



HIGHLIGHTS FROM THE 2009 SANTA FE BONE SYMPOSIUM

Learning Objectives

This activity is designed for physicians who treat postmenopausal women or other patients at risk for osteoporosis. There are no prerequisites for this activity. At the conclusion of this activity, participants should be able to:

- Describe the historic development of bisphosphonate therapy for treating osteoporosis and its current clinical application.
- Describe emerging therapies, including their mechanisms of action, efficacy, safety, and administration, for patients with osteoporosis.
- Employ effective strategies to successfully manage the treatment of skeletal disease in patients with chronic kidney disease (CKD) and heritable disorders of RANK–ligand/RANK/OPG signaling.
- Describe the clinical utility of FRAX and issues that are still to be addressed regarding its use.

CME Information

Release Date: December 4, 2009.
Valid for credit through December 3, 2010.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of **Indiana University School of Medicine and Health Focus, Inc.** **Indiana University School of Medicine** is accredited by the ACCME to provide continuing medical education for physicians.

Indiana University School of Medicine designates this educational activity for a maximum of 2 *AMA PRA Category 1 Credit(s)*.[™] Physicians should only claim credit commensurate with the extent of their participation in the activity.

To receive credit, participants must read the newsletter and submit the activity evaluation form and posttest (passing score = 70% or higher). A pdf of the newsletter with evaluation form and posttest may be found at www.2009santafebonesymposium.com.

Length of time to complete the activity: 2 hours.

Faculty Disclosure

In accordance with the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support, educational programs sponsored by **Indiana University School of Medicine** (IUSM) must demonstrate balance, independence, objectivity, and scientific rigor. All faculty, authors, editors, and planning committee members participating in an IUSM-sponsored activity are required to disclose any relevant financial interest or other relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services that are discussed in an educational activity. Dr. Lewiecki reported that he has received grant support from, or served as a consultant and/or speaker for Amgen Inc, Eli Lilly and Company, Hoffmann-La Roche Inc, GlaxoSmithKline, Merck & Co Inc, Novartis, and Procter & Gamble; and he also has financial interests in General Electric Company and Procter & Gamble. Dr. Bilezikian reported that he has served as a consultant for The Alliance for Better Bone Health, Eli Lilly and Company, Merck & Co Inc, and Novartis; and as a speaker for The Alliance for Better Bone Health, Eli Lilly and Company, and Novartis. Dr. Miller reported that he has nothing to disclose. Dr. Recker reported that he has served as a consultant for Allelix Biopharmaceuticals Inc, Amgen Inc, Eli Lilly and Company, GlaxoSmithKline, Hoffmann-La Roche Inc, Merck & Co Inc, Novartis, NPS Pharmaceuticals, Procter & Gamble, and Wyeth. Dr. Russell reported that he has served as a consultant for The Alliance for Better Bone Health, Amgen Inc, Novartis; and served as a speaker for The Alliance for Better Bone Health, Amgen Inc, Eli Lilly and Company, and Novartis.

CME Reviewer:

Statements of disclosure of relevant financial relationships have been obtained from Glenda Westmoreland, MD. Dr. Westmoreland has disclosed that she has no potential or actual conflicts of interest.

NOTICE: Indiana University School of Medicine advises the participant that this CME activity may contain reference(s) to unlabeled or unapproved uses of drugs or devices.

In recent years researchers have made remarkable strides toward understanding the biology of bone formation and resorption. These advances have already increased our knowledge of how bisphosphonates and other osteoporosis therapies work and permitted the development of improved therapies. Furthermore, entirely new approaches to the treatment of osteoporosis have been developed and studied in clinical trials or are currently in clinical trials. One such agent representing a novel and potentially powerful approach for treating osteoporosis is currently under review by the United States Food and Drug Administration (FDA). Researchers have also recently achieved great advances in our understanding of how chronic kidney disease (CKD) influences mineral metabolism and other aspects of bone formation, leading to the definition of a disease entity now known as chronic kidney disease–related mineral bone disease. Finally, world-wide epidemiologic studies have contributed to the creation of a fracture risk assessment tool (FRAX), which is now available for integration into the clinical setting. These and other advances were presented at the 2009 Santa Fe Bone Symposium, and selected highlights of this meeting are presented in this newsletter.

Bisphosphonates After 40 Years: The Beginning of the End or the End of the Beginning?

Graham Russell, PhD, MD, FRS

How has our understanding of the mechanism of action of bisphosphonates evolved in recent years?

The concept that bisphosphonates might be beneficial for bone arose from the natural ability of pyrophosphate to regulate bone mineralization.¹⁻⁵ Bisphosphonates are orally stable analogues of pyrophosphate, with the 2 phosphate groups joined by a carbon atom rather than an oxygen atom (Figure 1). Like pyrophosphate, bisphosphonates become attached to bone mineral.



FACULTY

Chair

E. Michael Lewiecki, MD

Clinical Assistant Professor of Medicine
University of New Mexico School of Medicine
Director
New Mexico Clinical Research & Osteoporosis Center
Albuquerque, NM



Faculty

John P. Bilezikian, MD

Professor of Medicine and Chief of Endocrinology
Columbia University College of Physicians and Surgeons
New York, NY



Paul D. Miller, MD

Distinguished Clinical Professor of Medicine
University of Colorado Health Sciences Center
Denver, CO
Medical Director
Colorado Center for Bone Research
Lakewood, CO



Robert R. Recker, MD

Professor of Medicine
Director, Osteoporosis Research Center
Creighton University School of Medicine
Omaha, NE



Graham Russell, PhD, MD, FRS

Professor of Musculoskeletal Pharmacology
The Botnar Research Centre and Oxford University Institute of Musculoskeletal Sciences
Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences
Nuffield Orthopaedic Centre, Headington
University of Oxford
Oxford, UK



IN THIS NEWSLETTER

- Bisphosphonates After 40 Years: The Beginning of the End or the End of the Beginning?
- Update on Rationale and Development of New Agents for Osteoporosis Treatment
- Discriminating the Cause of Fractures in Chronic Kidney Disease
- Fracture Risk Assessment and Treatment Guidelines: Highlights from the Panel Discussion

