Osteoporosis

This is a common disorder and yet there are still many important unanswered research questions which prevent us from knowing what constitutes best care.

Osteoporosis statistics:

- At age 50y, 1 in 3 women and 1 in 5 men will sustain a fracture in their remaining lifetime.
- 50% of patients with an osteoporotic fracture will sustain another and the risk rises exponentially with each fracture.
- In secondary prevention, although the relative risk reduction looks impressive (treatment reduces risk of a further fracture by 50%):
  - the NNT to prevent one vertebral fracture over 3y is 9–21 (that is 9–21 people must be treated for 3y to prevent one vertebral fracture)
  - the NNT to prevent one hip fracture over 3y is 48–91.

In primary prevention a significant absolute risk reduction has not yet been demonstrated.

Most of us have been using the 2014 NICE guidance on osteoporosis to guide our clinical management. However, these guidelines are now largely irrelevant. Published in several parts, the recommendations were based mainly on cost, and since then several of the drugs have come off patent and become significantly cheaper, whilst new drugs such as denosumab, have become much more widely used. NICE was due to publish an update in December 2015 but this has been postponed.

New guidance has been produced by SIGN (SIGN 2015, 142) and in some respects it is simpler and more relevant than the NICE guidance. For this reason we have summarised the SIGN guidance here followed by an explanation of where it differs from NICE. We have also attempted to address some of the questions that are raised, but not answered, by the guidance.

The references to the NICE guidance, for those who want to look them up are: NICE 2014, CG146; 2011, TA160 and TA161.

First some definitions:

<table>
<thead>
<tr>
<th>Osteoporosis definitions</th>
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</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>A disorder of reduced bone density and abnormal bone microarchitecture defined by a statistical construct where an individual has a bone mineral density (BMD) on DEXA scan of ≤–2.5 standard deviations from the mean of a healthy young woman (the T-score).</td>
</tr>
<tr>
<td>Severe osteoporosis</td>
<td>BMD T-score ≤–2.5 standard deviations from mean AND history of one or more fractures.</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Reduced BMD. T-score between –1 and –2.5 standard deviations from the mean.</td>
</tr>
<tr>
<td>Fragility fracture</td>
<td>Fracture caused by an injury insufficient to fracture a normal bone, e.g. a fall from standing height or less or no trauma at all.</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>Detecting patients at risk of osteoporosis based on clinical risk factors and determining whether to do a DEXA and then consider treatment. The aim is to identify reversible causes and reduce future fracture risk.</td>
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</tbody>
</table>
Key messages from the SIGN guidance

Primary prevention

- For primary prevention risk assess those aged ≥50y or over if they have clinical risk factors, using QFracture or FRAX tools. Do not risk assess if under 50y unless very strong risk factors (risk factors listed in table below).
- Do a DEXA scan if QFracture or FRAX suggests absolute risk of fracture ≥10% over 10y.
- Offer treatment to those who have both a fracture risk ≥10% over 10y AND T-score ≤−2.5.

Secondary prevention

- People aged ≥50y with a history of fragility fracture should be offered a DEXA scan and started on treatment if osteoporosis is confirmed (T-score ≤−2.5).

Treatment

- Oral bisphosphonates (alendronate or risendronate) remain first line options with IV zoledronate or denosumab alternatives if these are not tolerated.
- Where possible aim to get calcium from dietary sources (use a calcium calculator to see if achieving consumption of 700mg daily or more) and consider the need for vitamin D supplements.
- If calcium intake is inadequate, a combined calcium and vitamin D preparation may be prescribed.

SIGN 2015, 142 Osteoporosis: fracture risk assessment

Note SIGN focuses predominantly on post-menopausal women, the most commonly affected group and the group for which there is most evidence.

For men, or pre-menopausal women, assess risks, etc. as per this guidance, but think about whether further investigations/advice is needed, particularly in men where there is much more likely to be a cause for their osteoporosis.

Men, and those on glucocorticoid-induced osteoporosis, are discussed later in this article.
Risk factors
(used when deciding whether to do fracture risk assessment in primary prevention, see flow diagram above)

This table highlights the key factors to consider but allows clinical discretion - it isn't a tick box exercise, but that makes it tricky!

The risk factors in **bold** have the strongest evidence base of risk.

SIGN say that for those ≥50y the presence of one of these risk factors, should make you 'consider doing a fracture risk assessment, particularly in the presence of other risk factors'.

This is a bit vague. Do SIGN really want us to do a fracture risk assessment in every smoker aged 50y or more?

It is also at times contradictory (for example, in the non-modifiable risk factors box are 'female sex' but also 'age >65y in women'. So do you do a fracture risk assessment in a 60 year old woman or not?

In reality therefore we think we will interpret this as follows:

- ≥50y and 2 or more risk factors: seriously consider doing a fracture risk assessment.
- 1 risk factor only: base your decision on which risk factor (personally, for untreated early menopause I would risk assess, whereas I probably wouldn't for everyone who was inactive).

