County Durham and Darlington
Area Prescribing Committee

Guideline for the management of osteoporosis in primary care

This guideline has been prepared and approved for use within Sub ICB Locality County Durham

This guideline is not exhaustive and does not override the individual responsibility of health professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This guideline should be used in conjunction with the following guidelines:

- NICE TA160
- NICE TA161
- NICE TA204
- NICE TA464
- NICE CG146
- NOGG 2022
- SIGN142

Full details of contra-indications and cautions for individual drugs are available in the BNF or in the Summary of Product Characteristics (available in the Electronic Medicines Compendium) www.emc.medicines.org.uk

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Contents

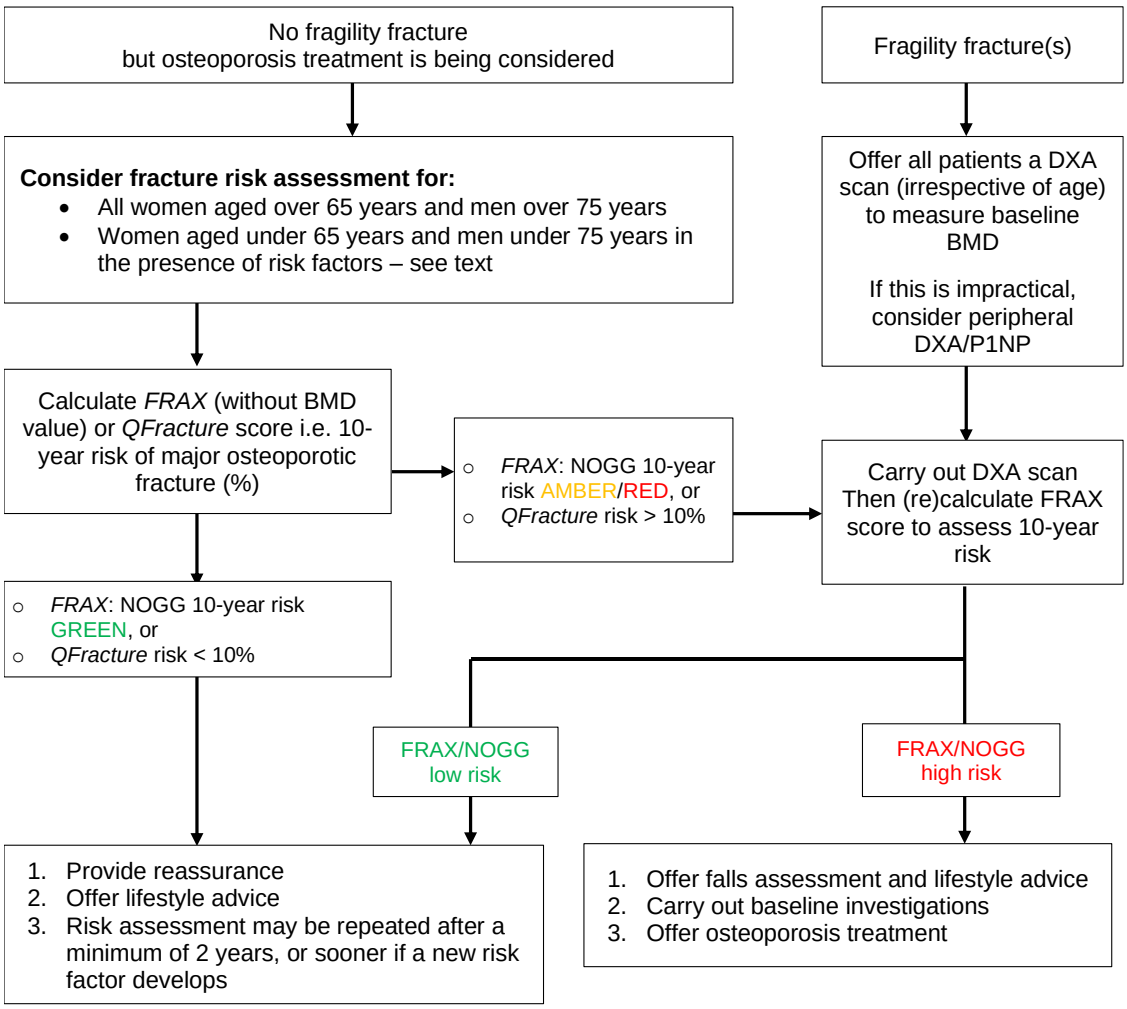
1 Introduction

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporosis leads to nearly 550,000 fragility fractures in the UK each year, costing the NHS in excess of £4.7 billion per year of which more than £1.7 billion to institutional care costs post-fracture. These costs are increasing year on year.
Loss of independence is common following a hip fracture with only 52% living in their own home after 120 days. Most major osteoporotic fractures are associated with reduced relative survival, part causally related and part due to associated co-morbidity (NOGG 2022).