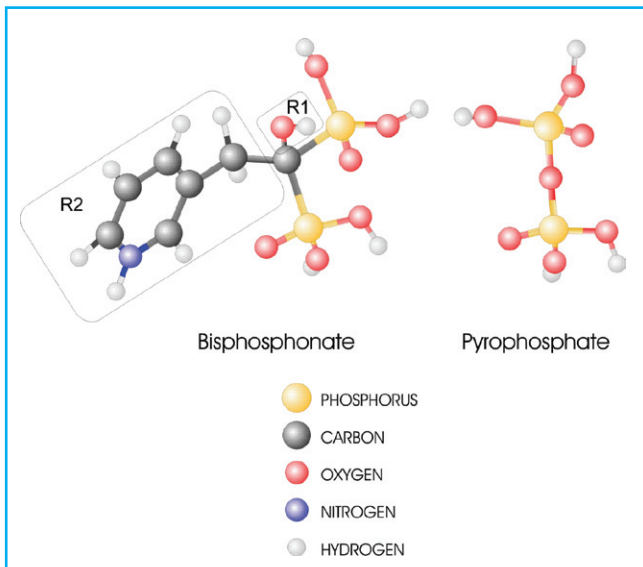


Figure 1. Chemical structures of a bisphosphonate and pyrophosphate.

Early theories implied that the physico-chemical interaction of bisphosphonates with bone mineral was the primary mode by which the drugs exerted their antiresorptive effects. We now know, however, that the more potent bisphosphonates—the bisphosphonates that contain a nitrogen atom (N) at a key location in their structure (including pamidronate, alendronate, risedronate, ibandronate, and zoledronate)—also have a highly selective antiresorptive effect on osteoclasts *in vivo*. This effect is mediated by the inhibition of farnesyl pyrophosphate synthase (FPPS), an enzyme in the mevalonate pathway of lipid biosynthesis. Inhibition of FPPS interferes with prenylation of key cellular GTP-binding proteins.⁶ Although the details are only partially understood, this effect is detrimental to osteoclast function, probably by affecting intracellular signaling and protein trafficking. There is evidence that the osteoclasts can persist, although with impaired functional capabilities.⁷ The importance of FPPS inhibition to the mechanism of action of bisphosphonates is supported by experiments showing that bisphosphonate inhibition of osteoclast function can be overcome by replacement of the reaction products of FPPS.⁵ Furthermore, among the N-containing bisphos-

phosphonates, there is a strong relationship between an agent's ability to inhibit FPPS and its ability to inhibit bone resorption.⁸ Indeed, much is now known about the crystal structure of FPPS and its binding to N-containing bisphosphonates.⁹

What accounts for the high selectivity of bisphosphonates for osteoclasts, given that FPPS is ubiquitous? Current evidence suggests that this selectivity is due to the high-affinity binding of the drugs to bone, where they are incorporated into bone mineral for extended periods. During bone resorptive activity, the drugs are released from the bone mineral and gain access to the osteoclast cytoplasm by a mechanism involving endocytosis.¹⁰ Hence, the bone mineral affinity of bisphosphonates acts as a “hook,” sequestering the compound inside bone until it is encountered by an osteoclast, at which time the drug inhibits osteoclast resorptive activity.⁵ The high-affinity binding of bisphosphonates to bone mineral also accounts for much of their safety, since the drugs are so rapidly adsorbed to bone that they have minimal opportunity to accumulate in other tissues. Overall, we have learned a great deal about how bisphosphonates work in recent years, but important questions still remain.

Are all bisphosphonates equivalent from a clinical standpoint?

Since the 1970s we have known that the bisphosphonates have important differences. The early agents, etidronate and clodronate, are the so-called simpler bisphosphonates because they lack an N atom in the side chain. Clodronate is still widely used among breast cancer patients outside of the United States, but etidronate is avoided because at high

doses it inhibits bone mineralization and causes osteomalacia.

The R1 and R2 side chains of the bisphosphonate molecule are important for bone mineral affinity, as well as the drug's ability to inhibit FPPS (Figure 1). R1 is almost always a hydroxyl group, but R2 is variable; agents that contain a constrained N in the appropriate location are especially potent. Indeed, the potent bisphosphonates—ibandronate, risedronate, and zoledronate—all have similar N distances from the phosphorus-carbon-phosphorus group. These compounds are several orders of magnitude more potent inhibitors of bone resorption than the simple, non-N-containing bisphosphonates. Thus, it can be easily demonstrated that there are pharmacologic differences among the bisphosphonates; some of these differences, such as speed of onset, reversibility, degree of reduction in bone turnover, and degree of interference with the parathyroid hormone (PTH) response, may be important in some clinical situations.

With regard to the speed of onset of anti-fracture efficacy, indirect comparisons suggest that the affinity of a bisphosphonate for bone can have intriguing effects on its speed of onset in different types of bone. For example, current evidence suggests that risedronate, which has a lower affinity for bone than zoledronate or alendronate, has a relatively quick effect to reduce fractures at all sites. In contrast, zoledronate, with a higher affinity for bone and a comparatively fast speed of onset for preventing vertebral fracture, seems to have a slower speed of onset for preventing hip fractures.¹¹ The explanation for this difference is not clear, but our current hypothesis is that zoledronate, because of its very high affinity for bone, is rapidly sequestered in trabecular bone and may have some difficulty in fully accessing cortical bone. Indeed, the concept is emerging that agents with lower bone

mineral affinity may achieve better distribution in bone than high-affinity agents that tend to become sequestered at the site of first contact.

The bisphosphonates also vary in their rate of reversibility after the discontinuation of treatment. After risedronate is discontinued, its antiresorptive effect is largely reversed after 1 year. In contrast, the effect of alendronate is only partially reversed 5 years after discontinuation. Zoledronate is dosed only once yearly, with evidence that it reduces bone resorption for prolonged periods. We believe these differences are also related to the affinity of the bisphosphonate for bone mineral,¹² although that is also unproven.

The different bisphosphonates also differ in the relative roles of bone mineral binding and FPPS inhibition to their efficacy. Comparing risedronate with alendronate, for example, risedronate has a lower binding affinity for hydroxyapatite, but higher potency for the inhibition of FPPS.^{8,12} Their comparative ability to inhibit bone resorption closely parallels their comparative ability to inhibit FPPS, reinforcing the importance of this mechanism for the inhibition of resorption.⁸ However, as discussed, bone mineral affinity affects the distribution of the agent in bone, as well as the duration of its effect after discontinuation. Bone mineral affinity can also contribute to an agent's potency. For example, ibandronate and alendronate are much weaker inhibitors of FPPS than risedronate and zoledronate, but some of this weakness is counteracted by higher bone mineral affinity. Hence, the clinically useful dose of any bisphosphonate represents the combination of both the FPPS affinity and the bone mineral affinity of that particular agent.

