“Chance favors only the prepared mind”

Pasteur

Bone quality in the treatment of osteoporosis: new approaches, new techniques, and new answers
The goal of quantitative fracture-risk prediction is to determine the threshold fracture probability at which intervention becomes cost-effective. Cost-effectiveness cutoffs vary with age. The FRAX® tool may help provide evidence of the fragility fracture risk in younger subjects, who are often in the osteopenic range and who represent 40% of all patients with fragility fractures. Future efforts should aim to offer a platform for future homogeneity in the choice of treatment thresholds in osteoporosis.

How innovations are changing our management of osteoporosis

by M. L. Brandi, Italy

Bone mineral density (BMD) was, for a long time, the only parameter that could be used for the diagnosis of osteoporosis in daily practice. However, after the first definition of osteoporosis was proposed in 1993, it was realized that other factors beside bone mass influence bone strength, particularly bone microarchitecture and clinical risks. Not surprisingly, in 2001, the revised definition of osteoporosis shifted the emphasis to changes in bone quality and, in 2008, the World Health Organization (WHO) released recommendations for the assessment of fragility fracture risk using clinical risk factors, with or without BMD. Even though bone mineral density is the single most important contributor to bone strength, qualitative factors also play a significant role. These include, in a hierarchical size distribution, the properties of organic and mineral materials, the degree of mineralization, turnover, and the manner in which bone mass is distributed in space, known as bone microarchitecture and macroarchitecture.

While many of the parameters that have been developed to describe structural bone properties can easily be assessed in vitro by histomorphometry, nondestructive and noninvasive techniques for use in vivo are at the forefront of radiological research in osteoporosis. A variety of innovative modalities, ranging from plain x-ray and DXA (dual-energy x-ray absorptiometry)-based hip structural analysis to computed tomography and magnetic resonance imaging, have been developed to assess bone structure, both at the micro and macro levels.

A second area of innovation is the WHO FRAX® fracture risk assessment algorithm, a simple, practical Web tool that integrates clinical information in a quantitative manner to predict a 10-year probability of major osteoporotic fracture for both women and men for a range of different countries.

Advanced imaging for the material and structural basis of bone strength

The strength of bone and its fragility are the result of its material composition and structure. Bone histomorphometry was developed in the 1950s by pioneer workers to explore various metabolic bone diseases. The microscopic technique was done on 2-D sections and, even though several mathematical formulations have been proposed to extrapolate 2-D measurements to the third, special dimension, the results are discordant.

Today, structural information about bone can be provided by noninvasive and/or nondestructive imaging techniques that include computed tomography (CT), particularly volumetric quantitative CT (vQCT), high-resolution CT (hrCT), micro-CT (mi-
Bone geometry is a relevant determinant of bone strength and fragility that can be evaluated using an automated DXA-based analysis of x-ray attenuation profiles, also known as hip structural analysis (HSA). This is easily derived from routine DXA scans that are elaborated by software provided by the manufacturers. This method has provided novel information on the correlation between hip geometry and risk of hip fracture, even though the contribution of hip geometry to the risk of hip fracture cannot be delineated using HSA independent of area BMD.

The only way to measure true volumetric density is through vQCT, a well-established method for assessing bone fragility and for monitoring BMD. As a volumetric measurement, vQCT can determine the bone mineral content of the entire bone or specific subregions, with a separate analysis of the trabecular and cortical compartments. The technique makes certain measurements possible, such as cross-sectional area and hip axis length, with derivation of the cross-sectional moment of inertia. Today, vQCT results can be applied to the analysis of finite elements, making it possible to identify the mechanisms of action of compounds whose effects are not apparent using DXA measurements.

Standard quantitative computed tomography techniques generate a spatial resolution of the order of 1 mm³ and are thus inadequate for detailed cortical and trabecular measurements. High-resolution imaging with multislice spiral CT (hrCT) provides a better depiction of trabecular and cortical morphology. hrCT can provide information that correlates to vertebral fracture risk, offering information distinct from that of a BMD measurement. A high-resolution peripheral QCT (hr-pQCT) system is available for the assessment of trabecular and cortical geometry at the distal radius and tibia. Muscle cross-sectional area can be assessed as well as the apparent density of muscles (pure muscle, fat) can be quantified using peripheral quantitative computed tomography.

Finite element analysis (FEA) was applied in solid mechanics to evaluate the behavior of complex and heterogeneous structures, like bone tissue, in response to applied loads. In FEA, the structure is decomposed into elements defined by reference points or nodes, which predict strength without using direct mechanical testing. When data from prospective studies of fracture risk become available, the prediction of fracture risk will be enhanced by the use of FEA.

Micro-CT analysis was developed to perform in vitro evaluation of small bone samples. This technique, using high radiation doses, makes it possible to visualize individual trabeculae, endosteal and periosteal surfaces, and cortical porosity. Only recently have in vivo micro-CT scanners (XtremeCT) become commercially available, providing quantitative and qualitative assessment of the distal part of the radius or tibia.

Magnetic resonance microscopy, which encompasses hrMRI and micro-MR, has received considerable attention as a potential technique to clinically evaluate bone fragility. Magnetic resonance imaging (MRI), whose availability is widespread, can provide three-dimensional images of bone tissue using nonionizing radiation. This advantage is counterbalanced by the high cost of the equipment, by the interference of metallic implants, and by the complexity of its interpretation. In combination with FEA, hrMRI offers high-quality interpretation of the trabecular bone microarchitecture and mechanical properties of bone tissue.

Nanoindentation, a technique widely applied in materials science, is capable of describing micromechanical properties, including hardness and elastic modulus, of material surfaces. The majority of studies have evaluated cortical bone, while relatively few studies have been devoted to trabecular bone. Correlations between these properties and bone mineral content may be evaluated using quantitative backscattered scanning electron microscopy in the future.

FRAX® and its application in patient management

FRAX® is a fracture risk assessment tool that was developed under the aegis of the World Health Organization by John Kanis and a group of epidemiologists. It was published in 2008, after being impatiently awaited for years, and is now universally accessible free of charge on the Internet (www.shef.ac.uk/FRAX). Kanis and coworkers studied 12 international, population-based cohorts, analyzing risk factors and their predictive values in about 60,000 individuals. The FRAX® algorithms give the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (hip, shoulder, forearm, or clinical spine fracture, but not radiological spine fracture without symptoms). The fracture risk variables are entered on the Web site. Femoral neck BMD can additionally be entered as a T-score. The obvious application of FRAX® is for the assessment of individuals to identify those who would be candidates for pharmacological intervention, and it has been widely used since the launch of the Web site. There are also challenges to be faced in the assessment of pharmaceutical agents for drug registration and in health economics.

The introduction of the FRAX® tool is expected to influence the assessment of patients. Until now, treatments were made based on the presence or absence of fractures and of a T-score of 2.5 SD or lower. Even though these criteria are applied by agencies responsible for drug reimbursement and are included in all the clinical guidelines, they leave out sev-
eral conditions encountered in clinical practice. It is relevant to recognize that FRAX® estimates fracture risk without changing the definition of osteoporosis, which is defined by T-score. Similarly, the Framingham Risk Index did not change the definition of hypertension.

In the UK, guidance for the identification of patients with a high fragility fracture risk has been based on an opportunistic case-finding strategy, where the presence of clinical risk factors associated with fracture makes the physician aware of the possibility of osteoporosis, with a consequent evaluation of BMD, followed by the treatment prescription needed. A similar approach has been used in several European countries and in the USA.

The FRAX® tool is easy to use, but it has limitations. First, several risk factors can be indicated only as present or absent (e.g., glucocorticoid therapy and previous fracture), without taking into account the time of exposure to a given fracture risk or the number of events that are expression of risk. Moreover, only femoral neck BMD is taken into account by FRAX®, an area where precision errors are more frequent and which means the exclusion of other areas, such as the lumbar spine, that are more frequently involved at younger ages. In addition, there are several risk factors, such as bone turnover, risk of falls, and previous pharmacological interventions, that are not incorporated into the assessment algorithms.

The goal of quantitative fracture-risk prediction is to determine the threshold fracture probability at which intervention becomes cost-effective. Cost-effectiveness cutoffs vary with age. The FRAX® tool may help provide evidence of the fragility fracture risk in younger subjects, who are often in the osteopenic range and who represent 40% of all patients with fragility fractures.

Given the worldwide variability of the reimbursement for antifracture drugs, it is not surprising to see different positions in the determination of treatment thresholds based on FRAX®. In summary, the cutoffs published up to now are only suggestions, and they are going to be changed based on findings from ongoing studies. Future efforts should aim to offer a platform for future homogeneity in the choice of treatment thresholds in osteoporosis.

Since 2006, the Committee for Medicinal Products for Human Use has been revising guidelines on the evaluation of drugs in the treatment of osteoporosis, and emphasis is now given to patients at risk of fracture. The few analyses conducted up to now on phase 3 clinical studies have shown that patients identified on the basis of clinical risk factors with FRAX® do respond to pharmacological interventions, even when BMD was not used to characterize risk.

All this renewed interest in osteoporosis, especially by general practitioners, is going to be good for the field. As happened for cardiovascular disorders, the opportunity of using an easy model to evaluate risk for the medical community will unearth novel possibilities for intervention in an area that is not getting enough attention from governments, physicians, or patients.

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References

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La densité minérale osseuse (DMO) a été pendant longtemps le seul paramètre disponible pour le diagnostic de l’ostéoporose en pratique clinique. Cependant, après que la première définition de l’ostéoporose ait été proposée en 1993, il est apparu que d’autres facteurs en dehors de la masse osseuse exerçaient une influence sur la résistance des os, en particulier la microarchitecture osseuse et les risques cliniques. Ces découvertes ont naturellement conduit en 2001 à une révision de la définition de l’ostéoporose davantage orientée sur les changements de la qualité osseuse. Enfin, en 2008, l’Organisation Mondiale de la Santé (OMS) a formulé les recommandations pour l’évaluation du risque de fracture par fragilité osseuse basée sur les facteurs de risques cliniques, avec ou sans la DMO. Même si la densité minérale osseuse constitue le facteur qui a lui seul contribue le plus fortement à la résistance osseuse, les facteurs qualitatifs jouent également un rôle significatif. Ils comprennent notamment, par ordre d’importance, les propriétés des matériaux organiques et minéraux, le degré de minéralisation, le renouvellement, et la manière dont la masse osseuse est distribuée dans l’espace, c’est-à-dire la microarchitecture et la macroarchitecture osseuse.

Bien que de nombreux paramètres développés pour décrire les propriétés structurelles osseuses puissent facilement être évalués in vitro par histomorphométrie, les techniques radiologiques non destructrices et non invasives utilisables in vivo sont les méthodes privilégiées dans le cadre de la recherche sur l’ostéoporose. Un certain nombre de modalités innovantes, qui vont de l’analyse structurelle de la hanche par radiographie sans préparation ou l’absorptiométrie biénergétique aux rayons X (dual-energy x-ray absorptiometry, DXA) à la tomodensitométrie et à l’imagerie par résonance magnétique, ont ainsi été développées pour évaluer la structure osseuse, au niveau microscopique et macroscopique.

Un second domaine d’innovation est constitué par l’algorithme d’évaluation des risques de fracture de l’OMS FRAX®. Il s’agit d’un utilitaire Internet simple et pratique, validé pour différents pays, intégrant les informations cliniques de façon quantitative afin d’établir une probabilité à 10 ans de fracture ostéoporotique majeure chez la femme et chez l’homme.

Techniques avancées d’imagerie pour l’évaluation des paramètres matériaux et structuraux de la résistance osseuse

La résistance de l’os et sa fragilité résultent de sa composition et de sa structure. L’histomorphométrie osseuse a été développée dans les années 1950 par des chercheurs explorant les différentes pathologies du métabolisme osseux. La
La seule manière de mesurer la densité volumétrique réelle passe par la TDM quantitative volumétrique, une méthode bien établie permettant l’évaluation de la fragilité osseuse et la surveillance de la DMO. Dans la mesure où il s’agit d’une mesure volumétrique, cette technique peut déterminer la teneur minérale osseuse de l’os entier ou de régions spécifiques, en analysant séparément les compartiments trabéculaires et corticaux. La technique rend certaines mesures possibles, notamment la surface transversale et la longueur de l’axe de la hanche, et permet d’en déduire le moment d’inertie transversal. À l’heure actuelle, les résultats de la TDM quantitative volumétrique peuvent être appliqués à l’analyse par éléments finis, permettant ainsi d’identifier les mécanismes d’action de médicaments dont les effets n’apparaissent pas à la DXA. Les techniques standard de tomodensitométrie quantitative permettent d’obtenir une résolution spatiale de l’ordre du mm², et donc incompatible avec des mesures corticales et trabéculaires détaillées. L’imagerie à haute résolution par TDM spirale passée par des études ont évoluté le tissu trabéculaire et cortical. La TDM spirale passée par des études ont évoluté le tissu trabéculaire et cortical. 

La géométrie osseuse est un facteur significatif de la résistance et de la fragilité osseuses, qui peut être évalué en utilisant une analyse automatisée par DXA des profils d’atténuation des rayons X, également dénommée analyse structurale de la hanche. Cette technique est facilement mise en œuvre à partir d’imageries de routine par DXA élaborées par des logiciels fournis par les fabricants. Cette méthode a permis de recueillir de nouvelles informations sur la corrélation entre la géométrie de la hanche et le risque de fracture de la hanche, même si le rôle de la géométrie de la hanche dans le risque de fracture de la hanche ne peut pas être précisé indépendamment de la DMO de surface.

La microscopie par résonance magnétique nucléaire, qui associe l’IRM à haute résolution et la micro-IRM, a fait l’objet d’un intérêt considérable comme technique susceptible d’évaluer cliniquement la fragilité osseuse. L’imagerie par résonance magnétique nucléaire (IRM), largement disponible, fournit des images en trois dimensions du tissu osseux en utilisant des rayonnements non ionisants. Cet avantage est tempéré par le coût élevé de l’équipement, par les interférences avec les implants métalliques, et la complexité de l’interprétation. En association avec l’analyse par éléments finis, l’IRM à haute résolution permet une interprétation de haute qualité de la microarchitecture de l’os trabéculaire et des propriétés mécaniques du tissu osseux.

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Santé par John Kanis et un groupe d’épidémiologistes. Il a été publié en 2008, après avoir été impatiemment attendu pendant plusieurs années[6,37] et il est désormais gratuitement accessible sur Internet (www.shef.ac.uk/FRAX). Kanis et coll. ont étudié 12 cohortes de population internationales afin d’analyser les facteurs de risque et leur valeur prédictive chez environ 80 000 personnes. Les algorithmes de FRAX® fournissent la probabilité à 10 ans de fracture de la hanche et la probabilité à 10 ans de fracture ostéoporotique majeure (hanche, épaule, avant-bras ou fracture clinique du rachis, mais non de fracture radiologique du rachis sans symptômes). Les paramètres du risque de fracture sont enregistrés dans le site Internet. La DMO du col fémoral peut en outre être enregistrée sous forme de score T. L’application évidente de FRAX®, qui a été largement utilisé depuis son lancement sur Internet, est l’évaluation des personnes considérées comme candidates à une intervention pharmacologique. Une autre application possible serait de contribuer à l’évaluation des agents pharmacologiques en vue de leur enregistrement, ainsi qu’à l’évaluation de paramètres pharmaco-économiques.

La diffusion de l’utilitaire FRAX® devrait avoir une influence sur l’évaluation des patients. Jusqu’à présent, la mise en œuvre des traitements était basée sur la présence ou l’absence de fracture, et une valeur de score T ≤−2,5 ET. Même si ces critères sont appliqués par les agences responsables du remboursement des médicaments et sont inclus dans toutes les directives cliniques, ils excluent un certain nombre d’affections rencontrées en pratique clinique. Il est significatif de constater que FRAX® estime le risque de fracture sans changer la définition de l’ostéoporose, basée sur le score T, de la même façon que l’indice de risque de Framingham n’a pas changé la définition de l’hypertension.

Au Royaume-Uni, les directives pour l’identification des patients présentant un risque élevé de fracture de fragilité sont fondées sur une stratégie opportuniste de recherche de cas, basée sur la présence de facteurs de risques cliniques associés aux fractures attirant l’attention du médecin sur l’éventualité d’une ostéoporose, suivie par une évaluation de la DMO, et par la prescription du traitement nécessaire[39]. Une approche similaire a été utilisée dans plusieurs pays européens[39] et aux États-Unis[40].

L’utilitaire FRAX® est facile à utiliser, mais il a ses limites. Tout d’abord, plusieurs facteurs de risque ne peuvent être indiqués que soit comme présents, soit comme absents (par exemple, un traitement par des glucocorticoïdes et des fractures antérieures), sans prendre en compte la durée d’exposition à un facteur de risque de fracture donné, ni le nombre d’événements qui sont l’expression du risque. En outre, seule la DMO du col fémoral est prise en compte par FRAX®, une région dans laquelle les erreurs de précision sont plus fréquentes, excluant ainsi d’autres régions, notamment le rachis lombaire, qui sont plus fréquemment atteintes chez les patients plus jeunes. En outre, il existe plusieurs facteurs de risque, notamment le renouvellement osseux, le risque de chute et de précédentes interventions pharmacologiques, qui ne sont pas incorporés dans les algorithmes d’évaluation.

L’objectif de la prédiction quantitative du risque de fracture est de déterminer la probabilité seuil d’une fracture pour laquelle une intervention présente un facteur coût-efficacité favorable. Les seuils coût-efficacité varient en fonction de l’âge[41]. L’utilitaire FRAX® peut fournir des éléments attestant d’un risque de fracture de fragilité chez des sujets plus jeunes, qui se trouvent souvent dans l’intervalle ostéopénique et qui représentent 40 % de l’ensemble des patients souffrant de fractures de fragilité.

Compte tenu de la variabilité mondiale en matière de remboursement des médicaments anti-fracture, il n’est pas surprenant de voir différentes positions dans la détermination des seuils de traitement basés sur l’utilitaire FRAX®[42-44]. En résumé, les seuils publiés jusqu’à présent ne sont que des suggestions, et ils sont susceptibles d’évoluer sur la base des résultats des études en cours. Les efforts futurs devraient conduire à offrir une plate-forme présentant une homogénéité dans le choix des seuils thérapeutiques dans l’ostéoporose.

Depuis 2006, le Comité des Médicaments à Usage Humain (Committee for Medicinal Products for Human Use, CHMP) révise les directives sur l’évaluation des médicaments dans le traitement de l’ostéoporose, en insistant dorénavant sur les patients à risque de fracture[45]. Les quelques analyses effectuées jusqu’à présent sur les études cliniques de phase 3 ont montré que les patients identifiés sur la base des facteurs de risque cliniques par l’utilitaire FRAX® pesaient de manière significative aux interventions pharmacologiques, même lorsque la DMO n’était pas utilisée pour caractériser les risques[46,47].

Tout cet intérêt renouvelé pour l’ostéoporose, en particulier par les généralistes, devrait s’avérer bénéfique pour ce domaine. Comme cela s’est produit pour les troubles cardiovasculaires, l’opportunité pour la communauté médicale d’utiliser un modèle simple permettant d’évaluer les risques mettra à jour de nouvelles possibilités d’intervention dans un domaine encore trop négligé par les gouvernements, les médecins ou les patients.

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Bone remodeling, a process by which bone resorption by osteoclasts is followed by bone formation by osteoblasts, is an essential physiological process regulating bone mass and strength. During growth, bone formation exceeds bone resorption, resulting in bone expansion. In the young adult, bone resorption is balanced by bone formation, resulting in maintenance of bone mass. The cellular mechanisms underlying the age-related alterations in bone resorption and formation are now better known. With aging, bone formation decreases due to reduction in osteoblast number, activity, and life span, whereas bone resorption increases as a result of sex hormone deprivation. These two mechanisms contribute to the decreased bone mass and increased risk of fractures seen in the aging population. Current effective antiresorbing drugs reduce bone remodeling in osteoporotic subjects. An ideal way to prevent age-related bone loss would be not only to reduce bone resorption, but also to promote bone formation. There is therefore an important need to develop therapeutic strategies capable of promoting bone formation in osteoporotic subjects. Current research efforts are focusing on strategies to target signaling pathways that positively control bone formation and bone mass. This may lead to the development of novel therapeutic approaches that promote osteoblastogenesis to counteract the defective bone formation and bone loss related to aging.

Osteoporosis: a disease of bone formation

by P. J. Marie, France

The skeleton is a unique tissue providing support and mineral balance for the organism. It is formed during growth and is maintained during adult life by continual renewal of the matrix, a process called bone remodeling. Bone remodeling is ensured by two cell types: osteoclasts, which resorb the calcified bone matrix, and osteoblasts, which are responsible for new bone matrix synthesis. During growth, bone formation exceeds bone resorption, resulting in bone expansion. In the young adult, bone resorption is balanced by bone formation, resulting in maintenance of bone mass. With aging and after the menopause, an imbalance in bone resorption relative to formation results in negative bone balance at the tissue level. This may lead to osteoporosis, a common skeletal disease characterized by reduced bone mass, deterioration of bone microarchitecture, and increased susceptibility to fractures. The causes of increased bone resorption relative to bone formation in women after the menopause are now better known (Figure 1). Estrogen deficiency in perimenopausal women (and to a lesser extent, the decline in testosterone levels in men) results in accelerated bone remodeling with bone resorption...
exceeding bone formation. This leads to an increased number of bone remodeling units, perforation of trabeculae, endocortical erosion (responsible for trabecular disconnection), alteration of trabecular microarchitecture, and reduced bone strength.\(^2,3\) Several mechanisms are involved in the acceleration of the bone remodeling occurring in estrogen deficiency, including increased cytokine production by monocytes, lymphocytes, and osteoblast/stromal cells in the bone microenvironment, as well as an increased receptor activated nuclear factor-\(\kappa\)B ligand (RANKL)/osteoprotegerin ratio that determines osteoclast differentiation.\(^2,3\)

Although the increased bone resorption activity associated with the menopause is related to increased bone formation due to the coupling phenomenon, bone formation remains insufficient to compensate for the increased bone resorbing activity (Figure 1). This is a key issue when considering the prevention and treatment of age-related bone loss, since once trabeculae are perforated, it is almost impossible to replace the missing trabeculae within the bone marrow and to rebuild appropriate connections with other trabeculae.

**Age-related defective bone formation**

Bone formation is a complex process involving the commitment of osteoprogenitor cells, their differentiation into preosteoblasts, and mature osteoblasts, whose function it is to synthesize bone matrix that becomes progressively mineralized.

Osteoblast commitment, differentiation, and function are all governed by several transcription factors, resulting in the expression of phenotypic genes and the acquisition of the osteoblast phenotype.\(^2\) The sequence of osteogenic differentiation is characterized by the expression of alkaline phosphatase and the synthesis and deposition of type I collagen and bone matrix proteins, followed by the onset of mineralization. At the end of bone formation, most osteoblasts become flattened lining cells, some become osteocytes, and others undergo apoptosis. A fraction of osteoblasts also die by apoptosis, a process that directly affects osteoblast life span and the duration of the bone formation phase.\(^5\) It has been established from animal models and human metabolic bone diseases that bone formation is more dependent on osteoblast number, which can be expanded, than on osteoblast activity, which is physiologically limited.\(^6\)

Aging is associated with decreased bone formation relative to bone resorption (Figure 1). There are two major causes that underlie the relative, age-related alteration in bone formation. As mentioned above, bone resorption increases as a result of hormone deprivation in the perimenopausal years. The coupling mechanism during bone remodeling results in increased bone formation, as reflected, for example, by the increase in bone remodeling markers occurring at menopause.\(^3\) However, the increased bone formation cannot compensate for the increased resorption, and this imbalance results in bone loss after menopause. Several mechanisms can be involved in the defective bone formation relative to bone resorption in estrogen deficiency. First, the osteoblast

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**Figure 1. Age-related alteration in bone mass.**

During growth, bone formation exceeds bone resorption, resulting in increased bone mass. In the young adult, bone resorption is balanced by bone formation, resulting in maintenance of bone mass. At menopause, bone remodeling increases with a relative imbalance in bone resorption versus formation, causing trabecular perforation and bone loss. Age-related trabecular thinning also contributes to deterioration of bone microarchitecture and bone deficit.
capacity of forming bone is limited, as evaluated by the mineral apposition rate, and this limited capacity to form bone matrix by osteoblasts is not increased in estrogen deficiency. Second, although the proliferative capacity of osteoblastic cells is increased by estrogen deficiency, most probably in response to the local release of growth factors from bone, this is not sufficient to compensate for the increase in bone resorption. A third mechanism underlying the relative lack of bone formation in estrogen deficiency is the alteration of osteoblast lifespan. Estrogens prevent osteoblast apoptosis, and estrogen deficiency results in increased osteoblast apoptosis that leads to a decrease in the duration of the bone formation phase. The decreased osteoblast life span does not allow bone to compensate for the increased bone resorbing activity of osteoclasts.

Age-related bone loss is associated with a second phenomenon, characterized by a slow, continuous decrease in bone forming activity, independent of sex hormone deficiency (Figure 1). This decreased bone forming activity that occurs with aging was first documented in humans as the decline in the amount of bone formed by osteoblasts in each remodeling unit. Although this slow decrease in bone matrix formed does not lead to perforation of trabeculae, the effect results in thinning of the bone trabeculae, increased trabecular separation, and decreased cortical thickness with age. This is an important and underestimated mechanism that contributes to the deterioration of bone microarchitecture and strength associated with fractures in osteoporotic subjects. ♦

**Cellular causes of age-related decrease in bone formation**

The development of appropriate therapeutic strategies in osteoporosis requires a better understanding of the mechanisms underlying defective bone formation occurring with aging and the menopause. Multiple mechanisms are believed to contribute to the age-related decline in bone formation (Figure 2). It is well known that mesenchymal stromal cells within the bone marrow are able to differentiate into osteoblasts or adipocytes under stimulation by hormonal or local factors, a process called cell plasticity. It has been found that the decreased osteoblastogenesis that occurs with aging may result from preferential differentiation of mesenchymal stromal cells into adipocytes, as a result of increased lipid oxidation causing oxidative stress and activation of the transcription factor peroxisome proliferator-activated receptor γ (PPAR-γ) that governs adipocyte differentiation. Pharmacological inactivation of PPAR-γ was consistently found to increase osteoblast differentiation and bone formation in mice.

A second mechanism that might contribute to defective bone formation with aging is a decrease in the preosteoblastic cell proliferative capacity. This decrease in cell proliferative capacity is likely to contribute to the age-related decline in osteoblast number in humans. Another important possible mechanism is the age-related intrinsic decrease in osteoblast function, possibly related to local decreases in the production of anabolic factors such as insulin-like growth factor 1 (IGF-1) or transforming growth factor β (TGF-β). Another like-
ly causative mechanism is the decreased maximal life span and accelerated senescence of bone marrow stromal cells with aging. This phenomenon may be linked to the age-related increase in oxidative stress in bone, or to the increased local cytokine production occurring in bone after the menopause. All these pathogenic mechanisms may concur to decrease osteoblast number and function and contribute to age-related decline in bone formation relative to bone resorption (Figure 2).

Besides these intrinsic causes, several exogenous factors may be involved in defective age-related osteostegogenesis. One well-known extrinsic factor that may alter osteoblast differentiation is the progressive decline in physical activity in aged subjects. Decreased mechanical strain is known to reduce osteogenic differentiation and to increase adipogenic differentiation of mesenchymal stromal cells, presumably by changes in the local production of growth factors and Wnt signaling. Thus, it is likely that the reduced physical activity that occurs with age reduces bone formation. Other important exogenous factors that may contribute to defective osteostegogenesis in the aging population include insufficient protein intake, excess alcohol and tobacco consumption, as well as medications, such as long-term glucocorticoid treatment. It is thus likely that the alterations in osteostegogenesis and the resulting decline in bone formation that occurs with aging result from multiple intrinsic and extrinsic causes.

**Promoting bone formation: an enduring therapeutic challenge in osteoporosis**

Given the fact that estrogen deficiency results in excessive bone resorption relative to bone formation, pharmacological compounds that decrease bone resorption are efficient at treating osteoporosis. Bisphosphonates are known to act by reducing bone remodeling (both resorption and formation), which leads to the prevention of bone loss and to a reduction in fracture incidence in osteoporosis. Denosumab, a fully human monoclonal antibody to RANKL that blocks its binding to receptor activated nuclear factor-κB and hence osteoclast differentiation, was recently shown to strongly reduce the risk of fractures in women with osteoporosis. Although efficient at decreasing bone remodeling activity, the long-term effects of bisphosphonates or denosumab on bone properties remain unknown.

Since age-related bone loss is associated with insufficient bone formation relative to bone resorption, a major advance in the therapeutic field would be to promote bone formation while reducing bone resorption. In this context, strontium ranelate was found to act by dissociating bone resorption and bone formation in vitro. A number of studies have shown that strontium ranelate activates osteoblast replication, differentiation, activity, and survival and reduces osteoclast function and survival. Accordingly, this drug was found to increase the mineral apposition rate, to improve trabecular microarchitecture, and to reduce fracture risk in osteoporotic subjects. This compound thus offers an ideal way of favoring bone formation without increasing bone resorption in age-related bone loss.

An enduring challenge in the prevention or treatment of age-related bone loss is whether one should prevent or protect the age-related decrease in bone formation. Up to now, the number of anabolic agents that promote osteostegogenesis has been very limited. Nature has provided us with some physiological tools to promote bone formation. For example, bone morphogenetic proteins (BMPs) are natural anabolic molecules that physiologically promote osteoblast differentiation in vitro and in vivo. However, BMPs can only be used as therapeutic agents for local bone repair because of their short half-life and possible side effects on nonskeletal stem cell development. Other natural skeletal growth factors such as IGF-1 or TGF-β have been shown to promote bone formation and reduce bone loss in experimental models of osteoporosis. However, these growth factors cannot be used easily in clinics because of their possible modulation of bone resorption as well as side effects. Two decades ago, fluoride, a mitogenic agent for osteoblastic cells, was tested in osteoporosis. Unfortunately, although fluoride is effective in increasing osteoblast replication in osteoporosis, osteoblast function is altered with fluoride treatment, which failed to improve bone strength. Finally, some statins have been shown to promote bone formation in experimental studies in animals. However, there is still no evidence for a clear anabolic effect on bone for these agents in humans.

A major step forward was the finding that, in contrast to continuous treatment, intermittent parathyroid hormone (PTH) increases bone formation in osteoporotic patients. At the cellular level, PTH acts on osteoblasts by activating protein kinase A (PKA), which phosphorylates the osteoblast transcription factor Runx2, which in turn upregulates the expression of osteoblast genes. Additionally, intermittent PTH activates extracellular signal-regulated kinase 1/2 (ERK1/2), mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase signaling, which upregulate osteoblast proliferation, differentiation, and survival (Figure 3, page 14). Furthermore, IGF-1, TGF-β, and fibroblast growth factor expression is upregulated by intermittent PTH, resulting in increased osteogenesis. All these mechanisms contribute to increase the recruitment of osteoblast progenitors and to decrease osteoblast apoptosis, resulting in increased bone formation relative to bone resorption.

At the tissue level, the increased bone formation induced by PTH (1-34) or (1-84) results in increased trabecular bone mass and cortical thickness, leading to a marked reduction in fracture risk in osteoporotic patients. This finding emphasizes the point that anabolic treatments may be more effective than antiresorbing drugs in the maintenance of bone.
Therapeutic perspectives in promoting bone formation

As emphasized above, there is still a need to develop efficient and safe drugs that are able to promote bone formation in osteoporosis. One possibility is to target the Wnt/β-catenin signaling pathway that was found to upregulate osteoblastogenesis.

Figure 3. Main signaling pathways involved in the anabolic effect of PTH on bone. PTH binding to its receptor activates PKA, PKC, and PI3K/Akt resulting in increased osteoblast proliferation, differentiation, and survival.

Abbreviations: cAMP, cyclic adenosine monophosphate; ERK, extracellular signal-regulated kinase; Gi, Gs, and Gq/G11, heterotrimeric G protein subunits; MAPK, mitogen-activated protein kinase; P38 MAP kinase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PTH, parathyroid hormone; Src, Src gene (proto-oncogenic tyrosine kinase family).

Figure 4. The canonical Wnt signaling pathway and control of bone formation. Binding of Wnt proteins to coreceptors LRP-5/6 and Frizzled leads to the recruitment of multiple proteins and GSK-3 phosphorylation, resulting in β-catenin accumulation and translocation into the nucleus, where it activates TCF/LEF transcription factors and osteoblast replication, differentiation, and survival. Based on this mechanism, targeting β-catenin using pharmacological GSK-3 inhibitors results in activation of bone formation.