Fragility fractures are often referred to as low-trauma fractures; that is, fractures sustained as the result of a force equivalent to the force of a fall from a height equal to, or less than, that of an ordinary chair. Osteoporotic fragility fractures occur most commonly in the vertebrae, hip and wrist, and are associated with substantial disability, pain and reduced quality of life.

2.1.1 Fracture Risk Assessment algorithm

Do not routinely measure BMD to assess fracture risk without prior assessment using FRAX (without a BMD value) or QFracture, unless the patient has evidence of fragility fracture(s).



Major risk factors:

- Oral corticosteroid treatment for more than 3 months (any dose) or if received 4 or more courses over a 12-month period
- Previous fragility fracture
- Untreated premature menopause at ≤ 45 years

Other risk factors include:

- BMI < 18.5 kg/m^2
- Current or history of smoking
- Alcohol intake ≥ 3 units/day (for both men and women)
- History of (recurrent) falls
- Discordantly low lumbar spine BMD
- Family history of hip fracture
- Secondary osteoporosis including endocrine, gastrointestinal (including coeliac and inflammatory bowel disease), rheumatological, haematological, respiratory, metabolic, chronic renal disease, prolonged immobility, organ transplantation or other iatrogenic causes (including sex hormone deprivation for treatment for breast or prostate cancer such as exemestane, anastrazole or letrozole)

Please note this list is not exhaustive – please see NOGG 2022 for more information.

Patients with osteoporosis and/or a fragility fracture should be investigated for underlying causes; this includes the need for routine blood tests – please see NOGG 2022 for recommended clinical investigations.

2.1.2 Fracture risk assessment

The FRAX tool (freely available at www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture and/or of major osteoporotic fracture. The tool has been externally validated in independent cohorts and can be used for patients between 40-90 years old.
The strength of FRAX is that femoral neck bone mineral density (BMD) measurements can be included in the assessment (not a mandatory field) whereas this is not possible for the QFracture algorithm. FRAX is therefore suitable for evaluating risk where DXA results are available to be taken into account.

The **QFracture** algorithm (freely available at www.qfracture.org/) is based on a UK prospective open cohort study of routinely collected data from general practices that takes into account numerous clinical risk factors and has, therefore, been extensively validated in the UK population, and estimates the 1–10-year cumulative incidence of hip and/or major osteoporotic fracture. It predicts fracture risk over a wider age range (30-84 years), predicts risk in different ethnic groups, provides a more accurate prediction in different groups including the elderly, dose/risk is modelled for alcohol and cigarette consumption, and a longer list of risk factors is included, notably recurrent falls and diabetes. However, it doesn't take DXA readings into account so can only be used as a screening tool pre-DXA, not as an outcome measure to assess patient's response to therapy and suitability for a treatment pause ("drug holiday").

NICE has recommended the use of fracture risk assessment tools (FRAX or QFracture) in the assessment of patients. Since FRAX and QFracture yield different outputs (probability of fracture accounting for mortality risk in the case of FRAX, and a cumulative risk of fracture in the case of QFracture), the two calculators cannot be used interchangeably.

National Osteoporosis Guideline Group (NOGG) intervention thresholds, recommended by NICE Quality Standards, are based on FRAX probability and thus cannot be used with fracture risk derived from QFracture or other calculators.

The estimated absolute risk of fracture in people aged over 80 years should be interpreted with caution, because predicted 10-year fracture risk may underestimate their short-term fracture risk. Patients above the upper age limits defined by these tools are considered to be at high risk.

Risk assessment tools may underestimate fracture risk in certain circumstances, e.g. if a person:

- has a history of multiple fractures
- has had previous vertebral fracture(s)
- has a high alcohol intake
- is taking high-dose oral or high-dose systemic corticosteroids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer)
- has other causes of secondary osteoporosis

In addition, fracture risk can be affected by factors that may not be included in the risk assessment tool, e.g. living in a care home or taking drugs that may impair bone metabolism (such as anti-convulsants, selective serotonin reuptake inhibitors, thiazolidinediones, proton pump inhibitors and anti-retroviral drugs).

2.1.2.1 Patients on corticosteroid treatment

Consider osteoporosis risk assessment prior to initiation of corticosteroid treatment, based on likely duration of therapy and patient's age, using FRAX or QFracture. Risk assessment should also be performed for patients who have been prescribed four or more courses of corticosteroids in a 12-month period, e.g. COPD rescue packs.

