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POSITION PAPER

# Goal-directed treatment of osteoporosis in Europe

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**Abstract**
*Summary* Despite the proven predictive ability of bone mineral density, Fracture Risk Assessment Tool (FRAX®), bone turnover markers, and fracture for osteoporotic fracture, their use as targets for treatment of osteoporosis is limited.
*Introduction* Treat-to-target is a strategy applied in several fields of medicine and has recently become an area of interest in the management of osteoporosis. Its role in this setting remains controversial. This article was prepared following a European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) working group meeting convened under the auspices of the International Osteoporosis Foundation (IOF) to discuss the feasibility of applying such a strategy in osteoporosis in Europe.
*Methods* Potential targets range from the absence of an incident fracture to fixed levels of bone mineral density (BMD), a desired FRAX® score, a specified level of bone turnover markers or indeed changes in any one or a combination of these parameters.
*Results* Despite the proven predictive ability of all of these variables for fracture (particularly BMD and FRAX), their use as targets remains limited due to low sensitivity, the influence of confounders and current lack of evidence that targets can be consistently reached.
*Conclusion* ESCEO considers that it is not currently feasible to apply a treat-to-target strategy in osteoporosis, though it did identify a need to continue to improve the targeting of treatment to those at higher risk (target-to-treat strategy) and a number of issues for the research agenda. These include international consensus on intervention thresholds and definition of treatment failure, further exploration of the relationship between fracture and BMD, and FRAX and treatment efficacy and investigation of the potential of short-term targets to improve adherence.

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## Introduction

The strategy of treating to a pre-specified target is a feature of several fields of medicine. The practice involves the identification of a biomarker for the disease process and defining a level of that biomarker that should be reached for optimal protection against the detrimental effects of the disease. The intent is to simplify and facilitate disease management decisions. International guidelines have established treatment targets for diabetes, hypertension, rheumatoid arthritis and hypercholesterolaemia, which have been widely applied in clinical practice. It has recently been proposed that a treat-to-target strategy would also be useful in osteoporosis [1, 2], though consensus on the issue has yet to be reached [3]. It was against this background that a working group meeting was convened by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) under the auspices of the International Osteoporosis Foundation in October 2013 comprising experts in the field of osteoporosis to discuss the feasibility of applying a treat-to-target strategy in osteoporosis in Europe. This article provides a summary of these discussions.

## Aims of treatment in osteoporosis

Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [4]. Although the diagnosis of the disease relies on the quantitative assessment of bone mineral density (BMD), which is a major determinant of bone strength, a variety of other skeletal and non-skeletal factors contribute to fracture risk [5]. In this respect, there are some analogies with other multifactorial chronic diseases. For example, hypertension is diagnosed by the measurement of blood pressure, whereas an important clinical consequence of hypertension is stroke. Notwithstanding, the risk of stroke is imperfectly captured by blood pressure readings in much the same way as the risk of fracture is imperfectly captured by measurement of BMD. In this context, the principal aim of treatment is to reduce the risk of fracture. If treatment-induced changes in BMD (or other relevant risk factors) presage a favourable clinical outcome, then so be it, but this does not change the aim of treatment. For treatment to target to be useful, the change in the variable measured or the level achieved in response to treatment must be proven to correlate with a meaningful reduction in fracture risk.

## Treat-to-target as a strategy: lessons from other fields

The aim of treat-to-target is to simplify management and, ultimately, reduce organ damage and improve clinical outcomes [1]. Its use implies that there is a well-demonstrated relationship between the target, frequently biological, measurable variable and clinically important endpoints for disease outcomes. It also implies that achievement of the target requires an action or other consideration. This could involve stopping the treatment, as would be the case for the use of antibiotics in infectious disease. Alternatively, the treatment could be modified in such a way as to maintain benefits or minimise adverse events. Finally, the treatment could be continued to maintain treatment benefits as, for example, in diabetes and hypertension. Alternatively, if the target is not achieved, this can mandate a change in therapeutic strategy.

