Osteoporosis- Secondary Prevention

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Declarations

- I have no financial interests or relationships to disclose regarding the subject matter of this presentation.

Introduction

- Background/Definitions
- Epidemiology
- Diagnosis & Screening
- Treatment decisions
- Treatment options & Safety Issues
- Future Treatment conundrums
- NHSCT FLS Overview

Osteoporotic Fracture

A fragility fracture is defined as one that occurs after only moderate trauma (equivalent to a fall from standing height or less).

The areas of fracture are typically in bones with higher levels of the spongy trabecular bone which is far more porous than compact bone formed of harder osteons.

Trabecular bone is found in the ends of long bones, vertebrae, and the flat bones of the axial skeleton, such as the pelvis.

This explains the typical distribution of osteoporotic fractures, which are more common in women and rates increase exponentially with age.

The facts

Epidemiology

- 1 in 2 women lifetime # Rx
- 1 in 5 men lifetime # Rx
- Rapid ↑ Fracture Rx age >60
- ↑ Rx spinal # women age >50
- ↑ risk hip #women age>70
- At age 80 1 in 4 women will # vertebrae **25%

Mortality

- 20% mortality at 1yr post hip #
- 50% patients previously mobile need mobility assistance after 1 fracture
- 1 in 5 hip # require permanent NH placement post #
- Spine fractures result in inc co-morbidities

Screening Tests/Risk factors

- Bone Profile/U&E/PTH/Vit D
- Testosterone
- Coeliac screen
- TFT
- Myeloma/MGUS
- Genetic disorders (prolactin/gonadotrophins)
- Eating disorders/Over exercising
- Diabetes/RA/IBD/Pancreatitis/COPD
- Alcohol
- Consider 24hr urinary Ca/dexamethasone suppression test/Bone Bx
- Other drugs eg. Aromatase Inhibitors- early dexa as rapid early bone loss

30% post menopausal women other cause found

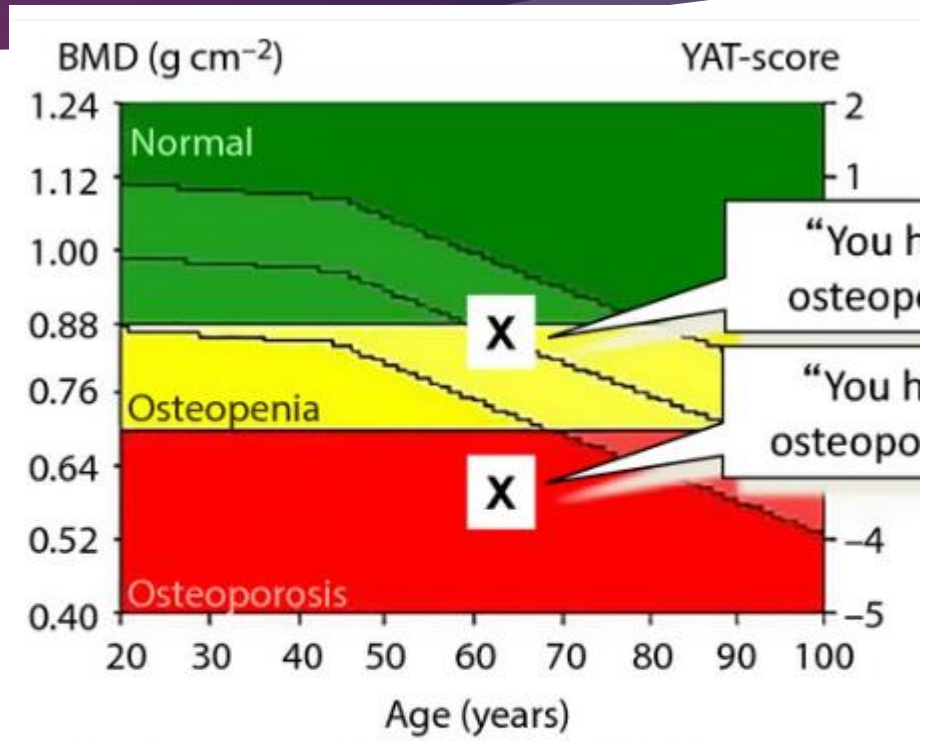
50% pre-menopausal women have a secondary cause

50-80% men have a secondary cause

Definition changes

- We have moved to assessing an individual's 5- or 10-year absolute risk of an osteoporotic fracture [2] through algorithm-based screening tools to better define and treat those with or at risk from osteoporosis, such as FRAX.

