North East and North Cumbria Integrated Care System Guideline for the management of osteoporosis in primary care

Endorsed for use within the North East and North Cumbria ICS by the NENC Medicines Committee	
NENC ICS Prescribing and Medicines Optimisation Committee (NTAG)	March 2024
NENC Medicines Committee	April 2024
Review Date	December 2025
Membership of the Guideline Development Group	Matthew Grove (Northumbria Healthcare NHS FT) Terry Aspray (Newcastle Hospitals NHS FT) Peter Bartholomew (Medical Physics, South Tyneside and Sunderland) Matt Bridges (County Durham and Darlington NHS FT) Chris Jewitt (Glenpark Medical Centre) Olwyn Jones (Gateshead Health NHS FT) Stephen Kirk (Whickham Cottage Medical Centre) Karen Little (Carlisle Healthcare) Kanchan Manchegowda (South Tyneside and Sunderland) Yousif Shanshal (Gateshead Health NHS FT) Lesley Sheik (Birbeck Medical Group) Louise Statham (Sunderland University) Lewis Sutherland (Northumbria Healthcare NHS FT) Nishanthi Thalayasingam (Newcastle Hospitals NHS FT) Stephen Tuck (South Tees Hospital NHS FT)

This guideline is not exhaustive and does not override the individual responsibility of health care 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[1]
- NICE TA161[2]
- NICE TA204[3]
- NICE TA464[4]
- NICE TA791[5]
- NICE CG146[6]
- NOGG guideline 2021[7]

Contents

Introduction

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

The NICE-accredited National Osteoporosis Guideline Group (NOGG) updated its detailed and comprehensive guideline[7] in 2021. This offers detailed, evidence-based advice on improving fracture risk assessment, long term treatment with denosumab, and bisphosphonate treatment pauses. The NOGG document is intended for all health professionals involved in management and commissioning of osteoporosis services, and as such includes a number of specific recommendations that apply more to secondary care than primary care services.

This document is an attempt to distil the NOGG guideline into a more practical form for deployment across the North East and North Cumbria (NENC) Integrated care system, with an emphasis on measures that need to be undertaken in primary care, and when it is appropriate to discuss patients with secondary care specialist services.

Notably, following NICE's approval of romosozumab[5] in May 2022 there has been a paradigm shift in secondary prevention of fracture, by promoting the first-line use of anabolic agents in very high fracture risk patients who are at imminent risk of further fracture.

Information has been included on secondary care prescribed anabolic agents (teriparatide and romosozumab) and zoledronic acid, as primary care practitioners will need some understanding of the issues around their use. The interested reader should refer back to the full guidelines if greater detail is required.

The NOGG guideline made one specific suggestion that has not been supported by the NENC Medicines board, notably that teriparatide should be used as a first line anabolic agent where romosozumab was contraindicated. There is currently insufficient evidence to support such usage as being cost effective.

NICE is currently reviewing their osteoporosis clinical guideline CG146. Publication is expected in January 2025 (GID-NG10216)[8]. This guideline may be subject to change after that date.

Figure 1: Flowchart for investigation and management of patients at risk of osteoporosis and fragility fracture

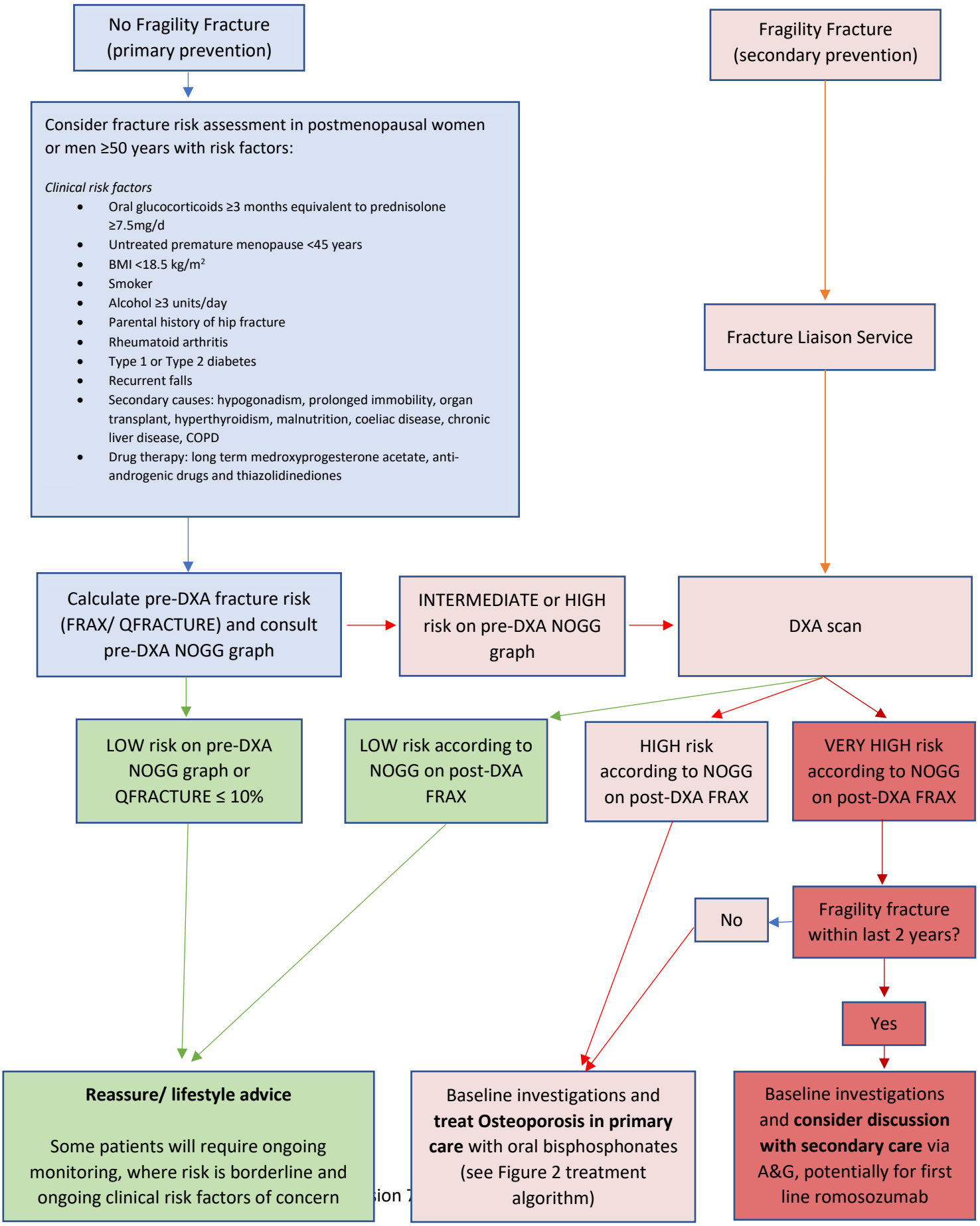


Figure 2: Oral bisphosphonates: Clinical Flowchart for long term treatment and monitoring (after NOGG 2021)