Where patients are at increased fracture risk, offer bone protective treatment at the onset of corticosteroid therapy.

Give vitamin D and calcium (see County Durham and Tees Valley formulary choices) while on long-term corticosteroids, regardless of osteoporosis risk.

If corticosteroids are stopped, withdrawal of bone protective therapy may be considered, but if corticosteroids are continued long term, bone protection should usually be maintained.

2.2 Investigations

Diagnostic assessment of individuals with osteoporosis should exclude diseases that mimic osteoporosis, identify the cause(s) of the osteoporosis, and include the management of any associated comorbidity.
Baseline investigations may include FBC, CRP, U&Es, LFTs, γGT, calcium, serum vitamin D, phosphate, TFTs, ESR (to exclude myeloma) and, where a DXA would not be possible, P1NP. TTG may be indicated where there is marked unexplained osteoporosis and/or suspicion of coeliac disease, as well as any other tests to exclude secondary causes of osteoporosis.

For more information, see NOGG 2022.

2.2.1 DXA scan

Ideally, all patients should have a DXA scan before treatment to confirm the diagnosis of osteoporosis and to establish a baseline bone density for measuring treatment effects. Primary care non-medical prescribers may request DXA scans (at CDDFT) as well as GPs. It must be ensured that the results of the DXA scan are sent back to the referrer and that these are actioned as appropriate.
Where a DXA scan is impractical, for instance in very elderly patients, a peripheral DXA or P1NP blood test may be done instead.

However, please note that it is no longer recommended to carry out DXA screening in isolation, i.e. without FRAX/NOGG risk assessment as this may miss other important clinical risk factors for fracture and, on its own, fails to accurately predict fracture risk.

2.2.2 P1NP testing

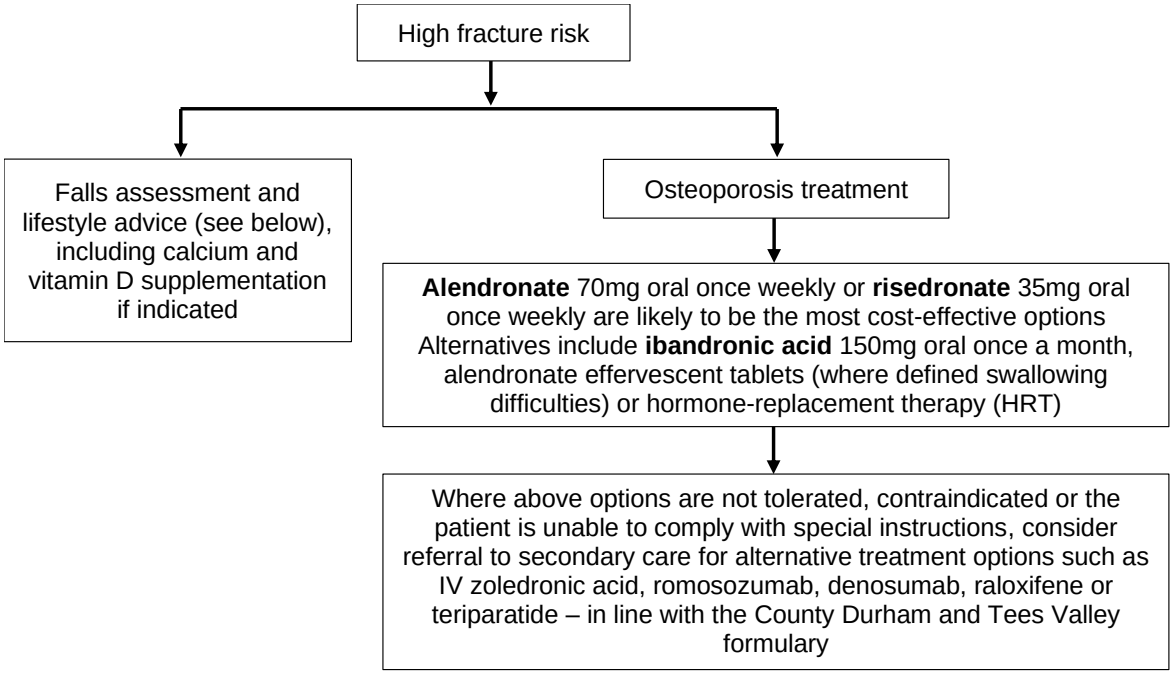
Type 1 collagen is the major collagen in the body and is mainly found in mineralised bone. There is a good correlation between P1NP serum levels and bone density and can be used in the assessment of bone turnover in osteoporosis. Plasma P1NP is increased in states of high bone turnover such as normal growth, healing fractures, Paget's disease, osteoporosis, hyperparathyroidism and hyperthyroidism and can be used to monitor therapy in osteoporosis.
Primary care can now request P1NP tests from CDDFT through ICE.