Old school!



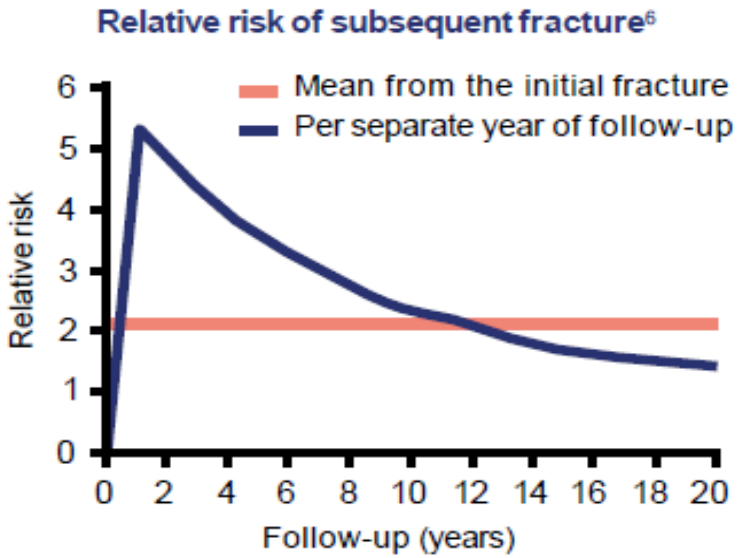
- *Epidemiology of Osteoporotic Fracture: an overview | ROS (theros.org.uk)*

Recognising MOFs

- Major Osteoporotic Fractures are Spine, hip, humerus and forearm
- Up to 50% of patients with MOF will re fracture within 2yrs
- Evidence: Biggest Rx of a # is having already had a vertebral #
- ●1 verbebral=3 fold ↑ Rx ● 2 vertebral #= 8 fold ↑ Rx

Imminent Fracture Risk

Subsequent fracture risk is not linear over time; relative risk of fracture is highest immediately after the initial fracture[6].



A recent fracture is a stronger risk factor for subsequent fracture than prior fracture[2].

Site of recent fracture influences imminent risk of subsequent fracture[2].

The fracture risk following **multiple fractures** is higher than that of patients with a single fracture[7]. The greater the number of fractures, the higher the risk of subsequent fracture[7].

Highest Rx is **within first year** of a fracture

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Arch Osteoporos. 2019 Feb 2; 14(1): 12.

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RESOURCE

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Imminent fracture risk assessments in the United Kingdom FLS setting: Implications and challenges

Rafael Pinedo-Villanueva,[1] Mata Charokopou,[2] Emese Toth,[2] Kerry Donnelly,[2] Cyrus Cooper,[1,3] Daniel Prieto-Alhambra,[1] Cesar Libanati,[2] and Muhammad K Javaid[1]

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Abstract

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With the recognition that a sentinel fracture leads to a high imminent risk of fracture, we discuss the implications and challenges of using imminent fracture risk in the secondary fracture prevention setting.

