

Gavel

Evidence-Based Medicine *in practice*

Management of postmenopausal osteoporosis

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- Osteoporosis is an extremely common condition among elderly people. In order to maximise both clinical effectiveness and cost-effectiveness, treatment should be targeted at those with the highest risk of fracture.
- Four strong independent predictors of fracture risk exist that can be applied to individual patients – sex, age, bone mineral density, and prior fracture history.
- All patients considered to be at risk of osteoporotic fracture should have their calcium and vitamin D intake assessed and, if necessary, supplemented. Once this has been addressed, consideration should be given to antiresorptive therapy.
- Although treatment is most commonly initiated at the time of the menopause, the evidence base relates principally to the use of antiresorptive agents in older women with prior vertebral fracture.
- Of the available treatments, only alendronate has been shown to prevent both vertebral and non-vertebral fractures and has NNTs that come within the bounds of a rational treatment strategy.
- Evidence relating to selective oestrogen receptor modulators is, as yet, preliminary and this group cannot yet be considered for inclusion in a rational management strategy.

Osteoporosis management

Introduction

From a position of relative obscurity, osteoporosis has emerged, over the past decade, as a disease area meriting active intervention within the context of primary care. Osteoporosis, particularly hip fracture, is associated with significant disability and mortality and accounts for considerable health resources. At any one time 20% of inpatient orthopaedic beds will be occupied by patients with hip fracture, at an annual cost of £250 million.¹ Once the longer-term care requirement has been taken into account, osteoporosis as a whole has been estimated to cost the NHS almost £1 billion per year.¹

Growing awareness of the scale of this problem has been fuelled, in part, by the availability of an ever-increasing number of drug therapies, all of which have been shown, to some extent, to influence the balance between bone formation and breakdown in the osteoporotic patient. The evidence base that underlies the management of osteoporosis is very patchy, however, with some accepted treatments being based on studies of marginal validity. Given the potential to treat large numbers of patients at considerable expense, it is essential that available resources are directed at managing this disease in a way that has been demonstrated to be effective.

In order to achieve this, two critical questions must be answered:

- Which patients should be targeted, in order to achieve significant clinical benefit for the individual, while keeping costs within reasonable limits?
- Which therapy should be used, once the decision has been taken to treat?

The first question is critical, given the large number of potential patients. It is clearly important that active treatment should be focused on those at greatest risk of fracture, if we are to reconcile both clinical effectiveness and cost-effectiveness. A large number of 'risk factors' have been identified, some of which

may be of value in carrying out this treatment stratification process.

Some risk factors, such as smoking habits, alcohol consumption, body weight and family history, have been derived from epidemiological studies but have proved to give disappointing results when predicting risk prospectively. Others, such as premature menopause, steroid use and immobility, may be important for treatment decisions in individual cases but are of limited value when deciding population treatment strategies.

There are four primary characteristics, however, that can be reliably used in populations, in order to predict their broad risk of osteoporotic fracture. These are:

- Sex.
- Age.
- Bone density.
- Prior fracture.

Sex

While the majority of osteoporotic fractures occur in women, a surprising number are also seen in men. It has been shown that 25% of all femoral neck fractures occur in men (Figure 1),² while the prevalence of vertebral deformity in the over-50s shows little difference between the sexes (Figure 2).³ It would therefore be useful to review treatment options for both men and women. However, virtually no research has been carried out into the management of osteoporosis in men, the vast majority of research having focused purely on postmenopausal women. In the absence of an evidence base, we must therefore restrict our review to this patient group.

Age

The absolute risk of sustaining a fragility fracture is closely associated with advancing age (Figures 1 and 2). Although this partly reflects a decline in bone density over time, this is only sufficient to explain part of the increase in risk.² As Figure 3 shows, for any given level of bone density, an older patient is

Figure 1. One-year cumulative incidence of hip fracture per 100,000 population (Netherlands, 1993)²

