> "The previous dichotomous selection [of patients who deserve to be treated], based only on a threshold of bone mineral density, will be replaced by the assessment of the individual 10-year absolute risk of fracture. Based on this evaluation of the absolute fracture risk and also on the willingness to pay of national or regional health authorities for the management of osteoporosis, the selection of patients to be treated will soon become scientifically robust, ethically correct, and economically sound."

National implementation of the ESCEO guidance and its consequences

Interview with J.-Y. Reginster, *Belgium*

Jean-Yves REGINSTER
MD, PhD
Bone and Cartilage Metabolism Research Unit, Centre Hospitalier Universitaire Centre-Ville Policliniques L. Brull
Liège, BELGIUM

The nonprofit European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) fosters interaction between clinical scientists, the pharmaceutical industry, regulators, and health policy makers to optimize management of osteoporosis and osteoarthritis within a comprehensive perspective of health resource utilization. In 2008, it issued guidance to help practitioners harmonize their prevailing national health economies with the latest evidence-based medicine findings. Using FRAX®, a Web-based World Health Organization tool that provides fracture probability algorithms, the ESCEO guidelines select treatment candidates based not on threshold bone mineral density (BMD), but on individual 10-year absolute fracture risk informed by clinical risk factors and age. Decisions to treat can then be modulated by the efficacy, cost, and side effects of treatment and on national health authorities' willingness to pay, making them scientifically robust, ethically correct, and economically sound. However, BMD retains its role as a marker of treatment response, most notably with strontium ranelate, which uniquely inhibits bone resorption while stimulating bone formation: changes in total hip or femoral neck BMD account for up to 74% of antifracture efficacy with strontium ranelate versus only 16% with bisphosphonates. Once the FRAX® tool identifies a patient as warranting osteoporosis treatment, strontium ranelate can be prescribed regardless of the level of risk identified by the algorithm. It is currently the only compound to show antifracture efficacy in such a widely scattered range of patients and absolute fracture risk.

Medicographia. 2010;32:67-70 (see French abstract on page 70)

What are the objectives of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)?

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) is a not-for-profit organization dedicated to fostering close interaction between clinical scientists dealing with rheumatic disorders, the pharmaceutical industry developing new compounds in this field, regulators responsible for the registration of such drugs, and health policy makers to integrate the management of osteoporosis and osteoarthritis within a comprehensive perspective of health resources utilization. The objective of the ESCEO is to provide practitioners with the latest clinical and economic information, allowing them to organize their daily practice; to provide an evidence-based medicine perspective with economic perception; and to remain at the forefront of science. The ESCEO Scientific

Address for correspondence:
Prof Jean-Yves Reginster, Bone and Cartilage Metabolism Research Unit, Centre Hospitalier Universitaire Centre-Ville, Policliniques L. Brull, Quai Godefroi Kurth 45, 9° Floor, 4020 Liège, Belgium
(e-mail: jyreginster@ulg.ac.be)

www.medicographia.com

Advisory Board is currently chaired by Professor René Rizzoli, one of the most prominent figures in the field of osteoporosis. Several working groups and expert consensus meetings have been and will be organized to provide practitioners with a clear synthesis of the most up-to-date science in various fields of interest, including—but not exhaustively—calcium and vitamin D requirements for postmenopausal women, osteonecrosis of the jaw linked to bisphosphonate use, adverse dermatological reactions with anti-osteoporosis treatments, the use of symptomatic slow-acting drugs for the management of osteoarthritis, the management of osteoporosis in the very elderly, and subtrochanteric fractures after long-term use of bisphosphonates. Furthermore, the ESCEO is the proud organizer of the European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ECCEO), the largest event fully dedicated to the clinical and economic aspects of the management of osteoporosis and osteoarthritis worldwide. The last congress took place in Athens, Greece, and saw more than 4200 delegates gathered. The next ECCEO Congress will be a joint venture with the International Osteoporosis Foundation (IOF). Together they will organize the IOF World Congress on Osteoporosis – ECCEO 10 Congress, which will take place in Florence, Italy, from May 5-8, 2010. All the information regarding this event can be obtained at: http://www.iofwco-ecceo10.org.