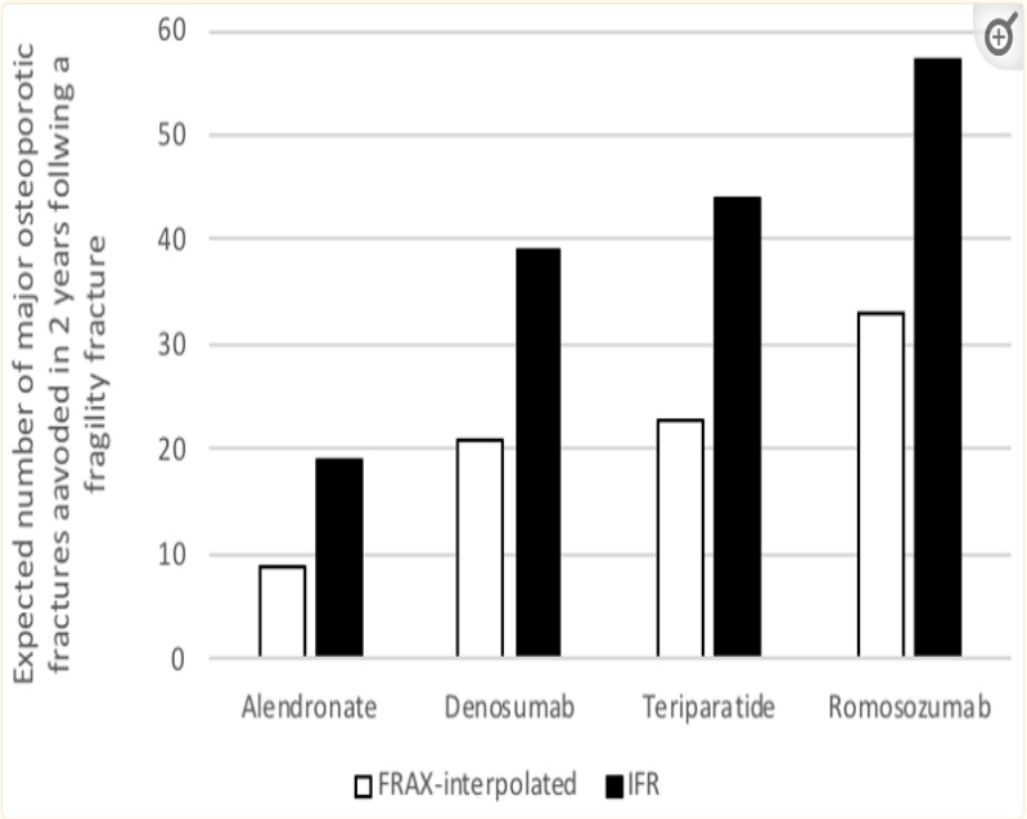


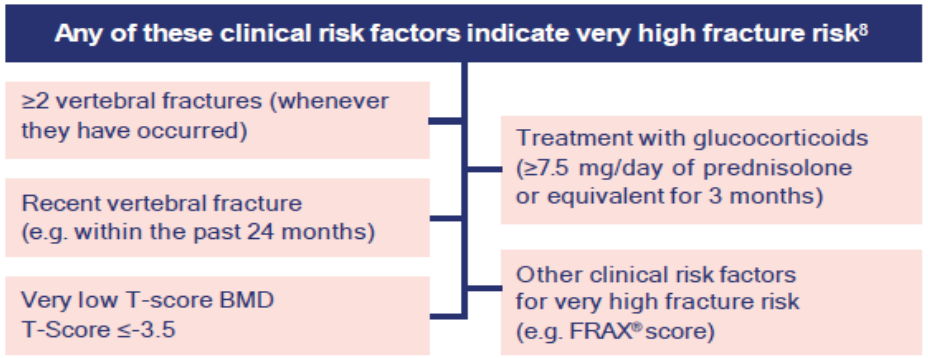
Figure 2

Expected number of major osteoporotic fractures prevented per 1,000 patients treated immediately following index fracture by different anti-osteoporosis medications using interpolated-FRAX vs. IFR after an index fracture[32]

Deciding when to treat/who to refer

- Age >80 with fragility fracture = treat *NICE guidelines
- **Commencing drug treatment without a DXA scan can be considered for people with a vertebral fracture.** *NICE guidelines
- Dexa (age >50 with fragility #, age <50 with 1 or more Rx factor)
- FRAX- this will help categorise to decide if onwards referral recommended

Think of ***"Imminent Fracture Risk"***



FRAX CALCULATOR

FRAX ® Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | CE Mar

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: Date of Birth: Y: M: D:
2. Sex — Male / Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture — No / Yes
6. Parent Fractured Hip — No / Yes
7. Current Smoking — No / Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Secondary osteoporosis — No / Yes
11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm²) — Select BMD

Clear | Calculate

Print tool and information

For USA use only

Consider FDA-approved medical therapies in postmenopausal women and men aged 50 years and older, based on the following:

- A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm
- Clinicians judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels

Country: UK Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 67 Date of Birth: Y: 1956 M: 7 D: 8
2. Sex — Male / Female
3. Weight (kg) 70.5
4. Height (cm) 162.4
5. Previous Fracture — No / Yes
6. Parent Fractured Hip — No / Yes
7. Current Smoking — No / Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Secondary osteoporosis — No / Yes
11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm²) T-Score -2.0

