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This e-newsletter presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Holly L. Thacker, MD, Chair-Elect, 2007-2008 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Thacker. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Less frequent dosing of parathyroid hormone increases bone density

Black DM, Bouxsein ML, Palermo L, et al, for the PTH Once-Weekly Research (POWR) Group. Randomized trial of once-weekly parathyroid hormone (1-84) on bone mineral density and remodeling. *J Clin Endocrinol Metab* 2008;93:2166-2172. **Level of evidence: I.**

Parathyroid hormone (PTH) given weekly for 11 months after daily treatment for 1 month, rather than the characteristic prolonged daily dosing, increases bone mineral density (BMD) in postmenopausal women with low BMD, found a double-blind, randomized, placebo-controlled trial of the hormone conducted in Maine. The results suggest that daily dosing may not be necessary to receive the full anabolic effect and that less frequent or shorter duration use of PTH may be as good as daily PTH for 2 years to strengthen bone and reduce fracture risk, the authors contend.

The study included 50 women aged 45 to 70 years (mean age, 58.2 ± 6.4 y) with femoral neck BMD T-scores between -1.0 and -2.0 . Participants received daily subcutaneous injections of 100 μ g PTH (1-84) or placebo for 1 month followed by weekly injections for 11 months. Both groups also received 500 mg calcium and 400 IU vitamin D daily. The primary

outcome measure was change in lumbar spine areal BMD as seen by dual x-ray absorptiometry. Secondary outcome measures were volumetric BMD at the spine and hip by quantitative computed tomography, trabecular bone microarchitecture as seen by magnetic resonance imaging (MRI) of the distal radius, and biochemical bone turnover markers. The aim of the study was to determine whether less frequent administration of PTH increases density of the lumbar spine.

Compared with placebo-treated women, spinal areal BMD increased by 2.1% ($P = 0.03$) and vertebral trabecular volumetric BMD by 3.8% ($P = 0.08$) in the women on PTH. Trabecular bone separation and number, assessed by MRI, significantly improved in the proximal regions of the distal radius in the group that received hormone ($P < 0.05$). There were similar trends for trabecular bone fraction and thickness in the proximal region. After 1 month of daily PTH, N-terminal propeptide of type 1 collagen increased by 98% in the treated group and declined slowly over the course of the 12 months.

Comment. Recombinant human parathyroid hormone (rhPTH 1-34), marketed as teriparatide (Forteo), received Food and Drug Administration (FDA) approval in 2002 for

treatment of the following groups at high risk of osteoporotic fracture: postmenopausal women and men with primary or hypogonadal osteoporosis. The first and only anabolic therapy, teriparatide offers an attractive alternative in the treatment of patients with severe osteoporosis or those in whom other osteoporosis therapies failed. Initial clinical concerns in regard to teriparatide included cost (approximately \$800/mo) and the required daily injections.

The treatment of osteoporosis is plagued by poor compliance rates. One study revealed compliance rates for three popular oral osteoporosis treatments of 23% (alendronate), 19.4% (risedronate), and 16.2% (raloxifene).¹

This study investigated a longer dosing interval for PTH. In a review of 76 studies across a variety of therapeutic areas, Claxton and colleagues concluded that simpler, less frequent dosing regimens improved compliance.² Despite this, the long-term (>1 y) compliance rates for osteoporosis therapies continue to be suboptimal at less than 50%.³

Although compliance with oral antiresorptive osteoporosis medications is extremely low, compliance with teriparatide is quite high. One study from the United Kingdom by Arden et al reported an 87% persistence rate at 12 months with teriparatide.⁴ A study by Adachi et al in Canada reported a high rate of compliance (82%-88%) with daily injectable teriparatide.⁵

The current study provides some interesting data and a look at the possible future of anabolic therapy for osteoporosis. Promising data in this study are the maintenance of the anabolic effect of injectable PTH with a weekly dosing interval, albeit with 1 month of a daily dose included. It is concerning that BMD at the spine increased yet there was a lack of effect on hip BMD. In addition, the study group was younger and without severe osteoporosis, which represents neither the typical nor FDA-approved population for teriparatide. Given that the study was not designed to provide treatment outcomes and there

is no routine clinical application to these findings, the results by Black et al set the stage for additional multicenter trials to determine fracture risk reduction and optimal dosing intervals for injectable PTH. Longer dosing intervals for PTH treatment can lessen medication exposure time, increase patient comfort, and potentially decrease side effects and the cost of treatment—all clinically relevant issues.

