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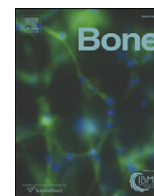
Review

Treatment of osteoporosis in men

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ABSTRACT

Summary: Aspects of osteoporosis in men, such as screening and identification strategies, definitions of diagnosis and intervention thresholds, and treatment options (both approved and in the pipeline) are discussed.
Introduction: Awareness of osteoporosis in men is improving, although it remains under-diagnosed and under-treated. A European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) workshop was convened to discuss osteoporosis in men and to provide a report by a panel of experts (the authors).
Methods: A debate with an expert panel on preselected topics was conducted.
Results and conclusions: Although additional fracture data are needed to endorse the clinical care of osteoporosis in men, consensus views were reached on diagnostic criteria and intervention thresholds. Empirical data in men display similarities with data acquired in women, despite pathophysiological differences, which may not be clinically relevant. Men should receive treatment at a similar 10-year fracture probability as in women. The design of mixed studies may reduce the lag between comparable treatments for osteoporosis in women becoming available in men.

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Introduction

Considerable progress has been made in understanding the pathophysiology and management of osteoporosis, though it remains under-diagnosed and under-treated [1], particularly in men [2]. Osteoporosis is widely considered to be much more prevalent in women, even though approximately 39% of new osteoporotic fractures estimated to have occurred worldwide in 2000 were in men [3]. Though the average age at which osteoporotic fractures occur in men is approximately 5–10 years later than in women depending on fracture type [4], men have greater morbidity and mortality rates due to hip fractures compared with women [5,6]. There is some lack of awareness among healthcare providers of the need to evaluate men for osteoporosis [7]. Among patients who have sustained a fragility fracture, men and women have a similar relative risk (RR) of sustaining a subsequent fracture [8,9], but men are less likely than women to receive therapy [10,11]. Treatment rates are very low in men (<10%), even in those with a prior fragility fracture. Moreover, the economic burden of osteoporosis is expected to rise due to ageing populations [12,13].

Progress has been made in the identification of men who should benefit from treatment (*e.g.* the FRAX management algorithm is applicable to men). However, controversies remain, for instance regarding the criteria by which to define osteoporosis in men on the basis of bone mineral density (BMD). Most information on osteoporosis is in women, and most treatments are developed and approved for use in women. Approved drugs in the US and Europe for osteoporosis treatment in men include bisphosphonates (alendronate, risedronate and zoledronic acid), and teriparatide. Strontium ranelate was recently approved in Europe. Denosumab and other drugs are expected to reach the market in the near future.

This review provides an overview of osteoporosis in men, available treatment options and potential future approaches to treatment.

Osteoporosis in men: is it different from postmenopausal osteoporosis?

Epidemiology of fractures

In untreated osteoporosis patients, low BMD is consistently associated with an increase in fracture risk. About 4–6% of men over the age of 50 years have osteoporosis. Estimates of lifetime fracture risk in men range from 13 to 25%, which is lower than estimates for women, who have a lifetime fracture risk of up to 50% [14]. The lower lifetime fracture probability arises because of a lower age-specific fracture incidence and shorter life expectancy in men compared to women. Studies on the impact of osteoporosis-related fractures in the United Kingdom have shown that the lifetime risk for hip, spine, and wrist fractures in women is 14, 28, and 13%, respectively, *versus* 3, 6, and 2% in men [15], although there is variation in reported incidence rates from country to country [16]. In Europe, estimates of the 10-year probability of hip fracture in men and women at the age of 50 range from 0.1 to 0.6% in men *vs.* 0.2 to 1.1% in women, and increase with advancing age [16].

Forearm fractures tend to increase in incidence in white women between the ages of 45 and 60 years, followed by a plateau or more attenuated rise thereafter, whereas rates in men commonly remain low, regardless of increasing age. The incidence of hip fracture increases exponentially with age in both men and women in most regions of the world. Most hip fractures are the result of a fall [17]. Population-based studies of vertebral fracture are difficult to compare, because of a lack of standardised diagnostic methods and criteria. Vertebral fracture prevalence tends to increase with age among men and women, with a steeper gradient among women [18] (Fig. 1). Other fractures associated with low trauma also increase in frequency with age among men, including fractures of the rib, clavicle, proximal humerus and pelvis. They add to the morbidity and mortality burden of osteoporosis in men.

