Trust Guideline for the Management of: Osteoporosis, Secondary Prevention of Fracture in Post-Menopausal Women

A clinical guideline recommended

For use in:	Postmenopausal women who have prior history of low trauma skeletal fractures
By:	Clinicians who practice in the osteoporosis field (primarily endocrinologists, rheumatologists, orthopaedic surgeons and Older People's Medicine (OPM) physicians)
For:	The secondary prevention of skeletal fractures in women who are known to have osteoporosis or who are at elevated fracture risk
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If Yes – does the strategy/policy deviate from the recommendations of NICE? If so, why?	No

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Glossary

ONJ	Osteonecrosis of the jaw
NOGG	National Osteoporosis Guideline Group
DEXA	Dual Energy X-ray absorptiometry
FRAX	on line fracture risk calculator
NOS	National Osteoporosis society
CTX	C terminal telopeptide / carboxy terminal collagen cross links
BMD	Bone mineral density
PTH	Parathyroid hormone

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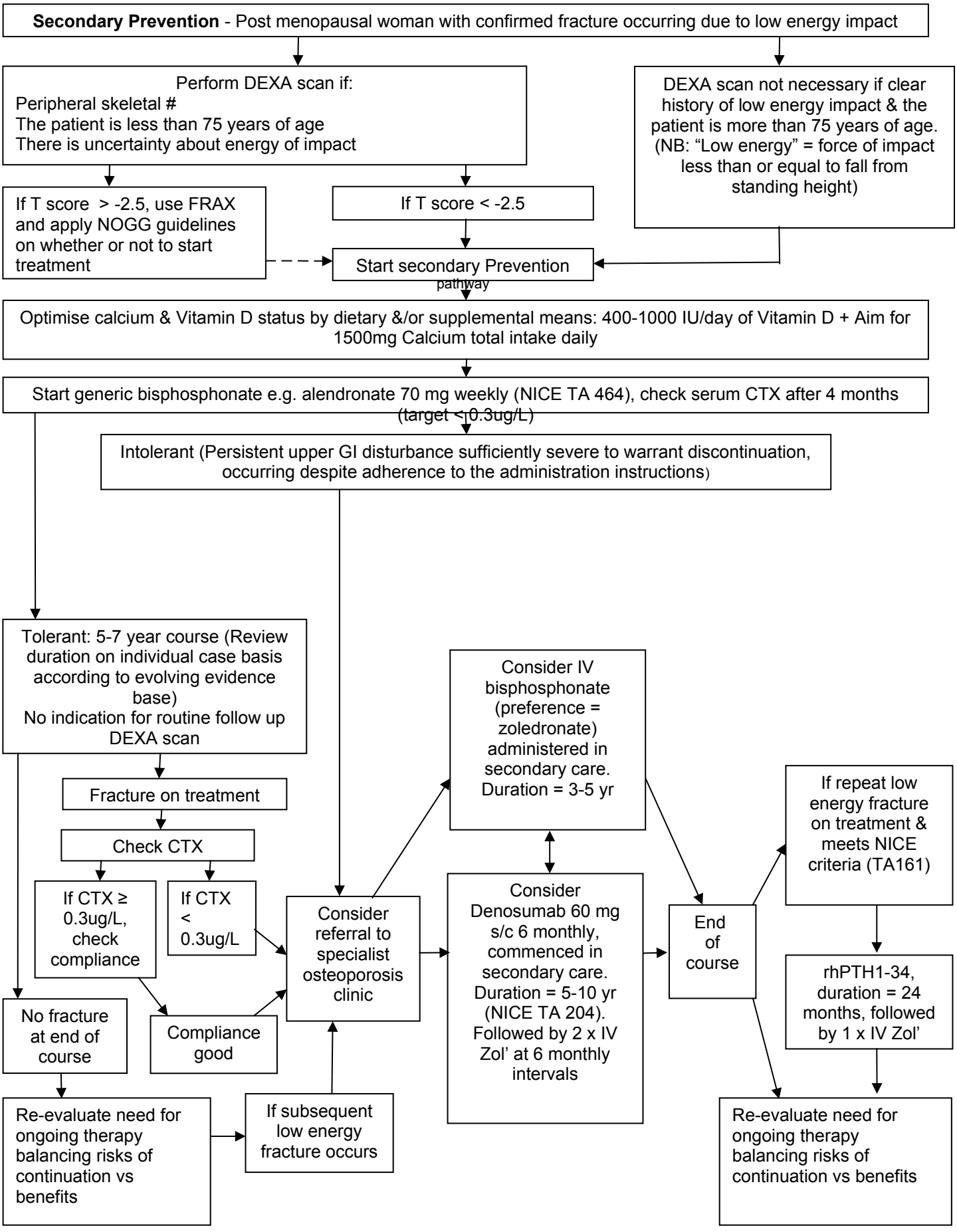