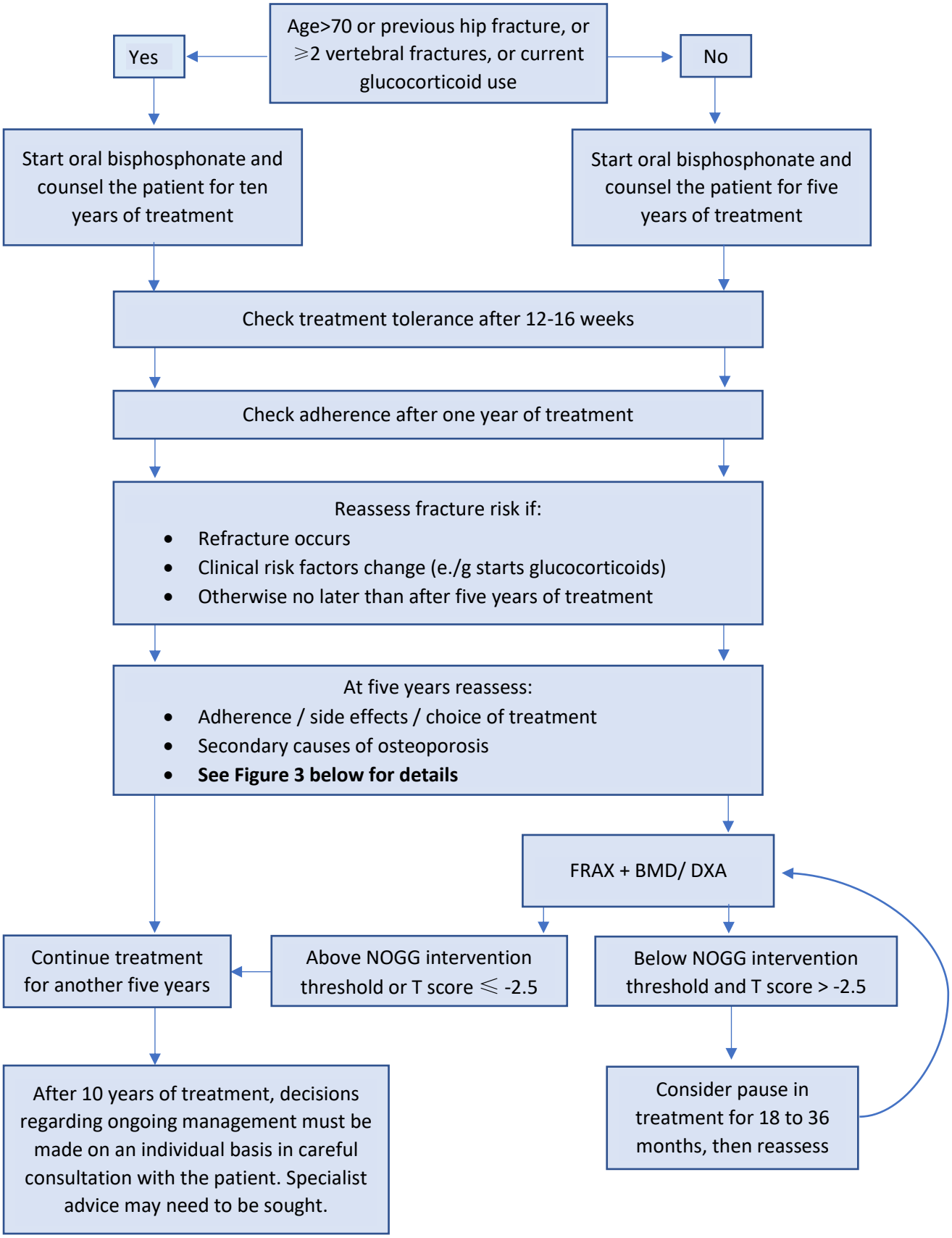
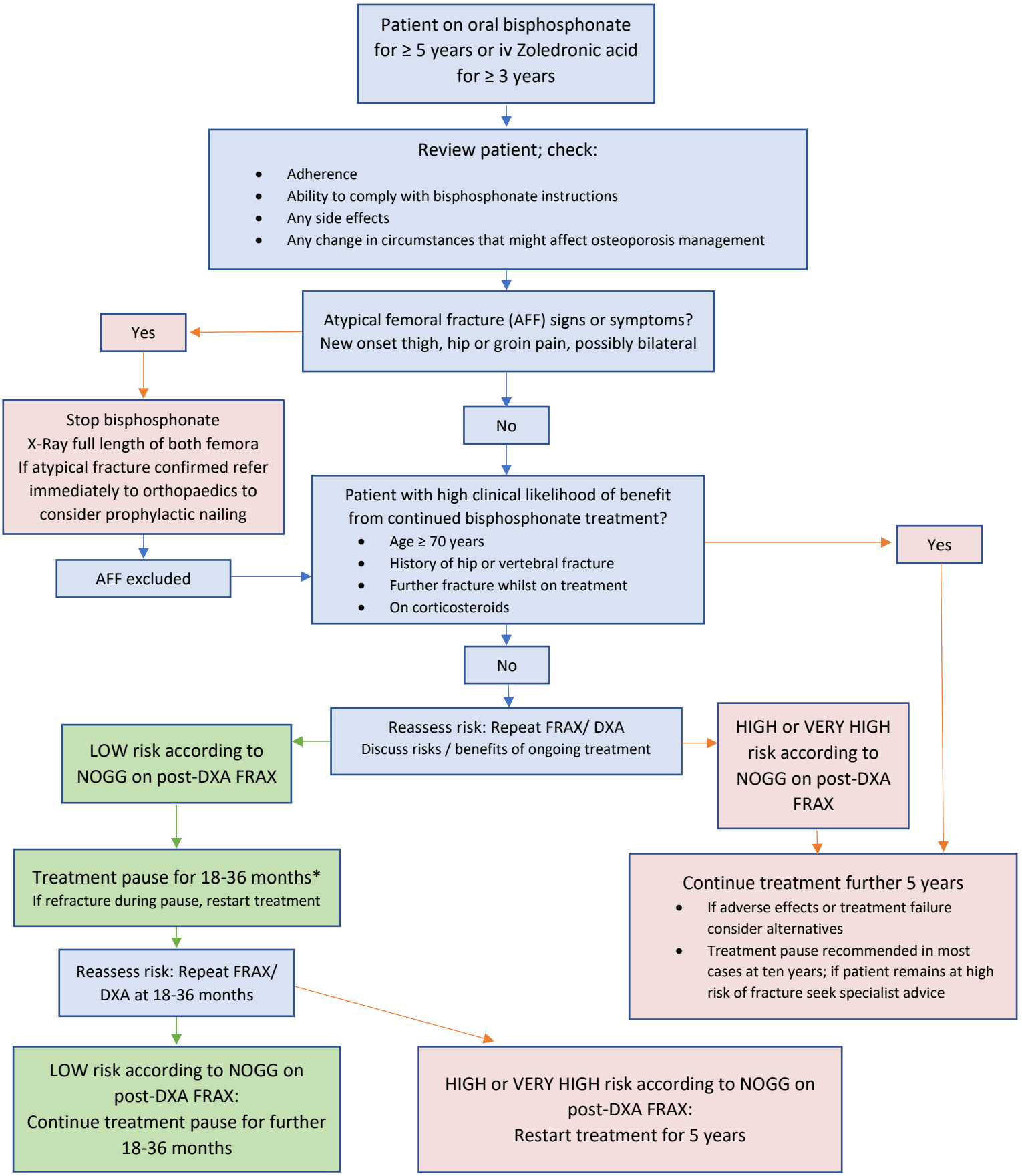