These data demonstrate that the bisphosphonates clearly have pharmacological differences and suggest that those dif-

ferences may impart clinically relevant differences in some treatment settings. Based on these differences, it is possible to subdivide the bisphosphonates into 3 groups according to their mechanisms of action: (1) The non-N-containing agents have lower potency and act by virtue of their bone mineral affinity and by acting in a different way on cellular biochemistry to generate ATP derivatives of bisphosphonates; (2) the alkyl-amino agents (such as pamidronate, alendronate, and ibandronate) have intermediate potency and act through reversible inhibition of FPPS; and (3) the heterocyclic N-containing agents (risedronate and zoledronate) have high potency and act through less reversible inhibition of FPPS. All 3 groups rely on high bone mineral affinity for their tissue specificity and prolonged duration of action.

We have reviewed this topic in more detail elsewhere,¹³ including the potential importance of effects of bisphosphonates on osteocytes.

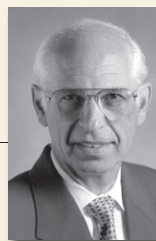
PUT IT INTO PRACTICE

- When choosing among the bisphosphonates, consider that some treatment settings may require the consideration of both mineral affinity and FPPS affinity.
- Take into account each agent's bone mineral affinity, because this may influence the time-to-onset of its antifracture efficacy, its distribution in different types of bone, and its reversibility.

Update on Rationale and Development of New Agents for Osteoporosis Treatment

John P. Bilezikian, MD

What is the current landscape for pharmacologic treatments of osteoporosis?



At the current time, the therapeutic landscape for osteoporosis is dominated by the class of drugs known as anti-resorptive agents. Although there are different types of antiresorptive drugs, they all act by impairing the activity of osteoclasts, the cells responsible for bone resorption.¹³ By indirect effects, the antiresorptive agents also impair the activity of osteoblasts, the cells responsible for bone formation. However, by inhibiting the osteoclasts to a greater extent than the osteoblasts, the antiresorptive agents rebalance the system to favor increases in bone formation and bone mass.¹⁴

The antiresorptive drugs approved in the United States are estrogens, raloxifene (a selective estrogen receptor modulator [SERM]), calcitonin, and the 4 bisphosphonates (alendronate, risedronate, ibandronate, zoledronate) discussed by Graham Russell. Some of these agents (estrogen, alendronate, risedronate, zoledronate) have been shown to reduce the risk of vertebral, nonvertebral, and hip fractures in randomized placebo-controlled clinical trials; for other agents, the evidence available from clinical trials is limited to vertebral sites.

The other general approach for osteoporosis therapy is to stimulate bone formation; drugs that use this approach have become known as osteoanabolic agents. The first member of the osteoanabolic class of drugs is teriparatide, which is recombinant human PTH (1-34).¹⁵ This agent is in widespread use for patients who have advanced osteoporosis and are at high risk for fracture. Teriparatide stimulates both bone formation and resorption, but it stimulates bone formation sooner than resorption, creating an "anabolic window" during which time bone formation predominates.¹⁶ This property is optimized by using teriparatide in a pulsatile fashion, namely, by daily sub-

cutaneous injection. Teriparatide reduces vertebral and nonvertebral fractures, and there is evidence that it improves bone microarchitecture.^{17,18}

Each of these agents is associated with adverse events, but they are generally considered to be well tolerated and safe. When used as part of a comprehensive treatment program that includes nutrition (calcium and vitamin D), exercise, lifestyle optimization, and measures to prevent falls, the available antiresorptive agents and teriparatide can be expected to reduce the incidence of fractures in most populations of patients with osteoporosis.

Another agent used to reduce fracture risk in osteoporosis is strontium ranelate, which is available in Europe and many other countries, but not in the United States. Evidence from animal models suggests that strontium ranelate exerts both antiresorptive and osteoanabolic actions;¹⁹ although it is not clear that such a dual effect explains the actions of the drug in humans. Nevertheless, strontium ranelate reduced the risk of both vertebral and nonvertebral fractures in clinical trials.^{20,21}

What new agents or treatment approaches are on the horizon?

Several new agents are in development for osteoporosis. In terms of new agents that fit into existing drug classes, there is ongoing research toward the development of low-dose estrogen preparations and new SERMS, such as lasofoxifene and bazedoxifene. However, I will focus on agents that take advantage of our improved understanding of the regulatory systems controlling bone formation and resorption.

Targeting the RANK/RANK ligand/OPG pathway with denosumab

One such regulatory system that has come to prominence recently is the RANK/

RANK ligand/OPG system, which is critical for intercellular bone signaling. RANK ligand (receptor activator of nuclear factor- κ B ligand) is expressed by osteoblasts and binds to its receptor (RANK) on the surface of osteoclasts and pre-osteoclasts. Activation of the RANK receptor by RANK ligand leads to bone resorption through stimulation of osteoclastogenesis and osteoclast action. Osteoprotegerin (OPG) functions as an important regulator of this system by acting as a decoy receptor for RANK ligand, making RANK ligand unavailable for binding to RANK.²² Early studies pursued the use of OPG as a therapeutic agent, but subsequent studies have focused on a human antibody to RANK ligand known as denosumab. By preventing RANK ligand from binding to RANK, denosumab reduces the activation and development of osteoclasts; thus, strictly speaking, denosumab is an antiresorptive agent. However, its mechanism of action is distinct from any other antiresorptive drug.

The phase II dosing studies of denosumab gave clear evidence of dose-related inhibition of bone resorption, as well as reductions in markers of bone formation. But the net effect was substantial and sustained increases in bone density at multiple skeletal sites.^{23,24} At the lumbar spine, bone density increases were similar to those seen with alendronate. But at the hip and distal one-third radius, denosumab was associated with greater increases in bone density than alendronate.²³ These promising results were followed by the FREEDOM trial, a double-blind, placebo-controlled, phase III trial of denosumab (60 mg subcutaneously every 6 months for 3 years).²⁵ Patients were postmenopausal women (N = 7868) with T-scores of less than -2.5 but greater than -4.0 at the lumbar spine or total hip. The primary end point was the incidence of new vertebral fractures over 3 years. The study

showed a significantly lower risk of vertebral fractures in the denosumab arm compared with the placebo arm (2.3% vs 7.2%; risk ratio = 0.32; 95% CI, 0.26–0.41; $P < .001$). Patients in the denosumab arm also experienced significantly lower rates of hip fracture (0.7% vs 1.2%; hazard ratio [HR] = 0.60; 95% CI, 0.37–0.97; $P = .04$) and nonvertebral fracture (6.5% vs 8.0%; HR = 0.80; 95% CI, 0.67–0.95; $P = .01$).²⁵ Denosumab was well tolerated and is currently under review by the FDA.