Objective/s

1. To provide guidance on the secondary prevention of low energy fracture in post menopausal women with known or suspected osteoporosis.
2. To standardise and unify this aspect of osteoporosis management throughout the NNUH.
3. To provide clear, evidence based, up to date guidance on osteoporosis management and secondary fracture prevention.
4. To reflect and incorporate current national guidance from opinion-leading bodies such as The National Institute for Health and Care Excellence (NICE) and National Osteoporosis Guideline Group (NOGG) in osteoporosis management but also to provide guidance on the use of newer agents such as rhPTH1-34, PTH and denosumab.
5. To reflect newer thinking in the osteoporosis world that has become more widely accepted since some of the existing guidance was written covering issues such as duration of treatment, role of repeat DEXA scanning, use of bone turnover marker blood tests and the risks/side effects of osteoporosis drugs, especially the bisphosphonates, such as atypical femoral fracture.

Rationale

There have been significant updates to several pieces of major national osteoporosis guidance since the last NNUH osteoporosis clinical guidelines were written. Specifically, NOGG guidance was updated in 2017 and two major new NICE documents have been released (TA464 and CG146). There have also been other important changes in the field including drugs coming off patent (Teriparatide, rhPTH1-34) and changes in thinking about recommended duration of treatment, especially with respect to the bisphosphonates.

Broad recommendations

Please refer to the “Quick reference guidelines” on page 2 in which the suggested pathway for treatment of post menopausal female patients with a low energy fracture history is outlined. This includes advice on whether or not a DEXA scan is required, how to interpret the latter, when to initiate treatment and with what agent. It furthermore recommends suitable treatment duration and when to consider referral to a specialist clinic.

The structure of the treatment pathway has, in essence, 3 components:

- Assessment of whether or not secondary prevention by pharmacological means is indicated. For all where there is a clear history of low energy impact and the patient is more than 75 years of age then pharmacological intervention will be indicated and in the majority of such cases, treatment can be started without DEXA scanning. There are a number of circumstances where DEXA scanning is indicated and these are specified in the flow chart on page 2.

- The second part is based on use of low acquisition cost, high efficacy, evidence based, orally active bisphosphonates such as weekly alendronic acid, for a limited time frame (5 – 7 years in the majority of cases).
- The patient should only progress to the third part of the pathway if they have true intolerance of oral bisphosphonate therapy or if they sustain a fracture while on treatment (fractures sustained very early on during a course of treatment eg within the first 12-18 months should attract less attention).

  The pathway should then involve referral to a specialist clinic, where further investigations will be performed and treatment will be escalated as set out in the quick reference guide pathway above. A parenteral bisphosphonate will usually be the first choice in the specialist clinic but other possibilities include denosumab and, after a fracture on treatment, anabolic agents such as rhPTH1-34 will be considered.

There are several key aspects of this guidance that we would draw the reader's attention to:

1. If there is a clear low trauma history to the index fracture and the patient is more than 75 years of age then we recommend commencing the secondary prevention pathway without recourse to DEXA scanning. This is in keeping with guidance in NICE TA464 and reflects the high likelihood of established osteoporosis being present in such patients.

2. If DEXA scanning is performed and the T score is -2.5 or lower, in the presence of appropriate fracture history, this should trigger automatic initiation of bone protection.

3. Bone Mineral density (BMD) is only 1 of several risk factors for fracture, we therefore recommend that if DEXA scanning is performed and the T score is above -2.5, the results of DEXA are integrated with other risk factors in order to predict a 10 year fracture risk, using the FRAX risk calculator available on the University of Sheffield web pages.

   This is analogous to the Q-RISK cardiovascular risk calculators available on line with which many colleagues are familiar. FRAX also provides advice on whether or not to recommend pharmacologic intervention based on NOGG guidance and for each FRAX calculation that is performed, a link is provided to individualised "treat or not to treat" guidance according to the patient's 10 year fracture risk.

4. Repeat DEXA scanning is no longer considered to be necessary in routine cases to assess response to treatment and should not be used as a matter of course. Indeed improvements in BMD only account for approximately 50% of fracture risk reduction with bisphosphonates.

   Re-scanning should however be considered if a patient sustains a low energy fracture while on treatment (unless very early during the treatment pathway), if they sustain a low energy fracture after a course of treatment has been completed, or by a specialist upon referral to a specialist osteoporosis clinic.

Re-scanning at intervals of less than 3 years is usually contra-indicated as the magnitude of bisphosphonate effect on BMD within this time frame is often smaller than the Coefficient of variance (CV) of the measurement on most densitometers.

