

NEWS Commentary

The following news items are reviews of important scientific articles with commentary that address clinical relevance. This material comes from the First to Know® program of The North American Menopause Society (NAMS), offered to its members via broadcast e-mail. You can receive the complete program by joining the Society (www.menopause.org). Please note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS.

Two studies find EPT-associated venous thrombosis risk elevated by age, weight, gene mutation, and type of estrogen

Cushman M, Kuller LH, Prentice R, et al, for the Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004;292:1573-80.

Oral estrogen plus progestin therapy (EPT) doubles the risk of venous thrombosis (VT), a risk further increased by older age, high body mass index (BMI), and presence of the factor V Leiden gene variant, according to data from the Women's Health Initiative (WHI), a double-blind, randomized, placebo-controlled trial, including an extended follow-up of 5.6 years, in comparison with the original report of 5.2 years. [WHI Writing Group, *JAMA* 2002]. The authors assessed data on VT risk, primarily deep vein thrombosis and pulmonary embolism, from 16,608 postmenopausal women between the ages of 50 and 79 who received either placebo or EPT consisting of 0.625 mg/day conjugated equine estrogens (CEE) plus 2.5 mg/day medroxyprogesterone acetate (MPA).

Overall, EPT recipients had a signifi-

cantly increased risk of VT (hazard ratio [HR], 2.06; 95% CI, 1.57-2.70). When analyzed for age compared with placebo recipients aged 50 to 59 years, EPT users aged 50 to 59 had an HR of 2.27 (95% CI, 1.19-4.33), EPT users aged 60 to 69 years had an HR of 4.28 (95% CI, 2.38-7.72), and EPT users aged 70 to 79 years had an HR of 7.46 (95% CI, 4.32-14.38). Having a high BMI significantly increased the VT risk associated with EPT in both overweight women (HR, 3.80; 95% CI, 2.08-6.94) and obese women (HR, 5.61; 95% CI, 3.12-10.11) when compared with normal-weight placebo recipients. Overweight was defined as a BMI of 25 to 30; obesity was defined as a BMI > 30.

In a nested, case-control study of WHI data, validated cases of VT and matched controls were analyzed for genomic DNA mutations using standard methods. Having factor V Leiden gene was found to significantly increase the VT risk. Compared with placebo recipients without the gene variant, EPT users with the mutation had an HR of 6.69 (95% CI, 3.09-14.49). Other genetic variants analyzed did not substantially increase the risk.

Smith NL, Heckbert SR, Lemaitre RN, et al. Esterified estrogen and conjugated equine estrogens and the risk of venous thrombosis. *JAMA* 2004;292:1581-7.

Current users of oral CEE alone—but not oral esterified estrogens (EE)—have a significantly increased risk of VT, according to this population-based, case-control study. Cases of first VT in peri- and postmenopausal women aged 30 to 89 (mean age, 69.4 years) were identified from records at a large health maintenance organization in Washington State. Cases were diagnosed between Jan 1, 1995 and Dec 31, 2001. A total of 586 cases of first VT were identified along with 2,286 controls matched for age and hypertension status. Multivariate logistic regression was used to analyze associations between current use of ET and risk of VT.

Compared with nonusers of hormones, the adjusted odds ratio for VT

risk among current users of any CEE-containing regimen was 1.65 (95% CI, 1.24-2.19). Among users of regimens containing EE, the OR was 0.92 (95% CI, 0.69-1.22). Adding a progestin (primarily MPA at 2.5 mg/day) to either regimen significantly increased the risk compared with estrogen alone (OR, 1.60; 95% CI, 1.13-2.26). Subgroup analyses showed that current users of EE alone, EE plus a progestin, and CEE alone had no significantly altered VT risk. Users of CEE plus a progestin, however, had a significantly increased risk (OR, 2.17; 95% CI, 1.49-3.14). Comparing the two estrogen groups showed a significantly higher risk among CEE users (OR, 1.78; 95% CI, 1.11-2.84). Users of CEE plus a progestin had an OR of 2.94 (95% CI, 1.60-5.40) compared with EE alone.

Most women (81%) used estrogen doses of 0.625 mg/day, defined as the modal dose. A dose-relationship analysis (low, modal and high) found that both modal and high doses of CEE were associated with significantly increased VT risks (OR, 1.68; 95% CI, 1.01-2.78 and OR, 3.80; 95% CI, 1.90-7.61, respectively) compared with modal doses of EE.

Comment. These two articles remind us that the use of ET/EPT is not without risk of VT. In the first article, the findings are consistent with prior data suggesting that age, obesity, and presence of the factor V Leiden gene mutation increase the risk. Inference for other gene mutations was plagued with small numbers of events. The authors suggest that it is probably not cost-effective to screen everyone for these mutations.

