NAMS
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Released September 13, 2005

The following news items present reviews of important, recently published scientific articles selected by members of 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. Note that opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS. Published news items may be viewed on the NAMS Web site (www.menopause.org/news.html).

ET/EPT may not increase breast cancer recurrence

von Schoultz E, Rutqvist LE, for the Stockholm Breast Cancer Study Group. Menopausal hormone therapy after breast cancer: the Stockholm Randomized Trial. *J Natl Cancer Inst* 2005;97:533-535. **Evidence level: I.**

Postmenopausal estrogen-containing therapy may not increase the risk of breast cancer recurrence in all women, according to this randomized study from Sweden. For this open-label study, investigators enrolled 378 postmenopausal women (median age, 57 years) who had undergone breast cancer surgery. Participants received either postmenopausal hormone therapy (HT; estradiol valerate with or without medroxyprogesterone acetate) or no hormone therapy. The primary end point was recurrence-free survival. Secondary end points were type of breast cancer recurrence, cause-specific mortality, and new primary cancers.

The trial was scheduled to last 5 years, but it was stopped after a median of 4.1 years because of an increased risk of breast cancer that occurred in the Hormonal Replacement Therapy After Breast Cancer — Is It Safe? (HABITS) trial. Although the trials had differences in study design, they were judged to be sufficiently similar to permit a joint analysis, which showed a statistically significant increase in relative hazard (RH) of 1.8 (95% CI, 1.03-3.10), leading to early termination of the trial. However, when the results were analyzed individually, the RH in the Stockholm trial showed an 18% decreased risk with HT (RH, 0.82; 95% CI, 0.35-1.9). In contrast, the HABITS trial showed a significantly increased RH of 3.3 (95% CI, 1.5-7.4).

In the Stockholm trial, 11 women in the HT group had breast cancer recurrence compared with 13 in the non-HT group. No between-group differences were observed for recurrence-free survival, type of recurrence, axillary lymph node status at primary surgery, or estrogen receptor-positive disease. The number of women using concomitant tamoxifen therapy or who had used HT in the past were also similar.

Investigators speculated that differences in design and clinical characteristics of the participants may have contributed to differences in results. The proportion of women with lymph-node positive tumors was smaller in the Stockholm trial than in HABITS (16% vs 26%, respectively), and more women received concomitant tamoxifen (52% vs 21%). Also, 73% used either estrogen alone or a long-cyclic regimen in which progestogen was administered for 14 days at 3-month intervals.

Comment. The results from this study are consistent with a number of studies examining the risks of HT after breast cancer. They suggest that short-term use of HT is probably not associated with a significantly increased risk of breast cancer recurrence.

It is important, however, to note that the need to use HT after breast cancer should be declining, as alternatives do exist. There are trials showing the efficacy of black cohosh extract [Osmers *Obstet Gynecol* 2005] as well as that of some antidepressants. [Loprinzi *Lancet* 2000] Also, a large international randomized controlled trial is under way comparing tibolone (2.5 mg/day), a non-FDA-approved drug, against placebo in breast cancer survivors (the LIBERATE trial). Some women

suffer hot flashes as a side effect of tamoxifen, and so stopping this drug, and perhaps trying an aromatase inhibitor, may help

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Comment. The issue of how to deal with distressing vasomotor symptoms in women following breast cancer is no small matter, and it has received little clarification from these two randomized controlled trials — Stockholm and HABITS — that many had hoped would provide some definitive answers regarding the effect of hormone therapy on breast cancer recurrence. This article by von Schoultz and colleagues presenting a more detailed account of the Stockholm trial carries few surprises.

When data from the two trials were combined for an interim safety analysis, an overall statistically significant increase in breast cancer events was seen in hormone recipients, leading to the premature closure of both trials. However, the Stockholm trial came to a strikingly different result from the HABITS trial regarding the RH for breast cancer recurrence — 0.82 (not significant) versus a significantly increased 3.3 for the HABITS trial.

It is necessary in clinical trials to adhere to sample size estimates to ensure that null findings can be accepted with confidence. In contrast, when an effect size is large, a difference between treatments may be seen before the full sample data are accrued, as happened in the HABITS trial, which only had data on 345 of 1,300 participants when the trial was closed. Although the Stockholm trial reported data on as many women (N = 378) as the HABITS trial, negative findings from the HABITS trial need to be viewed with caution because an adequate sample size was never reached.

