North of Tyne & Gateshead
Guideline for the management of osteoporosis in primary care and review of patients taking bisphosphonates for 5 years

Endorsed for use within North Tyneside, Northumberland, Newcastle and Gateshead by the North of Tyne and Gateshead Area Prescribing Committee	
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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

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

Introduction

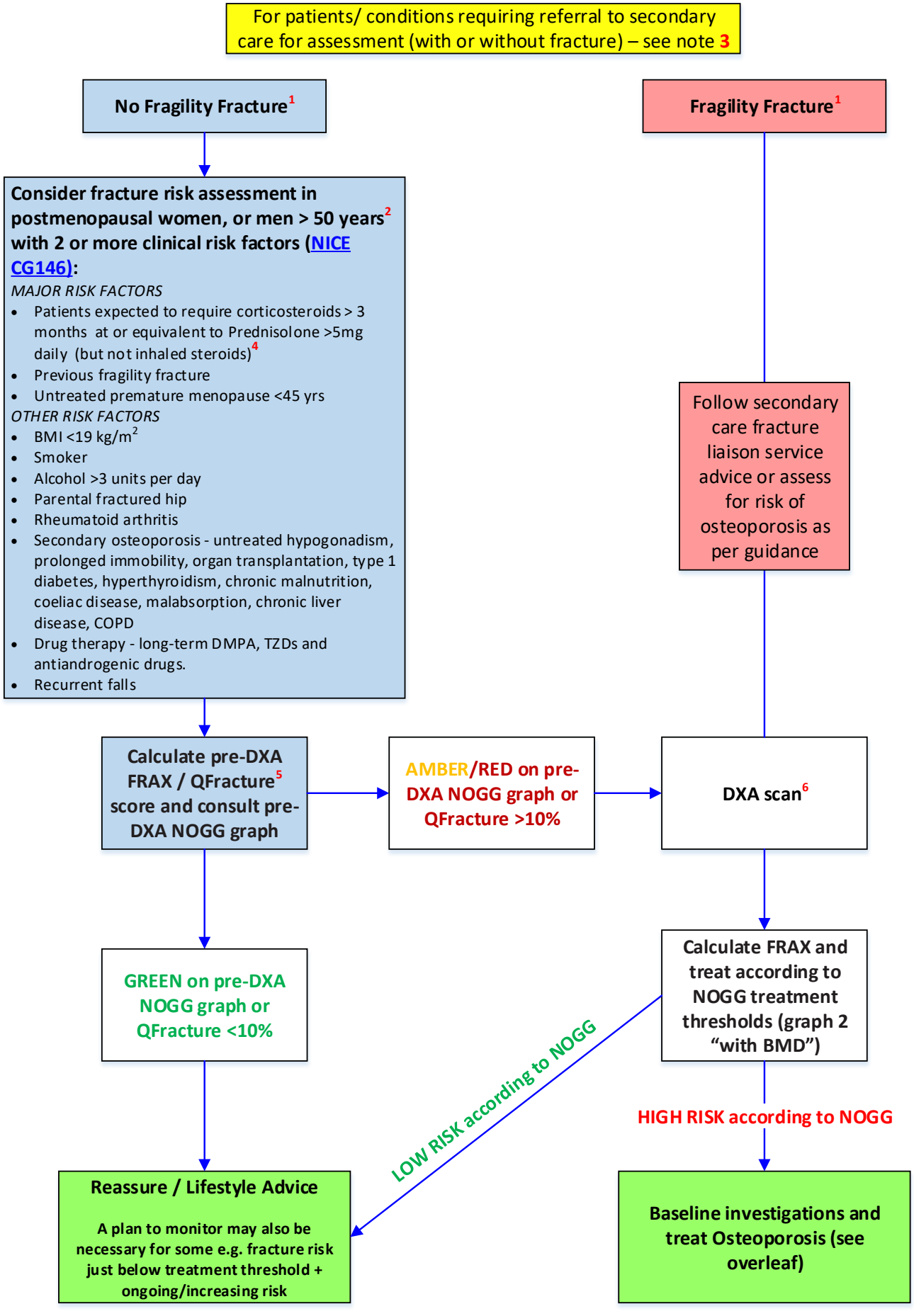
This guideline has been produced to advise primary care clinicians on the management of osteoporosis and of those at risk of osteoporosis.

