

Goal-directed treatment of osteoporosis in Europe

J. A. Kanis · E. McCloskey · J. Branco · M.-L. Brandi ·
E. Dennison · J.-P. Devogelaer · S. Ferrari ·
J.-M. Kaufman · S. Papapoulos · J.-Y. Reginster · R. Rizzoli

Received: 15 May 2014 / Accepted: 19 June 2014
© International Osteoporosis Foundation and National Osteoporosis Foundation 2014

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.

J. A. Kanis (✉) · E. McCloskey
Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, UK
e-mail: w.j.pontefract@sheffield.ac.uk

J. Branco
CEDOC, Department of Rheumatology, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, CHLO, EPE, Hospital Egas Moniz, Lisbon, Portugal

M.-L. Brandi
Metabolic Bone Unit, Department of Internal Medicine, University of Florence, Florence, Italy

E. Dennison
MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

J.-P. Devogelaer
Department of Rheumatology, Saint-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium

S. Ferrari · R. Rizzoli
Division of Bone Diseases, Faculty of Medicine, Geneva University Hospital, Geneva, Switzerland

J.-M. Kaufman
Ghent University Hospital, Ghent, Belgium

S. Papapoulos
Center for Bone Quality, Leiden University Medical Center, Leiden, The Netherlands

J.-Y. Reginster
Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium

E. Dennison
NIHR Nutrition Biomedical Research Centre, University of Southampton, Southampton, UK

Keywords BMD · Bone marker · FRAX · Management strategy · Osteoporosis · Target-to-treat · Treat-to-target

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

- | |
|--|
| <ul style="list-style-type: none"> • 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

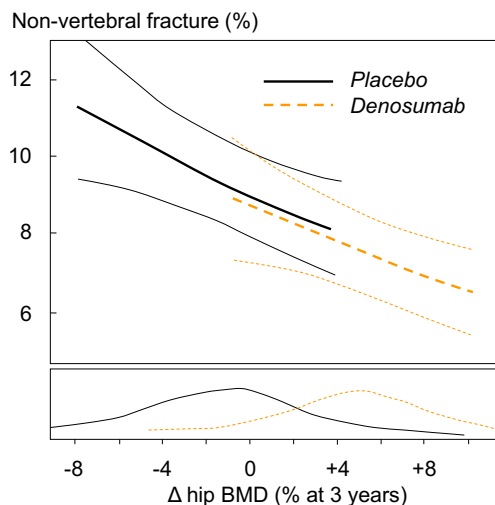


Fig. 1 Relationship between change in hip bone mineral density (BMD) at 3 years and rate of non-vertebral fracture in patients treated with denosumab or placebo (redrawn from reference [42])

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-PINP) 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 PINP [53], as shown in Fig. 2. However, a target of say a 50 % reduction in PINP 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

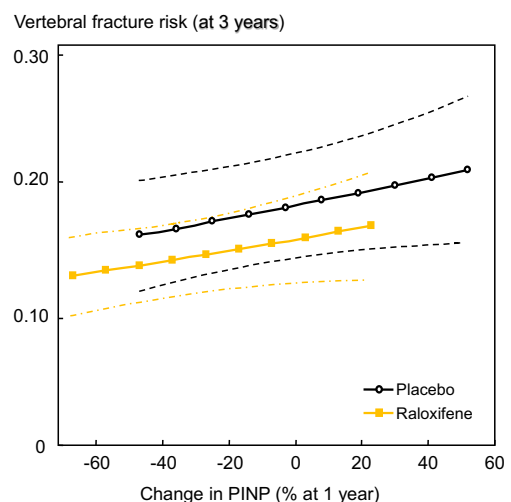


Fig. 2 The relationship between the change in s-PINP (serum procollagen type 1 N-terminal propeptide) and vertebral fracture risk (with 95 % confidence intervals) in women treated with raloxifene (redrawn from reference [53])