<table>
<thead>
<tr>
<th>Non-modifiable risk factors</th>
<th>Modifiable risk factors</th>
<th>Co-existing diseases</th>
<th>Drug risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65y in women</td>
<td>Known low bone density</td>
<td>Diabetes</td>
<td>Long term SSRIs</td>
</tr>
<tr>
<td>Age ≥75y in men</td>
<td>Alcohol intake &gt;3.5 units/d</td>
<td>Rheumatoid arthritis/SLE</td>
<td>Enzyme inducing anti-epileptics</td>
</tr>
<tr>
<td>Female sex</td>
<td>Low BMI &lt;20kg/m²</td>
<td>Inflammatory bowel disease</td>
<td>Aromatase inhibitors</td>
</tr>
<tr>
<td>Caucasian ethnicity</td>
<td>Smoking</td>
<td>Malabsorption syndromes including coeliac</td>
<td>GnRH agonists in men with prostate cancer</td>
</tr>
<tr>
<td>Any previous fracture (including non-fragility)</td>
<td>Physical inactivity</td>
<td>Institutionalised epilepsies</td>
<td>Long term DMPA (&gt;2y)</td>
</tr>
<tr>
<td>Parental history of osteoporosis</td>
<td></td>
<td>HIV on HAART treatment</td>
<td>Long term PPIs</td>
</tr>
<tr>
<td>Late menarche (&lt;16y)</td>
<td></td>
<td>Hyperthyroidism</td>
<td>Oral glucocorticoids</td>
</tr>
<tr>
<td>Untreated early menopause (&lt;45y)</td>
<td></td>
<td>Hyperparathyroidism</td>
<td>Glitazones</td>
</tr>
</tbody>
</table>

| Neurological disease (including dementia, stroke and Parkinson's, MS) | Moderate to severe CKD (if eGFR <30ml/min/1.73m² then specialist assessment bone health is needed! | | |
**Frequently asked questions**

As I stated at the beginning, the SIGN guidelines (SIGN 2015, 142) have simplified NICE previous offerings – here I will highlight significant differences and attempt to address some of the unanswered questions that remain a challenge in osteoporosis.
Which fracture risk assessment tool?

There are two widely available tools for assessing fracture risk; QFracture and FRAX.

**QFracture**
- Developed in the UK from the GP research database and can be used to predict absolute fracture risk over a chosen time frame from 1 to 10y.
- Has been independently validated in a cohort separate from its development.
- Includes more variables and particularly ethnicity, quantification of factors such as amount smoked/alcohol consumed, drug dosages, etc. It also separately considers the co-existing conditions that can result in secondary osteoporosis.
- It cannot, however, be recalculated to incorporate bone mineral density.
- It can be incorporated into many UK primary care computer systems and is freely available on the web.

**FRAX**
- FRAX was developed as part of a population cohort study based in countries across the world but including the UK.
- Available for free through the web and integrated into many primary care systems including EMIS, Vision and SystemOne.
- Allows, but does not require, incorporation of measured bone density.
- Calculates a 10y absolute fracture risk.

Which should we use?

NICE offer free choice of which tool to use and unhelpfully offer no guidance on how to use the tools to determine whether to perform a DEXA scan and whether to start treatment.

SIGN recommend the use of a risk assessment tool and proceeding to DEXA if absolute risk over 10y is 10% or more. They favour QFracture over FRAX for the following reasons:
- The underlying algorithm of FRAX has not been published in the public domain and it has therefore not been possible for it to be publicly validated.
- One available study comparing FRAX with QFracture suggests that it:
  - overestimates the risk of hip fracture in the UK population, particularly in those at low risk
  - underestimates the risk of fracture in older people.
- QFracture has been widely tested and validated in the UK population and is more accurate at predicting fracture risk. It has more extensive and comprehensive consideration of risk factors.

Treating without DEXA scans

This is an area where SIGN and NICE differ. SIGN favour the use of DEXA scans in almost all primary and secondary prevention situations. This is because the research studies which have shown benefits of treatment for osteoporosis did DEXA scans for all patients and have excluded patients who did not meet the criteria for osteoporosis, i.e. did not have reduced bone density. The benefits of treatment in patients who have not had a DEXA are therefore unknown.

NICE suggest it is acceptable in patients aged >75y with fragility fracture to presume osteoporosis without DEXA and treat accordingly in discussion with the patient.

These differences have resource implications.

Thresholds for starting treatment in primary prevention

Again, NICE and SIGN differ here.

**What do NICE say?**

The NICE guideline was published in 2008 and updated in 2011 (TA160, TA 161) and the guidance it offered about when to start treatment and which treatments could be considered was based on a complex interplay between number of risk factors and T-score values. They suggested using a fracture risk assessment tool but did not offer guidance on how to interpret the results.

Ultimately it was based on the cost of the different osteoporosis treatments at that time and this is largely irrelevant now as several of the drugs have come off patent and new drugs, e.g. denosumab have become more widely used. NICE was due to publish an update in December 2015 but this has been postponed.

As it stands, it is not particularly clinically useful in current practice and we feel SIGN is more straightforward to use.

**What do SIGN say?**

SIGN were much more prescriptive suggesting offering treatment to those with:

- A 10y fracture risk of 10% or more AND confirmed osteoporosis on DEXA scan.
In their full guidance they acknowledge that there is no study that has prospectively assessed the benefits of anti-osteoporosis medication in primary prevention based on risk scores.

However, retrospective application of risk scores to the big osteoporosis trials, e.g. FLEX and FREEDOM demonstrated that treatment significantly reduced the risk of fracture in patients with a risk of 10% or more AND low BMD.

We do not know if those at lower risk would have benefitted because they were not included in the studies.

*This is imperfect but it is the best information we have and fairly simple to use.*

### Choosing drug treatments

There are now a number of different options available that fall into three groups. First, a few general points:

- The vast majority of trials looking at drug treatments have been placebo-controlled so we have little in the way of head to head comparison to guide our choices.
- Where there are head-to-head comparisons, they often use surrogate markers, e.g. bone density or pain scores, or are indirect comparisons that are of low quality.

Therefore, we cannot conclusively say which drug is ‘the best’ and rather have to consider costs, individual patient preference and ability to manage the different preparations and the risk of harms. SIGN has made a ‘ladder’ recommendation of first to fourth line options shown in the summary of the guidance above. This is the best we have at the moment.