The intent of randomization is to ensure that possible confounding factors appear equally in both treatment and placebo arms. Although most important variables, such as age and years of follow-up, were well balanced between treatment arms in the HABITS trial, the HT group had slightly worse prognostic features than those assigned to placebo. Whether these minor differences could account for the differences between the trials seems doubtful.

Differences in characteristics of women enrolled in the two trials might also have contributed to the divergent results. What is unclear from the Stockholm trial is whether a group of breast cancer patients (based on diagnostic features or therapeutic adjuncts) can be identified for whom hormone therapy may safely be offered for control of vasomotor symptoms. Past observational studies [Col *J Clin Oncol* 2001] that showed no adverse effects of hormone therapy may have selected lower risk women to receive treatment than did the investigators in the HABITS trial.

Given the general ineffectiveness of treatments other than hormone therapy for severely distressed women, [Hickey *Lancet* 2005] affected women and their healthcare clinicians will continue to struggle with decisions regarding the use of hormone therapy. After counseling, it may still be appropriate to allow low-risk women to choose hormone therapy when vasomotor symptoms are severe and disruptive to their quality of life.

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Transdermal EPT has less effect than oral EPT on breast density

Harvey J, Scheurer C, Kawakami FT, Quebe-Fehling E, de Palacios PI, Ragavan VV. Hormone replacement therapy and breast density changes. *Climacteric* 2005; 8:185-192. **Evidence level: II-2.**

Estrogen plus progestogen therapy (EPT) administered transdermally is associated with a significantly lower incidence of increased mammographic breast density and breast tenderness than oral EPT, according to this randomized, open-label trial conducted in the United States and Switzerland. Data are presented from a subanalysis of 202 postmenopausal women (out of a total enrollment of 396) who had participated in a 1-year endometrial safety study and for whom pre- and poststudy mammograms were available. For the safety study, subjects aged 45 to 70 years and with an intact uterus were randomly assigned to receive either transdermal or oral EPT in a 3:1 ratio. Investigators used European products: a transdermal patch delivering 0.05 mg/day estradiol plus 0.14

mg/day norethisterone acetate (Estalis [CombiPatch in the United States]), and an oral tablet containing 2 mg/day estradiol plus 1 mg norethisterone acetate (Kliogest, not FDA-approved).

The primary end point for the subanalysis was breast density on mammogram after 1 year of treatment. Data showed that both the frequency and magnitude of breast density increases were significantly lower with transdermal EPT than with oral EPT. The mean adjusted breast density for women using transdermal EPT was 38.4% compared with 46.9% for oral EPT users (P <0.0001). Marked increases in breast density (defined as >25% increase) were noted in 4% of transdermal EPT users compared with 15.7% of oral EPT users, and no increase in breast density was noted in 39.1% versus 15.7%, respectively (P value not reported). The changes in breast density were reflected in changes paralleled by reports of breast tenderness. Overall, 36.0% of women using transdermal EPT reported having breast tenderness in some point during the study compared with 57.6% of women using oral EPT (P = 0.0002). Increasing age was a significant factor for increased breast density in both EPT groups, with women older than 65 years having the greatest increases from baseline.

Comment. Mammographic breast density is an important predictor of the accuracy of screening mammography. Hormone therapy has been associated with increased breast density, with greater increases seen with combined EPT than with estrogen alone.

This subanalysis presents data from eligible women whose mammograms were evaluated after the study by a radiologist blinded to EPT status. Results suggest that transdermal EPT use compared with oral EPT use has the potential to improve women's quality of life by reducing breast tenderness as well as to reduce the number of women with EPT-associated increased breast density.

These data should be considered preliminary, as I have methodologic concerns about this subanalysis. For example, were these comparative doses? In serum estradiol studies, a 50-µg transdermal estradiol dose is more equivalent to 1 mg of oral estradiol (one-half of the oral dose used in this study). Unfortunately, serum estradiol or estrone levels were either not measured or not presented. Previous studies have shown that both estrone and estradiol levels are elevated with oral doses of estradiol. Serum levels of norethisterone acetate and its metabolites may also vary between transdermal and oral administration. Thus, the difference could be due to differences in serum or tissue levels of estradiol, estrone, or progestogen — ie, due to levels of hormones rather than the route of administration. In addition, women with breast cancer have high sulfatase enzyme levels, 50 to 200 times more than aromatase. Conversion of estrone to estradiol in breast tissue could be biologically significant and affect mammographic breast density.

