

Top Ten Menopause Stories of 2007

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We've received so many positive comments about our "Top Menopause Stories of 2006" (January/February 2007, page 22) that we've decided to run an update! Similar to our approach last year, we attempted to identify the top new findings that improve the way we practice menopause medicine. While you may be familiar with many of these new findings, perhaps you'll find a few surprises.

Given that cardiovascular disease is the number-one killer of women, it seems fitting to emphasize recommendations for prevention as well as new findings that contribute to our understanding of the contradictions in the hormone therapy (HT) and heart disease story. Questions still persist about HT (dose, preparation, combinations, and effects on the breast), so relevant new studies made the list. New recommendations for maintaining bone health are included.

1. Saving Women's Hearts: Are we Doing all we Can?

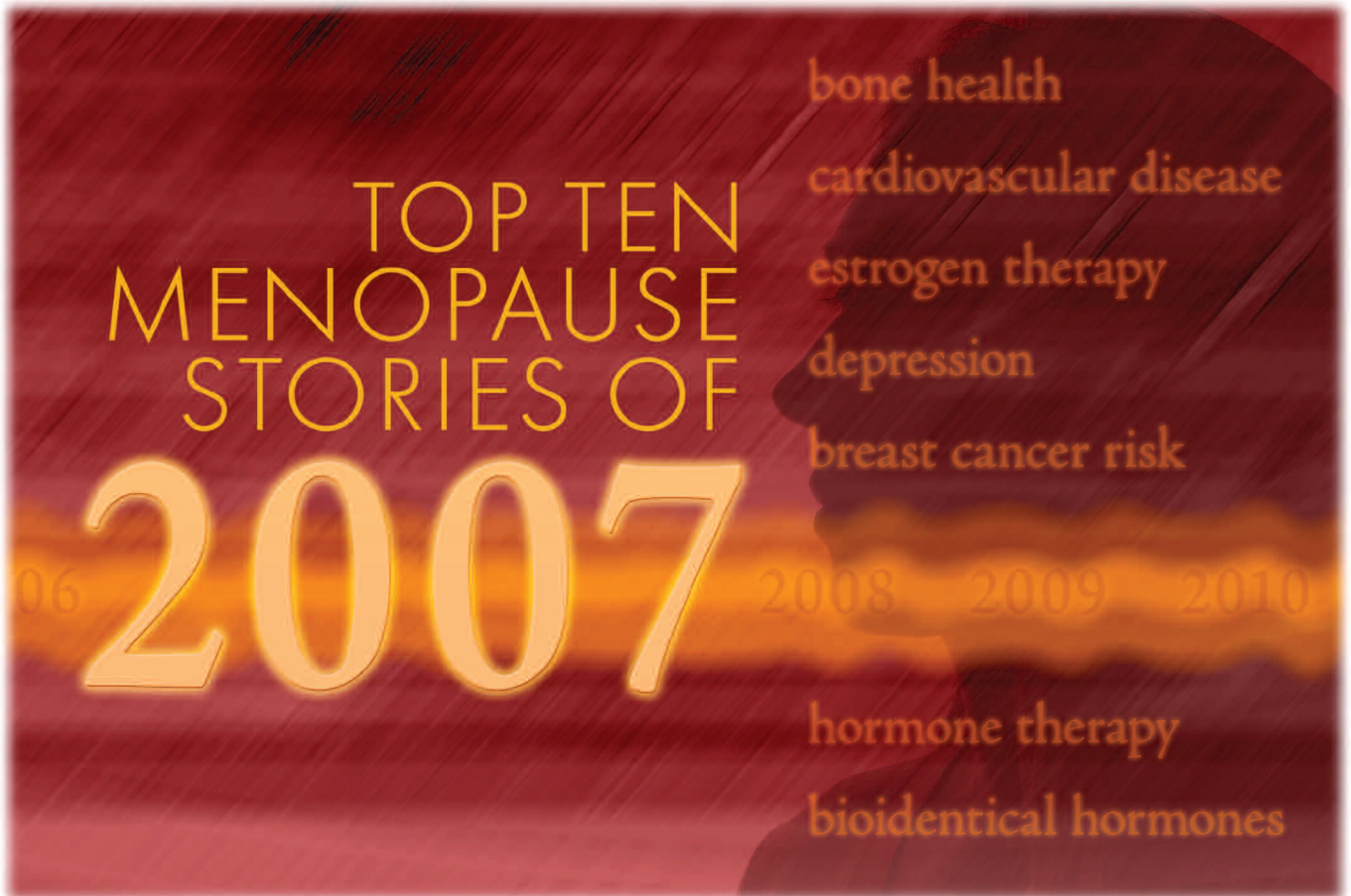
Fewer than one in five physicians appreciate the critical fact that more women than men die of coronary heart disease each year.¹ Concurrent with Heart Disease Awareness Month in February 2007, the American Heart Association (AHA) published updated recommendations for preventing heart disease in

women.² Crafted from a multidisciplinary panel and endorsed by a multitude of medical organizations (including The North American Menopause Society), this succinct evidence-based summary makes for quick but essential reading for anyone and everyone who advises women about their health.