2.3 Referral to secondary care

Consider requesting secondary care advice for managing complex patients at high risk of fractures. This may include patients requiring IV or subcutaneous treatment, men and pre-menopausal women.
Patient-specific advice will routinely be provided to primary care clinicians where relevant with the patient’s DXA results or on request.

2.4 Initiating treatment

2.4.1 Osteoporosis treatment algorithm



2.4.2 Falls assessment and lifestyle advice

- Adequate nutrition, especially with calcium and vitamin D (see section 2.4.2.1)
- Consider calcium and vitamin D supplementation for at risk patients (see section 2.4.2.1)
- Regular weight bearing exercise
- Avoidance of tobacco use and alcohol

2.4.2.1 Calcium and vitamin D supplementation

Offer calcium and/or vitamin D supplementation as an adjunct to anti-osteoporosis drug treatment, if dietary calcium is low and/or vitamin D insufficiency is a risk, respectively.

Estimate calcium intake and risk calcium deficiency

- Calculate the patient's estimated calcium intake using the Rheumatological Diseases Unit calcium calculator. A National Osteoporosis Society Healthy Bones patient information sheet may also be useful.
- Patients should ensure an intake of at least 700mg calcium/day.
- If their daily intake is less than 700mg/day, they should be advised on eating higher levels of calcium containing foods such as cheese and dairy products, oily fish and green vegetables.
  If an adequate calcium intake cannot be managed by diet, a combined calcium/vitamin D supplement should be sufficient – see County Durham & Tees Valley formulary
- If the patient's calcium intake is adequate, there is no need for supplementation unless there is concern about calcium malabsorption e.g. inflammatory bowel disease, corticosteroid treatment.
- Beware groups at risk of hypercalcaemia e.g. hyperparathyroidism and sarcoidosis, who must not receive calcium supplements.

Estimate risk of vitamin D deficiency

See local guidance on managing vitamin D deficiency and insufficiency.

Examples of groups at risk of vitamin D deficiency are:

- Non-white skin, lack of sunlight exposure (including concealing clothing, medications)
- Vegetarians (in particular non-fish eaters)
- Pregnant and breastfeeding women, babies, children and adolescents
- Older housebound or institutionalised people
- Liver and renal disease
- On medication that blocks the enterohepatic circulation of vitamin D (e.g. colesevelam or colestyramine)

If at risk of insufficiency, colecalciferol 10 microgram (400 units) daily should be recommended if lifestyle/dietary changes are unfeasible. Self-care may be appropriate for most patients.

Please note that low vitamin D levels attenuate the effectiveness of bisphosphonate treatment.

Vitamin D deficiency and insufficiency should be treated *prior* to initiation of parenteral anti-osteoporosis drug treatment, and *alongside* initiation of oral anti-osteoporosis drug treatment.

2.4.3 Osteoporosis treatment options for primary care

Clinicians should make every effort to share their decision-making with the patient, incorporating the patient's values and preferences as well as the best medical evidence. It may be appropriate to consider life expectancy of patient and other co-morbidities with their 10-year risk of fracture.

2.4.3.1 Oral bisphosphonates

Licensing status of bisphosphonates

For the prevention of osteoporosis, only risedronate 35mg once weekly is licensed. Alendronate 10mg daily is licensed for prophylaxis of glucocorticoid-induced osteoporosis. Alendronate 70mg once weekly, ibandronic acid 150mg oral once monthly and zoledronic acid 5mg IV annually* are licensed for the treatment of osteoporosis.
For more detail on prescribing indications, cautions, contraindications, side effects, interactions, patient advice and monitoring requirements, please see the electronic Medicines Compendium or BNF for drug class and under individual drugs.

Despite the above licensing statuses, NOGG 2022 recommends oral bisphosphonates (alendronate or risedronate) or intravenous zoledronate* as the most cost-effective options:

- Alendronate 70mg weekly for the *treatment* of osteoporosis in women with postmenopausal osteoporosis (PMO), men with osteoporosis, glucocorticoid-induced osteoporosis (GIO), and the *prevention* of PMO and GIO
- Risedronate 35 mg once weekly by mouth is recommended for the *treatment* of PMO, men with osteoporosis, GIO and the *prevention* of GIO in women

- Zoledronate 5mg once yearly by intravenous infusion* is recommended for the *treatment* of PMO, men with osteoporosis and men and postmenopausal women with GIO

*NB Red on CD&TV formulary, therefore requires referral to secondary care

Safety of bisphosphonates

- MHRA Alert 2014 regarding risk oesophageal reactions including oesophagitis, oesophageal ulcers, strictures or erosions
- MHRA Alert 2009 regarding risk osteonecrosis of the jaw
- MHRA Alert 2011 regarding risk atypical femoral fractures
- MHRA Alert 2015 regarding rare reports of osteonecrosis of the external auditory canal

During bisphosphonate treatment, encourage all patients to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling. For additional guidance, please refer to NOGG 2022.
During bisphosphonate therapy, advise patients to report any unexplained thigh, groin or hip pain and if such symptoms develop, the femur should be imaged (by full length femur X-ray, isotope scanning or MRI).