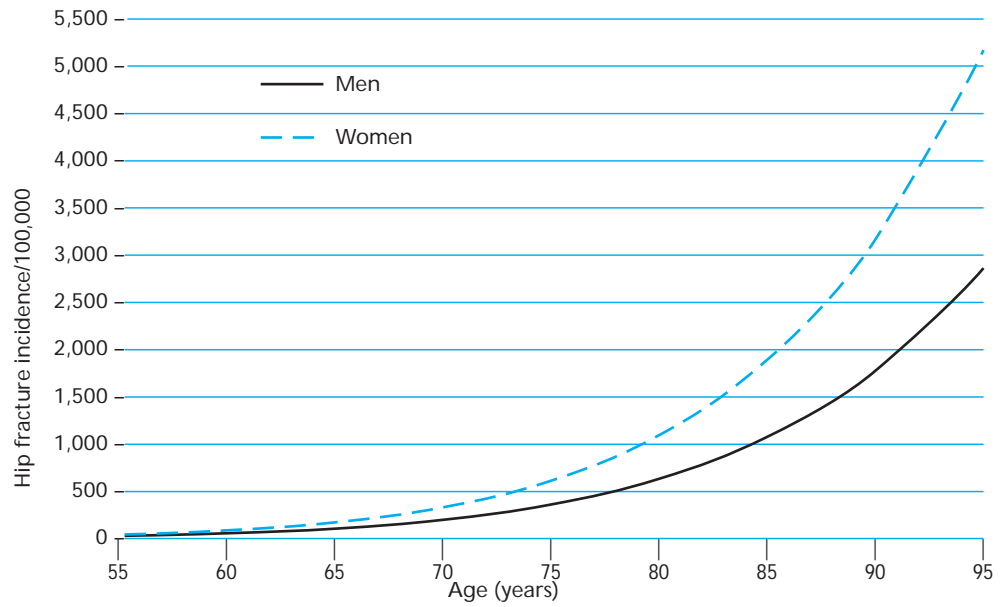


Figure 2. Prevalence of vertebral fracture by age and sex (Europe, 1990)³

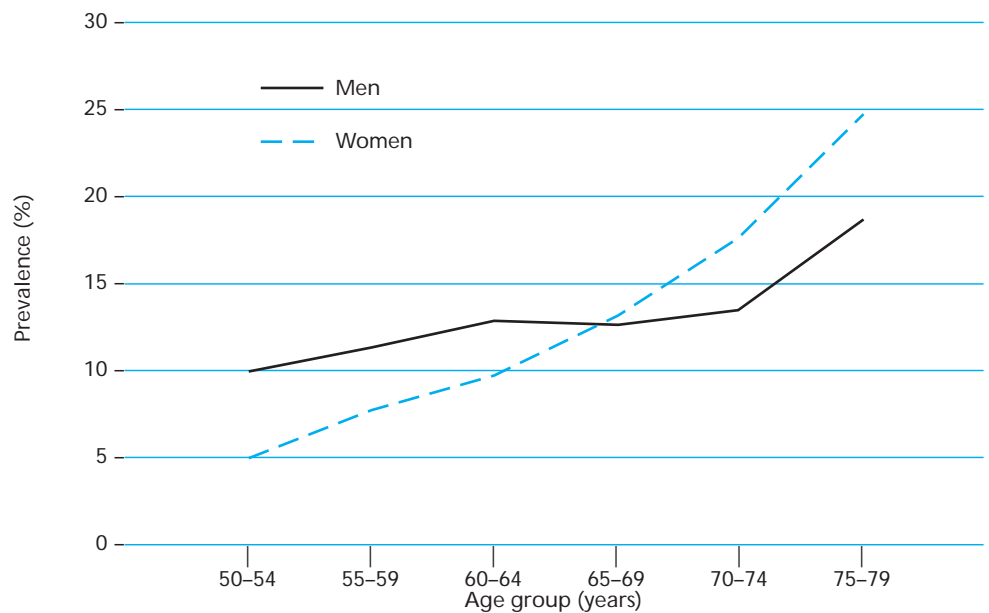
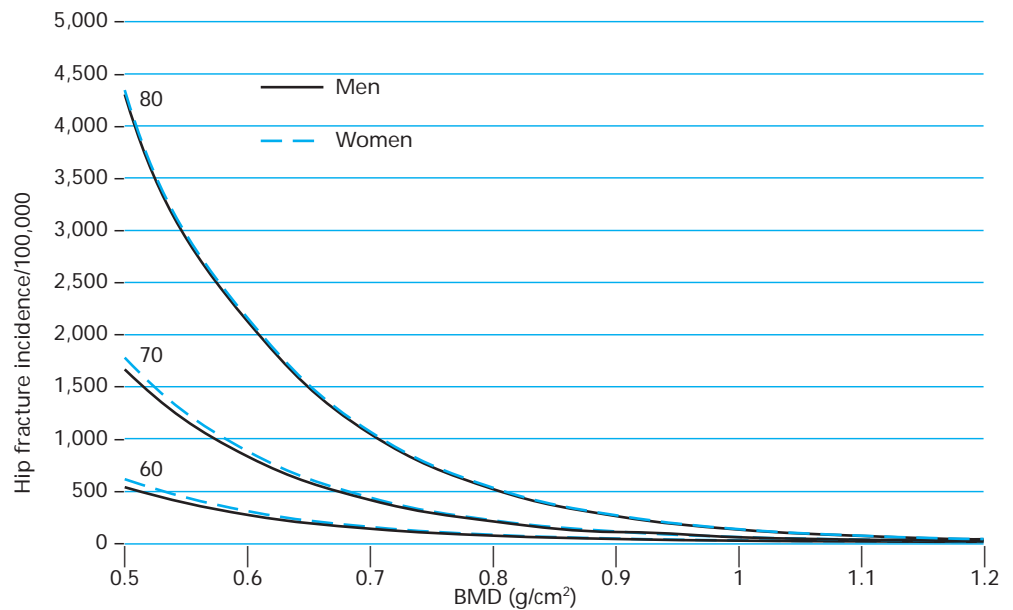


