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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 George A. Helmrich, MD, Chair-Elect, 2009-2010 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Helmrich. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Transdermal teriparatide for osteoporosis

Cosman F, Lane NE, Bolognese MA, et al. Effect of transdermal teriparatide administration on bone mineral density in postmenopausal women. *J Clin Endocrinol Metab* 2009 Oct 26. [Epub ahead of print] **Level of evidence: I.**

Osteoporosis treatment with a novel transdermal patch, giving a rapid, pulse delivery of teriparatide (PTH 1-34), may be a desirable alternative to daily subcutaneous injections. This study was designed to determine the safety and efficacy of a transdermal teriparatide patch compared to a placebo patch or the currently available 20- μ g subcutaneous injection in postmenopausal women with osteoporosis. The 6-month, randomized, placebo- and positive-controlled, multidose daily administration included 165 postmenopausal women (mean age, 64 y) with osteoporosis. The patches were available in a 20-, 30-, or 40- μ g doses or placebo patch and were self-administered daily for 30 minutes. The 20- μ g subcutaneous dose was injected daily. Mean percentage change in lumbar spine bone mineral density (BMD) from baseline at 6 months was the primary efficacy measure. The transdermal teriparatide significantly increased lumbar spine BMD versus the placebo patch at 6 months ($P < 0.001$). Compared to placebo and injection, the 40- μ g patch increased total hip BMD ($P < 0.05$). From

baseline, the bone turnover markers procollagen type I N-terminal propeptide and C-terminal cross-linked telopeptide of type I collagen showed an increase in a dose-dependent manner in all treatment groups and were all significantly different from placebo patch ($P < 0.001$). The authors concluded that transdermal patch delivery in postmenopausal women with osteoporosis for 6 months is safe and effective in increasing lumbar spine and total hip BMD.

Comment. Clinicians treating osteoporosis would like to provide a more convenient form of parathyroid hormone than the daily subcutaneous injection currently available (teriparatide). Several investigators have examined different schedules, routes, and formulations. This report of a phase 2 study compares teriparatide administered by a novel microneedle delivery system to the marketed drug. There are two key teaching points: first, to understand how a microneedle system works, and second, to look critically at short-term osteoporosis studies.

Imagine a microscopic bed of needles—just long enough to penetrate the upper layer of skin and get close to the capillary bed but short enough to avoid the pain receptors in the dermis. This new delivery system involves more than a thousand solid titanium needles,

each thinner than a hair, dipped in teriparatide and attached to a little plate held against the skin with a 1.3-inch-diameter patch. It provides excellent delivery of the drug into the circulation. This cutting-edge system, applied for 30 minutes (and then removed), produces the rapid rise and fall of plasma teriparatide needed to stimulate the anabolic bone response. The drug levels are not exactly the same in the two delivery systems (injection versus patch)—and the total amount of drug delivered by the 40- μ g patch is only 80% of that delivered by the 20- μ g injection—yet, this novel system holds great promise in being reliable, painless, and easily applied.

Short-term changes in bone density and bone turnover markers (eg, 6 months) are typically used to guide the choice of osteoporosis drug dose for subsequent 3-year fracture efficacy trials among thousands of patients that are ultimately required for FDA approval. We have numerous examples of osteoporosis drugs that looked fine in phase 2 but failed to have adequate efficacy and safety in phase 3. The 6-month bone density increases with the 40- μ g microneedle system look as good as 20- μ g subcutaneous teriparatide, but increases in bone turnover markers (indicating bone anabolic effect) are much lower with the patch—one half to one third as great as those seen with 20- μ g injection. I worry that the 40- μ g patch dose is suboptimal.

Many practical questions remain beyond the efficacy question. Will there be quality problems in large-scale manufacturing? Will the cost of this delivery system be in line with the usually prescribed osteoporosis drugs? Will skin reactions ultimately arise? (They were minimal in this 6-month study.) Will the elderly osteoporotic patient comply with the requirement to remove the patch after 30 minutes? At this point, we can admire the progress being made and keep alert for more microneedle system applications.