So, what's new? To start with, the panel refined risk assessment in

women because, as they explain, a Framingham global risk score of > 20% is useful to identify a woman at high risk, but a lower score is not sufficient to ensure that an individual is at low risk. The intermediate "at risk" population now includes women with one or more risks, such as physical inactivity, family history, evidence of subclinical vascular disease (such as an increased carotid intima-media thickness on ultrasound or coronary artery calcium on rapid computed tomography [CT] scan), and poor exercise capacity on a treadmill test. The panel also wanted to focus on lifetime risk rather than short-term, 10-year risk as defined by the Framingham global score.

Of note, a second (unrelated) group concurrently proposed a new algorithm for cardiovascular risk assessment in women that might be used in place of the Adult Treatment Panel-III risk scoring model. The Reynolds Risk Score, based upon 10 years of follow-up for 25,000 participants in the Women's Health Study, incorporates C-reactive protein and family history into the calculation of risk with the goal of assigning "intermediate-risk" women into low- or high-risk groups. The risk calculator is available on line at



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www.reynoldsriskscore.org.³ The AHA recommendations state that “the role novel [cardiovascular disease] CVD risk factors such as highly-sensitive C-reactive protein (hs-CRP) should play in guiding preventive interventions is not yet defined.”² Additional aspects of a woman’s reproductive history, such as preeclampsia and maternal placental syndromes, might also predict higher cardiovascular risk later in life.

In another new twist on risk factors, nonfasting triglyceride levels measured 2-4 hours postprandially had a stronger association with CVD in women than fasting levels,⁴ a story similar to risks of elevated postprandial versus fasting blood glucose levels. Formal recommendations for clinical use are pending.

What’s new in the AHA Guidelines from the standpoint of preventive therapies? Lifestyle interventions still head the list of clinical recommendations.² Omega-3 fatty acids in capsule form (~1000 mg of eicosapentanoic acid and docosahexanoic acid) may be considered in women with coronary heart disease (CHD). Higher doses (2-4 g) may be used for treatment of women with high triglyceride levels. Depression screening and treatment is also recommended for women with CHD. Major risk factor interventions (treatment of high blood pressure, and lipids and diabetes) closely follow previous recommendations.

Recommendations for aspirin therapy have been modified to reflect new clinical trial findings specific to women (and very different from findings in men). Aspirin therapy (75-325 mg/d) should be used in all high-risk women (those with a

Additional aspects of a woman’s reproductive history, such as preeclampsia and maternal placental syndromes, might also predict higher cardiovascular risk later in life.

calculated risk greater than 20% or a history of diabetes or vascular disease) unless contraindicated. Aspirin therapy (81 mg/d or 100 mg every other day) should be considered in all women age 65 years and older if blood pressure is controlled and benefit for ischemic stroke (~30% reduction) and myocardial infarction prevention (~33% reduction) is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke. In contrast, in women younger than 65 years, aspirin therapy appears to be beneficial only for prevention of ischemic stroke; routine use of aspirin in healthy women younger than 65 years is not recommended to prevent heart attack.

Finally, the AHA recommends that HT and selective estrogen receptor modulators (SERMs) not be used for the primary or secondary prevention of CVD. Neither is there a role for antioxidant supplements or folic acid in prevention of CVD. Earlier research indicating that soy protein has clinically im-

portant favorable effects on low-density lipoprotein cholesterol and other cardiovascular risk factors has not been confirmed.⁵ Because of lack of safety and efficacy data, use of isoflavone supplements in food or pills is not recommended.

It’s time for all healthcare practitioners who care for women to establish prevention of CVD as an absolute priority. Perhaps in the past, gender disparities in recommendations for preventive therapy were explained largely by the lower perceived risk for women versus men.¹ However, we no longer have any valid reason not to aggressively identify and treat cardiovascular risks in women. In spite of a desire to find a “magic bullet” to prevent heart disease, improvements in lifestyle measures, such as diet and exercise, continue to provide the greatest benefits.