Figure 3: Flowchart for review of patients taking long term bisphosphonates



*Duration depends on bone elution time: re-evaluate at 12-18 months (RIS, IBN), 24 months (ALN) or 36 months (ZOL)

Summary of main recommendations (adapted in large part from NOGG 2021)

Concerning assessment of fracture risk in postmenopausal women and men age ≥50

Conduct a FRAX[9] or QFRACTURE[10] assessment in people age ≥50 with a clinical risk factor for fragility fracture. When using FRAX, clinical judgement is needed when clinical risk exceeds those factors enterable into FRAX, such as multiple fragility fractures, very high glucocorticoid or alcohol dose, diabetes, and a history of falls, Parkinson's or other movement disorder. For diabetic patients the "Rheumatoid Arthritis" box within FRAX can be checked as a surrogate estimation of the increased risk incurred.

FRAX score may also be upwardly adjusted for patients who have recently (<2 years) sustained a fracture, or who have sustained multiple prior fragility fractures[11,12]. The online tool does not yet support these calculations, but risks may be recalculated by experienced practitioners to reflect these changes.

1. Measure BMD in people with intermediate (amber FRAX) risk to refine the estimate of ten-year risk
2. Measure BMD in people with high or very high fracture risk (red FRAX) to guide choice of drug and provide a baseline for BMD monitoring.
3. Patients with discordantly low lumbar spine BMD will be at higher risk of fracture than suggested by FRAX score calculated on neck of femur BMD. NOGG suggests increasing Major Osteoporotic Fracture risk by 10% for every T score unit difference between lumbar spine and femoral neck.
4. Consider imaging to look for vertebral fracture in people with acute onset back pain who have risk factors for osteoporosis, and/or in people with a history of ≥4cm height loss, kyphosis, recent or current long term oral glucocorticoid therapy, or who are known to be osteoporotic on DXA.
5. Assess falls risk in patients with osteoporosis and/ or fragility fractures and offer those at risk an exercise programme to improve balance and muscle strength. Patients who fall frequently have a relative risk of fracture 30% higher than suggested by FRAX.

Regarding drug treatment to prevent fractures in postmenopausal women, and men age ≥50

6. Offer drug treatment to people at high and very high risk of fracture, particularly those who have a history of prior and recent fragility fracture.
7. If BMD measurement is not practical (e.g due to frailty) use FRAX risk without BMD measurement and the online NOGG intervention thresholds to guide treatment decisions

When selecting drug treatments to prevent fractures in postmenopausal women and men age ≥50

8. Start treatment promptly after a fragility fracture, because the risk of re-fracture is highest immediately following a fracture.
9. Consider discussion of women classified as **Very High Risk by FRAX** via Advice & Guidance (A&G) with an osteoporosis specialist in secondary care. These patients may be eligible for first line romosozumab use if they fall into one or more of these groups:

a. Recent fragility fracture (vertebra, forearm, hip, humerus within last two years) – this is defined by NOGG as **Imminent Risk of Fracture** *or*
b. ≥2 vertebral fractures (whenever they have occurred) *or*
c. BMD T score ≤ -3.5

10. In other patients for whom treatment is indicated, offer antiresorptive therapy with oral bisphosphonates (weekly alendronic or risedronic acid, monthly ibandronic acid)
11. If first line bisphosphonates are unsuitable or not tolerated, consider discussion with secondary care via A&G for consideration of intravenous zoledronic acid or subcutaneous denosumab, or other alternative therapy.
12. Following treatment with first line romosozumab, patients will be switched to oral alendronic acid, iv zoledronic acid or denosumab to maintain BMD gain.