Here is a table summarising key facts that may be helpful. These details come from the SIGN full guideline (2015, 142) and a BMJ state of the review (BMJ 2015;351:h3783). For current doses, costs and monitoring requirements see the BNF.
### Antiresorptives

**Action:** to reduce the rate of bone turnover by inhibiting osteoclast activity

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Benefits/harms/disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Zoledronate (most potent)</td>
<td>Benefits: Alendronate, risedronate and zoledronate reduce all fractures compared with placebo &lt;br&gt; Harms: Concordance issues and GI side-effects with oral preparations; Osteonecrosis of the jaw is a rare side-effect; Atypical femoral fractures (more detail in next table)</td>
</tr>
<tr>
<td></td>
<td>Risedronate &lt;br&gt; Ibandronate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alendronate &lt;br&gt; Etidronate (least potent)</td>
<td></td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Denosumab (i.c. injection 6 monthly)</td>
<td>Benefits: Reduces risk of all types of fracture compared with placebo &lt;br&gt; Harms: Association with severe hypocalcaemia – requires monitoring &lt;br&gt; Caution in renal impairment &lt;br&gt; Cases of osteonecrosis of the jaw have been reported at high doses &lt;br&gt; Atypical femoral fractures have also been seen &lt;br&gt; Effects cease when treatment is stopped</td>
</tr>
<tr>
<td>Hormonal modulators</td>
<td>HRT &lt;br&gt; Tibolone &lt;br&gt; Reloxfene</td>
<td>Benefits: HRT and tibolone reduce vertebral and non-vertebral fractures compared with placebo during treatment &lt;br&gt;Raloxifene has only been shown to reduce vertebral fractures &lt;br&gt;Help with menopausal symptoms &lt;br&gt; Harms: Benefits cease on stopping treatment &lt;br&gt;Small risks of VTE, stroke, breast cancer &lt;br&gt;See HRT article (Women’s Health chapter) for discussion of this</td>
</tr>
</tbody>
</table>

### Anabolics

**Action:** to stimulate new bone formation by mobilising calcium from the skeleton and re-depositing it; with intermittent exposure, more bone is formed than resorbed

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Benefits/harms/disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone</td>
<td>Teriparatide</td>
<td>Benefits: Greater effect on the spine than long bones &lt;br&gt;Reduced vertebral fractures compared with placebo &lt;br&gt;No RCT evidence of reduction of non-vertebral fractures &lt;br&gt; Harms: Nausea, dizziness, leg cramps, mild hypocalcaemia</td>
</tr>
</tbody>
</table>

### Dual action (antiresorptive + anabolic)

**Action:** stimulates osteoblasts to deposit bone and inhibits osteoclasts from resorption

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Benefits/harms/disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strontium salts</td>
<td>Strontium ranelate &lt;br&gt; SPECIALIST PRESCRIBING ONLY</td>
<td>Benefits: More effective than placebo at reducing vertebral and non-vertebral fractures &lt;br&gt;No head-to-head comparisons with other osteoporosis drugs &lt;br&gt; Harms: Increased risk of VTE and CV events &lt;br&gt;Subject to MHRA warning to use only in severe osteoporosis and in patients who do not have: &lt;br&gt;○ IHD or PAD or cerebrovascular disease &lt;br&gt;○ uncontrolled hypertension</td>
</tr>
</tbody>
</table>

### Adverse effects of bisphosphonates

Because bisphosphonates are the most commonly prescribed osteoporosis treatments and have received significant press about potential adverse effects, we often get asked about these by patients, namely:

- Gastrointestinal side-effects.
- Oesophageal cancer.
- Atypical fractures.
- Osteonecrosis of the jaw and external ear canal.
- Atrial fibrillation.
- Uveitis and scleritis.
Here is a summary of the current evidence base relating to potential harms.