In Caucasians, geographical variations in hip fracture rate in women are mirrored by that in men. However, gender ratios are different in Latin America and Asia, with a blunting of female to male incidence ratios, but the rankings of high to low tend to remain consistent, even outside Europe [19]. Although female and male incidence rates are more approximate for India and China, they are very similar in terms of their rise with advancing age, and remain lower than hip fracture rates observed in most European countries [20,15,21]. In a Swedish study, more than twice as many women than men aged ≥50 years were hospitalised for hip fractures [22], and studies have reported higher mortality rates after hip fracture in men than in women. A Canadian study observed 71% of hip fractures in women and 29% in men, but in-hospital mortality of women was half that of men (5% and 10%, respectively) [23]. These
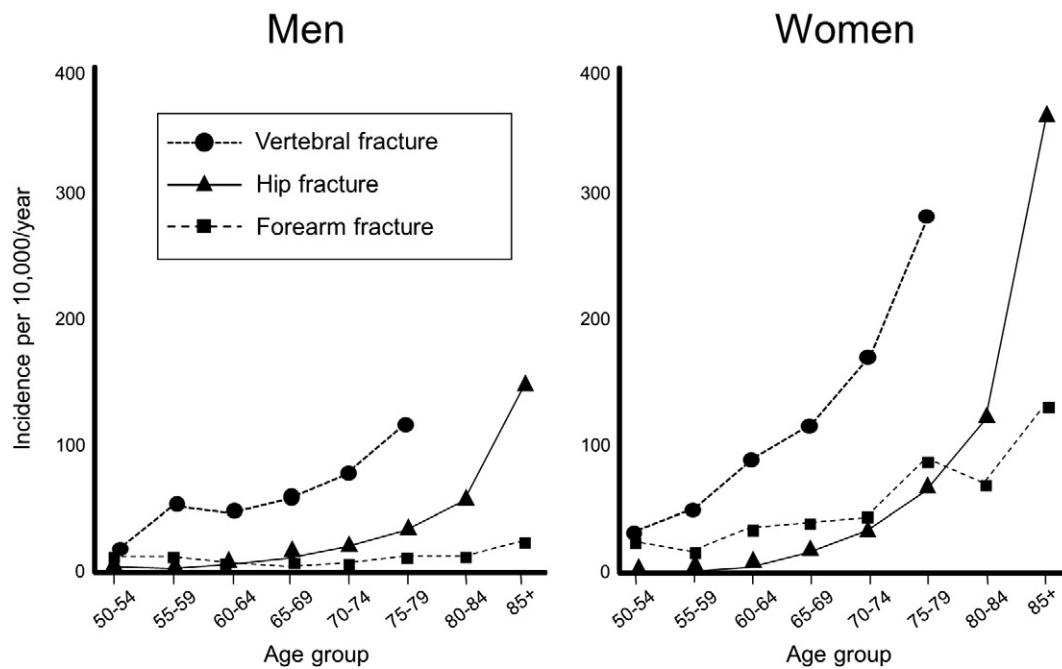
Fig. 1. Osteoporotic fractures in men and women: incidence of osteoporotic fractures in men and women. Adapted from [17].

differences persisted at one year [4,23] and related to pre-fracture health status and post-fracture complications.

Over the last few decades, temporal changes have been reported in the age-specific incidence of fractures in men and women. There does seem to be geographical diversity, particularly in the rate of rise in hip fracture incidence evident towards the end of the 20th century [18]. Hip fracture rates have now stabilised in some Western populations and, in some cases even decreased [24]. In contrast, some studies have suggested that rates are rising in other populations, particularly in Asia [21,25,26].

Relationship of fracture incidence to BMD

The diagnosis of osteoporosis relies on the quantitative assessment of BMD, usually by central dual energy X-ray absorptiometry (DXA) [27]. It was originally defined in postmenopausal women as a BMD value that is 2.5 standard deviations (SD) or more below the young female adult mean. The criteria were later broadened to include men and the femoral neck as the reference site [28] (based on the Third National Health and Nutrition Examination Survey [NHANES III] reference population of women aged 20–29 years) [29].

The use of a common reference range arises from several lines of evidence. A World Health Organization (WHO) systematic review and meta-analysis of data from 12 cohort studies including approximately 39,000 men and women assessed relationship between BMD and fracture risk. The data suggested a consistent increase in the RR of fracture for each SD decrease in femoral neck BMD. The gradient of risk was higher for hip fracture than for all osteoporotic fractures, but was the same in men as in women for both outcomes [8], so that the fracture risk in men and women at any given age was similar for a same absolute BMD value. The same study showed a decreasing gradient of risk for hip fracture with advancing age, but the age-dependency of fracture risk was similar in men and women [8]. The systematic review expressed absolute fracture risk as 10-year probability of hip fracture according to age and BMD T-score and concluded that the age-adjusted hip fracture incidence was identical in men and women of the same age and the same BMD [8].

Because the relationship between BMD and fracture risk changes with age [30], several studies investigating fracture risk in men and women have reached different conclusions [8,31–36]. However, the available studies show that the risk of hip and vertebral fracture is similar in men and women for any given BMD [8,30,35,37–39], supporting the use of a BMD value of 2.5 SD or more below the mean for young adult women for the diagnosis of osteoporosis in men.

Clinical risk factors and relationship to BMD

The prevalence of individual risk factors for osteoporotic fracture is commonly reported to be different in men compared to women. It is frequently suggested that osteoporosis in men often has secondary causes, the most common being corticosteroid use, excessive alcohol use, and hypogonadism (Table 1). Other causes that are gaining relevance are due to clinical problems related to hormone ablation for prostate cancer (discussed below), highly active anti-retroviral therapy in HIV-infected patients, and immunosuppressive therapy in organ transplanted patients [2]. Both in men and women, age, prior fracture and BMD capture a substantial proportion of fracture risk with further independent contribution of additional risk factors.

According to the MrOS study, which evaluated predictors of non-spine fracture in elderly men after adjusting for BMD, the following clinical risk factors were identified: previous fracture, age, a fall in the past year, use of tricyclic antidepressants, and inability to complete a walking test. The combination of multiple risk factors and low BMD was a powerful indicator of fracture risk. The study found that men who were in the lowest BMD tertile and had three or more clinical risk factors had a 15-fold greater fracture risk than those with no risk factors in the highest BMD tertile [40].

Considering osteoporosis in men as distinct from female osteoporosis might be misconceived. Clinical practice suggests that men are more often diagnosed with secondary osteoporosis, but there are no relevant population-based data to support this notion. It is difficult to distinguish between the multifactorial nature of female *vs.* male osteoporosis. A recently presented subanalysis of the MrOs cohort evaluated secondary causes of osteoporosis in subjects that had low BMD *vs.* those that did not have low BMD, and most were similar in terms of their risk factors [41]. It is thus not established that secondary osteoporosis really is more common in men. Men may be less likely to be referred for bone densitometry in the absence of specific risk factors for osteoporosis,

Table 1
Clinical risk factors used for the assessment of fracture probability in men.
Adapted from [50].

