

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.

Depression increases CVD risk in postmenopausal women

Wassertheil-Smoller S, Shumaker S, Ockene J, et al. Depression and cardiovascular sequelae in postmenopausal women: The Women's Health Initiative (WHI). *Arch Intern Med* 2004; 164:289-98.

In older postmenopausal women, symptoms of depression are significantly related to increased risk of cardiovascular disease (CVD) death and all-cause mortality, even after controlling for established CVD risk factors, according to data from the Women's Health Initiative Observational Study. A total of 93,676 postmenopausal women were followed for an average of 4.1 years. Depression was measured with a shortened form of the Center for Epidemiological Studies Depression (CES-D) scale. At baseline, 15.8% of women had depressive symptoms. Logistic regression analysis was performed to measure baseline predictors of depression. CVD risk factors were found to be significantly related to depression. Odds ratios for depression included 1.41 (95% CI, 1.35-1.47) for women with a history of any CVD, 1.45 (95% CI, 1.30-1.62) for myocardial infarction, 1.60

(95% CI 1.39-1.83) for stroke, and 1.84 (1.28-2.65) for aortic aneurysm. To measure CVD risk, investigators used Cox proportional hazards models and adjusted for multiple demographic, clinical, and risk factor covariates. Depression was significantly related to CVD risk and comorbidity. Specifically, among women with no history of CVD, depression was an independent predictor of CVD death (relative risk, 1.50; 95% CI, 1.10-2.03) and all-cause mortality (RR, 1.32; 95% CI 1.16-1.52). Among women with a history of CVD, depression was significantly associated only with an increased risk of stroke (RR, 1.45; 95% CI, 1.11-1.90). Antidepressant use did not affect the depression-associated risks.

Comment. The association between depression and cardiovascular events has been increasingly recognized in recent years. The association has been difficult to study because causality could go either way: depression could cause cardiovascular events or cardiovascular events could lead to depression (or a combination of both). The possibility even exists that depression is only a marker for some other factor that is, in turn, responsible for the association with adverse cardiovascular outcomes.

Strengths of this study include the careful statistical analysis techniques that took into account many potential confounders, confirmation of cardiovascular events using medical record review, and a prospective design, which lends strength to the notion that the depression precedes the cardiovascular risk. Moreover, this was the largest prospective cohort study ever conducted of older women, giving detailed information on depression and subsequent cardiovascular events.

Possible limitations include that estimates of some of the comorbidities, such as high cholesterol, relied on self-report rather than blood measurement. In addition, current depression was defined using a short version of the CES-D scale. While the tool is commonly employed in large-

scale epidemiologic studies and has been well validated, this instrument is a screening instrument and cannot make a clinical diagnosis of depression. Lastly, although the results were unchanged by separately analyzing women with no history of CVD, the authors recognize the possibility that, even among women without a history of CVD, undetected CVD may have been the cause of depression.

Although comparisons across past studies of this type are difficult, the bulk of the evidence supports the notion that depression represents an independent risk for CVD death and all-cause mortality. Why depressive symptoms would be a risk factor for CVD is unclear, although the authors discuss potential effects of depression on arrhythmia, sympathetic and parasympathetic tone, platelet aggregation, and inflammation. It is too early to say whether early recognition and intervention targeting subclinical depression will lower CVD risk.

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Bone density by itself does not accurately predict fracture risk (NORA data)

Siris ES, Chen Y-T, Abbott TA, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med* 2004;164:1108-12.

Most postmenopausal women who suffer fractures have peripheral bone T-scores better than -2.5, according to data from the National Osteoporosis Risk Assessment (NORA) study, a longitudinal observational study. A total of 149,524 postmenopausal Caucasian women, age 50 to 104 years (mean age, 64.5 years) were assessed for peripheral bone mineral density (BMD) at baseline, and followed for 1 year for incidence of new fractures. Bone density was measured at the heel,

forearm or finger, using single x-ray absorptiometry, ultrasonography, or dual-energy x-ray absorptiometry (DXA).

