details of potential conflicts of interest to the International Osteoporosis Foundation as follows: Roger Francis: Consultancy fees from Servier, Consilient Health and Amgen/GSK, and lecture fees from Servier, Amgen/GSK, Shire and Eli Lilly. David Reid: lecturer fees and/or consultancy fees for Amgen, Servier and Consilient Health. Alun Cooper: honoraria for Advisory Boards, Research Grants and/or Conference Invitations from Amgen, GSK, MSD, Novartis, Procter & Gamble, ProStrakan, Roche, Servier, and Shire Eugene McCloskey: Consultancy fees from Amgen, Medtronic, Tethys and lecture fees from Amgen, Bayer, GE Lunar, GSK, Hologic, Lilly, Medtronic, Merck, Novartis, Pfizer, Servier, Warner-Chilcott. Research Funding from Amgen, Innovus 3i, Lilly, Novartis, Pfizer Cyrus Cooper: consulting and/or lecture fees from Amgen, GSK, Alliance for Better Bone Health, MSD, Eli Lilly, Pfizer, Novartis, Servier, Medtronic and Roche. John Kanis: consultancy fees from Biointetica, Celtrix, D3A, General Electric, GSK, Hologic, Kissel, Lilly, Medimaps, Merck Research Labs, Pfizer, Roche, Sanofi-Aventis, Servier, UBS, Warner-Chilcott. Juliet Compston: consultancy and/or lecture fees from Novartis, MSD, Amgen, GSK, Servier, Medtronic, and Lilly and grant funding from Nycomed, Sanofi-Aventis, Acuitas, and Warner-Chilcott. Claire Bowring, Cyril Davies and Peter Selby – nothing to declare. David Marsh: consultancy and/or lecture fees from Servier, Lilly, GSK, Olympus, Amgen, Novartis, Synthes, Stryker, Biomet and Medtronic.

Funding

The guideline development process was conducted without financial support from any commercial organisation and the members of the National Osteoporosis Guideline Group have maintained complete editorial independence.

References

- [1] Compston J, Cooper A, Cooper C, et al. Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. *Maturitas* 2009;62:105–8.
- [2] Osteoporosis, Clinical guideline for prevention and treatment, www.shef.ac.uk/NOGG, Updated May 2013.
- [3] Kanis JA, on behalf of the World Health Organization Scientific Group. Assessment of osteoporosis at the primary health-care level. Technical report. University of Sheffield, UK: WHO Collaborating Centre; 2008.
- [4] Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX® and the assessment of fracture probability in men and women from the UK. *Osteoporosis International* 2008;19:385–97.
- [5] Kanis JA, McCloskey EV, Johansson H, et al. Case finding for the management of osteoporosis with FRAX® – assessment and intervention thresholds for the UK. *Osteoporosis International* 2008;19:1395–408.
- [6] Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. *Osteoporosis International* 2011;22:809–16.
- [7] Lekamwasam S, Adachi JD, Agnusdei D, et al. A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. *Osteoporosis International* 2012;23(9):2257–76.
- [8] Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;341:c3691.

- [9] Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 2011;342:d2040.
- [10] Abrahamsen B, Sahota O. Do calcium plus vitamin D supplements increase cardiovascular risk? *BMJ* 2011;342:d2080.
- [11] Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). *Heart* 2012;98:920–5.
- [12] National Osteoporosis Society. Vitamin D and bone health: a practical clinical guideline for patient management; 2013 www.nos.org
- [13] Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-Term Extension (FLEX): a randomized trial. *JAMA: The Journal of the American Medical Association* 2006;296:2927–38.
- [14] Ravn P, Christensen JO, Baumann M, Clemmesen B. Changes in biochemical markers and bone mass after withdrawal of ibandronate treatment: prediction of bone mass changes during treatment. *Bone* 1998;22:559–64.
- [15] Watts NB, Chines A, Olszynski WP, et al. Fracture risk remains reduced one year after discontinuation of risedronate. *Osteoporosis International* 2008;19:365–72.
- [16] Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment in osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *Journal of Bone and Mineral Research* 2012;27:243–54.
- [17] Leslie WD, Lix LM, Johansson H, et al. Does osteoporosis therapy invalidate FRAX for fracture prediction? *Journal of Bone and Mineral Research* 2012;27:1243–51.