<table>
<thead>
<tr>
<th>System</th>
<th>Issues and evidence</th>
</tr>
</thead>
</table>
| **Gastrointestinal side-effects** | Reflux and dyspepsia are common side-effects of bisphosphonate treatment. They seem to be most common with alendronate and oral ibandronate and least common with zoledronate. First check concordance. Instructions for taking bisphosphonates:  
  - Take on an empty stomach with a full glass of water.  
  - Remain upright for 30min and during this time do not eat or drink anything else.  
  **Do not use a PPI to treat reflux type symptoms caused by a bisphosphonate.** PPIs have been found to blunt the effectiveness of alendronate (Arch Int Med 2011;171:969) and theoretically will reduce calcium absorption too. Also some evidence that they increase risk of fractures in ex- and current smokers (BMJ 2012;344:e372). Lastly, the thinking goes that the symptoms will be due to bisphosphonate irritation to the oesophageal mucosa, rather than acid reflux and therefore unaffected by a PPI. |
| **Oesophageal cancer** | Two studies have looked at the possible link between bisphosphonate use and oesophageal cancer. Both used the same database but had different designs. Neither study demonstrates causality.  
  - The JAMA study used a cohort approach, comparing incidence of cancer in 42,000 bisphosphonate users with controls. It found no increased risk (JAMA 2010;304:657).  
  - The BMJ study identified 3000 cases of oesophageal cancer, matched them to controls and then looked at bisphosphonate use in the two groups. It showed that bisphosphonate use increased risk of oesophageal cancer (HR=1.93, CI 1.37–2.7) and a NNM=1000 for 5y of use (BMJ 2010;341:c4444).  
  An accompanying editorial (BMJ 2010;341:c4506) suggests that we should:  
    - Consider the risks vs. benefits for the individual patient.  
    - Ask patients about digestive disorders before prescribing.  
    - Regularly reinforce instructions for taking the drug to minimise irritation of the oesophagus.  
    - Tell patients to report difficulty swallowing, throat, chest or digestive discomfort so that they can be investigated promptly. |
| **Atypical fractures** | Atypical fracture is a new term for a particular type of femur fracture characterised by:  
  - Occurring in subtrochanteric or diaphyseal area, often bilateral.  
  - Fracture line is transverse unlike usual spiral or comminuted fractures of the femur.  
  - Rarely any history of trauma or fall.  
  - Typically these present with thigh pain (bilateral in almost half of cases).  
  Case reports have speculated that bisphosphonates may be implicated, but there is currently no established causal link. There have also been case reports for denosumab.  
  **A prospective Swedish cohort analysis and case–control study** looked at more than 12,000 women >55y who fractured their femurs in Sweden in 2008. They reviewed the X-rays and found 59 who had atypical fractures of the shaft, and compared bisphosphonate users vs non-bisphosphonate users (N55/M 2011;364:1728). Results:  
    - For women taking bisphosphonates for more than 2y, the number needed to harm (NNH) for one atypical fracture was 417 over a 3y period.  
    - Over that same 3y period, for each atypical stress fracture caused, 30 vertebral and 5 hip fractures will have been prevented.  
  A further *retrospective case–control study* has demonstrated that risk increases with length of bisphosphonate use (Arch Int Med 2012;172:930).  
  - The researchers noted that risk of atypical fracture increased with bisphosphonate duration, increasing by about 10% for each year of treatment.  
  - However, the authors point out that the actual incidence of atypical fractures they saw in their population was 32 per 1 000 000 person-years, 11 times less that the risk of classic femur fractures. The risk of these atypical fractures is small compared with the benefits of reducing more common osteoporotic fractures. It remains important to ensure women are taking bisphosphonates for a good indication. |
Summary

Bisphosphonates are effective drugs but have some fairly rare long-term harms. Their benefit in the secondary prevention of osteoporotic fracture is well researched (50% reduction in further fractures). The primary prevention of fracture in patients with a BMD T-score ≤−2.5 is well demonstrated with bisphosphonates too (FIT study: 36% reduction in fracture). The evidence base outside these parameters is less clear and we need to weigh up the benefits and harms and discuss these with our patients.

Calcium and vitamin D in osteoporosis treatment

Nearly all studies investigating the treatments for osteoporosis have included supplementary calcium and vitamin D as adjunctive treatments though there is a paucity of evidence that this is necessary in the presence of adequate dietary intake. In addition there is a dispute about the optimal doses of supplementation. There are no studies comparing the effectiveness of osteoporosis treatment with and without calcium and vitamin D supplementation.

There are also concerns that calcium supplementation may reduce adherence to osteoporosis treatments because of side-effects and may reduce its effectiveness because of being taken too close to bisphosphonate treatment.

A full discussion of the (lack of) merits and harms of combined calcium and vitamin D supplementation for fracture prevention can be found in the online handbook.

SIGN acknowledge these challenges in their guideline:

- They recommend considering vitamin D supplementation for those with risk factors for or confirmed deficiency.
- They recommend assessing calcium intake and only supplementing if it is less than 700mg daily.

If both are required a combined preparation is likely to improve.

Evidence for monitoring by DEXA

The evidence for monitoring progression of osteopenia, osteoporosis and response to treatment by DEXA scan is actually very limited.

Monitoring patients with osteopenia

NICE suggests that we should wait a minimum of 2y before reassessing a patient’s risk and then only if circumstances change. SIGN do not comment on how osteopenia should be followed.

This interesting paper in the NEJM offers some reassurance as to why this is appropriate (NEJM 2012;366:225).

They followed nearly 5000 women >67y with normal BMD or osteopenia and no history of fractures or previous osteoporosis treatment. They followed them up for over 16y and calculated the average time it would take 10% to develop osteoporosis at the femoral neck/hip for a given baseline T-score.

Results:
Average time for 10% to develop osteoporosis

<table>
<thead>
<tr>
<th>Initial DEXA result</th>
<th>Time (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or mild osteopenia at baseline (T-score &gt;–1.5)</td>
<td>15</td>
</tr>
<tr>
<td>Moderate osteopenia at baseline (T-score –1.5 to –2)</td>
<td>10</td>
</tr>
<tr>
<td>Advanced osteopenia at baseline (T-score –2 to –2.5)</td>
<td>1</td>
</tr>
</tbody>
</table>

Monitoring once treatment is started

NICE and SIGN differ on their recommendations, NICE advises not to monitor whilst SIGN suggest DEXA at 3y may be considered to identify a subgroup of patients who may be at greater risk of fracture. They acknowledge that further research is needed to determine whether BMD measurements made whilst on treatment should have any effect on clinical decision making.

An analysis of the Fracture Intervention Trial (FIT), one of the largest RCTs, which looked at the efficacy of alendronate in preventing fractures, provides some reassurance that monitoring may not be necessary (BMJ 2009;338:b2266). Women were having regular DEXA scans as part of this. They found:

- 97.5% of women demonstrated improved BMD over 3y.
- There was no significant difference in the extent of improvement between individuals taking account of concordance.

Like statins in primary prevention, NICE suggest we treat without monitoring the action of that treatment, safe in the knowledge that the drug functions regardless – in primary care the important markers are concordance, side-effects, falls and fractures and this is what we should review!