Targeting cathepsin K with odanacatib

Cathepsin K, a cysteine protease expressed in osteoclasts, degrades the organic matrix of bone, thereby helping to define the resorption pits that become bone remodeling units.²⁶ Inhibition of cathepsin K or deletion of the cathepsin K gene leads to shallower resorption pits and greater bone mass in animal models, though osteoclasts remain present and functional in other capacities, including signaling with osteoblasts.²⁷ Cathepsin K inhibitors have been proposed as a therapeutic target for osteoporosis, and one such inhibitor, odanacatib, is in phase III clinical trials. Results of a phase II trial of odanacatib were consistent with observations from animal models, indicating that bone resorption was inhibited to a greater degree than bone formation, and that bone formation was preserved to a greater degree than seen with bisphosphonates.²⁸ These observations suggest that odanacatib may preserve functional properties of osteoblasts better than other classes of antiresorptive agents.

Delivery of PTH

One limitation to the use of teriparatide is that it must be administered subcutaneously every day. Two approaches are now being studied with the goal of producing a better delivery system for teriparatide or endogenous PTH. A patch

system is being developed that could allow teriparatide to be administered transdermally.²⁹ The preliminary data suggest that this system achieves the pulsatile pharmacokinetic profile that is required for its efficacy.²⁹

The other approach aims to enhance secretion of endogenous PTH. This approach relies on the use of orally available inhibitors of the parathyroid calcium-sensing receptor. These so-called calcilytics stimulate the parathyroid cell to synthesize and release a pulse of endogenous PTH. Preliminary reports suggest that calcilytics may have promise for treatment of osteoporosis,³⁰ but the pharmacokinetic profile lacks the pulsatility that appears to be important.

New osteoanabolic pathways

The Wnt pathway is a complex and ubiquitous signaling pathway involved in numerous physiological processes, as well as embryogenesis, neurogenesis, and cancer. It is also a key pathway regulating the differentiation and activity of osteoblasts.³¹ Activity of the osteoblast Wnt pathway and, hence, bone formation, are down-regulated by the protein sclerostin, which is secreted by osteocytes.³¹ In this manner, sclerostin is thought to serve as an endogenous brake on bone formation.³² Indeed, studies of osteoporosis in animal models have shown that an antibody against sclerostin increases

bone formation and bone mass.³³ Drugs targeting other components of the Wnt pathway may also be attractive targets for osteoporosis therapy.

Discriminating the Cause of Fractures in Chronic Kidney Disease

Paul D. Miller, MD



In older patients with moderate declines in glomerular filtration rate (GFR), are increased fracture rates due to osteoporosis, or are they related to bone diseases usually associated with more severe CKD? How can these etiologies be distinguished clinically?

The stages of CKD are classified by GFR, with severe disease (stage 4 or 5) defined as a GFR of less than 30 mL per minute.³⁴ Several population-based studies have shown that severe disease is associated with substantial increases in the risk of fractures at all skeletal sites, with increases in the risk of hip fracture generally ranging from 7-fold to 14-fold compared with age-matched patients who do not have impaired renal function.³⁵ Furthermore, there is a growing body of literature suggesting that even patients with less-severe reductions in kidney function may have declines in bone remodeling^{36,37} and increased risk of fracture.³⁷ The pathophysiology of such declines may be related to changes in phosphorus clearance, elevations in fibroblast growth factor-23, elevated PTH levels with PTH resistance, or other effects of renal impairment.³⁶ So, the critical question is: How do we distinguish osteoporosis from the secondary effects of impaired renal function in older patients?

Both renal impairment and fracture risk increase with age. Data from the third National Health and Nutrition Examination Survey indicate that the prevalence of

concurrent osteoporosis and severe renal compromise (defined as a GFR of < 35 mL/min) increased from essentially 0% in women aged 50 to 59 years to 21.3% in women aged 70 to 79 years, and to more than 50% in older women.³⁸ Furthermore, the risk of hip fracture increases with age, even across individuals with similar T-scores,³⁹ indicating that other aspects of bone strength or quality decline with age. Although these data demonstrate a temporal relationship between CKD and fracture risk, it is clear that there is not a straight-forward cause-and-effect relationship.

Several bone diseases are more prevalent in patients with CKD and can account for much higher rates of fractures in these patients. These bone diseases include severe hyperparathyroidism (osteitis fibrosa cystica), adynamic bone disease, osteomalacia associated with impairment in mineralization and matrix formation, bone disease secondary to transplantation, and osteoporosis. The relative prevalence of these bone diseases in patients with stage 3 to stage 5 CKD-related mineral and bone disorder (CKD-MBD) is shown in Figure 2 (post-transplantation bone disease was not included in this analysis).³⁴ At this time, however, true adynamic bone disease and osteomalacia are thought to be less common in patients with early-stage CKD, and it is unclear if mild secondary hyperparathyroidism (PTH level between 65 and 300 pg/mL) is a significant risk factor for fractures.^{40,41} Thus, fractures in patients with early CKD (stages 1–3) are much more likely to be due to osteoporosis than a specific form of renal bone disease, a concept also supported by the Kidney Disease Improving Global Outcome Working Group (KDIGO) as long as there are no other biochemical abnormalities that might induce CKD-MBD.⁴²

Hence, diagnostic workup for suspected osteoporosis in patients with stage 1

PUT IT INTO PRACTICE

- Use available antiresorptive and osteoanabolic agents as part of a comprehensive treatment program that includes calcium and vitamin D intake, weight-bearing exercise, lifestyle optimization, and fall prevention.
- Recognize the potential for new agents to provide more options for tailoring treatment to individual patients and to enhance efficacy, safety, tolerability, and increased compliance.