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Lower-dose estradiol for advanced breast cancer patients

Ellis MJ, Gao F, Dehdashti F, et al. Lower-dose vs high-dose oral estradiol therapy of hormone receptor-positive, aromatase inhibitor-resistant advanced breast cancer: a phase 2 randomized study. *JAMA* 2009;302:774-780.

Level of evidence: I.

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CONTEXT: Estrogen deprivation therapy with aromatase inhibitors has been hypothesized to paradoxically sensitize hormone-receptor-positive breast cancer tumor cells to low-dose estradiol therapy. **OBJECTIVE:** To determine whether 6 mg of estradiol (daily) is a viable therapy for postmenopausal women with advanced aromatase inhibitor-resistant hormone receptor-positive breast cancer. **DESIGN, SETTING, AND PATIENTS:** A phase 2 randomized trial of 6 mg vs 30 mg of oral estradiol used daily (April 2004-February 2008 [enrollment closed]). Eligible patients (66 randomized) had metastatic breast cancer treated with an aromatase inhibitor with progression-free survival (\geq 24 wk) or relapse (after \geq 2 y) of adjuvant aromatase inhibitor use. Patients at high risk of estradiol-related adverse events were excluded. Patients were examined after 1 and 2 weeks for clinical and laboratory toxicities and flare reactions and thereafter every 4 weeks. Tumor radiological assessment occurred every 12 weeks. At least 1 measurable lesion or 4 measurable lesions (bone-only disease) were evaluated for tumor response. **INTERVENTION:** Randomization to receive 1 oral 2-mg generic estradiol tablet 3 times daily or five 2-mg tablets 3 times daily. **MAIN OUTCOME MEASURES:** Primary end point: clinical benefit rate (response plus stable disease at 24 weeks). Secondary outcomes: toxicity, progression-free survival, time to treatment failure, quality of life, and the predictive properties of the metabolic flare reaction detected by positron emission tomography/computed tomography with fluorodeoxyglucose F 18. **RESULTS:** The adverse event rate (\geq grade 3) in the 30-mg

group (11/32 [34%]; 95% confidence interval [CI], 23%-47%) was higher than in the 6-mg group (4/34 [18%]; 95% CI, 5%-22%; $P = .03$). Clinical benefit rates were 9 of 32 (28%; 95% CI, 18%-41%) in the 30-mg group and 10 of 34 (29%; 95% CI, 19%-42%) in the 6-mg group. An estradiol-stimulated increase in fluorodeoxyglucose F 18 uptake ($>$ or $=$ 12% prospectively defined) was predictive of response (positive predictive value, 80%; 95% CI, 61%-92%). Seven patients with estradiol-sensitive disease were re-treated with aromatase inhibitors at estradiol progression, among which 2 had partial response and 1 had stable disease, suggesting re-sensitization to estrogen deprivation. **CONCLUSIONS:** In women with advanced breast cancer and acquired resistance to aromatase inhibitors, a daily dose of 6 mg of estradiol provided a similar clinical benefit rate as 30 mg, with fewer serious adverse events. The efficacy of treatment with the lower dose should be further examined in phase 3 clinical trials.

Comment. The response of estrogen-receptor positive and progesterone-receptor positive recurrent breast cancer to treatment with estradiol (E_2) is contrary to expectations; however, therapy with E_2 in this study was in the context of recurrent disease following prior progression-free survival with treatment with an aromatase inhibitor (AI). This study shows that in approximately 29% of women whose breast cancer developed resistance to aromatase inhibition, E_2 treatment at either 6 mg or 30 mg daily produced clinical benefit (response plus stable disease at 24 weeks). The mechanism of action for E_2 in this clinical setting of breast cancer resistance to AI is unknown, although it may be related to apoptosis.¹ Of note, several patients who were initially sensitive to E_2 treatment but subsequently had disease progression responded to retreatment with AI, suggesting that E_2 therapy may in some cases result in re-sensitization to estrogen deprivation.