Evidence for duration of bisphosphonate treatment

This is a really important ‘known unknown’. Whilst SIGN suggest durations, these are based on poor quality or scanty evidence.

Bisphosphonates have a profound effect on bone metabolism. The risk–benefit balance is very unclear after initial treatment for 3–4y. Here we look at two papers that may help. The first a review article (CCJM 2011;78:619):

These are the salient points:

- When bisphosphonates are started osteoclasts are immediately inhibited from repairing and resorbing bone. For the next 6m or so osteoblasts continue to fill the pits left until there are none. These cartilaginous areas then gradually become mineralised over the next 3y.
- With bisphosphonate use bones become denser for the first 3y and then reach a plateau.
- Bisphosphonates remain retained in bone for over 10y and powerfully inhibit bone turnover.
- Most of the data we have on the efficacy of bisphosphonates are from studies that cover 3–4y.
- Osteoclasts are also responsible for repairing microscopic damage and their inability to do this may result in long-term adverse effects, e.g. atypical fractures.

The best evidence we have for long-term bisphosphonate use comes from the FLEX study (JAMA 2006;296:2927) and it is worth detailing.
FLEX was a randomised double-blinded extension of the FIT study (the seminal RCT that demonstrated that alendronate reduced fractures compared with placebo).

1000 women who had already received alendronate for 5y were randomised for a further 5y of either alendronate or placebo. Those who had a T score <-3.5 or fractured during the study were excluded (so the most severe/ bisphosphonate non-responders).

Outcomes:
- There was no difference in **radiological fracture rate** between the groups.
- **Physician-suspected** fracture rate was higher in the placebo group:
  - 5.3% vs. 2.4% (RR=0.45; CI 0.24–0.85); about 75% of these fractures were confirmed by per protocol X-rays done at the study centres
  - Bone turnover remained lower in the placebo group at 10y than it had been at the beginning of the study indicating that bisphosphonates continued to have some action 5y after stopping.
- Bone density at the hip decreased in both groups:
  - 3.4% in placebo group
  - 1% in alendronate group.

A post-hoc subgroup analysis was published later where patients were subdivided into 12 groups based on bone density and presence or absence of vertebral fracture at baseline (J Bone Miner Res 2010;25:976). Only one of these 12 subgroups showed a statistical difference between placebo and alendronate groups (the non-vertebral fractures in the subgroup who had not had a vertebral fracture at baseline and whose T-score was <-2.5). This statistical benefit to one subset is sometimes quoted in articles used to justify use to 10y.

Susan Ott, Professor of Medicine at Seattle, who wrote the review concludes that the principle of primum non nocere should be followed and bisphosphonates can be discontinued at 5y for most.

Another approach gaining traction is that when evaluating patients they should be categorised into low, medium or high risk of further fracture and managed accordingly. Nobody can agree, however, on how to establish who is in what category and what we should then do with them!

At GP Update we have done some asking around and the most coherent approach we could find was from a group of researchers from San Francisco writing in NEJM (NEJM 10.1056/NEJMp1202623).

They took data from the only two long-term studies we have (FLEX, as detailed in Susan Ott’s article above, and the HORIZON study, which was a 3y of zoledronic acid treatment study followed by 3 years of placebo or active treatment study (J Bone Miner Res 2012;27:243)) and noted that in both these studies bone density at the end of the active treatment was predictive of fracture risk later in the study.

Using the FLEX study on vertebral fractures they produced the following table:

<table>
<thead>
<tr>
<th>T score of femoral neck after 5 years treatment</th>
<th>NNT for 5y to prevent 1 vertebral fracture</th>
<th>Risk</th>
<th>Option suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ −2.5</td>
<td>24</td>
<td>High</td>
<td>Continue bisphosphonate?</td>
</tr>
<tr>
<td>&gt; −2.5 but ≤ −2</td>
<td>63</td>
<td>Medium</td>
<td>May benefit from further bisphosphonate?</td>
</tr>
</tbody>
</table>
Whilst this table is seductive in its simplicity note:

- It is based on a sub-set analysis: in some groups the numbers were very small making the confidence limits very wide and all just crossed into statistical insignificance! We have, however, included the table as published because we believe many specialists are using it to stratify risk in our patients and it is useful for you to see where it comes from.
- The FLEX study did not show any benefit in hip fracture prevention: we are just looking at vertebral fracture risk.
- These data are based on studies using alendronate and zoledronic acid, the authors suggest it should not be extrapolated to other bisphosphonates.

For me it does provide some narrative to help explain the situation to my patients, particularly because it allows me to compare the NNT figures for vertebral fractures from the FIT (first 5y of treatment) study (NNT=14 over 3–4y) with those after that time.

"We have very little knowledge of how much more benefit you will get from continuing your bisphosphonate after 5 years. Taking the most optimistic view, for vertebral fractures:

- In patients classified as high risk I will need to treat twice as many patients, as in the first 5 years, to prevent a vertebral fracture.
- In medium risk patients perhaps 5 times as many.
- And in low risk patients, 7 times as many.

In terms of hip fractures:

- I don’t know if any treatment beyond 5 years will add any extra benefit to prevent you fracturing your hip in the future."

In summary

The general consensus seems to be that a drug holiday could be considered after 5y depending on whether further fractures have occurred or new risk factors developed. Other points:

- Calcium and vitamin D should be continued life-long in all patients with osteoporosis.
- The role of bone turnover markers such as P1NP is still unclear.
- Involving our patients in these decisions will be of utmost importance.