2.4.3.2 Denosumab – specialist initiation

Denosumab (Prolia®) 6-monthly subcutaneous injections are approved for the *treatment* of PMO, men at increased fracture risk, *treatment* of bone loss associated with hormone ablation in men with prostate cancer at increased fracture risk, and GIO.

Denosumab is contraindicated in hypocalcaemia, therefore calcium levels must be corrected prior to treatment by adequate intake of calcium and vitamin D before initiating therapy – see section 2.5.

Before starting denosumab, it must be ensured that a long-term personalised osteoporosis management plan is in place and that both the patient and the primary care practitioner are made aware that denosumab treatment should not be stopped or delayed without discussion with a specialist**.**

For further cautions, contraindications, side effects, interactions and patient advice, please see the electronic Medicines Compendium or British National Formulary.

For more information on denosumab (Prolia®) prescribing and monitoring, see Appendix 2.

Safety of denosumab

- MHRA Alert 2015 regarding risk osteonecrosis of the jaw
- MHRA Alert 2014 regarding risk atypical femoral fractures
- MHRA Alert 2017 regarding osteonecrosis of the external auditory canal
- MHRA Alert 2022 regarding the use of denosumab in patients under the age of 18
- MHRA Advice 2014 regarding monitoring recommendations

During denosumab treatment, encourage all patients to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling.
During denosumab therapy, advise patients to report any unexplained thigh, groin or hip pain and if such symptoms develop, the femur should be imaged (by full length femur X-ray, isotope scanning or MRI).

2.4.3.3 Raloxifene – specialist initiation

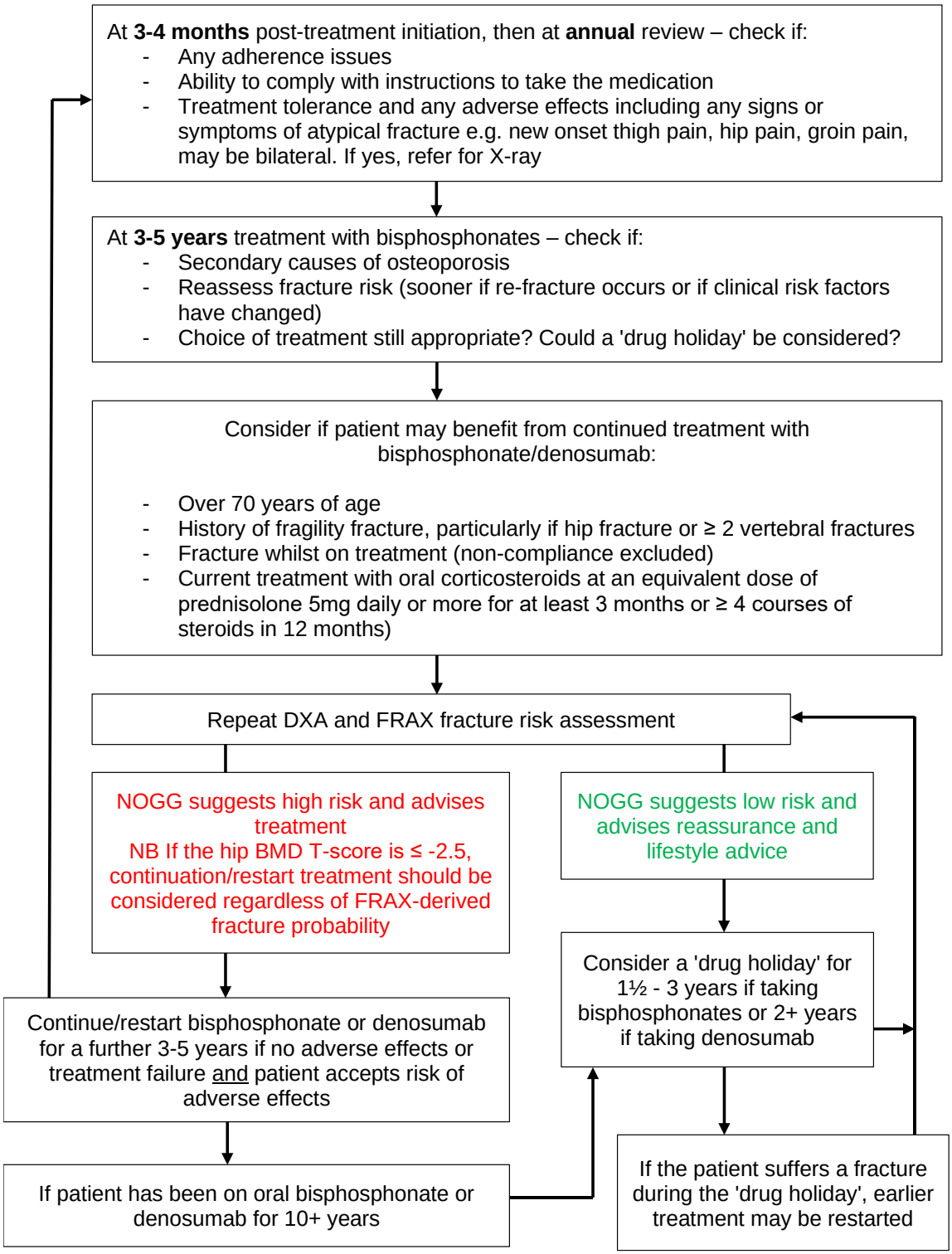
NICE TA160 recommends that raloxifene should not be used for the primary prevention of osteoporotic fragility fractures in postmenopausal women but may be used as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