- o Age
- o Sex
- o Low BMI (≤ 19 kg/m^2)
- o Previous fragility fracture, in particular of the hip, wrist and spine
- o Morphometric vertebral fracture
- o Parental history of hip fracture
- o Current glucocorticoid treatment (>5 mg prednisolone/day or equivalent for ≥ 3 months)
- o Current smoking
- o Alcohol intake of ≥ 3 units/day
- o Secondary causes of osteoporosis including: rheumatoid arthritis, untreated hypogonadism (*e.g.* bilateral orchidectomy, anorexia nervosa, hypopituitarism), inflammatory bowel disease (*e.g.* Crohn's disease and ulcerative colitis), prolonged immobility, organ transplantation, type I diabetes, thyroid disorders, chronic obstructive pulmonary disease
- o Falls

and there may be a general tendency by healthcare practitioners to look for the causes of secondary osteoporosis in men more carefully than in women.

Biochemical markers of bone turnover

Use of bone formation (serum procollagen type I N propeptide, sPINP) and bone resorption (serum C-terminal telopeptide of type I collagen, sCTX) markers are recommended by the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) as reference analytes for bone turnover markers (BTMs) in clinical studies. Levels of BTMs may predict fracture risk independently from BMD, and may provide data on treatment response and monitoring, although a stronger evidence base is needed.

Conflicting data on the association of BTMs with bone loss and fracture risk in men have been reported. A study in elderly men observed a decreased carboxylated serum osteocalcin to total osteocalcin ratio that was associated with increased subsequent fracture risk [42]. The Dubbo Osteoporosis Study of elderly men reported increased sCTX associated with an increased risk of osteoporotic fractures independent of BMD [43]. Finally, the MrOS cohort demonstrated that biochemical markers in men were predictive of bone loss in a similar manner as in women. Hip and non-spine fractures were associated with increased sPINP and sCTX, but the association no longer held true after adjusting for hip BMD [44]. On the other hand, the MINOS study found that serum concentrations of BTMs were not predictive of fractures [45]. The question of whether BTMs are predictive of accelerated bone loss or fractures in the clinical management of osteoporosis in men remains unanswered. The adoption of international reference standards would help to clarify uncertainties on their clinical use [46].

Pathophysiology of bone loss

Men have larger bones compared with women, resulting in greater bone strength. With age, bone size may increase in men by periosteal apposition more than in women, thus further increasing the sex difference in bone size (reviewed in [6]). One of the most noteworthy differences between male and female osteoporosis concerns bone microarchitecture. The patterns of bone loss in men seem to be different from those in women. Earlier trabecular loss was measured in men, with cortical loss starting after the age of 50 years, possibly linked to gonadal steroid decline (sex steroids are further discussed below) [7,47]. A deficiency in oestrogen or testosterone may be a unifying factor in the pathophysiology of the disease.

Men have a higher trabecular bone volume/tissue volume, which declines at a similar rate to women. Peripheral quantitative computed

tomography (CT) demonstrated that men seem to show a relative preservation of trabecular number, but more trabecular thinning [7,6], presumed to be secondary to reduced bone formation and correlated with indices of reduced bone formation.

Management algorithms

FRAX is a computer-based algorithm (http://www.shef.ac.uk/FRAX) launched in 2008. It calculates fracture probability from clinical risk factors (Table 1) and patient characteristics (age, weight, height, *etc.*) in both men and women. The output of FRAX is the 10-year probability of a hip fracture and of a major osteoporotic fracture (hip, clinical spine, humerus or wrist fracture) [48,49]. As is the case for women, there is presently no generally accepted algorithm for the management of osteoporosis in men [50], although FRAX is being increasingly incorporated into practice guidelines. An example for the UK is provided in Table 2.

Before the advent of FRAX, management algorithms for men were very similar to those used in postmenopausal women. In the UK, in the event of a previous fracture, a DXA would be performed or treatment would be considered in the absence of a BMD measurement. In the absence of a previous fracture, but if other clinical risk factors are present (Table 1), a DXA should be performed, and the subject recommended for treatment if their T-score was below −2.5 SD [51]. In other countries, other T-score thresholds have been used [2]. Although risks that justify treatment vary on a national basis, treatment is widely recommended in individuals with a prior history of fragility fracture [50].

Whereas the diagnosis of osteoporosis centres on the assessment of BMD at the femoral neck using DXA, other sites and validated techniques can be used for fracture prediction. The FRAX clinical risk factors contribute to fracture risk independently of BMD. The use of these risk factors in conjunction with BMD improves sensitivity of fracture prediction without adverse effects on specificity [52]. Thus, the FRAX algorithm may significantly impact clinical practice because it helps identify individuals at increased risk of fracture, while avoiding unnecessarily treating patients at low fracture risk.

Table 2
Example of management algorithm for the treatment of men in the UK.
Adapted from [49].

Men with a prior fragility fracture should be referred for BMD assessment.
  Men aged ≥ 50 years with clinical risk factors should have fracture probability assessed using the FRAX tool without measurement of BMD.
  Individuals with probabilities of a major osteoporotic fracture below the lower predefined assessment threshold can be reassured (range of probabilities for BMD testing according to age, see below). Assessments are recommended every five years or less depending on the clinical context.
  Individuals with probabilities of a major osteoporotic fracture above the upper predefined assessment threshold (see below) or with probabilities of a hip fracture above the upper limit can be treated without a prior BMD evaluation.
  Individuals with probabilities of a major osteoporotic fracture within the limits of the assessment thresholds and with probabilities of a hip fracture below the limit should have a BMD test and probabilities recomputed. If probabilities exceed the treatment threshold, intervention should be considered. Where probabilities fall below the treatment threshold, assessments are recommended every five years or less depending on the clinical context.
Predefined range of 10-year major fracture probabilities for BMD testing and intervention threshold by age:

Age (years)	Lower limit	Upper limit	Intervention threshold
50	5.7	9	7.5
55	7.5	12	10
60	10	14	12.5
65	14	20	15
70	11	25	20
75	14	29	25
80	18	34	30

Current European requirements for drugs used in osteoporosis in men

Treatment of osteoporosis in men at increased risk of fracture was first included in the latest revision of the European guidelines on the evaluation of medicinal products in the treatment of osteoporosis [53]. Previous guidelines were only for use in postmenopausal women. The guidelines state that, for women, an effect in reducing fracture risk must be demonstrated on both spinal and non-spinal fractures in a randomised, double-blind, placebo-controlled primary pivotal study with a minimum duration of two years to be conducted either in women with a BMD T-score below −2.5 SD or in women with prevalent fracture. For women to be included in a trial, a 10-year fracture probability range of 15–20% for spine, 5–7.5% for hip and 10–15% for major non-vertebral fractures is suggested as a clinically relevant and suitable inclusion criterion [53]. Of note, US guidance is slightly different (reviewed in [54]). In future, since the advent of the FRAX approach, studies may recruit patients with an increased 10-year probability of fracture, without distinguishing between prevention and treatment. Therefore, patients with various BMD values (including osteopenia) may be included in studies, provided their 10-year probability of fracture is increased. The main relevant issues arising from the revised guideline are summarised below:

- In the case of a new drug that has not previously been investigated in women, a two-year placebo-controlled study investigating fracture incidence as the primary endpoint is required to develop drugs for the treatment of osteoporosis in men at increased risk of fracture. Most compounds to treat osteoporosis in men have been developed in females. If a chemical entity has already shown efficacy (reduced fracture incidence) in women, a separate bridging study (vs. placebo in males) of the same drug (same formulation, dose and route of administration) may be carried out, provided that the duration is at least one year, and that BMD at the lumbar spine is the primary endpoint. Baseline fracture risk in the male population should be similar to the fracture risk of the women included in the pivotal study. Finally, the magnitude of BMD changes observed vs. placebo in males should be similar to that observed in postmenopausal women.
- In the majority of bridging trials that have been performed in men, the risk profile of the included study population did not match the fracture risk level in the pivotal trials in postmenopausal women. Moreover, since men with osteoporosis now have access to different treatment modalities, it may not be ethical to include men with high fracture risk in a placebo-controlled bridging study. Because more recent phase III studies have included women at lower risk than traditional studies, the data from these studies are more likely to provide a suitable basis for bridging to a male population with a lower risk

(to avoid bridging from a high-risk female population to a lower-risk male population).

Treatment of osteoporosis in men: available agents

Bisphosphonates

Bisphosphonates inhibit osteoclastic bone resorption and are the most widely used drugs in male osteoporosis. Studies of male osteoporosis include the evaluation of alendronate, risedronate, and zoledronic acid, as summarised below (Table 3). These agents are indicated to increase bone mass in men with osteoporosis.

Alendronate

In a two-year double-blind study, Orwoll et al. investigated 10 mg/day of alendronate or placebo in 241 men with osteoporosis aged 31–87 years (mean age 63 years). The study included men with femoral neck BMD at least 2 SD and lumbar spine BMD at least 1 SD below the male reference, or with femoral neck BMD at least 1 SD below male reference and at least one vertebral deformity or a history of an osteoporotic fracture. Half of the study population had established osteoporosis. At baseline, approximately 50% of patients had already sustained vertebral fractures [55].

Alendronate-treated men showed a similar increase in BMD as previously reported in postmenopausal women [56,57]. Lumbar spine BMD increased by $7.1 \pm 0.3\%$, whereas femoral neck BMD increased by $2.5 \pm 0.4\%$ [55]. The changes in BMD with alendronate were not affected by circulating levels of sex steroids (testosterone and oestradiol). Therefore, treatment and anti-fracture efficacy of bisphosphonate may potentially be similar in hypogonadal men and eugonadal men. In less extreme circumstances, this observation remains relevant in normal men whose testosterone levels decrease with ageing [58].

The alendronate study for the treatment of osteoporosis in men was a BMD endpoint study, and as such was not powered to determine anti-fracture efficacy. However, radiographic vertebral, clinical vertebral and non-vertebral fracture risks were numerically reduced in alendronate-treated men, without achieving a level of significance. The effect of alendronate on the change in height was significant. Men in the placebo group lost 2.4 mm in height, compared with 0.6 mm in the alendronate-treated men ($p = 0.02$). These data, although not conclusive, are consistent with anti-fracture efficacy [55].

Risedronate

A similar two-year BMD endpoint study was performed with risedronate 35 mg once a week in 284 men with osteoporosis aged 36–84 years (mean age 60) [59]. Men with a femoral neck BMD of at least 2 SD and lumbar spine BMD at least 1 SD below male reference

Table 3
Overview of studies in men with osteoporosis (approved agents).