Notably, the authors validated a biomarker that was a highly significant predictor of response by measuring metabolic flare, assessed by estradiol-induced changes in fluorodeoxy-glucose positron

emission tomography (FDG-PET) standardized uptake. A metabolic flare (12% increase in FDG uptake) had a positive predictive value for response of 80% and negative predictive value for nonresponse of 87%. In addition, progression-free survival was longer for patients with a metabolic flare. Given a total clinical response in 28% to 29% of patients, the availability of a biomarker to predict response is a major advance and a move toward personalized treatment. Patients who are more likely to benefit from E_2 therapy could be identified after 1 day of medication (FDG-PET E_2 stimulation test), avoiding prolonged treatment and its attendant side effects in those who do not show a metabolic flare and are much less likely to respond to E_2 or other endocrine treatment.

The authors use the term “lower-dose vs high-dose oral estradiol.” Caution should be employed when using relative terms such as low or high, as a dose of 6 mg of estradiol daily is more than 10 times the daily dose used in menopausal hormone therapy, thus might be considered relatively high. Both a daily dose of 6 mg E_2 and a daily dose of 30 mg E_2 produced equivalent responses, yet the 30-mg dose was associated with excess serious adverse events (high-grade nausea and vomiting, electrolyte disturbance, pleural effusion) compared to the 6-mg dose. Despite the exclusion of women at risk for deep vein thrombosis and pulmonary embolus from entry into the study, one thrombosis/embolic event was noted in each group. Since similar changes in FDG uptake were noted in both groups, it might be possible to lower the E_2 dose even further or administer E_2 transdermally to reduce side effects and maintain similar response rates. Clearly, this would need to be tested in future clinical trials.

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Reference:

1. Maximov PY, Lewis-Wambi JS, Jordan VC. The paradox of oestradiol-induced breast cancer cell growth and apoptosis. *Curr Signal Transduct Ther* 2009;4:88-102.

CVD associated with hip fracture risk

Sennerby U, Melhus H, Gedeberg R, et al. Cardiovascular diseases and risk of hip fracture. *JAMA* 2009;302:1666-1673. **Level of evidence: II-2.**

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CONTEXT: Recent studies indicate common etiologies for cardiovascular disease (CVD) and osteoporotic fractures. **OBJECTIVES:** To examine the relation between CVD and risk of hip fracture in twins and evaluate the relative importance of genetics and lifestyle factors in this association. **DESIGN, SETTING, AND PARTICIPANTS:** A cohort of all 31,936 Swedish twins born from 1914-1944 was followed up from the age of 50 years. The National Patient Registry identified twins with CVDs and fractures from 1964 through 2005. Time-dependent exposures using Cox proportional hazard regression models were evaluated. **MAIN OUTCOME MEASURE:** Time to hip fracture after diagnosis of CVD. **RESULTS:** The crude absolute rate of hip fractures was 12.6 per 1000 person-years after a diagnosis of heart failure, 12.6 per 1000 person-years after a stroke, 6.6 per 1000 person-years after a diagnosis of peripheral atherosclerosis, and 5.2 per 1000 person-years after a diagnosis of ischemic heart disease compared with 1.2 per 1000 person-years for those without a CVD diagnosis. The multivariable-adjusted hazard ratio (HR) of hip fracture after a diagnosis of heart failure was 4.40 (95% confidence interval [CI], 3.43-5.63); after a stroke, the HR was 5.09 (95% CI, 4.18-6.20); after a diagnosis of peripheral atherosclerosis, the HR was 3.20 (95% CI, 2.28-4.50); and after an ischemic heart disease event, the HR was 2.32 (95% CI, 1.91-2.84). Identical twins without heart failure and stroke also had, after their co-twins had been exposed to these respective diseases, an increased rate of hip fracture. These sibling twins pseudoexposed for heart failure had a multivariable-adjusted HR of 3.74 (95% CI, 1.97-7.10) for hip fracture, whereas pseudoexposure for stroke had an HR of 2.29

(95% CI, 1.20-4.35). **CONCLUSIONS:** A diagnosis of CVD was significantly associated with risk of subsequent hip fracture. Increased risks in co-twins without an index diagnosis suggest genetic factors in the association between CVD and osteoporotic fractures.