When postmenopausal women and men age ≥50 have started drug treatment

13. Regularly review patients' tolerance of, and adherence to, oral drug treatments
14. Plan to re-assess fracture risk after at least five years on oral bisphosphonates and three years on intravenous zoledronic acid
    a. Longer duration of treatment will be needed in older (≥70 years), or those who have sustained a hip or vertebral fracture, or are on high dose oral glucocorticoids, or have a further fragility fracture whilst on treatment
    b. In lower risk patients a treatment pause of 18 to 36 months can be considered after five years oral bisphosphonate or 3 years intravenous zoledronic acid
    c. Consider a treatment pause in all patients after ten years on bisphosphonate treatment, as ongoing therapy at this point is subject to diminishing returns and increased risk of complications. If concerned about ongoing fracture risk, specialist advice can be sought from secondary care regarding these patients.
    d. Reassess fracture risk 18 to 36 months after pausing drug treatment.
    e. Reassess fracture risk if a new fracture occurs whilst on treatment. This may indicate treatment failure, compliance or tolerability issues and hence a possible need to switch therapy.
15. Before starting denosumab ensure a long-term personalised osteoporosis management plan is in place. Do not stop denosumab treatment without a plan for ongoing therapy. Treatment pauses are not appropriate for patients on denosumab. Following discussion in the medicines guideline group and formulary committee, Denosumab has been classified AMBER (shared care). If considering stopping treatment seek specialist advice from secondary care. More detail can be found in the Denosumab shared care guideline document.

When postmenopausal women, and men age ≥50 are treated with oral glucocorticoids:

16. If starting ≥7.5mg/day prednisolone or equivalent for ≥3 months, start bone protective treatment at the same time (a DXA scan can follow later). This dose is equivalent to 30mg daily for four weeks within any three-month period.

17. Offer antiresorptive therapy with oral bisphosphonates (weekly alendronic or risedronic acid; monthly ibandronic acid); or discuss with secondary care via A&G for consideration of intravenous zoledronic acid or subcutaneous denosumab.
18. In patients known to have very low bone density (T score ≤ -3.5), or who are at Imminent Risk of Fracture (ie have sustained a fragility fracture within last two years) and whom are at Very High Risk of Fracture (as per FRAX), discuss with secondary care via A&G for consideration of first line anabolic treatment.

When advising on lifestyle and dietary measures:

19. Recommend a healthy, balanced diet, moderation of alcohol consumption and avoidance of smoking
20. Ensure sufficient dietary calcium and vitamin D intake; supplement vitamin D and calcium intake as necessary.
21. Encourage a combination of regular weight bearing and muscle strengthening exercises

Regarding fracture prevention services

22. All patients who sustain a fragility fracture should have access to a multidisciplinary, coordinator-based Fracture Liaison Service (FLS) to support timely fracture and falls risk assessment, investigation, treatment, and monitoring.
23. Diagnostic imaging services should routinely evaluate the spine in all imaging and report vertebral fractures using standardised measures.

Additional information for Figure 1: investigation and management flowchart

1. **Fragility Fracture** is defined as a fracture caused by falling from standing height or lower at walking speed or slower. It 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.
    a. *Stress fractures* are caused by repetitive minor trauma below the threshold usually required to break bone (e.g metatarsal fractures from running) and are not considered to be fragility injuries as they are not predictive of osteoporosis. Bone quality problems may still be present. If a patient has sustained multiple stress fractures measure serum vitamin D and seek advice from secondary care.

2. **Do not routinely assess fracture risk in patients <50 years**. Discuss with secondary care via A&G if patients under 50 years old are thought to be at significant osteoporotic risk.

3. **Do not routinely refer patients for DXA where their sole risk factor is an osteopenic appearance reported on plain XR.** Radiological osteopenia is a normal finding in the elderly. In the absence of other risk factors such as fracture, the osteopenic appearance is incidental to the original reason for the XR request. DXA is indicated only if other clinical risk factors are present.

4. **The following patients/ conditions may require discussion with secondary care via advice and guidance (A&G):**
    a. men under 50 years with osteoporosis
    b. patients with anorexia nervosa and other eating disorders
    c. patients failing to respond to oral therapies, i.e. continuing to fracture despite the patient being compliant with therapy for 1 year or more.
    d. patients who are intolerant/non-adherent to 1st line treatments
    e. patients with unexpectedly severe bone density loss or unusual patterns of loss (e.g. hip significantly different from spine) – the DXA report will advise if these should be discussed
    f. Patients with vertebral fractures (without suspicion of underlying malignancy) which are persistently painful >2 months post fracture or with difficult pain control, unstable or burst fractures and multiple vertebral fractures – consider referral to spinal surgery for vertebroplasty.
    g. Patients on breast or prostate cancer treatments should be investigated and managed according to relevant specialty guidelines.

5. **Corticosteroids** – where it is expected patients older than age 50 years will be on continuous treatment with oral prednisolone ≥7.5mg/day or equivalent for >3 months, then it is appropriate to start them on oral bisphosphonate therapy at the same time as the steroid course is started, pending results of DXA scan to better assess fracture risk.

6. **Discussion with secondary care for consideration of anabolic drug therapy**.
    a. Two anabolic agents are currently available: teriparatide and romosozumab.
    b. Both are administered by subcutaneous self-injection – teriparatide is a once daily injection for two years and romosozumab requires two injections once per month for one year.

c. These are RED drugs prescribed from secondary care and usually delivered under Homecare schemes.
d. Both agents are indicated for patients with severe osteoporosis at high risk of further fracture. Romosozumab is approved by NICE for first line before the patient is exposed to bisphosphonates, teriparatide is a 2nd or 3rd line agent.
e. They may not be suitable for patients who do not wish to consider self-injection, or may find this difficult, in which case oral bisphosphonates may still be preferable.
f. Both drugs are only used for a limited period (one year for romosozumab, two years for teriparatide) after which the patient will need to transition to a bisphosphonate or denosumab to maintain BMD gains. Anabolic agents should not be initiated if the patient is unsuitable for follow-on treatment.

7. Baseline investigations for osteoporosis
a. FBC, U&E, eGFR, LFT, Calcium and phosphate, ESR, CRP, Thyroid function
b. Coeliac screen
c. Serum Vitamin D in selected patients where there is clinical concern of frank vitamin D deficiency (malabsorption/ coeliac; non-white skin; inexplicably low bone density) or as a baseline where parenteral therapy is planned.