Abbreviations: Axin, axin gene; Dkk1, Dickkopf homolog 1 (Xenopus laevis) gene; Frat-1, frequently rearranged in advanced T-cell lymphomas 1 (gene); GSK-3, glycogen synthase kinase 3; LRP-5/6, low-density lipoprotein receptor–related protein 5/6; P, phosphate; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor transcription factors; Wnt, Wnt signaling pathway; osteosis, postnatal bone formation, and bone mass in animals and humans. How does Wnt signaling control bone formation? It was found that activation of the canonical Wnt/β-catenin pathway promotes osteoblastic cell proliferation and differentiation and reduces adipogenic differentiation from mesenchymal stromal cells through modulation of Runx2 and PPAR-γ2. Additionally, Wnt signaling promotes osteoblast survival (Figure 4). These effects, in addition to existing crosstalks between Wnt, BMP-2, and PTH signaling, contribute to the positive effects of Wnt signaling on osteoblastogenesis and bone mass. Interestingly, mechanical loading upregulates Wnt signaling and prevents adipogenic differentiation in mesenchymal stem cells. Moreover, attenuation of Wnt/β-catenin signaling contributes to age-related bone loss in mice, suggesting that the combination of reduced β-catenin signaling and mechanical stimulation may be involved in age-related decline of bone formation in humans.
Recent data have challenged the role of low-density lipoprotein receptor–related protein 5 (LRP-5) in the control of bone formation. Yadav et al. showed that LRP-5 may not play a major role in osteoblast function, but rather that bone mass is regulated by a β-catenin- and Wnt-independent effect of LRP-5 deletion on serotonin secretion from the gut. If confirmed, this discovery may lead to novel therapeutic approaches aimed at antagonizing serotonin synthesis in the gut and/or serotonin action on osteoblasts. Nevertheless, the fact remains that Wnt signaling in the bone microenvironment is likely to play a role in the control of bone mass. The important role of Wnt signaling in the control of bone mass suggests that this pathway may be a potential therapeutic target in osteoporosis. According to this concept, activation of canonical Wnt signaling using glycogen synthase kinase 3 inhibitors were shown to promote bone formation and to prevent bone loss in aged or ovariectomized osteopenic mice. However, the therapeutic use of Wnt signaling agonists in clinical settings is limited due to the potential activation of cancer cells. Future research is needed to determine whether pharmacological inhibition of natural antagonists of Wnt signaling, such as Frizzled or Dkk1, results in safe activation of Wnt signaling in bone. Alternatively, noncanonical Wnt signaling, which has been shown to promote bone formation, may be another target for developing new anabolic therapeutic approaches in osteopenic disorders.

Recent studies have opened a new area of translational research based on the clinical observation that the loss of function of sclerostin, the product of the SOST gene, results in increased bone mass. Sclerostin is produced by osteocytes and is a potent inhibitor of bone formation. It does this by antagonizing LRP-5 receptor signaling, Wnt signaling, and bone formation (Figure 5). Interestingly, sclerostin expression is negatively regulated by loading and PTH, suggesting that it may be a physiological modulator of bone formation. These findings led to the exciting concept that targeting sclerostin may lead to increased bone formation and bone mass in vivo. Indeed, targeted deletion of the sclerostin gene results in increased bone formation and bone strength in mice. More interestingly, a sclerostin antibody treatment was shown to increase bone formation, bone mass, and bone strength in a rat model of postmenopausal osteoporosis. This raises the hope that this novel therapeutic strategy may result in increased bone formation and bone mass in age-related osteopenic disorders.

**Figure 5. Mode of action of sclerostin on osteoblastogenesis.**

(A) Sclerostin, the product of the SOST gene expressed by osteocytes, is a physiological regulator of bone formation that is negatively regulated by loading and PTH. Sclerostin acts by blocking Wnt binding to LRP-5, thereby inhibiting Wnt signaling, which results in decreased osteoblast differentiation and survival and altered bone formation.

(B) Given that sclerostin inhibits bone formation, targeting sclerostin using a sclerostin antibody results in increased bone formation and bone mass.

**Abbreviations:** Wnt, Wnt signaling pathway; PTH, parathyroid hormone; LRP-5, low-density lipoprotein receptor–related protein 5; SOST, sclerostin gene.

**Conclusion and perspectives**

The available data indicate that aging is associated with impaired bone formation relative to bone resorption, indicating that osteoporosis is (also) a disease of bone formation. This has important implications for developing novel, efficient, anabolic therapeutic strategies in age-related bone loss.

Up to now, a limited number of molecules, including teriparatide and, to a lesser extent, strontium ranelate, have been shown to activate bone formation in clinical studies. Ongoing investigations are currently focused on targeting the Wnt signaling pathway that governs osteoblastogenesis and bone formation. It is hoped that this approach will lead to the development of safe anabolic agents that are able to promote bone formation in age-related osteopenic disorders.
References

27. Baron R. Wnt signaling, LRPs and gut serotonin: have we been targeting the right pathway for the wrong reasons? J Int Soc BoneRes. 2009;6:86-93.
L’OSTÉOPOROSE : UNE MALADIE DE LA FORMATION OSSEUSE

Le remodelage osseux, processus par lequel la résorption osseuse par des ostéoclastes est suivie d’une formation osseuse par des ostéoblastes, est un processus physiologique essentiel de régulation de la masse osseuse et de la qualité de la matrice osseuse. Pendant la croissance, la formation osseuse est supérieure à la résorption, permettant la croissance de l’os. Chez l’adulte jeune, la résorption osseuse est équilibrée par la formation osseuse et la masse osseuse se maintient. Chez l’adulte âgé, la résorption osseuse est supérieure à la formation, entraînant une perte osseuse. On connaît mieux maintenant les mécanismes cellulaires qui sous-tendent les changements liés à l’âge dans la résorption et la formation osseuses. Avec l’âge, la réduction du nombre, de l’activité et de la durée de vie des ostéoblastes entraîne une diminution de la formation osseuse alors que la chute des hormones sexuelles entraîne une augmentation de la résorption osseuse. Ces deux mécanismes participent à la diminution de la masse osseuse et à l’augmentation du risque de fractures dans la population âgée. Les traitements actuels efficaces diminuent le remodelage osseux chez les patientes ostéoporotiques. Cependant, une voie idéale de prévention de la perte osseuse serait non seulement de réduire la résorption osseuse mais aussi de favoriser la formation osseuse. Il est donc nécessaire de développer des stratégies thérapeutiques capables de favoriser la formation osseuse chez les sujets ostéoporotiques. Les efforts de recherche actuels se concentrent sur des stratégies ciblant les voies de signalisation qui contrôlent positivement la formation osseuse, ce qui pourrait aboutir à de nouvelles approches thérapeutiques destinées à favoriser l’ostéoblastogenèse pour contrerbalancer le défaut de formation osseuse et la perte osseuse liée à l’âge.
Long-term antifracture efficacy and safety of antiosteoporotic treatments: the hidden part of the iceberg

by J. B. Díaz-López and J. B. Cannata-Andía, Spain

Long-term antifracture efficacy and safety are the two major goals of any antiosteoporotic treatment. To date, several drugs have proved to be effective and safe during the 2-to-3-year period of a controlled clinical trial, but only a few of them have shown bone protection lasting up to 5 years, which is the minimum time period needed in order to ascertain if there is sustained fracture risk reduction. Raloxifene has shown efficacy in vertebral fracture risk reduction for up to 5 years, but no effect in nonvertebral fracture. The antifracture efficacy of risedronate versus placebo over 5 years has not been proven. Furthermore, although the bone mineral density (BMD) of women on alendronate increases up to 7 and 10 years, this increase is not associated with antifracture efficacy, especially in nonvertebral fractures. In contrast, strontium ranelate has demonstrated sustained fracture risk reduction up to 5 years in vertebral, nonvertebral, and hip fractures in double-blind, randomized, placebo-controlled trials. In addition, a complementary analysis of 8 years’ treatment has shown the same trend in vertebral and nonvertebral fracture risk reduction. In summary, several drugs have demonstrated long-term benefit on BMD, but only strontium ranelate has proven to be efficient on vertebral, nonvertebral, and hip fractures in the long term.

After beginning therapy, clinicians must confront the question of how long therapy should continue for and how we should evaluate its efficacy and safety. Unless there are obvious safety issues, long-term therapy is generally considered for chronic disorders such as osteoporosis; however, how many years “long-term” means has not yet been clearly defined. The second issue is how efficacy and safety should be evaluated. For both considerations, well-designed, randomized controlled trials are the answer. When compared with placebo, fractures determine efficacy outcomes, whereas a negative increment in morbidity defines safety outcomes. Postmarketing surveillance is also valid for safety.

Because of possible safety issues, long-term estrogen replacement therapy is not currently recommended for the management of postmenopausal osteoporosis, even though it has been demonstrated that estrogen therapy helps to prevent fractures. The optimal length of use of the other current medications for osteoporosis remains to be established. With respect to trials, a panel of experts representing the American Society for Bone and Mineral Research (ASBMR), the International Society for Clinical Densitometry (ISCD), and the National Osteoporosis Foundation...
(NOF)\(^2\) have provided an answer as to how many years the efficacy and safety an antosteoporotic agent should be evaluated for. They reached a consensus that trials should last at least 18 to 24 months to test efficacy with fracture end points, and 5 years to properly test safety and to demonstrate sustained fracture reduction.\(^3\)

Nowadays, many drugs have proven to be effective in reducing new osteoporotic fractures in postmenopausal women\(^3\)–\(^6\) (Table I). Most of these major clinical trials lasted no more than 3 years. In addition, in some of them (such as the calcitonin trial), only 46% of the initial participants completed the pre-programmed five-year follow-up; as a result, the grade of evidence was lower and just concerned the 200 IU nasal spray dose, but not the 100 IU and 400 IU sprays.\(^12\) Hence, any assumptions about long-term treatments based on the findings of any type of study, even with 3 years’ follow-up, should be made with great caution and by analyzing the strength of the evidence. Moreover, despite the fact that nonvertebral fractures are more prevalent and present a substantial burden for the patient, most of the osteoporosis treatments that have proven efficacy in reducing the risk of vertebral fracture have not shown reductions in nonvertebral fracture risk (Table I). Furthermore, information on the clinical efficacy and safety of several active antosteoporosis treatments at more than 4 to 5 years follow-up is limited. Currently, for a 5-year time period, the only treatment to have demonstrated its anti-fracture efficacy in a double-blind, randomized, placebo-controlled trial is strontium ranelate. However, information on bone mineral density (BMD) is also available with raloxifene, alendronate, and risedronate, but with different strengths of evidence as described below and summarized in Tables II and III (page 20).

**Table I.** Pivotal trials for osteoporotic fracture risk reduction in postmenopausal women.

<table>
<thead>
<tr>
<th>Drug/trials</th>
<th>Follow-up</th>
<th>Fracture risk reduction (vertebral / nonvertebral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate*</td>
<td>0-3 years</td>
<td>YES / YES</td>
</tr>
<tr>
<td>Liberman(^1)</td>
<td>0-3 years</td>
<td>Yes / -</td>
</tr>
<tr>
<td>FIT VF(^2)</td>
<td>0-3 years</td>
<td>Yes / -</td>
</tr>
<tr>
<td>FIT without VF(^2)</td>
<td>0-4 years</td>
<td>Yes / -</td>
</tr>
<tr>
<td>Risedronate*</td>
<td>0-3 years</td>
<td>YES / YES</td>
</tr>
<tr>
<td>VERT MN(^6)</td>
<td>0-3 years</td>
<td>Yes / -</td>
</tr>
<tr>
<td>VERT NA*</td>
<td>0-3 years</td>
<td>Yes / Yes</td>
</tr>
<tr>
<td>HIP(^3)</td>
<td>0-3 years</td>
<td>- / Yes</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>0-3 years</td>
<td>YES / -</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>0-3 years</td>
<td>YES / YES</td>
</tr>
<tr>
<td>HORIZON(^9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>0-3 years</td>
<td>YES / -</td>
</tr>
<tr>
<td>MORE(^3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitonin</td>
<td>0-5 years(^\dagger)</td>
<td>YES(^\ddagger) / -</td>
</tr>
<tr>
<td>PROOF(^12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strontium ranelate*</td>
<td>0-3 years</td>
<td>YES / YES</td>
</tr>
<tr>
<td>SOTI(^3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TROPOS((^14)</td>
<td>0-3 years</td>
<td>Yes / Yes</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>21 months</td>
<td>YES / YES</td>
</tr>
<tr>
<td>1-84 Parathyroid hormone</td>
<td>18 months</td>
<td>YES / -</td>
</tr>
<tr>
<td>TOP((^16)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Efficacy observed by meta-analysis of the major clinical trials. 
\(^\dagger\)Nearly significant. 
\(^\ddagger\)High rate of drop-out. 
\(^\ddagger\)Lower level of evidence and only with 200 IU.

**Table II**. Long-term antifracture efficacy and antiosteoporotic treatment safety – Díaz-Álvarez and Cunnata-Andía

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASBMR</td>
<td>American Society for Bone and Mineral Research</td>
</tr>
<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>BTM</td>
<td>bone turnover marker</td>
</tr>
<tr>
<td>DRESS</td>
<td>Drug Rash with Eosinophilia and Systemic Symptoms</td>
</tr>
<tr>
<td>FIT</td>
<td>Fracture Intervention Trial</td>
</tr>
<tr>
<td>FLEX</td>
<td>Fracture intervention trial Long-term EXTension</td>
</tr>
<tr>
<td>GP RD</td>
<td>General Practice Research Database</td>
</tr>
<tr>
<td>HORIZON</td>
<td>Health Outcomes and Reduced Incidence with Zoledronic Acid ONce yearly</td>
</tr>
<tr>
<td>ISCD</td>
<td>International Society for Clinical Densitometry</td>
</tr>
<tr>
<td>MO RE</td>
<td>Multiple Outcomes of Raloxifene Evaluation; PROOF; Prevent Recurrence Of Osteoporotic Fracture; SOTI; Spinal Osteoporosis Therapeutic Intervention; TROPOS; TREATMENT Of Peripheral OSTEoporosis; TOP; Treatment of Osteoporosis with Parathyroid hormone; VERT MN; Vertebral Efficacy with Risedronate Therapy (Multinational); VERT NA; Vertebral Efficacy with Risedronate Therapy (North America).</td>
</tr>
</tbody>
</table>

**Raloxifene**

Studies of raloxifene have shown a vertebral fracture risk reduction after 4 years similar to that after 3 years, and it has also shown benefit at 5 years in postmenopausal women not selected on the basis of osteoporosis or increased fracture risk.\(^17,18\) However, this latest study is different to the others as the incidence of vertebral fracture in the placebo group was very low (1.9% over 5 years), reflecting a low risk of fracture in the population included in the study, and thus difficulties in extrapolating these results to other studies in osteoporotic patients. Similar to what was shown in the pivotal trial, raloxifene had no effect on nonvertebral fracture risk after 5 and 8 years.\(^18,15\) In addition, the absence of effect of raloxifene on nonvertebral fracture was consistent across different subgroups, characterized by the presence or absence of risk fac-
tors at baseline (including a summary of nonvertebral fracture risk score). The effect on BMD observed after 3 and 4 years persisted when the drug was administered for 8 years. However, as was seen with estrogen replacement therapy, a sharp drop in BMD occurred upon raloxifene discontinuation. The long-term safety profile is also similar to that observed in the first 3 years, with an increase in the risk of deep vein thrombosis and a significant decrease in the incidence of invasive estrogen receptor–positive breast cancer. In contrast to the findings relating to estrogen replacement therapy, no evidence of coronary or cerebrovascular events has been found in postmenopausal osteoporotic women at relatively low risk of cardiovascular events.

**Bisphosphonates**

Long-term bone protection provided by alendronate and risedronate has been examined in a series of extensions of previously reported pivotal clinical trials. These trials included a limited number of patients and did not assess antifracture efficacy versus a placebo group. For instance, the long-term efficacy of risedronate was estimated by comparing the cumulative incidence of fractures during the last 2 years and the first 2 years of treatment in patients treated with risedronate for 7 years. The analysis was performed in 68 patients treated over 7 years with risedronate. Despite a similar incidence, the comparison limits a definitive conclusion on the long-term efficacy of risedronate. A similar approach to assess the efficacy of alendronate against fractures was used after 4 and 5 years in the Fracture intervention trial Long-term EXTension (FLEX) study. In the latter, the long-term effect of alendronate on BMD in patients treated first over 5 years with alendronate and then either switched to placebo or continued alendronate treatment was assessed. In absence of a “real” placebo group, any strong conclusion regarding the antifracture efficacy of alendronate in the long term is not possible. In fact, fractures were recorded as an “exploratory” outcome in the study. The results mentioned allow discussion on the possible long-term efficacy on vertebral fractures, but the efficacy on nonvertebral fractures is still missing.

### Table II. Studies and patient characteristics of placebo-controlled trials of osteoporotic fracture risk lasting at least 5 years.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Brief study description</th>
<th>Mean age (years)</th>
<th>Prior vertebral fracture (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene</td>
<td>Postmenopausal women (n=10101) with CHD* or multiple risk factors for CHD. Raloxifene 60 mg/d. Fractures as secondary outcome. Mean follow-up time 5.6 years.</td>
<td>67.5 – 67.5</td>
<td>Not determined</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Extension study from year 3 to year 5 in postmenopausal women (n=265) with established osteoporosis (1/3 of VERT study), 220 women completed the additional 2 years with risedronate 5 mg/d.</td>
<td>72.6 – 72.4</td>
<td>100</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Extension study in postmenopausal women (n=1099) (1/3 of FIT study), with a mean of 5 years prior alendronate treatment, randomized to placebo, alendronate 5 mg/d or 10 mg/d for 5 years.</td>
<td>73.7 – 72.8</td>
<td>34</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>Postmenopausal women (n=2714), 57% completed five years of the randomized TROPOS study with strontium ranelate 2 g/d.</td>
<td>76.8 – 76.7</td>
<td>33.6</td>
</tr>
</tbody>
</table>

### Table III. Vertebral and nonvertebral fracture incidence by treatment (trials described in Table II).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Type of fracture</th>
<th>Incidence (%)</th>
<th>Treatment effect RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo-treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Clinical vertebral fracture</td>
<td>1.9–1.3</td>
<td>0.65 (0.47–0.89) NS</td>
</tr>
<tr>
<td></td>
<td>Nonvertebral fracture</td>
<td>8.7–8.5</td>
<td>0.96 (0.84–1.10) NS</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Vertebral fracture</td>
<td>28.2–13.8</td>
<td>0.41 (0.21–0.81) NS</td>
</tr>
<tr>
<td></td>
<td>Nonvertebral fracture</td>
<td>8.5–5.2</td>
<td>0.59 (0.22–1.57) NS</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Clinical vertebral fracture</td>
<td>5.3–2.4</td>
<td>0.45 (0.24–0.85) NS</td>
</tr>
<tr>
<td></td>
<td>Nonvertebral fracture</td>
<td>19.0–18.9</td>
<td>1.00 (0.76–1.32) NS</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>Vertebral fracture</td>
<td>24.9–20.8</td>
<td>0.76 (0.65–0.88) NS</td>
</tr>
<tr>
<td></td>
<td>Nonvertebral fracture</td>
<td>20.9–18.6</td>
<td>0.85 (0.73–0.99) NS</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NS, nonsignificant; RR, relative risk.
With regard to bone mass, alendronate and risedronate maintained BMD gains for 10 and 7 years, respectively. Cumulative increases in BMD at the hip and spine and reductions in bone turnover markers (BTMs) were greater for women who kept receiving these aminobisphosphonates compared with those who discontinued it. However, in women who discontinued alendronate or risedronate who then subsequently received placebo in the extension studies, BMD remained high and BTM reduction was greater than values at baseline.

Overall, alendronate and risedronate were well tolerated during the 10 and 7 years of the extension studies. No new safety concerns were observed during the extension studies of alendronate and risedronate when compared with safety observations gathered during the first 3 years of the pivotal studies. Nevertheless, there is growing concern that long-term suppression of bone turnover with bisphosphonates may eventually lead to an accumulation of fatigue-induced damage and that it may be associated with a new form of insufficiency fracture of the femur.

In the last few years, there have been reports about the association between subtrochanteric and diaphyseal femur fractures and long-term alendronate treatment. However, we would advise caution. According to national observational register-based studies and recent case control studies, further trials are necessary to fully understand the pathophysiology of this side effect. The same comment is valid for osteonecrosis of the jaw — another potential side effect related to bisphosphonates — that was first reported following the administration of very high intravenous doses of aminobisphosphonates in cancer patients.

The report describing a significant increase in the risk of serious atrial fibrillation associated with once-yearly infusions of intravenous zoledronic acid in the Health Outcomes and Reduced Incidence with Zoledronic Acid ONce yearly (HORIZON) trial prompted an investigation into the possibility of increased atrial fibrillation risk with other bisphosphonates used to treat osteoporosis in postmenopausal women. The first report reviewing the Fracture Intervention Trial (FIT) did show a trend towards an increased risk of serious adverse events with alendronate that resembled the pattern observed in the HORIZON study, but there was no increase in atrial fibrillation. A later population-based case control study showed that the use of alendronate was never associated with an increased risk of incident atrial fibrillation in clinical practice.

As one of the features of bisphosphonates is a long residual time in bone and concerns about this have emerged, the concept of “drug holidays” has been coined for this kind of drug. Drug holiday time varies depending on the type of aminobisphosphonate. With alendronate, which appears to have a longer skeletal retention time than risedronate, the drug holiday period could be longer (up to 5 years), especially for women who were compliant for prolonged periods of time. Although we need more data before issuing any definitive recommendations regarding the optimal length of drug holiday for alendronate and risedronate, such strategies deserve consideration, especially if we take into account the recently reported side effects associated with long-term alendronate treatment.

**Strontium ranelate**

The antifracture efficacy of strontium ranelate has been documented across a wide range of patient profiles, including osteopenia and in very elderly women. Besides this, the reduction in fractures came together with a significant improvement in quality of life and an increase in the number of patients free of back pain.

Recently, the extension of up to 8 years of follow-up of the previous pivotal studies was presented (Figure 1, page 22). The efficacy of strontium ranelate in preventing fractures was analyzed by comparing the annual cumulative fracture incidence between the first and the last 3 years of the 8-year follow-up. The long-term results demonstrated that strontium ranelate maintains its antifracture efficacy with incidences of vertebral fractures (13.7%) and nonvertebral fractures (12.0%) after 8 years of treatment that were not significantly different to those obtained after 3 years of treatment (11.5% and 9.6%, respectively). The reduction in fracture risk was associated with a progressive BMD increase in the lumbar spine and over 6 years at the femoral neck.
incidence of venous thromboembolism (0.9% vs 0.6%) was observed at 3 years, and this remained unchanged from the third year on without any known underlying potential mechanism. A recent analysis of the General Practice Research Database (GPRD) database in the UK showed no difference in the incidence of venous thromboembolism events between patients treated with strontium ranelate and untreated patients. Furthermore, the incidence of thromboembolism events in the same study were similar in patients treated with strontium ranelate or alendronate, a treatment not known to increase this kind of risk. During postmarketing surveillance, very rare cases of hypersensitivity syndrome or DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) have been reported. The clinical manifestations typically occur within 2 to 6 weeks after initiating therapy and, in most cases, resolve upon discontinuation. This syndrome has been very rarely reported (1 case per 73,000 patient years). Nevertheless, due to the potentially fatal outcome linked to this syndrome, treatment should be discontinued immediately and permanently in case of skin rash, and medical follow-up should be initiated.

Summary
To date, many pharmacological agents having demonstrated their efficacy in decreasing fracture risk over 3 years, even though not all of them have demonstrated their efficacy in preventing nonvertebral fractures. In most other diseases, the equivalence of acute and chronic treatment is implicit; osteoporosis is, however, a rare example of a chronic disease in which controlled studies have been extended up to 10 years. Several studies have investigated the efficacy of these drugs, but their conclusions are limited by the designs of the studies and the low number of patients generally included. Alendronate or risedronate have demonstrated their efficacy on BMD in the long term, but only sparse data are available regarding their long-term efficacy on vertebral fractures and there is no strong data regarding nonvertebral fractures. At present, strontium ranelate is the only treatment to have proved its long-term efficacy in vertebral, nonvertebral, and hip fractures using the most rigorous approach. This long-term efficacy coupled with its wide spectrum of efficacy allows the use of strontium ranelate as a first-line intervention for the long-term treatment of postmenopausal women with osteoporosis.

Finally, two important practical remarks. Firstly, all the controlled studies with active antosteoporotic agents included supplementation with calcium and vitamin D; thus, adequate nutrition and optimal vitamin D dosage always seem to be necessary to maximize the response of all antosteoporotic drugs. Secondly, another crucial aspect to be borne in mind for any long-term treatment is adherence to the prescribed intervention.

In the context of clinical trials, the safety of strontium ranelate was good. The most common adverse events related to strontium ranelate were transient nausea and diarrhea during the first 3 months. A slight increase in the annual incidence of venous thromboembolism (0.9% vs 0.6%) was observed at 3 years, and this remained unchanged from the third year on without any known underlying potential mechanism. After treatment withdrawal, patients in SOTI who switched to placebo at 4 years experienced a progressive reduction in BMD, by 3.2% and 2.5% at lumbar spine and hip, respectively, reflecting the prompt clearance of strontium ranelate. According to the dual mode of action of the drug, a significant decrease in bone alkaline phosphatase and increase in the serum C-telopeptide cross-link of type 1 collagen was observed after treatment withdrawal. These changes were already detectable 3 months after treatment discontinuation, suggesting a relatively rapid release of strontium from bone.

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**Figure 1.** Reduction in the risk of vertebral, nonvertebral, and any osteoporotic fracture with strontium ranelate after 8 years of follow-up. Modified from reference 43: Reginster JY, Bruyere O, Sawicki A, et al. Bone. 2009;45:1059-1064. Copyright © 2009, Elsevier Inc.
Keywords: osteoporosis; fragility fractures; antiosteoporotic drugs; sustained antifracture efficacy
Efficacité et sécurité antifracturaires à long terme des traitements antiostéoporotiques : La partie immergée de l’iceberg

L’objectif principal de tous les traitements antiostéoporotiques est l’efficacité et la sécurité antifracturaires à long terme. Des études cliniques contrôlées de 2 à 3 ans ont à ce jour permis d’établir l’efficacité et la sécurité de plusieurs médicaments, mais seuls quelques-uns d’entre eux ont démontré une protection osseuse à 5 ans, durée minimale nécessaire pour affirmer une réduction prolongée du risque fracturaire. Le raloxifène a montré une réduction du risque des fractures vertébrales à 5 ans, mais pas des fractures non vertébrales. L’efficacité antifracturaire du risédronate versus placebo à 5 ans n’a pas été prouvée. Par ailleurs, si la densité minérale osseuse (DMO) des femmes sous alendronate augmente pendant 7 à 10 ans, mais cette augmentation ne s’associe pas à une efficacité antifracturaire, en particulier touchant les fractures non vertébrales. À l’inverse, au cours d’études en double aveugle, randomisées et contrôlées contre placebo, le ranélate de strontium a démontré une réduction du risque fracturaire prolongée à 5 ans pour les fractures vertébrales, non vertébrales et de la hanche. De plus, une analyse complémentaire à 8 ans a démontré la même tendance pour la réduction du risque des fractures vertébrales et non vertébrales. En résumé, plusieurs médicaments présentent des bénéfices à long terme sur la DMO, mais seul le ranélate de strontium est efficace à long terme sur les fractures vertébrales, non vertébrales et de la hanche.
Osteoporotic fragility fractures are associated with increased morbidity and mortality and are increasing in prevalence. Anti-osteoporotic treatments consisting of different classes of drugs and modes of delivery have broadly similar antifracture efficacy, but their benefit is hampered by nonadherence. Up to half of patients stop their treatment by the end of year one and are denied the optimal treatment benefit. The causes of nonadherence can be classified as factors relating to the medication, the patients themselves, or the doctor-patient relationship. The most common cause of nonadherence is real or perceived adverse effects caused by the medication. Although randomized trials do not show major problems, the apparent increase in adverse effects may be due to incorrect dosage administration or merely contemporaneous background incidence rates. In deciding the best treatment choice for the patient, careful consideration should be made of tolerability profiles, ease of administration, and the risk-benefit profile of the treatment. The patient’s own beliefs about osteoporosis and its treatment should be met with empathy and a frank discussion of the best clinical evidence available. Active patient involvement in their disease is to be encouraged in order to enable patient empowerment and better adherence. Finally, a good doctor-patient relationship aids all the factors discussed.

Medicographia. 2010;32:25-32 (see French abstract on page 32)

Osteoporosis affects 75 million individuals in Europe, the US, and Japan. Globally, the annual incidence of new osteoporotic fractures is estimated at 9 million, of which 1.6 million are hip fractures. The attendant morbidity and mortality pose a significant problem for any health-care economy. In Europe, osteoporosis causes more disability than rheumatoid arthritis, asthma, migraine, and all cancers, except for lung cancer. With a rising elderly population, osteoporosis is fast becoming a considerable public health disease with a significant personal and economic burden.

Over the last two decades, effective anti-osteoporotic treatments have been shown to reduce the risk of fractures by at least 30% to 50%. Early therapeutic or lifestyle interventions can now reliably be offered to individuals early in the course of their disease, with the help of the recent FRAX® assessment tool, which incorporates clinical risk factors in combination with bone mineral density (BMD) to predict absolute fracture risk. However, despite these improvements, actual fracture risk reduction may fall short of expectations due to nonadherence with treatment.
Nonadherence—prevalence and impact on fracture risk

In common with other chronic diseases, osteoporosis suffers from nonadherence.6,7 The majority of patients stop taking their antiosteoporotic treatment within the first 3 months; thereafter, adherence gradually falls to a rate of 44% to 65% at 1 year (Figure 1).8-10 At 2 years, just over a quarter of patients remain highly compliant, as defined by a means possession ratio (MPR) of over 80%. Since adherence rates in trials are typically above this level, only around a quarter of patients will realistically achieve the antifracture efficacy published in these initial trials. In these randomized control trials (RCTs), high adherence was possible by selecting motivated participants, giving frequent reminders of medication instructions and use, and by frequent contacts with health providers: conditions rarely encountered in practice. Large observational studies from the US and UK have shown that no benefit is observed with poor adherence rates of 50% or less.11,12 Above this rate, benefit gradually increases with compliance, reaching statistical significance at rates above 75% (Figure 2). Nonadherence is associated with an increase in fracture risk (21%) compared with the high-adherence group.13 The basis of these poorer outcomes has been shown to be due to less reduction in bone resorption13 and poorer gains in BMD.14

Reasons for nonadherence of antiosteoporotic treatments

There are many reasons why patients stop their medication (Table I). Clearly, it is challenging to address them preemptively in the initial consultation, but by encouraging greater patient involvement in their treatment plan, adherence can be improved and the patient will be more inclined to openly discuss some of these issues in subsequent meetings. Qualitative observational studies have identified several factors contributing to treatment nonadherence that are categorized into medication-related factors, patient factors, and factors related to the doctor-patient relationship.3,15 The most common reason by far is, however, medication-related factors, specifically side effects.

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**Table I. Reasons for nonadherence (Table I).**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Medication-related</td>
<td>Side effects, drug interactions, drug efficacy, cost</td>
</tr>
<tr>
<td>Patient factors</td>
<td>Perceived drug unpleasantness, patient beliefs, other medications</td>
</tr>
<tr>
<td>Doctor-patient</td>
<td>Communication, discontinuation of trial, expectations</td>
</tr>
</tbody>
</table>

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**Figure 1.** Cumulative compliance rate over a 5-year follow-up. Compliance is measured by means possession ratio, which is defined as the duration of prescription refills that covers up to the period of follow-up of interest. Red line = mean compliance level; gray lines = first and third quartiles. Modified from reference 10: Huybrechts KF, Ishak KJ, Caro JJ. Bone. 2006;38:922-928. Copyright © 2006, Elsevier Inc.

**Figure 2.** Relative risk of osteoporotic fractures as a function of compliance rate. The solid line represents the linear regression relationship across different levels of compliance from about 30% to 100%. Modified from reference 12: Gallagher AM, Pietrbrrok S, Olsson M, van Staa TP. J Bone Miner Res. 2008;23:1569-1575. Copyright © 2008 American Society for Bone and Mineral Research.

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**Selected Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>DRESS</td>
<td>Drug Reaction with Eosinophilia and Systemic Symptoms</td>
</tr>
<tr>
<td>DXA</td>
<td>dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>EMEA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>FIT</td>
<td>Fracture Intervention Trial</td>
</tr>
<tr>
<td>HORIZON</td>
<td>Health Outcomes and Reduced Incidence with Zoledronic Acid ONce yearly</td>
</tr>
<tr>
<td>HRT</td>
<td>hormone replacement therapy</td>
</tr>
<tr>
<td>LIFT</td>
<td>Long-term Intervention on Fractures with Tibolone</td>
</tr>
<tr>
<td>MORE</td>
<td>Multiple Outcomes of Raloxifene Evaluation</td>
</tr>
<tr>
<td>MPR</td>
<td>means possession ratio</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SERM</td>
<td>selective estrogen receptor modulator</td>
</tr>
<tr>
<td>SOTI</td>
<td>Spinal Osteoporosis Therapeutic Intervention</td>
</tr>
<tr>
<td>STEAR</td>
<td>selective tissue estrogen activity regulator</td>
</tr>
<tr>
<td>TROPOS</td>
<td>Treatment Of Peripheral OSteoporosis</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
</tr>
<tr>
<td>WHI</td>
<td>Women’s Health Initiative</td>
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</tbody>
</table>
Medication-related factors:
- Adverse effects.
- Dose frequency and administration preferences.

Patient-related factors:
- Belief in diagnosis and treatment.
- Perceived risk-benefit ratio.

Doctor-patient relationship:
- Trust and quality of care.
- Follow-up and monitoring.

Table I. Factors affecting oral antosteoporatic treatment adherence.
Based on references 3 and 15.

