# DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

# OSTEOPOROSIS GUIDELINE

- This guideline incorporates some of the recommendations from SIGN, NICE, National Osteoporosis Guideline Group (NOGG) and local expert opinion. It adopts a pragmatic approach to assess patients' risk of fracture in conjunction with the use of bone mineral density (BMD) measurement.

- The use of BMD alone to assess fracture risk has a high specificity but low sensitivity. This means that most osteoporotic fractures will occur in women who do not have osteoporosis as defined by a T-score of less than -2.5. Therefore, clinical risk factors and/or BMD can be considered for treatment.

- Patients with clinical risk factors should be considered for fracture risk assessment using FRAX® tool. In the absence of BMD patients are categorised into having very high, high, intermediate, or low fracture risks
  - Individuals with very high risk should be considered for advice & guidance/ referral to osteoporosis specialist for assessment and consideration of parenteral treatment. Oral treatment should be discussed with and commenced for the patient in meantime.
  - Individuals with high risk should be offered for treatment
  - Individuals with intermediate risk are considered for DXA and recalculation of the fracture risk.
  - Individuals with low risk are re-assessed in 5 years.

- For patients that are categorised as intermediate risk are unable to undergo bone densitometry due to any existing health condition, specialist opinion can be sought if required via the electronic referral system.

- Population screening for osteoporosis is not recommended. Do not routinely assess fracture risk in people under the age of 50 unless they have major risk factors (corticosteroid user, untreated premature menopause or previous fragility fracture) because they are unlikely to be at high risk.

- Patients who have sustained a clinically apparent osteoporotic fragility fracture will usually be reviewed by the Fracture Liaison service. A DXA scan may be arranged and clinical review offered. In other cases letters of advice are sent to the patients GP regarding treatment of osteoporosis.

- Osteoporosis may be assumed in women aged 75 years or older who have sustained fragility fracture if a DXA scan is considered to be clinically inappropriate or unfeasible. Local practice is that treatment rather than investigation with DXA benefits this patient group.

- Consultant will advise patients with breast cancer on aromatase inhibitor (e.g. anastrozole, exemestane, letrozole) regarding bisphosphate treatment at initiation. For male patients with prostate cancer, specialist will risk assess using FRAX and advice on treatment.

- Weekly oral bisphosphonate is the first-line treatment. Options include risedronate 35mg or alendronic acid 70mg. Patients should comply with administration instructions to minimise oesophageal irritation.

- Information regarding bisphosphonate treatment length/treatment breaks can be found in a separate guidance.

## Content



### Definitions

| | |
|---|---|
| **Osteoporosis** | WHO: A bone mineral density (BMD) of 2.5 standard deviations (SD) or more **below** the mean peak mass of average of young healthy women, as measured by dual-energy X-ray absorptiometry (DXA). (Reported as a T-score) |
| **Osteopenia** | As above with T-score between -1.0 SD and -2.5 SD |
| **Fragility fracture** | Fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level trauma (e.g. falling from a standing height or lower) |

### Abbreviations

| | |
|---|---|
| BMI | Body Mass Index |
| BMD | Bone mineral density |
| CKD | Chronic Kidney Disease |
| DXA (DEXA) | Dual energy X-ray absorptiometry |
| GNRH | Gonadotropin-releasing hormone |
| IBS | Irritable Bowel Syndrome |
| MS | Multiple Sclerosis |
| NOGG | National Osteoporosis Guideline Group |
| ONJ | Osteonecrosis of the jaw |
| PPIs | Proton Pump inhibitors |
| RA | Rheumatoid arthritis |
| SLE | Systemic Lupus Erythematous |
| SSRI | Selective Serotonin Re-uptake Inhibitors |

## 1. Adult Osteoporosis Treatment Pathway

**Fragility Fracture**

Fracture Liaison Service (FLS)

Perform fracture risk assessment, and if required, DXA, and review in clinic OR write to GP advising treatment

(Osteoporosis often assumed in women aged over 75 with fragility fracture where DXA inappropriate or unfeasible)

Exclude non-osteoporotic causes and causes of secondary osteoporosis

**On or commencing high dose oral corticosteroid (≥7.5mg prednisolone per day or equivalent) for ≥3 months**

**Clinical Risk Factors** – Consider assessment of fracture risk in patients with significant risk factor or **2** other risk factors.