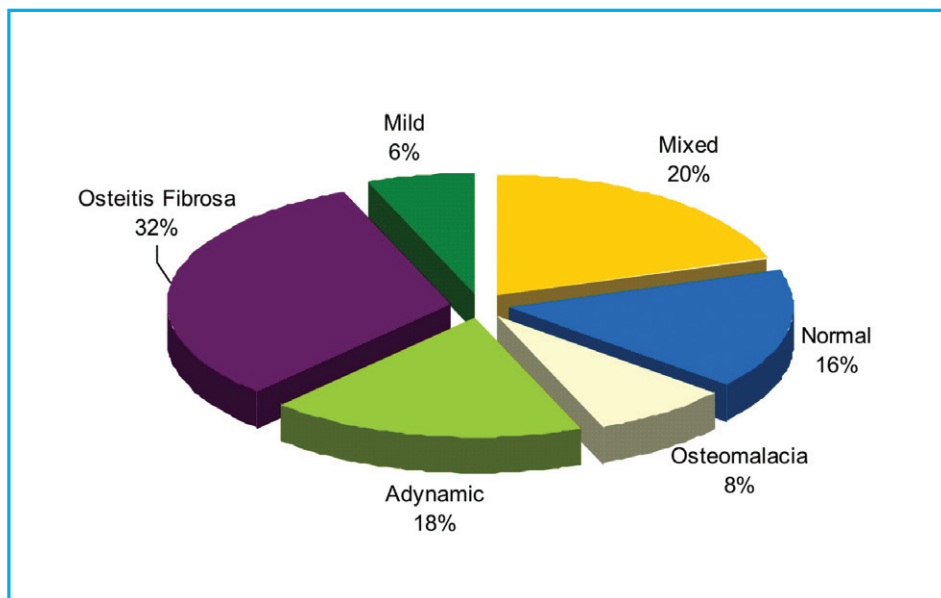


Figure 2. Relative prevalence of bone diseases in patients with concurrent bone disease and stage 3 to stage 5 CKD.³⁴

DEFINING CKD-MBD

Because of increased recognition of the link between CKD and bone disease (as well as vascular disease), an international working group has convened to define the disease entities involved and to develop guidelines for diagnosis and treatment. The working group is known as KDIGO (Kidney Disease: Improving Global Outcomes) and they have given the following definition to CKD-MBD:³⁴

A systemic disorder of mineral and bone metabolism due to CKD manifested by either 1 or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or other soft-tissue calcification

This definition is distinct from that for renal osteodystrophy, which is more narrowly defined as “an alteration of bone morphology in patients with CKD,” and “one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy.” The guidelines (www.kdigo.org) provide extensive information about the prevention, diagnosis, evaluation, and management of CKD-MBD.³⁴

to stage 3 CKD proceeds in much the same way as in postmenopausal women, *as long as there are no biochemical abnormalities suggesting CKD-MBD (see sidebar)*. Clinicians should also be attuned to the fact that patients with CKD often have additional risk factors for osteoporosis beyond the risk factors of the general population. Additional risk factors present in some patients with CKD include chronic heparin exposure among those receiving dialysis, chronic glucocorticoid exposure, hypogonadism, poor nutrition and associated vitamin D deficiency, hyperparathyroidism, and chronic metabolic or renal tubular acidosis.⁴³

How does the treatment of osteoporosis differ in patients with CKD from the treatment of patients with normal kidney function?

Pivotal clinical trials for osteoporosis treatments—including bisphosphonates, strontium ranelate, raloxifene, and teriparatide—enrolled patients with either estimated glomerular filtration rate (eGFR) or creatinine clearance as low as 30 mL per minute. Thus, the use of these same agents for patients with stage 1 to stage 3 CKD is consistent with the pivotal

clinical trials and current labeling.

Because of these same enrollment criteria, however, current FDA-approved labeling recommends these agents not be used in patients with a GFR of less than 30 mL per minute; essentially, there is very little data to support such use. Thus, in patients with stage 4 CKD (GFR between 15 mL/min and 30 mL/min), the use of these drugs constitutes an off-label use. Nevertheless, there are data from post hoc analyses supporting the efficacy and safety of risedronate, alendronate, and raloxifene in this setting. A retrospective analysis of 9 clinical trials found that risedronate (5 mg daily) preserved bone mineral density and reduced vertebral fracture risk without harming renal function for up to 3 years in osteoporotic women with severe renal impairment (creatinine clearance < 30 mL/min).⁴⁴ Likewise, a secondary analysis of the Fracture Intervention Trial (FIT) found that alendronate improved bone mineral density and reduced the risk of clinical and spinal fractures with no significant effect on adverse event rates in women with severe renal impairment (defined as estimated GFR < 45 mL/min in this trial).⁴⁵ Finally, small studies have also confirmed the safety of raloxifene in women with severe renal impairment.⁴⁶

The decision to use one of these agents for the treatment of osteoporosis in patients with stage 4 CKD must be individualized. In general, treatment may be considered for patients with confirmed osteoporosis without CKD-MBD and who are at very high risk for fractures or in whom the risk of death from fractures is high.

In patients with stage 5 or 5D CKD, there are no data supporting either the efficacy or safety of osteoporosis therapies, so caution is advised. Such therapies should be considered only in very specific circumstances and when a very clear diagnosis of osteoporosis is achieved, bearing in

mind that major fractures by themselves constitute a great risk for mortality. Furthermore, smaller doses should be considered and used for no longer than 2 to 3 years.⁴⁷

PUT IT INTO PRACTICE

- In patients with stage 1 to stage 3 CKD, diagnostic workup for suspected osteoporosis can proceed in the same manner as in postmenopausal women, as long as there is no biochemical evidence of CKD-MBD.
- Most approved therapies for osteoporosis can be used in patients with a GFR as low as 30 mL per minute. In patients with a GFR of less than 30 mL per minute, such treatment is off label.
- Remain vigilant about the substantially increased risk of fracture in patients with severe CKD, as this condition is associated with several bone diseases.
- Be alert for additional risk factors for osteoporosis in patients with CKD, such as chronic heparin exposure, glucocorticoid exposure, hypogonadism, hyperparathyroidism, and other factors.
- In a fracturing patient with stage 5 CKD, avoid any antiresorptive agent unless low bone turnover has been first excluded by biochemical markers of bone turnover or quantitative bone histomorphometry.

Fracture Risk Assessment and Treatment Guidelines: Highlights from the Panel Discussion

Moderator:

Robert R. Recker, MD



The World Health Organization, in collaboration with a number of investigators—particularly, Dr. John Kanis from the University of Sheffield, United Kingdom—has developed FRAX, a tool for evaluating an individual's risk of bone fracture during the next 10 years. The tool was developed

using population-based data from many parts of the world, and it incorporates clinical risk factors (such as age, smoking, glucocorticoid use, and other factors) in addition to bone mineral density at the femoral neck. An online version of the FRAX tool is available at www.shef.ac.uk/FRAX/.