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No clear difference in fracture risk found for various bisphosphonates

Cadarette SM, Katz JN, Brookhart MA, Sturmer T, Stedman MR, Solomon DH. Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture. *Ann Intern Med* 2008;148:637-646. **Level of evidence: II-3.**

(Continued)

A large observational study of the relative effectiveness of osteoporosis treatments to reduce nonvertebral fractures found little difference in fracture risk between risedronate, raloxifene, and alendronate. Calcitonin recipients may have a higher risk than alendronate recipients, however. The study compared nonvertebral fractures that occurred within 1 year of starting therapy for osteoporosis among enrollees in two statewide pharmaceutical benefit programs (New Jersey and Pennsylvania) for persons age 65 or older. The cohort included 43,135 patients who were new recipients of oral bisphosphonates, nasal calcitonin, or raloxifene between 2000 and 2005. Of these, 96% were women; mean age was 79 years (± 6.9 y). The primary outcome measure was nonvertebral fracture of the hip, humerus, radius, or ulna within 12 months of starting treatment. Secondary outcomes included nonvertebral fractures within 6 and 24 months of the start of treatment and hip fractures within 6, 12, and 24 months of starting treatment.

There were 1,051 nonvertebral fractures within 12 months of starting treatment. There was no large difference in nonvertebral fracture risk between risedronate (hazard ratio [HR], 1.01; 95% confidence interval [CI], 0.85-1.21) or raloxifene (HR, 1.18; 95% CI, 0.96-1.46) and alendronate (HR, 1.40; 95% CI, 1.20-1.63). Calcitonin recipients had more nonvertebral fractures than did alendronate recipients. Results were consistent when nonvertebral fracture rates at 6 and 24 months and hip fracture rates at 6, 12, and 24 months were compared. The authors warn that confounder adjustment was limited to healthcare utilization data, and confidence bounds of some comparisons were too wide to rule out potential clinically important differences between the drugs studied.

Comment. We have been fortunate recently to witness the emergence of many new therapeutic options for reducing osteoporotic fractures within the aging population. With the rising costs of medications, attempts to find the best of these treatment options are welcome. Cadarette et al try to fill this void of evidence with an attempted comparison of osteoporosis therapies. This study

also sought to measure what we care about most—fractures—rather than surrogate markers of bone mineral density and the resultant limitations of doing so. The size and cost of a randomized, controlled trial (RCT) measuring fractures as a primary outcome is usually prohibitive.

Several significant potential confounders in this study should be underscored, due to the use of a review of claims data that were not verified. Perhaps one of the most important factors affecting a medication's effectiveness and outcomes is a patient's persistence in taking it—a seemingly simple concept that is difficult to address in observational and cohort studies. Numerous studies to date have highlighted this factor's particular importance in osteoporosis management. This study readily acknowledges that adherence and persistence were not measured. Also, many prior studies have revealed outcome difference seen when these medications are used in the face of vitamin D and calcium insufficiencies, and this study does not seem to account for such potential differences.¹

In contrast to this study's results, individual trials on raloxifene, ibandronate, and calcitonin show no reduction in hip fractures. Another similar study, the REAL cohort trial, found fewer hip and nonvertebral fractures in the year following initiation among risedronate users versus those who took alendronate.² Also surprising, raloxifene performed equitably to bisphosphonates in preventing nonvertebral fracture, which has not been previously seen in other studies. The authors reveal that not only were participants in the raloxifene-treated group younger and healthier, but also more than twice as many of them were on recent or concomitant hormone therapy (HT), which can clearly skew results from being attributable to an agent by itself. The authors recognize the many limitations of their conclusions and the presence of multiple, very strong, and unrecognized confounders that likely account for these conflicting findings.