*Do not routinely test fracture risk in people under the age of 50 or premenopausal women (seek specialist advice)*

**Calculate 10 year fracture risk using FRAX® tool**

Very High or high risk | Intermediate | Low risk

**Risedronate 35mg once weekly** or
**Alendronic acid 70mg once weekly**
(effervescent tabs for dysphagia/long-term swallowing difficulties only. Do NOT use with thickener)

Take tablet as whole on arising, at least 30min before the first food or drink or other medicines, with full glass of water. Stay upright for at least 30min after

Be aware of relevant MHRA safety advice regarding oesophageal reactions, ONJ & atypical femoral fracture. Pregnancy should be excluded prior to starting treatment

Elderly patients that are housebound or living in residential/ nursing homes are likely to gain benefit from lifelong calcium + vitamin D supplementation

High risk patients less than 85 years old often benefit from a Bone Density scan pre-treatment as a baseline for further assessments whilst on treatment

***Refer*** if above treatments are not suitable or not tolerated
**Individual with very high risk - consider advice & guidance/ referral** for assessment & consideration of parenteral treatment. Discuss &commence oral treatment in the meantime.

**DXA & recalculate FRAX®**

**Then treat as very high, high, or low risk**

*If age-matched percentage <80% i.e. Z score <-2.0: exclude non-osteoporotic causes and causes of secondary osteoporosis (consider referral)*

Reassure reassess in 5 years or less depending on the clinical context

**Specialist referral**
Other treatment may be considered (denosumab, HRT, teriparatide, raloxifene, strontium, zoledronate)

***Investigate and address if underlying causes are suspected*** (especially in patients with vertebral fractures and in people with fragility fracture who are at low risk e.g. men, pre-menopausal women, women with premature menopause)

***Refer*** if no apparent cause found and severity of osteoporosis high

***Significant risk factors:***

- History of fragility fracture
- Parental history of hip fracture
- *Low BMI (<18.5kg/m$^2$)
- ≥3 months oral corticosteroid use

*Other risk factors*

- Women aged >65 or Men >75
- *Smoking
- *Alcohol intake per week >14 units
- Rheumatoid arthritis
- Diabetes
- Asthma/COPD
- Chronic liver disease
- Moderate to severe CKD (eGFR<60ml/min)
- Neurological diseases (alzheimers, parkinsons, stroke, MS)
- Recurrent falls
- inflammatory bowel disease, coeliac or malabsorption
- Institutionalised patients with epilepsy
- Primary hyperparathyroidism and endocrine diseases
- Drug therapy: antiepileptics, pioglitazone, GnRH agonists, aromatase inhibitors, long term depo progesterone acetate

* Modifiable risks- patients should be encouraged to achieve IBW, give up smoking & reduce alcohol intake.

Management strategy should be made on an individual basis after informed discussion about risk and benefit. See NICE decision support tool. NICE TA464: oral bisphosphonates are options for treating osteoporosis in patients who have been assessed as being at higher risk of osteoporotic fragility fracture and when bisphosphonate treatment is appropriate, taking into account risk of fracture, risk of adverse effects from bisphosphonates, and clinical circumstances and preferences.

## 2. Risk assessment Tool

The use of BMD has a high specificity but low sensitivity. This means that most osteoporotic fractures will occur in women who do not have osteoporosis as defined by a T-score of less than -2.5. For this reason population screening is not recommended and risk factors listed above are considered.

NICE CG146 recommends assessing fracture risk but does not specify a tool (FRAX® or QFracture®)
**The FRAX® tool (www.shef.ac.uk/FRAX) is the preferred risk tool recommended by JAPC**

FRAX® tool was developed based on extensive data on multiple cohorts, and a version calibrated to fracture epidemiology in the UK is available. It computes the 10 year probability of hip fracture or a major osteoporotic fracture, and can be calculated with or without BMD.
In absence of BMD NOGG recommends patients are categorised as having:-

- very high risk- patients with probability grossly above the upper assessment threshold
- High risk- patients with probability above the upper assessment threshold
- Intermediate risk- patients with probability between upper and lower assessment threshold
- Low risk- patients with probability below the lower assessment threshold

*Interpret the estimated 10-year fracture risk with caution in people aged 80 years and over*, as the short-term fracture risk may be underestimated.

The national osteoporosis society gives useful advice regarding repeating DXA scans. The decision as to whether and when to repeat a DXA scan depends on the initial results and the individual patient's circumstances. However, it is rarely helpful to repeat DXA scans within 2 years.