Thus, the finding of less increased breast density and less breast tenderness in the transdermal group could simply be an effect of giving a higher equivalent or biologic dose of estradiol with oral EPT than with transdermal EPT, an effect of estrone conversion by breast sulfatase to estradiol locally, or an effect of differential serum or tissue levels of progestogen absorption. A prospective, double-blind trial comparing the effects of oral estradiol alone against those of transdermal estradiol, with and without progestogen, as they relate to mammographic breast density as well as serum and, possibly, tissue levels of these hormones would help clarify these findings.

If comparative dosing confirms less breast density with transdermal than with oral administration, this will be important information to share with our patients, as increased breast density, in general, is considered an increased risk for breast cancer. Whether estrogen-associated increases in breast density correlate to increased risk of breast cancer is still to be proven.

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Oophorectomy with hysterectomy does not boost long-term survival

Parker WH, Border MS, Liu Z, Shoupe D, Farquhar C, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. *Obstet Gynecol* 2005;106:219-226. **Evidence level: II-3.**

Up to age 65 years, prophylactic oophorectomy with hysterectomy significantly decreases the rate of survival to age 80 in women with benign uterine disease, according to this review of published

studies. Investigators collected data on studies of hysterectomy in women aged 40 to 80 and published since 1990. Age-specific mortality rates, incidence rates, and case-fatality rates as they related to oophorectomy were compiled for five conditions: ovarian cancer, coronary heart disease (CHD), hip fracture, breast cancer, and stroke. Investigators used these data to develop a Markov decision-analysis model to estimate the effect of prophylactic bilateral oophorectomy on survival rates from age at surgery (40 and older) until age 80.

Overall, the risk of death from the five conditions was significantly greater with oophorectomy up to age 65. From then until age 80, the results were essentially the same. For women aged 50 to 54, oophorectomy was associated with an 8.58% excess mortality. For women aged 55-59, oophorectomy was associated with a 3.92% excess mortality. A sensitivity analysis did not find any survival benefit from oophorectomy.

Investigators provided specific results for the 50 to 54 age group. Their probability of survival to age 80 was 62.46% for those with oophorectomy conservation compared with 53.88% for those with concurrent oophorectomy. For the five conditions studied, the respective estimated mortality rates by age 80 were 3.38% versus 4.96% for hip fracture, 0.47% versus 0% for ovarian cancer, 1.82% versus 1.77% for breast cancer, 2.59% versus 2.47% for stroke, and 7.57% versus 15.96% for CHD.

Use of estrogen therapy by the 50 to 54 age group increased overall survival probabilities to 62.75% and 62.15%, respectively. For the specific conditions, estrogen therapy decreased mortality rates for hip fracture for both groups (to 2.06% and 3.17%, respectively) and CHD for the oophorectomy group (to 7.56%). Estrogen therapy increased the mortality rates for stroke for both groups (to 3.60% and 3.59%). Ovarian cancer and breast cancer rates remained essentially the same as did CHD for the ovarian conservation group.

Comment. One of the more difficult aspects of counseling women regarding the risks and benefits of prophylactic surgery is estimating future risk and presenting those numbers in a digestible format. In general, these conversations migrate to the most severe diseases or conditions possible. Although this is an important consideration, the goal of the informed-consent process is to provide some balance so that the most personalized decision can be made. The current study by Parker and colleagues provides some help in critically evaluating the risks of oophorectomy in the setting of benign disease — the real-life risks over time. Although these data are generated by "estimating" estimates of various outcomes, the power of this kind of statistical modeling allows a range of potential values to be considered in the overall "big picture."

What's most striking is the relative importance heart disease and osteoporosis play compared with the risk of cancer. While some criticism could be levied regarding the quality of the numbers used in the math, the robustness of the model suggests that these risks are much more important to survival than cancer. Also, although quality of life wasn't addressed, it is likely to favor the general conclusions of the trial. It is anticipated that these data will be frequently cited in future counseling sessions.

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Comment. There are several significant comments concerning this paper. First, it is not based on randomized controlled trials (RCTs) but rather on a decision-analysis model based on published age-specific data. But before *discounting* these data because they are not based on RTCs, remember that they are based on available data. One has to ask, what is the level of evidence on which the current practice of recommending routine oophorectomy by many clinicians is based? In this era of evidence-based medicine, what should the *default* mode be in the absence of good RTCs? Should it be what has always been done (ie, prophylactic oophorectomy)? Should the "challenger" have to provide the data? Or should the "active" arm (ie, removing ovaries) have to prove the benefit? I only ask these questions rhetorically because the answers are unclear.