Agent	N	Study duration	Main efficacy outcomes	Reference
Alendronate 10 mg/day	241	2 years	o LS-BMD increased by $7.1 \pm 0.3\%$, and FN-BMD increased by $2.5 \pm 0.4\%$.	[55]
Risedronate 35 mg qw	284	2 years	o Significant increase from baseline to endpoint in LS-BMD vs. placebo (4.5%, 95% CI: 3.5–5.6, $p < 0.001$). o Significant increases in hip BMD vs. placebo.	[59]
Zoledronic acid 5 mg once a year	1199	2 years	o Morphometric VF results showed a 67% reduction in risk of new VF. o LS-BMD increased from 4.7% at six months to 6.1% at two years. o Significant increases in LS-BMD vs. placebo.	[65]
Teriparatide 20 or 40 mcg/day	437	Premature termination (median total exposure 11 months)	o LS-BMD increased by 5.9% (20 mcg) and 9.0% (40 mcg) above baseline ($p < 0.001$ vs. placebo for both). o FN-BMD increased by 1.5% (20 mcg, $p = 0.029$) and 2.9% (40 mcg, $p < 0.001$).	[69]
Strontium ranelate 2 g/day	261	2 years (1 year to main analysis)	o LS-BMD increase at 1 year similar to that previously observed in core studies in postmenopausal women. o Significant increase at the femoral neck.	[97]

BMD, bone mineral density; CI, confidence interval; FN, femoral neck; LS, lumbar spine; qw, once a week; VF, vertebral fracture.

values or a femoral neck BMD at least 1 SD and lumbar spine BMD at least 2.5 SD below male reference values were included. At baseline, 35% and 34% of patients had prevalent vertebral fractures in the placebo and risedronate groups, respectively [59].

The study reported a significant increase from baseline to endpoint in lumbar spine BMD compared with placebo (4.5%, 95% CI: 3.5–5.6, $p < 0.001$). Significant increases in hip BMD were also observed compared with placebo. A 40% reduction in type 1 cross-linked N-telopeptide (NTX) was observed in risedronate-treated men, again similar to reports in post-menopausal women [60]. This study also showed that the effects on bone density and on NTX were not affected by circulating testosterone. The trial was not designed as a fracture-endpoint study; the number of fractures was small, as expected, because of the sample size and the study design. No statistically significant difference between treatment groups for the overall incidence of vertebral fractures or clinical fractures was observed. The cumulative incidence of clinical fractures was 7.7% in men on placebo *vs.* 4.9% in risedronate-treated men (RR 0.69 [0.25–1.93]). The positive effects of risedronate in men with osteoporosis were confirmed in an open-label, prospective, match-control trial [61].

Zoledronic acid

Approval of zoledronic acid for use in men was based on findings from the HORIZON Recurrent Fracture Trial (RFT), a study involving 508 men and 1619 women with a recent low trauma hip fracture that had been surgically repaired [62]. In this study, zoledronic acid (as an annual 5 mg infusion) showed a 35% reduced risk of new clinical fractures in the overall population compared with placebo, and no significant treatment-by-gender interaction was observed. More recently, an analysis of the subset of men participating in the HORIZON-RFT confirmed that the increase in BMD in men was statistically similar to that observed in women with recent hip fracture [63]. Low numbers of clinical fractures were observed in men in the HORIZON-RFT (16 [7.45%] and 20 [8.7%] for zoledronic acid and placebo, respectively), with no significant difference between the treatment groups. This lack of a statistically significant fracture reduction was expected, as the gender-based subset analysis was powered for a BMD endpoint and not for anti-fracture efficacy. In line with these findings, a head-to-head trial comparing once-yearly zoledronic acid with daily oral alendronate in men with low BMD also showed the expected effects of zoledronic acid on bone density and bone turnover [64].

Most recently, a fracture endpoint study in male osteoporosis investigated once-yearly intravenous (iv) zoledronic acid treatment in a randomised, multi-centre, double-blind, placebo-controlled, two year study. The primary efficacy endpoint was the reduction in vertebral fracture risk at the two-year endpoint of the trial. In all, 1199 patients were randomised to an annual infusion of either zoledronic acid 5 mg or placebo, and supplemented with calcium 1000–1500 mg and vitamin D 800–1200 mg/day. Patient inclusion and exclusion criteria were similar to previous bisphosphonate studies, in that men aged 50–85 years (mean age 65.8) with primary osteoporosis or secondary osteoporosis due to hypogonadism were included. Of note, this was a low-risk population compared to studies investigating postmenopausal women on zoledronic acid, because male reference values were used. The results of the study have recently been fully published [65]. Overall, the findings showed changes in surrogate outcomes (bone density and bone turnover) in line with those reported in pivotal trials of postmenopausal women [66]. Vertebral fracture risk reductions were similar in magnitude to those previously reported with iv zoledronic acid in postmenopausal osteoporosis.

Teriparatide

Teriparatide is classified as a parathyroid hormone (PTH) analogue that has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone. It is indicated to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture and in the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in men at high risk of fracture.

Teriparatide monotherapy

Initial indications that teriparatide was useful in male osteoporosis were published in the 1980s [67,68]. A placebo-controlled, double-blind trial subsequently led to its approval for the treatment of men in the US [69] (Table 3). This bridging study included 437 men with low BMD (hip or spine T-score < − 2.0 SD) without secondary causes of osteoporosis. Patients were randomised into three groups, and either received once daily subcutaneous 20 or 40 mcg teriparatide, or placebo. The patients were supplemented with calcium (1000 mg/day) and vitamin D (400 to 1200 IU) (continued during the subsequent follow-up observation phase). The study's primary endpoint was lumbar spine BMD. It was prematurely terminated (median total exposure 11 months), because osteosarcomas developed in rats during toxicological evaluation. This observation was, however, not considered predictive of an increased risk for humans treated for relatively short periods [70]. Baseline values showed that the study population was relatively young (58–59 years old), with relatively elevated spine BMD and low risk T-scores. About 40% of participants had vertebral fractures and half had low free testosterone values.

The patterns of biochemical marker changes in response to teriparatide were typical (dose-dependent increases in bone formation and resorption markers) and very closely mirrored similar data in women, albeit with a lower magnitude [69]. The changes in BMD were also very similar to those previously reported in women [71]. Both teriparatide doses led to the expected changes in spine, total hip and femoral neck BMD. When BMD responses to 20 mcg of teriparatide are compared in men and women, the absolute change in BMD is similar. Analyses showed consistent responses across the risk groups usually seen in male osteoporosis, in that responses did not differ according to baseline BMD, age, gonadal status, previous fracture status, smoking or alcohol consumption [69].