The treat-to-target strategy has been deemed to play an important role in several fields of medicine. Reducing blood pressure to below the recommended targets (140/90 mmHg) is known to reduce the risk of clinical events [6, 7]. In diabetes, the target of glycated haemoglobin ($HbA_{1C}$) <7 % is generally applied in patients with type 2 diabetes to reduce risk of microvascular and macrovascular events [8–11]. The actual target may vary from 6.5 to 8 % with more stringent targets set for patients with longer life expectancy or no significant hypoglycaemic events and less stringent targets for patients with advanced complications, limited life expectancy or a history of severe hypoglycaemia. The diabetes guidelines stress the importance of this individualization of treatment targets [10]. There is good evidence that correcting hypercholesterolaemia by reducing low-density lipoprotein (LDL) cholesterol is associated with a reduction in cardiovascular events [12], and current European guidelines suggest three targets according to underlying risk of heart disease (LDL cholesterol <1.8, <2.5 and <3.0 mmol/L for patients at very high, high and moderate risk, respectively) [13].

Although these targets are widely applied clinically, their use is a subject of ongoing debate [14–17]. The blood pressure targets in current use have never been formally validated [18]. Indeed, a meta-analysis of trials in hypertension covering more than 62,000 patients could not determine exactly to what extent blood pressure should be lowered to protect against cardiovascular events and cardiovascular mortality [6]. The setting of these targets—and even more stringent targets in high-risk patients, for example, the recommendation of older guidelines to lower blood pressure to <130/80 mmHg in patients with diabetes or a history of cardiovascular or renal disease—has recently come under critical scrutiny [19]. Zanchetti and colleagues concluded that the results of available trials show that the evidence is scanty for such recommendations, and simple trials should be designed to look for more solid evidence in favour of current recommendations. A similar conclusion was reached by a NICE Guideline

Development Group in its updated 2011 guidance [20] where the research recommendation concluded that "data on optimal blood pressure treatment targets, particularly for systolic blood pressure, are inadequate. Current guidance is largely based on the blood pressure targets adopted in clinical trials, but there have been no large trials that have randomised people with hypertension to different systolic blood pressure targets and that have had sufficient power to examine clinical outcomes."

Similarly, it has been argued elsewhere that there is no scientific basis to support LDL cholesterol targets, and their safety has never been proven [15]. These arguments are based on the absence of evidence from a major randomised clinical trial testing the strategy of treating patients to the LDL cholesterol targets in terms of both safety and efficacy in preventing cardiovascular events. Indeed, targets are often based on evidence from randomised clinical trials in restricted populations, which are then extrapolated to the general population [14]. Intriguingly, the recent American College of Cardiology/American Hypertension Association (ACC/AHA) guidance has abandoned the use of LDL and non-high-density lipoprotein (HDL) cholesterol targets as it was unable to find randomised controlled trial evidence to support continued use of such targets. Instead, they have recommended a strategy whereby treatment is targeted at those most likely to benefit, i.e. those at most risk, and have suggested that such individuals should receive the appropriate intensity of statin therapy to reduce their risk [21, 22]. They have recommended the use of an online risk calculator to assess cardiovascular risk over a 10-year timeframe [23].

In type 2 diabetes, the 2009 consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes [24] recognised that the most appropriate target levels for blood glucose and $HbA_{1C}$ have not been systematically studied. Rather, it recognised a general approach of achieving $HbA_{1C}$ values in the non-diabetic range with the target of <7 %, actually four standard deviations (SDs) above the non-diabetic mean, as a practical goal that would be associated with projected reductions in complications over time. It is important to note that even lower targets have been promulgated but not widely adopted partly because the results of studies with more aggressive glycaemic control failed to demonstrate a benefit of intensive glycaemic control on their primary cardiovascular outcomes [24]. The authors of the consensus statement were also mindful that even the <7 % goal for $HbA_{1C}$ would not be appropriate or practical for some patients so that clinical judgement would need to be applied for the individual patient.