Secondly, many would point out that oophorectomy with ET in this article had essentially the same overall survival as conservation of ovaries (at least in the 50-54 age group). Whether you believe the reasons are valid or not, the world has changed since the Women's Health Initiative. Fewer women will take ET, and that must be considered. If one looks carefully at the data, oophorectomy with ET

basically eliminates the 1 in 200 mortality from ovarian cancer associated with conservation, but carries an excess 1 in 100 mortality associated with hip fracture. Should we ask our patients to pick their poison?

Finally, the ACOG Guidelines [*ACOG Practice Bulletin* 1999; No. 7] still make the most sense. They state that the decision to perform prophylactic oophorectomy should be based not only on the patient's age but also on other factors that weigh individual risk for developing ovarian cancer against loss of ovarian function.

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Family history, age, and histology affect breast cancer risk in women with benign breast disease

Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. *N Engl J Med* 2005; 353:229-237. **Evidence level: II-2.**

In women diagnosed with benign breast disease, their risk for developing breast cancer is significantly affected by their family history of breast cancer, age at diagnosis, and histology of the findings, according to this long-term, observational cohort study. A total of 9,087 women (mean age, 54.1 years) who had been diagnosed with benign breast disease were followed for a median of 15 years. The histologic findings were defined as nonproliferative lesions (66.7% of the women), proliferative lesions without atypia (29.6%), and atypia hyperplasia (3.7%).

During the follow-up, 707 cases of breast cancer developed. The overall relative risk (RR) for cancer was 1.56 (95% CI, 1.45-1.68), and this increased risk persisted for at least 25 years after the initial biopsy. Women with atypia hyperplasia had the highest risk (RR, 4.24; 95% CI, 3.26-5.41) followed by those with proliferative changes without atypia (RR, 1.88; 95% CI, 1.66-2.12) and nonproliferative lesions (RR, 1.27; 95% CI, 1.15-1.41). The strength of a woman's family history of breast cancer, available for 4,808 participants, was found to be a significant risk factor independent of histologic findings. For women with no known family history, the overall RR was 1.18 (95% CI, 1.10-1.37). Women with a weak family history had an RR of 1.43 (95% CI, 1.15-1.75) and those with a strong family history had an RR of 1.93 (95% CI, 1.58-2.32). The investigators noted that although no significant interactions were found for family history and either age or histologic findings, women with nonproliferative lesions and a weak or nonexistent family history — 52% of the cohort with known family history — had essentially no increased risk (RRs, 1.12 and 0.89, respectively; 95% CIs, not significant).

Age and histologic findings were found to be significantly linked. In general, women with atypia tended to be older (mean age, 57.8 years) than those with nonproliferative findings (mean age, 49.9 years), a significant difference (P <0.001). For women with atypia, the RRs were 6.99 if it developed before age 45, 5.02 if it developed between ages 45 and 55, and 3.37 if it developed after age 55.

Comment. This study by Hartmann et al is quite important in defining the risk of breast cancer associated with benign breast disease. Prior to this article, comprehensive data correlating demographic factors and specific histologic lesions with the risk of breast cancer were limited and conclusions from existing studies ambiguous. For example, the National Surgical Adjuvant Breast Project (NSABP) data suggest that women with nonproliferative breast lesions have an increased risk of breast cancer. [Wang *J Natl Cancer Inst* 2004] The NSABP study, however, did not have sufficient data to distinguish proliferative from nonproliferative lesions and, instead, lumped them together.

A key finding was that nonproliferative lesions imparted no increase in breast cancer risk in women with no family history of breast cancer or with a weak family history. Only in women with a strong family history did this finding predict an increased risk, although the increase was likely due to family history rather than presence of the lesion itself.

On the other hand, proliferative lesions, particularly those with atypia, predicted a substantially increased risk of breast cancer. Specific lesions (as defined by the Page criteria [Dupont *N Engl J Med* 1985; Page *Cancer* 1985]) imparting increased risk included proliferative fibrocystic changes without atypia and proliferative fibrocystic changes with atypia

(atypical ductal hyperplasia, atypical lobular hyperplasia, or both). Notably, the data provided allow one to factor in the patient's age, family history, and histology in assessing risk.

Finally, the study provides inferential data regarding pathophysiology. During the first 10 years of follow-up, the proliferative lesions predicted an excess risk of breast cancers in the same breast, suggesting that these may be precursor lesions. Interestingly, there was an increase in contralateral breast cancer as well, suggesting that certain benign breast lesions may reflect an underlying propensity for breast cancer to develop at additional sites in the breast. In the past, this propensity was called a "field defect" and more recently a "mutator phenotype." [Santen *N Engl J Med* 2005]

In summary, this is a landmark study providing practical information for the clinician in interpreting what risk is imparted by the presence of benign breast disease.