In an 18-month follow-up study, about 80% of patients agreed to be observed without receiving study medication, but with the option to undertake other therapies [72]. After treatment discontinuation, BMD declined in both teriparatide treatment groups, particularly at the lumbar spine [72]. There was no difference in the rate of BMD decline as a function of testosterone concentrations [72]. From the original treatment trial baseline to the 18 months visit of the follow-up study, there was a lower incidence of moderate and severe fractures, in the combined 20 and 40 mcg teriparatide groups than in the placebo group ($p = 0.01$) [72]. However, these data should be interpreted with caution, because approximately 22% of the men reported the use of a bisphosphonate at some point during the follow-up study. Again, the point estimates for the reduction in vertebral fracture risk in men were essentially the same as in women [73], despite the smaller study size.

Of interest, Leder et al. investigated the effects of teriparatide treatment and discontinuation [74] in a small study involving 14 postmenopausal women and 17 eugonadal men with osteoporosis, aged 46–85 years, with lumbar spine or femoral neck T-scores < − 2 SD. Daily teriparatide (37 mcg) was administered subcutaneously for 24 months, followed by 12 months off therapy. The study observed that, following teriparatide discontinuation, the rate of BMD decline was greater in women than in men, possibly highlighting a difference in teriparatide response or in the drivers of BMD maintenance in men and women. The 5.9% female to male difference in trabecular BMD loss was statistically significant ($p = 0.037$; 95% CI, 11.2–0.4), but the difference in absolute trabecular BMD loss was not. The mechanisms underlying this potential relative resistance to post-teriparatide bone loss in men are unclear. This observation requires confirmation in larger studies and in men and women receiving the approved teriparatide dose of 20 mcg/day. One concern is that teriparatide appears to require continued administration for a sustained biological effect, unlike

bisphosphonates that have persistent effects on bone resorption many months after drug exposure [75–77]. However, Lindsay et al. also reported that women with postmenopausal osteoporosis showed sustained vertebral fracture risk reduction after withdrawal of teriparatide (at least 18 months) [73].

Finally, a post-marketing study on the use of teriparatide in the US, derived from the Direct Assessment of Nonvertebral Fracture in the Community Experience (DANCE) study, described gender differences for initiating teriparatide therapy. The drug was used more often in women, based on general frailty, low body mass and an inadequate response or intolerance to previous therapy. Chronic glucocorticoid therapy was the reason most often given by investigators for initiating therapy in men, and more often used as an indicator for therapy in men, illustrating the possibility that at least in the US, physicians view teriparatide use somewhat differently in men vs. women [78], and providing further evidence from a clinical practice setting that male osteoporosis is under-diagnosed and likely under-treated.

Teriparatide combination therapy

A study randomly assigned 83 men with low BMD to receive 10 mg/day alendronate, 40 mcg/day teriparatide subcutaneously, or both. Alendronate was administered for 30 months, and teriparatide was started after six months. Lumbar spine and femoral neck BMD increased significantly more in men on teriparatide monotherapy compared with the other groups. Changes in serum BTM were significantly greater in the teriparatide group than in the alendronate group or the combination therapy group ($p < 0.001$). As with BMD, a second study showed that alendronate impaired the action of teriparatide to increase bone turnover in men [79,80]. Previous studies in postmenopausal women also suggested that concomitant alendronate and PTH (1–84) reduced the anabolic effects of PTH [75,81]. These data may influence therapeutic choices after PTH discontinuation, because its use is limited to a maximum of two years [75].

Although these studies suggested that combination of teriparatide and bisphosphonates had no additive effect because alendronate diminished the teriparatide effect, zoledronic acid was shown not to block the anabolic effect of PTH. In a one-year partial double-blind randomised study of 412 postmenopausal women, Cosman et al. concluded that, while teriparatide increased spine BMD more than zoledronic acid, and zoledronic acid increased hip BMD more than teriparatide, combination therapy provided the best BMD improvement, both in spine and hip BMD [82].

Available treatments for osteoporosis in men: conclusions and discussion

The treatment response to oral bisphosphonates in male osteoporosis is similar to that observed in postmenopausal osteoporosis, in terms of bone density and bone remodelling. To date, conclusive anti-fracture evidence with alendronate and risedronate is unavailable in men, but fracture reductions are very consistent. With iv zoledronic acid, a recent report of fracture endpoint data in osteoporotic men indicates that zoledronic acid anti-fracture efficacy in men mirrored that observed in women. The approaches developed to treat and identify women at high risk (e.g. the FRAX approach) are likely to be equally useful in men.

Teriparatide studies concluded that the changes in biochemical markers, BMD, and vertebral fracture risk in response to 20 mcg teriparatide in men were essentially the same as in women. Studies have suggested that combination of teriparatide and alendronate diminished the teriparatide effect, but zoledronic acid was shown not to block the anabolic effect of PTH in women. Teriparatide appears to be an effective therapy in men with osteoporosis, yet maintenance of its effects after treatment cessation is not fully understood and may require subsequent initiation of bisphosphonate treatment.

Sex hormones

Several agents are known to have a positive effect on BMD in the extreme event of acute hypogonadism due to chemical castration, including bisphosphonates and denosumab (discussed below) [83,84]. It seems reasonable to use these agents to avoid bone loss in men receiving androgen deprivation therapy, particularly when baseline BMD is low or if other fracture risk factors are present.