More recently, the management of rheumatoid arthritis (RA) has been adapted to a treatment to target approach [25]. There is a marked contrast between the approach in RA and the other chronic diseases outlined above. In RA, the target focuses on joint inflammation [26] which is the consequence of the disease process rather than a risk factor or surrogate endpoint as used in hypertension, hyperlipidaemia and diabetes. The approach stems from the fact that joint damage and physical disability are the major adverse outcomes associated with reduction in quality of life and that disease activity—reflected by swollen joint counts, levels of acute phase reactants or composite indices of disease activity—is a good predictor of damage and physical disability [25]. Given that any joint involvement, even of a single joint, can cause morbidity, it would be reasonable to argue that complete remission should be the target of treatment; recognising that this may not be achievable in long-standing disease, the target comprises a state of low disease activity as the minimum target [25]. There is reasonable evidence that structured patient management aiming for low disease activity leads to better outcomes than traditional approaches [27, 28].

One overriding ideal is that physicians should be aiming for more personalised medicine and tailoring treatment to individual patient risk in a more evidence-based manner. Moreover, the treat-to-target strategy is not applied for all evidence-based medicine, for example, there is currently no target for the use of 100-mg/day aspirin for the secondary prevention of stroke. The lesson from other fields appears to be that the decision to implement a treat-to-target strategy in osteoporosis cannot be made simply by referring to other disease areas. It should instead consider the benefits and risks as they apply to the prevention of fracture.

## Treat-to-target as a strategy in osteoporosis

The ultimate goal of any management strategy in osteoporosis is the prevention of fracture. The main aim of a treat-to-target strategy would be to guide clinical decision-making in terms of when—or if—to stop or change treatment on the basis of an acceptable level of fracture risk (Table 1). As stated previously, treating to target implies that there is a surrogate measure that confirms that fracture risk is lower for the individual osteoporotic patient (within the realms of cost utility). There are a number of variables that have potential for a treat-to-target strategy in osteoporosis: BMD, Fracture Risk Assessment Tool (FRAX) probability, bone turnover markers (BTMs) or fracture itself.

**Table 1** Aims of treat-to-target strategy in osteoporosis

- Guide clinical decision-making regarding if or when to stop or change treatment on the basis of an acceptable level of fracture risk
- Reduce the risk of treatment-associated adverse events
- Improve adherence to treatment

## Fracture

The goal of treatment is to reduce the risk of fracture. To the patient, the hallmark of successful treatment is the absence of an intercurrent fracture. Insofar as available treatments reduce fracture incidence by 20 to 40 %, it is to be expected that fractures will occur on treatment. The occurrence of a fracture during treatment may arise for several reasons. First, it may reflect residual fracture risk in a patient receiving an effective treatment. Second, it could show evidence of quantitative or qualitative changes in risk factors, for example, those not influenced by the current treatment, such as falls, or a problem with compliance. Third, it may reflect suboptimal or failed treatment and indicate the need for a modification of the management strategy. There is currently no widely used definition of treatment failure, though the occurrence of two or more incident fractures in a treated patient may be an indication that the patient is not responding to treatment [29]. On the other hand, in practice, it is often difficult to maintain a patient on a specific osteoporosis treatment once there has been an incident fracture. In the light of these considerations, it does not appear to be realistic to apply the occurrence of incident fracture in a treat-to-target strategy. On the other hand, the absence of a fracture, though gratifying, cannot provide a signal to change management in the absence of safety concerns.

## Bone mineral density

Low BMD is highly predictive of fracture. A meta-analysis of 11 cohort studies, covering 90,000 person-years indicated that 1 SD reduction in vertebral BMD was strongly predictive of vertebral fracture (relative risk [RR] 2.3, 95 % confidence interval [CI] 1.9 to 2.8) and a 1 SD reduction in hip BMD was strongly predictive of hip fracture (RR 2.6, 95 % CI 2.0 to 3.5) [30]. In a more recent meta-analysis, the gradient of risk for hip fracture with BMD was 2.21 (95 % CI 2.03–2.41) and 1.56 (95 % CI 1.49–1.64) for other osteoporotic fractures [31]. Indeed, the predictive ability of BMD was comparable to that of a 1 SD increase in blood pressure for stroke and better than a 1 SD increase in serum cholesterol for cardiovascular disease [30].