Figure 3. One-year cumulative incidence of hip fracture in women by femoral neck bone density at ages 60, 70 and 80 (Netherlands, 1993)²



considerably more likely to suffer a fracture than is a younger one.² This probably reflects several issues, including declining overall activity, increasing coexisting disease, and deterioration in balance, coordination and general physical agility. Generally speaking, this means that there is a doubling in risk of hip fracture for every six-year increase in age,² while there is a doubling in risk of vertebral fracture for every ten-year age increase.³

Bone density

Although it does not account for total fracture risk, measurement of bone mineral density (BMD) remains one of the few objective means to assess fracture risk in an individual. The World Health Organisation defines any individual with a bone mineral density of more than 2.5 standard deviations below the level found in a young adult as having osteoporosis.⁴ While this definition is useful, in that it identifies a population at higher than average risk of fracture, it needs to be used with caution. Approximately 30% of all postmenopausal women will have osteoporosis by this definition,³ and, although many of these will ultimately suffer a fracture, this may not be for many years. At the same time, as many as 50% of women who suffer a fracture will not have a bone density within the osteoporotic range.¹

Broadly speaking, the predictive value of low BMD equates to that of high blood pressure as a predictor of stroke, or high cholesterol as a predictor of coronary heart disease. For every standard deviation (SD) decrease in BMD, the risk of fracture increases by between 1.5- and 2.5-fold.⁵ Every SD increase in diastolic blood pressure increases stroke risk 1.3- to 2.2-fold, while every SD increase in serum total cholesterol is associated with a 1.2- to 1.5-fold increase in coronary risk.⁵ Clearly, although all three of these objective measures are useful and important, they are far from perfect and none should be interpreted in isolation.

Prior fracture

Just as secondary prevention has become the prime objective for lipid-lowering therapy, there is a case for adopting a similar approach in osteoporosis, with active treatment being reserved for those with an existing osteoporotic fracture. A patient with one prior

vertebral fracture has a four- to five-fold increased risk of suffering a subsequent vertebral fracture, while those with multiple prevalent fractures experience a 12-fold increase in risk.⁶ At the same time, and perhaps more importantly, the presence of a vertebral fracture is associated with four-fold increased risk of a future non-vertebral fracture.⁷ The predictive capacity of a prior fracture history is therefore considerable when compared with BMD measurement and, although screening for asymptomatic disease is unlikely to prove a cost-effective exercise, the presence of a clinical vertebral fracture should be regarded as a strong indicator of future risk.

Evaluating treatment paradigms

Strategies for targeting specific groups for treatment all hinge on one or more of these risk groups and form the basis for clinical trials of treatment options. In considering which treatments should be used, the evidence must be examined in the context of three broad treatment targeting approaches:

- Treating women at the time of the menopause (with or without the aid of BMD measurement).
- Treating women with low BMD but no fractures at a more advanced age.
- Treating women after they have already experienced an osteoporotic fracture.

This consideration is important from the point of view of both clinical effectiveness and cost-effectiveness. A treatment that has to be proven to be effective in secondary prevention will not necessarily be effective in a primary prevention setting and, even if it is, such an approach may not prove economically viable, because of the inherent difficulties in identifying the at-risk group with a sufficient degree of accuracy.