Of the total new fractures reported, 82% occurred in women with *T*-scores better than -2.5; 67% occurred in those with *T*-scores better than -2.0. Although few fractures (18%) occurred in the group with the lowest *T*-scores (-2.5 or worse), they had the highest fracture rates: 35.7 osteoporotic fractures per 1,000 person-years and 8.8 hip fractures per 1,000 person-years. Nearly half of all fractures occurred in women meeting the treatment guidelines of the National Osteoporosis Foundation (ie, *T*-scores of -2.0 or worse, or *T*-scores of -1.5 or worse with one or more clinical risk factors); 45% of the osteoporotic fractures and 53% of the hip fractures occurred in this group. Their osteoporotic fracture rate was 24.7 per 1,000 person-years; their hip fracture rate was 5.1 per 1,000 person-years.

Miller PD, Barlas S, Brenneman SK, et al. An approach to identifying osteopenic women at increased short-term risk of fracture. *Arch Intern Med* 2004;164:1113-20.

Among postmenopausal women with *T*-scores between -1.0 and -2.5 (defined as osteopenia in this study), the greatest fracture risk occurs in those with previous fracture, peripheral *T*-scores of -1.8 or worse, poor health status, and poor mobility, according to this data analysis from the NORA study, a longitudinal, observational study. In all, data on 57,421 women with baseline peripheral *T*-scores of -2.5 to -1.0 and 1-year information on new fractures were assessed. Investigators evaluated the effect of 32 factors associated with increased fracture risk.

A multivariate analysis showed that women with previous fracture, regardless of their *T*-scores, had the highest increased risk of fracture in 1 year (4.1% risk). Women with *T*-scores of -1.83 or worse and those with poor health status were next. Both groups had 1-year fracture risks of 2.2%. The next highest increased fracture risk (1.9%) was in

women with poor mobility. Using those four factors, investigators created an algorithm that would have identified 74% of the women suffering a new fracture. Other factors significantly associated with increased fracture risk included advanced age, fracture in a first-degree relative, existence of a dowager hump, height loss (mean, 2.5 cm), low body mass index (<18.5 kg/cm²), menopause occurring before age 40, poor vision, use of certain medications (sedatives, antiepileptics, diuretics, cortisone), diabetes mellitus, current and past cigarette use (mean, 24 pack-years), and alcohol use.

Comment. These two papers explore additional aspects of the important Merck-funded NORA study. The study by Siris and colleagues suggests that most fractures in postmenopausal women occur in those who do not have bone density values consistent with osteoporosis (*T*-score -2.5 or worse). This is similar to other studies demonstrating that most women who experience nonvertebral fractures do not have osteoporosis by bone density criteria. This fact is important to appreciate but not surprising, since risk factors other than poor bone strength (such as falls) are determinants of nonspine fracture probability. The details of the Siris paper must also be interpreted in the context that the bone mineral density (BMD) measurements were acquired with peripheral bone density machines that often underestimate the lowness of bone density. Thus, the proportion of women who would have osteoporosis by central DXA testing might be higher than was reported in the paper.

The study by Miller and colleagues confirms important risk factors for fracture in postmenopausal women, including a history of prior fractures, predilection to falls, and poor health. Interestingly, age was not a strong predictor of fracture risk, in contrast to data from numerous studies showing that incidence of important fractures (spine and hip) increases with advancing age. The NORA study evaluat-

ed the occurrence of all fractures. Perhaps (likely, in my opinion), most of the fractures in the younger women in the study were minor peripheral fractures. It would be interesting to see the full spectrum of data in which the incidence of fractures is stratified by both age and fracture type.