The second article suggests that VT risk may be associated with CEE as opposed to EE, and that the use of a progestin may increase the risk with either preparation. A large HMO database was used to deal with potential disadvantages inherent in case-control methodology, including that hospitalized patients may not be as representative as outpatients. The description of the

methodology is not, unfortunately, sufficient to assure readers that these issues were completely dealt with. The authors correctly point out that additional studies are needed to replicate their findings.

The fact that these two articles attempt to determine the role of the progestin and the type of estrogen used as they relate to VT risk is to be applauded. While we await answers from future trials, we need to remind ourselves and our patients of the real, yet uncommon, risk of VT potentially with all forms of ET/EPT, and that these risks are compounded by aging, weight, immobility, etc. We can do a lot to help women become proactive by recommending physical activity, avoiding "stasis", and stopping ET/EPT before procedures associated with increased risk of thrombosis.

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Comment. In 2002, a systematic review and meta-analysis conducted for the US Preventive Services Task Force [Miller, *Ann Intern Med* 2002] concluded that menopausal estrogen therapy was associated with an increased risk for VT, with the highest risk in the first year of use. In the article by Cushman et al, new data from the WHI show a doubled VT risk associated with CEE plus MPA, with greater risk imparted by older age, overweight or obesity, and presence of factor V Leiden. In the study by Smith et al, observational data from a large HMO offer a hypothesis worthy of testing—that in contrast to CEE, EE is not associated with increased VT risk (adjusted). Dose-dependent VT risk with CEE was noted, as previously reported by others. However, selection and other biases of observational studies tend to overestimate benefit and underestimate risk. Clearly, randomized trial data for EE is needed to assess its

potential to enhance women's menopausal health. In the Smith et al paper, MPA increased VTE risk by 60%, which is comparable to the 62% increased risk with progestin in the randomized WHI data. A search for a safer progestin is equally mandated.

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Link between rapid tumor growth and mammography sensitivity supports 1-year screening interval

Buist DSM, Porter PL, Lehman C, et al. Factors contributing to mammography failure in women aged 40-49 years. *J Natl Cancer Inst* 2004;96:1432-40.

In women aged 40 to 49 years, rapid tumor growth in the breast contributes substantially more to decreased mammographic sensitivity at 24 months than at 12 months, indicating that a 12-month mammogram interval may be more appropriate in this patient population to identify these tumors, according to this cohort study. In all, 576 women diagnosed with invasive breast cancer were studied; 73 were aged 40 to 49 and 503 were older than age 50. The primary outcome was percentage of women with interval cancer by age. Interval cancers were defined as tumors diagnosed within 12 or 24 months after a negative screening mammogram and before the next mammogram.

The OR for interval cancer was significantly higher in younger women than in older women at both 12 months (OR, 2.36; 95% CI, 1.14-4.77) and 24 months (OR, 3.58; 95% CI, 2.15-5.97). Incidence rates for younger and older women were 27.7% and 13.9%, respectively, at 12 months, and 52.1% and 24.7%, respec-

tively, at 24 months. Investigators reported that in younger women, greater breast density was responsible for 67.6% of the decreased mammographic sensitivity at 12 months. At 24 months, 37.6% of the decreased sensitivity in younger women was attributed to breast density versus 30.6% to rapid tumor growth.

Comment. Buist and colleagues conclude that a 12-month screening interval may reduce the adverse impact of faster-growing tumors on mammographic sensitivity in younger women; however, their paper does not address the impact of such screening on recall rates in this population that is so susceptible to false-positive reporting.

Between ages 40 and 49, estimates suggest that 15 of every 1,000 women will develop breast cancer, and of these women, two will die from the disease. [Fletcher, *N Engl J Med* 2003] This contrasts with 21 women who will die from other causes during the same age-decade. The role of mammography as a breast cancer screening tool in women under age 50 remains controversial because of the following: 1) the low incidence of breast cancer at this age necessitates some 15,000 mammograms to prevent one breast cancer death, and 2) the increased breast density in premenopausal women leads to high false-positive rates (up to 20%). Data suggest that after 10 mammograms in women aged 40 to 69, as many as 49% will be recalled for further testing (most of these are false positives) and 18.6% will have had an open or needle biopsy [Elmore, *N Engl J Med* 1998]. These numbers would be even higher with annual mammography in premenopausal women, as suggested by Buist et al. False positives increase anxiety, resulting in more patients initiating healthcare visits for both breast-related and nonbreast-related concerns.