There are also three further critical factors to consider when evaluating the evidence. While these will apply equally to many other clinical areas, they are of particular relevance to the field of osteoporosis:

Is the study prospective or retrospective?

A number of high-quality retrospective studies in the field of osteoporosis have been

used to justify alternative treatment strategies. While these may provide interesting circumstantial support for a particular treatment, the lack of randomisation or blinding inherent in the retrospective methodology means that the results must be treated with great caution.

Does the study use a clinical or surrogate outcome?

While it is of value to know whether a treatment increases BMD, it is important to remember that this only constitutes part of the story when it comes to osteoporotic fracture (see Bone density section, above). If we are proposing to use a treatment to prevent fracture, then this must be supported by direct evidence of reduction in fracture risk, not simply an increase in BMD.

How is the fracture risk reported?

It may seem pedantic to distinguish between fracture risk and fracture rate, but there is actually a world of difference in their meaning. The term ‘fracture risk’ implies an assessment of the risk that any individual patient will sustain one or more fractures over a period of observation. The term ‘fracture rate’ implies a calculation of the number of fractures experienced over a standardised time period, typically expressed as the number of fractures per 1,000 woman-years. Unfortunately, because a patient who suffers

one fracture is far more likely than average to suffer a second fracture, these events cannot be regarded as independent. The assumption of independence is the fundamental principle that underlines most of the statistical tests that we use. Any assessment of risk reduction, numbers needed to treat (NNTs) or statistical significance will be invalid when applied to fracture rates.⁸ For our purposes, therefore, in line with the Royal College of Physicians Guidelines Group,¹ we will look exclusively at studies reporting fracture risk rather than fracture rate.

The evidence base

Treating women at the time of the menopause:

Hormone replacement therapy

The use of oestrogen replacement therapy, started at the time of the menopause, probably constitutes the most commonly adopted strategy for prevention of osteoporosis. It is therefore all the more surprising that there have been no prospective trials carried out investigating the impact of oestrogen on fracture in these patients. There is a considerable range of evidence, of varying quality, showing that the use of hormone replacement therapy (HRT) results in an increase in BMD, a consistent effect that is observed regardless of the type of HRT, the

Box 1. How to calculate NNTs

In order to compare clinical trials in a meaningful fashion, some measure of statistical comparison is required. Published papers use a range of statistical techniques, but these are generally difficult for the non-specialist to interpret. For this reason, *Gavel*, where possible, expresses trial results in terms of number needed to treat (NNT). NNTs are an estimate of the number of patients that would need to be given a therapy, in order to achieve the desired result.

For an outcome such as fracture, it is calculated very simply:

$$\text{NNT} = \frac{1}{\text{Proportion of patients with a fracture on placebo} - \text{Proportion of patients with a fracture on treatment}}$$

As an example, the fracture intervention trial,²⁴ described in this issue of *Gavel*, found the following:

- One hundred and forty-five patients out of 1,005 on placebo experienced a vertebral fracture (14.4%).
- Seventy-eight out of 1,022 patients on alendronate experienced a vertebral fracture (7.6%).

$$\text{NNT} = \frac{1}{0.144 - 0.076} = 14.7$$

This means that 15 patients need to be treated for three years to prevent one patient from suffering a vertebral fracture.

route of administration or the dosage regimen. There is also retrospective evidence⁹ to suggest that this increase in BMD results, in the long term, in a reduction in vertebral fracture risk. There are no studies currently published, however, that enable us to confirm, or quantify, this benefit.

That is not to say that HRT is ineffective when used in this patient group – indeed, it seems very likely that fractures will be prevented by this form of treatment. Equally, one must not forget the other potential benefits of HRT to the individual, in terms of climacteric symptom control and the possible, although unconfirmed, positive effect on risk of cardiovascular disease.¹⁰ The lack of prospective evidence, however, means that we are unable to assess the viability of this approach as a population strategy to prevent fractures.

Perhaps a more critical factor when considering HRT is the problem of discontinuation. In the Framingham study, a long-term observational follow-up of the population of a town in Massachusetts, the mean duration of use of HRT was five years following the menopause.¹¹ Measurement of spinal bone density in a cohort of elderly women (age 68–96, mean 76) showed that only those who had taken HRT for seven years or more had gained any advantage over those who had never taken HRT. In those aged over 75, this benefit was considerably attenuated, although still present.

