Fracture risk estimation may facilitate the treatment gap in osteoporosis

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INTRODUCTION: THE TREATMENT GAP

Osteoporosis is a systemic disease, characterised by low bone mass and a deteriorated microarchitecture, leading to an increased susceptibility to fractures.[1] SCOPE, a scorecard for osteoporosis in Europe, documents that the number of osteoporotic fractures in the 27 European Union (EU) countries will rise by 35% from 3.49 million in 2010 to 4.48 million in 2025.[2] The analysis was performed with the assumption that age-specific and gender-specific incidence rates of fractures will remain constant over the period of 15 years. It is possible that the incidence rate will increase even more, due to an unhealthy lifestyle (immobility) and/or vitamin D deficiency, while the incidence rate may flatten when physicians will be more capable of closing the treatment gap (the proportion of individuals with high risk of fracture with adequate treatment vs the proportion of individuals with high risk of fracture without adequate treatment). At the moment, the treatment gap for osteoporosis is substantial, and varies widely between EU countries, from 25% to 95%[2]; there is no evidence that the treatment gap is substantially lower in other parts of the world.

WHY DOES THE TREATMENT GAP PERSIST?

In theory, it is not too difficult to close the gap, since dual-energy X-ray absorptiometry (DXA) machines are widely available for diagnosing osteoporosis, and since effective, relatively safe and inexpensive (generic) drugs are currently available. With DXA, the bone mineral density (BMD) of the spine and hips is measured; a BMD $\geq$ 2.5 SD below the young female adult mean (T-score ≤ -2.5) at the lumbar spine or hip is (arbitrarily) defined as osteoporosis.[1] Earlier, it has been documented that the risk of osteoporotic fractures increases continuously as BMD decreases, resulting in a 1.5-fold to 3-fold increase in risk of fracture for each decrease in SD.[3] In addition, risk of fracture is elevated in patients with earlier non-vertebral fractures,[4] and in patients with subclinical and clinical vertebral deformities.[5] Alendronate, risedronate, zoledronic acid and denosumab, all antiresorptive drugs, have been shown to reduce the relative risk of vertebral fractures (by 40–70%), non-vertebral fractures (20–25%) and hip fractures (20–40%), in phase III trials.[6] In addition, exciting new drugs are under development that have a different working mechanism: cathepsin K inhibitors and monoclonal antibodies against sclerostin.[7 8]

Implementation of new diagnostic techniques and therapeutic options is often very difficult, since major difficulties arise when introducing evidence and clinical guidelines into routine daily practice. Passive dissemination of information (publication of consensus meetings in medical journals) is usually not an effective implementation strategy.[9] Effective implementation should focus on three basic issues for influencing the uptake of evidence: (A) attributes of evidence (eg, the phase III trials); (B) barriers and facilitators, and (C) effectiveness of dissemination and implementation strategies.[10]

The most important barriers are lack of awareness of the risk of future fractures in patients, and even in physicians (!), differences in the interpretation of the results of DXA measurements and safety issues of the antiosteoporotic drugs. Another important barrier is the lack of infrastructure to ensure the screening of patients with a recent fracture for underlying osteoporosis/elevated risk of fracture. Among the facilitators are validated tools on the absolute risk of fracture, which predict the risk of fracture over the coming 5–10 years. These tools may educate patients and physicians, and may help in answering the key question to which antiosteoporotic drugs should be prescribed.

Several initiatives that may facilitate the effectiveness of dissemination and implementation strategies have recently been started. The task force of the American Society of Bone and Mineral Research ('Making the first fracture the last fracture'),[11] and the International Osteoporosis Foundation ('Capture the Fracture'),[12] published guidelines and recommendations for patients 50+ years with a recent fracture. Patients with a fracture initially need acute care provided by an orthopaedic traumatologist. In a later phase, fracture prevention in patients identified at high risk for a subsequent fracture is also crucial; this is usually under the responsibility of rheumatologists or other medical experts. Therefore, close collaboration between all involved specialties is necessary, and a collaborative initiative from European League Against Rheumatisms and European Federation of Orthopaedics and Traumatology on fracture care has been started; they are expected to publish their recommendation in 2016.