1) Medication-related factors: adverse effects (Table II)

- Bisphosphonates

Experience with alendronate over the last decade has shown this commonly prescribed bisphosphonate to be well tolerated. In all the bisphosphonate trials, the overall tolerability of this class of treatment is similar when compared with placebo.\(^{16-21}\) Upper gastrointestinal symptoms, in particular, occur at similar rates in both treatment and placebo groups, provided strict administration instructions are followed: taking the tablet on an empty stomach in the morning with at least 8 fl oz of water and remaining upright for the next 30 minutes.

Nevertheless, postmarketing surveillance reveals the most common reason for nonadherence is upper gastrointestinal symptoms.\(^{22}\) Often, this has been shown to be due to a failure to adhere to the strict administration instructions. The most common mistakes are an inadequate duration of fasting leading to poor gastric absorption, an inadequate correct upright posture duration, and an inadequate ingestion of water with the tablet. These strict instructions pose significant adherence challenges, but these remain necessary to minimize the local irritant effect of the tablet on the mucosa and for optimal gastric absorption.

Despite taking the medication appropriately, up to 46% of patients on oral bisphosphonates still complain of gastrointestinal symptoms.\(^{16}\) This rate is observed in the large Fracture Intervention Trial (FIT), where patients with preexisting upper gastrointestinal symptoms were included for the study. An almost identical rate is also observed in the placebo group suggesting that this merely reflects the background prevalence of upper gastrointestinal symptoms in the elderly, where nonsteroidal anti-inflammatory drug use is common and contributory. Smaller studies with different inclusion criteria reported lesser rates of upper gastrointestinal symptoms, but all show rates that are statistically no different to those in the placebo group. Gastrointestinal symptoms, such as heartburn and dyspepsia, are generally mild, with only 2% of cases severe enough to lead to treatment withdrawal.\(^{16}\) Nonetheless, heightened awareness and vigilance may result in early withdrawal of the bisphosphonate in some cases. Interestingly, a multicenter, double-blind clinical trial that rechallenged these patients at a later date showed a recurrence in the rate of gastrointestinal symptoms no different to that of a placebo.\(^{23}\) It is not clear if the lack of difference versus placebo is a real effect or due to a highly motivated, selected healthy population. In a systematic review of RCTs, other common side effects of alendronate include back pain and headache,\(^{21}\) with the former occurring in 10% of the treatment group versus 3% in the placebo group in one study.\(^{24}\) Rare side effects occurring at a frequency of 1 in 1000 to 1 in 10,000 include skin reactions (such as photosensitivity and rash), eye inflammation (such as uveitis and scleritis), and hypersensitivity reactions.\(^{25}\) Very rare side effects occurring in less than 1 in 10,000 people include Stevens-Johnson syndrome and osteonecrosis of the jaw. The latter has attracted considerable public attention.

Osteonecrosis of the jaw is defined as the presence of exposed bone in the mouth which fails to heal despite appropriate treatment within 8 weeks.\(^{26,27}\) First described in 2003, bisphosphonate-related osteonecrosis of the jaw is largely confined to oncology patients who have received large cumulative doses of intravenous bisphosphonates. In these patients, an overall prevalence of 5% is observed in those treated for breast cancer, myeloma, or prostate cancer.\(^{28}\) It is believed that underlying malignancy predisposes patients to

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Common</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Upper Gl symptoms</td>
<td>Skin reactions</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
<td>Ocular inflammation</td>
<td>Osteonecrosis of the jaw</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Hypersensitivity</td>
<td></td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>Diarrhea</td>
<td>Local skin reactions</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Possible venous thromboembolism</td>
<td>DRESS syndrome</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Hot flushes</td>
<td>Venous thromboembolism</td>
<td></td>
</tr>
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<td></td>
<td>Leg cramps</td>
<td></td>
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<tr>
<td>Hormone replacement therapy</td>
<td>Abdominal cramps</td>
<td>Venous thromboembolism</td>
<td>Breast cancer</td>
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<td></td>
<td>Fluid retention</td>
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<td>Stroke</td>
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<tr>
<td></td>
<td>Breast tenderness</td>
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<td>Coronary artery disease</td>
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<td></td>
<td>Leg cramps</td>
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</table>

Table II. List of common oral antosteoporatic treatments and their adverse effects.
Abbreviations: DRESS, Drug Reaction with Eosinophilia and Systemic Symptoms; Gl, gastrointestinal.
the condition, which is made even more likely by risk factors such as tooth extraction, periodontal disease, and infection. When intravenous zoledronate was used to treat osteoporosis in the Health Outcomes and Reduced Incidence with Zoledronic Acid ONce yearly (HORIZON) trial, only 2 out of 7736 women developed osteonecrosis of the jaw: one in the treatment group and one in the placebo arm, both of whom responded with standard therapy for the condition.

In sharp contrast, oral bisphosphonates at the doses used in osteoporosis are associated with a far lower prevalence rate. A large German registry study has estimated a prevalence rate of 0.00038%, or less than 1 in 100 000 patient-years; a figure supported by postmarketing surveys. There is no evidence that this rate is any higher than the background population rate of spontaneous osteonecrosis of the jaw. A postal survey in Australia has recently shown a rate of 0.01% to 0.04%, but lack of adjudication of the diagnosis suggests these data need to be treated with caution. No specific preventative measures have been advocated by consensus, but it is reasonable to suggest the maintenance of good dental hygiene in all patients. It is clear that the benefit, in terms of fracture prevention, of oral bisphosphonates far outweighs the risk of this much overrated complication. However, it can be hard to change patients’ perceptions of risk with statistics.

Strontium ranelate

Strontium ranelate, which was licensed and marketed in 2004, has been shown to have significant vertebral and nonvertebral fracture protection in two large trials (SOTI and TROPOS), by virtue of its anabolic and antiresorptive properties. The overall incidence of side effects did not differ significantly from placebo, although diarrhea statistically increased in the treatment group in pooled data (6.5% versus 4.6% in placebo; relative risk [RR], 1.41; 95% confidence interval [CI], 1.15-1.72; P=0.0008). These symptoms are mild and transient—occurring for up to 3 months—and did not subsequently lead to significant treatment withdrawal in the trials. Other reported side effects from pooled analyses include venous thromboembolism and a transient elevation in creatinine kinase (RR, 1.42; 95% CI, 1.02-1.98; P=0.036; and RR, 1.68; 95% CI, 1.52-1.85; P<0.0001, respectively). The pathophysiology of these effects are uncertain.

Common reasons for stopping strontium ranelate include nausea, diarrhea, headaches, and skin reactions, which are sufficiently troublesome in 2.4%, 1.8%, 0.5%, and 0.1% of patients, respectively, although these rates are statistically no different to those of the placebo group. Hypersensitivity reactions that have been reported range from mild rash and pruritus to urticaria and angioedema, and, very rarely, the full Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. DRESS syndrome is a triad of rash, systemic symptoms, and significant eosinophilia occurring within 3 to 6 weeks of initiating treatment. In a European Medicine Agency (EMEA) report in 2007, only 16 strontium ranelate–related cases had been identified following a total of 570 000 patient-years of exposure worldwide. However, the mortality associated with this syndrome has led the EMEA to advise stopping strontium ranelate if a rash develops and to seek medical attention. Mild, isolated rashes without systemic symptoms are nevertheless common in the community, with a prevalence rate of 4.2% in a recent retrospective chart review of patients on strontium ranelate for up to 2 years’ duration. In the very rare instances of DRESS syndrome occurring whilst on strontium ranelate, it is safest to withdraw this treatment for that patient indefinitely.

Raloxifene

This selective estrogen receptor modulator (SERM) was the first of its kind for the prevention of fractures in osteoporosis. It is known to exert an estrogenic effect on bone and lipid metabolism, whilst acting as an estrogen antagonist on the breast and uterus. Increases in BMD were demonstrated at vertebral and nonvertebral sites, but antifracture efficacy is only evident in the vertebral (RR, 0.64; 95% CI, 0.54-0.78).

As such, its role is adjunctive in osteoporosis treatment. The Multiple Outcomes of Raloxifene Evaluation (MORE) study revealed that venous thromboembolism (VTE) is the only serious adverse effect, occurring up to 3 times more often when compared to placebo (RR, 1.78; 95% CI, 0.99-3.19) at a median of 40 months’ follow-up, similar in frequency to the rate observed in hormone replacement therapy (HRT). Hot flushes and leg cramps occur significantly more frequently with raloxifene than placebo (24.6% versus 18.3%; and 5.5% versus 1.9%, respectively). Nevertheless, these side effects were mild and did not lead to treatment withdrawal. On the other hand, the risk of developing all types of breast cancer is significantly reduced compared with placebo (RR, 0.38; 95% CI, 0.24-0.58), with no risk of endometrial pathology demonstrated. The role of raloxifene in cardiovascular protection is as yet unproven.

Hormone replacement therapy

In addition to relieving postmenopausal vasomotor symptoms such as hot flushes, hormone replacement therapy in the form of estrogen and combined estrogen and progestin has been shown to reduce the risk of developing vertebral and nonvertebral fragility fractures by approximately 25% to 40% in observational and randomized studies, such as the Women’s Health Initiative (WHI) trial. These positive effects are, however, offset by an increased overall mortality rate due to an increase in the rate of coronary heart disease, stroke, pulmonary embolism, and breast cancer, particularly in women taking the drug well after the menopause. These risks outweigh any benefits gained from fracture reduction, regardless of the severity of the osteoporosis. With the availability of other antosteoporotic treatments conferring similar

Bone quality in the treatment of osteoporosis: New approaches, new techniques, and new answers

Adherence to antosteoporotic treatment – Fung and Spector
antifracture efficacy, hormone replacement therapy should perhaps only be considered in postmenopausal women with osteoporosis and vasomotor symptoms, who benefit symptomatically.

Tibolone, a selective tissue estrogen activity regulator (STEAR), has been known to have beneficial estrogenic effects on bone and menopausal symptoms. Recently, the Long-term Intervention on Fractures with Tibolone (LIFT) trial, a large RCT of 4538 postmenopausal women aged 60-85, reaffirmed this, showing antifracture efficacy similar to other established antosteoporosis treatments at both vertebral and nonvertebral sites. Moreover, this study did not show any significant protection against hip fractures (relative hazard, 0.72; 95% CI, 0.32-1.63). Furthermore, although tibolone is not associated with cardiovascular or thromboembolic risks, the risk of developing stroke doubled at a median of 34 months’ follow-up, which would restrict its use to ideally postmenopausal women with no risk factors for stroke. There is a possible protective effect against colon cancer and breast cancer, although later studies have shown conflicting results and the mechanisms involved remain unclear.

2) Medication-related factors: dose frequency and administration preferences

There is ample evidence to suggest that patients find it a challenge to adhere to the strict administration instructions of bisphosphonates and, given a choice, most would prefer a weekly to a daily dosing regimen in order to minimize disruptions to their daily routines. It follows that less frequently taken oral formulations of bisphosphonates, such as ibandronate, might be expected to improve overall compliance. This notion—that patients always prefer less frequent dosing—has been refuted in a recent questionnaire-based population study that showed that patients value simplicity and ease of administration above dosing frequency. Just under half (45%) of the respondents would opt for a daily regime, such as that based on strontium ranelate, provided they could forego the strict instructions required of them by weekly and monthly bisphosphonates (opted for by 20% and 30%, respectively). The highest preference for daily dosing is found among those already on daily medication for other unrelated conditions. This is in keeping with the findings of a focus group study that showed that once a patient is able to adapt the dosing into their daily routine in a systematic fashion, it becomes easier to take the medication every day rather than once weekly. Furthermore, in a survey assessing patient preference for ibandronate or alendronate, most patients would prefer the latter, citing effectiveness as the most important factor above dosing procedure and dosage frequency.

In a small study of treatment-naïve osteoporotic patients, 65% prefer an annual infusion over oral weekly bisphosphonates. These patients tend to have a poor health status with a perceived high risk of fracture and the desire to avoid prescription drugs altogether. As suggested by the authors, this might be due to the view that an infusion theoretically offers superior efficacy compared with the oral formulation. This finding emphasizes the importance of involving patients in treatment decision-making and of discussing the risks and benefits of their chosen treatment. Further studies are required to see if patients on IV bisphosphonates continue to adhere to their annual infusion regimes beyond 2 to 3 years.

The adherence rates for antosteoporotic treatment gradually decline after the first few months, regardless of daily or weekly administration or the tolerability of the medication. Pharmacokinetics only partially explain this trend. This has led to a growing body of evidence that consistently shows that patients themselves and their interaction with their doctors play an integral, if not an equally important, role in adherence.

3) Patient factors: belief in diagnosis and treatment

Denial about their illness, lack of knowledge about osteoporosis, patients’ own views on how best they ought to be treated, and their perceptions of the appropriateness and risk-benefit judgment of initiating and continuing treatment are just some of the barriers to adherence. Being asymptomatic, many osteoporotic patients consider themselves in relatively good health, and the concept of future risk of developing fractures may be hard to grasp, although visual and objective tools, such as a FRAX score and DXA scan report, can help convey this message. Patient motivation and interest usually arise from a personal or family history of fractures or the fear of developing debilitating fractures in the future. Age and educational levels cannot be used to predict adherence, one way or another.

The reason why the biggest drop in adherence occurs within the first month of treatment (Figure 1) is that some patients do not even start their medication. A patient may not be ready to initiate treatment unless all lifestyle changes have been exhausted, and until a sufficient ‘watch and wait’ period has elapsed to convince them of the persistence of the disease. A clear discussion on the diagnostic process and a realistic outlook on the risk of nontreatment, together with better information on treatment options, will help to address these issues.

A distrust of all “artificial” medication is a common issue in many countries—the view that it is not good if it is not natural. This may arise from previous negative personal experiences or anecdotal reports from friends or family members or, indeed, from negative publicity in the media. The long list of side effects in the product leaflets has instilled many an anxiety, particularly among the risk-averse. Again, reassuring advice and knowledge about the prevalence and severity of side effects will allay many of these unfounded fears in some, but not all. In most cases, the benefits of treatment far outweigh the risks associated with antosteoporotic medication.
4) The doctor-patient relationship: trust, quality of care, and follow-up monitoring

The importance of the doctor-patient relationship as a framework for the treatment process discussed above cannot be overemphasized. The quality of care and trust fostered are arguably critical and key to adherence. Impartiality, the ability to listen and address the patient’s concerns, and sound practical advice are valued characteristics of a good consultation. Like all treatment in medicine, the treatment of osteoporosis involves making value judgements and elements of uncertainty, which can be shared with patients who wish to estimate the risk-benefit ratio of their treatment choices for themselves.

Polypharmacy patients with multiple comorbidities appreciate practical advice on issues concerning dosage instructions, such as timing and possible interactions of their medications. Wherever possible, dosing should be tailored to suit a patient’s lifestyle and routine to facilitate adherence. Nevertheless, at times, switching medications may become necessary.

As both the diagnosis and treatment benefit may not be apparent to the patient, regular feedback about progress is desirable to encourage continuation of treatment. BMD has been shown to positively influence adherence, but the results of feedback regarding biochemical markers of bone turnover are more complex. An improvement in levels of resorption markers (reduction) positively reinforced adherence, but a lack of improvement in these markers may worsen adherence in an already adherent patient.

The primary care family physician offers various aspects of medical care, and it is considered good practice to involve and update them on a patient’s treatment plan. Local and regional support groups are helpful sources of peer advice, with regular informal meets and talks. For the patient, a proactive approach is always to be encouraged in these activities (Table III).

<table>
<thead>
<tr>
<th>Table III. Strategies to improve adherence.</th>
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<tr>
<td><strong>Abbreviations:</strong> Dxa, dual-energy x-ray absorptiometry.</td>
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In some centers, the specialist nurse and pharmacist offer valuable advice and support to the overall care of the patient. Since most instances of nonadherence occur within the first few months of starting treatment, nurse-led telephone monitoring at 3 months, for example, could help address any patient concerns and promote adherence in the long term. This is increasingly being done in osteoporotic clinics where patients may not normally be seen for at least a year.

Summary

Good antifracture treatment efficacy requires adherence, which is often suboptimal. The most common reason for nonadherence is real or perceived intolerance to the medication. Although dosage frequency plays a significant role, pharmacokinetics is but one of many barriers to adherence. Patient-related factors are an important consideration, but a good doctor-patient relationship with clear communication can enable patients to make more-informed choices when deciding their treatment. It is possible to improve adherence, but a multimodal approach is needed to achieve this aim.

References

Bone quality in the treatment of osteoporosis: New approaches, new techniques, and new answers


Keywords: osteoporosis; adherence; adverse effects

Adherence to antosteoporotic treatment – Fung and Spector

Medicographia, Vol 32, No. 1, 2010
Observance du traitement antiostéoporotique : Une question de tolérance, de mode d’administration ou tout simplement de dialogue avec le patient?

Les fractures ostéoporotiques de fragilité s’associent à un accroissement de la morbidité et de la mortalité et leur prévalence augmente. Les différentes classes de traitements antiostéoporotiques et les modes de délivrance ont globalement la même efficacité antifracturaire, mais la non-observance entrave leurs résultats. Environ la moitié des patientes arrêtent leur traitement à la fin de la première année et refusent d’admettre le bénéfice du traitement. Les causes de non-observance peuvent être classées en facteurs liés au traitement, aux patientes elles-mêmes ou aux relations entre le médecin et la patiente. Des effets indésirables du traitement, réels ou perçus, sont la principale cause de non-observance. Bien que les études randomisées n’indiquent pas de problèmes majeurs, l’augmentation apparente des effets indésirables peut être due à un mauvais dosage ou simplement aux taux d’incidence concomitant. En choisissant le meilleur traitement pour la patiente, il faudra prendre soigneusement en compte la tolérance, la facilité d’administration et le rapport bénéfice/risque du traitement. Il faudra également appréhender avec empathie la propre connaissance de la patiente sur l’ostéoporose et son traitement et avoir une discussion franche sur les meilleures preuves cliniques. Il faut encourager un engagement actif des patientes afin de permettre leur responsabilisation et une meilleure observance. Finalement, une bonne relation médecin/patiente facilitera toutes les décisions. Une prise en charge soigneuse et une intervention opportune pour chaque patiente sera le gage d’un soin professionnel de bonne qualité.
FRAX® is an evolving body of work that will be constantly updated to improve its outreach and relevance as new data on epidemiology and clinical risk factors are available...The selection of the clinical risk factors used in FRAX® is based on a succession of meta-analyses that aimed to identify factors that are independently associated with osteoporotic fracture risk. These meta-analyses... comprised individual participant data from almost 60 000 men and women.”

FRAX® (http://www.shef.ac.uk/FRAX) is a web-based tool, developed by the World Health Organization (WHO) Collaborating Centre for Metabolic Bone Diseases, University of Sheffield (UK), that provides models for assessing fracture probability in men and women. These models, developed from studies in population-based cohorts in Europe, North America, Asia, and Australia, have been extensively validated in additional population-based cohorts with over a million patient years of observation. The algorithms in FRAX® integrate several well-validated clinical risk factors (CRFs)—age, body mass index, and dichotomized variables (eg, prior fracture, smoking, glucocorticoid use, rheumatoid arthritis), with or without bone mineral density (BMD). The models use Poisson regression to derive hazard functions of death and fracture that provide output as 10-year probabilities (hip fracture and major osteoporotic fracture of hip, spine, humerus, or forearm). Models are calibrated to specific countries where the epidemiology of fracture is known. This review addresses the translational practicalities of developing practice guidelines that apply the FRAX® tool at its intended primary-care level. The main applications are to identify patients requiring pharmacological intervention (CRFs alone suffice in some cases) and BMD testing. The practice guidelines that have incorporated FRAX® have set intervention thresholds that vary between countries, since considerations are not only clinical, but also economic. As for the FRAX® tool itself, it remains a work in progress that can only grow in strength, accuracy, and relevance as new databases on multiple other CRFs become available to enrich its algorithms.

Medicographia. 2010;32:33-40 (see French abstract on page 40)

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racture is the main clinical outcome for osteoporosis patients. The ability to accurately predict the risk of fracture in a patient is highly useful for clinicians in order to select the most appropriate treatment and management interventions. Bone mineral density (BMD) is considered as a major determinant of bone strength, and assessment of BMD at the femoral neck using dual-energy x-ray absorptiometry (DXA) is often performed to diagnose osteoporosis. The usual expression of BMD is as a T-score, which represents the number of standard deviations (SDs) by which the BMD of a patient differs from the mean BMD in young, healthy individuals. A patient has a clinical diagnosis of osteoporosis when their T-score is 2.5 SD or more below that of the young adult mean (T score ≤−2.5 SD).1 Although a T-score ≤−2.5 SD has been shown to accurately predict fracture risk in up to half of women aged over 50 years,2 the risk of fractures in osteoporosis is
also dependent on many other factors in addition to BMD. Indeed, many patients reported to be at low fracture risk according to their BMD assessment will still go on to experience fractures. Conversely, not all patients with a T-score \( \leq -2.5 \) SD will inevitably develop fractures. Treatment intervention thresholds based on only BMD therefore lack sensitivity and estimation of future fracture risk can be improved when other risk factors are taken into consideration.

The use of additional factors in fracture risk assessment is also advantageous in cases where BMD cannot be determined and in helping to decide the necessity of BMD assessments when health-care resources are limited. The World Health Organization (WHO) has developed statistical models that integrate information from BMD assessments and clinical risk factors for fracture to predict future fracture risk. \(^1,3\) These models can now be used clinically as the FRAX® tool (http://www.shef.ac.uk/FRAX), which is a computer-based program that calculates the 10-year probability of major osteoporotic fracture (hip, spine, humerus, or wrist) and the 10-year probability of hip fracture for a patient.

The selection of the clinical risk factors used in FRAX® is based on a succession of meta-analyses that aimed to identify factors that are independently associated with osteoporotic fracture risk. \(^1\) These meta-analyses used the primary data obtained from 12 prospective cohort studies and comprised individual participant data from almost 60,000 men and women. \(^4-18\) The use of primary data in the analyses allows the prognostic importance of each risk factor to be determined in a multivariable context, thereby also allowing interactions between risk factors to be analyzed. Ultimately, this improves the accuracy of the statistical models aimed at predicting fracture risk. It should also be noted that the risk of publication bias is absent with the use of primary data. The dichotomous risk factors identified from the meta-analyses included prior fragility fracture, parental history of hip fracture, current smoker, oral glucocorticoids, rheumatoid arthritis, and alcohol consumption greater than 3 units per day. In addition, body mass index (BMI) was identified as a continuous variable associated with fracture risk. All of these variables showed low to moderate heterogeneity between the different population cohorts and all fulfilled the criteria of being risk factors that were “reversible”, with the appropriate interventions. Each variable was investigated for interactions with sex, age, and BMD, as well as for interactions with the variable itself. With the exception of BMI, all variables were associated with fracture risk independently of BMD.

On the basis of the risk factors identified in these meta-analyses, four statistical models were constructed with the aim of predicting the probability of future fractures. \(^1\) These four models comprised the probability of hip fractures and the probability of other osteoporotic fractures, both with and without measurements for BMD. In each model, fracture was computed as a continuous hazard function using Poisson regression. All significant interactions of risk factors that were observed in the initial meta-analyses were entered into the model. In turn, any of these interactions that were found to be no longer significant for hip fracture and other osteoporotic fractures within the framework of the statistical models were omitted. In addition to the risk factors identified in the meta-analyses, provision was also made in the models for secondary causes of osteoporosis that have been consistently reported to be associated with a significant increase in fracture risk. These included untreated hypogonadism in men and women, inflammatory bowel disease, prolonged immobility, organ transplantation, type 1 diabetes, and thyroid disorders. \(^1\)

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>BMP</td>
<td>bone morphogenetic protein</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CRF</td>
<td>clinical risk factor</td>
</tr>
<tr>
<td>DXA</td>
<td>dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<tr>
<td>NOGG</td>
<td>National Osteoporosis Guideline Group</td>
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<tr>
<td>RCP</td>
<td>Royal College of Physicians</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>YAM</td>
<td>young adult mean</td>
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There is some uncertainty regarding the independence of these factors from BMD, but a conservative judgment was made that fracture risk was linked to a low BMD. However, in the absence of any measurements for BMD, the risk ratio for these other secondary causes was assumed to be similar to that of rheumatoid arthritis. The development of these statistical models forms the basis of the FRAX® tool. In the clinical setting, patient risk factors are easily obtained and can be input into the FRAX® Web site to give the probability of hip and other major osteoporotic fractures (Figure 1). Femoral neck BMD may be entered in addition as a T-score or as an absolute value.

It is important to note that besides clinical risk factors, the risk of fracture also varies with geographical location throughout the world. In order to calibrate the FRAX® models according to global region, algorithms have been developed based on average 10-year hip fracture probability according to epidemiological data for index countries. Global regions have been categorized according to hip fracture risk as follows:

(a) Very high risk (e.g., Denmark, Iceland, Norway, Sweden, USA).
(b) High risk (e.g., Australia, Austria, Canada, Finland, Germany, Greece, Hungary, Italy, Kuwait, Netherlands, Portugal, Singapore, Switzerland, Taiwan, UK).
(c) Moderate risk (e.g., Argentina, China, France, Hungary, Hong Kong, Japan, Spain).
(d) Low risk (e.g., Cameroon, Chile, Korea, Turkey, Venezuela).

Currently, FRAX® algorithms have been developed for Austria, China, Germany, France, Italy, Japan, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the USA. Therefore, in situations where there is no FRAX® algorithm specific to a particular country, a representative country should be chosen that is similar in terms of fracture risk.

Since its launch, the FRAX® tool has been extensively used and its Web site receives an average of 55 000 hits each day. One of the clear uses of FRAX® is the evaluation of the need for treatment intervention among osteoporosis patients in order to minimize the future risk of fractures. Despite its advantages, FRAX® does have some limitations, which must be borne in mind along when using it in the clinic. Furthermore, the development of algorithms that predict the future risk of osteoporotic fractures needs to be accommodated by the construction of new clinical guidelines. The remainder of this review focuses on the applications and constraints of FRAX® and also on the new challenges that this tool has brought to clinical guidelines for the management osteoporosis patients.

**Evaluation of patients for fracture risk**

The clinical guidelines for the management of osteoporosis in most countries are currently based on an opportunistic approach where certain clinical risk factors for fracture suggest the possible diagnosis of osteoporosis. The presence of these risk factors in a given patient is an indication for BMD assessment using DXA. Following this, treatment intervention is considered for patients with BMD values that are within the range of osteoporosis, as defined by the WHO (i.e., T-score ≤ -2.5 SD). Treatment is also recommended for women with a previous history of osteoporotic fracture, without necessarily the need for BMD assessment. With these clinical guidelines, the threshold for treatment intervention is largely dependent on the value of a patient’s BMD. However, several of the risk factors that indicate the need for BMD assessment do in themselves contribute independently to fracture risk. For example, at age 80 years, the 10-year probability of hip fracture is around 12% in women with a T-score of -2.5 SD, whereas, at age 50 years, the probability is only 2% for the women with the same T-score (Figure 2). Similarly, the 10-year probability for any major osteoporotic fracture (hip, forearm, shoulder, or clinical spine fracture) in women with a T-score of -2.5 SD ranges from 11% at the age of 50 years to 26% at the age of 80 years. These observations demonstrate that the age of a patient has a marked impact on the risk of osteoporotic fracture and that fracture risk can be more accurately assessed from age and BMD than by BMD alone. Similar observations were also noted for the other clinical risk factors identified for use in the FRAX® model that all have an impact independent from BMD on the future risk of fracture (Figure 3, page 36). The incorporation of these factors into the FRAX tool provides a means by which the future probability of fracture for patients can be predicted with more accuracy than with the use of BMD assessments alone.

**Limitations of FRAX® in clinical evaluations**

FRAX® has been primarily designed for use in most countries by primary-care physicians, who have relatively little expert knowledge in the management of patients with osteoporosis.
However, the FRAX® tool is not a substitute for a detailed clinical evaluation and physicians must be aware of its limitations when they interpret results in the clinic. Many of the risk factors used in FRAX®, such as cigarette smoking, alcohol consumption, and use of glucocorticoids, are dose dependent.²⁹-³² For these, FRAX® uses risk ratios based on an average dose. Similarly, the risk of fracture increases with the number of prior fractures,³³,³⁴ and a previous vertebral fracture is a particularly strong risk factor. Due to a lack of substantial clinical data, the clinician should also be aware that several risk factors for fracture have not been included in the FRAX® algorithm. These include factors such as biochemical markers of bone turnover, risk of falls, and previous pharmacological treatment. In the clinic, this information may also need to be taken into account if necessary.

The FRAX® tool allows the entry of several secondary causes of osteoporosis as risk factors for fracture. With respect to these secondary risk factors, the current evidence is unclear regarding the proportion of risk that they carry compared with BMD. Because of this, it is conservatively assumed that they all mediate fracture risk as a result of low BMD and that they are all left unweighted when entered into FRAX®.³⁵ Another secondary cause of osteoporosis is rheumatoid arthritis. However, it has been established that rheumatoid arthritis carries a fracture risk independent to that provided by BMD,³⁶ and this factor is therefore weighted accordingly in FRAX®. As mentioned above, when no BMD data is entered, the other secondary risk factors for osteoporosis are presumed to increase fracture risk in a manner similar to that of patients with rheumatoid arthritis.

Due to the large amount of clinical data currently available for BMD at the femoral neck, FRAX® is only compatible with BMD measurements from this site. The risk of fracture associated with BMD measurements from the femoral neck is the same in men and women at any given age.³⁷ One convenience of this is that, in accordance with current recommendations, the T-score can be obtained from a single reference standard, the National Health and Nutrition Examination Survey (NHANES) database for female Caucasians aged 20-29 years.¹,³⁸ However, it is important to consider that a range of
other bone assessments also provide pertinent information concerning fracture risk. These include biochemical indices of bone turnover,\textsuperscript{35} quantitative ultrasound or computed tomography assessments,\textsuperscript{40,41} and BMD measurements from other parts of the skeleton.\textsuperscript{42} Although the data from these assessments is too sparse for a meta-analysis of fracture risk that could be used in FRAX \textsuperscript{®}, they should be incorporated into future risk-assessment tools when more clinical information becomes available.

In summary, the present model of FRAX \textsuperscript{®} is able to enhance the assessment of osteoporosis patients through the integration of clinical risk factors with or without BMD measurements. Nevertheless, clinicians should not consider the FRAX \textsuperscript{®} tool as the ultimate means of assessing patients, but rather as a basis of assessment which will improve as more clinical data regarding osteoporotic fracture risk becomes available.

**Modifications to clinical guidelines to accommodate FRAX \textsuperscript{®}**

The advent of fracture risk prediction algorithms such as FRAX \textsuperscript{®} requires some adjustments to current clinical practice guidelines in terms of thresholds for BMD assessment and treatment intervention. In the United Kingdom, some changes have been introduced by the National Osteoporosis Guideline Group (NOGG), and previous opportunistic strategies to identify cases of osteoporosis are now incorporating a probability-based assessment of patients.\textsuperscript{43} The clinical risk factors for fracture that are now included in the NOGG guidelines are the same as those used in FRAX \textsuperscript{®} with the addition of a BMI less than 19 kg/m\textsuperscript{2}.

The general procedure for managing a patient presenting to the clinic is illustrated in Figure 4.\textsuperscript{1} Patient management starts with an initial assessment of fracture probability based on age, sex, BMI, and clinical risk factors. The NOGG management strategy classifies patients as being at high, medium, or low risk of future fractures. With the use of the FRAX \textsuperscript{®} tool, this categorization of patients is based on 10-year probabilities of osteoporotic fracture for women aged 50 to 80 years (Table I). In patients considered to be at high risk of future fracture, treatment is recommended, irrespective of BMD. For example, as with previous guidelines,\textsuperscript{20-26} the NOGG considers that women aged over 50 years with previous fractures should have treatment interventions without having to have BMD assessment.\textsuperscript{43} Based on the FRAX \textsuperscript{®} model, the treatment intervention threshold in the UK has been set to the equivalent to that of the 10-year probability of future fracture in women over the age of 50 years with prior osteoporotic fracture, but whose BMD is unknown. As can be seen in Figure 5, this treatment intervention threshold increases progressively with age. This is because age is an important independent determinant of fracture risk, and this was not

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Lower limit Major fracture (%)</th>
<th>Upper limit Major fracture (%)</th>
<th>Lower limit Hip fracture (%)</th>
<th>Upper limit Hip fracture (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>7.5</td>
<td>6.5</td>
<td>17.1</td>
<td>23.6</td>
</tr>
<tr>
<td>55</td>
<td>10</td>
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<td>28.8</td>
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<td>12.5</td>
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<td>80</td>
<td>30</td>
<td>5.2</td>
<td>41.3</td>
<td>46.5</td>
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</table>

Table I. Range of probabilities for BMD testing. The lower and upper limits for bone mineral density (BMD) assessment according to 10-year probabilities of major fracture and hip fracture for women with average body mass index are shown.


Figure 5. Management chart for osteoporosis. The darker shaded area in the left hand panel shows the limits of fracture probabilities for the assessment of BMD. The right hand panel gives the intervention threshold. Abbreviation: BMD, bone mineral density.

accounted for in the source guidelines. Compared with women of equivalent fracture risk, treatment interventions in men are largely similar in their efficacy,\textsuperscript{43} and therefore the same intervention threshold applies to men. It is also important to note that, if the resources are available, many clinicians would also perform a BMD test to gain additional information, such as a baseline measure to evaluate response to treatment. In patients considered to be at low risk (Figure 4), the probability of future fracture risk will be so low that a decision not to treat can be made without BMD assessments. An example of such a patient may be a woman at menopause with average BMI (24 kg/m²) with weak or no clinical risk factors, according to the Royal College of Physicians and European guidelines.\textsuperscript{20-25} The FRAX\textsuperscript{®} 10-year probabilities of a major fracture and hip fracture that exclude such women are shown in Table I for women with an average BMI.