Testosterone prevents bone loss and may increase bone mass in hypogonadal men, although there is little available long-term data and no fracture data. Despite testosterone's beneficial effects on the skeleton when initiated in the broader context of androgen replacement in established hypogonadism, it is not indicated for osteoporosis treatment as such [9]. A hypogonadal man with a high risk of fracture should receive classical osteoporosis medication [58], regardless of whether testosterone is being initiated on the basis of current hypogonadism treatment guidelines.

An important point concerns oestradiol, which may be more related to fracture than testosterone, and raises the question of oestradiol assay sensitivity and standardisation. Low oestradiol levels were associated with high bone remodelling and bone loss, whereas no such relationship was found for testosterone [85,86], and were also associated with increased fracture incidence [87]. In the MrOs cohort, sex steroids were measured using mass spectrometry in elderly men. Serum-free oestradiol but not testosterone, was independently associated with fracture risk [88]. In clinical practice, the potential implication is that measurement of serum sex steroid contribution could become standardised. These data provide a rationale for assessing the use of selective oestrogen receptor modulators (SERMs) in men. Although oestrogen or SERMs are currently not approved for use in men, raloxifene reduces bone turnover in men with low endogenous oestradiol levels [89,90] and increases BMD in prostate cancer patients undergoing gonadal suppression therapy [91], with the caveat that raloxifene increases bone turnover in men with serum oestradiol levels above the population median.

Agents in development for men

A number of drugs with anti-fracture efficacy in postmenopausal women are available and are likely to be applicable in men, provided that bridging studies are carried out. An overview of drugs in development demonstrates that the most promising novel treatments include combination treatments (as outlined above with bisphosphonates and teriparatide), denosumab, strontium ranelate, odanacatib (a specific inhibitor of the osteoclast protease cathepsin K), antibodies against endogenous inhibitors of bone formation sclerostin and dickkopf-1 (Dkk-1), and saracatinib (Src inhibitor), a cancer drug which has not yet been applied in osteoporosis (reviewed in [92]).

Therapies in late-stage development

Denosumab

The anti-resorptive denosumab is a monoclonal antibody that binds and neutralises the activity of human receptor activator of nuclear factor-κB ligand (RANKL), a key osteoclast cytokine, similarly to endogenous osteoprotegerin. This agent is indicated to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. Denosumab has been shown to increase BMD and reduce fractures in postmenopausal women with osteoporosis [93] and in men with prostate cancer on hormone ablation therapy. In a double-blind, randomised, multi-centre study, denosumab was investigated in men receiving androgen-deprivation therapy for nonmetastatic prostate cancer. Patients received 60 mg denosumab subcutaneously every six months or placebo (734 patients in each group). At 24 months, lumbar spine BMD increased by 5.6% in the denosumab group as compared with a loss of 1.0% in the placebo group ($p < 0.001$). The difference was significant as early as one month. Significant BMD increases were

also reported at the total hip, femoral neck, and distal third of the radius at all time points. At 36 months, denosumab-treated patients had a significantly decreased incidence of new vertebral fractures (1.5%, *vs.* 3.9% with placebo) (RR, 0.38; 95% CI, 0.19–0.78; $p = 0.006$), and markers of bone turnover were significantly decreased compared with placebo ($p < 0.001$) [84]. The efficacy and safety of denosumab in men with low bone mass at risk of fracture is being further evaluated in the ongoing phase III denosumab *vs.* placebo ADAMO trial [94].

Strontium ranelate

Strontium ranelate is an alternative orally active drug with opposite effects on bone resorption and formation, that has been demonstrated to significantly reduce vertebral and non-vertebral fracture risk in women with postmenopausal osteoporosis [95,96]. At time of submission of this review, Strontium ranelate was recently approved for treatment of osteoporosis in men, but the complete results of the main study in men have not yet been published. A two-year, controlled, double-blind bridging study has been performed in osteoporotic men. The objective was to study men with a similar risk profile as the postmenopausal women previously included in the pivotal phase 3 trials, therefore the BMD inclusion criterion was below a same absolute BMD threshold value as in the studies in women. In a preliminary communication of the results at one year (main study analysis), the authors reported that a same dosage of strontium ranelate with calcium and vitamin D supplementation resulted in similar strontium blood levels and a similar significant BMD gain at the spine and hip in osteoporotic men compared with osteoporotic postmenopausal women [97].

Of note, an open-label, prospective, controlled, BMD endpoint 12-month trial in male osteoporosis patients compared strontium ranelate 2 g/day (n = 76) *vs.* alendronate 70 mg/week, an agent already approved for male osteoporosis. Mean increases in lumbar spine and total hip BMD were greater with strontium ranelate compared with alendronate [98], although the increment in BMD is partly dependent on a treatment-induced artefact. These strontium ranelate data support the increases in BMD observed in the recent core bridging study.

Odanacatib

Odanacatib inhibits cathepsin-K, a protease that plays an important part in osteoclast function. A phase III odanacatib trial in men with osteoporosis is ongoing (NCT01120600). In postmenopausal women, the effect of odanacatib on biochemical markers of bone turnover (sCTX, bALP) and on change in lumbar spine and femoral neck BMD (*vs.* baseline) was promising at 24 and 36 months [99,100]. Femoral neck BMD decreased after odanacatib discontinuation, although it remained above baseline levels [100].

Therapies in early-stage development

Sclerostin inhibitors

Therapies currently in phase II development include sclerostin inhibitors [101]. Data obtained in sclerostin knock-out (KO) mice have shown that these have high bone mass and normal bone morphology, but with increased trabecular and cortical bone volume. Other than the bone phenotype, no additional biologically significant differences were observed between wild-type and KO mice. Based on micro CT imaging, female KO mice appeared to have increased bone volume compared with males [102]. Anti-sclerostin antibody was also shown to increase markers of bone formation and BMD in healthy men and postmenopausal women [103].