Despite the predictive value of BMD for fracture and the good correlation between fracture risk and BMD, there are a number of features that may make it a less than ideal choice for a target. First, the absolute value of BMD may have a high specificity for fracture at the threshold for osteoporosis, but it has a low sensitivity, i.e. many fractures will arise in individuals with normal BMD [32]. Second, for a given value of BMD, the risk for fracture increases markedly with age [33]. At age 50 years, the 10-year risk in women with a T-score of −2.5 is 4 % for vertebral fracture and 3 % for hip fracture; by the age of 80 years, the corresponding 10-year risks in women with the same T-score have raised to 10 and 24 % [33]. Age would therefore have to be taken into account if BMD were to be used as a target in a similar way as underlying heart disease risk is accounted for in the cholesterol targets. Third, the fracture probability risk for the same age and BMD in different countries vary widely due to geographical variations in mortality and hip fractures rates [34]. In addition, geographical variations in access to dual energy X-ray absorptiometry (DXA) machines [35] may modify the potential of BMD as a viable target in all countries. Finally, whilst most osteoporosis treatments tend to increase BMD up to a plateau—and this is associated with fracture risk reduction—it is unknown whether switching to another osteoporosis treatment to obtain even greater increases in BMD actually translates into additional fracture benefit [1]. On the other hand, there is some evidence that continuous, long-term gain in hip BMD is associated with further fracture risk reduction over time [36]. This is an important avenue for future research.

## Change in BMD

Another candidate variable is the treatment-induced change in BMD. This may be more promising than the absolute value of BMD since treatment-related improvements in BMD are associated with reductions in fracture risk [37–42]. Indeed, the change in BMD contributes to between 4 and 74 % of the reduction in fracture risk with treatment according to agent and method of analysis, with a significant correlation coefficient [41–46]. The problem is that even the best correlations are so poor that it is not possible to make even reasonably certain estimates in individuals (as opposed to populations) that the risk of fracture is decreased to a specific target level. Additional problems for the use of a change in BMD as a target are related to the differences in the modes of action of the various agents that will have variable effects at different skeletal sites. Other confounders are age, as described above [33], and the small size of the changes involved. In one study on the effect of bisphosphonates on BMD, 76 to 87 % patients had increased BMD at 1 year, but only 41 to 60 % had an increase of 3 % or more [47]. Indeed, the variations in BMD in many treated patients fall within the variability of the measurement. Thus, the absolute changes may not be sufficiently large to be useful as a target in the majority of patients. Moreover, even though there may be significant correlations between change in BMD and fracture risk, the correlations are too weak to be of predictive value in individuals. This considerably reduces the clinical value of any result based on a change in BMD over time (on or off treatment) in terms of monitoring the impact of a treatment. In phase 3 clinical trials, even in studies of the most potent anti-resorptives, there is a substantial overlap in changes in BMD between treated and untreated patients (Fig. 1). Even though this overlap concerns only a part of each population, it is a further indication that a change in BMD on

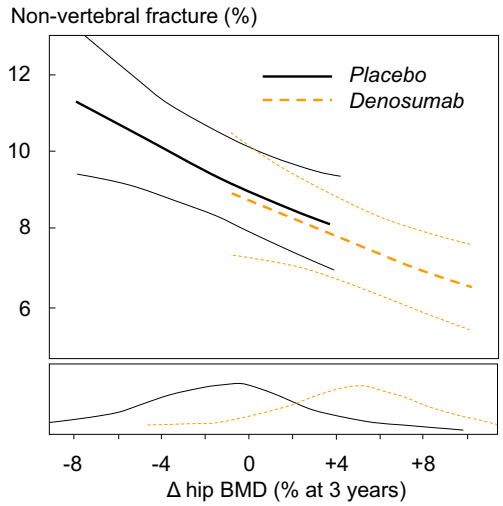


**Fig. 1** Relationship between change in hip bone mineral density (BMD) at 3 years and rate of non-vertebral fracture in patients treated with denosumab or placebo (redrawn from reference [42])

treatment has limitations as an appropriate target for individuals.