Additionally, several important therapeutic options were not included: HT, IV zoledronic acid, ibandronate, and teriparatide. With the Women's Health Initiative results showing hip fracture reduction, HT can no longer be looked at solely as a preventive medication for osteoporosis. The additional benefits of HT for a symptomatic menopausal patient in treating vasomotor symptoms and vaginal atrophy punctuate the necessity of assessing the patient as a whole and not overlooking HT as an important treatment option. A recent study of yearly IV zoledronic acid highlighted another important endpoint to consider when thinking about preventing and treating osteoporosis—a reduction in mortality.³

With generic formulations of alendronate now available, the pressure from insurance companies to choose the least expensive agent may override any desire for the “best” agent. This raises even more questions regarding true comparisons, as generics may have different bioequivalency, which even further complicates the matter. In the end, we are left considering all of the evidence to date and returning to an individualized assessment to determine the best treatment regimen for each patient.

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Perimenopausal women have higher mortality after mitral valve repair

Song HK, Grab JD, O'Brien SM, Welke KF, Edwards F, Ungerleider RM. Gender differences in mortality after mitral valve operation: evidence for higher mortality in perimenopausal women. *Ann Thorac Surg* 2008;85:2040-2045. **Level of evidence: II-3.**

During the ages that women undergo the menopause transition, mortality from mitral valve operation is 2.5 times greater in women than men who have similar risk factors, according to this retrospective study of outcomes of 24,977 patients (49% women) who had mitral valve repair or replacement. Outcomes were studied via records in the Society of Thoracic Surgeons National Cardiac Database for 2002 to 2005. The authors hypothesized that hormonal status may be an important factor in gender differences in outcomes after cardiovascular operations and sought to examine the influence of age and gender on risk during cardiac surgery by examining outcomes of this procedure, which is performed throughout the spectrum of middle and older age. Differences in mortality were examined by age and gender and compared by risk-adjusted analysis.

Data on patients aged 30 to 89 years who were not considered high risk and were undergoing mitral valve repair and replacement were analyzed. Men and women were subdivided into age decade groups to examine age and gender interaction. When not divided by age, mortality was higher in women than in men (3.9% vs 2.4%). When divided by age decade, the difference was accentuated in the 40s and 50s age groups for women versus men (1.7% vs 0.6% and 2.8% vs 1.2%, respectively). In the 30s age group, mortality in women and men was similar, as was that in the 60s, 70s, and 80s age decades. In patients aged 40 to 59 years, mortality was approximately 2.5 times higher in women than in men.

Comment. The strengths of this study were the large database evaluated (almost 25,000 patients) and the use of multiple centers. In addition, there were no differences between mitral valve repair and mitral valve replacement when evaluated. Potential problems include the lack of hormonal status reporting, the lack of data regarding causes of mortality, and the retrospective rather than prospective study design. In addition, there was no listing of the patients' lipid or lipoprotein status. It would of course be impossible to design a placebo trial.

The main message from this study is the potential importance of hormonal status, especially for women during perimenopause, to affect cardiovascular risk and outcomes of surgical procedures. Women in this age group, when risk-stratified using standard risk evaluators for cardiovascular status such as Framingham risk score, often have low 10-year risk scores but much higher lifetime scores. It is possible that many of these women, if stratified based on alternative scoring mechanisms and with more aggressive evaluations of lipid and lipoprotein status, may have been listed as higher risk, affecting the results. Physicians need to be aggressive in both evaluation and protection of women undergoing cardiovascular procedures during times of estrogen withdrawal, and alter risk stratification models to further identify those patients who may need more aggressive risk prevention during the perioperative time period.