## 3. Investigations for osteoporosis

Investigate and address if underlying causes are suspected as per detailed below. This is especially important in patients with vertebral fractures and in people with fragility fracture who are at low risk e.g. men, pre-menopausal women, women with premature menopause.

If no apparent cause found *and* severity of osteoporosis high (multiple fractures or significantly reduced bone density compared to that expected for age i.e. if age-match percentage <80% Z score <-2.0), referral to osteoporosis clinic may be appropriate for more thorough investigation. This is more likely to be the case for younger patients or men presenting with osteoporosis but the full detail of the case should be considered rather than having an age or sex based criteria for referral.

| Underlying Causes suspected | Investigations |
|---|---|
| Malabsorption, malignancy, inflammatory disease | FBC, ESR, coeliac antibodies |
| Osteomalacia, hyperparathyroidism, bone metastases | Calcium, phosphate, Alk Phos, vitamin D |
| Liver disease | LFT |
| Renal disease | Creatinine |
| Hyperthyroidism | TSH |
| Male Hypogonadism | Testosterone, SHBG |

| Causes of secondary osteoporosis | Non-osteoporotic causes & features for fragility fractures |
|---|---|
| • Endocrine conditions such as untreated premature menopause in women, hypogonadism in men, diabetes mellitus, hyperthyroidism, hyperprolactinaemia and Cushing's disease.<br>• Rheumatological conditions such as rheumatoid arthritis, and other inflammatory arthropathies.<br>• Gastrointestinal conditions that cause malabsorption such as Crohn's disease, ulcerative colitis, coeliac disease, and chronic pancreatitis.<br>• Chronic liver disease.<br>• Chronic obstructive pulmonary disease | • Metastatic bone disease - bone pain, history of cancer (especially lung, thyroid, prostate, kidney, or breast cancer), or symptoms of undiagnosed cancer (for example unexplained general malaise or weight loss).<br>• Multiple myeloma - bone pain, anaemia, recurrent infections, bleeding, symptoms of hypercalcaemia, or kidney disease.<br>• Osteomalacia - bone pain, muscle pain, or proximal muscle weakness.<br>• Paget's disease - bone pain or deformity |

## 4. Corticosteroid users

Patients commencing high dose corticosteroids (≥7.5mg per day prednisolone or its equivalent for ≥3 months) should be offered bone protection with bisphosphonate. Patients with additional risk factors may require a full treatment course of bisphosphonate beyond corticosteroid use. This would mean 5/10years referring to the treatment break guidelines. Indication for a full length of treatment should be determined by being high risk in a FRAX assessment at the start of treatment, or if new risk factors arise by the point corticosteroids complete.

Patients taking lower doses of oral corticosteroid long-term should be considered for fracture-risk assessment.

For patients starting on very high doses of steroids or a prolonged duration is anticipated, e.g. giant cell arteritis, it may be appropriate to commence bisphosphonates at the outset as significant bone loss occurs early on.

FRAX assumes an average dose of prednisolone and may underestimate fracture risk in patients taking higher doses, and overestimate risk in those taking lower doses.

Those aged 30-40 years of age who cannot be risk assessed using FRAX and taking 7.5mg or more per day of oral prednisolone for 3 months or longer require a BMD assessment using DXA. People under 30 would not yet have reached peak bone mass therefore DXA may not be appropriate.

## 5. Pharmaceutical management

**Bisphosphonates**

**Risedronate 35mg once weekly** (may have better gastrointestinal tolerance) or
**Alendronic acid 70mg once weekly**

An oral bisphosphonate is cost effective for treating osteoporosis in adults if the person is eligible for risk assessment on osteoporosis and has been assessed as being at higher risk of osteoporotic fragility fracture using FRAX or QFracture (NICE TA 464). Decision on treatment should be made on an **individual basis** after an **informed discussion** between the clinician and the patient about the advantages and disadvantages of the treatments available. (NNT at 1% risk is 200 for vertebral fractures and 333 for hip fractures) See NICE Patient decision aid and appendix 1.