2. Build Better Bone: Back to Basics with Calcium and Vitamin D

The role of calcium and vitamin D in maintaining bone health has long been emphasized. A new meta-analysis of 17 clinical trials, all designed with fractures as outcomes, finds that calcium supplementation is associated with a 12% reduction in all types of fractures in people 50 years and older.⁶ The trials include 52,635 persons, of whom 92% were women with an average age of 68 years. In the 4,508 participants in the eight trials with at least 80% compliance, fractures were reduced by 24%

($P < 0.0001$). The treatment effect was better with daily calcium doses of 1,200 mg or more and vitamin D doses of 800 IU or more.

In a small separate study, 168 healthy postmenopausal women recorded a 7-day food and supplement diary.⁷ When investigators correlated calcium intake with bone mineral density (BMD), they found that BMD was higher in women who consumed most of their calcium from food sources (average 830 mg/day) compared with women whose calcium intake stemmed largely from supplements, even though the women on supplements ingested more calcium (1,033 mg/day). The group in which the women ingested both dietary calcium and supplements had the highest BMDs (and calcium intake—1,620 mg/day). Women with more calcium in their food or who combined food with supplements had a higher ratio of urinary measures of nonestrogenic to estrogenic metabolites. The authors suggest that calcium from dietary sources is associated with a shift in estrogen metabolism that might produce more favorable effects on bone health.

Vitamin D, the other half of the equation, moves to the spotlight as new studies highlight the potential consequences of vitamin D deficiency on bone health as well as immune function, carcinogenesis,⁸ response to inflammation and total mortality.^{9,10} Vitamin D deficiency is defined as a 25-hydroxyvitamin D level less than 20 ng/mL; insufficiency falls into the range of 21 to 29 ng/mL. Current evidence is insufficient to make specific recommendations for vitamin D sup-

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plementation in all persons,¹¹ although daily supplementation of 700–800 IU of vitamin D significantly reduced hip fracture risk in a pooled analysis of 12 randomized trials in adults older than age 60 (primarily in elderly institutionalized women).

In July 2007, the National Osteoporosis Foundation updated their recommendations for calcium and vitamin D intake, advising that adults age 50 and over ingest 1,200 mg of calcium and 800–1000 IU of vitamin D₃ per day (www.nof.org; July 26, 2007).¹²

Practitioners should have a low threshold for measuring 25-OH-vitamin D and treating vitamin D deficiency. Adopting new recommendations for daily supplementation should reduce the prevalence of vitamin D deficiency. Continue to recommend calcium supplementation, particularly as food.

3. Hormone Therapy Presents Minimal Cardiovascular Risks in Younger, Recently Postmenopausal Women: A Sigh of Relief for Women Seeking Symptom Relief

In April 2007, the Women's Health Initiative (WHI) investigators published an analysis of combined data from the two original arms of the WHI trial, the estrogen-plus-progestin arm and the estrogen-only arm. The new analysis of 27,347 women examined the effects of HT on the incidence of cardiovascular risks relative to age by decade (50–59 years, 60–69 years and 70–79 years) and years since menopause (< 10 years, 10 to 20 years, and >20 years).¹³ The results showed a trend ($P = 0.02$) for increasing risk of CHD with increasing time since menopause, with no increased risk for women who started HT within 10 years of menopause. There was a borderline significant tendency for the effects of HT to lower total mortality in younger (age 50–59 years) women (P for trend = 0.06).

The higher risks of CHD in women more distant from menopause appeared to be concentrated in the small subset of women with moderate or severe vasomotor symptoms. Again, the authors suggest that the presence of moderate or severe vasomotor symptoms at older ages might signal the need for identification and treatment of risk factors for CHD.

The risk for stroke was increased overall by 32% and did not vary by age or time since menopause, although there was no increased risk of stroke in women ages 50–59 years. Because of low event rates in more recently menopausal women,

the absolute excess risk will be very small, even in the presence of some increased relative risk due to HT. The authors recommend that screening and treatment of risk factors for stroke would be advisable before considering HT.

The low or absent excess risk of CHD in women with less than 10 years since menopause is reassuring and contributes to the peace of mind of women (and their healthcare providers) considering the use of hormones in the first few years after menopause. Women with risk factors for CHD or stroke should be carefully counseled if considering HT. The intriguing link of vasomotor symptoms with increased CHD risk in older women merits further study. Given the uncertainties about prolonged use of HT as women age, the mantra of “lowest dose for shortest time” remains appropriate.

