

## Can we treat to target in osteoporosis?

“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 impact of drug holidays.”

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It has recently been proposed that a treat-to-target strategy could be useful in the management of osteoporosis [1,2]. The strategy of treating to a prespecified target in medical practice involves the definition of a level of a chosen disease biomarker that is associated with optimal protection against the detrimental effects of the particular disease. In many diseases, including diabetes, hypertension, rheumatoid arthritis (RA) and hypercholesterolemia, this has appeared to facilitate disease management decisions and increased uptake of therapies. The proposal of treat-to-target in osteoporosis has sparked discussions about the appropriateness of the biomarkers and the general approach [3,4].

### 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]. Thus, reducing blood pressure to below the recommended targets (140/90 mm Hg) reduces the risk of clinical events such as stroke [5]. In diabetes, the target of glycated hemoglobin (HbA<sub>1c</sub>) <7% is generally applied in patients with Type 2 diabetes to reduce risk of microvascular and macrovascular events [6]. Current European guidelines suggest three low-density lipoprotein (LDL) cholesterol targets according to underlying risk of heart disease (LDL cholesterol <1.8, <2.5 or <3.0 mmol/l for patients at very high, high and moderate risk, respectively) to reduce cardiovascular events [7].

Although these targets are widely applied clinically, their use is not supported by all. For example, in a 2011 NICE Guideline Development Group update, it was 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 randomized people with hypertension to different systolic blood pressure targets and that have had sufficient power to examine clinical outcomes’ [8]. Similarly, the research base supporting LDL cholesterol targets and their safety has also been questioned and the recent ACC/AHA guidance has abandoned the use of LDL and non-HDL cholesterol targets as it was unable to find RCT evidence to support continued use of such targets [9]. Instead they have recommended a strategy whereby treatment is targeted at those most likely to benefit, in other words, those at most risk, and have suggested that such individuals should receive the appropriate intensity of statin therapy to reduce their risk.

More recently, the management of RA has been adapted to a treatment to target approach [10,11]. In contrast to the other chronic diseases outlined above, the target in RA focuses on the consequence of the disease process, joint inflammation, rather than a risk factor or surrogate endpoint. The target comprises a state of low disease activity as the minimum target and there is reasonable evidence that achieving the latter leads to better clinical outcomes than traditional approaches [12].



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### Treat to target as a strategy in osteoporosis

The hallmark of successful treatment, particularly for the patient, is the absence of an intercurrent fracture. No therapy can reduce fracture risk by 100%, so it is to be expected that fractures will occur on treatment. The occurrence of a fracture during treatment may simply reflect residual fracture risk in a patient receiving an effective treatment, for example, a risk (e.g., falls) that is not modified by the current treatment. It may also reflect poor compliance or a true suboptimal response to the treatment with both perhaps indicating the need for a change in management strategy. Such complexities suggest it is unrealistic to apply the occurrence of incident fracture in a treat-to-target strategy. Furthermore, the lack of incident fracture, though gratifying, cannot provide a signal to change management.

As the ultimate goal of any management strategy in osteoporosis is the prevention of fracture, treating to target implies that there is a surrogate measure that confirms a lower fracture risk in the individual osteoporotic patient. Such surrogate measures might include BMD, bone turnover markers (BTMs) or FRAX® [13] probability.

### Bone mineral density

Despite the predictive value of BMD for fracture and the good correlation between fracture risk and BMD, a number of features make it a less than ideal choice for a target. First, many fractures arise in individuals with BMD that lies above the definition of osteoporosis [14]. Second, for a given value of BMD, the risk for fracture increases markedly with age, so that age would also need to be taken into account. More importantly, while 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]. Finally, while treatment-induced increases in BMD are associated with reductions in fracture risk, the correlations are sufficiently 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. In Phase III clinical trials, even in studies of the most potent antiresorptives, there is a substantial overlap in changes in BMD between treated and untreated patients [15].

### Bone turnover markers

Contrary to the position of BMD, there is no consensus on the characterization of high and normal bone turnover. In a recent meta-analysis, the predictive value of 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-CTX was 1.18 (95% CI: 1.05–1.34) [16]. These gradients of risk are substantially lower than those reported for the use of femoral neck BMD in the prediction of fracture. Nonetheless, the decrease in fracture risk on anti-resorptive treatment is associated with significant reductions in BTMs [17]. However, data from clinical and population based studies have proved difficult to translate into accurate targets for individuals and the use of BTM targets has not been widely translated into clinical practice.

### 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 with bone volume, trabecular architecture or cortical thickness considered as targets for treatment. Limitations include the invasive nature of traditional assessments (e.g., transiliac crest bone biopsies) or newer techniques (e.g., microindentation [18]) and the relative cost and radiation exposure of other techniques (e.g., computed tomography and finite element analysis). 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, in a subset of patients from the FREEDOM study of denosumab, finite element analysis showed significant improvements in bone strength at both the spine and hip in the active treatment group but the correlation between sites was weak ( $r = 0.38$ ) [19].

### FRAX probability

The FRAX tool, most widely accessed through the online site [13], produces an estimation of 10-year probability of fracture risk. Several treatments have had efficacy evaluated in terms of FRAX score at baseline, indicating either a greater antifracture efficacy at higher risk or no interaction between antifracture 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 reduction in fracture risk [20]. A recent analysis of a subset of the same cohort, comprising more than 11,000 women undergoing baseline and follow-up DXA scans, 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 ( $p = 0.3$ ) [21].

These findings reflect the fact that FRAX was constructed to estimate risk from a range of parameters, some of which are not modifiable by osteoporosis treatments (e.g., age, sex, weight and height, prior fracture etc.). 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.

## Conclusion

The ultimate goal of treating osteoporosis is to prevent fracture and reduce associated morbidity and mortality. 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 impact of drug holidays. The question of whether a treat to target strategy will improve osteoporosis management remains an area for further research. None of the most likely surrogate parameters

currently available in the field of osteoporosis appears to be ready for use in a treat-to-target strategy. Until further research provides compelling evidence for such a shift in approach, the current target remains one of directing appropriate and effective treatments to those at highest risk of fracture.

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