NICE's 2012 clinical guideline (NICE CG146) made specific recommendations as to who should have their fracture risk assessed and advised that this should be done using a validated tool such as FRAX. In so doing it created a conflict with it's 2011 technology appraisal guidance (NICE TA160/161) which had advised a much more cumbersome approach to treatment thresholds. Subsequent clinical guidelines such as SIGN 142 (March 2015) and NOGG (revised 2017) have suggested more practical treatment thresholds, but ones that had not been rigorously cost-assessed.

In it's recent technology reappraisal of bisphosphonates (NICE TA464, August 2017) NICE explains that because of price reductions in this group of drugs it can no longer detect a treatment threshold below which they are not cost effective. This updates their TA guidance and brings it in line with the clinical guideline, abolishing the previous cumbersome treatment thresholds suggested in 2011. In so doing NICE has endorsed treatment thresholds set out in more recent guidelines as cost-effective, and has tacitly suggested that the (NICE- accredited) 2017 NOGG guideline thresholds provide a reasonable basis for treatment in clinical practice.

The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient. Fracture risk assessment including DXA may still help patients decide whether or not they wish to take up the offer of treatment. **In this guideline therefore we suggest using the National Osteoporosis Guideline Group graphs to guide shared decisions about treatment with the patient.**

FRACTURE RISK ASSESSEMENT/ OSTEOPOROSIS TREATMENT THRESHOLD ALGORITHM



NOGG is available at www.shef.ac.uk/NOGG/manual_data_entry.html

ADDITIONAL INFORMATION FOR TREATMENT THRESHOLD ALGORITHM

The most important risk factors for osteoporosis are advanced age (in both men and women) and female sex. Because of increased bone loss after the menopause in women, and age-related bone loss in both women and men, the prevalence of osteoporosis increases markedly with age, from 2% at 50 years to more than 25% at 80 years in women. As the longevity of the population increases, so will the incidence of osteoporosis and fragility fracture.

1. **Fragility Fracture** is defined as a fracture caused by falling from standing height or lower at walking speed or slower. It also includes vertebral and hip fracture even if there is no history of trauma. Fractures of the skull, facial bones, or digits are not included. The terms low trauma fracture and osteoporotic fracture have an identical meaning for the purpose of this guidance.

2. **Do not routinely assess fracture risk in patients <50 years unless major risk factors are present** (see flowchart). Refer to secondary care (either for advice and guidance or clinic appointment) if patients under 50 years old are identified.

3. **The following patients/ conditions may require referral to secondary care for assessment (with or without fracture) either for advice and guidance or clinic appointment**
   - Refer (either for advice and guidance or clinic appointment):
     - men under 50 years with osteoporosis
     - patients with anorexia nervosa at significant risk of osteoporosis
   - Consider referral for:
     - patients failing to respond to oral therapies, i.e. continuing to fracture despite the patient being compliant with therapy for 1 year or more.
     - patients who are intolerant/non-adherent to 1st line treatments
   - The DXA report may advise referral of patients with unexpectedly severe bone density loss or unusual patterns of loss (e.g. hip significantly different from spine)
   - Vertebral fractures, without suspicion of underlying malignancy, which are not settling - persistent pain two months post fracture, those with difficult pain control, unstable or burst fractures and multiple vertebral fractures – consider referral to spinal surgery for vertebroplasty
   - Patients on breast or prostate cancer treatments should be investigated and managed according to relevant specialty guidelines

4. **Corticosteroids** – Consider osteoporosis assessment in advance based on likely duration of therapy. For those on steroids calculate FRAX or QFracture score and treat accordingly. Consider vitamin D and calcium while on steroids (refer to North of Tyne & Gateshead formulary)

5. **Quantifying the risk of fracture.** Fracture risk assessment should be carried out, prior to DXA in patients with clinical risk factors for osteoporosis and in whom anti-osteoporosis treatment is being considered. QFracture or FRAX can be used. The FRAX and QFracture risk-assessment tools are freely available at https://www.shef.ac.uk/FRAX/tool.aspx?country=1 and http://www.qfracture.org/
   If using risks generated by either tool, NOGG thresholds can be manually entered at: https://www.sheffield.ac.uk/NOGG/manual_data_entry.html

6. **The ideal is that all patients should have DXA scan before treatment to confirm osteoporosis**, but there may be examples where clinicians can use their clinical judgement on whether to start treatment without DXA scan, for example in extreme age following hip fracture.