4. HT for Symptom Relief: How Low can you Go?

A few years ago the results of the Women’s Health, Osteoporosis, Progestin, Estrogen (HOPE) study established that HT with conjugated estrogens (CE) in an oral dose of 0.3 mg/day accompanied by medroxyprogesterone acetate (MPA) 1.5 mg/day was as effective at reducing vasomotor symptoms as the preparations used in the WHI (CE 0.625 mg with MPA 2.5 mg daily).¹⁴ CE alone at the 0.3-mg dose also reduced vasomotor symptoms but not quite to the extent of the “usual”

In one new study, a 0.014-mg transdermal patch (delivering approximately half the dose of the CE 0.3-mg equivalent) was reported to relieve hot flashes in postmenopausal women.¹⁵

0.625-mg dose. In response to those findings and the FDA adage to use the lowest dose for the shortest time, most estrogen preparations on the market are currently available at doses equivalent to CE 0.3 mg. What about lower-dose therapy?

In one new study, a 0.014-mg transdermal patch (delivering approximately half the dose of the CE 0.3-mg equivalent) was reported to relieve hot flashes in postmenopausal women.¹⁵ The 12-week trial in over 400 women compared the micro-dose patch to a 0.023-mg/d 17- β estradiol and 0.0075 mg/day levonorgestrel patch or placebo. At the 12-week endpoint, 41.3% of women receiving micro-dose E2 were treatment responders compared with 24.2% in the placebo group. In the micro-dose group, the mean reduction in moderate and severe hot flashes from baseline was approxi-

mately 50% after 2 weeks, 70% after 4 weeks, 90% after 8 weeks, and 95% after 12 weeks. Adverse events did not vary between groups. This preparation has previously been shown to preserve BMD in women ages 60 to 80 years while achieving E2 blood levels of 8.6 pg/mL.¹⁶

Earlier in the year, the FDA approved a new 0.1% estradiol gel (Divigel, Upsher-Smith) for the treatment of moderate to severe hot flashes. The lowest approved dose of the gel (0.25 g of gel with 0.25 mg of estradiol) achieves serum estradiol levels of 9.8 pg/mL. In clinical trials, this dose significantly reduces the median daily frequency and the median daily severity of hot flashes by week 7 of administration (Divigel package insert, Upsher-Smith, 2007).¹⁷

The bottom line for women is that very low doses of estrogen can improve vasomotor symptoms, especially if the patient has patience and is aware that the maximal effect might take 2 to 3 months. Whether exposure to lower doses is also associated with lower risks has not been established in clinical trials.

5. Decline in Breast Cancer Incidence in 2003: Fallout (from the WHI) or Fluke?

“An initial analysis of data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) registries shows that the age-adjusted incidence rate of breast cancer in women in the United States fell sharply (by 6.7%) in 2003, as com-

pared with the rate in 2002.... Regression analysis showed that the decrease began in mid-2002 and had begun to level off by mid-2003.”¹⁸ Thus began *The New England Journal of Medicine* article laying out the details of an observation met with cynicism on some parts and nods of tacit understanding among others. The premise of this paper was that the substantial decline of HT prescriptions following the announcement of the WHI results in July of 2002 led to a fall in breast cancer incidence within just 1 year. Is this plausible? Is this possible?

A closer look at the data reveals that the decrease in breast cancer was evident only in women 50 years of age or older and primarily among estrogen-receptor positive cancers. For women between the ages of 50 and 69 years, estrogen-receptor-positive tumors declined by 14.7% while estrogen-receptor-negative tumors declined by 1.7%. An analysis of the California Cancer Registry also found that rates of breast cancer reduction correlated with declines in HT use.^{19,20} Since these publications, a number of other groups have reported similar findings.²¹⁻²³

The authors propose that the drop in breast cancer might suggest that “clinically occult breast cancers stopped progressing or even regressed soon after discontinuation of the therapy.”¹⁸ They offer other potential explanations for the drop in breast cancer incidence, including a SEER reporting flaw, a decrease in screening mammography, enhanced lifestyle or increased use of other drugs that might curb breast cancer (tamoxifen or raloxifene, nonsteroidal anti-inflammatory drugs,

statins, and calcium and vitamin D). While there is some concern about a trend toward a decline in screening mammography,²⁴ none of the alternative explanations seem adequate to explain the magnitude or the time course of the drop in breast cancer incidence in the year following publication of the WHI.

Postmenopausal women concerned about the increase in breast cancer risk while taking HT for relief of menopausal symptoms might find the possible reduction in breast cancer following cessation of HT somewhat comforting. The 3-year follow up of WHI participants after trial end and discontinuation of HT should be reported soon and might shed additional light on the intriguing findings of these observational studies.^{18,25} In the meanwhile, it is important to continue to recommend mammographic screening to women of appropriate age according to current recommendations, regardless of past or present HT use.