A panel discussion was held addressing the issues of how the FRAX tool will affect clinical practice and how it will integrate with guidelines for the diagnosis and treatment of osteoporosis. This section of the newsletter will summarize the key points of this discussion and address some of the lingering questions and issues surrounding the use of the FRAX tool in clinical practice.

What are the advantages of using the FRAX risk calculation tool?

One of the main advantages of the FRAX tool is that it allows clinicians to obtain a more refined assessment of fracture risk in patients who are at risk but who do not satisfy existing definitions of osteoporosis. For example, many patients have T-scores in the intermediate range between normal and osteoporosis (between -1.0 and -2.5) and no history of fractures, but have other risk factors that place them at high risk for fractures. The FRAX tool allows clinicians to recognize which of these patients are at high risk of fracture and may be candidates for therapy. The converse is also true: Some patients may have satisfied previous criteria for treatment based on bone mineral density alone, but are actually at low risk for fracture according to the FRAX tool. Overall, the FRAX tool allows for a more refined assessment of 10-year fracture risk than bone mineral density measurements alone.

Will insurance reimbursement for osteoporosis treatment be tied to specific FRAX risk thresholds?

It is important that clinicians, reimbursement entities, and guideline-forming

bodies understand that FRAX is not intended to replace clinical experience or a physician's judgment. For example, the National Osteoporosis Foundation (NOF) recommends that treatment be considered in postmenopausal women or men older than 50 years if they have "low bone mass (T-score between -1.0 and -2.5) and 10-year probability of hip fracture greater than or equal to 3% or 10-year probability of major osteoporosis-related fracture greater than or equal to 20%" based on FRAX calculations. However, both the NOF guidelines and the FRAX instructions note that they are intended to *guide, but not replace* clinician judgment and patient preference. Furthermore, the FRAX tool does not incorporate known dose-dependence of certain risk factors (such as glucocorticoid use), necessitating the need for clinical judgment in the interpretation of results from FRAX. Laboratory results for markers of bone turnover that are not included in the FRAX model may also indicate more or less risk, and clinical judgment is required to incorporate these results into an overall assessment of a patient's risk. In general, the FRAX tool is an important step forward and one that has been scientifically developed and validated, but it cannot incorporate all of the important factors that may affect an individual patient's risk of fracture.

The FRAX-based treatment thresholds cited in the NOF's *Clinician's Guide* (20% and 3% 10-year risk of major osteoporosis-related fracture or hip fracture, respectively) were determined with a heavy emphasis on cost-effectiveness. As the prices for osteoporosis therapies decline, these thresholds may have to be reevaluated.

Is the FRAX tool appropriate for all patients?

No. FRAX is validated for use in *untreated* men and women between the ages of 40 years and 90 years. However,

according to the NOF's *Clinician's Guide*, FRAX is applicable for making treatment decisions only in untreated postmenopausal women and men older than 50 years who have T-scores at the femoral neck or lumbar spine between -1.0 and -2.5.⁴⁸ It is important to recognize that the *Clinician's Guide* recommends consideration of initiating pharmacological therapy to reduce fracture risk in other situations, such as existing osteoporosis (T-score -2.5 or below at the femoral neck or lumbar spine) or prior hip or vertebral fracture (clinical or morphometric), regardless of FRAX score.

FRAX should not be used in patients being treated for osteoporosis. Treatment may improve bone mineral density and thereby reduce a patient's FRAX risk score to below treatment thresholds. But that does not justify cessation of treatment, just as antihypertensive therapy that effectively lowers blood pressure to below

target levels does not justify cessation of antihypertensive therapy. Thus, once a patient starts therapy for osteoporosis, their baseline FRAX calculation should remain on their chart as the justification for treatment. Recalculation of FRAX after treatment has started should not factor into decisions about whether treatment should be continued.

The FRAX tool does not address the prevention of osteoporosis. Thus, patients who may soon experience events that cause significant bone loss (such as menopause) are in need of more comprehensive counseling and assessment directed at minimizing or preventing such loss. The NOF's *Clinician's Guide* provides prevention recommendations for the general population related to calcium and vitamin D intake, weight-bearing exercise, prevention of falls, and avoidance of tobacco and excessive alcohol consumption.⁴⁸

PUT IT INTO PRACTICE

- Implement the FRAX risk assessment tool as a guide for evaluating risk in appropriate patients, with continued use of experience and clinical judgment regarding factors that may alter an individual patient's risk beyond those incorporated into FRAX.
- Use FRAX for making treatment decisions with the NOF guidelines only in untreated postmenopausal women or men older than 50 years with osteopenia who do not meet other treatment indications.
- Since FRAX-based risk calculations use only 1 of 3 criteria for recommending the use of osteoporosis therapies according to NOF guidelines, don't overlook other criteria (existing osteoporosis by T-score classification or prior hip or vertebral fracture).

Read this newsletter and receive 2.0 hours of CME credit.

To access a pdf of this newsletter with evaluation form and posttest, and the complete meeting proceedings, go to: www.2009santafebonesymposium.com.

© 2009 Indiana University and Health Focus, Inc. All rights reserved.

REFERENCES

1. Fleisch H, Neuman WF. Mechanisms of calcification: role of collagen, polyphosphates, and phosphatase. *Am J Physiol*. 1961;200:1296-1300.
2. Fleisch H, Bisaz S. Isolation from urine of pyrophosphate, a calcification inhibitor. *Am J Physiol*. 1962;203:671-675.
3. Fleisch H, Russell RGG, Straumann F. Effect of pyrophosphate on hydroxyapatite and its implications in calcium homeostasis. *Nature*. 1966;212:901-903.
4. Russell RG. Excretion of inorganic pyrophosphate in hypophosphatasia. *Lancet*. 1965;2(7410):461-464.
5. Russell RG. Bisphosphonates: mode of action and pharmacology. *Pediatrics*. 2007;119(suppl 2):S150-S162.
6. Luckman SP, Hughes DE, Coxon FP, Graham R, Russell G, Rogers MJ. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. *J Bone Miner Res*. 1998;13(4):581-589.
7. Weinstein RS, Roberson PK, Manolagas SC. Giant osteoclast formation and long-term oral bisphosphonate therapy. *N Engl J Med*. 2009;360(1):53-62.
8. Dunford JE, Thompson K, Coxon FP, et al. Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther*. 2001;296(2):235-242.
9. Kavanagh KL, Guo K, Dunford JE, et al. The molecular mechanism of nitrogen-containing bisphosphonates as antiosteoporosis drugs. *Proc Natl Acad Sci U S A*. 2006;103(20):7829-7834.
10. Thompson K, Rogers MJ, Coxon FP, Crockett JC. Cytosolic entry of bisphosphonate drugs requires acidification of vesicles after fluid-phase endocytosis. *Mol Pharmacol*. 2006;69(5):1624-1632.
11. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356(18):1809-1822.
12. Nancollas GH, Tang R, Phipps RJ, et al. Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. *Bone*. 2006;38(5):617-627.
13. Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int*. 2008;19(6):733-759.
14. Bilezikian JP, Matsumoto T, Bellido T, et al. Targeting bone remodeling for the treatment of osteoporosis: summary of the proceedings of an ASBMR workshop. *J Bone Miner Res*.