Calcilytics

The stimulation of spontaneous endogenous PTH secretion, using calcium receptor agonists that tend to reduce serum calcium (calcilytics), has been proposed as an alternative approach to teriparatide administration. Examples of such compounds include ronalcaleret and JTT-305. Ronalcaleret had no effect on BMD, possibly because of a prolonged

stimulation of PTH secretion [104]. JTT-305 was tested over three months in 154 postmenopausal osteoporotic women randomised to three groups: placebo (n = 51), 10 mg/day (n = 50) and 20 mg/day (n = 53). Some differences in spine BMD and effects on P1NP and CTX markers, were found [105]. Interesting data on newer calcilytic drugs may emerge in the near future [92].

Drugs in pre-clinical development

Wnt/beta-catenin pathway

Advances in the molecular understanding of processes involved in the bone-anabolic pathway have highlighted the canonical Wnt/beta-catenin pathway as a key regulator of bone formation [106], which is negatively regulated by Wnt inhibitors such as Dkk-1 and sclerostin [107]. The Wnt pathway is composed of multiple potential drug targets involved in its activation (19 Wnts, 10 Frizzled, 3 LRPs) or inhibition (4 Sfrp, Dkk-1, sclerostin). Some components such as catenin, Rho, or PKC also interact with multiple pathways that are not specific for bone, which complicates matters in the context of targeted therapy. Importantly, interference with Wnt inhibitory factor 1 (WIF1) is associated with a potential risk of neoplastic development (osteosarcoma) [108]. Moreover, the reversibility or duration of the effect is not fully established. If therapy is stopped once good bone forming activity has been achieved, it is not clear whether this effect should be maintained with the administration of bone resorption inhibitors.

Selective androgen receptor modulators

Selective androgen receptor modulators (SARMs) have been shown to improve muscle strength and body composition, and to prevent bone loss in orchidectomised rats [109]. These agents display tissue-selective pharmacologic activity and may have an advantage over steroidal androgen therapy. Yarrow et al. demonstrated that trenbolone had advantages over testosterone in orchidectomised rats, supporting the need for future studies examining its potential in androgen replacement therapy [110]. Overall, these data do not display a very high magnitude of effect on bone strength. Moreover, the effects of respective SARMs on endogenous oestrogen levels and on the skeleton may diminish the clinical potential of these agents [9].

Agents in development for men: conclusions and discussion

Potential drugs for the treatment of osteoporosis in men include two broad categories, either of bone resorption inhibitors or of bone formation stimulators, as reviewed elsewhere [92]. Several additional agents are expected to be approved for the treatment of osteoporosis in men in the near future. Strontium ranelate has recently been approved in Europe for treatment of osteoporosis in men, but publication of complete results of the core study is still awaited. Denosumab is approved for use in men receiving androgen deprivation therapy for nonmetastatic prostate cancer who are at high risk of fracture. Data on the effect of denosumab in men with low bone mass at risk of fracture are also on the horizon. Other promising therapies at different stages of development include odanacatib, sclerostin inhibitors, or calcilytics.

Overall discussion and conclusions: who should be treated?

There is general agreement on the diagnosis of osteoporosis in men. In terms of assessment algorithms, different approaches have been used, either a traditional approach or a fracture probability-based approach, as is the case in the UK (Table 2). FRAX is, however, increasingly used in guidelines as they undergo revision.

The treatment algorithm and clinical guidance, which this panel wishes to support, aim to treat men at a similar 10-year fracture risk as in women, because the morbidity and mortality associated with major osteoporotic fractures in men are substantial. Available evidence suggests that treatment algorithms in women are also applicable to

men. In practice, this is likely to involve the use of FRAX and clinical risk factors (Table 1). The use of fixed intervention thresholds is viewed as counter-intuitive to current practice, because the risk is to exclude too many younger patients and, conversely, to include too many older patients above a threshold value.

The available level of evidence that treatment decreases the risk of fracture in men is lower than for women. As such, the US Endocrine Society is of the opinion that there is currently not enough information in men to make a recommendation, because too few fractures have been recorded in men to link BMD changes with anti-fracture efficacy. Additional fracture data are needed to endorse the clinical care of osteoporosis in men. However, this panel believes that this view can be countered, based on available epidemiological and clinical efficacy data in male subjects, which display similarities with data acquired in women, in terms of treatment effects on BMD, biochemical markers of bone turnover, and fracture endpoint, despite the recorded differences in pathophysiology of bone loss and bone microarchitecture. Overall, empirical data from men and women are so similar that differences in morphology may not be clinically relevant.

Despite the wealth of available data from numerous studies in women, the current strategy of drug development for the treatment of osteoporosis in men is such that there is a delay of several years before clinical trial data in men become available. Perhaps the lag between comparable treatments becoming available for female and for male osteoporosis can be reduced. The situation is not unlike coronary artery disease, which was initially thought to be principally a male disease, but for which female treatment was made more rapidly available. A logical conclusion would eventually be to design mixed studies, as recommended by the WHO [111]. From a pragmatic point of view, it is unlikely that drugs for the specific treatment of osteoporosis in men will be developed.

One area of research that deserves more attention is the hormonal and non-hormonal factors influencing bone loss in men. There appears to be potential in measuring serum oestradiol levels, in addition to testosterone levels in men with low BMD. We wish to encourage the development of standardised mass spectroscopy assays for the assessment of sex steroid contribution in male osteoporosis.

Awareness of osteoporosis in men is improving, although it remains under-diagnosed and under-treated. It is important to highlight this population of patients and to define treatment options and intervention strategies, in order to reduce mortality, improve treatment and care, and make sure that treatments reach those who most need it.

Conflict of interest

Acknowledgments

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