6. The Yin and the Yang of Estrogen Therapy and Prevention of Coronary Heart Disease. Where Are We Now?

In the discussion of the combined WHI trials, the authors comment that “hormone therapy has a putative beneficial effect on early atherosclerosis, no effect on advanced atherosclerosis, and an early increase in risk of CHD events when advanced atherosclerosis may be present.”¹³ They also say that “estro-

gen may have dual and opposing actions, retarding the earlier stages of atherosclerosis through beneficial effects on endothelial function and blood lipids, but triggering acute events in the presence of advanced lesions through procoagulant and inflammatory mechanisms.”¹³ Several new studies lend additional support to this hypothesis.

In an ancillary study of the estrogen-alone arm of the WHI trial, 1,064 women (ages 50 to 59 years at randomization) underwent CT of the heart after a mean of 7.4 years of estrogen treatment. The mean coronary artery calcium (CAC) score after trial completion was lower among women receiving estrogen therapy (ET) ($P=0.02$). For CAC scores of more than 300 (vs. <10), the multivariate odds ratio was 0.39 ($P=0.004$) among women with at least 80% adherence.²⁶ The effects of ET on CAC in women 60 years or older was not examined. In spite of these intriguing findings, the authors concluded that “in the meantime, hormone therapy should not be initiated (or continued) for the express purpose of preventing cardiovascular disease in either younger or older postmenopausal women.”²⁶

The Women’s International Study of long Duration Oestrogen after Menopause (WISDOM) trial, conducted in the UK, Australia and New Zealand, was similar in design to the WHI, used identical hormone therapies, and was halted when the results of the WHI were revealed.²⁷ As in the WHI, women in WISDOM were a mean age of 63 years; however, follow up was limited to an average of 11.9 months. The results confirm an elevated risk of CHD in

women randomly assigned to combined HT, consistent with the increased risk reported in older women in the WHI and other secondary prevention trials.²⁷

How might progressive atherosclerosis disrupt the beneficial effect of estrogen in young healthy arteries? In animal studies, a cholesterol metabolite (27-hydroxycholesterol [27HC]) is elevated in hypercholesterolemia and present in atherosclerotic lesions. The 27HC competitively inhibits estrogen-dependent production of nitric oxide by vascular cells and interferes with carotid artery re-endothelialization.²⁸ An elevation of 27HC may contribute to the loss of estrogen protection from vascular tissue as atherosclerosis evolves.

Whether the risk of pulmonary or venous thromboembolic events (VTEs) translates to risk of coronary artery thrombosis has not been well established. An extension of the Estrogen and Thromboembolism Risk (ESTHER) study, a large case-control study conducted in France, showed that the odds ratio for VTE was 4-fold greater in users of oral estrogens than in women using transdermal preparations.²⁹ Though this finding has not been confirmed in randomized controlled trials, the evidence from this large observational study suggests that the risk of VTE might be less with transdermal preparations. From the standpoint of cardiovascular disease, however, recall that in the Papworth trial, transdermal estrogen increased the risk of cardiovascular events in women with a history of cardiovascular disease.³⁰ The Kronos Early Estrogen Prevention Study

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(KEEPS), currently under way, compares oral to transdermal estrogen and measures carotid intima-media thickness as a trial endpoint.

These intriguing new findings will undoubtedly lead to additional research in an effort to learn more about the mechanisms of estrogen action. The recent recommendations of the AHA and NAMS (both issued within the first few months of 2007) conclude that postmenopausal HT should not be used for primary or secondary prevention of cardiovascular disease in women,^{2,31} positions in agreement with current FDA labeling and the authors of these important studies.³²

7. Secondary Prevention of Fractures: Just Do It

In spite of available therapies, few patients with a history of fracture are treated to prevent future fractures. This holds even for patients who have experienced a hip fracture, with its attendant morbidity, mortality and enhanced risk for future fractures (up to 1 in 10 patients

per year). According to the Healthcare Effectiveness Data and Information Set (HEDIS) data,³³ only about 20% of women age 67 years and older who have suffered hip fractures have either been treated or have had a bone density study within 6 months of the fracture.

A year ago, one of our “Top Stories” reported that intravenous (IV) bisphosphonates (ibandronate and zoledronic acid) reduced fractures in women with postmenopausal osteoporosis. Since that story, the Horizon Study, showing a reduction in vertebral, hip and nonvertebral fractures with an annual infusion of IV zoledronic acid, was published.³⁴ In August 2007, the FDA approved the use of zoledronic acid for treatment of postmenopausal osteoporosis.