TREATMENT ALGORITHM

Basic investigations, lifestyle advice, and osteoporosis treatment

Falls assessment and lifestyle advice

- Adequate calcium and vitamin D
- Regular weight bearing exercise
- Avoid tobacco and excess alcohol
- Care home patients, housebound, frail elderly and patients in sheltered accommodation should be considered for calcium and vitamin D therapy.

Patient information leaflets are available from the National Osteoporosis Society. www.nos.org.uk/resources

Osteoporosis treatment

Please refer to the appropriate manufacturers SPC and/or BNF entry for further information on cautions, contraindications and administration instructions.

FIRST LINE

Alendronate 70mg once weekly or

Risedronate 35mg once weekly

Patients should be reviewed after 5 years of bisphosphonate treatment (see section on reviewing bisphosphonate therapy). Refer if eGFR <30 ml/min/1.73m² and patient has confirmed osteoporosis.

SECOND LINE if intolerant / compliance issues

For specialist initiation only in line with the North of Tyne & Gateshead Formulary. Prior to referral MUST check corrected calcium, vitamin D and eGFR. **Contraindicated** in hypocalcaemia. Check serum 25OH Vitamin D and if <50nmol/L correct according to local advice. Review after 5 years

6 monthly s/c Denosumab Initiate in secondary care then continue in primary care (see separate denosumab leaflet)

Yearly IV Zolendronate in secondary care

THIRD LINE OPTIONS

Specialist only - see additional information. Raloxifene can be intitiated in primary care if recommended by specialist

Basic investigations

- FBC, CRP, U&Es, LFTs, eGFR, bone chemistry, serum vitamin D, TFTs, ESR

Investigations to consider if secondary cause suspected

Depending on the results from the basic investigations, consider excluding secondary causes

- PSA – male vertebral or pathological fractures
- PTH
- Serum/ urine electrophoresis and free light chains to detect multiple myeloma/other B cell malignancies
- tTGA –to detect coeliac disease

OSTEOPOROSIS TREATMENT - ADDITIONAL INFORMATION

At all times, where possible, shared decisions about treatment should be made between clinicians and patients, 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.

MHRA / CHM advice Bisphosphonates: Osteonecrosis of the Jaw (October 2007 and November 2009)

The risk of developing ONJ in association with oral bisphosphonates seems to be low. The risk of ONJ is substantially greater for patients receiving intravenous bisphosphonates for cancer indications than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease.

Patients who are prescribed bisphosphonates should have a dental examination, prior to treatment, if they have poor dental health. During bisphosphonate treatment patients should maintain good oral hygiene, receive routine dental checkups, and report any oral symptoms.

The MHRA and EU recommend issuing patient reminder cards for denosumab and intravenous bisphosphonates to minimise the risk of ONJ in patients taking denosumab or bisphosphonates. See link

The cards can be obtained directly by calling Amgen (*Prolia*®) on 01223 436 441.

MHRA / CHM advice Bisphosphonates: Atypical femoral fractures (June 2011)

Atypical femoral fractures have been reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis. The risk of this complication appears to be increased in patients with rheumatoid arthritis and/or on steroids.

- Atypical femoral fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture
- Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated, and should be based on an assessment of the benefits and risks of treatment for the individual
- Patients should be advised to report any thigh, hip, or groin pain. Any patient who presents with such symptoms should be evaluated for an incomplete femur fracture
- The need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on an assessment of the benefits and risks of treatment for individual patients, particularly after 5 or more years of use.