8. Further investigations depending on results of baseline tests
a. Serum protein electrophoresis and serum free light chain analysis
b. PTH level
c. Sex hormone screen in men with unexplained low BMD
d. PSA in men with vertebral fractures

9. When discussing a patient with secondary care employ Advice and Guidance (A&G) in the first instance
a. Many problems can be resolved via A&G and don't necessarily require full referral or outpatient review
b. It is extremely helpful to provide details of previous bone protection therapies, particularly details regarding how long the patient was treated for as this will constrain future therapy.

Additional information regarding review of patients taking long term bisphosphonates

- Patients on bisphosphonates experience a rise in bone density due to suppression of bone breakdown (anti-resorptive effect).
- After ten years on treatment, this rise in bone density reaches a plateau, due to inhibition of bone synthesis.
- This state is associated with rare but serious adverse side effects due to inhibition of bone microfracture repair, notably atypical femoral fractures (AFF)[13] and osteonecrosis of the jaw (ONJ)[14] or external auditory canal[15].

The risk of these complications increases with duration of treatment and dose of drug. They are consequently seen most frequently in patients taking high doses of intravenous bisphosphonates for oncological indications, and far less often in patients receiving treatment with oral bisphosphonates for osteoporosis.

- AFF incidence varies from 1.8/100,000 person-years to 113/ 100,000 person years bisphosphonate exposure, for patients on osteoporosis therapy <2 years to 8-10 years respectively.
- Overall number-needed-to-harm is around 2000[16].
- Poor dental hygiene increases the risk of ONJ; an excellent guideline is available on reducing the risk of this complication from NHS Scotland[21].
- Both rheumatoid arthritis and oral glucocorticoid use increase the risk of AFF and ONJ.

Stopping bisphosphonates results in resumption of bone turnover and a fall in bone density. Different bisphosphonates elute more slowly from bone: resumption of turnover occurs within 1-2 years of stopping ibandronic or risedronic acid, 2-3 years after stopping alendronic acid, and may take 3 or more years from stopping zoledronic acid.

This has led to the pragmatic suggestion that treatment should be paused once it is felt that the patient is unlikely to benefit from continuing therapy, allowing skeletal turnover to resume (and hence repair microfractures), then restart therapy before a major osteoporotic fracture is sustained.

NOGG suggests that treatment should be reviewed at five years for patient on oral bisphosphonates (alendronic, risedronic and ibandronic acid) and three years for patients on intravenous zoledronic acid.

- If the drug is tolerated, compliance seems reasonable and there is no concern over side effects then treatment should be continued for a further 3-5 years in these high-risk groups:
    - Age ≥70 at point bisphosphonate was started.
    - Previous history of hip and/ or vertebral fracture.
    - Currently treated with oral glucocorticoids ≥7.5mg prednisolone per day or equivalent.
    - Patients who have experienced a further fragility fracture during the first five years of treatment.
- At ten years, if patients have been compliant with therapy it is likely that bone turnover will be significantly reduced. There will need to be a careful discussion regarding the risks and benefits of continuing treatment, compared to the risk of stopping and allowing bone turnover to resume.

Once treatment is stopped, fracture risk should be re-evaluated after an interval. In most cases risk will remain high and restarting treatment should be considered.

- Re-evaluation should be considered early (one year) in patients who have been on risedronic or ibandronic acid,
- After two to three years in patients exposed to long term alendronic acid,
- After three years in patients who have been on zoledronic acid.

We have pragmatically proposed using DXA to re-evaluate risk in patients finishing a treatment pause. The evidence base for this is lacking; similarly, although using bone turnover markers to assess loss of drug effect offers an attractive rationale, the evidence that this is useful in clinical practice is slight.

Detailed information regarding drug treatments for osteoporosis

The section below discusses individual drugs in detail. A few agents are included that are classified RED for secondary care use only; these are mentioned primarily for information, detailed guidance regarding their use is out of scope of this guideline.

Calcium and vitamin D (GREEN)

- All patients being treated with bisphosphonates or denosumab should receive routine vitamin D supplementation of at least 800 units daily. Bisphosphonates and denosumab are hazardous and contraindicated in hypocalcaemic or vitamin D deficient patients

- In selected patients where there is clinical concern of frank vitamin D deficiency (malabsorption/ coeliac; non-white skin; inexplicably low bone density) it may be appropriate to formally measure vitamin D levels.

- Measurement of vitamin D levels also recommended in all patients starting on denosumab or intravenous zoledronic acid; these should be corrected if deficient or insufficient prior to starting antiresorptive therapy. An accelerated regime of 20,000 units daily for ten days can be used to minimise delay to next denosumab dose.

- Local vitamin D guidelines available from South Tyneside[17], North of Tyne, Gateshead and North Cumbria[18] and County Durham and Tees Valley [19]APCs for more detail if required.

- 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.

- Dietary calcium intake can be estimated (online calculator from University of Edinburgh[20]). If calcium intake >700mg per day there is no need for supplementary calcium, unless there is clinical concern of malabsorption e.g. IBD, steroids.

Oral bisphosphonates (Alendronic, Risedronic and Ibandronic acid) (GREEN)

- Once-weekly oral bisphosphonates are cheap and effective inhibitors of bone resorption.
    - They also suppress bone synthesis, but their effect on resorption is greater, so overall they increase bone density whilst reducing bone turnover.

- Oral bisphosphonates are contraindicated in patients with hypersensitivity to bisphosphonates, or who are hypocalcaemic.

- Side effects include
    - gastroesophageal reflux and dyspepsia.
    - Aggravation of incipient osteomalacia in vitamin D deficient or insufficient patients, causing musculoskeletal pain.
    - Rarely, uveitis and scleritis.

- Oral bioavailability of bisphosphonates is extremely poor (less than 1%), and effectively nil if the drug is ingested with food or other medication.
    - Because of this, and because of the gastroesophageal side effects, they should be taken on an empty stomach, with a glass of water but no other medication, and the patient should remain upright for at least half an hour afterwards. Other medication can then be taken after a half-hour interval.
    - Oral bisphosphonate compliance is notoriously poor; it should be checked at follow up appointments and enquired into in cases of apparent treatment failure.