It is clear from these (and other) data that assessing women simply on the basis of having osteoporosis by BMD testing will not accomplish the objective of preventing most fractures. BMD is but one (although an important one) of several determinants of fracture risk in older adults. As clinicians, we should not simply treat *T*-scores. Instead, we should treat individuals who are at moderate to high risk of fracture. The challenge is to select risk factors that identify women at increased risk *and* that are indicative of a salutary response to therapy. The Miller paper points out that a history of poor health is a risk factor for fractures. However, no study has demonstrated that treating nonosteoporotic women in poor health leads to fracture protection. Women selected on the basis of advanced age and fall-related risk factors did not have a significant reduction in fracture risk when treated with risedronate [McClung. *N Engl J Med* 2004]. Before suggesting that any clinical risk factor for fracture be used as an indication for treatment requires evaluation in a clinical trial.

Fortunately for our field, a very robust and clinically useful strategy for estimating fracture probability in an individual and for determining treatment thresholds based on fracture risk is being developed by a working group of the World Health Organization (WHO). When available next year, this strategy will use bone density in combination with other validated risk factors to identify individuals at moderate to high fracture risk who will be candidates for treatment. Many of them will not have osteoporosis by bone density criteria. The WHO strategy will address the important issues emphasized in the Siris and Miller papers. It will also allow clinicians to move away from *T*-score-based guidelines for

intervention, toward making an important conceptual distinction between diagnostic criteria for osteoporosis (based on BMD values) and treatment thresholds determined by the level of risk. This will be an important advance in our field.

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Low-dose levonorgestrel IUS provides endometrial protection

Wildemeersch D, Schacht E, Wildemeersch P, et al. Endometrial safety with a low-dose intrauterine levonorgestrel-releasing system after 3 years of estrogen substitution therapy. *Maturitas* 2004;48:65-70.

A low-dose levonorgestrel-releasing intrauterine system (IUS) can effectively protect the endometrium of postmenopausal women and suppress uterine bleeding during 3 years of estrogen-alone therapy, according to this prospective clinical trial from Belgium. A total of 24 postmenopausal women with a thin endometrium (<5 mm) were enrolled. Women received continuous 17 β -estradiol at a percutaneous dose of 1.5 mg/day or an equivalent dose, either orally or by patch. After 1 month of estrogen therapy, an IUS releasing levonorgestrel at 14 μ g/day (FibroPlant-LNG; not available in North America) was inserted. The IUS was left inserted for 36 months. End points included histologic and ultrasonographic evidence of endometrial suppression. After 3 years, endometrial specimens showed endometrial suppression with glandular atrophy and no sign of hyperplasia. Uterine bleeding was suppressed in all women.

Comment. The concept of suppressing the endometrium with local rather than systemic progestin in women taking estrogen for menopausal symptoms is appealing for two reasons. First, the Women's Health Initiative, as well as data from

observational studies in the United States, Sweden, and the United Kingdom, have shown that the progestin component of combination estrogen plus progestogen (EPT) is largely, if not exclusively, responsible for the increased risk of breast cancer in women using EPT. Second, systemic progestin is associated with unpleasant side effects, including mood changes, in some women. Accordingly, preventing endometrial neoplasia without use of systemic progestin is a desirable goal.

The study by Wildemeersch and colleagues assessed endometrial outcomes in postmenopausal women taking continuous estrogen during approximately 3 years of using a frameless IUS. The system releases 14 μ g/day levonorgestrel rather than the 20 μ g/day released by Mirena, the only progestin-releasing IUS available in the United States. To facilitate insertion, women with genital tract atrophy took unopposed estrogen for 1 month before IUS insertion. Local anesthesia was used for some insertions. On sonography, endometria were noted to be thin in all cases, and all biopsies revealed inactive endometria. Mirena also has been found to prevent endometrial hyperplasia in postmenopausal women taking continuous estrogen.

Intrauterine delivery of progestin represents an appealing approach to endometrial protection in women taking estrogen for relief of menopausal symptoms. Although the Mirena system is small enough for safe insertion in some but not all postmenopausal women, the availability of smaller intrauterine progestin delivery systems, appropriate for smaller uteri in postmenopausal women, would enhance therapeutic options in a positive way.