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

Reproduced from reference [79], with kind permission from Springer Science and Business Media

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

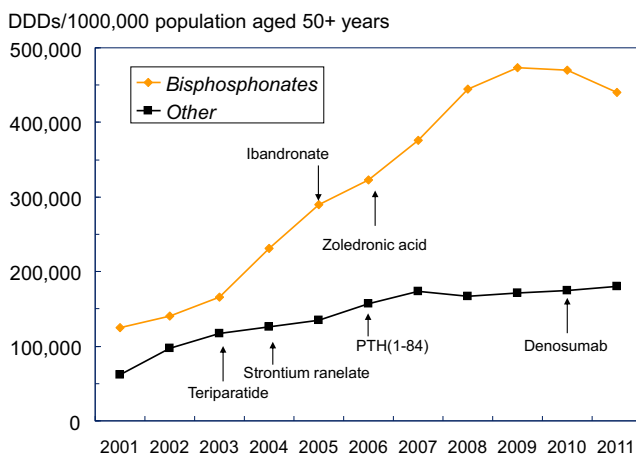


Fig. 3 Estimated use of osteoporosis treatments (defined daily doses [DDDs]/100 population aged ≥ 50 years) from 2001 to 2011 (reproduced from reference [78], with kind permission from Springer Science and Business Media)

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

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”.

Acknowledgments We are grateful to the Committee of Scientific Advisors of the International Osteoporosis Foundation and the Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis for their review and endorsement of this paper.

Conflicts of interest JA Kanis has received consulting fees, advisory board fees, lecture fees and/or grant support from the majority of companies concerned with skeletal metabolism. E McCloskey has received consultancy, lecture fees, research grant support and/or honoraria from Active Signal, Alliance for Better Bone Health, Amgen, Bayer, Consilient Healthcare, GE Lunar, Hologic, Internis Pharma, Lilly, MSD, Novartis, Pfizer, Roche, Servier, Tethys, UCB and Univadis. ML Brandi has received consulting fees, paid advisory boards, lecture fees and/or grant support from Amgen, Eli Lilly, Merck Sharp & Dohme, Novartis, Servier, Spa, Stroder and NPS. E Dennison declares lecture fees from Lilly. S Ferrari has received consulting fees, advisory board fees, lecture fees and/or grant support from Amgen, GSK, MSD, Eli Lilly, Novartis and Bioiberica. J-M Kauffman has received consulting fees, paid advisory boards, lecture fees and/or grant support from Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Procter & Gamble, Roche,

Sanofi Aventis, Servier and Warner Chilcott. S Papapoulos has received consulting/speaking fees from Axsome, Amgen, Eli Lilly, GlaxoSmithKlein, Merck, Novartis and Roche. J-Y Reginster on behalf of the Department of Public Health, Epidemiology and Health Economics of the University of Liège, Liège, Belgium, received consulting fees or paid advisory boards from Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Theramex, UCB. Lecture fees when speaking at the invitation of a commercial sponsor: Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed, Novo-Nordisk. R Rizzoli received lecture fee and paid advisory boards from Merck Sharp and Dohme, Eli Lilly, Amgen, Servier, Takeda and Danone. JC Branco and JP Devogelaer have no conflict of interest.