- They should be used with caution in patients who have pre-existing oesophageal problems, or who will have difficulty complying with the instructions for use.

- Their use is problematic in chronic kidney disease
    - Alendronic acid is contraindicated in patients whose eGFR is <35ml/min.
    - Risedronic and oral ibandronic acid are contraindicated at eGFR <30ml/min, so are preferred over alendronic acid in patients with borderline renal function with eGFR range 30-35ml/min

- Long term treatment with bisphosphonates is associated with greatly reduced bone turnover, and the rare side effects of AFF, ONJ and osteonecrosis of the external auditory canal mentioned above.
    - Patients should be warned to report any new hip, thigh or groin pain or any persistent discharge from the auditory canal.
    - Good dental hygiene is crucial to reducing the risk of osteonecrosis of the jaw: the Scottish Dental Clinical Effectiveness Programme has published an excellent document on measures to take to reduce the incidence of this complication[21].
    - Patients with risk factors for osteonecrosis of the jaw (poor dental hygiene, smokers, on steroids or immunosuppressive drugs) should be advised to see a dentist as soon as possible when starting bisphosphonates.

Intravenous Zoledronic acid (RED)

- Intravenous zoledronic acid is a potent aminobisphosphonate that has a prolonged antiresorptive action following a single intravenous infusion of 5mg.
- Zoledronic acid appears to be more effective than weekly oral bisphosphonates, not least because it does not cause gastroenterological problems and is fully bioavailable.
- It is therefore a useful alternative to oral bisphosphonates in osteoporotic patients at risk who cannot tolerate oral medication because of gastrointestinal comorbidity or side effects.
- It allows for treatment of patients with osteoporosis by annual day case infusion; studies suggest that the infusion interval can be safely increased to eighteen-monthly with no loss of effect[22].
- The commonest side effect is a febrile, flu-like reaction immediately after infusion and lasting 24hr-72hr. This can usually be managed with paracetamol; the incidence of the reaction declines with subsequent infusions.
- An increase in symptomatic atrial fibrillation was observed in phase III studies.

- Zoledronic acid is contraindicated in hypocalcaemic patients and in patients with GFR <35ml/min.
    - The MHRA recommends use of calculated creatinine clearance rather than eGFR to assess suitability for treatment in patients >75 years or at the extremes of BMI.
    - For purposes of simplicity the guideline group preferred to retain eGFR for use in patients on oral bisphosphonate therapy

- Calcium and phosphate levels, and vitamin D levels should be checked before each infusion and vitamin D supplemented pre-infusion if necessary.

- Patients with risk factors for osteonecrosis of the jaw (poor dental hygiene, smokers, on steroids or immunosuppressive drugs) should be advised to have a dental check-up, ideally before starting treatment.

- Treatment with zoledronic acid following hip fracture in men and women is associated with fewer subsequent clinical fractures but also a 28% relative reduction in all-cause mortality at three years[23].
    - For this reason NOGG proposes that first line zoledronic acid should be considered in all patients following hip fracture.
    - The logistics of this recommendation are beyond the scope of this guideline but likely to be implemented via secondary care orthogeriatrics services and may just involve a single infusion in frail elderly hip fracture patients.

Denosumab (PROLIA™) (AMBER)

- Denosumab is a monoclonal antibody directed at RANK ligand, which regulates osteoclast activity.
- It is licensed for the treatment of osteoporosis in men and women at increased risk of fractures, and within glucocorticoid exposure.
- Denosumab is given as a six-monthly subcutaneous injection of 60mg which can be done in primary or secondary care.
- It is a potent antiresorptive agent, and similar to bisphosphonates in that it also suppresses bone synthesis, and consequently long-term treatment can cause AFFs, ONJ and osteonecrosis of the external auditory canal as seen with potent bisphosphonates.
    - The incidence of ONJ may be higher with denosumab than with bisphosphonates, particularly in patients who switch from a bisphosphonate to denosumab[24].

- Denosumab differs crucially from bisphosphonates in that it has a rapid offset, with any delay in the treatment dose resulting in rapid loss of drug effect (after as little as eight months from the previous dose).
- This offset is associated with rebound increase in bone turnover to levels above those seen at baseline, a rapid fall in bone density, and a relatively high incidence of multiple vertebral fractures (so called rebound vertebral fractures)[25].

This has a number of consequences:

- Denosumab should not be initiated or stopped without prior discussion with a secondary care osteoporosis specialist. To this end the drug has been reclassified as AMBER and patients should be treated under a formal shared care agreement with a secondary care osteoporosis specialist.
- Denosumab is suitable for initiation in primary care under specialist advice, providing baseline investigations have been undertaken. See denosumab shared care documentation for details. It may be possible for some patients to self-inject the drug with specific training.
- The drug may be suitable for older patients who are cognitively intact and well-motivated to take responsibility for organising regular appointments - and chasing these up when cancelled due to service capacity constraints.
- The manufacturer offers an on-line support program for patients (the PROLONG programme, accessible from www.prolia.co.uk) that includes reminders for patients as to when their next injection is due.
- It is extremely important that the six-monthly dosing regime is adhered to.
    - The injection schedule should not be changed to accommodate dental surgery, as the risk of rebound fracture greatly outweighs the risk of ONJ.
- It is unclear if the drug can safely be stopped at all. The necessity for potentially indefinite treatment should be explained to the patient before the drug is started, and a long-term treatment plan should be in place before initiation.
    - This is particularly important with younger patients who may therefore expect to be on treatment for a very long time.
- NOGG has proposed that patients stopping denosumab should be switched to a potent bisphosphonate; “lock in” with zoledronic acid or oral bisphosphonates have been proposed.
    - A number of mostly small-scale observational studies of this approach[26] suggest it may be partially successful in mitigating some of the post-denosumab bone loss and reducing rebound fracture risk, although bone loss still occurs.
    - A randomised trial of scheduling zoledronic acid lock-in according to change in bone turnover markers[27] showed patients still experienced a significant loss of bone density, with no difference observed between the different treatment strategies.
    - A substantial portion of patients on denosumab were started on the drug specifically because concerns over renal function argued against using a bisphosphonate. For these patients bisphosphonate lock-in will not be an option.
    - Secondary care will advise on how best to undertake bisphosphonate lock in when required.
- Unlike bisphosphonates, denosumab does not exhibit tachyphylaxis at ten years and bone density continues to rise – which implies long term treatment may have ongoing benefits that mitigate risks, and indefinite treatment may be the preferred approach.