5. A course of bisphosphonate treatment should not be considered to be open-ended or completely risk-free. Patients on bisphosphonates are at elevated (albeit small) risk of atypical femoral fractures and osteonecrosis of the jaw (ONJ). Other potential risks associated with bisphosphonates are starting to emerge (e.g. possible elevated carcinoma of the oesophagus risk, although the effect size and strength of association are still unknown).
   It is therefore important that benefit outweighs risk and therefore duration of treatment of 5 - 7 years is recommended in most cases. Case-specific factors should however be included in decision making around individual circumstances.

6. Interpretation of C terminal telopeptide (CTX) results: To assess compliance with and efficacy of bisphosphonate therapy, the guideline recommends routinely checking the serum CTX level after the first 4 months of bisphosphonate therapy. If the drug is being taken and absorbed then a significant suppression of CTX level will be observed confirming that bone resorption is being effectively suppressed. Level less than 0.3 microgram/L indicates effective treatment. This is considered to be a quicker, more reliable, and more cost-effective way of assessing treatment efficacy than is waiting 3 years to perform a repeat DEXA scan.

7. Although not included in the pathway on page 2, consideration should be given to the use of HRT in specific groups of post menopausal women. As with all agents, careful consideration of the risk benefit ratio needs to be undertaken.

   However, in post menopausal women under the age of 60 who are intolerant of other agents, and especially if they have undergone premature ovarian failure or surgically induced menopause, HRT remains an option for osteoporosis treatment and fracture prevention. Its use under these circumstances should probably only be undertaken after specialist opinion has been sought. Further guidance is available from the Royal Osteoporosis Society. Similarly, a limited role also exists for use of the selective oestrogen receptor modulator drug Raloxifene as outlined in TA161(https://www.nice.org.uk/Guidance/TA161)

8. There is growing awareness that at the end of a course of Denosumab therapy many patients exhibit a rebound fall in BMD which is associated with a concomitant rise in fracture risk (reference 9). There is no definitive evidence on how best to manage this challenge but one possible way to handle this situation based on currently available evidence is to administer two sequential zoledronate infusions within the first 12 months after the end of the course of Denusumab (reference 10)

9. Note on management of fracture risk in steroid treated patients: These comments pertain to those on 7.5 mg/day or more of prednisolone (or equivalent doses of other glucocorticoid) for 3 months or more. It should be borne in mind that a higher T score cut off is conventionally employed for marking out high fracture risk individuals on steroids and conventionally T < -1.5 is considered significant in this context. However, fracture risk is thought to abate quite rapidly upon cessation of steroid therapy if this possible.

The greatest evidence base for managing fracture risk in steroid treated patients relates to the use of bisphosphonates, however, there is also an evidence base supporting the use of rhPTH1-34 in this situation (reference 11) and especially now that generic rhPTH1-34 is available this option should be considered where bisphosphonates have been unsuccessful or are contraindicated.

Clinical audit standards

We suggest that compliance with the guideline in respect of parameters such as 10 year maximum bisphosphonate duration, absence of routine repeat DEXA scanning, 12 month CTX assessment and use of second line agents only where strictly indicated by the guideline be audited. We suggest a 90% adherence standard.

Summary of development and consultation process undertaken before registration and dissemination

The authors listed above drafted this guideline on behalf of NNUH osteoporosis working group who have agreed the final content. During its development it has been circulated for comment to: directorates of endocrinology, rheumatology, older people's medicine and orthopaedics.

This version has been endorsed by the Clinical Guidelines Assessment Panel.

Distribution list/ dissemination method

Available via the NNUH intranet trust guidelines pages.

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Appendix 1

Denosumab:

- GP referral to secondary care specialist OP clinic required:
  - To be initiated in secondary care ONLY

- If used for PRIMARY prevention (i.e. no prior fragility fracture):
  - Must ADDITIONALLY fall into one of the categories below (***NICE guidance***):

Age	No. independent risk factors for fracture		
	0	1	2
65-69	-	T-4.5	T-4.0
70-74	T-4.5	T-4.0	T-3.5
≥75	T-4.0	T-4.0	T-3.0

(NICE: TA204 denosumab for the prevention of osteoporotic fractures in postmenopausal women)

Where clinical risk factors for fracture are considered to be:

- Parental history hip fracture
- Alcohol intake ≥4 units/day
- Rheumatoid arthritis

Appendix 2

Teriparatide:

In keeping with NICE guidance, teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women:

- who are unable to take alendronate and risedronate, or have a contraindication to or are intolerant of alendronate and risedronate **or** who have had an unsatisfactory response to treatment with alendronate or risedronate **and**
- who are 65 years or older and have a T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, **or** who are aged 55–64 years and have a T-score of –4 SD or below plus more than two fractures.

For the purposes of this guidance, independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.

For the purposes of this guidance, intolerance of alendronate or risedronate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly.

For the purposes of this guidance, an unsatisfactory response is defined as occurring when a woman has another fragility fracture despite adhering fully to treatment for 1 year and there is evidence of a decline in BMD below her pre-treatment baseline.