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NAMS NEWS

Hormone Therapy Report Available Soon

The plethora of new clinical trial data regarding postmenopausal hormone therapy (HT) published over the last few years prompted NAMS to develop reports on HT use in October 2002 and September 2003. The overall objective of these reports has been to present clinical recommendations for use of HT in peri- and postmenopausal women.

During 2004, the NAMS Board of Trustees convened a third HT Advisory Panel to develop a new report. It will be available on October 6, 2004, at the NAMS Annual Meeting—then posted on the NAMS Web site and published in *Menopause*.

NAMS is grateful to the following individuals who served on the Panel, advising the NAMS Board of Trustees: Wulf H. Utian, MD, PhD (Chair); David F. Archer, MD; J. Chris Gallagher, MD; Margery L.S. Gass; Morrie L. Gelfand, CM, MD; Victor W. Hen-

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Poster Session at Annual Meeting

While attending the NAMS Annual Meeting, October 6-9, be sure to view the scientific posters. The dedicated poster viewing time is Friday, October 8, from 3:45 to 4:45 PM. Not only will authors be available for questions during that time, refreshments (popcorn) will be served, courtesy of a grant from The Alliance for Better Bone Health.

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Upcoming NAMS Events

All the events listed here will be held at the Marriott Wardman Park Hotel, Washington, DC

Menopause Basics Course
October 6 (8 AM-Noon)

Competency Exam
October 6 (2:30-4:30 PM)
(July 28 Application Deadline)

NAMS 2004 Annual Meeting
October 6 (5:30 PM) to
October 9 (2:30 PM)

CME on NAMS Web Site

Log on to the NAMS Web site for an opportunity to earn CME credit. Two programs are now posted: (1) Position Statement on the treatment of vasomotor symptoms and (2) Satellite highlights from the 2003 Annual Meeting. There is an administrative charge of \$50 per program for participants who are not NAMS members; there is no fee for members—providing another reason to join.

New Professional Guidebook Available Soon as a CME Activity

NAMS is pleased to announce that its leading professional resource—the *Menopause Core Curriculum Study Guide*—is being updated and renamed *Menopause Practice: A Clinician's Guide* to more clearly reflect its purpose.

“This new book represents a timely and valuable resource for all clinicians who care for menopausal women,” said Andrew M. Kaunitz, MD, Chair of the NAMS Professional Education Committee. “Whether one’s focus is understanding the latest about hormone therapy from the Women’s Health Initiative, choosing the most appropriate treatment for osteoporosis, or advising women regarding alternative options for

Future NAMS Meeting

17th NAMS Annual Meeting
October 11–14, 2006
Nashville, TN

relieving menopause symptoms, *Menopause Practice: A Clinician's Guide* has the answers clinicians need.”

With an estimated length of 300 pages, the new book will premier at the NAMS 2004 Annual Meeting. Review chapters will be posted on the NAMS Web site. The cost (including shipping) will be \$69 for NAMS members, \$109 for nonmembers.

“Not only is this guidebook an excellent clinician reference, it’s also been designated a NAMS CME activity,” said Wulf H. Utian, MD, PhD, Chair of NAMS CME Committee. “A total of 19 credit hours can be earned.”

This guidebook will also be provided free of charge to all those who register to sit for the NAMS Menopause Practitioner competency examination during 2005 and to those who apply to renew their credential before the end of 2005.

Spotlight on Menopause Education:

Consumer Menopause Education in Braille

NAMS offers an unprecedented array of professional and consumer education materials. The spotlight this issue is on the braille edition of the NAMS 60-page consumer booklet, the *Menopause Guidebook*. Thanks to an educational grant from Berlex Laboratories, Inc., copies of the two-volume braille edition of this leading consumer resource are available free of charge from the National Braille Press (617/266-6160).