In a retrospective study carried out in Sweden, the risk of hip fracture was assessed in relation to current or prior use of HRT.¹² They found that current users of HRT were significantly less likely to suffer a hip fracture than those who had never been on HRT, an effect that was independent of the age of the patient. Some degree of benefit was maintained in long-term users of HRT for up to five years after discontinuation of treatment, but, after more than five years had elapsed, there was no significant difference in hip fracture risk between past users and those who had never taken HRT.¹²

Given that most significant osteoporotic fractures occur in older women, the implications of these observations are important. If we wish to reduce the risk of fracture within our population by means of postmenopausal HRT, it appears that

treatment needs to be continued for considerably longer than is currently advised. This benefit must, of course, be weighed against the small but significant increase in breast cancer risk that accumulates with long-term use of oestrogen replacement therapy.

Other treatments

There is no evidence, circumstantial or otherwise, to support the use of any other pharmacological treatment in the immediate postmenopausal period.

Treating women with low BMD but no fractures at a more advanced age:

A logical approach to the problem of osteoporosis is to focus treatment efforts on a target group of patients at increased risk of fracture, who are therefore more likely to benefit from intervention. The first method of refining the treatment group is by age of onset. By delaying the start of treatment until the patient has reached her 60s, it may prove possible to circumvent the problem observed in the Framingham study and thereby ensure that patients are on treatment at their time of greatest fracture risk. At the same time, by focusing on patients with a low BMD, treatment will be more targeted on those who are most likely to benefit.

HRT

Once again, there are no prospective fracture data relating to HRT, although there is good evidence that there is a continued benefit, in this age group, on BMD.^{13–15}

Bisphosphonates

Two good quality studies have investigated the impact of the bisphosphonate alendronate in this patient group. The first studied the impact of treatment on a group of 4,432 women (mean age 68), none of whom had suffered a previous fracture.¹⁶ Mean BMD was just below normal (T score = -1.6), with approximately one-third having a measurement in the osteoporotic range (T score < -2.5). The second was somewhat smaller, involving 994 women (mean age 64).¹⁷ All the women were osteoporotic (T score < -2.5) and a minority (21%) had evidence of prior vertebral fracture.

The results of both these studies appear in Table 1 (opposite).

Table 1. Prevention of vertebral fracture in older postmenopausal women

Treatment	n (control/active)	Duration (years)	Fractures (control)	Fractures (active)	NNT
Alendronate ¹⁶ all patients	4,432 (2,218/2,214)	4.25	3.5%	1.9%	64
Alendronate ¹⁶ low BMD	1,631 (812/819)	4.25	5.4%	2.7%	37
Alendronate ¹⁷	994 (397/597)	3	5.5%	2.8%	37
Raloxifene ¹⁸ 60 mg data	5,064	3	4.3%	1.9%	42

Selective oestrogen receptor modulators

This new group of agents mimics many of the actions of oestrogens, while avoiding some of the adverse effects associated with HRT. One of these, raloxifene, is now licensed for use in the UK. There are, as yet, no published data relating to raloxifene's impact on fracture, although the preliminary results of a large trial, involving 5,064 women (mean age 67), have been presented at an international meeting.¹⁸ For the sake of completeness, these data have been included in Table 1 but, because the study has not yet been exposed to peer review, the results should be treated with a degree of caution. Patients in this study were given either placebo, raloxifene 60 mg or raloxifene 120 mg daily. As the higher dose is not licensed for use in the UK, only data relating to the 60 mg dose are reported here.

Two clear conclusions can be drawn from this somewhat limited evidence base. First, as expected, the identification of patients with low BMD significantly enhances our ability to target the patients most able to gain from active intervention. Second, however, even with this BMD-enhanced selection, the NNTs remain on the high side. It is difficult to justify, on either clinical or financial grounds, treating 40 patients for three to four years in order to prevent one from suffering a vertebral fracture. It is clearly necessary to refine the treatment group even further.

Treating women after they have already had an osteoporotic fracture:

Osteoporosis is a progressive condition, with multiple fractures occurring in women with established disease. Several studies have

therefore investigated the hypothesis that, by identifying and treating those women with prevalent vertebral fractures, one might be able to prevent further progression, while at the same time targeting treatment at the group in which it would potentially be most cost-effective.