All guidelines and recommendations strongly advocate considering secondary fracture prevention in patients with a recent fracture within the Fracture Liaison Service (FLS).[11–14] Nowadays, FLS is the preferred clinical pathway, in which in all patients of 50 years and over, the future risk of fracture can be estimated by combining the results of DXA measurements, imaging of the spine (either with conventional radiographs and/or lateral vertebral assessment), fall risk evaluation and by systematically looking for underlying diseases. Obviously, individuals at a high risk of fracture will be offered pharmacological and non-pharmacological treatment options, usually for 5 years. In patients with severe osteoporosis and in patients with treatment failure with antiresorptive drugs, the prescription of osteoanabolic drugs, such as teriparatide, could be an attractive option.

WHICH PATIENTS SHOULD BE TREATED WITH ANTIOSTEOPOROTIC DRUGS?

Unfortunately, the interpretation of DXA in individual patients is not always straightforward. With DXA, a two-dimension areal BMD measurement is performed, which does not fully represent microarchitecture and bone strength. The microarchitecture can be estimated with peripheral quantitative CT at the forearm and lower tibia, but these machines are not widely available, at least partly because of the high costs.[15 16]

As mentioned above, osteoporosis is diagnosed when the T-score is <-2.5, but how can the clinical consequences of a T-score of -2.7 be explained to the patient? The relative risk for fractures is roughly two times higher than in a patient with a T-score of -1.7, and four times higher than in a patient with a T-score of -0.7, but what is the (absolute) fracture risk?

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A T-score of −2.7 in a woman aged 53 years, in the absence of other risk factors, corresponds according to fracture risk assessmnet tool (FRAX)[17] with a low 10-year hip fracture risk of 0.3% and a low 10 year major fracture risk of 2.2% (her height is 1.65 m and her weight 65 kg). This is not uncommon nowadays: several relatively young individuals are worried and confused because of their low T-score, while their absolute fracture risk is low, and thus, their indication for drug treatment is weak.

The absolute fracture risk is very helpful for treatment decisions and it gives the physician and the patient, in a model of 'shared decision making', the tools to make understandable decisions.[18] Since osteoporosis is associated with a low adherence to therapy, it can be argued that a shared decision is crucial and may have a substantial and positive effect on adherence to therapy.[18] Suppose the relative risk reduction of vertebral fractures is around 50%, it makes a difference when this drug is prescribed in patients with a 15% risk of incident vertebral fractures over 3 years, as in one of the earliest alendronate trials,[19] or in a patient with a 3% risk of having a fracture: in the first patient the risk decreases from 15% to 7.5%, while in the latter patient the risk only decreases marginally (an absolute fracture reduction of 7.5% vs 1.5%).

The strength of the T-score is that it has been widely accepted as an arbitrary cut-off point for diagnosing osteoporosis, but it is often not always useful in daily practice. The absolute fracture risk data, which predict the future risk over the coming 5 years or 10 years, have additional value, but unfortunately, there is still no worldwide consensus on the threshold value of fracture risk above which antiosteoporotic treatment should be started.

WHAT IS THE OPTIMAL METHOD TO ESTIMATE THE FRACTURE RISK?

For the reasons described above, the systematic review and meta-analysis from Marques *et al*[20] about tools to quantify the absolute risk of fracture over 5 years and/or 10 years is very welcome. They included 45 studies, evaluating 13 different tools. Studies that have not been externally validated or were only designed and tested in specific situations were excluded. The second part of the manuscript focuses on the 3 studies that had been tested in more than 3 populations: FRAX (26 studies in 9 countries),[21] Garvan (6 studies in 3 countries)[22] and QFracture (3 studies, all in UK).[23]

The main outcome was the area under the curve (AUC) and 95% CIs obtained from receiver operating characteristic analyses. The authors concluded that the overall efficacy is satisfactory, with an AUC >0.70. However, some differences were observed: in postmenopausal women with BMD measurement, the overall AUC-score of the five studies testing FRAX in 115.611 individuals (0.79; 95% CI 0.73 to 0.85) was slightly higher than in the two studies using Garvan in 5.574 individuals (0.74; 95% CI 0.61 to 0.87). In women and men without a BMD measurement, QFracture seems to have a better score than FRAX: 0.89 (95% CI 0.88 to 0.89) after being investigated in 1.779.164 individuals, versus 0.74 (95% CI 0.68 to 0.80) in 131.224 individuals (only data presented in women). This is more or less in line with an earlier systematic review from 2013, in which it was concluded that simple tools (including Garvan) often did as well as the more complex tools (among them FRAX and QFracture).[24]

HOW TO INTERPRET THE DATA OF THE META-ANALYSIS?