MHRA / CHM advice Bisphosphonates: Osteonecrosis of the auditory canal (December 2015)

- Benign idiopathic osteonecrosis of the external auditory canal has been reported very rarely with bisphosphonate treatment, mainly in patients receiving long-term therapy (2 years or longer).
- The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections or suspected cholesteatoma.
- Risk factors for developing osteonecrosis of the external auditory canal include: steroid use, chemotherapy, infection, an ear operation, or cotton-bud use.
- Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during treatment with a bisphosphonate.

Calcium and Vitamin D for patients taking bisphosphonates

Estimate calcium intake. These resources can help:
Healthy Bones The National Osteoporosis Society
Rheumatological Diseases Unit calcium calculator

Only give calcium supplementation if dietary intake inadequate and not possible to have a calcium rich diet. Most people manage an adequate dietary calcium intake.

- Evaluate dietary calcium intake is at least 700mg calcium per day
- If >700mg there is no need for extra calcium, unless there is concern about calcium malabsorption e.g. IBD, steroids.
- If calcium intake is low, one tablet of a combined calcium/vitamin D supplement should be enough.
- Beware groups at risk of hypercalcaemia: primary e.g. hyperparathyroidism and sarcoidosis, who must not receive calcium supplements.

Estimate risk of vitamin D insufficiency/deficiency. Common groups at risk of vitamin D deficiency / insufficiency

- Non-white skin, lack of sunlight exposure (including concealing clothing)
- Vegetarians (in particular non-fish eaters)
- Pregnant & breastfeeding women, babies, children and adolescents
- Older housebound or institutionalised people
- Liver and renal disease
- On medication that affect vitamin D metabolism, such as anticonvulsants, rifampicin, Highly active antiretroviral therapy (HAART)
- On medication for which sunlight-avoidance in mandated due to skin cancer risk (e.g. azathioprine), or photosensitivity-risk (e.g. Docetaxel; Demeclocycline).
- On medication that blocks the enterohepatic circulation of vitamin D (e.g. Colesevelam, or Colestyramine).
- If at risk of insufficiency – Colecalciferol 20microgram (800 units) daily.

FIRST LINE - Oral bisphosphonates
Alendronate 70mg once weekly or Risedronate 35mg once weekly

Contra-indications

Abnormalities of oesophagus, factors which delay gastric emptying, hypocalcaemia, uveitis, scleritis. Patients should be vitamin D replete, as bisphosphonates can aggravate osteomalacia. Avoid if eGFR less than 35ml/minute/1.73m^2 (alendronate), 30ml/minute/1.73m^2 (risedronate)

Counselling

Take on an empty stomach at least 30 minutes before breakfast or other medicines. Swallow whole with plenty of water (at least 200mL) while sitting or standing and remain upright for at least 30min after taking. Advise patients on the rare risk of osteonecrosis of the jaw, osteonecrosis of the auditory canal, and atypical fractures.

Adherence with bone protection treatments:

- Ask if the patient adherent with bisphosphonate.

- Ensure the patient understands what is being treated and is aware of the risks of non-adherence. The risks of not treating osteoporosis are greater than the risks associated with treatment.
- Ask if the patient able to comply with specific instruction to take bisphosphonates.
- Do not refer the patient for a DXA if the patient has been significantly non-adherent (the bone clinic uses bone turnover markers to assess this).
- Ask if the patient suffering from any adverse effects.

Gastrointestinal effects with bisphosphonates e.g. dyspepsia or reflux:

- Complying with the administration directions can help reduce GI adverse effects.
- If GI side effects intolerable on alendronate, consider switching to risedronate as Prescription Event Monitoring observational studies suggest GI side effects are rarer (32.3 consultations for GI adverse effects per 1000 patient months for alendronate and 26.9 for risedronate in month 1 reducing to 10.9 for alendronate and 8.1 for risedronate in month 2).
- If patients develop upper oesophageal pathology during treatment (e.g. stricture, achalasia, Barrett's) on bisphosphonates; STOP the bisphosphonate and refer for consideration of other parenteral bone sparing agents

SECOND LINE - If intolerance or compliance issues with first line therapy - for specialist initiation only