HRT

There is one small prospective study that examines the role of HRT in secondary prevention of osteoporotic fracture.¹³ Seventy-eight patients with previous vertebral fractures were randomised to receive transdermal oestrogen or placebo for one year. Although there appeared to be a benefit in terms of vertebral fracture rate, the trial was too small to demonstrate any significant benefit on individual fracture risk.

A much larger study (n=2,763), whose prime intention was to investigate the impact of HRT on recurrent cardiovascular events, also collected fracture data.¹⁹ Over a mean follow-up period of 4.25 years, the investigators did not demonstrate any significant benefit. Event rates were low (2.3% per year) and, given that fracture was not a primary outcome of the study, one should probably not read too much into this negative result. Of perhaps greater interest was the fact that the study was also unable to demonstrate any positive impact on cardiovascular events, which certainly was a primary outcome measure.²⁰

Bisphosphonates

Two drugs in this class, etidronate and alendronate, have been investigated in a secondary prevention role.

A small study using cyclical etidronate for three years in 66 women with prior vertebral fracture suggested a potential impact on future risk of fractures.²¹ The trial was small, with only 40 women completing the study, and insufficient data are presented to comment on the magnitude of any effect.

A second, considerably larger, study (n=423) investigated the effect of treatment over two years,²² (extended to three years²³). This was a complex trial design, with four subgroups, investigating various combinations of etidronate and sodium-potassium phosphate treatment. It remains, however, the only published prospective study of cyclical etidronate with a fracture outcome. The results at the end of three years' treatment showed a trend towards a reduction in vertebral fracture risk, although the study was too small for this to reach statistical significance.

Alendronate usage in secondary prevention has been investigated in one large, well-designed study.²⁴ This involved 2,027 women with low BMD and prior vertebral fracture being randomised to receive treatment with either alendronate or placebo. At the end of a three-year period, there was a significant reduction in the risk of both vertebral (Table 2) and non-vertebral fractures (Table 3).²⁴

Selective oestrogen receptor modulators

In a secondary prevention arm of the raloxifene study, 2,641 patients with prior fracture were randomised to receive either placebo, raloxifene 60 mg or raloxifene 120 mg for three years. Subject to the caveats that must be accorded to unpublished work, we have included the data relating to the 60 mg

Table 2. Secondary prevention of vertebral fracture

Treatment	n (control/active)	Duration (years)	Fractures (control)	Fractures (active)	NNT
Etidronate ^{23*}	431 (212/211)	3	15.1%	13.3%	55
Alendronate ²⁴	2,027 (1,005/1,022)	3	14.4%	7.6%	15
Raloxifene ¹⁸ 60 mg data	2,641	3	20.2%	14.1%	16

* Not significant

Table 3. Prevention of non-vertebral fracture

Treatment	n	Duration (years)	Fractures (control)	Fractures (active)	3-year NNT
Alendronate 5/10 mg ^{24*} (any non-vertebral)	2,027	3	14.7%	11.9%	36
Alendronate 10mg ²⁵ (any non-vertebral)	1,908	1	3.9%	2.0%	18**
Raloxifene ^{18*†} (any non-vertebral)	2,641	3	9.3%	8.5%	125
Alendronate ²⁴ (hip fracture)	2,027	3	2.2%	1.1%	90
Raloxifene ^{18*†} (hip fracture)	2,641	3	0.7%	0.8%	-1,000

* Not significant. ** Inferred from one-year data. † Combined 60 mg and 120 mg data

dose in Table 2. There was an apparent reduction in the risk of vertebral fracture, although its significance level cannot yet be calculated with the data available. There was no impact on non-vertebral fracture (Table 3, previous page).

On the face of it, this evidence would appear to support a strategy of secondary prevention using either alendronate or, if the published data prove robust, raloxifene. One must avoid drawing conclusions too rapidly, however. Vertebral fracture is a useful indicator of osteoporotic disease progression and undoubtedly causes considerable suffering. Many vertebral fractures, however, are asymptomatic and are only found coincidentally on x-ray. It is non-vertebral fractures – particularly femoral neck fractures – that incur greatest morbidity, mortality and expenditure within the NHS. Before adopting any treatment as a standard approach, therefore, it is important to be sure that they are likely to impact on the risk of clinically apparent osteoporotic fractures.