This is a question that needs to be answered urgently, particularly as the shadow of long-term harms hangs over these drugs. There is currently considerable ad hoc and misplaced advice being offered and I am not sure the SIGN guideline really helps.
Osteoporosis in men

Osteoporosis in men has an underlying cause in more than 50% of cases, e.g. hypogonadism, prostate cancer treatment, steroid use and alcohol excess. Many of the treatments used to treat post-menopausal osteoporosis have investigated in men but using small, poorer quality ‘bridging studies’ which have demonstrated similar effects on bone density but been too small to show fracture reduction.

The NEJM has recently published an RCT on the effect of zoledronic acid on fracture risk in men aged 50–85y, who either had osteoporosis, or had osteopenia and a past history of fracture (NEJM 2012;367:1714). The study involved 1199 men over 2y with the primary endpoint being new X-ray detected vertebral fractures.

This study was funded by Novartis, the manufacturer of zoledronic acid, and was a ‘modified intention to treat’ design (which can introduce bias into the results).

Results

- 1.6% of the treated group suffered an X-ray detected vertebral fracture compared with 4.9% of the placebo group. RR=0.33 (CI 0.16–0.70; P=0.002). That works out as a NNT of 33 over 2y.
- However, there was no significant difference in clinical fracture rate between the groups.
- Whilst the number of adverse events was recorded as similar in both groups at a seemingly high incidence of 25%, there were 9 MIs in the treatment group vs. 2 in the placebo group (and this difference is statistically significant). This issue was not addressed in the study.

SIGN recommend that men be referred for specialist assessment.

Corticosteroid induced osteoporosis

Corticosteroids can cause and exacerbate osteoporosis affecting bone quality as well as bone density.

The risk of fracture (typically vertebral) rises immediately and returns to normal about 12m after stopping. The extent depends on the dose used and the duration of treatment (DTB 2010;48:98).

- A significant steroid load is >1g prednisolone over a year, e.g. 1m of 30mg/d or 25d of 40mg/d.
- The risk is immediate so, if possible, assess risk and consider treatment prior to starting steroids.

FRAX and QFracture include steroid use when calculating risk. NICE recommend using this.

SIGN are concerned it may underestimate risk (Interestingly if you input data for a female aged 65y, taking regular steroids with no other factors into FRAX and QFracture you get a 10y risk of 13% and 5.6%, respectively – this stark difference in risk suggested by the two different tools presents us with a challenge!)

- SIGN recommend following the RGP guidelines when starting steroids which suggest:
  - start bone protection without further assessment on anyone aged >65y or with a history of fragility fracture
  - do a DEXA in everyone else and start bone protection if T-score <-1.5 S.D.

Ensure all get lifestyle advice.
- Alendronate, risedronate, etidronate, zoledronate and teriparatide are licensed for the prevention of glucocorticoid-induced osteoporosis.

Calcium supplementation and cardiovascular risk

Do calcium supplements with or without vitamin D increase the patients’ risk of cardiovascular disease?

Two meta-analyses (detailed below) sparked a widespread media frenzy at the time.

- The first showed an increased risk of non-fatal MI but not other cardiovascular endpoints in those taking calcium WITHOUT vitamin D (BMJ 2010;341:c3691). This was not felt to be relevant to UK practice because the vast majority of our patients were prescribed a combination of calcium and vitamin D.
- The second, by the same authors, analysed data from those taking calcium WITH vitamin D, in the WHI trial (BMJ 2011;342:d2040). This showed NO increased cardiovascular risks. However, they realised the data were affected by the fact that some women were taking supplements outside the trial. So when they analysed the data again, accounting for this, they found a small increased risk in MI rates but not other cardiovascular endpoints. However, as the accompanying editorial pointed out, the methodology is imperfect.

Two further meta-analyses have since been published. Importantly, the second one accounted for TOTAL calcium intake – whether from dietary intake or supplementation.

- EPIC–Heidelberg study: this large prospective cohort compared fatal and non-fatal cardiovascular risks in 24 000 adults aged 35–64y over 11y of follow-up (Heart 2012;98:920). Users of calcium supplements had an increased cardiovascular risk compared with non-users and this was more pronounced in those who took calcium supplements WITHOUT vitamin D (HR=2.39, CI 1.12–5.12).
- Swedish long-term cohort study: in this Swedish study 39 000 women were monitored over 19y (BMJ 2013;346:f228). Dietary intake was established by questionnaire and total calcium intake calculated.
The researchers found risk was associated with total calcium intake, not with use of calcium supplements. Compared with women whose total intake was between 600 and 1000mg/d of calcium, those whose intake was above 1400mg/d had a higher all-cause death rate (HR=1.40, CI 1.17–1.67). Use of calcium tablets alone was not associated with any increased risk per se. The risk was linked to total calcium intake in excess of 1400mg/d from any source (hazard ratio for all-cause mortality = 2.57, CI 1.19–5.55).

It looks like taking too much calcium in your diet (from whatever source) is associated with excess mortality.

What does this mean for us in practice?

- Calcium and vitamin D supplements should not be prescribed without good indication.
- We should assess dietary calcium more carefully and only prescribe calcium supplement in patients with an inadequate diet. Now we have vitamin D supplements available separately there is an opportunity to tailor the supplementation for patients with osteopenia or osteoporosis more effectively.

How can I assess the calcium intake of a patient?

- There are now a number of online intake calculators. For example this one from Edinburgh: [www.rheum.med.ed.ac.uk/calcium-calculator.php](http://www.rheum.med.ed.ac.uk/calcium-calculator.php)

**Calcium supplements and bone health**

In those NOT on bisphosphonates, what benefit is there from calcium supplementation?