Other considerations

- Denosumab can cause dangerous hypocalcaemia; calcium and phosphate levels should be checked prior to treatment. Risk of hypocalcaemia is highest in patients who are vitamin D deficient (even if normocalcaemic)[28] or have chronic kidney disease.
    - we recommend checking vitamin D levels prior to each treatment, so patients on this drug will require six-monthly vitamin D level measurement.
- Denosumab is not nephrotoxic so has been proposed as an alternative to bisphosphonates in patients with low bone density and chronic kidney disease. This is not straightforward and such treatment should be undertaken only by metabolic bone or renal specialists.
- Biosimilar Denosumab is likely to become available within the next two years. At least one product has already been approved by the EMA. It is unclear at this time whether patients

should adhere to one brand or whether different denosumab brands can be used interchangeably. Whether biosimilar manufacturers will offer patients support similar to the PROLONG programme is also unclear.

Romosozumab (EVENITY™) (RED)

- Romosozumab is a monoclonal antibody targeted at sclerostin, a regulator of bone breakdown. When administered subcutaneously monthly it rapidly boosts bone synthesis whilst reducing bone breakdown.

- This results in a larger increase in bone density within twelve months than with any other drug currently available, and a very significant reduction in fracture risk.

- The effect is not maintained, so after twelve months patients should be switched to either bisphosphonates or denosumab to maintain bone density gains. It is therefore not suitable as a treatment for patients who cannot tolerate bisphosphonates or denosumab.

- Romosozumab is most effective in treatment-naïve patients; patients who have had prior exposure to bisphosphonates or denosumab (both of which reduce bone synthesis) demonstrate a blunted therapeutic effect.

- Only a single one year course of treatment will be offered; repeated courses are not effective.

Romosozumab has been endorsed by NICE for use only in postmenopausal women with a recent major osteoporotic fracture (within the last two years) who are at very high risk of imminent fracture. Potentially eligible women include:

- Vertebral and/ or other fragility fracture (forearm, hip, humerus) within last two years
- ≥2 vertebral fractures (whenever they have occurred)
- BMD T score ≤ -3.5
- FRAX risk in the Very High Fracture Risk range

Ideally such patients should be discussed with secondary care for consideration of anabolic agents, before being trialled with a bisphosphonate. In practice many will be picked up and referred directly from fracture liaison services.

- Romosozumab has a good safety profile, although there was a small but statistically significant increase in the risk of cardiovascular adverse events (MI and stroke) in one of the phase III trials. It is consequently contraindicated in patients with a history of myocardial infarction or stroke, and also with hypocalcaemia.
- No ongoing monitoring is needed.
- Because of its mechanism of action it is not expected to increase the risk of ONJ or AFFs; there were a handful of cases of these within the phase III trial population, but all had prior bisphosphonate exposure.

Teriparatide (RED)

- Teriparatide is recombinant human parathyroid hormone [1-34].
    - Biosimilars are now available (MOVYMIA™ and TERROSA™) which offer some cost saving over the originator FORSTEO™.
- Teriparatide is given by daily sc injection for a two year course.
- It increases both bone synthesis and bone breakdown; synthesis outweighs breakdown resulting in a net positive effect on bone mass.
- The therapeutic effect of teriparatide is most evident in trabecular bone (vertebrae) rather than in cortical sites such as at the hip.
    - It is ideal for patients with vertebral osteoporosis and fractures
    - In patients with cortical / hip fracture or at high risk of hip fracture, iv zoledronic acid may be preferable.

- Teriparatide is contraindicated in patients who are hypercalcaemic or hyperparathyroid (even if normocalcaemic at baseline).
- No monitoring is required.
- It is not associated with either AFF or ONJ, indeed has been proposed as a potential treatment for these conditions
    - evidence for benefit in this scenario is confined to case studies and short case series, and it is currently not approved for this indication.

- Courses of teriparatide are limited to two years in length and should not be repeated. Patients completing two years of therapy should transition to an antiresorptive agent to maintain bone density gains.

- Teriparatide was approved by NICE[2] in 2008 for the secondary prevention of osteoporotic fragility fracture in both men and women with severe osteoporosis.

- Although NOGG[7] has suggested teriparatide be used first line as an alternative anabolic agent in patients who are not otherwise suitable for romosozumab, there is insufficient evidence for cost-efficacy of this approach and it is currently not supported by the Medicines board.

Hormone Replacement Therapy (GREEN)

- 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[29,30].

- A recent narrative review concluded that overall, the benefit-risk profile supports the use of HRT in the management of osteoporosis in women < 60 years old, who have recently (within 10 years) become menopausal, who have menopausal symptoms and have low baseline risk for adverse events[31].

- HRT is the preferred option for primary prevention of osteoporosis in women with premature menopause or <60 years

    - For women who have sustained a fragility fracture, or are at unusually high risk of fracture, or with contraindications to HRT, discussion with secondary care via A&G is recommended

- HRT use beyond age 60 is not recommended; bisphosphonates are preferred for primary and secondary prevention of osteoporosis in this group.

Raloxifene (GREEN+)

- Raloxifene is a selective oestrogen receptor modulator; it has oestrogenic effects in bone but anti-oestrogenic effects in the breast and ovary.
- It inhibits bone resorption, reducing the risk of vertebral fracture but without increasing the risk of breast cancer. It has not been shown to affect the risk of non-vertebral fracture.
- It is licensed for use in postmenopausal women, but should be used with caution in women with a history of stroke or with risk factors for stroke.
- It may be useful as a follow-on therapy for romosozumab or teriparatide in women with contraindications to bisphosphonates.