The proportion of patients considered to be at intermediate risk (Figure 4) will vary between different countries and depends partly on available resources. It is in this group of patients that a BMD evaluation could be potentially useful in order to further assess future risk of fracture. The NOGG has included 10-year probabilities of future fractures that represent upper and lower thresholds for BMD assessment across a range of different ages over 50 years (Figure 5). Patients above the upper probability threshold are recommended for treatment intervention regardless of their BMD. This threshold prevents a patient classified as being at high risk on the basis of clinical risk factors being reclassified as low risk due to information gleaned from BMD assessments.\textsuperscript{19} For patients below the lower assessment threshold, neither treatment nor BMD evaluation is considered necessary. This threshold has been seen set to exclude a requirement for BMD testing in patients who have minimal risk of future fractures. In the United Kingdom, the upper assessment threshold has been arbitrarily set at 1.2 times the intervention threshold and determines the number of patients who would be eligible for BMD testing.\textsuperscript{45} Excluding patients with a previous history of osteoporotic fracture, these assessment thresholds imply that, depending on their age, 15% to 30% of patients should undergo BMD assessment.\textsuperscript{43} Assessing this proportion of the population presenting at the clinic makes the most of the predictive power of BMD measurements, especially with respect to hip fracture.\textsuperscript{50}

In the light of these recommendations for treatment intervention and BMD assessment, the NOGG has summarized the following proposals for patient management:\textsuperscript{43}

1. Postmenopausal women with a previous history of osteoporotic fracture should be considered for treatment. BMD measurement may sometimes be appropriate for these patients, particularly in younger postmenopausal women. Men with a history of osteoporotic fracture should be referred for BMD assessment.

2. Men aged 50 years or more and all postmenopausal women with a WHO risk factor or a BMI <19 kg/m\textsuperscript{2} should have their future probability of fracture evaluated using the FRAX\textsuperscript{®} tool without measurement of BMD.

3. Individuals with probabilities of a major osteoporotic fracture below the lower assessment threshold shown in Figure 5 can be reassured. A further evaluation using FRAX\textsuperscript{®} is recommended in 5 years or less, depending on the clinical context.

4. Individuals with probabilities of a major osteoporotic fracture above the upper assessment threshold given in Figure 5 or with probabilities of a hip fracture above the upper limit in Table I can be treated without BMD testing.

5. Individuals with probabilities of a major osteoporotic fracture within the limits of the assessment thresholds given in Figure 5 and with probabilities of a hip fracture below the upper limit in Table I should have a BMD test, and probabilities for future fracture risk should be recalculated with FRAX\textsuperscript{®}. If the recalculated probabilities exceed the treatment threshold, treatment intervention should be considered. Where probabilities fall below the treatment threshold, a further assessment is recommended in 5 years or less, depending on the clinical context.

If the clinician has no access to computer facilities, the above guidelines can be broadly followed using simplified paper charts that summarize management decisions on the basis of clinical risk factors and age.\textsuperscript{46}

The integration of a probability-based assessment of future fracture risk using FRAX\textsuperscript{®} is currently being introduced into clinical guidelines for other countries.\textsuperscript{47-51} The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) guidelines now apply the same treatment intervention and assessment thresholds (Figure 5).\textsuperscript{52} However, one difference of the ESCEO guidelines is that BMD measurements are recommended for all patients with future fracture probabilities above the lower assessment threshold. The Japanese Society for Bone and Mineral Research defines a diagnosis of osteoporosis requiring treatment as a BMD less than 70% of the young adult mean (YAM) and less than 80% of the YAM for patients with previous fracture.\textsuperscript{49} In order to integrate the FRAX\textsuperscript{®} algorithm into Japanese guidelines, T-score equivalents to 70% and 80% of YAM BMD for Japanese people were used.\textsuperscript{53}

Using the NHANES III reference for BMD at the femoral neck in Caucasian women aged 20-29 years, these T-scores were -2.7 SD and -1.8 SD, respectively.\textsuperscript{54} With these data, the treatment intervention thresholds based on 10-year probabilities of future fractures were highly concordant with the intervention thresholds developed for the UK and Europe (Figure 5).
Conclusions

The development of the FRAX® tool enables physicians working in primary health care to calculate the future risk of osteoporotic fractures in patients through the integration of a range of clinical risk factors with or without BMD measurements. This improves the sensitivity of future fracture risk assessments based on BMD measurements alone. The incorporation of the FRAX® tool into practice guidelines around the world provides an updated means of categorizing patients requiring treatment for osteoporosis and/or BMD assessments.

Nevertheless, the FRAX® tool should not replace detailed clinical evaluation, and additional clinical factors that are not currently included in the FRAX® models may need to be considered by the physician, if necessary. In this regard, FRAX® is an evolving body of work that will be constantly updated to improve its outreach and relevance as new data on epidemiology and clinical risk factors are available.

Acknowledgement: The work on intervention thresholds has been supported by the National Osteoporosis Guideline Group (NOGG) and the International Osteoporosis Foundation.

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FRAX®, a new tool for assessing fracture risk – Kanis and others


Keywords: FRAX®, fracture probability; osteoporosis; treatment guidelines

APPLICATIONS CLINIQUES ET SEUILS D’INTERVENTION DU FRAX® : UN NOUVEL OUTIL D’ÉVALUATION DU RISQUE DE FRACTURE

FRAX® (http ://www.shef.ac.uk/FRAX) est un outil informatique mis au point par le centre de collaboration de l’Organisation Mondiale de la Santé (OMS) pour les maladies métaboliques osseuses, à l’université de Sheffield (RU), qui fournit des modèles pour l’évaluation de la probabilité des fractures chez les hommes et les femmes. Ces modèles, développés à partir d’études sur des cohortes de population en Europe, en Amérique du Nord, en Asie et en Australie, ont été largement validés sur d’autres cohortes de population avec plus d’un million de patients/année d’observation. L’algorithme de FRAX® intègre plusieurs facteurs de risque clinique bien validés (FRC), comme l’âge, l’indice de masse corporelle et d’autres variables (comme une fracture antérieure, le tabagisme, l’utilisation de corticoides, une arthrite rhumatoïde), avec ou sans évaluation de la densité minérale osseuse (DMO). Les modèles utilisent la régression de Poisson pour dériver la fonction du risque de décès et de fractures qui établit le rendement en probabilités à 10 ans (fracture de la hanche et fracture ostéoporotique majeure de la hanche, du rachis, de l’humérus ou de l’avant-bras). Les modèles sont calibrés pour chaque pays pour lequel l’épidémiologie de la fracture est connue. Cet article s’intéresse aux aspects pratiques translationnels pour permettre de développer les directives qui s’appliquent à l’outil FRAX® à son niveau voulu des soins primaires. Les principales applications sont l’identification des patients qui ont besoin d’une intervention pharmacologique (les FRC seuls suffisent parfois) et la DMO. Les recommandations pratiques qui ont mis en place l’outil FRAX® ont établi des seuils d’intervention qui varient entre les pays, les préoccupations n’étant pas seulement cliniques mais aussi économiques. Comme pour l’outil FRAX® lui-même, des progrès restent à faire pour améliorer la puissance, l’exactitude et la pertinence des nouvelles bases de données, d’autres nombreux FRC devenant alors disponibles pour enrichir son algorithme.
The last 15 years have seen considerable development in the therapeutic arsenal available for the treatment of osteoporosis. While this is good news, it also implies that therapeutic choices prescribers are required to make are not always easy. Analyzing the major pivotal studies reported in the literature is of great help when faced with these choices. However, the level of proof is not the same for all available molecules, especially as regards prevention of nonvertebral fractures as a whole and hip fractures in particular. Nevertheless, there are several efficient treatments for the prevention of vertebral fractures, nonvertebral fractures as a whole, and hip fractures in particular. Where several possible treatments seem to be efficient, a choice needs to be made. Besides tolerance to antiosteoporotic treatments, which is generally satisfactory, and the practical aspects of administration, other tools need to be employed. Molecules cannot be compared directly since there are no randomized studies in which their efficacies are directly compared. Nor is it possible to consider the reduction in relative risk, since doing so would lead to an error in interpretation as the inclusion criteria for the various studies are not strictly identical. On the other hand, a review of the data from the major pivotal studies shows that the reduction in relative risk depends on the severity of osteoporosis. Thus, when that type of analysis was possible, it was shown that the reduction in relative risk was greater when osteoporosis was less severe. It would be appropriate, therefore, in these conditions, to take into account the improvement in absolute fracture risk (defined as the difference between fracture risk in placebo and treatment groups). This parameter varies widely from one molecule to the next, even though all of the drugs at our disposal have proven antifracture efficacy (for vertebral fractures, in any case), which justified their being granted full market approval. This parameter can also be used to calculate the number needed to treat to prevent a fracture event, defined as the inverse of the reduction in absolute fracture risk, an asset to practitioners for translating clinical trial results into benefits for patients.

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Within the last 15 years, substantial progress has been made in the understanding and treatment of osteoporosis. With the considerable development of the therapeutic arsenal at their disposal, practitioners now find themselves having to choose from among the many different molecules available. The choices they are faced with are not easy, since all of the available molecules have been granted full market approval and have, by definition, demonstrat-
ed their usefulness. One of the problems stems from the fact that, as far as osteoporosis is concerned, no head-to-head trials have ever been carried out to evaluate antifracture efficacy. In practice, the practitioner must make a choice, and this will depend on the antifracture efficacy of the molecule for all types of fractures, since this may differ from one molecule to the next. In intertrial comparisons of antifracture efficacy with respect to a placebo group, relative risk is generally taken into account. This approach is open to criticism in that the reduction in relative risk may depend on the severity of the disease in the selected population. In other words, quite frequently, the reduction in relative risk is found to be greater in less severe cases of osteoporosis. More generally, the lack of strict similarity across trial populations is a serious criticism of this approach. Within the last few years, as observed in other domains and particularly cardiovascular pathology, absolute risk reduction has emerged as a factor to be taken into account. In some situations, for instance, it can serve as the basis for deciding which antosteoporotic treatment to administer.

Given the broad scope of this topic, we will restrict our discussion to postmenopausal osteoporosis. In doing so, we can suppose that the diagnosis of osteoporosis is established. In other words, initial testing would have already been carried out to eliminate malignant and benign bone fragility diseases other than osteoporosis (osteomalacia, primary hyperparathyroidism). Similarly, in this paper, we will only address the drug treatment of osteoporosis, even though it is clear that non-drug aspects of therapy must be taken into account, regardless of the drug used. Likewise, we will not be considering vitamin D, which is widely used in the treatment of osteoporosis, but in more of a supplementary role (in association with another antosteoporotic treatment) than as a treatment in its own right.

In the first part of this paper, we will explore the antifracture effects of various treatments, expressed in terms of reduction in relative fracture risk. In the second part, we will examine the concept of absolute risk, and the reduction of the latter during antosteoporotic treatment. Lastly, we will consider the corollary of absolute fracture risk, i.e., the number needed to treat (NNT) to prevent a fracture event. The antifracture efficacy of various antosteoporotic treatments was the subject of a recent update,1 the main results of which are summarized in Table I.1

Antiestrogenic drugs are generally classified into three groups, according to their mechanism of action: bone resorption inhibitors, bone anabolic agents, and uncoupling agents. Bone resorption inhibiting drugs include drugs used in menopausal hormone treatment, selective estrogen receptor modulators (SERMs), and bisphosphonates. We will not consider menopausal hormone replacement therapy (HRT) in this paper for two reasons: firstly, the WHI (Women’s Health Initiative) study has clearly demonstrated that its benefit/tolerance ratio is poor; and, secondly, given the wide range of therapeutic solutions available today, it is now very rare to prescribe HRT as part of the treatment of osteoporosis. Where bone-forming drugs are concerned, we will focus particular attention on teriparatide. Lastly, strontium ranelate is the only uncoupling agent at our disposal.

**Bone resorption inhibitors**

*Selective estrogen receptor modulators (SERMs)*

The only SERM currently available is raloxifene. Although base-doxifene and lazofoxifene have recently been granted market approval in Europe, they are not yet available to prescribers in the major European countries.

Raloxifene was examined in MORE (Multiple Outcomes of Raloxifene Evaluation).2 At the end of 3 years of treatment, a reduction in vertebral fracture risk was found in a population of osteoporotic women—defined as such according to densitometric criteria and/or the presence of at least one vertebral fracture—compared with a placebo group. However, fracture risk reduction varied according to the initial data. Thus, risk reduction was 55% in women without vertebral fractures at inclusion (relative risk [RR], 0.45; 95% confidence interval [CI], 0.29–0.71). On the other hand, in women who had at least one vertebral fracture at inclusion, risk reduction was lower (30%; RR, 0.70; 95% CI, 0.56–0.86). The study was extended for a further year, with the double-blind procedure being maintained. During the fourth year, a 50% reduction in fracture risk was observed in women who had no initial vertebral fractures, as opposed to a 38% reduction in women with a preva-

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**Table I.**  

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>BONE</td>
<td>oral ibandronate osteoporosis fracture trial in North America and Europe</td>
</tr>
<tr>
<td>FIT</td>
<td>Fracture Intervention Trial</td>
</tr>
<tr>
<td>HIP</td>
<td>Hip Intervention Program</td>
</tr>
<tr>
<td>HORIZON PFT</td>
<td>Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly Pivotal Fracture Trial</td>
</tr>
<tr>
<td>HORIZON RCT</td>
<td>Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly Randomized Controlled Trial</td>
</tr>
<tr>
<td>HRT</td>
<td>hormone replacement therapy</td>
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<tr>
<td>MORE</td>
<td>Multiple Outcomes of Raloxifene Evaluation</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
</tr>
<tr>
<td>RUTH</td>
<td>Raloxifene Use for The Heart (study)</td>
</tr>
<tr>
<td>SERM</td>
<td>selective estrogen receptor modulators</td>
</tr>
<tr>
<td>SOTI</td>
<td>Spinal Osteoporosis Therapeutic Intervention (study)</td>
</tr>
<tr>
<td>TROPOS</td>
<td>Treatment Of Peripheral OSteoporosis (study)</td>
</tr>
<tr>
<td>VERT MN</td>
<td>Vertebral Efficacy with Risedronate Therapy, Multi-national (study)</td>
</tr>
<tr>
<td>VERT NA</td>
<td>Vertebral Efficacy with Risedronate Therapy, North America (study)</td>
</tr>
<tr>
<td>WHI</td>
<td>Women’s Health Initiative (study)</td>
</tr>
</tbody>
</table>
lent vertebral fracture. However, efficacy was not demonstrated either in preventing nonvertebral fractures as a whole or hip fractures in particular. Through the MORE study, raloxifene was shown to be effective in preventing breast cancer, but its efficacy varied according to the type of cancer and duration of follow-up (~70%). It was found to be effective only in osteoporotic. On average, at inclusion, the women had osteopenia and, in most cases, without a prevalent fracture. In a subanalysis of the trial, it was demonstrated that when women with densitometric osteoporosis (T-score <-2.5) were considered, alendronate was also effective in preventing wrist and hip fractures. However, as was the case in the FIT-1 trial (and in the subpopulation of women with densitometric osteoporosis), alendronate was not found to be effective in preventing nonvertebral fractures as a whole.

**Risedronate**
Risedronate has also proven its efficacy in preventing vertebral fractures. After being administered for 3 years, it was found to reduce vertebral fracture risk by between 41% and 49%, depending on the authors. It has also been shown to be effective in preventing nonvertebral fractures. However, findings concerning its efficacy vary according to different studies. Thus, the reduction in nonvertebral fracture risk was significant in one of the two pivotal studies (~36%). In the other pivotal study conducted in Europe, the reduction was not significant (~33%). In a specific study on the efficacy of risedronate in preventing hip fractures, the authors reported a global 30% reduction in fracture risk. However, the efficacy of the drug was most apparent in women aged 70 to 79 years old, in whom femoral neck bone density had substantially declined (T-score <-3, and presence of at least one hip-fraction risk factor). Under these conditions, a 40% reduction in hip fracture risk was observed after 3 years of treatment. A comparative meta-analysis of alendronate and risedronate was performed to evaluate their efficacy in preventing nonvertebral fractures, given the results observed in the pivotal studies. The meta-analysis showed that both molecules were effective: RR values for alendronate and risedronate were 0.86 (0.76-0.97) and 0.81 (0.71-0.92), respectively.

**Bisphosphonates**
Bisphosphonates—structural analogues of pyrophosphates—are powerful inhibitors of bone resorption. Elicidrone will not be considered in this review, on account of its modest efficacy.

**Alendronate**
Alendronate was the first available bisphosphonate to demonstrate antifracture efficacy. Thus, in FIT-1 (Fracture Intervention Trial 1), which evaluated patients with at least one vertebral fracture at inclusion, a significant reduction in the risk of vertebral fractures (~47%), wrist fractures (~50%), and hip fractures (~51%) was observed. However, the efficacy of the treatment was not demonstrated when nonvertebral fractures were considered globally. In the FIT-2 study, alendronate was only found to be effective in preventing morphometric vertebral fractures. The study population, however, was not cancers in which estrogen receptors were present. The initial findings on the prevention of cardiovascular morbidity were not confirmed by the RUTH (Raloxifene Use for The Heart) study. On the other hand, unlike estrogens, raloxifene has not been demonstrated to have harmful cardiovascular effects.

**Table I. European guidelines for the diagnosis and management of osteoporosis in postmenopausal women.**

<table>
<thead>
<tr>
<th>Effect on vertebral fracture risk</th>
<th>Effect on nonvertebral fracture risk</th>
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<tr>
<td><strong>Osteoporosis</strong></td>
<td><strong>Established osteoporosis</strong></td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>(including hip†)</td>
</tr>
<tr>
<td>Alendronate</td>
<td>(including hip†)</td>
</tr>
<tr>
<td>Risedronate</td>
<td>+</td>
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<tr>
<td>Ibandronate</td>
<td>+</td>
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<tr>
<td>Zoledronic acid</td>
<td>+</td>
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<tr>
<td>HRT</td>
<td>+</td>
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<tr>
<td>Raloxifene</td>
<td>+</td>
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<tr>
<td>Teriparatide and PTH</td>
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</tbody>
</table>

<table>
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<tr>
<th><strong>Established osteoporosis</strong></th>
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<tr>
<td>(including hip†)</td>
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<tr>
<td>(including hip†)</td>
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<td>+†</td>
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</table>

* women with a prior vertebral fracture
† in subsets of patients

Abbreviations: HRT, hormone replacement therapy; PTH, parathyroid hormone.
preceding their inclusion in the study), a 69% reduction in nonvertebral fracture risk was observed in the former case and a 60% reduction in the latter.

**Zoledronate**

It was recently demonstrated that zoledronic acid could reduce vertebral fracture risk by 70% (95% CI, 62% to 76%) in patients with osteoporosis, defined either in densitometric terms or by the presence of at least one vertebral fracture. In the same study, the drug was found to be effective in preventing both nonvertebral fractures (-25%) (95% CI, 13% to 36%) and hip fractures (-41%) (95% CI, 17% to 58%). In a study involving a population of men and women with recent hip fractures, zoledronate was found to reduce the risk of clinical fractures by 35% (RR, 0.65; 95% CI, 0.50-0.84). In the same study, the drug was also shown to be effective in preventing clinical vertebral fractures (-46%) (95% CI, 8% to 28%). Lastly, in a secondary analysis of their data, the authors also found the treatment to be effective in reducing the death rate (-28%; RR, 0.72 [0.56-0.93]).

**Optimal bisphosphonate treatment duration**

This is a difficult question to answer insofar as the pivotal studies were conducted over a period of 3 years. A 5-year data from the TROPOS study have recently been published. The 5-year data from the TROPOS study have recently been published. In that study, the authors showed that the efficacy of treatment: (i) remained unchanged during the 5th year when compared to the previous years, but (ii) declined significantly during the 5th year when compared to the results observed in the placebo group. Lastly, a follow-up study of the effect of alendronate on bone mineral density (BMD) was published in 2004, the maximum treatment duration of which was 10 years. In that study, group sizes were small, and, over such a long period of time, the double-blind procedure was not maintained. Nonetheless, the authors were able to demonstrate that the evolution in nonvertebral fracture risk between the 1st and the 3rd year and the 6th and the 10th years was identical, suggesting that efficacy did not decline over time. However, the methodology can be criticized, and it is difficult to draw definitive conclusions.

**Bone formation stimulants**

**Parathyroid hormone**

The leading drug in this category is teriparatide, which is the 1-34 fragment of parathyroid hormone. At a dose of 20 µg/day, teriparatide has been shown to be capable of reducing vertebral fracture risk by 65% (after 18 months of treatment, on average) when compared with the results observed in a placebo group. At the end of that period, an equally significant reduction in nonvertebral fracture risk (-53%) was also demonstrated. Moreover, its vertebral antifracture efficacy seemed to be more pronounced in women who had at least two vertebral fractures at inclusion, and it is for this reason that teriparatide is generally indicated for the treatment of the most severe osteoporosis. Parathyroid hormone (1-84) has also been evaluated. After 18 months of treatment, a 60% reduction in vertebral fracture risk was observed, but without a significant effect on nonvertebral fracture risk.

**Strontium ranelate**

Strontium ranelate has an original mode of action in that it stimulates bone formation while at the same time inhibiting bone resorption. This has been demonstrated in vitro as well as in vivo by measuring changes in bone-remodeling markers and analyzing bone biopsies. Strontium ranelate has been the subject of a vast development program comprising two pivotal studies: namely, the SOTI (Spinal Osteoporosis Therapeutic Intervention) study, which sought to evaluate the efficacy of strontium ranelate in preventing vertebral fractures; and the TROPOS (TREATment Of Peripheral OSteoporosis) study, whose main purpose was to evaluate the efficacy of the molecule on nonvertebral fractures. In the SOTI study, after four years of strontium ranelate treatment, a 33% reduction in vertebral fracture risk was observed when compared with the results observed in the placebo group. The 5-year data from the TROPOS study have recently been published. In that study, the authors observed a significant reduction in nonvertebral fracture risk (-15%). The reduction was somewhat higher (-18%) when major nonvertebral fractures alone were considered. A significant reduction (43%) in hip fracture risk was also observed in patients with low bone densities (T-score < -2.4 at the spine and femoral neck). Strontium ranelate was also found to be effective in patients over 80 years old, in whom a global reduction of 30% in both vertebral and nonvertebral fracture risk was observed. Lastly, in a very recent study, strontium ranelate was shown to be effective in osteopenic women, regardless of whether they had vertebral fractures at inclusion or not.

**Toward a more judicious approach: absolute fracture risk reduction**

Globally, these various data show that there are currently several antosteoporotic molecules with proven therapeutic value. In practice, the question is how does one know which of these molecules is the most relevant for a given patient. The previously mentioned therapeutic trials, in focusing on relative risk only, cannot always provide an answer. Indeed, as mentioned earlier, not all of the molecules were found to be effective in preventing nonvertebral and hip fractures. However, some of the molecules mentioned earlier have clearly been shown to be capable of reducing both vertebral and nonvertebral fracture risks. For practical purposes and to assist prescribers with their choices, appropriate tools are needed. Unfortunately, in the field of osteoporosis, there are no comparative studies on the antifracture efficacy of the various treatments. And given the sizes of the populations required for such studies and the cost of the latter, there is little likelihood that such studies will be undertaken.
Furthermore, it is not possible to compare the reduction in relative risk across different studies. Indeed, the criteria for inclusion in the studies seeking to evaluate the efficacy of a given molecule were quite variable. In some of them, patients with at least one vertebral fracture were included. In others, only patients with densitometric osteoporosis were included. And in other studies, both of these criteria were taken into account. In practice, therefore, other tools are needed to help determine the benefits patients can expect in a given situation. As is the practice in other medical disciplines, the evaluation of absolute risk—and consequently the reduction thereof with treatment—is an important factor to take into consideration.

The evaluation of absolute fracture risk is now possible on an individual basis, thanks to the FRAX® tool. More specifically in therapeutic terms, besides what has been previously mentioned, the use of relative risk presents at least two drawbacks. In clinical practice, by definition, there are no placebo groups. The reduction in relative risk observed in certain conditions is therefore of little relevance. Moreover, by definition, the concept of relative risk does not take account of the frequency of the event that one wishes to predict (in our case, the fracture). Taking into consideration relative risk alone to guide therapeutic choices could lead to the treatment of populations in which fracture risk is very low, as illustrated in the article by P. Alonso-Coello. Another approach consists of considering the reduction in absolute fracture risk, defined as fracture incidence in the placebo group minus fracture incidence in the treatment group. The reduction in absolute risk can also be used to calculate the number needed to treat to prevent the occurrence of the event being considered (in this case, the fracture). This is defined as the inverse of the reduction in absolute risk (expressed as a raw value and not as a percentage).

Figure 1 shows the reductions in absolute vertebral fracture risk expressed as percentages for the major clinical trials mentioned in the first part of this paper.

As regards the reduction in absolute hip fracture risk, less data is available in the literature. A summary of this data is shown in Figure 2. While, by definition, the reduction in absolute hip fracture risk with ibandronate is nil, it is identical and low (~1%) with zoledronate, risedronate, and alendronate. It is most pronounced with strontium ranelate (a 2% reduction in absolute hip fracture risk).

From reduction in absolute fracture risk to number needed to treat to prevent a fracture event
As mentioned earlier, the NNT to prevent a fracture event is defined as the inverse of the reduction in absolute fracture risk. This approach has been adopted by several authors within the framework of the major therapeutic trials to eval-
uate the efficacy of the various treatments. A recent report \textsuperscript{28} reviews the therapeutic modalities for the prevention and treatment of osteoporosis. One of the interesting things about this report is that it provides NNT values for the studies referred to in the first part of this paper. As an example, it is classically reported that HRT—which was not mentioned previously—given the fact that the reasons for not prescribing HRT are numerous—is the only treatment whose antifracture efficacy has been established in the general population. This is true, but aside from the poor benefit/risk ratio of HRT, it is certainly not useful to treat all women with HRT to prevent hip and vertebral fractures. Indeed, for the latter two conditions, the NNTs are 216 and 225, respectively.

As regards the other drugs and following the order in the first part of this paper, the results are as follows: for raloxifene, through the MORE study and taking into consideration the population as a whole, the NNT is 29. Where the bisphosphonates are concerned, the results depend on the molecule. Thus, for alendronate within the framework of the FIT-1 study, the NNT to prevent a vertebral fracture at inclusion, the NNT is 37 for vertebral fractures, 91 for hip fractures, and 53 for wrist fractures. In the FIT-2 study, a post hoc analysis was immediately performed on patients with a T-score <-2.5. When all clinical fractures were taken into consideration, the NNT was 15. For clinical vertebral fractures, the NNT was 34. For risedronate in the VERT NA (Vertebral Efficacy with Risedronate Therapy, North America) study, the NNT to prevent vertebral fracture was 20. In the VERT MN study, it was 10. One explanation for this is that vertebral fracture risk in the placebo group was much higher in the VERT MN study than in the VERT NA study (29% and 16%, respectively). In the previously mentioned HIP (Hip Intervention Program), the NNT was 91. In the BONE study evaluating the efficacy of ibandronate, the NNT for the prevention of vertebral fracture was 20.

The most recent bisphosphonate to receive market approval, i.e., zoledronate (HORIZON PFT [Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly Pivotal Fracture Trial]) has an NNT of 13 for vertebral fractures, 91 for hip fractures, and 37 for nonvertebral fractures. These marked differences are not always comparable with the reduction in relative risk. For example, the reduction in hip fracture risk in the HORIZON PFT study was 41%, while the reduction in nonvertebral fracture risk was markedly lower (~25%). In the HORIZON RCT (Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly Randomized Controlled Trial), the NNT to prevent a clinical fracture was 19. This increased to 48 when clinical vertebral fractures alone were taken into consideration. When all nonvertebral fractures were taken into account, the NNT was 32. As mentioned earlier, in the HORIZON RCT study, a 28% reduction in mortality was observed, corresponding to an NNT of 27.

For strontium ranelate, the NNT (SOTI study) to prevent the occurrence of a vertebral fracture was 9, \textsuperscript{18} and 59 (TROPOS study) to prevent a peripheral fracture.\textsuperscript{29} In the latter study, the NNT to prevent a hip fracture in women at high risk of fracture at the upper end of the femur was 48.

**Conclusion**

Studies on osteoporosis are always conducted versus a placebo group. Currently, several antosteoporotic drugs exist with different mechanisms of action and modalities of administration. These molecules have all demonstrated their usefulness in preventing the occurrence of vertebral fractures, and to a lesser degree—but this is highly dependent on the molecule in question—nonvertebral fractures in general and hip fractures in particular. Taking into consideration the reduction in relative fracture risk alone to guide prescribers’ choices is not sufficient. However, no comparative studies have been conducted with the main goal of evaluating antifracture efficacy. It is known that the populations selected for inclusion in the pivotal studies were quite different. Given these conditions, taking the reduction in absolute fracture risk into consideration seems appropriate.

As mentioned earlier, the reduction in absolute fracture risk varies from one molecule to the next. It is also possible, using this parameter, to calculate the NNT to prevent a fracture event, thus translating the results of clinical trials into current medical practice. These parameters deserve to be taken into consideration as tools to allow a fair and complete comparison of the efficacy of the antosteoporotic treatment.

**References**


5. Barlet-Conor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascul-
Réduction du risque absolu et efficacité des traitements anti-ostéoporotiques en l’absence d’études comparatives

L’arsenal thérapeutique du traitement de l’ostéoporose s’est considérablement développé ces 15 dernières années. Cependant, cette bonne nouvelle au revers en ce qu’il n’est pas toujours facile pour les prescripteurs de faire un choix. Dans ce contexte, les principales études pivot de la littérature sont certainement d’une grande aide, même si le niveau de preuve n’est pas le même pour toutes les molécule, surtout si l’on se réfère à la prévention des fractures non vertébrales en général et à celle des fractures de hanche en particulier. Néanmoins, des traitements efficaces pour la prévention des fractures vertébrales, non vertébrales et de la hanche existent bel et bien, et il faut en choisir un. Pour ce faire, outre la tolérance des traitements anti-ostéoporotiques, qui est généralement bonne, ou les aspects pratiques de l’administration du médicament, il faut s’aider d’autres critères. Il est impossible de comparer des molécules directement car il n’existe pas d’études randomisées pour cela. Il n’est pas possible non plus de prendre en compte la réduction du risque relatif car, si faisant, l’interprétation serait erronée, les critères d’inclusion des différentes études n’étant pas strictement identiques. Toutefois, une revue des données issues des principales études pivot, lorsqu’elle est possible, montre que la réduction du risque relatif dépend de la sévérité de l’ostéoporose et qu’elle est d’autant plus grande que l’ostéoporose est moins sévère. Dans ces conditions, le paramètre le plus approprié à prendre en compte serait l’amélioration du risque absolu de fracture (défini comme la différence entre le risque de fracture entre les groupes placebo et traité). Ce paramètre montre de larges variations d’une molécule à l’autre, même si chacune d’entre elles dispose d’une efficacité anti fracturaire avérée (pour les fractures vertébrales, en tous cas) justifiant leur autorisation de mise sur le marché. Ce paramètre peut être aussi utilisé pour calculer le nombre de personnes à traiter pour prévenir une fracture, nombre défini comme l’inverse de la réduction du risque absolu de fracture et qui permet aux médecins de traduire les résultats des études cliniques en bénéfices pour les patients.

Keywords: absolute risk reduction; fracture risk; antiosteoporotic treatment; nonvertebral fracture; vertebral fracture


Is BMD measurement still useful with the advent of the FRAX® fracture risk assessment tool?

The FRAX® fracture risk assessment algorithm developed by Kanis et al at the World Health Organization Collaborating Centre for Metabolic Bone Diseases at the University of Sheffield, UK, is able to integrate clinical risk factors independently of bone mineral density (BMD) to derive hazard functions of death and fracture as 10-year probability outputs. Our experts examine the impact FRAX® has had on fracture risk assessment and whether BMD still has a role to play in the future.

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3. J. K. Lee, *Malaysia*
4. W. Lems, *The Netherlands*
5. R. Nuti, C. Caffarelli, and S. Gonnelli, *Italy*
6. M. E. Simões, *Portugal*
7. G. Skarantavos, *Greece*
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9. C. Horváth, *Hungary*
1. M. Chandran, Singapore

Though estimating relative risks and lifetime risk of fractures is of value in evaluating the burden of osteoporosis in populations and the effects of intervention strategies, they are less relevant with regard to individual risk assessment. The FRAX® tool computes the 10-year probability of fractures from clinical risk factors with or without the measurement of femoral neck bone mineral density (BMD).