	Effect on vertebral fracture risk		Effect on nonvertebral fracture risk	
	Osteoporosis	Established osteoporosis*	Osteoporosis	Established osteoporosis*
Alendronate	+	+	NA	+ (including hip)
Risedronate	+	+	NA	+ (including hip)
Ibandronate	NA	+	NA	+†
Zoledronic acid	+	+	NA	NA (+)‡
HRT	+	+	+	+
Raloxifene	+	+	NA	NA
Teriparatide and PTH	NA	+	NA	+
Strontium ranelate	+	+	+ (including hip)	+ (including hip)

* Women with a prior vertebral fracture.
† In subsets of patients.
‡ Mixed group of patients with or without prevalent vertebral fractures.
+ = effective drug.

Table I. *Comparison of the antifracture efficacy of common osteoporosis treatments.*
Antifracture efficacy of the most frequently used treatments for postmenopausal osteoporosis when given with calcium and vitamin D, as derived from randomized controlled trials.
Abbreviations: *HRT, hormone replacement therapy; NA, no evidence available; PTH, parathyroid hormone.*
Adapted from reference 1: *Kanis JA, Burlet N, Cooper C, et al.* Osteoporos Int. *2008;19:399-428.*

What changes will the ESCEO guidance bring to the diagnosis of osteoporosis?

In 1997, the European Foundation for Osteoporosis and Bone Disease (which later joined the International Federation for Societies on Skeletal Diseases to form the International Osteoporosis Foundation) published guidelines for the diagnosis and management of osteoporosis. At that time, the diagnosis of osteoporosis was based on the World Health Organization (WHO) operational definition of osteoporosis, ie, a T-score of bone mineral density (BMD) measured by dual-energy x-ray absorptiometry below -2.5 at the lumbar spine or at the total hip. Since then, there have been significant advances in the field of osteoporosis. These include the development of many new techniques for measuring bone mineral, improved methods of assessing fracture risk, and new treatments that have been shown to significantly reduce the risk of fractures at vulnerable sites. The objective of the new guidance document published by the ESCEO is to incorporate these new scientific developments and to provide a new concept of the selection of patients who deserve to be treated. The previous dichotomous selection, based only on a threshold of bone mineral density, will be replaced by the assessment of the individual 10-year absolute risk of fracture. Based on this evaluation of the absolute fracture risk and also on the willingness to pay of national or regional health authorities for the management of osteoporosis, the selection of patients to be treated will soon become scientifically robust, ethically correct, and economically sound.

Selected abbreviations and acronyms

BMD	bone mineral density
ECCEO	European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis
IOF	International Osteoporosis Foundation
WHO	World Health Organization

What are the treatment modalities recommended in ESCEO guidance?

The effect of major pharmacological interventions on vertebral and hip fracture risk have been summarized in the ESCEO document. Currently, the most frequently used treatments for postmenopausal osteoporosis include inhibitors of bone resorption (ie, bisphosphonates, selective estrogen receptor modulators, and hormone replacement therapy), stimulators of bone formation (peptides from the parathyroid hormone family), and, more recently, strontium ranelate, a chemical entity that has a unique mode of action that concomitantly inhibits bone resorption, while stimulating bone formation *(Table I).*[1] The ESCEO guidance document recommends the selection of a treatment option based on

its ability to reduce fractures at various skeletal sites (including hip) and in the population being specifically considered (ie, osteopenia, osteoporosis, or severe osteoporosis).

How can we monitor treatment efficacy with respect to the different therapeutic classes?

Monitoring of treatment can be done with biochemical markers of bone turnover or bone mineral density assessment. Whether the long-term antifracture efficacy of antiosteoporotic drugs is dependent on the extent to which treatment can increase or maintain BMD is controversial. Meta-regressions, based on summary statistics, demonstrate a stronger correlation between change in BMD and fracture risk reduction than results based on individual patient data. For bisphosphonates, 16% of the vertebral fracture risk reduction after treatment with alendronate was attributed to an increase in BMD at the lumbar spine. Larger increases in BMD at both the spine and hip observed with alendronate were associated with greater reductions in the risk of nonvertebral fractures. However, for patients treated with risedronate or raloxifene, changes in BMD predict the degree of reduction in vertebral or nonvertebral fractures even more poorly. For bone-forming agents, increases in BMD account for approximately one third of the vertebral fracture risk reduction with teriparatide. A larger proportion (up to 74%) of the antifracture efficacy of strontium ranelate is explained by changes in total hip or femoral neck BMD. Strontium ranelate appears to be the first agent for which BMD measurement after one year can be used as a valid tool for monitoring the long-term response to treatment. For markers of bone turnover, a significant association has been reported between the short-term decrease and the absolute level of markers of bone turnover with the use of antiresorptive agents, on the one hand, and the magnitude of the reduction of the risk of vertebral and nonvertebral fractures, on the other hand. During bone-forming therapy with teriparatide, serum P1NP increases two-to-three–fold within 1 to 3 months, a change that correlates with a subsequent increase in BMD.