CME POSTTEST & ACTIVITY EVALUATION

Highlights from the 2009 Santa Fe Bone Symposium

E. Michael Lewiecki, MD, John P. Bilezikian, MD,
Paul D. Miller, MD, Robert R. Recker, MD, Graham Russell, PhD, MD, FRS

MD DO Other

Name

Mailing Address

Phone Fax Email

**To Earn CME credit, complete BOTH sides of this survey and submit via Fax: 650-963-3520
or Mail: Health Focus, Inc., P.O. Box 2090, Mountain View, CA 94042-2090**

A. POSTTEST

	True	False
1. The tissue selectivity of bisphosphonates for bone is believed to be explained by their high binding affinity and rapid adsorption to bone mineral.....	<input type="checkbox"/>	<input type="checkbox"/>
2. Bisphosphonates obtain access to osteoclast cytoplasm by passive diffusion across the cell membrane.....	<input type="checkbox"/>	<input type="checkbox"/>
3. As a general property, the antiresorptive agents affect only markers of bone resorption and have no effect on markers of bone formation.....	<input type="checkbox"/>	<input type="checkbox"/>
4. RANK ligand stimulates both osteoclastogenesis and osteoclast activity by binding to RANK.....	<input type="checkbox"/>	<input type="checkbox"/>
5. Denosumab binds to osteoprotegerin, preventing it from binding to RANK ligand.....	<input type="checkbox"/>	<input type="checkbox"/>
6. Odanacatib interferes with osteoclast action by inhibiting cathepsin K, a cysteine protease important for degrading bone matrix.....	<input type="checkbox"/>	<input type="checkbox"/>
7. Pulsatile delivery of teriparatide is less effective at improving bone mass than constant administration.....	<input type="checkbox"/>	<input type="checkbox"/>
8. Mild secondary hyperparathyroidism is an established risk factor for bone fracture.....	<input type="checkbox"/>	<input type="checkbox"/>
9. CKD-MBD can manifest as calcification of vascular tissue, as well as bone disease.....	<input type="checkbox"/>	<input type="checkbox"/>
10. Trials of bisphosphonates for osteoporosis have included patients with stage 3 CKD.....	<input type="checkbox"/>	<input type="checkbox"/>
11. No patient with a FRAX-calculated 10-year risk of hip fracture below 3% should be considered eligible for osteoporosis therapy.....	<input type="checkbox"/>	<input type="checkbox"/>
12. Patients with high exposure to glucocorticoids may have a 10-year risk of osteoporosis-related fracture that may be higher than that calculated by FRAX.....	<input type="checkbox"/>	<input type="checkbox"/>

B. ACTIVITY EVALUATION

1. Please indicate the degree to which this activity may help you:	Excellent	Very Good	Good	Satisfactory	Poor
a. Describe the historic development of bisphosphonate therapy for treating osteoporosis and its current clinical application.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Describe emerging therapies, including their mechanisms of action, efficacy, safety, and administration, for patients with osteoporosis.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Employ effective strategies to successfully manage the treatment of skeletal disease in patients with chronic kidney disease (CKD) and heritable disorders of RANK-ligand/RANK/OPG signaling.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Describe the clinical utility of FRAX and issues that are still to be addressed regarding its use.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Highlights from the 2009 Santa Fe Bone Symposium/December 2009

2. Fair balance and professional effectiveness

- | | Strongly Agree | Agree | Disagree | Strongly Disagree |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| a. Course was free from commercial bias..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b. Content was fair-balanced..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c. Activity is relevant to my practice..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d. What I learned may help improve patient care..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Yes

- e. I agree to participate in a brief outcomes survey within 6 months of this activity.....

3. Outcomes (Check all that apply)

- | | What are the most important things you learned from this activity? | In what areas related to this topic do you still have questions? | In what areas of practice would you consider making changes? |
|---|--|--|--|
| a. Current treatment strategies..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b. New treatment options..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c. Side-effect management..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d. Clinical trial results and their significance to practice..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e. Screening and prevention..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f. Diagnostic strategies..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g. Quality-of-life issues..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h. Patient education..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

C. GENERAL NEEDS ASSESSMENT

1. Please indicate how important each of the following areas would be to you in future CME newsletters: (1 = least important; 5 = most important)

- | | 1 | 2 | 3 | 4 | 5 |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a. New pharmacologic agents..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b. Approaches to common clinical challenges..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c. Approaches to common therapeutic strategies..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d. Implementing guidelines..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e. How to educate patients..... | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

2. Suggested topics and faculty for future CME newsletters:

.....

.....

3. What factors do you consider when choosing to participate in a specific CME activity? (Check all that apply)

- | | |
|--|--------------------------|
| a. General interest in topic/keep up-to-date with advances in the field..... | <input type="checkbox"/> |
| b. Importance of topic to my clinical practice..... | <input type="checkbox"/> |
| c. Topic is based on specific problems encountered in my practice..... | <input type="checkbox"/> |
| d. Faculty expertise..... | <input type="checkbox"/> |
| e. Format..... | <input type="checkbox"/> |
| f. Convenience..... | <input type="checkbox"/> |
| g. Number of CME credit hours offered..... | <input type="checkbox"/> |
| h. Cost..... | <input type="checkbox"/> |

D. CERTIFICATION OF PARTICIPATION

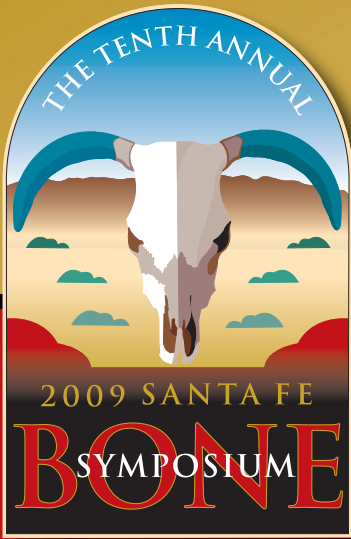
1. I claim credit (up to 2 AMA PRA Category 1 Credit(s)TM).