When discussing the reasons why BMD measurement is still useful even in the era of FRAX®, thought has to be given to the distinction between diagnosis of osteoporosis and assessment of fracture risk. This in turn implies a distinction between diagnostic and intervention thresholds. FRAX® is meant to be a fracture risk assessment tool. However, BMD measurement using dual-energy x-ray absorptiometry (DXA) remains the core concept in osteoporosis diagnosis and is the most clinically recognized and validated method currently. The World Health Organization (WHO) definition of osteoporosis is based on the results of BMD. The International Osteoporosis Foundation and the National Osteoporosis Foundation suggest that individuals with a history of fragility fracture have high osteoporotic risk and should receive BMD examination. In women aged 70-80 years, the “BMD screening for all” strategy has been found to be more cost effective in preventing hip fracture than either no screening or screening in women with at least one risk factor.¹

A low BMD is an important risk factor for future fractures. Many prospective studies with DXA indicate that the risk of fracture approximately doubles for each standard deviation (SD) reduction in BMD. The increase in fracture risk for a specific change in BMD depends on the technique used for measuring BMD, the site measured, and the fracture of interest. The ability to predict hip fracture—for instance, by BMD measurement—is as good as that of blood pressure in predicting stroke and better than the use of serum cholesterol to predict coronary artery disease.² BMD measurement may also help in identifying individuals, especially premenopausal women and men who have experienced a fragility fracture and who are likely to have a secondary cause of osteoporosis. Differing levels of BMD—for instance, low Z scores less than –1—could indicate the possibility of a secondary cause.

BMD is also a good indicator when monitoring treatment response. The Fracture Intervention Trial (FIT) has shown that women whose BMD increased by more than 3% in the first 2 years of alendronate treatment were found to have the lowest incidence of new vertebral fractures.³ The Spinal Osteoporosis Therapeutic Intervention (SOTI) and TReatment Of Peripheral OSteoporosis (TROPOS) studies have shown that the beneficial effects of strontium ranelate in fracture risk reduction are related to the increases in BMD seen with this agent.⁴,⁵

Even given all the above, however, the sensitivity of BMD measurement is low, and approximately 50% of all fractures would be missed if BMD measurement alone is relied upon, since they occur in patients who have a BMD T-score in the osteopenic or normal range. The predictive value of BMD can be enhanced by the use of other clinical factors, such as age, previous fragility fracture, premature menopause, a family history of hip fracture, the use of oral corticosteroids, etc. FRAX® puts low BMD into perspective as one of the many risk factors for fractures. Though FRAX® assessment without BMD is of some value with the performance characteristics being similar to the use of DXA for the prediction of nonhip fractures, the value of BMD in case finding is improved when combined with the use of clinical risk factors with the FRAX® algorithm.⁶

In conclusion, even in this current era of fracture risk assessment using FRAX®, measurement of BMD still plays a very important role in the diagnosis of osteoporosis for fracture prediction (in which case its value can be enhanced by combining it with other clinical risk factors) and for the follow-up and management of treated patients. Where facilities for BMD testing are limited, consideration should be given to the judicious and selective use of this important tool, so as to optimally deploy resources and appropriately identify individuals above or below an intervention threshold.

References
Will the addition of BMD measurements improve identification of those at risk of osteoporotic fractures?

The World Health Organization (WHO) diagnosis of osteoporosis is largely based on the DXA (dual-energy x-ray absorptiometry) assessment of central bone mineral density (BMD). Despite a specificity of 85%, DXA has a poor sensitivity, and numerous studies have shown that less than 50% of fragility fractures occur in subjects with DXA-confirmed osteoporosis (T-score < –2.5). The WHO classification also does not take cognizance of causes of a low BMD other than osteoporosis, nor does it recognize the importance of bone quality or extraskeletal factors, like falls, in the development of fracture.

The knowledge that many women at risk of fracture will not be identified on the basis of a BMD measurement has rekindled interest in clinical risk factors (CRFs). Advanced age, a previous fragility fracture, a family history, excessive leanness, bone toxins, and certain diseases have been shown to predispose to fracture, largely independent of BMD. FRAX®, the latest fracture risk assessment tool, uses these CRFs. 1

Vertebral fracture (not included in FRAX®), age, and BMD have the highest gradient of risk and may predict fracture risk as well as, if not better than, FRAX®. 2,3 Moreover, the lack of country-specific data on the epidemiology of osteoporosis seriously limits the scientific use of risk assessment tools like FRAX®. There can be little doubt that the combined use of two independent fracture risk factors like BMD and CRFs will complement our ability to identify those at risk of an osteoporotic fracture.

Will it alter your decision to intervene with a bone-active drug?

The efficacy of pharmacologic intervention has largely been demonstrated in patients with a low BMD or a prior fracture, but their efficacy in patients with other CRFs remains unknown. The history of a major osteoporotic fracture is an important predictor of fracture and would negate the need for a BMD measurement before initiating therapy. The mere presence of a number of CRFs in the absence of significant fracture or low BMD would, however, support the need for a BMD measurement in order to decide on pharmacological intervention.

Will it influence treatment?

BMD data have had little influence on the type of osteoporosis treatment. Although bisphosphonates have been shown to be effective in patients selected solely on the basis of prior fractures, risedronate was ineffective in preventing fracture in elderly women with a BMD T-score above –2.5, suggesting that alternative therapeutic strategies may have to be considered in those with CRFs and less severe bone loss. Conversely, an extremely low BMD (eg, T-score < –4.0) may argue against the use of antiresorptive agents, which only modestly increase BMD, and instead suggest the use of anabolic agents.

Will it impact on compliance and adherence?

Little evidence exists that compliance can be improved with reinforcement in subjects who have already sustained a fracture. However, in those without a history of fracture, reinforcement strategies using BMD data do suggest that adherence can be improved.

Will it influence monitoring of treatment?

Changes in BMD following initiation of treatment with antiresorptive agents (ARAs) account for <20% of the variance in fracture risk reduction. BMD monitoring is therefore of limited value in subjects treated with ARAs. Drugs with anabolic actions, however, significantly increase BMD. Changes in BMD following treatment with strontium ranelate have been shown to explain 75% of the antifracture efficacy of this drug. 4

Summary

Osteoporosis is a complex syndrome which is best managed when CRFs, a history of prior fracture, and BMD measurements are combined to optimize treatment. The need to determine the importance of different CRFs in a community and to establish local intervention thresholds is emphasized.

References

3. J. K. Lee, Malaysia

Improvement in vertebral stiffness and strength after vertebroplasty has been found to depend highly on BMD. Individuals with higher BMD might have a higher leakage rate when given a higher cement volume; whereas ex vivo biomechanical study showed that low BMD (<0.7 g/cm³) may have least improvement in mechanical properties after vertebroplasty. The cement volume should be restricted to the amount needed for fracture reduction only. Therefore, it might be appropriate for patients with osteoporotic fractures with different BMDs to receive different treatment strategies to prevent recurrent fracture and subsequent complications.

FRAX® only provides us with the ten-year fracture probability or absolute risk to assist us in deciding whether to initiate treatment in an untreated individual. The value of absolute risk before initiating treatment is useful for clinicians. However, in clinical practice, many patients do not appreciate a single value for the absolute fracture risk or the 10-year probability of them sustaining fractures. Comparisons of absolute risk cannot be calculated in treated individuals based on FRAX®, as FRAX® is only applicable in untreated individuals.

The use of clinical risk factors together with BMD improves sensitivity of fracture prediction without adverse effects on specificity and provides a mechanism for the effective and efficient delivery of health care to individuals at high risk and the avoidance of unnecessary treatment to others. There are other clinical uses of BMD measurement which are not possible and cannot be replaced with FRAX®. Therefore, the measurement of BMD, wherever it is available and accessible, is still very important in managing our patients with osteoporosis.

References
B one mineral density (BMD) measurement is advocated in elderly patients with clinical risk factors for osteoporotic fractures, such as low body mass index, familiar osteoporosis, the use of glucocorticoids, etc. Usually, in the work-up of patients with (possible) osteoporosis, a dual-energy x-ray absorptiometry (DXA) scan of the lumbar spine and the hips is performed. Suppose that a 61-year-old woman with a height of 165 cm and a body weight of 59 kg—without other obvious causes of (secondary) osteoporosis—has T-scores of −1.8 for the lumbar spine and of −2.6 for the hips. Should you treat her with antosteoporotic drugs or not? Because the T-score of the hips is lower than −2.5, the diagnostic threshold for osteoporosis, many of our colleagues would start antosteoporotic treatment, but is that realistic? What is her fracture risk and what is the risk reduction that can be expected, based on the literature? For the first question, the FRAX® scoring system is very helpful: for this patient, the 10-year probability of having a major fracture is 9.9% and her 10-year hip fracture risk is 2.8%. A lot of our colleagues and several patients are probably hesitating about whether their preliminary treatment decision based on low BMD is correct.

The FRAX® scoring system is particularly useful for both physicians and patients to get information about the future untreated fracture risk. It has been suggested that, since compliance with antosteoporotic drugs is low, a model of shared decision-making between physician and patient with the use of the absolute future fracture risk may be helpful.

Unfortunately, there are limitations with the use of absolute fracture risk according to FRAX®:

- Although 90% of nonvertebral fractures are related to falls, falls are not included in the algorithm;
- Vertebreal morphometric deformities are also not included in the algorithm;
- The use of glucocorticoids (GCs) is a yes-no phenomenon, which is certainly also a limitation since GCs are prescribed in different dosages in clinical practice and the side effects of GC on bone are dose-related;
- The FRAX® database is based on several cohorts from 9 countries: other countries have been encouraged to submit their country-specific data, if available, to the FRAX® organizers; and
- The most important limitation is that consensus about the thresholds for both diagnosing and treating osteoporosis are lacking. It has been suggested that a pharmacoeconomic analysis should be made for each country.

It is possible to calculate an absolute fracture risk score according to FRAX® with or without BMD measurement. Obviously, this is an advantage in countries in which DXA is not available. The question is, however, whether it is useful to perform a DXA measurement in patients for whom a FRAX® score has already been determined, if DXA machines are widely available. There are four reasons that support additional DXA measurements in these patients:

1. Measuring BMD gives additional information about future fracture risk, making the risk score more precise. That can easily be seen in the model: low T-scores are associated with slightly higher fracture risk scores for major fractures and for hip fractures, etc.
2. With a DXA measurement at baseline, the possibility of performing repeated measurements after some years to evaluate the effect of (drug) treatment in the individual patient remains;
3. Since modern DXA machines are also equipped with lateral vertebral assessment (LVA), it is possible to perform additional morphometry of vertebrae height in the thoracolumbar spine; and
4. A low BMD measurement can confirm a diagnosis of osteoporosis, which might be important in patients with a high trauma fracture. In contrast, a finding of normal BMD in a patient with a vertebral or nonvertebral fracture may induce hesitation about whether or not antosteoporotic treatment is indicated.

References
For at least two decades, bone mineral density (BMD) has formed the cornerstone not only for the diagnosis of osteoporosis, but also for the assessment of fracture risk and the monitoring of treatment. However, although the risk of fractures approximately doubles for each SD reduction in BMD, there is a growing conviction that assessment with BMD alone captures a minority of the fracture risk. In fact, half or more osteoporosis-related fractures occur in patients with T-scores better than -2.5, which are in the osteopenic or normal range.

The use of clinical risk factors (CRFs) that add information on fracture risk independently of BMD improves the sensitivity of fracture risk assessment. The FRAX® tool computes the 10-year probability of a major osteoporotic fracture or a hip fracture on the basis of CRFs identified from baseline and follow-up data from ten prospective population-based European cohorts. These CRFs comprise a prior history of fragility fracture, body mass index, parental history of hip fracture, long-term use of glucocorticoids, rheumatoid arthritis, current smoking, and alcohol intake of 3 or more units daily. BMD can be included, but the model also works without it.

The development of the WHO FRAX® calculator represents a major achievement and is currently the gold standard fracture model. FRAX® may be one of the few resources available for fracture risk assessment in countries where facilities for BMD measurement are limited (for example, India where dual-energy x-ray absorptiometry [DXA] equipment was limited to 6 towns in 2004).

At this point, it is crucial to correctly define the real value of FRAX® assessment without BMD. A recent study examined the effects of using CRFs alone, BMD alone, or a combination of both in FRAX® to detect women at risk of hip fractures. The use of BMD alone showed improved sensitivity with respect to CRFs, but at the expense of a reduction in predictive value, positive predictive value, and an increase in the number needed to treat (NNT) value. In this study, the combination of CRFs and BMD selected women at higher risk than either CRFs or BMD alone, yielding the lowest NNT.

Moreover, the combined test identified women with a lower mean T-score than BMD tests alone and a substantially lower T-score than with CRFs alone.

These findings support the view that fracture risk is optimally characterized when BMD results are used with FRAX®. However, where facilities for BMD are limited, as happens in most European countries, it has been suggested that a triage system might be utilized. According to this approach, BMD testing would not be necessary in individuals categorized by CRFs to be way above or way below a threshold risk for fractures, whereas BMD would be measured in individuals categorized as being close to the threshold risk. In these cases, the inclusion of BMD for a better classification of fracture risk is supported by the fact that BMD reflects several important and independent risk factors for fracture that are not included in FRAX®, such as vitamin D status, bone turnover, previous treatment for osteoporosis, and medication that induces bone loss (antiepileptic drugs and aromatase inhibitors).

Traditionally, a limitation of FRAX® without BMD was that patients identified on the basis of CRFs with FRAX® would not respond to pharmacological interventions. Nevertheless, two recent studies showed that in patients treated with clodronate or bazedoxifene, high FRAX® probabilities were associated with higher efficacy, even when BMD was not used to characterize the fracture risk. Finally, BMD testing continues to be the best method for following up patients treated with antosteoporotic drugs.

In conclusion, the use of FRAX® with BMD increases the performance characteristics of fracture risk assessment compared with the use of CRFs alone. Further studies are needed to define the cost-effectiveness of such a strategy, which on the one hand requires more resources, but on the other improves the budget impact by limiting treatment only to high-risk patients.

References
In the last 15 years, our medical rationale for evaluating fracture risk has been bone mineral density (BMD)-based. According to the dual-energy x-ray absorptiometry (DXA) operational definition of osteoporosis, we tended to classify, and therefore to treat, individuals with T-scores lower than −2.5 as osteoporotic and consequently at high risk of fracture. After a while, this approach was demonstrated to be inefficient and inappropriate; a great part of the population classified as being osteopenic would miss out on treatment if medical thinking was based uniquely on DXA. In fact, we now know, thanks to the results of epidemiological studies like the National Osteoporosis Risk Assessment (NORA) study,¹ that in a real population, the majority of fractures develop in individuals classified as osteopenic (partially because this is the real state of the majority of the fracture population).

Perhaps the bigger issue is that low BMD is only one of the risk factors for fracture; other factors like bone architecture, quality, and bone remodeling (all difficult to quantify) were not taken into account in our clinical judgement previously. Last but not least, clinical risk factors for osteoporosis and fractures were used in an empirical and unorganized manner and tended to be put at the back of the stage when compared with the importance of DXA. This bias has also been demonstrated not to be very correct, as the majority of opinion leaders on osteoporosis now believe that osteoporosis clinical risk factors account for about 60% of the osteoporotic fracture determinism.² In fact, all the local and best known osteoporosis guidelines draw attention to clinical risk factors for osteoporosis and the need, for accessibility and economic reasons, to limit BMD testing in clinical prescreened populations.³

In this scenario, the appearance of a diagnostic and evaluating tool in which clinical risk factors were put in their right place and weighed according to their relative importance was anxiously awaited by the scientific and clinical community. FRAX® emerged to answer the majority of these questions; in fact, it is simple, validated, available, and adjustable (for some countries), allowing the calculation of risk, and thus an intervention threshold, in osteoporosis. It allows us to calculate fracture risk in the presence or absence of BMD values. Applying FRAX® and accepting that our ten-year intervention threshold risk of hip fracture is at least 3% (and perhaps a total risk of 10%)⁴ may shift our therapeutic intervention toward patients who really do need it; it means, for instance, not treating perimenopausal women without clinical risk factors just because they have low BMD. Why test it in the first place? It also means treating all women if they are over 76, regardless of BMD (as age is a big determinant of risk fracture). Finally, it means treating women with low-energy fractures, even if the T-score is −2.

But, as with other subjects in medicine, not everything is purely black or white… there is a “twilight” zone. Because FRAX® is not perfect, there are some factors that are underweighted by this tool: falls, number of fractures, magnitude and duration of smoking and drinking, vitamin D status, bone remodeling, and vertebral osteoporosis… . And it is for these twilight zone cases that measuring BMD can be useful; for those individuals considered at intermediate risk when calculating FRAX®, for all cases of secondary osteoporosis (this is one area that FRAX® underestimates), probably for everyone above 65 years of age, and whenever the clinician believes that reassessing fracture risk could be useful. In addition, monitoring BMD during osteoporosis treatment is considered a valuable process according the majority of guidelines. We must always remember that there is no guideline, guidance, or tool that should override good clinical judgement!

References
Is BMD measurement still useful with the advent of the FRAX® fracture risk assessment tool?

The World Health Organization (WHO) Consensus Conference defines osteoporosis as a condition of bone deterioration in which individuals have “a bone mineral density (BMD) that lies 2.5 standard deviations or more below the average value for young healthy women,” and the Surgeon General’s report adds to this definition increased risk of fracture. BMD, while associated with fracture risk, is not fully predictive of who will experience a low impact fracture. Large epidemiological studies have shown that BMD accounts for only ≈60% of the fracture risk and have suggested that other “bone quality” parameters may account for why two individuals with similar lifestyles and equivalent BMDs may have different fragility fracture histories. Although measurable decreases in BMD in untreated patients have been associated with increased risk of fragility fracture, areal BMD changes account for less than half of the improvement in fracture risk seen in osteoporotic patients treated with anticatabolic and anabolic agents.

FRAX® is a computer based algorithm that provides models for the assessment of fracture probability in men and women. The approach uses easily obtained clinical risk factors to estimate 10-year fracture probability. Clinical risk factors include age, low body mass index (BMI), previous fracture, parent’s osteoporotic fracture, corticosteroid use, rheumatoid arthritis, secondary osteoporosis, low BMD, excess alcohol consumption, and smoking. The estimate can be used alone or with femoral neck BMD to enhance fracture risk prediction.

The use of FRAX® with the generation of a number does not, however, replace clinical judgment. For example, several of the clinical risk factors identified take no account of dose-response, but give risk ratios for an average dose or exposure. By contrast, there is good evidence that the risk associated with excess alcohol consumption, cigarette smoking, and the use of glucocorticoids is dose-responsive. In addition, the risk of fracture increases progressively with the number of prior fractures. These limitations should be recognized when interpreting a FRAX® result in the clinic. It should also be acknowledged that there are many other risk factors for fracture that are not incorporated into assessment algorithms. Examples include the biochemical markers of bone turnover.

The obvious application of FRAX® is in the assessment of individuals to identify those who would be candidates for pharmacological intervention. Experts in the care of patients with osteoporosis are used to integrating information derived from multiple risk factors. By contrast, primary care physicians in most countries have little expert knowledge, and it is for this constituency that FRAX® has been primarily designed. Physicians should not consider the FRAX® tool as a gold standard, but rather as a platform technology on which to build as new validated risk indicators become available.

In clinical practice, areal BMD can only be useful in determining if a patient is healthy, osteopenic, or osteoporotic at first visit according to the WHO criteria, but does not answer questions about the patient’s fracture risk and treatment decisions. The FRAX® model is an aid to enhance patient assessment by the integration of clinical risk factors alone and/or in combination with BMD. Other tools, such as determination of bone turnover, can provide physicians with further valuable information for treatment, when available.

References
Is BMD measurement still useful with the advent of the FRAX® fracture risk assessment tool?

**References**

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Osteoporosis is a collective name for diseases with different pathomechanisms, but with a common clinical output: fragility fracture. Bone fragility is predominantly determined by mineral content, but other bone properties also contribute toward ensuring mechanical competence. The collagen network, microstructure of bone tissue, trabecular network, and size and macrostructure of bones are accepted as important, while the role of elasticity, the osteocyte network (vectorially governing bone turnover), and other contributors to bone quality are only recently becoming clear. As most of these factors cannot be evaluated in daily practice, the link between pathophysiological knowledge and patient management remains a point of controversy. Little is known about the relation of bone properties to widely used clinical risk factors (CRFs), while bone mineral density (BMD) has more or less of an impact on bone quality.

Until now, the diagnostic criteria for osteoporosis (T-score < –2.5) has also been used as an intervention threshold. This method has poor cost-effectiveness. The risk/benefit ratio has also proven inappropriate as half of fractures occur in patients with normal BMD or osteopenia. FRAX®, the new 10-year fracture risk assessment tool, has provided an elegant solution to this problem, with a limited number of CRFs tested on robust databases of thousands of people. Using this tool new health economic strategies can be formulated for each country and more precise treatment decisions can be made for individual patients. While FRAX® is convincing and accepted worldwide, some limitations have been highlighted by the original authors and others.

Firstly, one needs to recognize that BMD is not the main point of a FRAX® calculation. Only hip BMD is involved and, moreover, a fracture probability can even be obtained without BMD at all. Does this suggest that BMD will be unnecessary with the advent of FRAX®?

First of all, BMD is still an existing basis for the definition of osteoporosis (T-score < –2.5), like blood pressure measurement is for the diagnosis of hypertension. This is not a medical, but a financial way of selecting patients for treatment at a currently acceptable level of cost-effectiveness. A relationship between BMD measured and fracture risk (twofold increase per T-score SD) also exists. Moreover, fluctuations and variability in BMD of different bones depend on a patient’s genetic profile and individual lifestyle (physical activity). This is why the International Society for Clinical Densitometry (ISCD) recommends testing BMD in a range of bones and using the lowest value for diagnosis. Young postmenopausal women with low vertebral but normal femoral BMD provide a good example of why this recommendation exists.

The clinical risk factors of FRAX® have been carefully evaluated for their relationships to BMD. Thanks to these associations, FRAX® provides a more relevant indication for intervention in osteopenia, which is a big step forward in osteoporosis management. However, BMD can help in cases where FRAX® has limitations, eg, dosage of glucocorticoids or severity of previous fractures (site, number, and type). The exclusive role of hip BMD was due to technical limitations, so the involvement of other bones remains to be evaluated. A more promising approach is the use of nonmass methods like quantitative bone ultrasound (elasticity + trabecular integrity), for which the 10-year fracture probability has been calculated by Kanis et al. Involving turnover markers seems to be an exciting step, too. Risk due to vitamin D deficiency has also not been incorporated in FRAX®, but is partly reflected by BMD. Bone density has an effect on fracture risk independent of some clinical risk factors, but related to others. Not surprisingly, the fracture probability calculated from clinical factors and BMD T-score < –2.0 was higher than the probability calculated using only clinical risk factors. In contrast, a normal or slightly decreased BMD (T-score > –2.0) decreases calculated fracture risk (unpublished results of our study).

In summary, the advent of FRAX® does not mean the end of BMD. In fact, wider use of BMD and nonmass bone testing methods could help FRAX® provide a more precise risk assessment.

References
Osteoporosis is a common insidious disease seen typically in middle-aged and elderly women due to the postmenopausal fall in estrogen levels. The combination of progressive bone loss and decreased bone quality increases the risk of vertebral, nonvertebral, and hip fracture, causing major morbidity and mortality. In spite of this apparent simple picture, treatment confronts clinicians with three major challenges: first, drugs against osteoporosis have been around for 40 years, but few have proved effective in preventing fractures at all sites; second, the increase in fracture risk in postmenopausal women with osteoporosis is due to a variety of risk factors, whose combination results in a great number of different profiles, obliging clinicians to select a drug that is effective for their patient’s particular profile; third, solid evidence of long-term efficacy is required when treating a chronic disease such as osteoporosis. As an antiosteoporotic agent with a unique mode of action, Protelos (strontium ranelate) is the first drug to meet these challenges. It has a unique mode of action, by means of which it increases bone formation and reduces bone resorption, thus rebalancing bone turnover in favor of bone formation. Protelos builds strong new bone in osteoporotic women, providing protection against vertebral, nonvertebral, and hip fractures. Protelos has been shown to be effective across a variety of profiles: from the youngest to the oldest patients, and from those with osteopenia to those with the most severe osteoporosis. The 2008 European Guidance acknowledged Protelos as the treatment with the most robust evidence of comprehensive antifracture efficacy and, hence, as an unequivocal first-line choice in the treatment of postmenopausal osteoporosis.

Medicographia. 2010;32:59-66 (see French abstract on page 66)
Protelos: comprehensive efficacy against vertebral, nonvertebral, and hip fracture

Treatments of osteoporosis are generally assessed by their ability to prevent two types of fracture: vertebral fractures (the most common type) and hip fractures (the most serious type in terms of morbidity and mortality, especially in the elderly). Surprisingly, few treatments among the armamentarium available to clinicians have proved effective against both vertebral and hip fractures.

Two pivotal efficacy trials, both multinational, randomized, double-blind, and placebo-controlled have confirmed the efficacy of Protelos on each fracture type in a total of 6740 postmenopausal women, all of whom received concomitant calcium/vitamin D supplementation at a dose tailored to the degree of deficiency (calcium 500/1000 mg, vitamin D3 400/800 IU).

The efficacy of Protelos against vertebral fracture was assessed in the Spinal Osteoporosis Therapeutic Intervention (SOTI) trial in 1649 postmenopausal women aged ≥50 years with ≥1 vertebral fracture(s) and lumbar spine bone mineral density (BMD) ≤0.840 g/cm² (Hologic: www.hologic.com). Protelos decreased new vertebral fracture risk by 49% after only 1 year (relative risk [RR], 0.51; 95% confidence interval [CI], 0.36–0.74; \( P<0.001 \)). Clinical vertebral fractures, defined as vertebral fracture coupled with back pain and/or height loss ≥1 cm, fell by 52% also as early as the first year of treatment (RR, 0.48; 95% CI, 0.29–0.80; \( P=0.003 \)). Reductions in vertebral and clinical vertebral fractures at 3 years (41%; RR, 0.59; 95% CI, 0.48–0.73, and 38%; RR, 0.62; 95% CI, 0.47–0.83, respectively; both \( P<0.001 \)) further confirmed the long-term efficacy of Protelos (Figure 2).

The second study, TReatment Of Peripheral Osteoporosis Study (TROPOS), assessed the efficacy of Protelos against nonvertebral and hip fractures in 5091 postmenopausal women with femoral neck BMD equivalent to a T-score below −2.5 SD (centralized normative data analysis; Dr D. O. Slosman, Geneva, Switzerland) and age ≥74 years or 70 to 74 years with an additional fracture risk factor. At 3 years, Protelos decreased the risk of nonvertebral fractures by 16% (RR, 0.84; 95% CI, 0.702–0.995; \( P<0.05 \)) and the risk of major nonvertebral fractures by 19% (RR, 0.81; 95% CI, 0.69–0.95; \( P<0.05 \)).

Figure 1. Three key criteria for the treatment of osteoporosis.

Figure 2. The effects of Protelos on the risk of vertebral fracture in women with postmenopausal osteoporosis in the SOTI study.

Figure 3. Significant decreases in the relative risks of nonvertebral, major nonvertebral, and hip fractures with Protelos vs placebo in the TROPOS study.

fractures (hip, wrist, pelvis, sacrum, ribs-sternum, clavicle, and humerus) by 19% (RR, 0.81; 95% CI, 0.66-0.77; P<0.05). Special attention was paid to the effect of Protelos on hip fractures, because of their devastating consequences in terms of morbidity and mortality. In the subgroup of patients at highest hip fracture risk, ie, those aged ≥74 years with femoral neck T score ≤−2.4 SD, Protelos decreased the risk of hip fractures by 36% (RR, 0.64; 95% CI, 0.412-0.667; P=0.046) over 3 years (Figure 3). At the same time, TROPOS confirmed the SOTI data by showing that Protelos decreased the risk of new vertebral fractures over 1 and 3 years by 45% (RR, 0.55; 95% CI, 0.39-0.77; P<0.001) and 39% (RR, 0.61; 95% CI, 0.51-0.73; P<0.001), respectively, versus placebo.

Protelos is thus effective against osteoporotic fractures at all major sites in postmenopausal women, regardless of disease severity, as recently acknowledged in the European Guidance for the Treatment and Management of Osteoporosis in Postmenopausal Women (Table I).4

**Risk factors**

BMD remains the main fracture risk factor and the basis for diagnosis. Independently of other risk factors, Protelos de-

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<tr>
<th>Prevention of vertebral fracture</th>
<th>Prevention of nonvertebral fracture</th>
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<tr>
<td>Women with osteoporosis</td>
<td>Women with osteoporosis + vertebral fracture</td>
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<td>Protelos</td>
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<td>Alendronate</td>
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<td>Teriparatide and PTH</td>
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In subsets of patients only (post hoc analysis).
† Mixed group of patients with or without prevalent vertebral fractures.
+ = effective drug.

Table I. Protelos is the only treatment to have demonstrated its efficacy on vertebral, nonvertebral, and hip fractures, whatever the severity of osteoporosis. Abbreviations: HRT, hormone replacement therapy; NA, no evidence available; PTH, parathyroid hormone. Adapted from reference 4: Kanis JA, Burlet N, Cooper C, et al. Osteoporos Int. 2008;19:399-428. Copyright © 2008, Springer London.
creases vertebral fracture risk by 39% (RR, 0.61; 95% CI, 0.53-0.70; \(P<0.001\)) in osteoporotic women with hip/lumbar spine T-score ≤-2.5 SD. It is also the only treatment to reduce vertebral fracture risk in osteopenic women (hip/lumbar spine T-score between -1 and -2.5 SD) by a margin as high as 72% (RR, 0.28; 95% CI, 0.07-0.99; \(P=0.045\)). Efficacy is independent of the number of prevalent fractures: in osteoporotic women with no, one, or two prevalent fractures, Protelos reduced vertebral fracture risk by 48% (RR, 0.52; 95% CI, 0.40-0.67; \(P<0.001\)), 45% (RR, 0.55; 95% CI, 0.41-0.74; \(P<0.001\)), and 33% (RR, 0.67; 95% CI, 0.55-0.81; \(P<0.001\)), respectively. Similarly, in osteopenic women with and without prevalent fractures, Protelos decreased vertebral fracture risk by 38% (RR, 0.62; 95% CI, 0.44-0.88; \(P=0.008\)), and 59% (RR, 0.41; 95% CI, 0.17-0.99; \(P=0.039\)).

Bone markers, which allow estimation of the level of bone remodeling in postmenopausal women, are sometimes used to confirm the diagnosis of osteoporosis. Even though the relationship between bone markers and fracture risk has not been established, a treatment that works whatever the level of bone markers can only bolster clinician confidence. In the pooled SOTI and TROPOS populations, Protelos decreased vertebral fracture risk by a significant 31% to 42% (nonsignificant difference) across all ranges of the bone formation marker bALP (bone alkaline phosphatase). Similar decreases, from 37% to 47%, were achieved across all ranges of the bone resorption marker sCTX (serum cross-linked C-telopeptides of type I collagen). The two markers can be combined to differentiate patients into low- and high-turnover groups. Protelos decreased vertebral fracture risk by 33% (RR, 0.67; 95% CI, 0.47-0.95; \(P=0.023\)) and 49% (RR, 0.51; 95% CI, 0.37-0.70; \(P<0.001\)) in low- and high-turnover women, respectively.

Finally the efficacy of Protelos has been shown to be independent of family history of osteoporosis, body mass index, and smoking.

**Young patients with severe osteoporosis**

Osteoporosis is one of the most common disorders in young postmenopausal women. Bone loss, due to a dramatic increase in bone turnover, can be rapid in the first decade after the fall in estrogens. This explains why treatment needs to be initiated early if it is to maximize its effect and prevent more devastating consequences. In postmenopausal women aged 50-65 years, Protelos reduced vertebral fracture risk by 47% (RR, 0.53; 95% CI, 0.33-0.85; \(P=0.006\)) over 3 years and this effect was found to be sustained over a further year, as shown by a 40% reduction in vertebral fracture risk at 4 years (RR, 0.60; 95% CI, 0.39-0.92; \(P=0.017\)). Efficacy was also independent of age in the pooled SOTI and TROPOS populations: 3-year vertebral fracture risk fell by 37% in women <70 years (RR, 0.63; 95% CI, 0.46-0.85; \(P=0.003\)) and by 42% in those aged 70-80 years (RR, 0.58; 95% CI, 0.48-0.68; \(P<0.001\)).

**Elderly and frail patients**

Women over the age of 80 are particularly prone to fractures due to the frequent combination of risk factors in that age group. These women represent about 8% of the postmenopausal population, but account for over 30% of fragility fractures and over 60% of hip fractures. These have particularly debilitating sequelae in terms of delayed fracture healing, functional impairment, loss of autonomy, as well as increased consumption of nursing homes resources, financial cost, and mortality.

In patients over 80, Protelos reduced vertebral fracture risk by 59% (RR, 0.41; 95% CI, 0.22-0.75; \(P=0.002\)), clinical fractures by 37% (RR, 0.63; 95% CI, 0.44-0.91; \(P=0.012\)), and nonvertebral fractures by 41% (RR, 0.59; 95% CI, 0.37-0.95; \(P=0.027\)) after 1 year, and by 32% (RR, 0.68; 95% CI, 0.50-0.92; \(P=0.013\)), 22% (RR, 0.78; 95% CI, 0.61-0.99; \(P=0.040\)), and 31% (RR, 0.69; 95% CI, 0.52-0.92; \(P=0.011\)) after 3 years. Protelos is the only treatment to have shown long-term efficacy in the elderly, with decreases of 31% in vertebral fracture risk (RR, 0.69; 95% CI, 0.52-0.92; \(P=0.010\)) and 26% in nonvertebral fracture risk (RR, 0.74; 95% CI, 0.57-0.95; \(P=0.019\)) over 5 years.