References

- Lewiecki EM, Cummings SR, Cosman F (2013) Treat-to-target for osteoporosis: is now the time? *J Clin Endocrinol Metab* 98:946–53
- Cummings SR, Cosman F, Eastell R et al (2013) Goal-directed treatment of osteoporosis. *J Bone Miner Res* 28:433–8
- McCloskey E, Leslie WD (2013) Goal-directed therapy in osteoporosis. *J Bone Miner Res* 28:439–41
- (1993) Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 94:646–650
- Kanis JA, on behalf of the World Health Organization Scientific Group (2007) Assessment of osteoporosis at the primary health care level. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK, Sheffield, Technical Report
- Staessen JA, Wang JG, Thijs L (2001) Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 358:1305–15
- Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 34:2159–219
- UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–53
- The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–86
- Inzucchi SE, Bergenstal RM, Buse JB et al (2012) Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 55:1577–96
- IDF Clinical Guidelines Task Force (2013) Global Guideline for Type 2 Diabetes. www.idf.com. Accessed 17 July 2013
- Cannon CP (2005) The IDEAL cholesterol: lower is better. *JAMA* 294:2492–4
- Catapano AL, Reiner Z, De BG et al (2011) ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Atherosclerosis* 217(Suppl 1):S1–44
- McAlister FA, van Diepen S, Padwal RS et al (2007) How evidence-based are the recommendations in evidence-based guidelines? *PLoS Med* 4:e250
- Hayward RA, Krumholz HM (2012) Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. *Circ Cardiovasc Qual Outcome* 5:2–5
- Ledford H (2013) Cholesterol limits lose their lustre. *Nature* 494:410–1
- Krumholz HM (2013) Target cardiovascular risk rather than cholesterol concentration. *BMJ* 347:f7110
- National Institute for Health and Clinical Excellence (NICE)—British Hypertension Society (BHS) (2006) Hypertension: management of hypertension in adults in primary care. www.nice.org.uk/CG034guidance. Accessed 31 July 2013
- Zanchetti A, Grassi G, Mancia G (2009) When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. *J Hypertens* 27:923–34
- National Institute for Health and Clinical Excellence (2011) Hypertension: The clinical management of primary hypertension in adults. August 2011. <http://www.nice.org.uk/nicemedia/live/13561/56007/56007.pdf>. Accessed 13 Jan 2012
- Goff DC Jr., Lloyd-Jones DM, Bennett G et al (2013) 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*
- Stone NJ, Robinson J, Lichtenstein AH et al (2013) 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*
- Kane SP (2014) Pooled cohort equations to predict 10-year risk of first cardiovascular event. <http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx>. Accessed 7 April 2014
- Nathan DM, Buse JB, Davidson MB et al (2009) Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 32:193–203
- Smolen JS, Aletaha D, Bijlsma JW et al (2010) Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 69:631–7
- Schoels M, Wong J, Scott DL et al (2010) Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 69:995–1003
- Feldmann M, Maini RN (2003) Lasker Clinical Medical Research Award. TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases. *Nat Med* 9:1245–50
- Grigor C, Capell H, Stirling A et al (2004) Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 364:263–9
- Diez-Perez A, Adachi JD, Agnusdei D et al (2012) Treatment failure in osteoporosis. *Osteoporos Int* 23:2769–74
- Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 312:1254–9
- Johnell O, Kanis JA, Oden A et al (2005) Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 20:1185–94
- Kanis JA, Johnell O, Oden A et al (2000) Risk of hip fracture derived from relative risks: an analysis applied to the population of Sweden. *Osteoporos Int* 11:120–7
- Kanis JA, Johnell O, Oden A et al (2001) Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int* 12:989–95
- Kanis JA, Oden A, McCloskey EV et al (2012) A systematic review of hip fracture incidence and probability of fracture worldwide. *Osteoporos Int* 23:2239–56