2. Please provide your signature:



REFERENCES (continued from page 8)

- 2009;24(3):373-385. 15. Canalis E, Giustina A, Bilezikian JP. Mechanisms of anabolic therapies for osteoporosis. *N Engl J Med.* 2007;357(9):905-916. 16. Bilezikian JP, Rubin MR. Monitoring anabolic treatment. In: Seibel MJ, Robins SP, Bilezikian JP, ed. *Dynamics of Bone and Cartilage Metabolism*. 2nd ed. San Diego, Ca: Elsevier Academic Press; 2006:629-647. 17. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344(19):1434-1441. 18. Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Eriksen EF. Recombinant human parathyroid hormone (1-34) [teriparatide] improves both cortical and cancellous bone structure. *J Bone Miner Res.* 2003;18(11):1932-1941. 19. Reginster JY, Deroisy R, Neuprez A, Hilgsmann M, Zegels B, Bruyere O. Strontium ranelate: new data on fracture prevention and mechanisms of action. *Curr Osteoporos Rep.* 2009;7(3):96-102. 20. Reginster JY, Felsenberg D, Boonen S, et al. Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: Results of a five-year, randomized, placebo-controlled trial. *Arthritis Rheum.* 2008;58(6):1687-1695. 21. Meunier PJ, Roux C, Ortolani S, et al. Effects of long-term strontium ranelate treatment on vertebral fracture risk in postmenopausal women with osteoporosis. *Osteoporos Int.* 2009;20(10):1663-1673. 22. Vega D, Maalouf NM, Sakhaee K. CLINICAL Review #: the role of receptor activator of nuclear factor-kappaB (RANK)/RANK ligand/osteoprotegerin: clinical implications. *J Clin Endocrinol Metab.* 2007;92(12):4514-4521. 23. Lewiecki EM, Miller PD, McClung MR, et al. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. *J Bone Miner Res.* 2007;22(12):1832-1841. 24. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med.* 2006;354(8):821-831. 25. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* 2009;361(8):756-765. 26. Stoch SA, Wagner JA. Cathepsin K inhibitors: a novel target for osteoporosis therapy. *Clin Pharmacol Ther.* 2008;83(1):172-176. 27. Pennypacker B, Shea M, Liu Q, et al. Bone density, strength, and formation in adult cathepsin K (-/-) mice. *Bone.* 2009;44(2):199-207. 28. McClung M, Eisman JA, Bone HG, et al. Odanacatib treatment in postmenopausal women with low bone mineral density: 24-month results. *Bone.* 2009;44(suppl 2):S438. 29. Cosman F, et al. Rapid pulse transdermal delivery of PTH[1-34] (ZP-PTH) is effective in increasing bone mineral density of the lumbar spine and hip in postmenopausal women with osteoporosis. *Osteoporos Int.* 2009;20(suppl 2):S228. 30. Fitzpatrick L, et al. Ronacaleret, a novel calcium-sensing receptor antagonist demonstrates potential as an oral bone-forming therapy in healthy postmenopausal women. *J Bone Miner Res.* 2008;23:Abstract 1174. 31. Kubota T, Michigami T, Ozono K. Wnt signaling in bone metabolism. *J Bone Miner Metab.* 2009;27(3):265-271. 32. Hoepfner LH, Secreto FJ, Westendorf JJ. Wnt signaling as a therapeutic target for bone diseases. *Expert Opin Ther Targets.* 2009;13(4):485-496. 33. Li X, Ominsky MS, Warmingtton KS, et al. Sclerostin antibody treatment increases bone formation, bone mass, and bone strength in a rat model of postmenopausal osteoporosis. *J Bone Miner Res.* 2009;24(4):578-588. 34. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int.* 2009;113(suppl):S1-S130. 35. Alem AM, Sherrard DJ, Gillen DL, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int.* 2000;58(1):396-399. 36. Hruska KA, Saab G, Mathew S, Lund R. Renal osteodystrophy, phosphate homeostasis, and vascular calcification. *Semin Dial.* 2007;20(4):309-315. 37. Nickolas TL, Leonard MB, Shane E. Chronic kidney disease and bone fracture: a growing concern. *Kidney Int.* 2008;74(6):721-731. 38. Klawansky S, Komaroff E, Cavanaugh PF Jr, et al. Relationship between age, renal function and bone mineral density in the US population. *Osteoporos Int.* 2003;14(7):570-576. 39. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int.* 2001;12(12):989-995. 40. Coen G. Adynamic bone disease: an update and overview. *J Nephrol.* 2005;18(2):117-122. 41. Moe S, Drueke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2006;69(11):1945-1953. 42. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. *Kidney Int Suppl.* 2009 Aug;(113):S1-130. 43. Gal-Moscovici A, Sprague SM. Osteoporosis and chronic kidney disease. *Semin Dial.* 2007;20(5):423-430. 44. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res.* 2005;20(12):2105-2115. 45. Jamal SA, Bauer DC, Ensrud KE, et al. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. *J Bone Miner Res.* 2007;22(4):503-508. 46. Yanik B, Bavbek N, Yanik T, et al. The effect of alendronate, risedronate, and raloxifene on renal functions, based on the Cockcroft and Gault method, in postmenopausal women. *Ren Fail.* 2007;29(4):471-476. 47. Miller PD. Diagnosis and treatment of osteoporosis in chronic renal disease. *Semin Nephrol.* 2009;29(2):144-155. 48. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC; 2008. Available at: http://www.nof.org/professionals/NOF_Clinicians_Guide.pdf. Accessed November 18, 2009.



E. Michael Lewiecki, MD



John P. Bilezikian, MD



Paul D. Miller, MD



Robert R. Recker, MD



Graham Russell, PhD, MD, FRS

Highlights from the 2009 Santa Fe Bone Symposium

Health Focus, Inc.
PO Box 2090
Mountain View, CA 94042-2090

**Earn up to
2 hours
CME credit.**

Presorted
First Class
U.S. POSTAGE
PAID
Elmwood Park, NJ
Permit #99