Contraindicated in hypocalcaemia, correct prior to treatment by adequate intake of calcium and vitamin D before initiating therapy. Check serum 25OH Vitamin D and if <50nmol/L correct according to local advice

Denosumab 60mg SC pre filled syringe every 6 months **GREEN PLUS drug – secondary care initiated, GPs continue (see information sheet)**

Zoledronic acid intravenous infusion 5mg once a year **RED drug – secondary care must prescribe**

THIRD LINE - For specialist initiation only - Teriparatide 250mcg/ml, 2.4ml prefilled syringe - 20mcg daily **RED drug – secondary care must prescribe In line with NICE TA161**

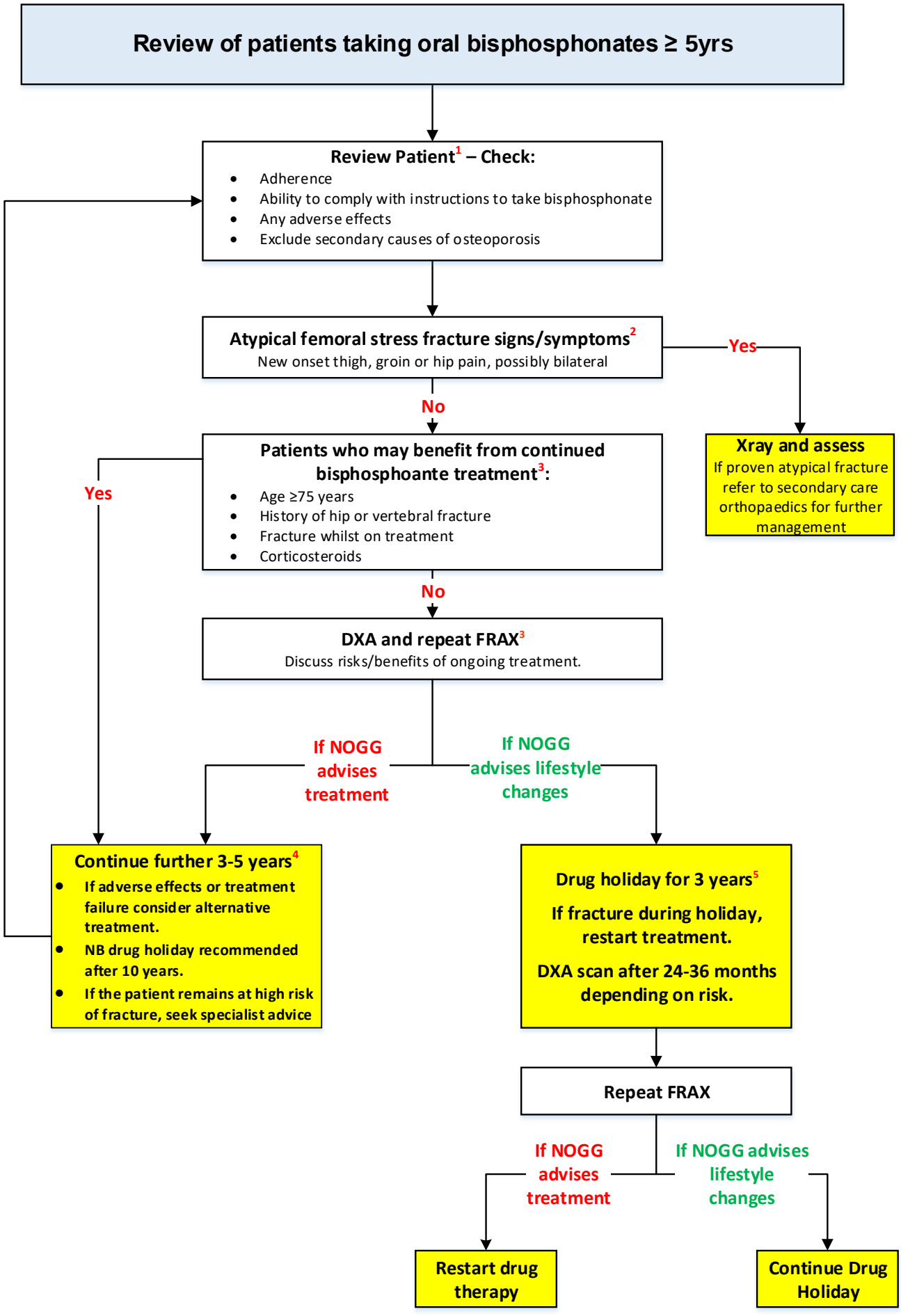
Raloxifene 60mg once daily

Contraindications

History of venous thromboembolism, undiagnosed uterine bleeding, endometrial cancer, cholestasis. Caution in mild to moderate renal impairment; avoid in severe impairment. Avoid in hepatic impairment. Use with caution for: patients with risk factors for venous thromboembolism (discontinue if prolonged immobilisation); risk factors for stroke; breast cancer (manufacturer advises avoid during treatment for breast cancer); history of oestrogen-induced hypertriglyceridaemia (monitor serum triglycerides); avoid in acute porphyria.

Counselling

Advise patient of the increased risk of developing a blood clot whilst on treatment. The risk is a similar to that of hormone replacement therapy (HRT) or the contraceptive pill containing oestrogen.


Review of patients taking oral bisphosphonates ≥ 5yrs
Review Patient[1] – Check:
Adherence
Ability to comply with instructions to take bisphosphonate
Any adverse effects
Exclude secondary causes of osteoporosis
Atypical femoral stress fracture signs/symptoms[2]
New onset thigh, groin or hip pain, possibly bilateral
Yes
No
Xray and assess
If proven atypical fracture refer to secondary care orthopaedics for further management
Patients who may benefit from continued bisphosphoante treatment[3]:
Age ≥75 years
History of hip or vertebral fracture
Fracture whilst on treatment
Corticosteroids
Yes
No
DXA and repeat FRAX[3]
Discuss risks/benefits of ongoing treatment.
If NOGG advises treatment
If NOGG advises lifestyle changes
Continue further 3-5 years[4]
If adverse effects or treatment failure consider alternative treatment.
NB drug holiday recommended after 10 years.