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Low vitamin D levels associated with increased cardiovascular mortality

Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med* 2008;168:1340-1349. **Level of evidence: II-2.**

Low levels of 25-hydroxyvitamin D (25[OH]D) and 1,25-dihydroxyvitamin D (1,25[OH]₂D) are associated with increased risk for all-cause and cardiovascular mortality, according to the Ludwigshafen Risk and Cardiovascular Health study, conducted in southwestern Germany. The prospective cohort study included 3,258 consecutive male and female patients (mean age, 62 [\pm 10] y) who were scheduled for coronary angiography at a single center. Serum levels of 25(OH)D and 1,25(OH)₂D were determined and separated into quartiles for each month that blood was drawn. Because vitamin D levels fluctuate throughout the year, individual patients' levels were divided into quartiles on the basis of 202 to 358 vitamin D measurements of study patients each month. Patients were followed for a median of 7.7 years. The main outcomes were all-cause and cardiovascular mortality.

At the end of follow-up, 737 persons had died, with 463 deaths from cardiovascular causes. Those patients in the lower half of the vitamin D range (the two lower 25(OH)D quartiles—7.6 ng/mL and 13.3 ng/mL) had a hazard ratio of 1.53 to 2.08 for all-cause mortality after adjusting for cardiovascular risk factors. The relationship of vitamin D level to mortality was consistent regardless of comorbidities, level of physical activity, or New York Heart Association functional class. Hazard ratios for cardiovascular mortality in patients in the lower half of vitamin D quartiles were 1.82 to 2.22. Low vitamin D levels correlated with markers of inflammation, oxidative burden, and cell adhesion. These included C-reactive protein, interleukin 6, serum phospholipids levels, glutathione levels, vascular cell adhesion molecule 1 levels, and intercellular adhesion molecule 1 levels. Cardiovascular risk markers improved for patients in the higher quartiles of 25(OH)D and 1,25(OH)₂D.

Comment. The higher the latitude at which a person lives, the higher the risk they have of hypertension. Living at higher latitude increases risk of vitamin D deficiency because the zenith angle of the sun is more oblique,

causing the skin to be less efficient in producing vitamin D. When hypertensive adults were exposed to simulated sunlight in a tanning bed, which raised their blood levels of 25(OH)D (the measure for vitamin D status) by 100%, their blood pressure returned to normal. The active form of vitamin D, 1,25(OH)₂D, decreases the renal synthesis of the blood pressure hormone renin. Vascular smooth muscle cells and cardiomyocytes have a vitamin D receptor and 1,25(OH)₂D influences vascular smooth muscle and cardiomyocyte proliferation. In addition, 1,25(OH)₂D is a potent immunomodulator, and thus may influence the inflammatory activity associated with arteriosclerosis.

Vitamin D plays an important role in heart health. There have been several studies reporting that vitamin D deficiency is associated with congestive heart failure, and patients who are vitamin D deficient are at higher risk of having a myocardial infarction. Thus, it comes as no surprise that low serum 25(OH)D levels were associated with an increase in all-cause and cardiovascular mortality. However, what is of interest and needs to be confirmed is the observation that lower 1,25(OH)₂D levels were also associated with all-cause and cardiovascular mortality. Often, when patients are vitamin D deficient, (ie, 25(OH)D level <20 ng/ml), there is a compensatory rise in PTH levels that results in

an increase in the renal production of 1,25(OH)₂D. Thus, patients who are vitamin D deficient often have a normal or elevated level of 1,25(OH)₂D. Since 1,25(OH)₂D regulates renin production and alters vascular smooth muscle and cardiomyocyte function, it is possible that a reduction in the renal production of 1,25(OH)₂D could also increase risk of cardiovascular mortality. It is also known that living at higher latitudes increases risk of developing and dying of deadly cancers, autoimmune diseases, and type 2 diabetes, all of which can increase mortality and thus could help explain the significant increase in all-cause mortality that the authors reported.

To treat vitamin D deficiency, 50,000 IU of vitamin D₂ once a week for 8 weeks followed by 50,000 IU of vitamin D₂ every 2 weeks thereafter is effective and will not cause toxicity. Alternatively, taking 1,000 to 2,000 IU of vitamin D per day will help ensure that both children and adults remain vitamin D sufficient throughout the year.

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The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

Level I	Properly randomized, controlled trial.
Level II-1	Well-designed controlled trial but without randomization.
Level II-2	Well-designed cohort or case-control analytic study.
Level II-3	Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
Level III	Meta-analyses; reports from expert committees; descriptive studies and case reports.

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