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EDITORIAL

Treat-to-target—mainstream or marketing?

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'Treat-to-target' is an approach to the management of chronic disease that was initially developed in cardiovascular medicine. Informed by epidemiological data, individual risk factors for which treatments were available were identified (hypertension, dyslipidemia and diabetes in the case of cardiovascular disease). Calculators that incorporate these and other risk factors such as age and smoking were developed to estimate the risk over 5 to 10 years of major cardiovascular events (myocardial infarction, stroke and cardiovascular death). Informed by clinical trial data, treatment thresholds are determined and suitable and potentially attainable targets for each risk factor selected, though these may undergo revision in light of new data. The role of clinicians is to estimate their patients' risk, persuade them that this is a worthwhile strategy and, based on periodic biomarker assessment (for example, blood pressure, LDL cholesterol and glycated haemoglobin), to amend the drug regimen to keep as close to the targets as possible. Although the therapeutic armamentarium is generally effective, issues of cost, safety and adherence mean that not everyone reaches the targets. However, there is a mass of evidence that such an approach can reduce the rate at which cardiovascular events happen.

In the osteoporosis field, a treat-to-target strategy was first mooted in 2013 [1, 2]. In this context, the events we are trying to prevent are fractures and the main risk factors are age, frailty, falls, bone quality and bone mass—some, but not all, of which are incorporated into the widely used FRAX risk calculator. However, the analogy with cardiovascular medicine falls down at a number of points: we have limited ability to affect the major risk factors, there are few biomarkers, no empirically defined targets to aim at and no clinical trial data supporting a treat-to-target approach.

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The drugs we do have are targeted at bone mass—either inhibitors of bone resorption (generally inexpensive) or anabolic agents (generally expensive). They are moderately effective, reducing fracture incidence by 20–40%, but of course do not impact on age, frailty and falls. The biomarkers that have been suggested as a potential target include bone turnover markers, bone mineral density or a change in the FRAX score. All have major drawbacks. FRAX scores increase over time (primarily reflecting age), and although this trend can be attenuated by treatment, it is uncommon for someone's FRAX score actually to diminish [3]. Higher levels of bone turnover markers are associated with increased fracture risk, but the gradient of the risk is substantially lower than those reported for the use of femoral neck BMD [4] and interventions that elicit very different responses (bisphosphonates vs teriparatide, for example) can each reduce fracture risk. BMD itself as a target is also problematic. Many fractures arise in people with normal BMD [5], and for any given value of BMD, the risk of fracture varies markedly with age [6]. Treatment-induced improvements in BMD are correlated with reduced fracture risk, but the correlations are weak so are not useful in making individual decisions about treatment doses, duration or change of therapeutic agent [4].

The current edition of the journal reports the deliberations of a 'Delphi panel' of European physicians and surgeons who were asked to consider a number of questions pertaining to a treat-to-target strategy for osteoporosis [7]. The Delphi process, originally developed for use in estimating or forecasting, consists of asking panellists to rate their agreement with, and to comment on, individual statements, with responses being used to formulate subsequent rounds of questions. The aim is to reduce the range of answers such that the group converges on the 'correct' answers. All the authors agreed that a treat-to-target stratagem was required, and that total hip BMD was the most appropriate biomarker with 75% of the panellists favouring a target T-score of − 1 to − 2.

There are some issues with this. Most effective osteoporosis treatments increase BMD to a plateau (with an associated reduction in fracture risk) and it is unknown whether changing to another osteoporosis treatment to obtain a greater increase

in BMD will translate into additional anti-fracture efficacy. Of the agents currently available, the anabolic drug romosozumab has greatest effects on bone density at the hip [8]. The Endocrine Society currently recommends romosozumab use in postmenopausal women with severe osteoporosis at very high risk of fracture (defined as T-score less than − 2.5 and a prior fracture or a history of multiple vertebral fractures). In the trial of Saag et al. in postmenopausal women with osteoporosis similarly defined, the mean total hip BMD T-score before treatment was − 2.78 [9]. The reported 6–7% increase in hip BMD after romosozumab treatment would raise the mean T-score only to − 2.6, and an increase of 28% would be required to reach a T-score of − 2. So it is evident that for people with severe osteoporosis we do not yet have the means to reach the panellists' target.

In light of this, and the knowledge that no current target is suitable and no trial evidence supports a treat-to-target strategy, what should we to make of the consensus view of the panellists? Might they simply have failed to observe Mark Twain's dictum that "Whenever you find yourself on the side of the majority, it is time to reform, or pause and reflect", or is there some other explanation? The European Delphi panel was convened by the Brussels based pharma company UCB. As is unfortunately typical with such expert panels (which rank on the lower rungs of the evidence-based medicine ladder), the range of opinion drawn upon is narrow, with no input from patients, primary care, public health or health economists. UCB paid an honorarium to all the panellists, the corresponding author of the paper is employed by UCB, and the paper was written with the assistance of a medical consulting firm that "provides specialised market access and medical communication services to the pharmaceutical industry". Another author was an employee of a company that provides "bespoke solutions for whole brand building, driving visibility, relevance, and purpose in (the) marketplace". These overt commercial interests should certainly raise a red flag or two [10, 11]. Perhaps this is why a number of panellists did not accept the invitation of co-authorship.

Some background may be important here. In 2019, the US FDA approved romosozumab for use in severe postmenopausal osteoporosis. The European Medicines Agency initially declined a similar application by UCB to market it in Europe, primarily because of concerns about safety, though it was eventually approved in December 2019. One might be forgiven for thinking that in trying to raise the profile of 'treat-to-target', the real purpose of this paper is to promote an unproven treatment strategy for osteoporosis, in a way that might create a market niche, and demand, for romosozumab. There is no doubt that there is need for more effective and affordable treatment for osteoporosis, but it is important that commercial interests follow the science and do not try to dictate it.

Compliance with ethical standards

Conflict of interest Tim Cundy declares that he has no conflict of interest.

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