Clear | Calculate

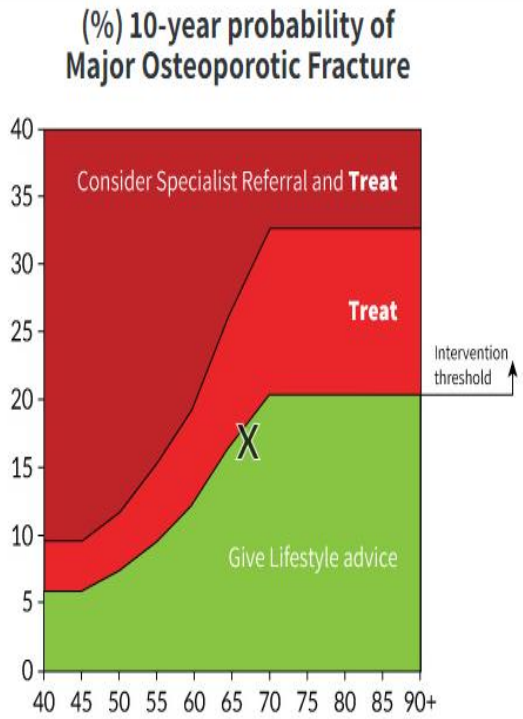
BMI: 26.7
The ten year probability of fracture (%)
with BMD