The concept of frailty takes into account a variety of health status factors in addition to age, including decreased strength, tiredness, involuntary weight loss, slowness, and inactivity. Frail osteoporotic women are more vulnerable when exposed to stressors and more likely not only to fall, but to fracture as a result. In frail patients from the SOTI and TROPOS populations, Protelos decreased vertebral fractured risk by 58% (RR, 0.41; 95% CI, 0.23-0.73; \(P=0.002\)) and overall osteoporotic fracture risk by 28% (RR, 0.72; 95% CI, 0.49-1.04; \(P=0.08\)) after 3 years.

Thus, Protelos is similarly effective in reducing the risk of vertebral and nonvertebral fractures in young and elderly postmenopausal women and in the frail elderly, suggesting that the earlier it is introduced after menopause onset, the greater the anticipated benefit.

**Protelos: the only antosteoporotic treatment with long-term antifracture efficacy proven beyond 3 years**

Only treatments with proven long-term efficacy can hope to be effective in treating a lifelong disease such as osteoporosis. Despite this obvious requirement, there are long-term fracture data for few, if any, treatments. At best, they tend to be BMD data and/or fracture data in open studies or calculated as an annual incidence, rather than in terms of efficacy over time. Protelos is alone in having proven antifracture efficacy beyond 3 years, as shown by the findings from TROPOS, which evidenced efficacy sustained over 5 years, and even as much as 8 years in an open-label extension study in a subgroup of SOTI and TROPOS patients.
Protelos, the logical response to osteoporosis – Halbout

Protelos: unique in being effective over 5 years
Proof of the efficacy of Protelos was afforded by TROPOS, a randomized, double-blind, multicenter, placebo-controlled study with preplanned analysis over 5 years in the intention-to-treat population \( n=2714 \).

During that period, Protelos reduced nonvertebral fracture risk by 15% (RR, 0.85; 95% CI, 0.73-0.99; \( P=0.032 \)) and the risk of new major nonvertebral osteoporotic fracture by 18% (RR, 0.82; 95% CI, 0.69-0.98; \( P=0.025 \)) versus placebo.

In a high-risk subgroup \( n=1128 \); \( \geq 74 \) years and lumbar/femoral neck T-score \( \leq -2.4 \) SD), Protelos reduced hip fracture risk by 43% versus placebo over 5 years (RR, 0.57; 95% CI, 0.33-0.97; \( P=0.036 \)) and vertebral fracture risk by 24% (RR, 0.76; 95% CI, 0.65-0.88; \( P<0.001 \)). Overall, Protelos reduced the risk of osteoporotic fracture by 20% versus placebo independently of location (RR, 0.20; 95% CI, 0.71-0.90; \( P<0.001 \)). Only 21 patients needed to be treated with Protelos to prevent 1 new osteoporotic fracture; safety was similar to that over 3 years, with mostly mild and transient side effects. Rates of venous thromboembolism were comparable to those on placebo (2.7% vs 2.1%; odds ratio 1.30).

Protelos and bone architecture

*Protelos improves bone architecture*
Treatment strategy used to focus on decreasing bone resorption, but this strategy had limitations: strong downregulation of bone resorption hindered repair of normal stress-induced microcracks, while there is an inevitable decrease in bone formation induced by antiresorptive treatment due to the coupling between osteoblast and osteoclast activity. Protelos is currently alone among antosteoporotic agents in decreasing bone resorption while increasing bone formation. The net balance is the creation of new bone. Benefits on bone were first shown in bone biopsies from SOTI and TROPOS patients. Treatment for 3 years resulted in bone microarchitecture benefits, as evidenced by increased cortical bone thickness of 18% (\( P=0.008 \)) and trabecular number by 14% (\( P=0.05 \)), while decreasing trabecular separation by 16% (\( P=0.004 \)). These improvements were associated with a change in bone structure from "rod-like" on placebo to "plate-like" on Protelos (Figure 5, page 64).

These benefits of Protelos in terms of bone architecture result from increased osteoblast activity, shown by increases in mineral apposition rate (+9%; \( P=0.019 \)) and osteoblast sur-
face (+38%; \( P=0.047 \)), and a 10% trend toward a decrease in osteoclast surface. Bone biopsy analysis at 5 years revealed no abnormalities in structure or mineralization.\(^{19} \)

\[ \text{Protelos: unique dual mode of action} \]

The experimental evidence accumulated for the dual mode of action of Protelos, notably on osteoblasts, osteoclasts, and bone architecture, has been reviewed elsewhere (Figure 8).\(^{22} \)

An intensive effort is underway to elucidate the molecular basis of its innovative mode of action. Studies in various models have shown that Protelos has a direct effect on both osteoblasts and osteoclasts by increasing osteoblast replication, differentiation, and activity,\(^{23-26} \) while simultaneously downregulating osteoclast differentiation and activity.\(^{26-29} \) A recent Australian study also shows that Protelos promotes osteocyte differentiation into osteoblasts.\(^{30} \)

Protelos modulates the level of two major factors closely involved in regulating osteoclastogenesis by osteoblasts. Osteoprotegerin (OPG) and receptor activator nuclear factor-κB ligand (RANKL) are both expressed by osteoblasts. The OPG/RANKL ratio governs osteoclastogenesis: a low ratio promotes osteoclastogenesis, a high ratio downregulates it. Two studies in human osteoblasts have shown Protelos to increase mRNA expression of OPG, while simultaneously decreasing mRNA expression of RANKL. This is highly predictive of subsequent downregulation of osteoclastogenesis.\(^{30,31} \) In the same studies, Protelos increased the replication and differentiation


\[ \text{Figure 6.} \text{ Comparison of the changes in cortical thickness and the ratio of bone volume to total volume for Protelos and alendronate. Abbreviations: C.Th, cortical thickness; BV/TV, bone volume/total volume. Modified from reference 20: Rizzoli R, Felsenberg D, Laroche M, et al. Ann Rheum Dis. 2009;68(suppl 3):669. Abstract SAT0388.} \]
Protelos, the logical response to osteoporosis—Halbout

of human osteoblasts, which are similarly highly predictive of subsequent enhancement of bone formation. This was the first evidence to show that Protelos modulates both bone formation and bone resorption by acting directly on human osteoblasts, suggesting that osteoblasts play a key role in the drug’s mechanism of action.

A remarkable mouse model of severe osteoporosis and spontaneous fracture recently confirmed the link between the benefits of Protelos on bone architecture and osteoporotic fracture prevention. Protelos decreased the number of new fractures by 60% vs controls after 9 weeks. Spontaneous fracture prevention was related to a net improvement in both trabecular and cortical microarchitecture.32

Bone marker monitoring in clinical trials has consistently confirmed the dual mode of action revealed in the in vitro studies. In women receiving Protelos in both SOTI and TROPOS, bALP (a marker of bone formation) independently increased, while sCTX (a marker of bone resorption) decreased. These effects were detected as early as after 3 months of treatment (bALP, +8.1%; P<0.001; and sCTX, −12.2%; P<0.001) and were sustained over 3 years.3 These trials thus confirmed the clinical benefits of the dual mode of action of Protelos: new bone formation, improved bone quality, greater bone strength, and lower fracture risk.

Conclusion

Protelos has proved its efficacy against vertebral, nonvertebral, and hip fractures. This treatment is the only one to have also proven its efficacy across a wide spectrum of patient profiles. In addition, Protelos is the only treatment to have proven its efficacy over 5 years, which is sustained for up to 8 years. Furthermore, this long-term efficacy was associated with very good safety and tolerability. These unique benefits are explained by the ability of Protelos to build new, strong bone, thanks to its unique dual mode of action. The benefits on the microarchitecture have been proven consistently, with improvement in both cortical and trabecular bone (the main determinants of hip and vertebral fractures, respectively). Protelos has all the characteristics of a major treatment and must be considered a first-line treatment in the armamentarium of clinicians concerned with the treatment of osteoporosis.

References

7. Roux C, Reginster JY, Fechtenbaum J, et al. Vertebral fracture risk reduction with strontium ranelate in women with postmenopausal osteoporosis is inde-
U NE IMPORTANTE EFFICACITÉ ANTIFRACTURAIRE COUPLÉE À DES BÉNÉFICES OSSEUX ORIGINAUX :
PROTELOS, LA RÉPONSE LOGIQUE À L’OSTÉOPOROSE

L’ostéoporose est une pathologie courante et insidieuse caractéristique des femmes d’âge moyen et élevé due à la chute post-ménopausique des taux d’estrogènes. L’association de la perte osseuse progressive et de la diminution de la qualité osseuse augmente le risque de fracture vertébrale, non vertébrale et de la hanche, source de morbidité et de mortalité importantes. Malgré ce contexte apparemment simple, les médecins sont confrontés à trois défis thérapeutiques majeurs : premièrement, en dépit de la disponibilité de médicaments antiostéoporotiques depuis quelque 40 ans, peu d’entre eux se sont montrés efficaces à tous les sites de fractures ostéoporotiques ; deuxièmement, de nombreux facteurs augmentent le risque de fracture chez les femmes ménopausées ostéoporotiques, aboutissant à un grand nombre de profils différents, obligeant ainsi les médecins à sélectionner un médicament efficace pour chaque patient en particulier ; troisièmement, il faut des preuves fiables d’efficacité à long terme pour traiter une maladie chronique comme l’ostéoporose. Protelos (ranélate de strontium) est le premier médicament antiostéoporotique qui répond à ces critères : son mode d’action original lui permet d’augmenter la formation osseuse et de diminuer la résorption osseuse, rééquilibrant ainsi le métabolisme osseux en faveur de la formation. Protelos construit un nouvel os solide chez les femmes ostéoporotiques, assurant ainsi une protection contre les fractures vertébrales, non vertébrales et de la hanche. Protelos se montre efficace quels que soient les profils des patientes : des plus jeunes aux plus âgées, et des ostéopénies aux ostéoporoses les plus sévères. Protelos a été reconnu par les recommandations européennes 2008 comme le traitement possédant la démonstration la plus complète d’efficacité antifracturaire et représente ainsi sans conteste un traitement de premier choix de l’ostéoporose ménopausique.

Keywords: strontium ranélate; osteoporosis; treatment guidelines; Protelos
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 economics 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.

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
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.

**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. Previous dichotomous selection, based on the 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.

**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). The ESCEO guidance document recommends the selection of a treatment option based on

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**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 |

**Table I. Comparison of the antifracture efficacy of common osteoporosis treatments.**

<table>
<thead>
<tr>
<th>Osteoporosis</th>
<th>Established osteoporosis*</th>
<th>Osteoporosis</th>
<th>Established osteoporosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>+</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>Risedronate</td>
<td>+</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>+</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>HRT</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>+</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>Teriparatide and PTH</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>+</td>
<td>+</td>
<td>+ (including hip)</td>
</tr>
</tbody>
</table>

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

+ = effective drug.
monitoring of treatment can be done with biochemical markers of bone turnover or bone mineral density assessment. Whether the long-term antifracture efficacy of antosteoporotic 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.

**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-

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

<table>
<thead>
<tr>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Low body mass index</td>
</tr>
<tr>
<td>Previous fragility fracture, particularly of the hip, wrist, and spine</td>
</tr>
<tr>
<td>Glucocorticoid treatment (&gt;5 mg prednisolone daily or equivalent for 3 months or more)</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>Alcohol intake of 3 or more units daily</td>
</tr>
<tr>
<td>Secondary causes of osteoporosis</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Untreated hypogonadism in men and women, eg, premature menopause, bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy for breast cancer, hypopituitarism</td>
</tr>
<tr>
<td>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)</td>
</tr>
<tr>
<td>Prolonged immobility, eg, spinal cord injury, Parkinson’s disease, stroke, muscular dystrophy, ankylosing spondylitis</td>
</tr>
<tr>
<td>Organ transplantation</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Thyroid disorders, eg, untreated hyperthyroidism, overtreated hypothyroidism</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
</tbody>
</table>
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.

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 candidatures 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.
Although osteoporosis is less prevalent in men, it has been estimated that 30% of all hip fractures occur in males and that one in eight men older than 50 years will experience an osteoporotic fracture. The reported prevalence is further increasing due to the increasing life expectancy of men, measuring bone mineral density more frequently in men with back pain, and probably due to general changes in nutrition and lifestyle with a negative impact on calcium metabolism and the skeleton.

Osteoporosis in men

J. D. Ringe, Germany

Osteoporosis in men is today recognized worldwide as an important and growing public health problem. Although osteoporosis is less prevalent in men, 30% of all hip fractures occur in males and the prevalence of vertebral fractures—half of that in women—is still substantial. Loss of trabecular bone in aging men is associated with changes in the insulinlike growth factor 1 (IGF-1) regulation system leading to trabecular thinning, rather than the reduced trabecular connectivity seen in women after the menopause. Cortical bone loss in men, however, starts later in life and is associated with a decrease in physical activity and bioavailability of both sex hormones. Alendronate was the first bisphosphonate to be approved for the treatment of male osteoporosis based on consistently positive effects on bone mineral density (BMD) and vertebral fractures from two independent studies in men on a daily dosage of 10 mg. Just two years ago, risedronate followed suit with its once-weekly dosage and, recently, 5 mg zoledronic acid IV once yearly and teriparatide—as the first osteaanabolic agent for men—were approved. Up till now, etidronate and ibandronate have been insufficiently studied in men. Pilot study data show that the lumbar spine and total hip BMD increases seen with strontium ranelate are consistent with those found previously in postmenopausal women. A randomized, placebo-controlled trial testing this innovative dual-action drug in a purely male population has been set up to confirm these preliminary results and will soon be finished.

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The rather exclusive focus on postmenopausal osteoporosis in the past has undoubtedly led to an underreporting of osteoporosis in men. Fifteen years ago, it was shown that 29% of men and 56% of women, if they are currently 60 years old and receive no preventive measures, will experience fractures during their remaining lifetime. Only in the past decade has attention been focused upon the increasingly important problem of osteoporosis in men. Efforts devoted to the issue have been successful. There is today a much better understanding of the disorder, and effective diagnostic, preventive, and therapeutic strategies have been developed. Today, osteoporosis in men is recognized as an important public health problem and has developed into a very active research issue. Male-female differences have been revealed that in turn have had positive effects on our understanding of bone biology in general. Drugs that have been developed primarily for the treatment of postmenopausal osteoporosis have been studied and approved for male osteoporosis with a typical delay of several years.
The magnitude of the problem

Although osteoporosis is less prevalent in men, it has been estimated that 30% of all hip fractures occur in males and that one in eight men older than 50 years will experience an osteoporotic fracture.\(^3,4\) Moreover, studies have shown that the mortality rate after fracture in men is higher compared with that in women.\(^5,7\) The reported prevalence is further increasing due to the increasing life expectancy of men, measuring bone mineral density more frequently in men with back pain, and probably due to general changes in nutrition and lifestyle with a negative impact on calcium metabolism and the skeleton.\(^3,8\) In our outpatient department today, already 20% of patients presenting for diagnosis and treatment of osteoporosis are men. Nevertheless, the disease remains largely underdiagnosed and undertreated.\(^9,10\)

**Epidemiology of fractures**

The incidence of fractures is bimodal in both sexes with peaks of fracture incidence in adolescence and young adulthood, lower rates in middle age, and dramatic increases thereafter. Figure 1 clearly shows that men have a higher “juvenile peak”, possibly due to a higher risk of traumatic impacts. The sharp increase in later life in men is as dramatic as in women, but occurs about 10 years later in life.\(^11\) In younger men, long bone fractures are more common, whereas vertebral and hip fractures predominate in the elderly, where skeletal fragility, frailty, and falls are major factors.\(^12\) The age-adjusted incidence of hip fractures in men is one third to one half that of women. There is less information concerning vertebral fracture rates in men. According to data from the European Prospective Osteoporosis Study (EPOS), the age-adjusted incidence in men seems to be rather high, reaching 50% of that in women.\(^13\)

**Pathogenesis of male osteoporosis**

According to results of longitudinal studies, bone loss accelerates in men after the age of 70 and rapid bone loss is more common with deficient testosterone and estradiol levels.\(^14,15\) In contrast to women developing reduced trabecular connectivity due to a loss of trabeculae, men show trabecular thinning secondary to reduced osteoblastic formation.\(^16,17\) The better preservation of spongic bone microstructure may explain their 50% lower lifetime risk of fractures.\(^1\) The loss of trabecular bone in men starts after reaching peak bone mass in association with changes in the insulin-like growth factor 1 (IGF-1) regulation system. Cortical bone loss, however, starts later in life and is associated with decreasing physical activity and bioavailability of both sex hormones, causing increased bone remodeling. Up to 85% is lost after age 50.\(^18\) As important differences between men and women, it was always stated that men lose less bone than women from the endosteal envelope and that they gain more bone on the periosteal envelope with advancing age. Recent evidence challenges these observations and further research is requested.\(^19-21\) Data from the MINOS study on 796 elderly men showed that low muscle mass in men is associated with narrower bones, thinner cortices, and a consequent decreased bending strength.\(^12\)

The cause of osteoporosis in men is much more heterogeneous than in women; 50% to 60% of men with osteoporosis are diagnosed as secondary cases, ie, the disease is associated with one or more relevant medical conditions, medications, or lifestyle factors that may result in bone loss and reduced bone strength.\(^2,22\) The reported pattern of identified risk factors in men varies largely between centers due to differences in the respective patient sources.\(^23\) In our own earlier study on 500 unselected men, we found that 52% had primary idiopathic and 48% secondary osteoporosis.\(^2,8\) Among the latter, we identified a subgroup of monoetiological (n=124) and another of polyetiological origin (n=116). In Table I, the frequency of risk factors in these 240 males is shown in terms of mono- and polyetiological subgroups. It becomes obvious that some factors are “strong” pathogenetic risks, which lead to secondary osteoporosis on their own (for example, numbers 1, 4, 5, 11, and 21 in Table I), while other “weak” risk fac-
tors only cause osteoporosis when in combination (for example, numbers 2,3,6,7,8, and 10 in Table I). In an important fraction of osteoporotic men, hypercalcemia can be detected as an underlying disorder. In our study, we found this risk factor in 34 patients (Table I). Interestingly, idiopathic hypercalcemia is an uncommon risk factor in osteoporotic women.

**Diagnosis of osteoporosis in men**

There are important sexual differences in skeletal biology that may influence bone density measurement. In particular, bone size is larger in men. For diagnostic purposes, gender differences are addressed by the use of sex-specific T-scores, but this practice remains controversial. Epidemiologic data suggest that for any given absolute bone mineral density (BMD) value at the spine or hip, the risk of fracture is similar among women and men of the same age. Since the prevalence of degenerative changes in men at the lumbar spine with increasing age is very high, measurements of bone mineral density at the femoral neck or total hip are preferable to spinal assessments. The average BMD in men who fracture a hip, however, is higher than in women, suggesting that other factors such as bone microarchitecture or trauma may contribute to fractures more in men than in women. Until safety data are available to confidently link fracture risk to BMD measurements in men, the use of male-specific reference ranges has to be adopted. Today in most guidelines, bone densitometry is recommended in men aged 70 or older or earlier in men with major risk factors for osteoporotic fractures. That means male patients should be assessed routinely for risk factors for osteoporosis and for clinical symptoms of secondary osteoporosis.

Additional examinations to obtain a definite diagnosis of osteoporosis are not very different from the procedures used in women. When proving a BMD z-score below –2.0 (2 SD below the age-related mean), a clinical examination and further laboratory testing for secondary osteoporosis is indicated. In our osteoporosis center, we use a 25-question questionnaire as a first source of information. The answers are verified by taking a thorough personal history of the patient, with an evaluation of possible underlying diseases, medications, risk factors of lifestyle, and finally a physical examination. The results are a basis to judge the extent of additional blood and urine examinations and any further diagnostic program. Since hypogonadism is often difficult to detect on the basis of a patient’s history and physical examination, measurement of total testosterone and sex hormone-binding globulin (SHBG) is recommended in all men with osteoporosis. 25-Hydroxyvitamin D should be measured in patients reporting low exposure to sunshine and/or with low-normal serum calcium, hypocalcemia, or increased parathyroid hormone. There are only limited data relating markers of bone turnover to fracture risk in men. Because they show high biological variability, routine use of these markers cannot be recommended. They may, however, be useful in men with no apparent cause of osteoporosis and in men with very low BMD for detecting low levels of bone formation.

**Table I. Risk factors in men with secondary osteoporosis.**

<table>
<thead>
<tr>
<th>Frequency of risk factors in 240 males with secondary osteoporosis</th>
<th>Total (n=240)</th>
<th>Monoetiological (n=123)</th>
<th>Polyetiological (n=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Long-term GC therapy</td>
<td>82</td>
<td>35</td>
<td>47</td>
</tr>
<tr>
<td>2. Chronic alcoholism</td>
<td>56</td>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>3. Heavy smoker</td>
<td>54</td>
<td>0</td>
<td>54</td>
</tr>
<tr>
<td>4. Hypogonadism</td>
<td>49</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>5. Idiopathic hypercalcium</td>
<td>34</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>6. Chronic liver disease</td>
<td>19</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>7. Asthma (without GCs)</td>
<td>17</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>8. Crohn’s disease (without GCs)</td>
<td>17</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>9. Gastric surgery</td>
<td>17</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>10. Anticonvulsive therapy</td>
<td>12</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>11. Multiple myeloma</td>
<td>11</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>12. Low-calcium diet</td>
<td>10</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>13. Immobilization</td>
<td>10</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>14. Diabetes mellitus</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>15. Primary hyperparathyroidism</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>16. Thyrotoxicosis</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>17. Rheumatoid arthritis (without GCs)</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>18. Thyroxine therapy</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>19. Heparin therapy</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>20. Familial osteoporosis</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>21. Mastocytosis</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>22. Hypophosphatemia</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>23. Lymphoproliferative disease</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>24. Cushings’s syndrome</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>25. Cardiac transplantation</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>26. Bone marrow metastases</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>27. Osteogenesis imperfecta</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>28. Hypopituitarism</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>29. Celiac disease</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Pattern and frequency of risk factors in 240 men with secondary osteoporosis distinguishing between mono- and polyetiological subgroups.

Abbreviation: GC, glucocorticoid.

Prevention of osteopenia and fractures in men

Measures to avoid bone loss and associated fractures in men are similar to those in women. In early life, a combination of good nutrition, regular exercise, and a healthy lifestyle should aim to produce a high peak bone mass. Reducing modifiable individual risk factors of diet and lifestyle, including alcohol, nicotine, and physical inactivity, remain important throughout life.30

For men with one or more diseases or medical conditions associated with a high risk of developing secondary osteoporosis (Table I), early detection and counteracting measures are important. Examples include a reduction of glucocorticoid dosage if possible, substitution of androgen in hypogonadism, thiazides in idiopathic hypercalciuria, or early surgical treatment of primary hyperparathyroidism.2,30

In the elderly at risk of falls (eg, reduced muscle strength, poor balance, frailty, and history of previous falls), attempts to increase strength and balance or the use of a hip protector may be beneficial. Due to positive effects on muscle mass and function, vitamin D supplementation of at least 800 IU per day reduces the risk of falls.31,32 There are still conflicting data on the benefits of calcium and vitamin D in osteoporosis, but more recent meta-analyses favor beneficial effects on falls and fractures.33,34 Table II summarizes general recommendations for the prevention of bone loss and osteoporotic fractures in men.

- Long-term regular physical activity and exercise.
- Maintenance of adequate calcium and vitamin D intake throughout life by diet and/or supplementation (total intakes 1000-1500 mg calcium and 800-1200 IU vitamin D per day).
- Routine calcium/vitamin D supplementation after age of 70.
- Limit alcohol intake and smoking.
- Recognize and treat testosterone deficiency.
- Identify other risk factors (Table I) and consider specific prophylactic measures.
- Advice to avoid falls and selective use of hip protection in elderly frequent-fallers.

Table II. General measures for prevention of bone loss and osteoporotic fractures in men.

The therapeutic dilemma of male osteoporosis

Even today, not all drugs available for women with postmenopausal osteoporosis are also approved treatments for osteoporosis in men. This is due to the fact that data from earlier trials on mixed female-male populations have not been accepted and that the requested randomized controlled studies on purely male cohorts are always smaller and often contain insufficient fracture reduction evidence.

Earlier drugs were approved for osteoporosis in general, without separate trials in men being asked for (eg, calcium, fluoride, calcitonin, and alfacalcidol). These are still available for treating osteoporosis in men in some countries. Starting with the bisphosphonates, health authorities only approved new substances for postmenopausal osteoporosis, arguing that the respective phase 3 trials had been performed in this population. Furthermore, it was suggested that significant differences in bone biology might exist between the sexes, with consequent clinically relevant differences in therapeutic response.

Accordingly, nowadays the approval for using a new drug in men follows after several years’ delay in general or never, if the respective pharmaceutical company considers a new independent study in men as being too expensive given the limited time of their patent protection. This is a severe therapeutic disadvantage for men with osteoporosis. To prescribe innovative drugs to men with established osteoporosis “off label” is often difficult because insurers tend to be reluctant to reimburse the costs in many countries. Interestingly, so far for all drugs studied in men, similar therapeutic results to those seen in women in terms of BMD, bone turnover markers, and fracture-reducing potency have been reported, disproving the argument that relevant basic differences exist in the bone biology of the female and male skeleton.30

Osteoporosis therapy in men

- Causative therapy in secondary osteoporosis

Since about 50% of men are diagnosed as having secondary osteoporosis, an etiologically tailored treatment is more important in male than in postmenopausal osteoporosis. In hypogonadal men with secondary osteoporosis, androgen replacement therapy is effective.36-37 We recommend a combination with calcium and vitamin D and found that subcutaneous or transdermal testosterone therapy, especially in advanced osteoporosis, is not sufficient per se to significantly improve BMD.2 A combination with another bone turnover-modifying substance is very often mandatory. Contraindications for androgen use (lipid pattern, prostatic cancer risk) have to be taken into consideration.

Other examples of a causative therapy have been mentioned above under prevention. In glucocorticoid-induced osteoporosis, a premature reduction in corticoids may increase the risk of osteoporosis, since an insufficient immunosuppressive effect will favor further loss of bone tissue by proinflammatory cytokines.38 Furthermore, insufficient disease control is associated with less mobility. For the majority of secondary osteoporoses (see Table I), no causative therapies are available, ie, therapeutic strategy is the same as that for idiopathic osteoporosis.

- Treatment of idiopathic osteoporosis

In men with secondary osteoporosis without options for etiology-related treatment and in all primary or idiopathic cases of osteoporosis, an individually tailored therapeutic strategy has to be planned. A prerequisite for devising this long-term strategy is information about the history and present situation.
In a prospective controlled 3-year trial in 60 men with primary osteoporosis, we found a significantly lower vertebral fracture rate with low-dose intermittent fluoride therapy when compared with controls receiving only calcium plus vitamin D. Alendronate was shown to be effective for the treatment of male osteoporosis and was the first bisphosphonate to be approved for this indication. The positive evidence was mainly based on two large trials. The first trial was a two-year multicenter randomized placebo-controlled US study on 241 men with primary osteoporosis or secondary osteoporosis due to hypogonadism. In the second trial, an open prospective controlled study by our group, 134 men with only idiopathic osteoporosis were treated over 3 years. Both studies proved that the therapeutic results on BMD and fracture incidence with 10 mg alendronate daily are consistent with the effects known for postmenopausal osteoporosis. Although similar effects on BMD and significant decreases in bone turnover markers could be demonstrated with alendronate 70 mg once weekly, this dosage was never approved for male osteoporosis.

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**Calcitonin, fluoride, and alfacalcidol**

There are only older case reports or small studies for these treatments in male osteoporosis. In a double-blind, placebo-controlled study testing the physiological osteoclast inhibitor calcitonin, 28 men received either 200 IU salmon calcitonin via nasal spray plus 500 mg calcium per day or placebo via nasal spray plus calcium. A significant lumbar spine BMD increase of 7.1% in the calcitonin group vs 2.4% in the controls was found in parallel with a higher decrease in bone resorption markers with calcitonin. In another study, 28 men with glucocorticoid-induced osteoporosis were treated with 200 IU salmon calcitonin via nasal spray plus 500 mg calcium per day or placebo via nasal spray plus calcium. A significant lumbar spine BMD increase of 7.1% in the calcitonin group vs 2.4% in the controls was found in parallel with a higher decrease in bone resorption markers with calcitonin. In a prospective controlled 3-year trial in 60 men with primary osteoporosis, we found a significantly lower vertebral fracture rate with low-dose intermittent fluoride therapy when compared with controls receiving only calcium plus vitamin D. Further relevant studies with fluoride in men were not undertaken mainly due to the low cost of the substance and the lack of patent protection.

Only recently, it was shown that treatment with the active D-hormone analogue alfacalcidol plus calcium is superior to plain vitamin D plus calcium in male osteoporosis.

**Bisphosphonates**

There are only two small uncontrolled studies using the typical intermittent cyclical therapeutic regimen with etidronate in men with osteoporosis that show significant effects on BMD, but no fracture results.

Alendronate was shown to be effective for the treatment of male osteoporosis and was the first bisphosphonate to be approved for this indication. The positive evidence was mainly based on two large trials. The first trial was a two-year multicenter randomized placebo-controlled US study on 241 men with primary osteoporosis or secondary osteoporosis due to hypogonadism. In the second trial, an open prospective controlled study by our group, 134 men with only idiopathic osteoporosis were treated over 3 years. Both studies proved that the therapeutic results on BMD and fracture incidence with 10 mg alendronate daily are consistent with the effects known for postmenopausal osteoporosis. Although similar effects on BMD and significant decreases in bone turnover markers could be demonstrated with alendronate 70 mg once weekly, this dosage was never approved for male osteoporosis.

The first evidence that risedronate is also effective in men came from a large subgroup of male patients with glucocorticoid-induced osteoporosis. We were the first to investigate
the therapeutic efficacy of risendronate in a purely male population (n=316) with primary and secondary osteoporosis. Patients were randomized to risendronate or controls, stratified by the presence of prevalent vertebral fractures at baseline. All patients in the bisphosphonate treatment arm received 5 mg risendronate plus 1000 mg calcium and 800 IU vitamin D daily. Patients in the control group received 1 µg alfalcacidol plus 500 mg calcium daily if they had prevalent vertebral fractures and 1000 IU plain vitamin D plus 800 mg calcium per day if they did not. After 12 and 24 months, we found significantly higher increases in lumbar spine and total hip BMD with risendronate compared with the combined controls. The relative risk reduction of patients with new vertebral fractures with risendronate was 60% after the first and 61% after the second year of intervention.

We concluded from the CASIMO trial that strontium ranelate—treated patients compared with alendronate, at both sites (Figure 3), and were consistent with the respective average 12 month increases from the pivotal fracture studies with strontium ranelate in postmenopausal osteoporosis. Interestingly, there was a significantly steeper reduction in back pain in strontium ranelate–treated patients.

We concluded from the CASIMO trial that strontium ranelate is at least as potent if not superior in men with established osteoporosis as alendronate, which has received approval for this indication. A multicenter international trial with strontium ranelate in men is due to finish soon.

Figure 3. Effect of year-long osteoporosis therapy on BMD. Average increases in lumbar spine and total hip BMD after 12 months with strontium ranelate or alendronate (the CASIMO trial).

Abbreviations: BMD, bone mineral density; CASIMO, Comparing Alendronate and Strontium ranelate In Male Osteoporosis; LS, lumbar spine; TH, total hip.


Risedronate 35 mg per week was studied in an international randomized placebo-controlled study. Some 192 patients received once weekly risedronate and 93, placebo. All patients received additional supplementation of 1000 mg calcium and 400-500 IU vitamin D. After 2 years, there was a significant increase in lumbar spine BMD of 5.8% in the risedronate group versus 1.2% in controls. Concerning all new fracture events documented as adverse events, there was a positive trend in favor of risedronate, but no significant difference (7.7% placebo vs 4.9% risedronate). Risedronate 35 mg once weekly was the second bisphosphonate to be approved for the treatment of men at high fracture risk, and its fracture reducing potency was recently underlined by a meta-analysis. There are no relevant studies on pamidronate and ibandronate in men. Zoledronic acid 5 mg once yearly by infusion, however, was approved recently for male osteoporosis. In a subset of 508 men from the Health Outcomes and Reduced Incidence with Zoledronic Acid ONce yearly (HORIZON) recurrent fracture trial, significant increases in total hip BMD and a reduction in the rate of new clinical fractures could be demonstrated.

A large purely male study comparing once yearly zoledronic acid versus placebo is currently being performed.

**Teriparatide and strontium ranelate**

There are two trials that have studied the osteoanabolic effect of parathyroid hormone (PTH) in men with osteoporosis. The first one was a small pilot study (n=23) with daily injections of 400 IU teriparatide (rhPTH[1-34]) in 10 patients and placebo injections in 13. After 18 months, average lumbar spine BMD had increased 13.5% in the PTH group and was unchanged in the placebo group (P<0.001). This mean rate of gain in BMD was consistent with the rate seen in the pivotal fracture trial in postmenopausal osteoporosis. A larger international trial of 437 men with osteoporosis (20 µg or 40 µg rhPTH daily or subcutaneous placebo) over 11 months plus 18 months' follow-up found similar effects on BMD and a significantly lower rate of vertebral fractures for the pooled PTH groups.

With strontium ranelate in postmenopausal osteoporosis, significant effects on all fracture types over the whole age range from early postmenopausal to advanced age could be demonstrated. In the open-label, controlled, prospective CASIMO (Comparing Alendronate and Strontium ranelate In Male Osteoporosis) trial, we randomly included 152 men (mean age 59.8 years) with prevalent vertebral fractures and T-score values of lower than –3.0 SD at lumbar spine and lower than –2.5 SD at total hip. Patients of group A (n=76) received 2 g strontium ranelate plus 800 IU vitamin D and 1200 mg calcium per day. The 76 men of group B were treated with alendronate 70 mg once weekly and the same daily amounts of vitamin D and calcium. After 12 months, the average lumbar spine–bone mineral density (LS-BMD) increase was 5.8% and 4.5% in the strontium ranelate and alendronate patients, respectively. The corresponding mean changes at total hip amounted to 3.5% and 2.7%.