The question arises whether treatment-induced changes in BMD are associated with commensurate changes in bone strength. For example, does a patient achieving a BMD T-score of say −1 SD from a lower value regain the fracture risk of an untreated with the same T-score, all other things being equal? This seems unlikely since treatments (or at least the ones we have now) do not restore bone structure to reverse this component of bone weakness. This is an important topic for future research.

## Bone turnover markers

Contrary to the position of BMD, there are no consensus views to characterise high and normal bone turnover. For some analytes, the pre-menopausal reference range has been used to define a normal range, but there is a wide overlap between pre- and postmenopausal women, and a large overlap between those who will fracture compared with those that remain fracture free [48]. In a recent meta-analysis, the predictive value of serum procollagen type 1 N-terminal propeptide (s-P1NP) was a 1.23 (95 % CI 1.09–1.39) increase in fracture risk per SD increase in analyte. The hazard ratio per SD increase in risk of fracture for s-serum C-telopeptide crosslinks (CTX) was 1.18 (95 % CI 1.05–1.34) [49]. These gradients of risk are substantially lower than those reported for the use of femoral neck BMD in the prediction of fracture [30, 31, 50]. For example, in a large meta-analysis, the gradient of risk for hip fracture with BMD was 2.21 (95 % CI 2.03–2.41) and 1.56 (95 % CI 1.49–1.64) for other osteoporotic fractures [31]. The poor gradient of risk and the fact that different interventions elicit different responses to treatment (e.g. the bisphosphonates and teriparatide [51]) suggest that absolute values for BTMs are not suited as treatment targets, at least with current technologies.

## Change in bone turnover markers

The decrease in fracture risk on anti-resorptive treatment is associated with significant reductions in BTMs [37]. In one meta-analysis, there was a 40 % reduction in fracture risk for a 70 % reduction in bone resorption over 1 year of treatment with an anti-resorptive agent [37]. These data from phase 3 studies are difficult to translate into accurate targets for individuals. With raloxifene, for example, treatment is associated with a 30 % decrease in vertebral fracture risk [52]. The decrease in fracture risk was significantly associated with a decrease in the marker P1NP [53], as shown in Fig. 2. However, a target of say a 50 % reduction in P1NP is an effect that is seen in a substantial minority of placebo-treated patients. Such observations suggest that changes in BTMs will not provide adequate targets to assess the adequacy of treatment.

It has been suggested that an appropriate target is to lower BTMs to the pre-menopausal range [54]. In the 50 % of women who have normal levels, the objective is to induce changes in BTMs by the least significant change [55]. Unfortunately, expert opinion has not been translated into empirical observation.

BTMs may show large and rapid responses to the treatments used for osteoporosis, and their measurement has proved useful for drug development. In the case of anti-resorptive interventions, the decrease in marker values, particularly the indices of bone resorption, occurs within days or weeks of starting treatment. In contrast, the change in BMD occurs over months or years so that BTMs may give earlier

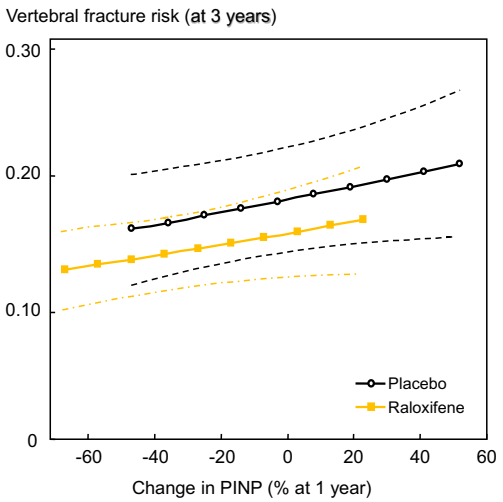


**Fig. 2** The relationship between the change in s-P1NP (serum procollagen type 1 N-terminal propeptide) and vertebral fracture risk (with 95 % confidence intervals) in women treated with raloxifene (redrawn from reference [53])

information on the response to treatment than BMD. Moreover, the decrement in marker values is large in the case of bisphosphonates (e.g. by 50 % or more), whereas the increment in BMD is modest (e.g. 5 %) [48]. The responsiveness of the markers to intervention provides a rationale for their early use to explore issues of compliance early in the treatment regimen. There is thus the prospect of the use of BTMs as a short-term target as an index of compliance shortly after the onset of treatment. This, however, defines target in a different way.