If the patient remains at high risk of fracture, seek specialist advice
Drug holiday for 3 years[5]
If fracture during holiday, restart treatment.
DXA scan after 24-36 months depending on risk.
Repeat FRAX
If NOGG advises treatment
If NOGG advises lifestyle changes
Restart drug therapy
Continue Drug Holiday

Review of patients taking bisphosphonates for 5 years – additional information

This guidance is proposed as a pragmatic approach to the patient who has been compliant with oral bisphosphonate therapy for 5 years. By this point, 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 benefit over risks of therapy therefore becomes less favourable and a period off therapy ("holiday") may be considered.

NB Fracture risk may still be high; the principle here is that fracture risk has been reduced and that there is sustained reduction in fracture risk even after discontinuing bisphosphonate therapy.

Evidence is limited as to how long the effects of bisphosphonates continue and the optimal period of time before treatment should be restarted.

At review, the following should be discussed (numbers correspond to those on algorithm):

1. **Check Adherence with therapy**

If the patient is significantly non-adherent to the point where it is felt they are unlikely to have taken effective therapy for the past few years, then consideration should be given to alternative more acceptable forms of therapy rather than a drug holiday.

2. **Check for Atypical Fractures**: Does the patient have any signs or symptoms of an atypical fracture (new onset thigh, groin or hip pain, possibly bilateral)?

At initiation of therapy patients should be advised of the small risk (1/1,000 / year) of atypical femoral fracture and advised to seek medical advice at new onset hip or thigh pain. Atypical femoral fractures are a specific kind of stress fracture that can occur after no or minimal trauma in a very small number of patients. Symptoms include new onset thigh, hip or groin pain, and can be bilateral. The diagnosis is made by radiological confirmation of certain specific features, including site of fracture, transverse or oblique configuration, non-comminution etc. All patients should be screened at their 3-5 year review for possible atypical fractures and an x-ray of both hips and both femora requested if symptoms are present.