Reflux and dyspepsia are common side-effects of alendronate. Patients presenting should be checked for concordance and asked to follow instructions – tablet to be taken whole on arising with full glass of water, at least half an hour before the first food or drink (except water) in the morning. Patients should not lie down or return to bed after taking the medication. *PPIs should **not** be used to treat reflux type symptoms.*

MHRA has issued guidance on the use and safety of bisphosphonate. Side effects and concerns:

- Atypical femoral fractures reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis (MHRA 2011 )
- Osteonecrosis of the jaw (ONJ) is a recognised complication of antiresorptive treatments- risk with oral bisphosphonates is low. Cancer patients should have a dental check-up before bisphosphonate treatment (MHRA 2009)
- Oral formulations with serious oesophageal adverse reactions
- Very rare reports of osteonecrosis of the external auditory canal (MHRA 2015)

Patients should be advised to:

- Stop taking the bisphosphonate and seek medical advice if they experience any signs or symptoms of possible oesophageal reaction, for example dysphagia, pain on swallowing, retrosternal pain, or new/worsened heartburn.
- Have a regular dental check-up and to tell their dentist that they are taking a bisphosphonate, particularly if they are going to undertake invasive dental procedures.

- Report any pain in the thigh, hip, or groin, as 'incomplete' atypical femur fractures can occur, with some people experiencing pain weeks to months before presenting with a completed fracture

Alendronic acid 70mg effervescent tablets (Binosto) may be considered for patients with dysphagia/ long-term swallowing difficulties. Follow manufacturer's administration direction. Patients should not swallow the undissolved effervescent tablet, should not chew the effervescent tablet or allow the effervescent tablet to dissolve in their mouths because of the risk for oropharyngeal irritation. Not to be used with thickening agent.

**If an oral bisphosphonate is not tolerated or is contraindicated, consider specialist referral.** Specialist treatment options include denosumab, HRT, teriparatide, raloxifene, strontium ranelate & zoledronic acid.

Bisphosphonate length of treatment in osteoporosis (see JAPC local guidance )
Data suggests that the longer-term use of oral bisphosphonate treatment may be associated with increased risk of drug-related side effects, in particular, atypical femur fracture. It has been suggested that patients on oral bisphosphonates may benefit from 'drug breaks' following a spell on treatment (particularly after 5 or more years of use) in the hope that this may reduce the risk of skeletal adverse effects. If treatment is discontinued, fracture risk should be re-assessed after a new fracture; or if no new fractures, after 2 years.

## Calcium and vitamin D

Combination treatment (Calcium + Vitamin D)
Patients should aim for 1000 mg Calcium daily. Use Calcium calculator https://www.iofbonehealth.org/calcium-calculator

Calcium supplementation alone should not be recommended as a means of fracture prevention in those not on a bisphosphonate.

If there is adequate Calcium and vitamin D intake, then no supplementation is required. Elderly patients that are housebound or living in residential/ nursing homes are likely to gain benefit from lifelong calcium + vitamin D supplementation. A combination treatment of calcium and vitamin D is recommended if both are required and to aid compliance. However, compliance and persistence with supplementation is poor.

Formulary choices:

| Brand and dose | Dose | Formulation |
|---|---|---|
| Calci-D<br>(calcium 1000mg + VitD3 1000units) | Take one daily | Chewable tablet (as an option for patients with compliance issue) |
| Accrete D3 tabs<br>(calcium 600mg+ VitD3 400units) | Take one twice daily | Film coated tablets |
| Evacal D3<br>(calcium 600mg+ VitD3 400units | Take one twice daily | Chewable tablet |
| Adcal D3 CAPLET<br>(calcium 300mg + VitD3 200units) | Take TWO twice daily | Caplet (smaller size if unable to swallow tablets/capsules; stability in a MCA for up to 14days) |
| Adcal D3 Dissolve<br>(calcium 600mg + vit D3 400iu) | Take one twice daily | Effervescent tabs* (option for patients with swallowing difficulties) |

*contains approx. 42mg sodium per tablet, equivalent to 2.1% of the WHO recommended max. daily intake of 2 g sodium for an adult

Calcium supplements should not be taken within two hours of bisphosphonates. As the dose is supplemental, routine monitoring is not thought necessary except in patients with renal impairment where caution is advised. Avoid in patients with hypercalcaemia, metastatic calcification and a history of calcific renal stones.

**The following treatments may be considered by specialist if first/second line treatments are not suitable or not tolerated**

**Denosumab** AMBER

Denosumab 60mg (injected every 6 months) may be used under the shared care agreement. Compliance with NICE TA 204 criteria (listed below) from the specialist should be evidenced.