With the advent of FRAX®, should case finding strategy be adapted to take clinical risk factors into account?

As of today, there is no universally accepted policy for population screening in Europe to identify patients with osteoporosis or those at high risk of fracture. In the absence of such policies, patients are identified opportunistically using a case-finding strategy based on the finding of a previous fragility fracture or the presence of significant risk factors *(Table II)*.[1] The discovery that the presence of clinical risk factors and age modulate risk (and therefore cost-effectiveness) reinforces the view that treatment should be directed on the basis of fracture probability, rather than on a single BMD threshold. Risk factors that are used for clinical assessment include age, sex, low body mass index, previous fragility fracture, parental history of hip fracture, glucocorticoid treatment, current smoking, increased alcohol intake, and secondary causes of osteoporosis.

How will FRAX® impact health economics?

There is an increased need for management strategies to be placed in an appropriate health economic perspective for guideline development and for reimbursement. Algorithms that integrate the weight of clinical risk factors for fracture risk, with or without information on BMD, have been developed by the WHO Collaborating Center for Metabolic Bone Diseases in Sheffield, England. This algorithm, FRAX®, calculates the 10-year probability of hip fracture or major osteoporotic fracture. Probabilities can be computed for an index of European countries, categorized for different levels of risk. The intervention threshold can be defined as a fracture probability at which intervention becomes acceptable. Decisions about the need for treatment depend not only upon the fracture probability, but also on efficacy, costs, side effects of treatment, and willingness to pay. Developments in the ability to assess fracture probability in individuals rather than in pop-

Risk factor
Age
Sex
Low body mass index
Previous fragility fracture, particularly of the hip, wrist, and spine (including morphometric vertebral fractures)
Parental history of hip fracture
Glucocorticoid treatment (>5 mg prednisolone daily or equivalent for 3 months or more)
Current smoking
Alcohol intake of 3 or more units daily
Secondary causes of osteoporosis
Rheumatoid arthritis
Untreated hypogonadism in men and women, eg, premature menopause, bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy for breast cancer, and hypopituitarism
Inflammatory bowel disease, eg, Crohn's disease and ulcerative colitis (it should be noted that the risk is partly dependent on the use of glucocorticoids, but an independent risk remains after adjustment for glucocorticoid exposure)
Prolonged immobility, eg, spinal cord injury, Parkinson's disease, stroke, muscular dystrophy, ankylosing spondylitis
Organ transplantation
Type 1 diabetes
Thyroid disorders, eg, untreated hyperthyroidism, overtreated hypothyroidism
Chronic obstructive pulmonary disease

Table II. *Clinical risk factors used for the assessment of fracture probability.*

After reference 1: Kanis JA, Burlet N, Cooper C, et al. Osteoporos Int. *2008; 19:399-428. Copyright © 2008, International Osteoporosis Foundation and National Osteoporosis Foundation.*