Comment. Sennerby et al describe an excellent and innovative study using a very large number of twins from Sweden to evaluate the relationship between CVD events and risk of hip fracture and to dissect the potential impact of environmental and medical factors versus genetic factors. Cerebrovascular and coronary heart disease events are associated with increased risk of hip fracture. This has been presumed to be on the basis of increased risk of subsequent falls, which have been shown to play a key role in increased risk of fragility fractures¹ and the implied association of immobilization and loss of muscle mass, due to limited mobility, resulting in both increased risk of falls and loss of bone density. The striking findings in this study are the 4.4 to 5.1-fold increase in hazard ratio (HR) after heart failure and stroke, respectively, in the population analysis. Other CVD, including peripheral atherosclerosis and ischemic heart disease, were associated with a 2.3- to 3.2-fold increase in HR.

If the presumed falls and bone loss mechanisms were correct, such findings would not necessarily be remarkable. However, by contrast with typical epidemiological studies, this current approach makes it possible to dissect the potential roles of environmental and genetic factors in the increased risk. It is possible to match an affected twin, who has actually suffered one of these CVD events, with an unaffected twin. It is then possible to examine the risk of fracture for the “pseudo-affected” twin for both monozygotic and dizygotic twins. As in all other twin studies, given that monozygotic twins share all of their genes and dizygotic twins have half their gene variants in common, any genetic relationship is expected to be stronger in monozygotic than dizygotic twins.

A remarkably large part of the increased HR for hip fracture, particularly after heart failure, peripheral atherosclerosis, and ischemic heart disease, could be explained by common genetic factors contributing to both outcomes rather than any direct effect of the cardiovascular events per se. This was very clearly the case for heart failure, in which there was also a much greater effect on hip fracture risk in monozygotic than dizygotic twins. Thus, most, if not all, of the increased risk of hip fracture after heart failure diagnosis was due to shared genes rather than any effect on intermediate factors, such as falls, immobilization, and accelerated bone loss. A proportion of the increased hazard ratio with peripheral atherosclerosis and ischemic heart disease also appeared to be genetic, but was not higher in monozygotic than in dizygotic twins.

With stroke, which carried the highest HR for hip fracture, a proportion of this effect could be explained by genetic factors but much less than for the other factors. This is also consistent with the Kaplan-Meier analysis, in which the increased risk of hip fracture occurred almost immediately after the stroke event and thus was most likely related to falls. Nevertheless, a proportion even of that increased risk of hip fracture also appeared to be genetically related. Importantly, the increased HR for risk of hip fracture after stroke was substantially higher in

men than in women, consistent with other studies showing that, although men have lower risk of fragility fractures, they have a greater increase in risk of a second fracture and also have higher premature mortality.²

The importance of this study is that it not only reminds us that clinicians must be more aggressive in prevention and treatment in osteoporosis in individuals with CVD but also recognize that, as with osteoporosis in general, there is a strong inherited component and that family history of osteoporosis and fragility fracture warrant very careful attention (perhaps particularly in men).

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References:

1. Nguyen T, Sambrook P, Kelly P, et al. Prediction of osteoporotic fractures by postural instability and bone density. *BMJ* 1993;307:1111-1115.
 2. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA* 2009;301:513-521.
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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.

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| 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. |

2010 Call for Abstracts

Don't miss the opportunity to submit your research abstracts to NAMS for presentation at the 21st Annual Meeting (October 6-9, 2010) in Chicago, IL.

- Submit your abstracts through the NAMS Web site:
www.menopause.org
- Information submitted for consideration must not be identical to that presented at any meeting prior to the NAMS meeting, and the study must have been published as of April 30, 2010
- The abstract submission deadline is April 30, 2010
- Top abstracts will be accepted for oral presentation and up to four poster prizes will be awarded (top prize: \$1,000)
- All accepted abstracts will be published in the NAMS journal, *Menopause*, after the meeting

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