- Primary prevention of osteoporotic fragility fractures in patients who are intolerant, contraindicated, or unable to comply with special instructions for administrating alendronate and risedronate ***and*** who have a combination of T-score, age and number of independent clinical risk factors for fractures as indicated in the following table.

| | **Number of independent clinical risk factors for fracture** (parental history of hip fracture; alcohol intake of 4 more units per day; rheumatoid arthritis) | | |
|---|---|---|---|
| Age (years) | 0 | 1 | 2 |
| 65-69 | NOT recommended | −4.5 | −4.0 |
| 70-74 | −4.5 | −4.0 | −3.5 |
| 75 or older | −4.0 | −4.0 | −3.0 |

- Secondary prevention of osteoporotic fragility fractures in patients who are intolerant, contraindicated, or unable to comply with special instructions for administrating alendronate and risedronate.

It is important to check calcium & vitamin D levels before each dose due to risk of severe hypocalcaemia (MHRA 2012). ONJ occurs rarely with denosumab (MHRA 2014) and good oral hygiene practices should be maintained during treatment. There is an increased risk of multiple vertebral fractures after stopping or delaying on-going treatment with denosumab (MHRA 2020).

**Hormone Replacement Therapy**

HRT is recommended by the National Osteoporosis Society for women under the age of 60 years when the benefits of treatment outweigh the risks. There are a large number of formulations of oestrogen or oestrogen plus progestagen combinations, some of which are licensed. The unfavourable risk/benefit balance in older postmenopausal women, suggest that the use of HRT for osteoporosis prevention is mostly restricted to younger postmenopausal women who are at high risk of fracture and also have menopausal symptoms.

**Parathyroid hormone (teriparatide)** RED

This is licensed for the treatment of osteoporosis but should be reserved for specialist advice. It has been designated a RED drug in Derbyshire and will be under the care of secondary care. Duration of treatment is to 2 years.

**Romosozumab** RED

Romosozumab is recommended as an option for treating severe osteoporosis in people after menopause who are at high risk of fracture, only if:

- they have had a major osteoporotic fracture (spine, hip, forearm or humerus fracture) within 24 months (so are at imminent risk of another fracture) and
- the company provides romosozumab according to the commercial arrangement.

**Selective oestrogen receptor modulator (Raloxifene)** GREEN after specialist initiation

Licensed for the treatment of post-menopausal osteoporosis but should be reserved after consultant initiation at a dose of 60mg per day taken at any time without regard to meals. Treatment is likely to be more effective if calcium and vitamin D is also given.

**Strontium Ranelate** RED

Reserved for patients who have had an atypical femur fracture that do not fulfil criteria for teriparatide. Advice by the MHRA (March 2014) is that strontium should only be prescribed to patients who do not have a history of heart problems and if the patient is unable to take other medicines for this condition.

The EMA also advised that the patients' risk of developing cardiovascular disease should be evaluated before starting treatment and on a regular basis thereafter, generally every 6 to 12 months.

Strontium should not be started in people who have or have had :-

- Ischaemic heart disease
- Peripheral arterial disease
- Cerebrovascular disease
- Uncontrolled hypertension

**Zoledronic acid** **RED**

Intravenous bisphosphonates are options for treating osteoporosis in adults who have been assessed as being at higher risk of osteoporotic fragility fracture as per NICE TA464. Choice of treatment is made on an individual basis after informed discussion with a specialist.

Zoledronate has been associated with renal impairment, therefore in patients at risk e.g. pre-existing renal disease, renal function monitoring should be considered.

## 6. Biochemical markers of bone turnover in osteoporosis

The place of biochemical indicies of skeletal turnover still requires further research before used in routine clinical practice. In secondary care the use of N-terminal propeptide of type 1 procollagen (PINP) and C-terminal telopeptide of type 1 collagen (CTX) are internationally recognised as useful to guide decision making.

## Reference


1. NICE CG146. Osteoporosis: assessing the risk of fragility fracture- August 2012, last updated Feb 2017
2. SIGN 142: Management of osteoporosis and the prevention of fragility fractures. March 2015, revised Jan21
3. JAPC-Guidance on the prevention, diagnosis and management of Vitamin D deficiency in primary care
4. NICE TA 204 Denosumab for the prevention of osteoporotic fractures in postmenopausal women. October 2010
5. NOGG Clinical guideline for the prevention and treatment of osteoporosis. 2017, updated July 2019
6. NICE TA464 Bisphosphonates for treating osteoporosis. August 2017, last updated July 2019