For cautions, contraindications, side effects, interactions, patient advice and monitoring requirements, please see the electronic Medicines Compendium or British National Formulary.

2.4.3.4 Hormone Replacement Therapy (HRT)

HRT comprises a large number of oestrogen formulations or oestrogen plus progestogen combinations, some of which are approved for the prevention of osteoporosis in postmenopausal women at risk of fragility fracture.
Because of the unfavourable risk/benefit balance in older postmenopausal women, the use of HRT for osteoporosis is generally restricted to younger postmenopausal women (age ≤ 60 years) who are at high risk of fracture and also have menopausal symptoms and who have low baseline risk for adverse malignant and thromboembolic events. Discuss continued use of HRT after the age of 60 years with the patient, with treatment based on an individual risk-benefit analysis.

2.5 Treatment review, including calcium and vitamin D intake


At 3-4 months post-treatment initiation, then at annual review – check if:
- Any adherence issues
- Ability to comply with instructions to take the medication
- Treatment tolerance and any adverse effects including any signs or symptoms of atypical fracture e.g. new onset thigh pain, hip pain, groin pain, may be bilateral. If yes, refer for X-ray
At 3-5 years treatment with bisphosphonates – check if:
- Secondary causes of osteoporosis
- Reassess fracture risk (sooner if re-fracture occurs or if clinical risk factors have changed)
- Choice of treatment still appropriate? Could a 'drug holiday' be considered?
Consider if patient may benefit from continued treatment with bisphosphonate/denosumab:
- Over 70 years of age
- History of fragility fracture, particularly if hip fracture or ≥ 2 vertebral fractures
- Fracture whilst on treatment (non-compliance excluded)
- Current treatment with oral corticosteroids at an equivalent dose of prednisolone 5mg daily or more for at least 3 months or ≥ 4 courses of steroids in 12 months)
Repeat DXA and FRAX fracture risk assessment
NOGG suggests high risk and advises treatment
NB If the hip BMD T-score is ≤ -2.5, continuation/restart treatment should be considered regardless of FRAX-derived fracture probability
NOGG suggests low risk and advises reassurance and lifestyle advice
Consider a 'drug holiday' for 1½ - 3 years if taking bisphosphonates or 2+ years if taking denosumab
Continue/restart bisphosphonate or denosumab for a further 3-5 years if no adverse effects or treatment failure and patient accepts risk of adverse effects
If patient has been on oral bisphosphonate or denosumab for 10+ years
If the patient suffers a fracture during the 'drug holiday', earlier treatment may be restarted

2.5.1 Treatment review of patients taking bisphosphonates, denosumab or raloxifene

Good practice recommends that patients' treatment acceptability, adherence and any side effects are reviewed after around 3-4 months, then annually (or sooner if indicated).

Treatment benefits should be reviewed after a maximum of 5 years. Once a patient has been taking oral bisphosphonates or denosumab therapy for 3-5 years, the majority of the fracture risk reduction benefit has already accrued and the risk of atypical fractures and other long-term complications of therapy begins to increase. The risk-benefit balance of therapy therefore becomes less favourable and a treatment pause ("drug holiday") should be considered where appropriate.