Major osteoporotic	17
Hip Fracture	3.2

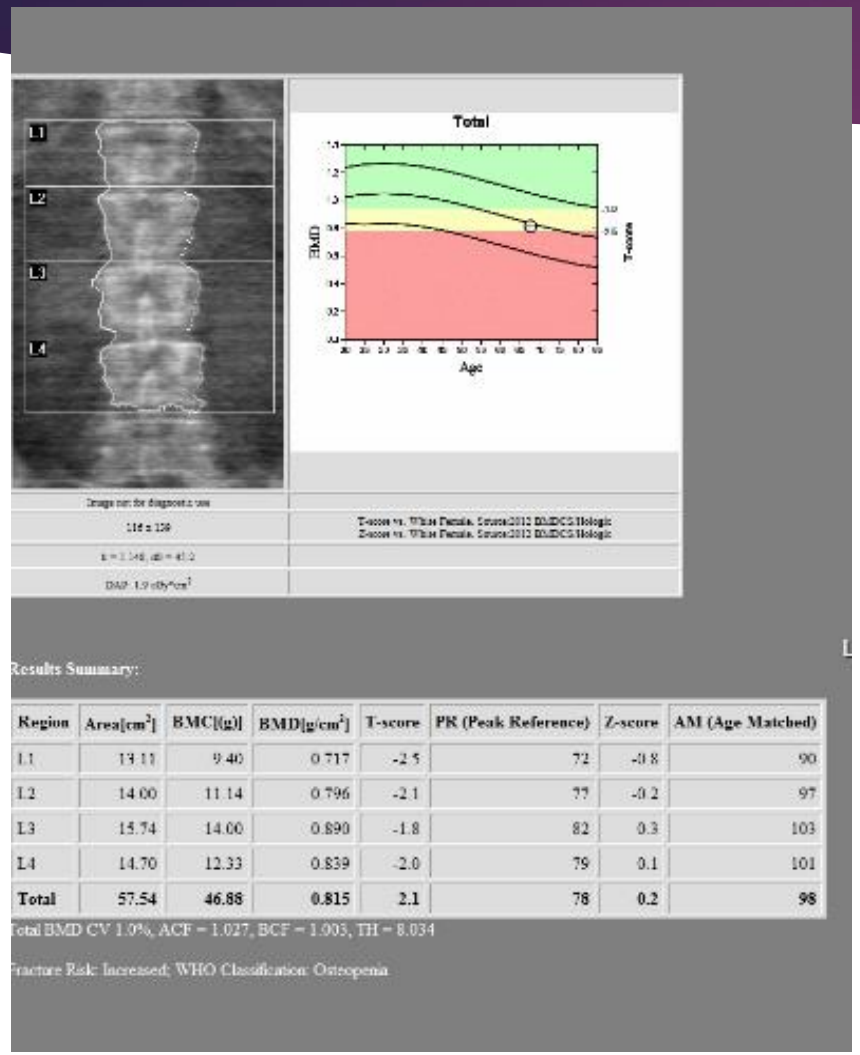
View NOGG Guidance

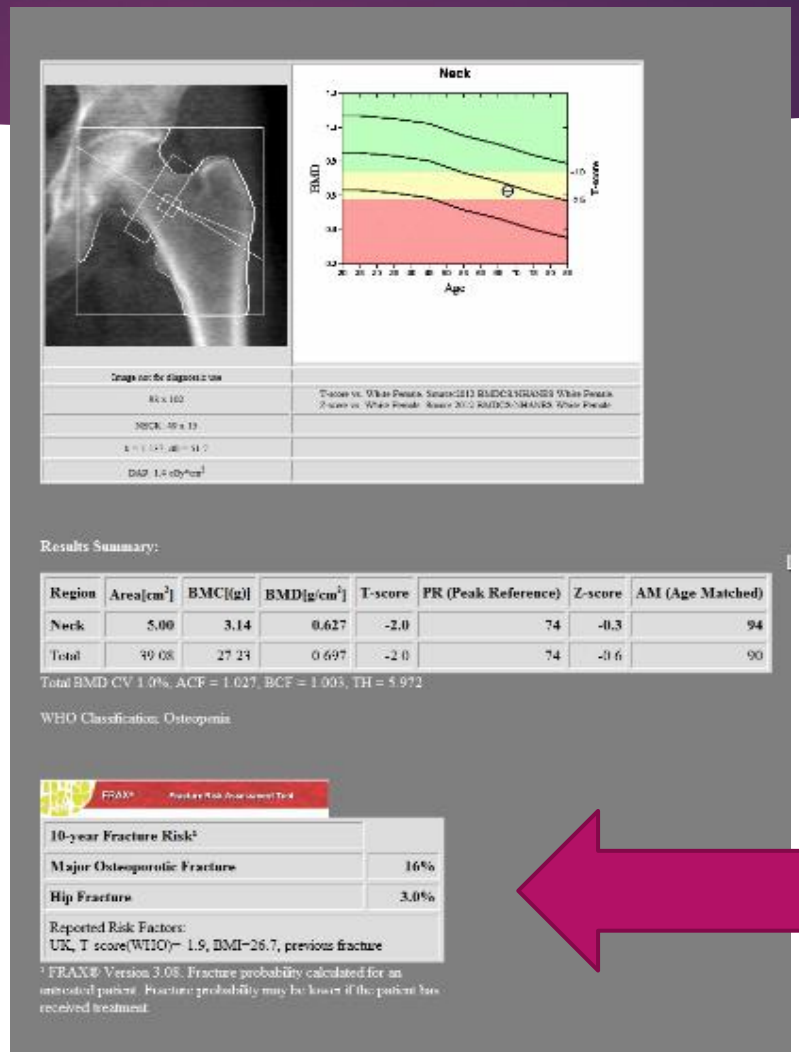
If you have a TBS value, click here: Adjust with TBS

NOGG
National Osteoporosis Guideline Group • UK



It's mostly done for us now!