### Indices of bone strength

As fragility fracture is a consequence of impaired bone strength, an obvious related target could be the restoration of bone strength. Some treatments have bone-forming properties and improve bone microstructure and strength [56–62] and induce greater gains in BMD than anti-resorptive agents [59]. This suggests that variables such as bone volume, trabecular architecture or cortical thickness and porosity could be considered as targets for treatment [63, 64]. Limitations include the invasive nature of traditional assessments (e.g. transiliac crest bone biopsies) and the cost, though newer techniques, such as high resolution quantitative computed tomography and finite element analysis (FEA), may be promising alternatives [65–67]. In terms of fracture prediction, the added value of these approaches above that of simple measurement of areal BMD appears limited, whether the same holds true for assessing the response to therapy has been the focus of a few studies. For example, changes in areal BMD were poorly correlated with FEA-modelled changes in vertebral compression strength, with a much stronger relationship for anabolic therapy (teriparatide) than for alendronate [66]. In a subset of patients from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study of denosumab, FEA analysis showed significant improvements in bone strength at both spine and hip in the active treatment group, but the correlation between sites was weak ($r$=0.38). These techniques appear to have promise in the early assessment of potential therapies, but the need for computed tomography scans limits their clinical applicability at present.

### FRAX probability

One possibility for a treatment target is to use FRAX probability [68] since it produces an estimation of 10-year fracture risk. Several treatments have had efficacy evaluated in terms of FRAX score at baseline [69–73], indicating either a greater anti-fracture efficacy at higher risk or no interaction between anti-fracture efficacy and baseline risk. In a single study, FRAX has been shown to perform similarly in treated and untreated patients, suggesting that the impact of treatment on fracture risk may be difficult to detect and that FRAX may have a low sensitivity for treatment-induced reductions in fracture risk [74]. A recent analysis of a subset of the same cohort, comprising more than 11,000 women undergoing baseline and follow-up DXA scans, not only confirmed that FRAX scores were strongly predictive of incident major fracture and hip fracture over 4 years of treatment but also reported that the change in FRAX score on treatment was not independently associated with the subsequent risk of a major fracture ($P$=0.8) or hip fracture ($P$=0.3) [75].

These findings are not surprising. First, FRAX was constructed to estimate risk from a range of parameters that are generally intrinsic to the patient rather than the disease (e.g. age, sex, weight and height), and a treatment that cannot influence these parameters will produce little change in the FRAX score. In particular, age is very dominant in FRAX, reducing the sensitivity of the tool to indicate change. The major component of FRAX affected by osteoporosis treatment is the change in BMD which, as discussed, has a poor relation with fracture risk reduction. This is particularly true for BMD at the femoral neck, which is the input variable for FRAX.

This lack of responsiveness reduces the feasibility of using FRAX score as a treatment target. A more appropriate target for treatment may be achievement of a stable FRAX score, i.e. a treatment that attenuates an age-related increase in fracture probability. Further research is needed before this could be applied in clinical practice.

## Target-to-treat or treat-to-target?

The foregoing observations indicate that a treat-to-target strategy for osteoporosis is currently an unrealistic and, for many patients, unattainable goal and remains firmly within the realm of research. The most pressing problem facing the osteoporosis field is the failure to initiate therapy in those at high risk of fracture (target-to-treat). In contrast to the literature reviewed above, there is an enormous and compelling evidence base for the efficacy and safety of therapies to significantly reduce fracture risk. Despite this and the wide availability of treatment, observational studies suggest that, even if BMD indicates that the patient has osteoporosis, it only leads to prescription of drugs in 25 % of cases [76]. Indeed, few patients leave the hospital after fracture with an appropriate osteoporosis treatment even after hip fracture [77]. There is therefore a large treatment gap between the number of individuals who reach an intervention threshold for osteoporosis and the number who actually receive a treatment. A recent pan-European study assessed the treatment gap as the difference in the number of patients receiving treatment (as judged from sales data and adjusted for compliance) and the number of individuals at high risk (defined by FRAX) [78]. The treatment gap