At annual and 3-5 year review, the following should be discussed:

- Adherence with therapy
- Treatment tolerability and any complications, including atypical fractures
- Eligibility for continued treatment

<u>Continuing treatment with a bisphosphonate or denosumab after 5 years for people at continued high risk of a fragility fracture</u>

NOGG 2022 recommends bisphosphonate treatment for up to a total of ten years in the following high-risk patients:

- Age > 70 years at the time the bisphosphonate was started
- Previous history of hip or vertebral fractures
- Taking oral corticosteroids ≥ 5mg prednisolone/day or equivalent
- One or more low impact trauma fracture(s) during treatment (exclude poor adherence and secondary osteoporosis causes)
- DXA scan post-treatment hip BMD T-score ≤ -2.5

There is currently no evidence to support continued prescribing beyond 10 years of continued treatment. All patients on bisphosphonate treatment for ≥ 10 years should be reviewed for the continued need for treatment on an individual basis.

<u>Stopping treatment</u>

Review whether the treatment can be stopped, either completely or for a treatment pause, at the following intervals:

- Five years for alendronic acid, risedronate sodium, and ibandronic acid
- Five years for denosumab

If the patient has two or more comorbidities (NICE NG56 and PrescQIPP Bulletin 231) or if a fracture occurs during treatment, this review should be brought forward to a maximum of 3 years.

When the decision to stop therapy has been made, bisphosphonates can be stopped immediately without the need to taper treatment because of their lasting therapeutic effects after treatment is stopped.

Denosumab **should not** be stopped without considering alternative treatment, e.g. bisphosphonates, in order to prevent rapid BMD loss and a potential rebound in vertebral fracture risk.

Patients should continue taking calcium and vitamin D supplementation while their osteoporosis treatment has been (temporarily) discontinued e.g. during a treatment pause.

Reassessment of the patient's bone health following temporary treatment discontinuation/ pause or permanent discontinuation

During a treatment pause, assess the need for recommencing the bisphosphonate at the end of the following intervals or sooner if there is a new fracture (DXA scan and fracture risk reassessment):

- 18 months for risedronate sodium or ibandronic acid
- 24 months for alendronic acid
- 18 months for denosumab

It is recommended leave a period of at least 18 months between DXA scans to ensure that small changes are attributable to discontinuation of drug treatment and not technical or natural variations.

If biochemical markers of bone turnover (e.g. P1NP) indicate relapse from suppressed bone turnover and BMD has decreased following withdrawal, resumption of treatment should be considered.

Some patients may have stable BMD and/or ongoing suppression of bone turnover well beyond two years; it is appropriate for these patients to remain off therapy with ongoing monitoring.

Discontinuation of denosumab leads to rapid reductions in BMD and elevations in bone turnover to levels above those seen before treatment initiation and patients who discontinue denosumab have an increased risk of sustaining multiple vertebral fractures.

Restarting treatment after a treatment pause

The evidence is limited as to how long the effects of bisphosphonates continue and what the optimal period of time before treatment may be restarted is.

If there are signs of deteriorating bone health on the DXA scan, then a further risk assessment using FRAX should be undertaken to decide whether it is appropriate to restart therapy for a further 5 years. The Osteoporosis Treatment algorithm (see section 2.4.1) should be followed again to guide choice of treatment.

3. References and resources

1. NICE CG146: Osteoporosis – assessing the risk of fragility fracture (2017)
2. NICE TA160: Raloxifene for the primary prevention of osteoporotic fragility fractures in postmenopausal women (2018) – under review
3. NICE TA161: Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (2018) – under review
4. NICE TA204: Denosumab for the prevention of osteoporotic fractures in postmenopausal women (2010) – under review
5. NICE TA464: Bisphosphonates for treating osteoporosis (2019)
6. NICE QS149: Osteoporosis (2017)
7. National Osteoporosis Guidelines Group: Clinical guideline for the prevention and treatment of osteoporosis (2021): NOGG 2022
8. Reid DM et al (2008). Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. Cancer Treat Rev. 2008;34 Suppl 1:S3-18 [online]. Available from https://strwebprdmedia.blob.core.windows.net/media/uuunj31y/management-of-breast-cancer-treatment-induced-bone-loss.pdf [25/04/2022.
9. Scottish Intercollegiate Guidelines Network SIGN142: Management of osteoporosis and the prevention of fragility fractures (2020)
10. PrescQIPP Bulletin 231: Bisphosphonate treatment for osteoporosis (2019)
11. Specialist Pharmacy Service: NICE Bites no. 100a: Osteoporosis – assessing the risk of fragility fracture NICE CG146 (2018)
12. Collier JD, Ninkovic M, Compston JE (2002). Guidelines on the management of osteoporosis associated with chronic liver disease. Gut 2002; 50 (Suppl I): i1–i9 [online]. Available from <https://www.bsg.org.uk/wp-content/uploads/2019/12/BSG-guidelines-on-the-management-of-osteoporosis-associated-with-chronic-liver-disease.pdf> [22/04/2022].