These increases were significantly higher for the strontium ranelate–treated patients compared with alendronate, at both sites (Figure 3), and were consistent with the respective average 12 month increases from the pivotal fracture studies with strontium ranelate in postmenopausal osteoporosis. Interestingly, there was a significantly steeper reduction in back pain in strontium ranelate–treated patients.
Conclusion
Although the causes of osteoporosis are more heterogeneous in men than they are in women (about 50% of cases in men are diagnosed as secondary cases), the options for prevention and basic therapy of osteoporosis are the same as those in postmenopausal women. Initially, modifying and counteracting existing negative risk factors, especially those relating to diet, physical exercise, and calcium and vitamin D supplementation, is recommended. The current treatments available for male osteoporosis are alendrone, risedronate, and zolendronate, but strontium ranelate has good potential with some promising results. More news about strontium ranelate will shortly be available after the completion of an ongoing international multicenter study.

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Focus

OSTÉOPOROSE MASCULINE

L’ostéoporose masculine est aujourd’hui reconnue dans le monde entier comme un problème de santé publique important et en croissance. Malgré une moindre prévalence de l’ostéoporose masculine, 30 % de toutes les fractures de hanche ont lieu chez les hommes et la prévalence des fractures vertébrales (la moitié de celles des femmes) reste importante. La perte d’os trabéculaire des hommes âgés s’associe aux modifications du système de régulation du facteur de croissance analogue à l’insuline de type 1 (IGF-1), conduisant à un amincissement trabéculaire, plutôt qu’à une réduction de la connectivité trabéculaire telle qu’elle est observée chez les femmes après la ménopause. La perte d’os cortical chez les hommes commence cependant plus tard dans la vie et s’associe à une diminution de l’activité physique et de la biodisponibilité des deux types d’hormones sexuelles. Deux études indépendantes chez l’homme ont montré que l’alendronate à la dose quotidienne de 10 mg était le premier bisphosphonate à avoir des effets positifs cohérents sur la densité minérale osseuse (DMO) et les fractures vertébrales dans l’ostéoporose masculine. Il y a juste 2 ans, le dosage hebdomadaire du risedronate a été validé et récemment, l’acide zolédronique IV à 5 mg une fois par an et le tériparatide (comme premier anabolisant osseux masculin) ont été approuvés. L’étidronate et l’ibanronate ont jusqu’à maintenant été insuffisamment étudiés chez les hommes. Les données d’une étude pilote montrent que l’augmentation de la DMO observée avec le ranélate de strontium au niveau du rachis lombaire et de la hanche totale est cohérente avec celle trouvée antérieurement chez les femmes ménopausées. Une étude randomisée, contrôlée contre placebo, testant cette double action innovante dans une population exclusivement masculine, sera bien-tôt achevée et devrait confirmer ces résultats préliminaires.

Keywords: osteoporosis; men; risk factors; prevention; therapy
Fracture healing is an extremely important biological process that is necessary for the survival of the animal. Fracture healing failure is associated with serious impairment of the locomotor system as well as a decline in quality of life. Postfracture deformities after poor reduction of the fractured extremity, e.g., leg shortening or angulations, are associated with serious functional incapacity. Fracture healing should ideally fully return bone strength to its prefracture state. Fracture healing is a unique biological event that takes a considerably long period of time to complete. A short phase of endochondral external callus formation is followed by a prolonged remodeling period. There is a danger of nonunion and possible refracture occurring during the endochondral callus formation phase. As fractures are more common in people with osteoporosis who may already be undergoing long-term treatment with antiosteoporotic medication, it is of great clinical importance to know whether these drugs have a positive or negative effect on the biological process of fracture repair. Surprisingly, the existing literature, especially clinical studies, is limited. Prospective trials in patients receiving antiosteoporotic medications prior to and/or after a fracture would be helpful, especially for orthopedic surgeons, and would aid their care of osteoporotic patients before and following fracture. In this review, the existing knowledge is presented with an emphasis on the practical issues related to the clinical applications in orthopedic surgery.

G. P. Lyritis, Greece

Fracture healing: a three-step process

Fracture healing is an important biological process that is necessary for the survival of the injured animal. Bone is a unique tissue and its repair process of great biological importance, as it aims to fully restore lamellar bone to its original condition thereby regaining initial bone strength. Fracture is usually understood as being the complete disruption of a long bone after a fall, but many people ignore the fact that trabecular bones, especially in osteopenic patients, may suffer microfractures, which are automatically restored by minicallus formation, as shown in Figure 1 (page 80). Repair of a fractured long bone typically progresses in three consequent stages.

Stage 1 (inflammatory phase)
This follows immediately after fracture and is associated with the activation of wound healing pathways usually observed after a soft tissue injury (bleeding, development of a hematoma with macrophages and other inflammatory cells) and the gradual
development of capillary clotting, several cytokines and growth factors, including transforming growth factor β (TGF-β) and vascular endothelial growth factor (VEGF), facilitate the recruitment of additional inflammatory cells and the invasion of multipotent mesenchymal stem cells from the periosteum and the bone marrow. During this stage, a primitive callus develops, reducing uncontrolled mobility at the fracture site. The inflammatory stage of fracture healing is fast and lasts up to a week after fracture.

Stage 2 (reparative phase)

This phase starts within the first days of the inflammatory one and continues for several weeks. A gradually developing hard callus is formed—usually around the fracture site—that imitates a large internal splint around the fractured bone. The formation of the external callus is stimulated by instability at the fracture site. Micromotion enhances callus maturation and its transformation from a cartilaginous to a hard osseous model, while local strains become gradually smaller. The simultaneous removal from the injured area of avascular bone and the production of fresh bone occur during the reparative phase, with the action of cartilage and differentiated osteoblasts coming directly from precursor cells (intramembranous ossification). Within the fracture gap and at its periphery, abundant cartilage formation occurs in a manner similar to the endochondral ossification observed at the growth plate. Chondrocyte proliferation and differentiation are stimulated by the expression of growth factors including TGF-β2, platelet-derived growth factor (PDGF), insulinlike growth factor 1 (IGF-1), and some bone morphogenetic proteins (BMPs), ie, BMP-2, -4, -5, and -6. The reparative external callus, which is typically composed of woven bone, now connects the fragment ends, offering limited mechanical strength at the fracture site. The first two stages of fracture healing (inflammatory and reparative) and external callus formation are considered mechanisms necessary for the survival of the injured animal, which after a reasonable consolidation of the fracture can partially return to its usual activities. Of course, this solution by no means offers bone strength equal to that in the prefracture period, and the possibility of a refracture is still high. The full restoration of the initial mechanical condition occurs after a prolonged period of time through the well-known mechanism of bone remodeling. During the callus remodeling phase, woven bone is gradually replaced by lamellar bone, according to the laws of the mechanostat that Frost described many years ago.

Stage 3 (remodeling phase)

This is a nonemergency phase and can be considered as a gradual adaptation of the fractured bone to the usual strains of everyday life. As a paradigm for the adaptive biological mechanism of fracture remodeling, we have taken the story of the restoration of the walls of the Acropolis of Athens following the destruction of the city during the Persian Wars and their urgent rebuilding with the ruins of the walls destroyed by the Persians (Figure 2).

Does osteoporosis affect fracture healing?

Fractures in the osteoporotic elderly are more frequently associated with complications and invalidity during the period of rehabilitation. Experimental studies on the effect of osteoporosis on fracture repair in the ovariectomized rat model have shown delayed fracture healing and a diminution of the mechanical strength of bone after the completion of the healing process. The final outcome is the union of the fracture; non-union is very uncommon. On the other hand, there is only anecdotal evidence that osteoporosis may delay fracture healing in humans. Taking into consideration that bone modeling and fracture healing have similar mechanisms and that osteoblastic modeling is usually suppressed in advanced age and in osteoporotic patients, it seems normal that fracture repair in elderly people should take longer. In the corticosteroid-induced osteoporosis animal model, fracture healing was found to be delayed. In conclusion, there is still a question mark over whether postmenopausal and senile osteoporosis affects fracture healing in humans. Nevertheless, mechanical

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>BMP</td>
<td>bone morphogenetic protein</td>
</tr>
<tr>
<td>CGRP</td>
<td>calcitonin gene–related peptide</td>
</tr>
<tr>
<td>IGF-1</td>
<td>insulinlike growth factor 1</td>
</tr>
<tr>
<td>NOS</td>
<td>nitric oxide synthase</td>
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<tr>
<td>PDGF</td>
<td>platelet-derived growth factor</td>
</tr>
<tr>
<td>PTH</td>
<td>parathyroid hormone</td>
</tr>
<tr>
<td>S-CTX</td>
<td>serum collagen C-telopeptide</td>
</tr>
<tr>
<td>S-TRACP</td>
<td>serum tartrate-resistant acid phosphatase</td>
</tr>
<tr>
<td>TGF-β</td>
<td>transforming growth factor β</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
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and biological factors involved in the healing process of bone are influenced by age and osteoporosis, in the way estrogen deficiency has a biological effect on bone.\textsuperscript{12}

- \textbf{Does high bone turnover affect fracture healing?}

It is well known that posttraumatic osteopenia is the result of high bone turnover and that fracture healing is associated with increased biochemical bone markers, especially those of bone resorption.\textsuperscript{13} Women who have recently sustained fracture have higher levels of bone markers, in particular serum tartrate-resistant acid phosphatase 5b (S-TRACP-5b) and urine osteocalcin. Even two years after fracture, biochemical formation and resorption markers such as serum bone alkaline phosphatase and serum collagen C-telopeptide (S-CTX) are elevated, compared to prefracture period levels.\textsuperscript{15} Scintigraphy also demonstrates hot areas at fracture sites, presumably a result of existing long-term high bone turnover at the fracture site. This is a possible explanation as to why a history of preexisting fracture is an indicator of high risk for a new fracture.\textsuperscript{14}

\textbf{Pharmaceutical treatment of osteoporosis and its effect on fracture healing}

Fractures are common in osteoporotic patients. According to epidemiologic studies, the incidence of fractures of long bones exponentially increases with age, representing a major cause of morbidity and mortality in elderly people.\textsuperscript{15} While antiestrogenic therapies significantly lower the risk of a fracture, almost half of elderly people experience a new fracture in their lifetime.\textsuperscript{16} Fracture healing in patients already being treated is therefore a problem of clinical importance. The effect of osteoporotic therapies on fracture healing has been studied experimentally, but the existing clinical studies are rather limited. Osteoporosis treatments are nowadays classified into three groups: anticatabolic, anabolic,\textsuperscript{17} and dual action (anabolic and anticatabolic, mainly represented by strontium ranelate) categories. Each group of antiestrogenic therapy has different mechanisms of action on bone cells, but it is true that most of them also influence other bone cells, either directly or indirectly, via the coupling phenomenon.\textsuperscript{18} Based on the characteristics of fracture repair and the type of fixation, an antosteoporotic drug may be chosen to accelerate fracture healing, to assist the recovery of the patient, or to avoid any fracture complications. An evaluation of the complication rates after fracture fixation of the proximal femur shows that patients with suspected osteoporosis have an increased rate of refracture or fixation failure.\textsuperscript{19} While preclinical studies support the fact that pharmacological agents can augment fracture union,\textsuperscript{20} it is not clear if this translates into clinical benefit and offers patients with osteoporosis or at high risk of delayed union a better chance of fracture healing.\textsuperscript{21} To ensure that antosteoporotic agents have a beneficial effect on fracture healing (especially for diaphyseal and metaphyseal fractures of long bones), biomechanical, histologic, and radiographic differences must be shown between individual patients and nontreated injured persons.\textsuperscript{18} This means that prospective clinical studies should be designed to demonstrate a positive medicinal effect.

- \textbf{Preclinical evaluation of the effect of osteoporosis therapies}

A reduced capacity in osteoporosis to heal a fracture has been shown in several animal models. Experimental data show a 40% reduction in the cross-sectional area of fracture callus as well as a 23% reduction in bone mineral density (BMD) in healing ovariectomized rat femoral fractures.\textsuperscript{22} Mechanical properties of callus are impaired, and the fixation stability of the implants deteriorates dramatically.\textsuperscript{23} Some drugs, in particular corticosteroids, decrease the healing process remarkably.\textsuperscript{11} It would be of great interest to know the effect of osteoporosis therapies on the fracture healing process. For convenience, both preclinical and clinical data will be presented.

- \textbf{Clinical studies and experience of the effect of bisphosphonate treatment on fracture healing}

Bisphosphonates have a marked inhibitory effect on osteoclasts and bone resorption, especially in the case of high bone turnover conditions. The effect of bisphosphonates on fracture healing depends on the type of substance as well as the duration and the prefracture administration dosage. In a canine model of closed, transverse radial fracture treated with alendronate, increased callus formation was found, due to slower callus formation, and no inhibition of bone formation or decrease of callus strength was observed.\textsuperscript{24} A larger callus with increased bone mineral content was also found in a sheep animal fracture model treated with pamidronate, but again no effect on the mechanical properties of the callus was detected.\textsuperscript{25} Incadronate given to growing rats with a femoral shaft fracture, which also produced a larger callus, increased stiff-
ness and ultimate load of the callus, too. A similar effect (larger callus and increased torsional mechanical strength) was also found after the administration of ibandronate in ovariectomized rat. Zoledronic acid administered in rats that sustained a closed femoral fracture and that were examined using different methods (nanoindentation, histology, and biomechanical after local application of zoledronic acid) suffered no delay of callus formation and no effect on the mechanical properties of the callus. By the absence of interference with mechanical status, one can speculate that in animal models, different bisphosphonates do no practical harm to the fracture healing outcome, but delay endochondral ossification.

There is a surprising lack of evidence and prospective clinical studies on fracture healing in patients treated with bisphosphonates, especially over a long period of time. One year of alendronate treatment did not alter fracture healing at the distal radius in a small group of postmenopausal osteoporotic women. In another small group of patients, one in 9 patients treated with alendronate who had sustained a fracture had a problem with fracture healing. All these 9 patients were found to have histological evidence of severe depression of bone formation. It was speculated from this small amount of evidence that alendronate treatment in osteoporotic patients who had sustained a fracture of the appendicular skeleton does not delay fracture union. As it is possible that bisphosphonate treatment may suppress bone turnover and promote microfracture accumulation, it is questionable whether this type of treatment can also facilitate the development of stress fractures. Bone microdamage is critical in the understanding of bone quality. Assessment of microdamage is technically difficult, especially in humans. The clinical impact of microdamage accumulation, potentially induced by bone drugs, has been demonstrated in experimental studies, but is still controversial in humans. In clinical practice, orthopedic surgeons with concerns about the depression of bone turnover during the period of fracture healing may wish to stop bisphosphonates in order to avoid impairment of the bone healing process. But on the other hand, initiating antosteoporotic treatment in untreated people who have suffered a fracture could prevent consequent macrofracture.

Atypical subtrochanteric fractures and bisphosphonates
During the last few years, a series of case reports have drawn our attention to an unusual type of subtrochanteric or diaphyseal femoral fracture, especially in alendronate patients. The high number of reported cases in a short period of time suggests that many similar fractures were treated previously by orthopedic surgeons, who either did not notice the association with alendronate treatment or never reported it. All these fractures have some common clinical and radiological features. The majority of the patients received alendronate for a long period of time, some of them had atypical pain in the broken thigh months before femoral fracture, and some of them were taking additional drugs, commonly corticosteroids. Radiologically, all these fractures are surprisingly almost identical to unusually thick femoral cortices with a transverse fracture line and a cortical peak at the medial distal femoral fragment. Because of the longstanding preexisting femoral pain, some patients were examined and, in the prefracture radiograph, there was a suspicion of a stress fracture of the medial cortex (Figure 3). Scintigraphy in some prefracture cases also revealed a hot spot at the site of the future fracture. The biggest retrospective controlled study of the atypical fractures reports a long prefracture period with alendronate. As this category of fractures is a new scientific finding, more epidemiologic and laboratory studies are needed. Suppressed (frozen) bone turnover could be speculated, but high levels of active osteoclasts were detected in one case with bone biopsy at the fracture site.

Effect of PTH (1-34) and strontium ranelate on fracture healing
The amino terminal active form of human parathyroid hormone (PTH [1-34], teriparatide) has an anabolic effect on both
cortical and trabecular bone. Animal studies on fracture healing suggest that PTH signaling improves the biomechanical properties of fracture callus and accelerates callus formation, endochondral ossification, and bone remodeling. Based on these data, PTH (1-34) is likely to be a potent agent for enhancing fracture healing in patients with poor fracture healing potential, such as those with osteoporosis, prolonged steroid use, or recalcitrant nonunion. It is also recognized that daily PTH administration is an effective therapy for increasing BMD and preventing fractures in both male and female osteoporosis patients. More recently, a growing body of evidence supports the conclusion that PTH would also be an effective anabolic therapy for the enhancement of bone repair following fracture. Treatment with PTH results in significant increases in BMD, production of bone matrix proteins, new bone formation, and increased mechanical strength, indicating that PTH can enhance and accelerate normal fracture healing.

Several animal studies have demonstrated that PTH therapy consisting of daily subcutaneous injections during bone repair leads to increased callus volumes and a more rapid return of bone strength. Although no human clinical trial data are yet available, the role of PTH and of teriparatide in fracture healing is currently under investigation. The magnitude of the increase in the animal group treated with teriparatide was found to be two times higher than at the nonosteotomy site. It is difficult to extrapolate a positive effect to humans, as there is no evidence in humans suffering recent fracture and because the doses administered to animals are several times higher than the human dosage (20 µg/day). Theoretically, its anabolic effect on bone formation could explain the significant decrease in vertebral fractures observed in clinical studies.

Strontium ranelate was found to stimulate bone formation and inhibit bone resorption. This dual-action (formation and resorption) medication can also be considered as a possible therapeutic agent for accelerating fracture healing and increasing its mechanical properties. In an intact, closed femoral fracture male rat model, healing was studied radiologically and histologically. Both studies showed an increase in effect with time. Local application of strontium salts in implants used in fracture fixation has been suggested for fracture repair promotion. Prospective studies in humans are necessary to show this healing acceleration also occurs in man. Recently, it was reported that strontium ranelate as well as teriparatide can increase the callus volume in a closed femoral fracture experimental rat model, while callus torsional strength is improved by strontium alone. However, further studies are necessary to confirm these encouraging results in humans.

Effects of estrogen, raloxifene, and vitamin D and its analogues on fracture healing
The effect of estrogens and raloxifene on fracture healing was studied in the ovariectomized closed tibial fracture rat model. It was found that both medications improve fracture healing histologically and mechanically. Apart from the animal study, there is no evidence for the clinical use of estrogens and raloxifene in fracture healing in humans, especially over a prolonged period of time.

Several animal studies have shown that vitamin D₃ treatment promotes both fracture healing and mechanical strength in the callus. However, no adequate studies on the role of vitamin D and calcium treatment in fracture healing are currently available in humans. One study focused on the healing process in osteoporotic/osteopenic fractures and investigated the potential of an oral calcium and vitamin D₃ supplement at mitigating some of the problems associated with the osteoporotic fracture healing process, such as delayed or insufficient healing.

The increase in BMD in the fracture region was interpreted as a positive impact by vitamin D₃ and calcium on the fracture healing process, thanks to a higher concentration in the cellular environment of these agents. The supplement potentially facilitates osteoblasts in building Ca²⁺ and producing callus via an increase in the rate of osteoblast/osteoclast turnover from osteogenic cells. Despite a high concentration of calcium in the animal study, the callus had little bending strength, so it is therefore possible that although vitamin D₃ and calcium increase the calcium concentration in the fracture area, it still yields brittle bone. More investigation is necessary, but it seems likely that osteoporotic women might benefit from oral calcium plus vitamin D₃ supplementation during the fracture healing process.

Calcitonin is found to promote the cartilaginous phase of fracture healing. However, examination of the innervation of callus reveals an extensive distribution of sensory fibers containing calcitonin gene-related peptide (CGRP), a neuropeptide with potent vasodilatory actions. In a rabbit animal model with a defect of the mandible, there was a positive correlation between the expression and activity of CGRP and nitric oxide synthase (NOS) and fracture healing. It has therefore been speculated that CGRP may promote fracture healing via the regulation of the expression and activity of NOS.

New strategies for the evaluation of antosteoporotic treatments are needed
Therapeutic strategies for the prevention and treatment of the nontraumatic fractures, especially those of the appendicular skeleton, must seriously consider the importance of the high incidence of fracture healing delay or failure in the elderly, especially, as well as the increased incidence of refracture after a fracture. Both the disturbance of fracture healing as well as the possibility of fracture reoccurrence at the site of the mechanically immature callus are important for osteoporotic patients, especially those of advanced age. Antosteoporosis medication enhances the healing process in general, but it is surprising that there is a lack of evidence in prospective clin-
Fracture healing and antosteoporotic treatments—lytis

U pdate

References


Keywords: antiosteoporotic treatment; fracture healing; bone remodeling; bisphosphonate; strontium ranelate

Cicatrisation fractureuse et traitements antiostéoporotiques

La cicatrisation des fractures est un processus biologique extrêmement important, indispensable à la survie animale. Lorsque celle-ci est défaillante, le système locomoteur et la qualité de vie se trouvent sévèrement altérés. Les déformations post-fracturaire qui résultent d’une mauvaise réduction de l’extrémité fracturée, comme un raccourcissement ou des déviations des membres, sont associées à de sévères incapacités fonctionnelles. Idéalement, la cicatrisation fractureuse aboutit à une solidité osseuse identique à celle antérieure à la fracture. La cicatrisation fractureuse est un processus biologique qui nécessite une très longue période pour s’accomplir. Elle débute par une courte phase de formation d’un cal externe endochondral, suivie par une période prolongée de remodelage. C’est au cours de la formation du cal qu’il existe un risque d’absence d’union et de refracture. Les fractures survenant plus souvent chez les personnes ostéoporotiques, les fractures survenant plus souvent chez les personnes ostéoporotiques susceptibles d’avoir déjà été traitées depuis longtemps avec des médicaments antiostéoporotiques, il est très important de savoir si ces derniers ont un effet positif ou négatif sur le processus biologique de cicatrisation des fractures. La littérature existante, et surtout les études cliniques, est de façon surprenante, très réduite. Des études prospectives effectuées chez des patients traités par des médicaments antiostéoporotiques avant et/ou après une fracture seraient utiles pour permettre une meilleure prise en charge des patients ostéoporotiques avant et après fracture par les chirurgiens orthopédiques. Cet article présente les connaissances actuelles en soulignant les questions pratiques liées aux applications cliniques en chirurgie orthopédique.
A TOUCH OF FRANCE

Under this heading, each issue of *Medicographia* features two cultural articles. The first one touches on the history of medicine, based around great figures from French history, while the second one addresses broader aspects of France’s heritage, such as history, art, literature, and the description of museum collections.

The Big Blue: a touch of French underwater medicine

C. Régnier, France

The diving suit created in 1715 by the knight Pierre Rémy de Beauve.

Photo Alain Wérl © Collections Musée Frédéric Dumas – Ville de Sanary-sur-Mer

France, a pioneer of underwater archaeology

D. Camus, France

A riddle at the bottom of the Mediterranean Sea found during underwater exploration of the Lighthouse of Alexandria.

© Stéphane Compoint.
No conditions exist in nature where man and air-breathing creatures are subjected to the influence of a stronger pressure than that exerted by the atmosphere on the seas,” wrote Paul Bert, the French physiologist and expert in nitrogen narcosis, in 1878. This observation marked the beginning of underwater medicine and the complex study of the physiological phenomena linked to decompression. Other than pearl fishermen and breath-hold divers (apnea divers) hunting fish in Asia or Polynesia, extended underwater diving using a system of artificial breathing dates back to the first industrial revolution in the middle of the 19th century. In the 18th century, the first diving suits were connected to the surface by a hose through which air was transported via the use of a bellows or a manual pump located at the surface. In 1865, the first autonomous diving suit, designed by three French engineers (Benoît Rouquayrol and Augustus and Louis Denayrouze), appeared; it was fitted with a regulator and reserve of air. It was then that the era of underwater diving truly began, but both this and increasingly ambitious civil engineering projects requiring the use of pressurized caissons were taking their toll of decompression accidents. It was therefore essential to improve the equipment, but above all to gain an understanding of the biophysics of blood gas dissolution and depressurization. Several European and American contributions helped further the quest by establishing diving tables outlining the stages of decompression, by carrying out studies on the composition of diving gases, and by designating rules to follow while descending into the depths and returning to the surface. With the partial resolution of diving equipment and safety questions by the middle of the 20th century, the exploration of the sea and river depths commenced. Several French pioneers, namely Philippe Tailliez, Jacques-Yves Cousteau, and Frédéric Dumas, were instrumental in the forging of this new path of scientific adventure and also in raising awareness in our collective consciousness about the protection of marine ecosystems.

Nowadays underwater diving, which boasts 15 million divers worldwide, makes use of techniques and equipment that are a result of technology that has been under continuous development since the middle of the 19th century. The diving suit used most often today is the independent, flexible, self-contained model, while rigid suits and helmets are also occasionally used. A breathable circuit can be one of two types; an open circuit is one where a diver produces bubbles each
time an exhalation is ejected into the sea, while a closed circuit is one where each exhalation is recycled to produce more oxygen, which then enters the same supply circuit of breathable gas as before.\textsuperscript{1,2}

On the medical front, doctors were confronted early on with diving accidents that were the result of large variations in pressure that had affected the hollow cavities of the body. The main factor affecting a diver’s body in these cases is the pressure exerted by seawater. Pressure increases by one bar for every ten meters’ depth. Because most of the components of the human body are incompressible, the body’s cavities that come in contact with inhaled air, such as the ears, sinuses, teeth, and intestines, are particularly vulnerable.\textsuperscript{3,4}

This can have several serious implications. For example, a difference in pressure or unequal pressure in the middle ear is likely to cause alternobaric vertigo, which can be fatal if it causes a diver to panic. In order to compensate for barometric pressure variations in the internal ear during descent, the diver must perform the maneuver described by the Italian surgeon Antonio Maria Valsalva (1666-1723), which now carries his name, the Valsalva Maneuver. Additionally, the air contained in the lungs expands as the diver ascends, which can cause serious tissue lesions. Secondly, the narcotic properties of some gases (argon, nitrogen), which are responsible for “drunkenness of the deep,” are counteracted by the use of a gaseous mixture rich in oxygen, such as Nitrox, the composition of which is adjusted according to the depth of the dive.\textsuperscript{4,5}

Finally, the main problem that doctors faced in the 19th century was decompression. An inert gas (e.g., nitrogen, helium, or hydrogen) dissolves in a liquid—in this case, the blood of the diver—according to its partial pressure (Henry’s Law), which increases with the depth of the dive. Inversely, during ascent, gas escapes into the liquid causing bubbles to form, which can bring on circulatory accidents, paralysis, and particular or joint pain, which are typical types of decompression disturbance. The diver must therefore ascend carefully in defined stages to avoid the onset of such effects.\textsuperscript{3,6}

For centuries, the pearl fishermen of Polynesia have been familiar with the risks involved in ascending too quickly after immersion at 40 meters. The knowledge and stories passed on by the elders and ancestors of the fishermen comprised one crucial rule, the establishment of decompression stages. This was done in order to appease the Ocean God, who was held responsible for such diving mishaps. The same instinctive mastery of decompression rules is attributed to the Ama apnea divers in Japan and the Haenyo from the province of Jeju-do in Korea.\textsuperscript{3,7}

The first recorded observation of the physiological consequences of decompression, now known as decompression illness (DCI), was made in 1667 by the Irish physicist and chemist Robert Boyle (1627-1691), when he put a viper in a vacuum under a bell jar. Boyle was one of the pioneers, along with Thomas Hobbes (1588-1679), who carried out experiments in a vacuum. Besides the respiratory distress of the
snake, “which struggled furiously,” the scholar noticed that bubbles appeared inside the cornea of the reptile. He attributed this first degassing incident to abrupt decompression. Independently of one another, Robert Boyle and the French physicist abbé Edme Mariotte (1620-1684) both described the law of thermodynamics linking the absolute pressure and volume of a gas to an initial and final state, \( p_1 \times V_1 = p_2 \times V_2 \). The Boyle-Mariotte Law only applies to ideal or perfect gases. Following Boyle’s findings, other scientists made related empirical observations:

- The Englishman Dr Henshaw used a pressurized chamber he invented—the domicilium—to treat pulmonary and intestinal disturbances in 1662;
- Edmund Halley dived to a depth of 18 meters for 90 minutes in a diving bell experiment in 1689.1-3,5

In 1803, the physicist and chemist William Henry (1775-1836) made his law public: at a constant temperature and at saturation, the quantity of gas dissolved in a liquid is proportional to the partial pressure the gas exerts on the liquid. In his law, Henry added a specific factor for each gas taking into account its ability to dissolve in a liquid. Henry’s Law found an immediate application in underwater diving and made it possible to understand why decompression accidents occurred when rising to the surface.1-3

In the middle of the 19th century, England, the United States, and France suffered a large number of fatal accidents with divers, laborers working in caissons in naval shipyards, and coal miners in pressurized atmospheres. In 1847, the notion of decompression was clarified by the French occupational health doctors Pol and Watelle. They observed that being in a high pressure environment immediately following a stay in the deep considerably improved the undesirable symptoms, which opened the way to the perfection of decompression chambers. In 1861, Bucquoy issued the first hypothesis on bubbles in the blood of the divers:

> Gases of the blood pass back to a free state under the influence of decompression... and cause accidents comparable to those of an injection of air in the veins.” His recommendation was “…to take all necessary precautions for slow decompression...”1,3,5

Disturbances linked to stays in the deep are called the bends, an English word meaning “to fold” or “to bend over”. It was used by Triger in 1841 to describe the problems suffered by the tube laborers working on the big American bridges in San Francisco and Mississippi. After a seven-hour stay in tubes with a pressure of three bars, the workers came out bent in two or folded over because of agonizing joint pain. These rheumatological manifestations could also be accompanied by urinary retention, paralysis, palpitations, loss of consciousness, and marrow lesions. The complete clinical chart was drawn up in 1859 by Dr François, who recorded 133 cases of the bends in laborers working on the pile foundations for the bridge from Strasbourg to Kehl.5,9,10

In 1879, in his monumental 1800-page classic La pression barométrique (Barometric Pressure), Paul Bert (1833-1886), a French physician and politician, explained the role of nitrogen and carbon dioxide gas in decompression accidents. He also described the neurotoxicity of oxygen at high pressure, known as the Paul Bert effect. He was the first to set forth decompression rules for divers:

> …have them maintain position for a good quarter of an hour at the mid-way point and when they return from a dive at 4 atmospheres of pressure, make them breathe some oxygen immediately upon return to the surface… They pay only when they get out!9,10

Haldane and his tables: debates and controversy

In 1906, with the development of submarines and a corps of military divers, the British Admiralty entrusted the Scottish doctor John Scott Haldane (1860-1936) with the task of studying ways to decrease underwater accidents. He chose to use goats as the experimental model because their lean-fat ratio was relatively similar to that of humans; in addition, goats have a rate of perfusion close to that of man.

Using Henry’s Law (1803), the scholar established a formula to determine the different coefficients of gas absorption in the tissue of an organism. The Scottish scholar continued the work of Paul Bert and confirmed the theory and benefits of a slow ascent by proving that the partial pressure of nitrogen was related to external pressure. To ensure a safe ascent without accidents or adverse effects, he deemed it necessary to respect the following rule: the pressure of nitrogen blood saturation must always be less than or equal to twice the ambient pressure.
ent pressure. But in the end, Haldane departed from the hypothesis that the absorption and elimination rate for gases in tissue were identical.1,2,6

In 1908, in *The Journal of Hygiene*, Haldane presented the Royal Navy with his famous diving decompression tables that established stages during ascent to the surface from a depth of up to 62 meters. These tables took into account the age and stoutness of the diver. Haldane’s views contrasted with the theories of Heller, Mager, and von Schrotter, who recommended a slow and uniform ascent of 20 minutes per atmosphere of pressure.

Haldane was the first to provide a mathematical model of decompression and divers adopted his decompression tables rapidly, which resulted in a considerable decrease in diving accidents. “Haldane’s method, thanks to its approximation and the indeterminate nature of its parameters, makes it adaptable to all situations,” wrote Dr. Stephane Loiseau in his 2002 memoir of subaquatic and hyperbaric medicine.5,7,8

Following Haldane, many other models were presented. These took into account tissue specificity (Hempelman, Royal Navy, 1952), the variability of thresholds of critical sursaturation in depth (Workman, US Navy, 1965), and the Doppler-detected presence of circulatory venous bubbles (Spencer, US Navy, 1970).2,8

Scottish physiologist John Scott Haldane (1860-1936) invented the first gas mask used in World War I. After experimenting with the effect of toxic gases on himself, he designed a decompression apparatus to help make deep-sea divers safer and produced the first decompression tables after extensive experiments with animals. One of these tables, from the *Journal of Hygiene* (Cambridge) 1908;8:343-443, is reproduced here. © Cambridge University Press.