35. Kanis JA, McCloskey EV, Johansson H et al (2013) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 24:23–57
36. Ferrari S, Adachi J, Lippuner K et al (2013) Further reductions in nonvertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years. *Abstr J Bone Miner Res* 28:1017
37. Hochberg MC, Greenspan S, Wasnich RD et al (2002) Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. *J Clin Endocrinol Metab* 87:1586–92
38. Bjarnason NH, Sarkar S, Duong T et al (2001) Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal osteoporosis. *Osteoporos Int* 12:922–30
39. Bauer DC, Black DM, Garnero P et al (2004) Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial. *J Bone Miner Res* 19:1250–8
40. Eastell R, Barton I, Hannon RA et al (2003) Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *J Bone Miner Res* 18:1051–6
41. Jacques RM, Boonen S, Cosman F et al (2012) Relationship of changes in total hip bone mineral density to vertebral and nonvertebral fracture risk in women with postmenopausal osteoporosis treated with once-yearly zoledronic acid 5 mg: the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 27:1627–34
42. Austin M, Yang YC, Vittinghoff E et al (2012) Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. *J Bone Miner Res* 27:687–93
43. Bruyere O, Roux C, Detilleux J et al (2007) Relationship between bone mineral density changes and fracture risk reduction in patients treated with strontium ranelate. *J Clin Endocrinol Metab* 92:3076–81
44. Sarkar S, Mitlak BH, Wong M et al (2002) Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. *J Bone Miner Res* 17:1–10
45. Li Z, Meredith MP, Hoseyni MS (2001) A method to assess the proportion of treatment effect explained by a surrogate endpoint. *Stat Med* 20:3175–88
46. Chen P, Miller PD, Recker R et al (2007) Increases in BMD correlate with improvements in bone microarchitecture with teriparatide treatment in postmenopausal women with osteoporosis. *J Bone Miner Res* 22:1173–80
47. Rosen CJ, Hochberg MC, Bonnick SL et al (2005) Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. *J Bone Miner Res* 20:141–51
48. Vasikaran S, Eastell R, Bruyere O et al (2011) Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int* 22:391–420
49. Johansson H, Oden A, Kanis JA et al (2014) A meta-analysis of reference markers of bone turnover for prediction of fracture. *Calcif Tissue Int* 94:560–7
50. Kanis JA, Oden A, Johnell O et al (2007) The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 18:1033–46
51. Arlot M, Meunier PJ, Boivin G et al (2005) Differential effects of teriparatide and alendronate on bone remodeling in postmenopausal women assessed by histomorphometric parameters. *J Bone Miner Res* 20:1244–53
52. Ettinger B, Black DM, Mitlak BH et al (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. Results from a 3-year randomized clinical trial. *JAMA* 282:637–45
53. Reginster JY, Sarkar S, Zegels B et al (2004) Reduction in PINP, a marker of bone metabolism, with raloxifene treatment and its relationship with vertebral fracture risk. *Bone* 34:344–51
54. Garnero P, Hausherr E, Chapuy MC et al (1996) Markers of bone resorption predict hip fracture in elderly women: the EPIDOS Prospective Study. *J Bone Miner Res* 11:1531–8
55. Bergmann P, Body JJ, Boonen S et al (2009) Evidence-based guidelines for the use of biochemical markers of bone turnover in the selection and monitoring of bisphosphonate treatment in osteoporosis: a consensus document of the Belgian Bone Club. *Int J Clin Pract* 63:19–26
56. Marcus R, Wang O, Satterwhite J et al (2003) The skeletal response to teriparatide is largely independent of age, initial bone mineral density, and prevalent vertebral fractures in postmenopausal women with osteoporosis. *J Bone Miner Res* 18:18–23
57. Neer RM, Arnaud CD, Zanchetta JR et al (2001) Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 344:1434–41
58. Jiang Y, Zhao JJ, Mitlak BH et al (2003) Recombinant human parathyroid hormone (1–34) [teriparatide] improves both cortical and cancellous bone structure. *J Bone Miner Res* 18:1932–41
59. Saag KG, Shane E, Boonen S et al (2007) Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med* 357:2028–39
60. Arlot ME, Jiang Y, Genant HK et al (2008) Histomorphometric and microCT analysis of bone biopsies from postmenopausal osteoporotic women treated with strontium ranelate. *J Bone Miner Res* 23:215–22
61. Rizzoli R, Laroche M, Krieg MA et al (2010) Strontium ranelate and alendronate have differing effects on distal tibia bone microstructure in women with osteoporosis. *Rheumatol Int* 30:1341–8
62. Rizzoli R, Chapurlat RD, Laroche JM et al (2012) Effects of strontium ranelate and alendronate on bone microstructure in women with osteoporosis: results of a 2-year study. *Osteoporos Int* 23:305–15
63. Bala Y, Zebaze R, Ghasem-Zadeh A et al. (2014) Cortical porosity identifies women with osteopenia at increased risk for forearm fractures. *J Bone Miner Res*
64. Silva BC, Leslie WD, Resch H et al (2014) Trabecular bone score: a noninvasive analytical method based upon the DXA image. *J Bone Miner Res* 29:518–30
65. Keaveny TM, Bouxsein ML (2008) Theoretical implications of the biomechanical fracture threshold. *J Bone Miner Res* 23:1541–7
66. Keaveny TM, Donley DW, Hoffmann PF et al (2007) Effects of teriparatide and alendronate on vertebral strength as assessed by finite element modeling of QCT scans in women with osteoporosis. *J Bone Miner Res* 22:149–57
67. Kopperdahl DL, Aspelund T, Hoffmann PF et al (2014) Assessment of incident spine and hip fractures in women and men using finite element analysis of CT scans. *J Bone Miner Res* 29:570–80
68. Kanis JA, Borgstrom F, De Laet C et al (2005) Assessment of fracture risk. *Osteoporos Int* 16:581–9
69. Kanis JA, Johansson H, Oden A et al (2011) A meta-analysis of the effect of strontium ranelate on the risk of vertebral and non-vertebral fracture in postmenopausal osteoporosis and the interaction with FRAX((R)). *Osteoporos Int* 22:2347–55
70. McCloskey EV, Johansson H, Oden A et al (2012) Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX. *J Bone Miner Res* 27:1480–6
71. Kanis JA, Johansson H, Oden A et al (2010) A meta-analysis of the efficacy of raloxifene on all clinical and vertebral fractures and its dependency on FRAX. *Bone* 47:729–35