Appendix 1 – Glossary

BMD	Bone Mineral Density
BMI	Body Mass Index
BNF	British National Formulary
CRP	C reactive protein
DXA	Dual energy X-ray Absorptiometry
ESR	Erythrocyte sedimentation rate
FBC	Full blood count
ɣGT	ɣ glutamyl transferase
GFR	Glomerular filtration rate
GIO	Glucocorticoid-induced osteoporosis
HRT	Hormone-replacement therapy
LFTs	Liver function tests
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NICE	National Institute for health and Care Excellence
NOGG	National Osteoporosis Guidelines Group
PMO	Osteoporosis in post-menopausal women
P1NP	Type I Procollagen N-terminal Peptide
SIGN	Scottish Intercollegiate Guidance Network
TFTs	Thyroid function tests
TTG	Tissue transglutaminase
U&Es	Urea and electrolytes

Appendix 2 – Denosumab (Prolia®) prescribing and monitoring guidance

General information

Denosumab is licensed for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures.

The recommended dose of denosumab is 60mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.

No dose adjustment is required in elderly patients or patients with mild to moderate renal impairment (see below for recommendations relating to monitoring of calcium).
No data is available in patients with long-term systemic glucocorticoid therapy and severe renal impairment (eGFR < 30 mL/min). The safety and efficacy of denosumab have not been studied in patients with hepatic impairment

The patient must have been supplied with the contact details for the initiating specialist team (e.g. Rheumatology Department or secondary care physician with special interest in metabolic bone disease) and a patient information leaflet.

Precautions for use

Patients must be adequately supplemented with calcium and vitamin D.

Additional risk factors for hypocalcaemia:

- untreated vitamin D deficiency
- severe renal impairment and dialysis
- concomitant glucocorticoid treatment

All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.

The Prolia® needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Treatment with denosumab should not be stopped without specialist review due to developing an increased risk of multiple vertebral fractures (MHRA Drug Safety Update August 2020).

Monitoring

The following blood tests should be carried out prior to *each dose* (i.e. every six months):

- serum calcium and adjusted calcium levels (should be normal)
- vitamin D levels (should be > 50 nmol/L)
- U&Es
- Patient assessment with regards to tolerability (any issues with last dose?) and any emerging safety issues such as:
    - symptomatic hypocalcaemia (see MHRA Drug Safety Update 2014)
    - skin infections
    - osteonecrosis of the jaw (see MHRA Drug Safety Update 2015)
    - osteonecrosis of the external auditory canal (see MHRA Drug Safety Update 2017)
    - atypical fractures of the femur (see MHRA Drug Safety Update 2013)

  Please see the Summary of Product Characteristics for more information on potential side effects.
- Provide routine counselling incl. good oral hygiene and regular dental check-ups
- The patient should also be reminded to maintain their calcium and vitamin D supplementation throughout treatment with denosumab

Ideally, the blood tests should be done two weeks prior to the next dose but tests within 3 months may be acceptable.
Please contact the initiating specialist team (e.g. Rheumatology Department) if any of these are out of range, or if the prescriber has any questions.

If the patient has renal impairment (eGFR < 30/min), then serum calcium also needs to be measured 1-2 weeks post-dose. Also monitor calcium levels if the patient presents with symptoms indicative of hypocalcaemia.

Repeat DXA scan at 3-5 years (as indicated by specialist) and copy the results to the initiating specialist team for review.

Treatment duration and next steps

The MHRA advise that the optimal duration of denosumab treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically (normally after 3-5 years) based on the expected benefits and potential risks of denosumab on an individual patient basis (MHRA Drug Safety Update August 2020) and, in some cases, treatment may be continued for up to 10 years.

Re-referral to secondary care

While the patient is receiving their denosumab doses and monitoring in primary care, the patient may not always require ongoing regular reviews by secondary care although specifics will be set out by the referring specialist. At any point, the GP may contact the referring specialist for advice or refer into secondary care for an unplanned review.

In order to reduce the risk of rebound bone loss and fracture, it is essential that the patient is reviewed by a specialist clinician prior to stopping denosumab so that treatment cessation and alternative treatment initiation (if any) can be planned.