**Table 2** Number of women eligible for treatment, treated and treatment gap in 2010 [8]

| Country | Number potentially treated (000s) | Number exceeding fracture risk threshold (000s) | Difference (000s) | Treatment gap (%) |
|---|---|---|---|---|
| Austria | 139 | 282 | 143 | 51 |
| Belgium | 214 | 402 | 188 | 47 |
| Bulgaria | 13 | 240 | 227 | 95 |
| Czech Republic | 79 | 330 | 251 | 76 |
| Denmark | 87 | 190 | 103 | 54 |
| Estonia | 7 | 48 | 41 | 86 |
| Finland | 53 | 172 | 119 | 69 |
| France | 1,390 | 2,437 | 1,047 | 43 |
| Germany | 730 | 3,231 | 2,501 | 77 |
| Greece | 333 | 482 | 149 | 31 |
| Hungary | 238 | 332 | 94 | 28 |
| Ireland | 91 | 124 | 33 | 26 |
| Italy | 1,069 | 2,635 | 1,566 | 59 |
| Latvia | 12 | 80 | 68 | 85 |
| Lithuania | 11 | 109 | 98 | 90 |
| Luxembourg | 9 | 16 | 7 | 43 |
| Netherlands | 242 | 605 | 363 | 60 |
| Poland | 245 | 1,127 | 882 | 78 |
| Portugal | 269 | 425 | 156 | 37 |
| Romania | 100 | 599 | 499 | 83 |
| Slovakia | 75 | 148 | 73 | 49 |
| Slovenia | 35 | 62 | 27 | 44 |
| Spain | 1,277 | 1,709 | 432 | 25 |
| Sweden | 100 | 358 | 258 | 72 |
| UK | 1,064 | 2,298 | 1,234 | 54 |
| EU27 | 7,881 | 18,441 | 10,560 | 57 |

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varied from 25 % in Spain to 95 % in Bulgaria. Large treatment gaps were identified in countries with populations at both high and low risk of fracture (Table 2). In total, in the EU, it was estimated that, out of the 18.4 million women that exceed the risk level, 10.6 million were untreated. These figures are conservative since an undetermined proportion of low risk women will have received treatment.

Treatment uptake has risen in Europe in the last decade, but there are signs of a decrease since 2010 (Fig. 3) [78, 79]. The reasons for the downturn are not completely clear, but may be linked to concerns over rare but serious side effects of treatments, as well as differing approaches to health technology

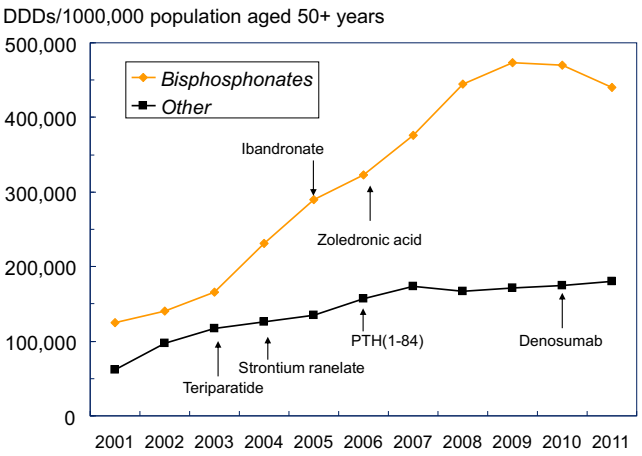


**Fig. 3** Estimated use of osteoporosis treatments (defined daily doses [DDDs]/100 population aged ≥50 years) from 2001 to 2011 (reproduced from reference [78], with kind permission from Springer Science and Business Media)