## Reviewed in consultation with

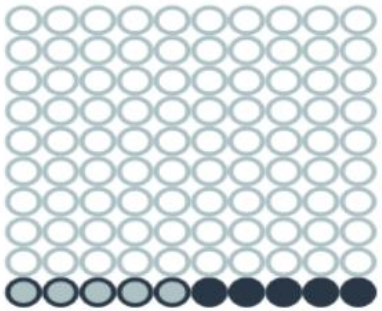
Michelle Hui, Antonia Ugur, Ram Laxminarayan, Puneet Srivastava, Sarah Broadhurst, Peggy Katambi, Gemma O'Hara and Emma Stanley, UHDB, and Keven Fiarburn on behalf of CRHFT.

| Document control | Date |
|---|---|
| Clarification for high dose steroids added page 5 | July 2022 |
| Adcal D3 dissolve replaces Calfovit sachets | December 2022 |
| Advice for 'very high risk' category from FRAX added; treatment flow chart updated to include very high risk | March 2023 |
| Oral weekly risedronate and alendronic acid both listed as first line option | May 2023 |

**Appendix 1: Effect of bisphosphonates on the risk of fractures**
**(see NICE patient decision aid- [Bisphosphonates for treating osteoporosis])**

## Effect of bisphosphonates on the risk of vertebral (spinal) fractures

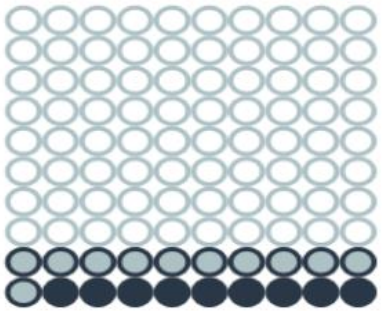
### 10 in 100 (10%) baseline risk



On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:

- about 90 people will not have a vertebral fracture and would not have done anyway
- about 5 people avoid getting vertebral fractures because they have bisphosphonate treatment
- about 5 people get vertebral fractures even though they have bisphosphonate treatment.

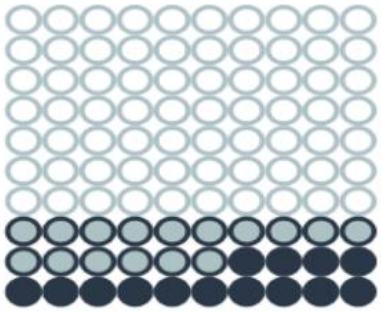
### 20 in 100 (20%) baseline risk



On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:

- about 80 people will not have a vertebral fracture and would not have done anyway
- about 11 people avoid getting vertebral fractures because they have bisphosphonate treatment
- about 9 people get vertebral fractures even though they have bisphosphonate treatment.

### 30 in 100 (30%) baseline risk



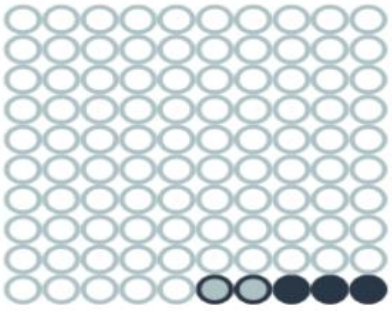
On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:

- about 70 people will not have a vertebral fracture and would not have done anyway
- about 16 people avoid getting vertebral fractures because they have bisphosphonate treatment
- about 14 people get vertebral fractures even though they have bisphosphonate treatment.

**It is not possible to know in advance what will happen to any individual person**

## Effect of bisphosphonates on the risk of hip fractures

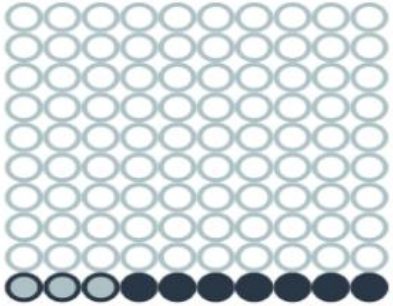
### 5 in 100 (5%) baseline risk



On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:

- about 95 people will not have a hip fracture and would not have done anyway
- about 2 people avoid having a hip fracture because they have bisphosphonate treatment
- about 3 people have a hip fracture even though they have bisphosphonate treatment.

### 10 in 100 (10%) baseline risk



On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:

- about 90 people will not have a hip fracture and would not have done anyway
- about 3 people avoid having a hip fracture because they have bisphosphonate treatment
- about 7 people have a hip fracture even though they have bisphosphonate treatment.

### 20 in 100 (20%) baseline risk

On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:

- about 80 people will not have a hip fracture and would not have done anyway
- about 7 people avoid having a hip fracture because they have bisphosphonate treatment
- about 13 people have a hip fracture even though they have bisphosphonate treatment.

**It is not possible to know in advance what will happen to any individual person**