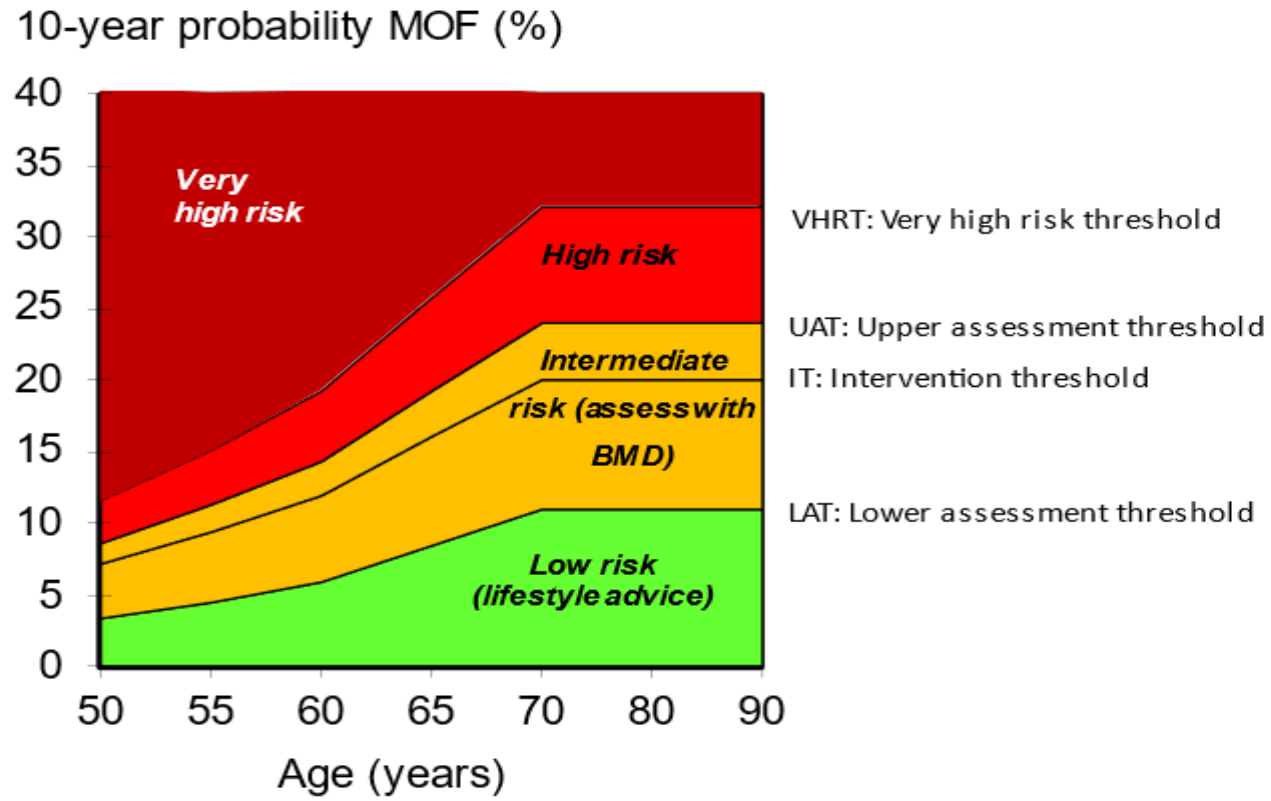
FRAXplus now out

The FRAX score for high fracture risk is defined as a 10-year major osteoporotic fracture probability of ≥20% or a 10-year hip fracture probability of ≥3%.

NOGG Guidelines

FRAX assessment thresholds for ten-year probability of fracture

a. The approach recommended for decision-making is based on fracture probabilities derived from FRAX and can be applied to men and women [78]. This approach is underpinned by cost-effectiveness analysis with oral or intravenous bisphosphonates as the intervention [111, 112]; **(Evidence level Ib)**. FRAX assessment thresholds for ten-year probability of a major osteoporotic fracture (MOF) are shown in Figure 1.



Treatments
Bone Strength = Quality + Density

- **Drugs:**
- Bisphosphonates
- Teriparatide
- Denosumab
- Romozosumab
- HRT
- Abaloparatide now NICE approved

- **Lifestyle:**
- 22 mins brisk activity/day or 75mins high intensity/week
- Avoid excessive flexion in yoga/pilates
- Adequate ca
- Reduce Falls:
  - Muscle strengthening
  - Balance retraining
  - Sufficient duration >6/12

Bisphosphonates

- Inhibit Osteoclastic bone resorption
- Attach to binding sites on bony surfaces, especially surfaces undergoing active resorption
- Osteoclasts absorb the bisphosphonate which slows down their activity and therefore reduces bone breakdown
- Reduce Ca being released from bone can cause a small decrease in serum Ca and compensatory rise PTH
- Proven to reduce fractures in both **Vertebral and Hip** sites

Alendronic Acid 50% reduction in vertebral & hip # Liquid form (BINOSTO)

Risedronate eGFR >30, Alendronate eGFR >35

Horizon Trail for IV Zol Sept 2023

Call to action: a five nations consensus on the use of intravenous zoledronate after hip fracture

Antony Johansen,[✉] Opinder Sahota, Frances Dockery, Alison J Black, Alasdair M J MacLullich, M Kassim Javaid, Emer Ahern, and Celia L Gregson

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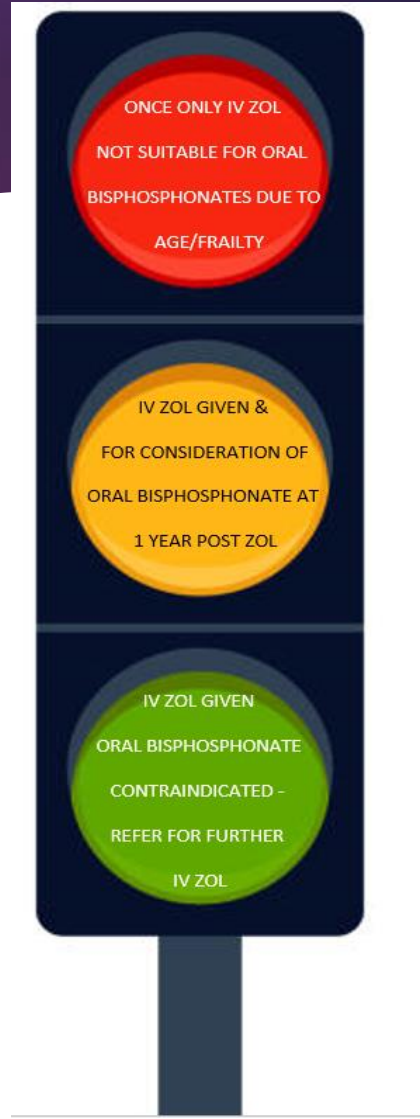
How often does IV Zol need to be given?