No study of either alendronate or raloxifene has specifically set out to investigate this endpoint, although there is relevant data to be gleaned for both drugs. Event rates in all the studies are relatively low, as non-vertebral fractures tend to occur in older age groups than were investigated for vertebral fracture. This means that NNTs will tend to be large and confidence intervals wide. We are, none the less, able to draw broad implications regarding the impact of a treatment on this important group of osteoporotic fractures (Table 3, previous page).

A recently published study relating to alendronate also offers an interesting new perspective. All the main alendronate trials to date^{16,17,24} have used a range of doses, with the majority of patients being on 5 mg per day, half the licensed dose, for most of the treatment duration. The most recent study, however, used a dose of 10 mg in a mixed group of 1,908 patients, all of whom had low bone density but whose prior fracture status was unspecified.²⁵ The study only lasted for one year and did not collect data on vertebral fracture but the results were, none the less, surprising, given the timescale. Achieving an NNT of 54 within one year would suggest a three-year figure of between 15 and 20. In isolation this might be regarded as a freak

result but, in combination with the other alendronate data, it provides fairly solid confirmatory evidence of efficacy.

Prospective data relating to etidronate is lacking in respect of non-vertebral fracture. A retrospective analysis of GP data has suggested that there may be an impact on hip fracture associated with etidronate use,²⁶ although the inherent limitations of the study design make this difficult to confirm or refute.

Calcium and vitamin D

It will not have escaped the reader's notice that no mention has so far been made of the role of calcium and vitamin D supplementation in preventing osteoporotic fracture. This may be considered surprising, as one of the largest and best-designed studies in the field demonstrated an impressive benefit.^{27,28} In a three-year trial, 3,270 elderly ladies (mean age 84 years) resident in nursing homes or sheltered accommodation were randomised to receive either 1.2 g calcium plus 800 IU vitamin D or placebo daily. Although there were large numbers of dropouts – only 1,765 completed the trial – the benefit was substantial. Eleven percent of patients on placebo suffered a hip fracture, compared with 8% on active treatment, equating to an NNT of 40. Similar results were reported in a smaller study looking at a somewhat younger (mean age 71) community-living cohort.²⁹ A comprehensive review of all other trials of calcium and vitamin D, whether alone or in combination, failed to reveal any other well-constructed trials yielding a positive result.³⁰

The benefits of this form of treatment seem genuine in certain groups of patients but probably do not reflect any impact on the osteoporotic process itself. In both cases, the placebo-treated population was vitamin D and calcium deficient, with consequent secondary hyperparathyroidism. This condition is also associated with an increased risk of hip fracture, independently of any coexisting osteoporosis.³¹ Correction of underlying calcium and vitamin D deficiency is therefore an important step in the prevention of fracture. What we do not know, because it has not been investigated, is whether the use of supplementation in patients with normal parathyroid function has any additional benefit.

Certainly, in the major trials of antiresorptive therapy,^{16-18,23-25} steps have been taken to ensure that all patients, whether on active treatment or placebo, are calcium and vitamin D replete, thereby ensuring that any observed differences in fracture risk are genuinely associated with the treatment under investigation.

Conclusions

It is reasonable to suggest that any patient at high risk of osteoporotic fracture should be assessed for adequacy of calcium and vitamin D intake and appropriate steps taken to correct this where necessary. The more difficult decision that then has to be taken is which patients should be considered for active antiresorptive therapy. Based on the available evidence:

- Initiating preventive treatment at the time of the menopause is superficially attractive but lacks any clear support in the evidence base. Where there are other indications for treatment and there is a likelihood that the woman will remain on treatment for seven years or more, there is circumstantial evidence to support the use of HRT to prevent osteoporosis at this time.
- Delaying the onset of treatment until the late 60s means that the chances of preventing a fracture are considerably enhanced, although the NNTs remain considerably higher than one would wish. Targeting therapy at those with a low BMD considerably enhances the power of this approach, although it would be difficult to justify even this strategy on economic grounds.
- All patients considered to be at risk of osteoporotic fracture should have their calcium and vitamin D intake assessed and, if necessary, supplemented. Once this has been addressed, consideration should be given to antiresorptive therapy.
- There is good evidence to support the use of antiresorptive agents in patients who have already suffered a vertebral crush fracture, with several studies demonstrating a reduction in both vertebral and (in the case of alendronate) non-vertebral fracture risk.
- Evidence relating to the use of selective oestrogen receptor modulators remains limited, although it appears that their effect is exerted preferentially at the spine rather than the hip. Until peer-reviewed data have been published their position within a rational strategy must remain undefined.

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