**Table 3** Issues for the research agenda

- Consensus on intervention thresholds
- Further research into the relationship between fracture (particularly hip fracture) and changes in BMD
- Investigation of whether switching therapy to further increase BMD is beneficial in terms of fracture risk reduction
- Integration of FRAX or other validated risk engines into new randomised controlled trials to link measurement of efficacy to fracture probability
- Consensus on how to identify and measure treatment failure
- Further research into the potential of using biomarker measurement to improve adherence

assessment [78]. The most important point is that it leaves a large proportion of European patients unprotected from the risk of osteoporotic fracture. The decrease in treatment uptake is even more marked in the USA where treatment gaps for patients with hip fracture increased significantly over a 10-year interval from 59.8 % in 2002 to 79.5 % in 2011 [80].

There will be many reasons for the large treatment gap, but the problem is compounded by the fact that there is currently no international consensus on who should be treated. In Europe, a common view is that treatment can be recommended in women with a prior fragility fracture. For this reason, European guidelines have promoted a FRAX-based approach where the treatment threshold is equal to or greater than that of a woman with a prior fragility fracture [35]. The application of FRAX in individual countries is, however, heterogeneous and a worldwide consensus on who to treat would help promote equity of the access to treatment. An example is the international promotion of fracture liaison services by the IOF to better identify and service patients who have had a fragility fracture [81].

## Conclusions

The ultimate goal of treating osteoporosis is to prevent fracture and reduce associated morbidity and mortality, i.e. to improve absolute fracture risk. Effective management strategies need to balance the aim of continuing treatment in patients at risk of fracture against issues such as the long-term effects of treatment, the relevance and weight given to rare side effects and the effects of drug holidays. All of this is set against a background of diminishing treatment uptake.

The question of whether a treat-to-target strategy will improve osteoporosis management remains an area for further research. We have reviewed the most likely surrogate parameters currently available in the field of osteoporosis; BMD, BTM, FRAX and bone strength and none appears to be ready for use in a treat-to-target strategy. All of these targets would be unattainable in many patients even if a target could be agreed upon and validated. Additionally, applying a treat to target strategy in individual patients is problematic because of the small treatment-induced changes in the candidate parameters. The inability to extrapolate from statistically significant correlations in large clinical trials to make treatment decisions in individual patients further limits the applicability of this concept in daily clinical practice.

The IOF-ESCEO discussions highlighted a number of themes for the research agenda, which are summarised in Table 3. These include further research into the relationships between fracture risk and BMD and/or FRAX score in patients who are receiving osteoporosis treatment.

A review of the manner in which targets have been developed in other fields indicates that the scientific basis of targets is questionable with the exception of RA. In RA, the target focuses on joint inflammation, which is the consequence of the disease process rather than a risk factor or surrogate endpoint as used in hypertension, hyperlipidaemia and diabetes and proposed for osteoporosis. The inability to set targets should not be negatively interpreted: Targets are not applied in all fields (e.g. aspirin), which implies that the decision not to implement targets is a clear option in a debate on targets in osteoporosis.

Another important field of research is the better definition of treatment failure, i.e. whether the occurrence of a fracture on treatment should be considered as treatment failure. Further consensus is needed on how to identify and measure treatment failure in osteoporosis [29] and how to address it clinically. In this context, we note that the International Osteoporosis Foundation has defined inadequate response to treatment [29], albeit on a non-scientific basis, but has never defined adequate response.

## Summary

The fundamental purpose of osteoporosis treatment is to reduce the risk of fracture. There is no validated quantitative marker that monitors risk reduction in the individual patient. Available treatments are effective but reduce fracture incidence only by 20 to 60 %, and it is to be expected, therefore, that fractures will arise during treatment. Given a difficulty in defining treatment failure, it is no surprise that the definition of treatment success is problematic.

The IOF and ESCEO consider that the goal in osteoporosis should be to prescribe osteoporosis treatment to the people who need it and to ensure that those who are taking treatment continue to do so. This aim could be summed up, not as treat-to-target, but as “target-to-treat”.

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