The HORIZON recurrent fracture trial specifically focused on patients with hip fracture [14]; three annual doses of 5 mg led to a 35% reduction in clinical fracture risk [44]. Annual 5-mg dosing for 3 years is therefore the standard regimen. The first dose of IV Zol is the most important, and a single dose may suffice for those with more severe frailty and comorbidities associated with high 1-year mortality or when the therapeutic burden of attending a clinic or other external facility to receive further IV Zol appears unrealistic. Notably, the BMD effects of a single dose of IV Zol are maintained for several years in frail nursing home residents and in postmenopausal women [45, 46]. A subgroup analysis of the two HORIZON trials showed people who received just one dose of IV Zol experienced a similar fracture risk reduction after 3 years as those who had all three [47]. Although, the subgroups were different at baseline, those who received one dose had more fracture risk factors. Given the wide confidence intervals for fracture outcomes, it cannot be concluded that a single dose is equivalent to three consecutive annual doses. The HORIZON-PFT Extension continued treatment for a further 3 years and saw a greater vertebral fracture risk reduction in those at higher fracture risk, lending weight to the benefit of repeated IV Zol [48].

RVH Orthogeris Initiative

- Mid Dec 2023
- 481 patients by Sept 2024
- Approx 50% requiring FU

- CrCl >35
- PO Vit D 50,000IU daily for 3-5/7 (guidelines 150,000-250,000)
- 300,000IM if swallowing issues
- Along with maintenance Vit D



Reid IR et al NEJM 2018: 18monthly Zol

Randomized Controlled Trial > N Engl J Med. 2018 Dec 20;379(25):2407-2416.
doi: 10.1056/NEJMoa1808082. Epub 2018 Oct 1.

Fracture Prevention with Zoledronate in Older Women with Osteopenia

Ian R Reid [1], Anne M Horne [1], Borislav Mihov [1], Angela Stewart [1], Elizabeth Garratt [1], Sumwai Wong [1], Katy R Wiessing [1], Mark J Bolland [1], Sonja Bastin [1], Gregory D Gamble [1]

Affiliations + expand

PMID: 30575489 DOI: 10.1056/NEJMoa1808082

Abstract

Background: Bisphosphonates prevent fractures in patients with osteoporosis, but their efficacy in women with osteopenia is unknown. Most fractures in postmenopausal women occur in those with osteopenia, so therapies that are effective in women with osteopenia are needed.

- 18 monthly IV Zol- 4 doses
- 37% ↓ in osteoporotic #
- 34% ↓ in NVF
- 55% ↓ in VFs
- 35% ↓ in death
- 39% ↓ in MI
- 33% ↓ in cancer esp breast
- No. needed to treat 10-15

Denosumab

- Monoclonal Antibody
- Binds to the cytokeine RANKL
- RANKL inhibition blocks osteoclast maturation , function and survival
- Reduces bone absorption
- More potent effect than bisphosphonates
- Rapid onset
- 6 monthly SC injection (half life 26 days)
- **Vertebral and hip # reduction (Vertebral>hip)**

Issues with Denosumab

- Caution in eGFR<30, *can* give if eGFR>15
- Dialysis use does happen
- Do not use if PTH high: accumulative dosing causes inc PTH with each dose
- Low Ca can be profound and prolonged in CKD Stage 5
- Rapid bone density reduction on stopping or late doses
- Need an exit strategy ?age suitability
- Shared care requirement
- Ideally self injection programmes in future

Safety Issues

- Osteonecrosis jaw (external auditory canal):1 in 10,000 Risk ONJ **vs** 1 in 1000 # risk
- Hypocalcaemia esp with Vit D/eGFR
- Atypical # (Denmark Study)- **Bilateral imaging obligatory
- CV Risk: Bone fragility is a marker of cardiovascular risk and vice versa
  - Rx of MI significantly higher within first 30 days of #hip
  - Rx of stroke significantly higher for 10years

HRT

- In majority if women age <60 benefits of HRT outweigh Rx (ideally age 40-50)
- Risks:
  - Breast Ca (age/preparation): Oestrogen only lower Rx than continuous combined
  - Ovarian Ca (small review)
  - VTE (preparation dependent, PO oestrogen 2-4 fold inc Rx in 1st yr of use, dermal or vaginal preparation no inc risk)
  - CVA (age dependent/preparation)
  - Endometrial Ca (cyclical HRT 'safe' for up to 5yrs, gives a monthly bleed)

Teriparatide

NICE-

1.4 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 (as defined in section 1.6), **or** who have had an unsatisfactory response (as defined in section 1.8) 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.