New this year is the publication of a randomized clinical trial in 2,127 patients, mean age 74.5 years, who had suffered a hip fracture surgically repaired within the prior 3 months.³⁵ Patients who were unable or unwilling to take oral bisphosphonates were randomly assigned to IV zoledronic acid or placebo. Because so many subjects were found to be vitamin D deficient, the protocol was modified to provide for a loading dose of vitamin D in all patients, regardless of the level of serum 25-hydroxyvitamin D at baseline. Of interest, only 41.8% of the patients, all with documented hip fractures, had a *T* score of less than -2.5 SD at the femoral neck.

After a median follow-up of 1.9 years, patients randomized to zoledronic acid (5 mg IV annually) had fewer new clinical fractures. The

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rates of any new clinical fracture were 13.9% in the placebo group versus 8.6% in the zoledronic acid group, a 35% risk reduction ($P=0.001$). Non-vertebral fractures were significantly reduced by 27% (from 10.7% to 7.6%), and vertebral fractures decreased by 46% (from 3.8% to 1.7%). The incidence of hip fractures declined from 3.5% in the placebo group to 2.0% in the treatment group, but the 30% reduction did not reach statistical significance. Significant divergence in the fracture-free survival curves between the two groups for all clinical fractures was evident as early as 12 months ($P=0.02$). No adverse effects on healing of fractures were noted.

The other remarkable finding in this trial was a 28% reduction in mortality, down from 13.3% in the placebo group to 9.6% in the zoledronic acid group ($P=0.01$). In contrast to reports from other trials, atrial fibrillation was not increased in the group assigned to zoledronic acid. No cases of osteonecrosis of the jaw were reported.

The moral of this story is that now more than ever there really is no excuse not to aggressively treat fracture patients. For those patients who do not tolerate oral bisphosphonates, the once-yearly infusion of zoledronic acid might provide a better therapeutic option. The long duration of oral bisphosphonate effects on preventing fractures has also been reported with alendronate

Both circulating sex steroid levels and mammographic density appeared to be strongly and independently associated with the risk of breast cancer.

therapy.³⁶ Following 5 years of drug treatment in the Fracture Intervention Trial Long-term Extension (FLEX) study, fracture reduction persisted for another 5 years after discontinuation of therapy. Women should be vitamin D replete prior to initiating bisphosphonate therapy. The reported reduction in mortality with IV zoledronic acid is new and merits further study.

8. Mammographic Density and the Risk of Breast Cancer

It's not news that dense breasts are associated with an increased risk of breast cancer, but over the past year a more critical look at breast density and detection of breast cancer, the relationship of hormone levels to breast density, and evidence for a genetic contribution to breast density all made the news.

With data from three case-control studies, Boyd et al³⁷ showed that, as compared with women with

dense tissue affecting less than 10% of their mammogram, women with dense tissue in 75% or more had a 4.7-fold increased risk of breast cancer. The risk of breast cancer in dense breasts remained elevated for as long as 8 years after study entry, thus strongly suggesting a biologic connection between breast density and breast cancer.³⁸ Dense breasts might also mask an existing tumor, accounting for the 17-fold odds of detecting a cancer by nonscreening methods within a year after a screening examination in a woman with dense breasts compared with one whose breasts were less dense.³⁷

A nested case-control study within the Nurses' Health Study examined the relationship between breast density and circulating sex steroid levels in postmenopausal women.³⁹ The investigators reported that breast density was associated with a ~4-fold increased risk of breast cancer, similar to Boyd et al's findings. Coming as no surprise, endogenous levels of both estradiol and testosterone were associated with a doubling of breast cancer risk. Both circulating sex steroid levels and mammographic density appeared to be strongly and independently associated with the risk of breast cancer.

A group from the Mayo Clinic conducted a genome-wide linkage scan to identify genes contributing to mammographic density.⁴⁰ DNA was obtained from 889 relatives from 89 families. The analysis suggested a common locus on chromosome 5p.

That breast density correlates with breast cancer incidence, appears to contribute to breast cancer risk independently from endogenous hormones, and likely has a

genetic component all strengthen the case for incorporating mammographic breast density into algorithms for breast cancer risk assessment. Determination of breast cancer risk by including mammographic breast density with other known risk factors might enhance the ability to identify women who would benefit from pharmacologic measures to prevent breast cancer.⁴¹

Future refinement of techniques and increased availability of digital technology for more accurately measuring mammographic breast density will enhance our clinical use of this important determinant for breast cancer risk.