72. Kanis JA, Johansson H, Oden A et al (2009) Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed with FRAX. *Bone* 44:1049–54
73. Donaldson MG, Palermo L, Ensrud KE et al (2012) Effect of alendronate for reducing fracture by FRAX score and femoral neck bone mineral density: the Fracture Intervention Trial. *J Bone Miner Res* 27:1804–10
74. Leslie WD, Lix LM, Johansson H et al (2012) Does osteoporosis therapy invalidate FRAX for fracture prediction? *J Bone Miner Res* 27:1243–51
75. Leslie WD, Majumdar S, Lix LM et al (2014) Can Change in FRAX score be used to “treat-to-target”? A population-based cohort study. *J Bone Miner Res* 29:1074–1080
76. Canoui-Poitrine F, Jaglal S, Chapurlat R et al (2010) Has reimbursement of bone mineral density testing and anti-osteoporotic treatments improved management of osteoporosis in France? *Bone* 47:790–4
77. Jennings LA, Auerbach AD, Maselli J et al (2010) Missed opportunities for osteoporosis treatment in patients hospitalized for hip fracture. *J Am Geriatr Soc* 58:650–7
78. Hernlund E, Svedbom A, Ivergard M et al (2013) Osteoporosis in the European Union: medical management, epidemiology and economic burden: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos* 8: 136
79. Kanis JA, Borgstrom F, Compston J et al (2013) SCOPE: a scorecard for osteoporosis in Europe. *Arch Osteoporos* 8:144
80. Solomon DH, Johnston SS, Boytsov NN et al. (2014) Osteoporosis medication use after hip fracture in U.S. Patients between 2002 and 2011. *J Bone Miner Res*
81. Akesson K, Marsh D, Mitchell PJ et al (2013) Capture the Fracture: a Best Practice Framework and global campaign to break the fragility fracture cycle. *Osteoporos Int* 24:2135–52