Before referring for DXA, consider if appropriate - clinical judgment required if DXA scan would not change clinical management e.g. end of life decision to stop treatment.

3. **For those aged <75 - Repeat DXA, repeat FRAX and discuss the risks / benefits of continuing treatment** Repeat DXA to enable calculation of current FRAX score – this is particularly if they were started on therapy before FRAX scores were widely used. (see also Note 4).

   NOGG suggests that "continuation of bisphosphonate treatment beyond 3-5 years can generally be recommended in individuals age ≥75 years, those with a history of hip or vertebral fracture, those who sustain a fracture while on treatment, and those taking oral glucocorticoids (≥7.5mg prednisolone/day or equivalent)"

There are two options at this stage: either to continue therapy for a further 5 years or to stop for a period ("drug holiday") with the intention to possibly restart when conditions are right.

4. Continuing treatment with a bisphosphonate after 5 years for people at continued high risk of a fragility fracture

This is based on (expert opinion by NOGG and FLEX Extension study):

- Women with a T Score of less than -2.5 after 5 years of treatment have fewer non-vertebral fractures if they continue for up to 10 years
- Continuing treatment with alendronate after 5 years of treatment, for a further 5 years, is associated with a small reduction in clinically apparent vertebral fractures but no difference overall in fracture incidence at least for the 1st 2 years.

Some adverse events have been reported with long-term bisphosphonates. These are based on observational and post-marketing studies; there is a possible association but not proven causality with bisphosphonate use. Incidence of all is very rare.

Further information can be found at
http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con120237.pdf

5. Stopping bisphosphonate treatment for a "drug holiday" after 5 years

This is based on:

- Evidence that a drug holiday after 5 years of treatment with alendronate is associated with only a small increase in clinically apparent vertebral fractures, but no increase in other types of osteoporotic fractures.
- Evidence of rare but serious adverse effects of bisphosphonates, with an increasing incidence of these adverse effects with continuing treatment
- In patients who have taken continuous oral alendronate for 10 years, a drug holiday is strongly recommended.

Assessment of bone health during a "drug holiday"

The principle here is to attempt to assess changes in the patient's skeleton whilst off therapy to inform decisions about future. Little evidence exists for how this should best be done; a pragmatic approach based on clinical consensus is suggested here.

Serial DXA scans may show a fall in BMD off bisphosphonate therapy, but absolute changes are small (1-2% fall per year) and may be close to the precision error and co-efficient of variation of the scanner. Large changes are required to be sure the effect seen is genuine, so a period of 24-36 months should be allowed between scans. Availability of serial scanning may be difficult in North Northumberland and technically tricky in frail elderly patients with previous fractures.

After 3 years off bisphosphonate therapy, if there are signs on DXA of deteriorating bone health then a further assessment using FRAX should be undertaken, to decide whether it is appropriate to restart therapy for a further 5 years. Choice of agent is the same as set out in the treatment algorithm on page 5. Note that patients should continue with calcium / vitamin D supplementation during the drug holiday.

Some patients may have stable BMD and/ or ongoing suppression of bone turnover well beyond 2 years; it is appropriate for these patients to remain off therapy with ongoing monitoring of DXA.

References

NICE Osteoporosis – primary prevention (TA160) (January 2011)
NICE Osteoporosis – secondary prevention including strontium ranelate (TA161) (January 2011)
NICE Osteoporotic fractures – denosumab (TA204) (October 2010)
NICE Bisphosphonates for treating osteoporosis (TA464) (August 2017)
NOGG Osteoporosis. Clinical guideline for prevention and treatment (May 2013)
SIGN 142 Management of osteoporosis and the prevention of fragility fractures (March 2015)
Bone and Tooth Society of Great Britain. National Osteoporosis Society. Royal College of Physicians.
Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment. London: Royal College of Physicians (2002)
The University of Sheffield School of Health and Related Research. Adverse effects and persistence with therapy in patients taking oral alendronate, etidronate or risedronate: systematic reviews. 2006.
Drug Safety Update February 2013, vol 6, issue 7: A1
European Medicines Agency new recommendations for contraindications and revised warnings for Protelos/Osseor