9. Feeling Sad may be Bad for Bones: The Depression/SSRI Link

Depression is common in women, and selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat depression. In papers from two separate North American populations, SSRIs were associated with an increased rate of bone loss at the hip⁴² and a two-fold increased risk of clinical fragility fractures.⁴³ The use of SSRIs was also associated with a doubling in the risk for falls.⁴³ What contributes to bone loss—depression, the SSRIs, or both?

In an animal model of depression, evidence suggests that the sympathetic nervous system mediates the skeletal effects of stress-induced depression.⁴⁴ The depression-triggered bone loss is associated with a substantial increase in bone norepinephrine levels and reduced osteoblast number. Bone loss can be blocked by

propranolol, a β -adrenergic antagonist. Therapy with a tricyclic antidepressant prevented both the depression and bone loss.

In studies of premenopausal women with depression, bone mineral density was diminished compared with nondepressed women, and serum cortisol levels were increased,⁴⁵ as were proinflammatory cytokines.⁴⁶

Other lifestyle factors might contribute to compromised bone strength. A depressed woman may be less likely to exercise, take supplemental calcium and vitamin D, and more likely to smoke or drink, all measures associated with compromised bone mass.

When evaluating a depressed patient, it is important to consider bone health. If SSRI antidepressants are prescribed for the treatment of depression in older postmenopausal women, bone density should probably be measured. Following current recommendations for calcium and vitamin D supplementation is important. Whether SSRIs prescribed for treatment of vasomotor symptoms also compromise bone density has not been clearly established, but measuring bone density and reinforcing conservative measures seems prudent.⁴⁷

10. Premarin has a New Partner: The Bazodoxifene/CE Paradigm

Bazodoxifene (BZA, Wyeth Pharmaceuticals) is an “estrogen agonist-antagonist” (formerly referred to as a SERM until the FDA changed the

terminology in September 2007) currently under review by the FDA for prevention and treatment of osteoporosis (Wyeth press releases).⁴⁸ “Clinical studies have shown favorable effects on the skeleton, with prevention of bone loss in postmenopausal women without osteoporosis and reduction in vertebral fracture risk in women with osteoporosis, without stimulation of endometrium or breast.”⁴⁹

According to a press release, in a 3-year randomized placebo- and active-controlled clinical trial enrolling 7,492 postmenopausal women with moderate to severe osteoporosis, BZA significantly reduced the relative risk of new vertebral fractures by approximately 40% (absolute risk 2.4% on BZA versus 4.1% on placebo).⁵⁰ Subgroup analysis of 1,782 women at higher risk for fracture showed that BZA significantly reduced the incidence of non-vertebral fractures by 46% (absolute risk of ~3.4% on BZA and 6.3% on placebo). A non-statistically significant increase in the incidence of venous thromboembolic events was observed in all active treatment groups compared with the placebo group.

A persistent concern regarding the use of estrogen for relief of vasomotor symptoms is the need to counteract the effect of estrogen on the endometrium. With the addition of a progestin, side effects such as breast tenderness and vaginal bleeding occur; risks of breast cancer and vascular events increase. Accordingly, other options for endometrial protection have been sought. BZA has been shown to decrease endometrial thickness in postmenopausal women.⁵¹ BZA has been

combined with conjugated estrogens as a tissue-selective estrogen complex (TSEC) and studied in postmenopausal women.

At the NAMS meeting in October 2007 the safety and efficacy of BZA with CE for treatment of vasomotor symptoms was presented.⁵² After 12 weeks of treatment, postmenopausal women (average age, 53.4 years) taking BZA 20 mg with CE 0.625 mg reported 80% fewer hot flashes; those receiving BZA 20 mg with CE 0.45 mg cited 74% fewer incidents; women assigned to placebo reported 51% fewer hot flashes. Symptom relief was evident within 14 days of starting therapy. Investigators reported a statistically significant improvement in time to fall asleep and feeling rested after sleep. No difference in uterine bleeding or breast pain between study groups and placebo occurred. No cases of endometrial hyperplasia were detected. The most common side effects of BZA are headache and joint pain.

In a separate report, the effects of BZA and CE on vulvar/vaginal atrophy and sexual function were presented.⁵³ Similar doses were studied. Both BZA/CE regimens were significantly more effective than placebo or BZA alone in improving vaginal pH, superficial cells and parabasal cells, lubrication, and vasomotor and sexual function.