- PTH analog
- New bone formation
- Stimulation of osteoblastic over osteoclastic activity
- **Daily SC injection for 2 years**
- 'one' off treatment course
- Must followup with antiresporptive
- Biososimilars now available: Movymia, Terrosa (launched 2019)
- Avoid if paraprotein band/skeletal malignancy
- **Initial reduction in hip BMD in first 6/12 then improves both hip and spine**

Romosozumab

- Monoclonal Antibody sclerostin inhibitor
- Inhibits bone formation and stimulates bone resorption "dual effect"
- **2 injections SC once/month for 12 months**
- Not licensed for men
- Contraindicated in stroke or MI
- Increased CV risk: 1% risk difference (1 in 100 additional event over 1yr period in studies which didn't exclude MI/Stroke patients)
- QRisk3 Calculator
- **Spine and hip efficacy**

Romo NOGG Guidelines

NOGG/ROS Advisory statement on the prioritisation of romosozumab in clinical practice

Building on NOGG 2021 recommendations, [2] we suggest that referral for, and consideration of treatment with romosozumab, is prioritised **in postmenopausal women who have had a MOF within 24 months, with any one of the following:**

- a BMD T-Score ≤-3.5 (at the hip or spine), or
- a BMD T-score ≤-2.5 (at the hip or spine) and either
  - vertebral fractures (either a vertebral fracture within 24 months or a history of ≥2 osteoporotic vertebral fractures), or
  - very high fracture risk (*e.g.*, as quantified by FRAX).

Following the approved duration of treatment with romosozumab (12 months), treatment with alendronate, zoledronate or denosumab should be initiated without delay.

Abaloparatide

- PTH1 Receptor but with higher affinity than PTH
- No ONJ and less Rx hypercalcaemia
- 18monthly SC injection
- No fridge needed

- T-score between -2.5 and -4.9 at the lumbar spine or femoral neck and radiological evidence of 2 or more mild, or 1 or more moderate, lumbar or thoracic vertebral fractures or history of low-trauma non-vertebral fracture within the past 5 years
- aged over 65 years with the same fracture criteria as the group above, and a T-score between -2.0 and -4.9
- aged over 65 years who did not meet the fracture criteria whose T-score was between -3.0 and -4.9.

Future Treatment Conundrums

Prolia® fracture risk reduction Vs zoledronic acid[1]

Data are derived from real-world sources and not from a controlled clinical study

Major osteoporotic fracture

As early as year 1, Prolia was superior to zoledronic acid in decreasing the risk of major osteoporotic fracture[1]

The benefit increased over time in the study

- Major osteoporotic fracture defined as nonvertebral fracture and hospitalized vertebral fracture
- Average follow-up was longer for Prolia® (mean: 1.52 years, median: 1.18 years) compared to zoledronic acid (mean: 1.44 years, median: 1.16 years)
- *$p < 0.05$

- When to treat
- What order of drug therapy to use
- Duration of Treatments
- New biosimilars emerging
- Patients living longer
- 80 year olds can be amazing…is 80 the new 60…???
- Cost of this and lack of services

NHSCT FLS

- Virtual Nurse Led Screening Service
- Not supported by an Osteoporosis Service as yet
- Active recruitment rather than referral process
- Age 50-80
- eGFR>30
- 1 Virtual Cons clinic/month for complex cases
- Remember IV Zol in RVH to be noted on letters
- Fracture.LiaisonService@northerntrust.hscni.net

Conclusion

- Background/Definitions
- Epidemiology
- Diagnosis & Screening
- Treatment decisions
- Treatment options & Safety Issues
- Future Treatment conundrums
- NHSCT FLS Overview

Other Reading

- Secondary Causes of Osteoporosis
- Steroid dosing and secondary prevention
- Interpreting dexas
- Early onset osteoporosis
- Bone turnover markers

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- **NOGGClinicalguidelineforthepreventionandtreatmentofosteoporosis (2021).**Availableat:https://www.nogg.org.uk/full-guideline(Lastaccessed:August11,2023