The use of the FRAX-score as the first choice in patients in whom a BMD is available can be advocated, since it is certainly a robust score, has been tested in many studies and has country-specific data. However, FRAX also has some limitations; for example, fall risk is not incorporated, while the number of fall events is one of the five risk factors in the Garvan scoring method. Thus, it can be preferred for routine performance of the FRAX-score, while in frequent fallers the Garvan-score should (also) be performed three or four times per year or even more.[25] The dosage of glucocorticoids (GCs) is also not specified, while it is well known that bone loss and fractures are dose related in GC users.[26] An adjustment model was published later, in which a decrease in the estimation of fracture risk by 20% was suggested in patients treated with low dose GC, and for high dosages (>7.5 mg per day), the estimated value of risk probabilities could be increased by 15%.[27]

In patients without BMD measurement, the QFracture seems to be at least as good as the FRAX-score, or even better. While the FRAX-score is well-known, the QFracture is, at least outside the UK, relatively unknown. The QFracture was specifically designed for integration into electronic records as part of routine care of GPs in UK. Although the system might be very convenient and may have a good predictive value, the tool is not easy to reproduce elsewhere, which is a large contrast with the widely available FRAX tool.

LIMITATIONS

The interpretation of the data from the meta-analysis is hampered by the differences in designs of the tools. Differences were found in the age and gender of patients, both clinically relevant risk factors. There was also variation in the observation time, and even the type of (major) fracture varied between the studies. A very important issue is that the data were derived from cohort studies in the general population, while FRAX and other scores are often used in other populations, for instance in elderly patients with a recent fracture.

Another issue is the large variation in risk factors: the QFracture contains 31 items, Garvan only 5, and FRAX 11. Thus, the QFracture is more time-consuming than FRAX, but the predictive value of a tool increases when the number of (strong) risk factors is larger. Several risk factors for future fractures are checked in QFracture but not in FRAX: previous falls, ethnicity, diabetes mellitus (DM) type 1 and DM type 2, cardiovascular disease, gastrointestinal disease, the use of hormonal replacement therapy, and even the presence or absence of SLE. It is surprising that SLE is on the list of risk factors, since SLE certainly has a multifactorial and negative effect on BMD and fractures,[28] but the incidence of the disease is very low.

Looking more in detail at the risk factors in the fracture risk prediction tools, it is remarkable that previous falls and the use of GCs, both very important risk factors, are only scored in 5 out of 12 tools. Physical exercise is only scored in one prediction tool, probably because there is no widely accepted definition, while vertebral fractures and/or loss of height are counted in none of the prediction tools.

SUMMARY

The treatment gap for patients at high risk of fractures is substantial, but recent new initiatives, such as by the American Society of Bone and Mineral Research and the International Osteoporosis Foundation, and the introduction of FLS, are important instruments that may help to close the gap. Validation tools on the absolute fracture risk, which predict the risk of fracture over the coming 5–10 years, are among the facilitators of the implementation of optimal fracture prevention in high-risk patients. The systematic review and meta-analysis of the accuracy of estimation

of osteoporotic fracture risk provides valuable information on the estimation of the prediction of fractures based on different tools. Comparisons between the studies are hampered by differences in study design (including gender, age and type of fractures), number of risk factors and observation time. Another limitation is the absence of a widely accepted consensus on 5-year or 10-year absolute fracture risk above which antiosteoporotic treatment should be started. Nevertheless, the use of a fracture risk prediction tool can be very informative for patients in daily practice: the widely used FRAX-score can be used as the primary model, while in patients with recurrent falls the Garvan model maybe of added value.

Acknowledgements Dr Jos Hoes and Dr Nathalia Kuchuk read the manuscript, and suggested improvements to the manuscript.

Competing interests The author received speaker's fee from Amgen, Eli Lilly, Merck, Will Pharma, Servier, and Novartis.

Provenance and peer review Commissioned; externally peer reviewed.

To cite Lems WF. *Ann Rheum Dis* 2015;**74**:1943–1945.

Received 22 August 2015
Revised 1 September 2015
Accepted 6 September 2015
Published Online First 25 September 2015

► http://dx.doi.org/10.1136/annrheumdis-2015-207907

Ann Rheum Dis 2015;**74**:1943–1945.
doi:10.1136/annrheumdis-2015-208245

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