A TSEC provides a novel approach to treatment of menopausal symptoms while avoiding some of the concerns of progestin therapies. Each estrogen agonist-antagonist studied to

date has unique properties—BZA will be no exception. From a safety standpoint, candidates for this combination will exclude women with increased risk of blood clots or markedly elevated triglycerides. No safety data have been reported in women with prior estrogen-dependent neoplasms such as breast cancer or uterine cancer. Finally, while these agents are under evaluation by the FDA, the package insert for raloxifene advises against adding oral estrogen to raloxifene therapy; in one reported clinical trial, raloxifene 60 mg with oral 17- β estradiol 1 mg resulted in signs of endometrial stimulation including hyperplasia and atypia.⁵⁴

Postscripts to a Few of the 2006 Stories...

Is there a shining star for breast cancer prevention? Last year we wrote about the findings of the Study of Tamoxifen and Raloxifene (STAR), a head-to-head breast cancer prevention trial in women at high risk for breast cancer. In response to the findings from the STAR trial and other long-term trials of raloxifene, in September 2007 the FDA approved raloxifene for reducing the risk of breast cancer in postmenopausal women with osteoporosis and postmenopausal women at high risk for invasive breast cancer.

Regulation of Compounding Pharmacies and Bioidentical Hormones: Who's Minding the Store?

In October 2006 The Endocrine

Society issued a policy statement on bioidentical hormones.⁵⁵ The statement, endorsed by NAMS, recognized that a few “bioidentical hormones”—those available from retail pharmacies, such as estradiol and progesterone—are produced under FDA supervision and are monitored for dosage and purity as are preparations of traditional hormones. “However, even FDA-monitored ‘bioidentical hormones’ have not been examined in long-term studies such as the WHI and therefore, have unproven safety and efficacy.”⁵⁵ The Endocrine Society supports FDA regulation and oversight of all hormones regardless of chemical structure or method of manufacture. This should include:

- Surveys for purity and dosage accuracy
- Mandatory reporting by manufacturers of adverse events
- A registry of adverse events
- Inclusion of uniform information for patients, such as warnings and precautions in packaging

In November 2006 the American Medical Association (AMA) adopted a resolution calling for FDA oversight of bioidentical hormones. The resolution, introduced by The Endocrine Society, American Association of Clinical Endocrinologists, and American Society for Reproductive Medicine, urges the FDA to follow the recommendations of The Endocrine Society statement. The AMA added the caveat urging the FDA to prohibit the use of the term “bioidentical hormones” unless the preparation has been approved by the FDA. In the Spring of 2007 the Senate Special Committee

on Aging heard testimony, although a formal ruling is still pending.

Alternative Treatments for Hot Flashes

One of the agents mentioned last year is desvenlafaxine succinate, known as Pristiq, a serotonin and norepinephrine reuptake inhibitor manufactured by Wyeth Pharmaceuticals. In clinical trials, presented at the American College of Obstetricians and Gynecologists in May 2007, the drug reportedly reduced hot flashes as well as nighttime awakenings due to night sweats.⁵⁶ However, the findings were not consistent in all trials presented. In July 2007 the FDA issued an Approvable Letter requiring additional clinical trial data regarding the potential for serious adverse cardiovascular and hepatic effects associated with the use of Pristiq in this indication.⁵⁷ Pristiq is also under consideration by the FDA for treatment of major depressive disorder. ■

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This article includes discussion of off-label use of medications.

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Top Ten Menopause Stories of 2007

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From the Editor

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involve addressing their concerns based on scientific _____ while also being respectful and considering _____. (Answer, p. 277.)

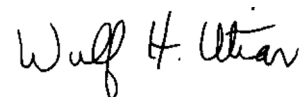
Take the Next Step

This has really been a teaser. But hopefully it will give you a tantalizing glimpse into the scope and detail of the contents of this quite remarkable publication. The book is also a CME activity and offers a maximum of 25 AMA PRA Category 1 Credits through NAMS, which is an ACCME-accredited organization. No administrative fee is required.

Finally, remember that acquiring, reading and digesting the contents of the book is only

part of an ongoing self-education process. As knowledge about and the need to manage menopause increase at a phenomenal pace, I encourage you to join NAMS and take advantage of the multiple offerings that will keep you up to date and on the front lines of this exciting and rewarding area of medical practice. Visit the NAMS Web site (www.menopause.org) to sample the offerings, and remember the member's section offers even more.

My very best wishes to you and yours for a healthy, happy, peaceful and prosperous New Year.



Wulf H. Utian, MD, PhD, DSc(Med)

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The North American Menopause Society