Studies in Norway and Sweden [Zahl, *BMJ* 2004] have reported a dramatic 50% rise in breast cancer incidence among women aged 50 to 69 after the nationwide introduction of mammographic screening,

but no corresponding fall in breast cancer incidence after age 69. This led them to conclude that one-third of all cancers detected by mammographic screening were over-diagnosed. They concluded that women cannot make an informed choice on screening unless the level of over-diagnosis is properly explained to them.

A recent US survey [Schwartz, *JAMA* 2004] found unbridled enthusiasm for cancer screening among the lay public because of the prevalent belief that early detection was synonymous with cure. Although only 6% were aware that mammography might detect nonprogressive breast cancer, 56% said they would want to be tested for "pseudodisease" (cancers growing so slowly they would never cause problems). The authors conclude that the public's enthusiasm for cancer screening stems, in large part, from the success of public health campaigns for widely recommended cancer screening tests. However, they note that these can be misleadingly simple messages that discourage meaningful discussions regarding prudent use of tests. The challenge is to balance messages and reduce the public's risk for overtesting and overtreatment.

The merits of annual mammography in premenopausal women, as proposed by Buist et al, must be carefully weighed against the negative effect of much higher numbers of recalls for false-positive findings and overdetection of early-stage disease. Physicians need to develop better ways to communicate these shortcomings of mammography to the public.

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Forum

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with and without medroxyprogesterone acetate on bone in early postmenopausal women. *JAMA* 2002;287(20):2668-2676.

7. Wasnich RD, Bagger YZ, Hosking DJ, et al. Changes in bone density and turnover after alendronate or estrogen withdrawal. *Menopause* 2004;11:622-630.

8. Reid IR, Brown JP, Burckhardt P, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med* 2002;28;346:653-661.

9. McClung MR, Lewicke EM, Bolognese MA, et al. AMG 162 increases bone mineral density (BMD) within 1 month in postmenopausal women with low BMD. *J Bone Miner Res* 2004; S20.

10. McClung M, Omizo M, Weiss S, et al. Comparison of lasofoxifene and raloxifene for the prevention of bone loss in postmenopausal women. *J Bone Miner Res* 2004; S96.

11. McClung MR, Wasnich RD, Hosking DJ, et al. Prevention of postmenopausal bone loss: six-year results from the Early Postmenopausal Intervention Cohort Study. *J Clin Endocrinol Metab* 2004;89:4879-4885.

12. Kanis JA, Johnell O, Oden A, et al. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int* 2001;12:989-995.

The presence of risk factors, particularly low body weight (< 127 lbs) and a history of previous fracture, lowers the threshold for intervention to a *T*-score less than -1.5

There are no systematic studies of any bone active agent on bone loss in women with an early menopause; this group may need larger doses.

Estrogen. Because a woman with an early menopause suffers from estrogen deficiency, the physician also has to consider the potential for developing premature heart disease. There are also symptomatic problems of vaginal dryness and vasomotor symptoms. If the patient has menopausal symptoms, then estrogen should be the number-one choice. It is highly effective at preventing bone loss and fractures, and the Women's Health Initiative (WHI) study suggests that it may be the most effective agent for preventing fractures in women with low bone mass/osteopenia. Recent data show that lower doses of estrogen (eg, conjugated equine estrogens 0.45 mg and 0.30 mg, transdermal estradiol 0.025 µg) prevent bone loss in women in their mid fifties. The type of hormones used (estrogen only or estrogen/progestin) may depend

on whether early menopause is surgically induced or natural. Treatment should be continued for at least 10 years. The WHI study showed that the risk for cardiovascular events, stroke and breast cancer are not increased in women within 10 years of menopause who receive estrogen only (conjugated equine estrogens 0.625 mg). For women who received estrogen and progestin, there was no significant risk in the first 10 years for cardiovascular events and strokes; however, there was a small increase in breast cancer.

Bisphosphonates (*Alendronate, Risedronate, Ibandronate*). These agents would be the first choice for women who cannot take estrogen for medical reasons (eg, history of breast cancer, venous thrombosis).

There are no data on the dose needed to prevent bone loss in women with an early menopause. Most studies have been carried out in women in their sixties. All of these agents prevent bone loss and there are emerging data that this group may prevent fractures in women with low bone mass. Much of the data are derived from retrospective post hoc analysis. However, bone loss is more rapid in the first 5 years post-menopause and more data in this group for bisphosphonates are needed. There do not seem to be any increased problems after 10 years use of alendronate; however, assessment of safety is not as comprehensive as for estrogens. Any ongoing history of gastric symptoms would count against their use, however new monthly, rather than weekly, regimens may overcome the gastric problem

SERMs. Raloxifene was the first of this group of compounds to be tested in postmenopausal women. There are no studies in an early menopause group, but Raloxifene prevents bone loss in women in their early fifties. Its potency on bone is almost equal to that of lower estrogen



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