The Rouquayrol-Denayrouze diving apparatus: a step towards autonomy

In 1865, Benoît Rouquayrol (1826-1875) and Augustus Denayrouze (1837-1883), both natives of the Aveyron area of France (Midi-Pyrénées region), completed construction of the first independent underwater breathing apparatus equipped with an
Rouquayrol, a mining engineer for the Company of Coalmines and Foundries of the Aveyron, embarked upon research on ways to help victims of mine disasters, such as fire-damp explosions or miners trapped in galleries flooded by gases or water. Between 1860 and 1863, he submitted three patents for a salvaging device to save miners in gaseous environments. These devices were regulators of compressed gas, a mask with nose clip and mouth piece in vulcanized rubber, and a special air pump that compressed air without excessively heating it.\textsuperscript{3,11,12}

Denayrouze was a Lieutenant in the Navy. Ineligible for active duty after a serious ailment contracted in the region of Cochinchina in southern Vietnam, he spent time recovering in Espalion in southern France, where he met Rouquayrol in 1864. The naval officer immediately grasped that the mining engineer’s rescue device could be adapted for underwater diving.\textsuperscript{11,12}

The two men set to work and came up with the “Rouquayrol-Denayrouze diving apparatus,” for which they registered a patent on June 27, 1864. The regulator was fitted with an antireturn valve for the supply of compressed air. One technical improvement was the addition of a whistle to alert the diver to when the air supply was running low. The first trials were carried out in the Lot area by “cabussairs”, Aveyron poachers who dive into rivers to capture fish trapped in the tall grass. Even though the trials were conclusive, two major technical problems quickly became apparent: the lack of eye protection and the cold temperature of the water, which rapidly paralyzed the divers. Rouquayrol and Denayrouze quickly set about making diving suits using vulcanized rubber from the American Charles Goodyear. To this, they also added goggles based on a design for railway engineer goggles. This diving suit conjured up images of a frogman, but without the flippers. The divers, at this point in time, were still just moving up and down.\textsuperscript{11,12}

In February 1865, a company was created to sell this innovative equipment to national navies and fishing associations. Two years later, the diving apparatus of the two Aveyronnais inventors was awarded the gold medal at the 1867 Exposition Universelle (World Fair). The renowned French novelist Jules Verne (1828-1905) used this type of equipment to outfit his hero, Captain Nemo, in his novel Twenty Thousand Leagues under the Sea (1869-70). More than 1500 sets of “Rouquayrol-Denayrouze diving apparatus” were sold, and their equipment remained in use for nearly sixty years.\textsuperscript{5,11,12}

Augustus Denayrouze entrusted his brother Louis, a Polytechnicien (a postgraduate of France’s premier engineering university), with managing the French Society of Sponge Fishing in the Mediterranean (Société Française de Pêche des Éponges en Méditerranée), based in Smyrne, which he founded in 1865. Louis Denayrouze (1848-1910) invented the underwater ear trumpet, the first medium of communication under the sea, and the “aerophone”, an underwater watertight gas lamp supplied by air from the diver’s air reservoir.\textsuperscript{11,12} The Rouquayrol-Denayrouze company also produced a diving suit with an integrated, bolted-on helmet that was connected to the surface by a safety rope and rubber tubing. This equipment made extended underwater stays possible, but the hoses and ropes limited the movement of the diver.\textsuperscript{11}

Adventures of the “Trois Mousquemers”: the Silent World

In modern times in France and throughout the world, three Frenchmen have made an indelible mark on underwater diving: Philippe Tailliez (1905-2002), Frédéric Dumas (1913-1991), and Jacques-Yves Cousteau (1910-1997), nicknamed the “Trois Mousquemers” (the Three Musketeers of the Sea). They were undisputed pioneers in the continuous improvement of diving techniques, the development of underwater exploration, the making of documentaries, and in proclaiming the fragility of marine environments. Cousteau declared, “In our team, I was the organizer, Tailliez was the poet and visionary, and Dumas was the star.”\textsuperscript{8,13}

At this time at the end of the 1930s, divers still had rudimentary equipment. The “Rouquayrol-Denayrouze diving apparatus” had been forgotten, and divers now favored an open-circuit diving suit made by Gaston Le Prieur and Maurice Ferréz (1926), which was equipped with a “manodétendeur” (flow-meter), continuous air flow, and a compressed air supply in a Michelin bottle. The diver also had a basic mask with a port-hole. The drawbacks to this equipment were that a lot of air was wasted and autonomy was very limited, with only 10 minutes dive time at 12 meters.\textsuperscript{8,13,14}

It was in this environment that Philippe Tailliez—the son of a sailor, student of the Naval School of Brest, and swimming champion—moved to Toulon, where he indulged his passions.
**SYNOPSIS OF DIVING EQUIPMENT**

1715 - The knight Pierre Rémy de Beauve creates a diving suit. An iron corset protects the chest from the water pressure, a helmet fits on the girdle, two hoses are linked to the surface, and air is delivered by a bellows. Watertightness is ensured by a leather jacket fastened at the back, and the diver wears lead-ballast shoes.

1765 - The abbot of Chappelle carries out a trial in the Seine with his underwater cork suit, which he names “scaphantre” from the Greek *skaphe*, meaning a small boat, and *andros*, meaning man.

1772 - Fréminet provides a model of a diving suit in which the diver drags behind him a reservoir of air.

1805 - Touboul's autonomous apparatus is fitted with a tap for the entry of air.

1825 - The Englishman William H. James invents an independent system with a reservoir of air situated around the waist of the diver.

1830 - The German scholar Augustus Siebe invents a brass diver's helmet with three port-holes and, seven years later, the first diving suit "with heavy feet" that is entirely watertight and linked to a pump.

1831 - The autonomous diving suit, invented by the American Charles Condet, is made with semisubmersible rubber (semidry suit); it is fitted with an air compressor. In August 1832, the inventor dies at a depth of seven meters while testing his suit.

1838 - The doctor Theodore Guillaumet d’Argentan registers the patent for the first regulator supplied by an air pump at the surface. The diver has an inflatable bladder for buoyancy.

1855 - The hatter Joseph-Martin Cabirol adopts Siebe's diving dress model, which he makes using rubberized canvas; a fourth porthole is added to the helmet, which is equipped with an adjustable valve to evacuate stale air. Diving suit approved by the French Imperial Navy.

1864 - Augustus Denayrouze and Benoît Rouquayrol invent the "diving apparatus," the first independent diving suit without an integrated helmet. Equipped with a nose clip, "snout-mask," and mouth piece, the system is portrayed by Jules Verne in his science fiction novel *Twenty Thousand Leagues under the Sea* (1869-70).

1905 - Maurice Fernez begins his research on breathing under water with the aid of a rubber tube fitted with a "no-return" valve, for air exhaled to the surface.

1918 - The Japanese Ohgushi designs a closed-circuit air recycler that allows divers to descend hundreds of meters, thanks to an air reserve filled to 150 bars and equipped with a manual valve.

1920 - Fernez introduces his face mask with glass and his subaqueous glasses that Philippe Taillez, Frédéric Dumas, and Jacques-Yves Cousteau wear in the 1930s. Fernez joins Le Prieur to work on an independent, self-contained diving suit with a continuous air supply from an air reserve. The diver can now swim in a horizontal position.

1933 - Rubber swim fins by Louis de Corieu.

1934 - In Marseilles, Georges Beuchat founds a society, Beuchat International, that develops the Tarzan speargun, a surface buoy, and an isothermic suit.

1949 - The Australian Ted Eldred manufactures the Porpoise regulator.

1951 - The American researcher Hugh Bradner invents the first neoprene wetsuit.

1958 - Based on Dumas’s model, the first underwater safety harness appears.

1960 - First IBM dive computer to measure decompression stages.

1971 - First buoyancy vest connected to the diver’s air reserve.
for apnea diving, underwater hunting, and undersea scenery. On board the battleship Condorcet, where he was a torpedo boat officer, he met a young Lieutenant, a gunner by the name of Jacques-Yves Cousteau, whom he quickly initiated into the world of diving. In 1938, off the islands of Embiez, he met the engineer Frédéric Dumas, an adept underwater hunter and inventor, and the dynamic trio was formed. In 1942, Cousteau set about improving the currently available, but rudimentary, diving equipment. Drawing inspiration from the apparatus used by Georges Commelinès to establish his 53-meter underwater diving record in Marseilles, he designed a new type of miniature automatic regulator made from Bakelite (although, in reality, it was still based on the Rouquayrol-Denayrouze system). This particular model of streamlined diving apparatus made by Cousteau and Emile Gagnan, a French-Canadian engineer specializing in gases, included a pressure gauge, alarm, and steel or aluminum bottles—which the inventors called an “Aqualung.” It was using this apparatus that Frédéric Dumas established a new 72-meter diving record. 8,13,15

In 1942, the first French underwater film, *Par dix-huit mètres de fond (18 Meters Deep)*, was created by Cousteau, who filmed Dumas while diving. The film won him the Congress of Documentary Film’s first prize in 1943. The following year a second film was made, *Épaves (Shipwrecks)*, which detailed the exploration of the boats of the French fleet that had sunk near Toulon. Cousteau, enthralled by underwater images and different perspectives, put a 35-mm camera in a watertight box, conceived by the engineer Léon Vèche (the first model was made in 1893 by the French biologist Louis Boutan [1859-1934]), and the rest is history. 8,13,15

**FRENCH DIVING MUSEUMS**

- **The Frédéric Dumas International Diving Museum** in Sanary-sur-Mer (Var).
  It was opened in 1994 by the members of the Frédéric Dumas Association. The museum is located on two sites: rue Lauzet Aïné and the Roman tower on avenue Gallieni. The museum contains unique pieces from around the world, including the diving suit of the knight Pierre Rémy de Beauve (1715), the monoglass mask constructed by Dumas in the 1930s with the inner tube of a truck, and the first model of Fenzy’s buoy (1961). Every year the museum organizes l’Art Bleu (Blue Art), an arts salon dedicated to the underwater world.
  
  Rue Lauzet Aïné and avenue Gallieni, 83110 Sanary-sur-Mer, France
  Tel: 04.94.74.01.04 (tourist office). Fax: 04.94.07.42.13
  E-mail: lorida.gerard@orange.fr

- **The Diving Suit Museum** in Espalion (Aveyron).
  The museum, founded in 1977, is set up in two ground floor rooms of the former Saint Jean-Baptiste Church. On display is the only known model of the Rouquayrol-Denayrouze diving apparatus as well as many German, English, and Canadian models of feet-heavy suits (diving suits with lead soles), civil and military diving equipment (post-1945), diving turrets, recompression chambers, small submarines, etc.
  
  38 rue Droite, 12500 Espalion, France
  Tel: 05 65 75 82 10. Fax: 05.65.73.64.70
  E-mail: muriel.peissik@museeduscapandre.com

*Unlikely setting: an ancient Gothic church in Espalion, in the Aveyron department in the southern part of the Massif Central mountains, housing the “Diving Suit Museum” (Musée du Scaphandre). © Musée du Scaphandre, Espalion, France.*
In 1945, the GRS (Groupe de Recherche Sous-Marine [Underwater Research Group]) was created under the direction of Philippe Tailliez, who had at his side both Dumas and Cousteau. On board the sloop Elie Monnier, the GRS team carried out its first extensive scientific investigations: underwater archaeology, minesweeping, exploration of the sea floor, oceanographic filming, and research with bathyscaphes (free-diving, self-propelled deep-sea diving submersibles).

In 1949, Philippe Tailliez wrote the first manual on underwater diving with a diving suit. In France and throughout the world, he remains the discrete instigator of environmental awareness regarding the fragility of the marine depths: “Every man has two homelands: his own and the sea.”

Dumas continued to improve the diving equipment by inventing a safety collar (or safety harness) in 1950, which was the first stabilizing buoyancy compensator with an air reserve separate to that of the main air supply. He also designed a groin strap, to make the carrying of air bottles easier. Dumas was also the coauthor of and the main actor in many of the films created by Cousteau on board the Calypso. 7,8,13,15,16

Jacques-Yves Cousteau: an ecological pioneer
Jacques-Yves Cousteau, the son of a lawyer, discovered the sea in the deep, rocky inlets near Marseilles where his family lived. He married Simone Melchior in 1937, and they had two children, Jean-Michel (born in 1938) and Philippe (born in 1940). Cousteau studied at the Naval School of Brest before joining the French Naval Intelligence Service. He was sent to Shanghai and Japan in 1938, to the USSR in 1939, and participated in a commando raid against the Italian intelligence services in France in 1943.

In 1948, with the filmmaker Marcel Ichac (1906-1994), he made the first underwater archaeology film, while exploring a Roman shipwreck off the coast of Mahdia (Tunisia). The film, Carnet de plongée (Diving Log), was presented at the 1951 Cannes Film Festival, where it was received with great acclaim and swept up awards. 7,8,16

The following year, Cousteau founded the COF (Campagnes océanographiques françaises [French Oceanographic Campaigns]) and took possession of the legendary laboratory ship Calypso, which was acquired and equipped with the help of Loel Guinness (1906-1988), a descendant of Samuel Guinness, the younger brother of the Guinness brewery founder Arthur Guinness. This event marked the start of a multitude of exploratory expeditions across the oceans, seas, and rivers of the world. In the 1950s, with the help of Jean Mollard, he created the Soucoupe Plongeante SP-350, an easy-to-handle underwater “diving saucer” able to reach a depth of 350 meters. In 1956, he was awarded the Palme d’Or (Golden Palm) at the Cannes Film Festival for his film Le Monde du Silence (The Silent World), which he made with Louis Malle (1932-1995). During filming, the filmmaker suffered a barotrauma of the tympanic membrane. 7,16,17 In 1957, Cousteau was elected to the board of the Oceanographic Museum of Monaco and entered the American Academy of Sciences. His popularity continued to grow and he fought for marine ecology, organizing a press campaign in October 1960 to oppose the dumping of radioactive waste in the Mediterranean by the Commissariat à l’Énergie Atomique (French Atomic Energy Commission). During a visit to Monaco, General de Gaulle (1890-1970) asked him to be “kind” to the learned French atomic physicists. Cousteau countered: “It is up to your atomic physicists to be kind to us.”
Commander Cousteau and his crew donned red caps like those worn by the convicts from Toulon prisons forced to labor underwater, at the beginning of their underwater odyssey, which started in the early 1960s. The most media-savvy of the underwater divers, Cousteau had enormous success in the United States and, in 1977, he was awarded the United Nations Prize for the Environment. Eleven years later in 1988, he was inducted into the distinguished French body l’Académie française (French Academy). In explaining his philosophy, he declared: “My goal is not to instruct; I am neither a scientist nor a teacher. I am a discoverer, and my aim is to fill people with wonder. We love what fills us with wonder, and we protect what we love.”

Cousteau created a new genre of scientific communication that mainly targeted the general public, the production of which enabled him to defend his beliefs and views on marine ecosystem conservation. His ability to amaze his audience helped introduce environmental adventure films to the genre of film documentaries.

References


France is at the forefront of underwater exploration, thanks to the efforts of leaders like Jacques-Yves Cousteau and institutions like the Department for Underwater and Undersea Archaeological Research in Marseilles. French underwater archaeologists have made many remarkable finds over the first few decades of scientific exploration of the ocean depths, but there are over 3 million wrecks worldwide that remain undiscovered, according to UNESCO.

Who has not thrilled to a seafaring tale of newfound passages and far-flung landfalls, pirates and plunder, mutiny and marooning, or to the Raft of the Medusa and the “Convergence of the Twain”? But what of the hapless, silenced by the sea? Are their tales to remain forever untold, their spirits drifting mute like flotsam on the boundless main? Long inaccessible, hidden away in Davy Jones’s locker, the imprint of humankind in the silence of the depths is now being deciphered by marine archaeologists. Theirs is a discipline that long struggled to establish itself, hampered by the difficulties of reaching underwater sites and by captious dry land archaeologists contending that the sea bears no trace of the past, has no memory. Yet submerged sites, oftentimes the aftermath of shipwrecks or seismic events, are time capsules of human interaction with seas, lakes, and rivers. With its 11 million square kilometers of territorial waters and maritime borders with 30 countries, France not surprisingly was the first country to invest in underwater archaeology. In 1966, André Malraux, the then French Minister of Culture, created the Department for Underwater and Undersea Archaeological Research in Marseilles, which, with the aid of its 30-meter boat L’Archéonaute, has since mapped over 900 sites in its mission to protect and preserve France’s underwater cultural heritage.

Taking the plunge

Working underwater is hazardous and complex. Diving equipment is burdensome—breathing apparatus, isothermal combination, flippers, diving weights, buoyancy compensator—comfort relative, and the breathing of compressed air means that a diver is less efficient than when working on dry land. Beyond a depth of 10 meters, tissue nitrogen uptake forces a diver to limit time spent underwater or to undergo gradual decompression, either by resurfacing in successive stages or by using a decompression chamber. Strict observance of safety rules is therefore key to successful underwater exploration of archaeological sites.

Famous early discoveries

Remarkable finds in the 1900s spurred archaeologists’ interest in shipwrecks. Two cargoes of Greek artworks were discovered a few years apart: in the Aegean Sea at Antikythera (including a large 4th century BC bronze statue of Hermes), and then off the coast of Tunisia near Mahdia.
The Mary Rose, an English Tudor warship built in Portsmouth (1509-1510), is the only 16th-century warship on display anywhere in the world. The ship was thought to have been named after King Henry VIII’s sister, Mary, and the Tudor emblem, the rose. It was one of the first warships to be able to fire a full broadside of cannons. Oil on canvas (20th century). © Richard Wills (contemporary artist)/private collection/ The Bridgeman Art Library.

A 2nd-century bronze statue of Hermes, the messenger of the Gods in Greek mythology, found during underwater excavations at Mahdia, Tunisia. © Musée National du Bardo, Le Bardo, Tunisia/Giraudon/The Bridgeman Art Library.

A team of divers handling a 2-ton, eight-sided calcite block with the utmost care, as the slightest slip could have severe consequences. After the inscriptions on it were studied, it was determined that it comes from the era of Sethi I (1290-1278 BC), the father of Ramses II. © Stéphane Compoint.

The Mary Rose, an English Tudor warship built in Portsmouth (1509-1510), is the only 16th-century warship on display anywhere in the world. The ship was thought to have been named after King Henry VIII’s sister, Mary, and the Tudor emblem, the rose. It was one of the first warships to be able to fire a full broadside of cannons. Oil on canvas (20th century). © Richard Wills (contemporary artist)/private collection/ The Bridgeman Art Library.
These exceptional finds prompted the Italian authorities to undertake excavations near Rome on the bed of Lake Nemi, which since the 15th century had been known to be the last resting place of two ships built for the Roman Emperor Caligula in the first century AD. From 1928 to 1932, the lake was drained and the wrecks, which had already been plundered, were studied scientifically for the first time. One ship served as a temple dedicated to Diana, the goddess of the hunt; the second was a floating palace, with heated, mosaic floors and baths, inspired, it is believed, by Caligula’s fascination with the opulent lifestyles of the Hellenistic rulers of Syracuse and Ptolemaic Egypt.

The Mary Rose is the only 16th century warship on display anywhere in the world. One of the first warships able to fire a full broadside of cannons and the pride of the English fleet, she was built for Henry VIII in 1509-1510 and was manned by a crew of 200 sailors, 185 soldiers, and 30 gunners. After serving for over thirty years, she sank in the Solent during an engagement with the French fleet in July 1545, not it seems because of enemy fire. It would appear that in firing from the port side first and then turning sharply to fire from starboard, the Mary Rose heeled and water flooded in through the open gunports. Her plight was worsened because the upper decks were crowded with soldiers in full armor, thus raising the ship’s center of gravity, and she capsized. The wreck was rediscovered nearly three centuries later, but the location was subsequently forgotten and new searches begun in the 1960s culminated with the lifting of the Mary Rose in 1982.

In August 1628, on her maiden voyage from Stockholm, the Swedish warship Vasa ran straight into a violent storm and foundered before it could even leave the harbor, in full view of thousands of Stockholmers eager to see the great ship set sail. After much searching through the archives, Anders Fransen relocated the Vasa in the 1950s, at a depth of 32 meters in a busy shipping lane just outside Stockholm harbor. Exceptionally well preserved because of the low salinity of the Baltic Sea, the Vasa was recovered in 1961 and is now housed in a purpose-built museum in Stockholm, where it offers a fascinating insight into life aboard a 17th century warship.

The Mediterranean

Marseilles has played a key role in the history of archaeological diving. Studies by Jacques-Yves Cousteau of the wreck of the Grand Congloué in the Harbor of Marseilles in the 1950s are regarded as a world first. The divers used scuba equipment, developed by Cousteau, and a suction dredge to clean the site. The expedition’s archaeologist, Fernand Bencit, remained aboard the support ship Calypso, while the divers, albeit untrained in archaeology, searched the wreck and recovered artifacts. Not being a diver, Bencit was unable to observe first hand the positions of the wrecks, and this led to thirty years of controversy regarding the dating of one thousand Roman amphoras and a large cargo of black, glazed dishware and Greco-Roman amphoras. Only later was it realized that the cargoes were actually from two superimposed wrecks of vessels that had sunk almost a century apart.

In the 2nd century BC, when Rome had conquered the wine- and pottery-producing regions of Latium and Campania, there was extensive trading between Italy, Gaul, and the Iberian Peninsula. As Michel L’Hour, the Director of the Department for Underwater and Undersea Archaeological Research (DRASSM) in Marseilles, points out, “one third of the ancient shipwrecks currently inventoried in the Mediterranean bear witness to this huge trade and together account for some 13,000 pieces of dishware and double that number of amphoras”.

Further evidence of this trade emerged during the excavation of a shipwreck off the harbor of Madrague de Giens, near Hyères, in what is considered the first scientific underwater excavation conducted in France (1972 to 1982). This 1st century BC sailboat (40 meters long, 9 m wide; approximately 400 tons) was carrying wine from Italy in thousands of amphoras of the Dressel 1B type, as well as hundreds of black, glazed vases.
The Mediterranean also boasts the cave with the oldest cave paintings in the world: the Cosquer Cave, located near Cap Morgiou, not far from Marseille in France. The cave, named after Henri Cosquer, the professional diver who discovered it in 1985, is the only underwater cave with Paleolithic cave paintings in the world. The entrance to the cave is located 37 m below sea level because of changes in the relative altitudes of land and sea since prehistoric times. During the peak of the last major glaciation era approximately 20,000 years ago, the Würm period, the shoreline of the Mediterranean would have been several kilometers away. It contains paintings from two distinct Upper Paleolithic eras. The first set comprises 65 hand stencil paintings, which date back approximately 27,000 years (Gravettian epoch), while the second set consists of 177 animal drawings, which date back 19,000 years (Solutrean epoch). Both land animals, such as bison and horses, and marine animals, like seals and penguins, are represented in the latter set. Interestingly, ancient stencil hand paintings, which are all of adult hands in the Cosquer Cave, have been found throughout the world, from Australia to Africa and from Asia to the Americas.

♦ The English Channel and the Atlantic

Long discounted because of its depressions and dangerous currents, the English Channel and the Atlantic off the French coast became of focus of great interest in the 1980s. When archaeologists from DRASSM were called in to work on a wreck discovered five miles from Ploumanac’h, they found that it contained an astonishing cargo of lead ingots covered with inscriptions in Latin characters. Epigraphic study of the 271 ingots showed that the shipwreck was ancient. Michel L’Hour explains that:

Until then there had never been any tangible evidence of the sea trade in raw materials in the English Channel before and after the Roman Conquest of Britain. The Ploumanac’h wreck offered the first opportunity to study this trade. In terms of its cargo and chronology, this shipwreck is still the only one of its kind in Northern and Western Europe.

In 1994, a Breton diver discovered the La Natière site off Saint Malo. An initial survey revealed an extensive site, almost 50 meters from East to West and from North to South. As the excavations advanced, the archaeologists found four shipwrecks and Michel L’Hour qualified the site as “one of the most attractive in the world. A veritable underwater Pompeii. The sites were unchanged since the time of the sinking”. After eight years of work, two shipwrecks were identified. La Dauphine was a large royal frigate that disappeared on 10 December, 1704, when returning with a captured English ship, The Dragon. It was remarkably well preserved, with objects from daily life aboard, such as Norman and German pottery, arms, pewter pots, swords, sabers, pistols, and a surgeon’s instrument case. And at the La Natière II site, there was the wreck of L’Aimable Grenot, a privateer frigate lost at
sea on 6 May, 1749, with its cargo of Breton cloth to be sold at Cadiz. In 1692, at the height of the War of the League of Augsburg, when Europe was opposed to French ambitions, Louis XIV sought to help his cousin King James II of England regain his throne, which he had lost to William III of Orange. Louis offered to make his fleet and men available, under Vice Admiral de Tourville. After initial success off Barfleur on 29 May, when Tourville defeated an Anglo-Dutch fleet, English ships destroyed three of the largest French vessels in Cherbourg Harbor and, a few days later, burnt twelve French ships anchored in Hougue Bay. This defeat sounded the death knell for the ambitions of Louis XIV and James II to invade England.

In 1985, a Norman diver reported these wrecks and the local French authorities called on the expertise of DRASSM, with a view to setting up a maritime museum on Tatihou Island. From 1990 to 1995, Michel L’Hour and Elisabeth Veyrat codirected the excavations at a depth of 4 to 9 meters. Some 5000 hours of underwater work revealed five wrecks from Admiral Tourville’s fleet during the reign of Louis XIV, a pivotal period in the evolution of ship hull design.

◆ The high seas
Shipwrecks in shallow water suffer the ravages of time, erosion, and human activity, but those resting at greater depths are magically preserved and are most commonly discovered while drilling for oil. In 1985, while exploring Gabonese territorial waters, the company Elf Gabon discovered an archaeological site at a depth of twelve meters. The French authorities lost no time in dispatching a team from DRASSM, led by Michel L’Hour and Luc Long. With logistic backup from Elf Gabon, an exhaustive three-month study of the site identified the Mauritius, a three-masted Dutch vessel (40 to 45 meters long) built in 1601-1602 for the Dutch East India Company. In addition to cannon, instruments from a surgeon’s trunk, a bronze bell, and white and blue porcelain, the archaeologists discovered 140 tons of pepper and 20,000 zink disks, a cargo that gives us a glimpse of 17th century trade between Asia and Europe.

On 24 May, 1997, an autonomous underwater vehicle was exploring the coastal waters of the Sultanate of Brunei for TotalFinaElf, when piles of dishes and jars suddenly appeared in its light beams. Excavations overseen by DRASSM lasted three months and involved a multidisciplinary team 172 strong (archaeologists, caterers, divers, artists, experts in gas mixtures, physicians specialized in diving accidents), 70 of whom were French. Two submarines—Jules and Jim—fitted with three 450-watt projectors and several cameras, enabled the archaeologists to work in excellent conditions at a site that had probably never been plundered because of its distance (22 nautical miles) from the coast. Every day, the Royal Brunei Navy ferried the team from the shore to a barge anchored near the site. Another land-based team received over 13,200 objects retrieved from the sea, which they sorted, restored, drew, photographed (20,000 digital photos), and inventoried on a daily basis. These sunken treasures of Brunei, it was established, were lost in the South China Sea during a commercial voyage of a vessel (22 meters long and 8 meters wide) probably dating from the late 15th or early 16th century.

French underwater archaeologists have made many remarkable finds in the ocean depths, and will no doubt in the future uncover many more of the three million or more wrecks and hundreds of submerged rock art sites, cities, and monuments that the United Nations Educational, Scientific, and Cultural Organization (UNESCO) estimates remain undiscovered around the world.

◆ Fascinating finds
◆ An exceptional discovery: the bust of Caesar at Arles
Luc Long, curator at DRASSM, has for twenty years been exploring the bed of the Rhone River, a task complicated by poor visibility and strong currents. For a decade, he and his team have been diving at Arles, where they have discovered hundreds of amphoras and pottery that bears witness to a booming river trade in Roman times. In September 2007, Long and his team recovered a veritable treasure trove of marble sculptures (Neptune, Asclepius), architectural fragments, magnificent bronzes (including a gold-plated Victory), and a 40 cm-high white marble bust of Julius Caesar, which he believes was sculpted from real life. If so, it is one of the most important historical discoveries in France since the 1960s. “That it was found here is not surprising,” says Long, “as Caesar founded Arles in 46 BC. After his assassination, the bust may have been thrown in the Rhone by partisans of Pompey.”

◆ Alexandria: metamorphosis, preservation, and rebirth
In 1912, the French engineer Gaston Jondet was the first to publish maps of underwater ruins at Alexandria, discovered during work to enlarge the western port. In 1990, the French archaeologist Jean-Yves Empereur created the Centre d’Études Alexandrines.
Soon after, the center was asked by the Egyptian Antiquities Department to study the waters around the Citadel of Qaitbay. Between 1994 and 1996, in the sector where Jondet conducted his first explorations, Jean-Yves Empereur’s team from the Centre d’Études Alexandrines (CEAlex) drew up a digital map of over 3000 pieces of stonework (some weighing 75 tons) of archaeological interest, spread over 2 hectares under only 8 meters of water. These blocks of granite, statues, columns of different shapes, capitals, and parts of obelisks are probably vestiges of one of the Seven Wonders of the Ancient World, the Lighthouse of Alexandria. Early on the morning of October 4, 1995, archaeologists from CEAlex pulled a 12-ton granite torso over 4 meters high from the seabed and, using further finds of the crown, head, and legs, pieced together a 12-meter statue that used to stand guard at the main door to the lighthouse. This statue was of Ptolemy II, the
The mystery of the Lapérouse Expedition

As he mounted the scaffold on 21 January, 1793, Louis XVI is reputed to have called out “Have we any news of Monsieur Lapérouse?”. Apocryphal or not, his inquiry reflects the fascination of the time engendered by the mysterious fate five years before of the explorer Lapérouse and his two ships, La Boussole and L’Astrolabe (The Compass and The Sextant), which disappeared with all hands in the Solomon Islands, east of Papua New Guinea.

In appointing Jean-Baptiste Lapérouse to lead an expedition around the world, Louis XVI hoped to complete the mapping of the planet, establish new trading posts, open up new sea...
routes, and enrich scientific knowledge and collections. The expedition’s two frigates, La Boussole and L’Astrolabe, left Brest in August 1785 with 220 men aboard. For nigh on three years, they sailed the high seas to Easter Island, the Sandwich Islands, the Philippines, Brazil, Chile, and Japan before vanishing one day in 1788 in a violent Pacific storm after calling at Botany Bay, Australia.

Some forty years later in September 1827, Peter Dillon, a South Seas trader, shed the first light on the fate of Lapérouse and his men when he happened upon the wreckage of the expedition north of Vanuatu. He recovered the bell of L’Astrolabe and the bronze muzzle-loading cannon, but there was no trace of La Boussole. Dillon later recounted in his Narrative and Successful Result of a Voyage in the South Seas, to Ascertain the Actual Fate of Lapérouse’s Expedition how local inhabitants had told him that both ships had been thrown onto reefs by a tempest, that some survivors had later built a boat from the wreckage and sailed away, and that two survivors had remained on the island, but had since died.

It was not until well over a century and a half later that new evidence emerged. In the mid-1980s, the two wrecks were identified—L’Astrolabe had foundered on rocks not far from La Boussole, which had run aground on the reefs of Vanikoro. Numerous objects were brought to the surface, land-based digs revealed a camp of the survivors, and the skeleton of an unknown member of Lapérouse’s crew was recovered. These findings came more than two centuries too late to satisfy Louis XVI’s eleventh-hour curiosity, but, as the last pieces of the jigsaw fall into place, we can now affirm: “Yes, we do have news of Monsieur Lapérouse.”

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**LA FRANCE, pionnière de l’archéologie sous-marine**

Qui n’a jamais frissonné aux récits marins de nouvelles voies de passage et de territoires éloignés, de pirates et de leur butin, de mutineries et d’abandons sur une île déserte ou devant le Radeau de la Méduse et le tragique naufrage du Titanic ? Mais qu’en est-il des infortunés, réduits au silence par les flots ? Leur histoire restera-t-elle à jamais lettre morte, leurs âmes dérivant en silence comme une épave sur l’océan infini ? L’empreinte de l’humanité, longtemps inaccessible, cachée dans les fonds abyssaux, est désormais déchiffrée par les archéologues sous-marins dans le silence des profondeurs. Leur discipline a longtemps lutté avant de s’imposer, entravée par de multiples difficultés pour atteindre les sites sous-marins et par des archéologues terrestres et chicaniers prétendant que la mer ne témoinne d’aucune trace du passé, qu’elle n’a pas de mémoire. Certains sites jusqu’à présent immergés, conséquences de naufrages ou de séismes, sont des bulles temporelles, reflets de l’interaction de l’homme avec les mers, les lacs et les rivières. Forte de ses 11 millions de kilomètres carrés d’eaux territoriales et de frontières maritimes avec 30 pays, il n’est pas étonnant que la France ait été la première nation à s’investir dans l’archéologie sous-marine. Le Département des Recherches Archéologiques Subaquatiques et Sous-marines (DRASSM) de Marseille, créé en 1966 par André Malraux, alors ministre de la culture, a répertorié plus de 900 sites à l’aide de son bateau de 30 m, L’Archéonaute ; il a pour mission de préserver l’héritage culturel sous-marin de la France.
Instructions for authors

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- Manuscripts should be provided by e-mail (judit.siklosi@fr.netgrs.com) or by CD double-spaced, with 2.5-cm margins. Pages must be numbered. Standard typed page = 25 lines of 90 characters (including spaces) double-spaced, 2.5-cm margins = a total of about 320 words per page.
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