A recent meta-analysis found (BMJ 2015;351:h4183):

- Increasing calcium intake either by diet or supplements had only a small and non-progressive impact on bone mineral density. No benefit at all was seen after the first year. This is unlikely to translate into meaningful clinical benefits.
- This conclusion held true even where low serum vitamin D or poor baseline calcium intake were issues.

The same authors then went on to look at the more important issue of whether supplements actually reduced fractures. There were fewer studies looking at this outcome and they were heterogeneous so only a systematic review was possible (BMJ 2015;351:h4580).

- Increasing calcium intake either by diet or supplements did not show consistent benefits in fracture prevention.
- The only study showing consistent benefits was the 1992 paper by Chapuy which demonstrated benefits in very elderly women in nursing homes with persistent low calcium intake and low vitamin D levels.
- Calcium supplementation should not be recommended as a means of fracture prevention in those not on bisphophonates.

The accompanying editorial reminds us that this conclusion was first reached 25y ago but was strongly refuted at the time (BMJ 2015;351:h4825).

- It suggests that if an individual is meeting the recommended dietary intake of 700–900mg/d additional supplementation is not likely to be beneficial.
- It suggests that it is time to stop the mass medicalisation of elderly people!
Osteoporosis

- Use QFracture or FRAX to assess fracture risk in those aged >50y with risk factors for osteoporosis.
- Offer a DEXA scan to all those with a 10y fracture risk ≥10% and those who have had fragility fractures.
- Consider underlying causes and treat these if possible.
- Offer lifestyle advice to everyone.
- Oral bisphosphonates remain first line treatment but if not tolerated, consider zoledronate infusions or denosumab.
- Consider dietary calcium intake and only supplement if inadequate; offer separate vitamin D supplements to those at risk of deficiency.
- Bisphosphonates have some long term risks – reassess after 5y.
- The optimal duration of treatment and what to do next remains unclear
- Assess osteoporosis risk for anyone starting long-term corticosteroids and offer preventative treatment as soon as possible.
- Strong evidence now suggests that high total calcium intake is associated with raised mortality risk.
- Targeting calcium supplementation to those who are unable to take adequate levels through their diet is probably more appropriate.

How do you give instructions about taking bisphosphonates and reporting adverse effects?
Could you change your written instructions on the dispensing label?
Audit all patients on repeat scripts for steroids or who have collected three or more scripts for steroids in the past year:
- Have they been offered bone protection?
- Do you use the bisphosphonate preparation with the lowest acquisition cost?
- How do you check concordance and side-effects?
- Have you reviewed patients on strontium?

For professionals:

A calcium calculator to work out daily intake can be found at: http://tinyurl.com/GPU-Calciumcalculator.
The RCGP/NOS resource can be found at: www.osteoporosis-resources.org.uk
The NOGG offer free access to the FRAX tool: www.shef.ac.uk/FRAX/tool.jsp?locationValue=1
The QFracture Score can be found at: www.qfracture.org/

For patients:
The National Osteoporosis Society website has lots of useful information and support forums for patients: www.nos.org.uk/
To calculate dietary calcium intake try: www.rheum.med.ed.ac.uk/calcium-calculator.php

We make every effort to ensure the information in these pages is accurate and correct at the date of publication, but it is of necessity of a brief and general nature, and this should not replace your own good clinical judgement, or be regarded as a substitute for taking professional advice in appropriate circumstances. In particular check drug doses, side effects and interactions with the British National Formulary. Save insofar as any such liability cannot be excluded at law, we do not accept any liability for loss of any type caused by reliance on the information in these pages.
ALL OUR 2016 COURSES

Our comprehensive one-day update courses for GPs, GP STs, and General Practice Nurses.
We do all the legwork to bring you up to speed on the latest issues and guidance.

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- GPs, trainers and appraisers preparing for appraisal and revalidation or wanting to keep up to date across the whole field of general practice.
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- GPs who want to be brought up to speed following maternity leave or a career break.
- General Practice Nurses, especially those seeing patients with chronic diseases.

What’s included?
- 6 CPD credits in a lecture based format, with plenty of time for interaction, humour and video clips, to keep you focused and awake.
- A printed copy of the relevant Handbook including the results of the most important research in primary care over the last 5 years and covering the subjects more extensively than possible in the course.
- 12 months subscription to www.gpcpd.com. With three times the content of the handbook, it allows you to capture CPD credits as you read on the site and use it in consultations! It also comes with focussed learning activities to double your CPD credits…at the end of the year you simply upload everything ready for your appraiser!
- Buffet lunch and refreshments throughout the day!

What’s not included? Our courses contain NO theorists, NO gurus, NO sponsors, NO reps on the day! Just real life GPs who will be back at the coal face as soon as the course has finished.

www.gp-update.co.uk
The GP Update Course – our flagship course!

With the amount of evidence and literature inundating us, it can be hard to know which bits should change our practice, and how. The GP presenters summarise and discuss the results of the most important new evidence and guidance, concentrating on what it means to you and your patients in the consulting room tomorrow.

**Bristol**  Wed 11 May
**Exeter**  Thur 12 May
**London**  Fri 13 May
**London**  Sat 14 May
**Newcastle**  Wed 18 May
**Sheffield**  Thur 19 May
**Manchester**  Fri 20 May
**Birmingham**  Sat 21 May
**Norwich**  Tue 24 May
**Chelmsford**  Wed 25 May
**London**  Thur 26 May
**Belfast**  Wed 8 June
**Oxford**  Fri 30 Sep
**Southampton**  Sat 1 Oct
**Cardiff**  Wed 5 Oct
**Exeter**  Thur 6 Oct
**London**  Fri 7 Oct
**London**  Sat 8 Oct
**Leeds**  Wed 12 Oct
**Liverpool**  Thur 13 Oct
**Manchester**  Fri 14 Oct
**Birmingham**  Sat 15 Oct
**Cambridge**  Tue 18 Oct
**London**  Wed 19 Oct
**Nottingham**  Thur 20 Oct
**Inverness**  Wed 2 Nov
**Edinburgh**  Thur 3 Nov
**Glasgow**  Fri 4 Nov

The Women’s Health Update Course

From the pill to pelvic pain, periods and prolapses, this one day women’s health update is a comprehensive guide to understanding and managing common gynaecological problems in general practice. The subjects are covered in a much greater depth than is possible on the GP Update course and includes simple ideas which we as GPs have found helpful in our consultations.