Strontium Ranelate (RED)

- Strontium ranelate is provided as a 2g sachet of granules, to be suspended in water and taken two hours after food.
- It substitutes for calcium within hydroxyapatite and has weak anti-resorptive and anabolic effects.
    - As it is incorporated into the bone matrix and has a higher atomic number than calcium, it artefactually increases observed bone density; serial DXA scans require careful interpretation in patients on this drug.
- It is approved for use in both men and women and reduces the incidence of vertebral and nonvertebral fractures.
    - the manufacturer advises against use when eGFR <30ml/min.
    - In phase III trials it increased the risk of venous thromboembolism, and post-marketing surveillance showed an increase incidence of cardiovascular, cerebrovascular and thromboembolic disorders.

- Because of the VTE and cardiovascular side effects its original manufacturer suspended sales. It has been relaunched but is only approved for use by osteoporosis specialists, after careful discussion of cardiovascular risks with the patient.

Conclusions

- Osteoporosis is a common cause of preventable disability and mortality

- For primary prevention, a case-finding approach with formalised clinical evaluation of fracture risk, backed up by selective DXA scanning and oral bisphosphonate therapy for patients found to be at high risk remains the standard management strategy.

- Fracture Liaison Services play a key role in identifying and assessing patients who have sustained a fragility fracture, are at Imminent Risk of further fracture and may require urgent treatment.

- NICE and NOGG recommend first line treatment with romosozumab for secondary prevention in patients who are both at Very High Risk of Fracture *and* at Imminent risk of fracture (ie have sustained a fragility fracture within the last two years), particularly if they have sustained vertebral fractures. These patients will require discussion with secondary care.

- For secondary prevention patients who are not at Very High risk, or who have already completed a course of anabolic therapy, oral bisphosphonates remain the standard management strategy.

- Annual intravenous zoledronic acid may be a useful agent for patients who cannot tolerate oral bisphosphonates or for patients who have sustained a hip fracture.

- Subcutaneous denosumab may be useful in certain carefully selected patients but cannot be safely stopped or delayed. All patients who are to be started on denosumab should have a long-term personalised osteoporosis management plan in place, with discussion of an exit strategy before treatment is initiated. If denosumab is to be stopped within primary care this should only be after discussion with a secondary care osteoporosis specialist. Such patients should be managed under a formal shared care agreement.

- HRT is useful for primary prevention of fractures in younger post-menopausal women (<60 years) who have a low baseline risk for adverse malignant and thromboembolic events. Use beyond age 60 should be carefully discussed with the patient.

- All patients receiving anti-osteoporosis treatment should be routinely offered vitamin D supplements, and supplementary calcium if needed.

References

(links all correct as of 15th August 2023)

[1] Raloxifene for the primary prevention of osteoporotic and fragility fractures in postmenopausal women (NICE TA160, updated 2018)

[2] Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (NICE TA161, updated 2018)

[3] Denosumab for the prevention of osteoporotic fractures in postmenopausal women (NICE TA204, published 2010, updated 2014, under review as of August 2022)

[4] Bisphosphonates for treating osteoporosis (NICE TA464, updated July 2019)

[5] Romosozumab for treating severe osteoporosis (NICE TA791, May 2022)

[6] Osteoporosis: assessing the risk of fragility fracture (NICE CG146, updated Feb 2017)

[7] National Osteoporosis Guideline Group (NOGG): Clinical guideline for the prevention and treatment of osteoporosis (Sept 2021)

[8] Osteoporosis: risk assessment, treatment and fragility fracture prevention (update). NICE, Guideline in development (GID-NB10216) expected publication 20 Jan 2025.

[9] FRAX online Fracture Risk Assessment Tool (UK)

[10] QFracture 2016 online Fracture Risk Assessment Tool

[11] FRAX: readjustment or re-think. Yasser , El MiedanyArch Osteoporosis 2020; 15(1)

[12] Adjusting conventional FRAX estimates of fracture probability according to the number of prior fractures. Kanis et al, Osteoporosis International 2022(12)

[13] Medicines and Healthcare products Regulatory Agency (MHRA): Bisphosphonates: atypical femoral fractures (June 2011)

[14] Medicines and Healthcare products Regulatory Agency (MHRA): Bisphosphonates: osteonecrosis of the jaw (December 2014)

[15] Medicines and Healthcare products Regulatory Agency (MHRA): Bisphosphonates: very rare reports of osteonecrosis of the external auditory canal (December 2015)

[16] Managing Osteoporosis in patient on long-term bisphosphonate treatment: Report of a Task Force of the American Society for Bone and Mineral Research. Adler et al., JBMR 2015

[17] Management of Vitamin D deficiency and insufficiency in adults. Medicines Optimisation team, South Tyneside CCG, August 2021

[18] Quick Reference Guide: Primary Care management of Vitamin D deficiency. North of Tyne, Gateshead and North Cumbria APC, January 2020

[19] County Durham and Tees Valley Primary Care Management of Vitamin D deficiency, January 2023

[20] Online Calcium Calculator available from:
https://webapps.igmm.ed.ac.uk/world/research/rheumatological/calcium-calculator/

[21] Oral Health Management of Patients at risk of medication-related osteonecrosis of the jaw. SCDEP March 2017

[22] Fracture Prevention with Zoledronic acid in Older women with osteopenia. Reid et al., NEJM December 2018

[23] Zoledronic acid and clinical fractures and mortality after hip fracture. Lyles et al., NEJM 2007

[24] Risk of osteonecrosis of the jaw under denosumab compared to bisphosphonates in patients with osteoporosis. Everts-Graber et al., JBMR November 2021

[25] Denosumab (Prolia): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment. MHRA Drug Safety Update 26th August 2020

[26] Discontinuing Denosumab: can it be done safely? A review of the literature. Tay and Tay, Endocrinology and metabolism 2022; 37(2); 183-194

[27] Treatment with Zoledronic acid subsequent to denosumab in osteoporosis: a randomized trial. Solling et al., J Bone Min Research 2020 (October)

[28] Should vitamin D level be measured before denosumab in patients with castration-resistant metastatic prostate cancer to prevent hypocalcaemia? Demiray et al., Eurasian Journal of Medical Investigation 2021

[29] Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2012; (7): CD004143.

[30] Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002; 288(3): 321- 33.

[31] Rozenberg S, Al-Daghri N, Aubertin-Leheudre M, et al. Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis? Osteoporos Int 2020; 31(12): 2271-86.