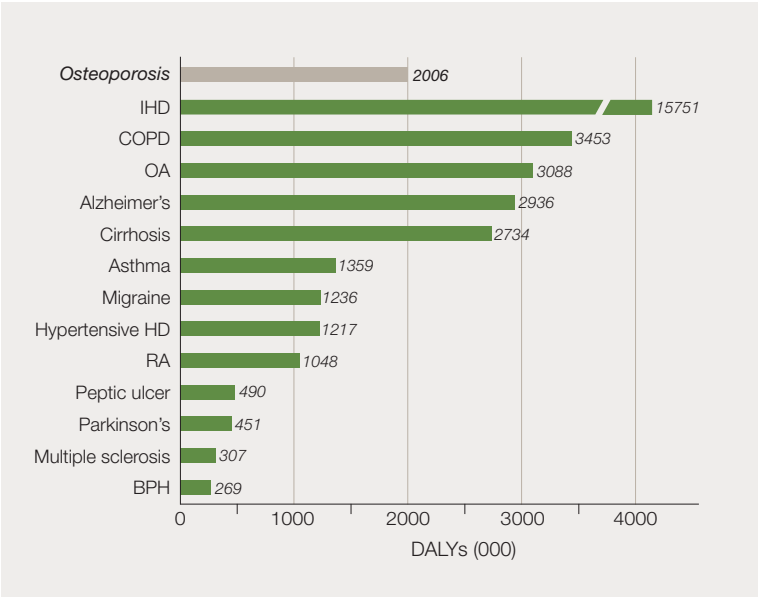

Figure 1. *The health impact of osteoporosis versus that of other diseases. The relative burdens of a selection of noncommunicable diseases in Europe estimated using disability-adjusted life years (DALYs).*
Abbreviations: *BPH, benign prostatic hyperplasia; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; OA, osteoarthritis; RA, rheumatoid arthritis.*
Modified from reference 2: *Johnell O, Kanis JA.* Osteoporos Int. *2006;17:1726-1733. Copyright © 2006, International Osteoporosis Foundation and National Osteoporosis Foundation.*

ulations provide new challenges for the health economic evaluation of interventions *(Figure 1).*[2] These developments mean that previous estimates of intervention threshold based on cost-effectiveness need to be revised using models that integrate the weights of influence of different clinical risk factors on the risk of fracture and death.

How does Protelos' effectiveness independent of the level of risk factors represent an advantage for practitioners?

Strontium ranelate has shown an antifracture efficacy at all skeletal sites, including spine, non-spine, and hip. It is the only compound to have so far shown antifracture efficacy at the hip level after five years of treatment in a preplanned, placebo-controlled, double-blind, randomized study. The antifracture efficacy of strontium ranelate has also been tested across a wide scatter of populations, including early postmenopausal, osteopenic, osteoporotic, and severe osteoporotic patients, and subjects over the age of 80. Similarly, the ability of strontium ranelate to decrease the risk of fracture is not influenced by the presence or absence of various risk factors for fracture, including—but not exhaustively—the severity of prevalent fractures, the number of prevalent fractures, being a current smoker, low body mass index, parental history of fracture, and the level of bone turnover at baseline. Strontium ranelate is currently the only compound that has shown antifracture efficacy in such a widely scattered range of patients and absolute fracture risk. ■

References

1. Kanis JA, Burlet N, Cooper C, et al; European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int.* 2008;19:399-428.
2. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int.* 2006;17:1726-1733.

Keywords: ECCEO; ESCEO; osteoporosis; osteoarthritis; IOF; bone mineral density; FRAX®

MISE EN PLACE NATIONALE DES RECOMMANDATIONS DE L'ESCEO ET SES CONSÉQUENCES

L'organisation à but non lucratif ESCEO, (European Society for Clinical and Economic aspects of Osteoporosis and Osteoarthritis), *encourage les relations entre cliniciens, industrie pharmaceutique, régulateurs et administrateurs de santé afin d'optimiser la prise en charge de l'ostéoporose et de l'arthrose dans le vaste contexte de l'utilisation des ressources de santé. En 2008, des recommandations furent mises en place pour aider les médecins à harmoniser leurs économies de santé nationales avec les données EBM* (evidence-based medicine = *médecine basée sur les preuves) les plus récentes. Les recommandations de l'ESCEO utilisant FRAX® (outil Internet de l'OMS calculant des algorithmes de probabilité de fractures), sélectionnent les candidates au traitement non sur une valeur-seuil de la DMO (densité minérale osseuse) mais sur le risque absolu de fracture d'un individu à 10 ans, basé sur les facteurs de risque cliniques et sur l'âge. Les décisions de traiter peuvent ensuite être modulées selon l'efficacité, le coût et les effets secondaires du traitement tout en tenant compte de l'accord ou non des autorités nationales de santé à en couvrir les frais. C'est à ces conditions que les décisions seront scientifiquement valables, éthiquement correctes et économiquement saines. La DMO garde néanmoins son rôle de marqueur dans la réponse au traitement, surtout avec le ranélate de strontium qui inhibe la résorption osseuse et stimule la formation osseuse de façon unique : les modifications de la DMO au niveau de la hanche totale ou du col fémoral comptent pour 74 % dans l'efficacité antifracturaire du ranélate de strontium* versus *seulement 16 % avec les bisphosphonates. Une fois une patiente identifiée par FRAX® comme ayant besoin d'être traitée, le ranélate de strontium peut être prescrit quel que soit le niveau de risque identifié par l'algorithme. C'est actuellement le seul composé à avoir une efficacité antifracturaire sur un tel éventail de patientes et sur un risque absolu de fracture si largement dispersé.*