The day is designed for all GPs and GP STs – not just those with a special interest!

**Edinburgh**  Thur 23 Jun
**Newcastle**  Fri 24 Jun
**Birmingham**  Thur 30 Jun
**London**  Fri 1 Jul
**Exeter**  Thur 3 Nov
**London**  Fri 4 Nov
**Leeds**  Thur 10 Nov
**Manchester**  Fri 11 Nov

The Cancer Update Course

Since 2012, Red Whale | GP Update has joined forces with Macmillan Cancer Support to provide a course that gives all GPs the knowledge and inspiration they need when dealing with cancer. From cancer prevention, screening, diagnosis and treatment to palliative care.

2015 has seen the biggest shake up in cancer in the last 10 years with the publication of the updated NICE guidelines on suspected cancer. If, like many of us in England & Wales, you are still finding your way around them, then this course will definitely help!

**Leeds**  Thu 16 June
**Birmingham**  Fri 17 June
**Bristol**  Thu 23 June
**London**  Fri 24 June
**Manchester**  Thu 10 Nov
**Birmingham**  Fri 11 Nov
**Cambridge**  Thu 17 Nov
**London**  Fri 18 Nov
Lead. Manage. Thrive! – The NEW management skills course for GPs.

Sometimes it feels like the thriving GP is an endangered species – demands on limited time and resources have never been higher. Our practices run in ever more complex ways and our teams extend beyond the practice walls. Often we get that instinctive feeling that there must be a better way to do things but creating the space to make it happen can be difficult.

As usual Red Whale has done all the legwork to bring you a concise, practical and actionable one day course and handbook. Not only have we trawled through lots of relevant management, leadership and development literature, but we have also distilled its content through the lens of real GPs, enabling you to apply it to the reality of your practice.

Manchester  Fri 24 June
London   Fri 1 July

Our Consultation Skills Courses

One day small group courses designed for GPs, GP STs and General Practice Nurses.

The courses have a practical focus and lots of engaging exercises allowing delegates to rehearse the most effective consultation behaviours. But don’t worry, there won’t be any role playing in front of everybody!

The Telephone Consultation Course

With the increased importance of telephone consultations this course aims to deliver practical skills which can be put to use immediately. The telephone is being used more and more by nurses as well as doctors in primary care, for triage, consultation and follow-up; in the daytime as well as out of hours. Our goal is to help you overcome difficulties and leave you with concrete ideas to enhance your own telephone contacts with patients.

Leeds  Tue 10 May
Birmingham  Fri 20 May
London  Thu 9 June
London  Thu 6 Oct
Manchester  Thu 13 Oct

The Effective Consultation Course

The Course focuses on behaviours which enhance effective use of time in the consultation. Efficient consultations reduce clinical risk and lower the risk of complaints and lawsuits. The course uses the rich evidence base on which consultation behaviours enhance effectiveness and how to go about learning them. We focus on actions and you will leave with many practical tips to use in your consulting room the following day.

London  Fri 13 May
Manchester  Thu 19 May
Leeds  Wed 5 Oct
London  Fri 25 Nov

The Medically Unexplained Symptoms Course

A significant proportion of patients who present to us will turn out to have symptoms that are medically inexplicable. We all know that there is no magic solution with these patients and sometimes they leave us feeling defeated and not sure what to do. However, there is evidence which can help address the issue.

London  Thu 12 May
London  Thu 20 Oct

Prices:

GP Update Course:
GP £195 | GP Registrar £150 | Nurse £150

All other courses:
£225 or £210 for members of www.gpcpd.com

(GPCPD members, please log in and then click on the relevant button within the 'Member information' box on the right of the home screen to get your discount code)
I would like to come on the following course(s) (please write legibly!):

- The GP Update Course (location).............................................................   (date).........................
- The Women's Health Update Course (location).............................................................   (date).........................
- The Cancer Update Course (location).............................................................   (date).........................
- Lead. Manage. Thrive! The management skills course (location).............................................................   (date).........................
- The Telephone Consultation Course (location).............................................................   (date).........................
- The Effective Consultation Course (location).............................................................   (date).........................
- The Medically Unexplained Symptoms Course (location).............................................................   (date).........................

I can't attend a course but would like to order your Handbook or DVD
- GP Update Handbook and 12 months access to GPCPD £150
- GP Update Handbook, DVD and 12 months access to GPCPD (pre-order for shipment mid May 2016) £225
- Women’s Health Update Handbook £70
- Cancer Update Handbook £70

For downloadable information on becoming a presenter with us please visit: www.gp-update.co.uk/team Or email team@gp-update.co.uk

We are looking for practising GPs to start making big, bold waves in primary care education as Red Whale presenters.

You will be trained in presenting one-day, lecture-based courses to audiences of 50-300 delegates.

GP Update – Red Whale is a market leading educator for GPs, Nurses and Pharmacists. We are looking to expand our team of enthusiastic presenters and continue making our courses relevant, challenging and fun.