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Acupuncture improves urinary urge incontinence

Emmons SL, Otto L. Acupuncture for overactive bladder: a randomized controlled trial. *Obstet Gynecol* 2005;106: 138-143. **Evidence level: I.**

Acupuncture treatment can significantly improve bladder capacity, urgency, frequency, and quality-of-life scores, according to this randomized, single-blind, placebo-controlled trial. A total of 85 women (median age, 51 years; 56% were postmenopausal) with symptoms of overactive bladder with urge incontinence were enrolled to receive acupuncture or placebo acupuncture four times, once per week. The treatment group received acupuncture at sites designed to improve incontinence. The placebo group received acupuncture at sites designed for relaxation.

The primary end point was number of incontinent episodes over 3 days, based on a voiding diary. Secondary end points included voiding frequency and urgency, voided volume and bladder capacity based on cystometric testing, and scores on the urinary distress inventory and incontinence impact questionnaire.

Compared with baseline, women in both groups had significant decreases in number of incontinent episodes (59% vs 40% for treatment and placebo groups, respectively), a nonsignificant between-group difference. Women in the treatment group, but not the placebo group, had significant improvements from baseline in urinary frequency (14% reduction), proportion of voids associated with urgency (30% reduction), maximum voided volume (13% increase), and maximum cystometric capacity (13% increase). Significant between-group differences were found for scores on both the urinary distress inventory and the incontinence impact questionnaire, although both groups had significant improvements from baseline for both measures.

Comment. This well-designed and well-executed trial assessed the effectiveness of acupuncture specific for urinary urgency, frequency, and urge incontinence against a placebo acupuncture. The results reported here, while somewhat limited by size and lack of statistical power, are promising. Overall, the percent reduction of urge incontinence episodes in women treated with acupuncture was not statistically different from placebo; however, treatment appeared to reduce urgency and frequency symptoms and improve the scores on both the urinary distress and incontinence impact questionnaires. The percent reductions in urgency, frequency, and urge incontinence symptoms and the percent increases in bladder capacity are similar to those reported for behavioral therapy and anticholinergic medication. Additionally, while patients reported some discomfort with acupuncture needle placement, there were no significant adverse effects.

About 16% of adult women report urinary urgency, frequency and or/or urge incontinence (overactive bladder), and the prevalence of these symptoms increases with age. Expanding treatment options for these conditions is imperative. The current effective treatments for overactive bladder are limited to behavioral and physical therapies, which require adherence to a daily regimen, as well as anticholinergic medications, which can have bothersome side effects. Although the results of this study should be interpreted with some caution given the small sample size, they do suggest that acupuncture

may be as effective as some of the standard treatments for urgency and frequency symptoms.

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Comment. This study demonstrates that acupuncture has the potential for offering an alternative treatment to either medication or behavioral therapy for urge urinary incontinence in midlife women. The strengths of this study include use of a blinded, randomized design. In particular, the blinding of both study participants and evaluators adds rigor. The measurement of multiple outcomes, including urodynamics, self-reported bladder function (bladder diary), and quality of life, is consistent with the International Continence Society recommendations for urinary incontinence intervention studies.

Some areas of concern include the relatively short duration of treatment, the use of active acupuncture for the placebo control rather than a sham needle approach, and the lack of a long-term (greater than 4 weeks) follow-up period. As the authors note, the low number of study participants may have contributed to the lack of statistically significant differences in incontinence frequency changes between the experimental and control groups. The power calculation based on a 75% reduction in urinary incontinence in the experimental group is likely an unrealistic estimate, thereby leading to an underpowering of the study. However, the 59% reduction in urinary accidents in the experimental group, while not statistically significant, is clinically meaningful. Coupled with the significant reductions in urinary frequency and urgency, these results suggest that acupuncture may be an effective treatment option for urge urinary incontinence. Additional research is needed to confirm these findings.

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Two studies find lipid levels predictive of coronary events

Ridker PM, Riai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B_{100}, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA* 2005;294:326-333. **Evidence level: II-2.**

The ratio of total cholesterol to high-density lipoprotein cholesterol (HDL-C) as well as levels of non-HDL-C provide clinical data predicting risk of cardiovascular (CV) events in women that are as accurate as other lipid measures and inflammatory biomarkers, according to this prospective cohort study. Using a cohort derived from participants in the Women's Health Study of aspirin and vitamin E in the prevention of cardiovascular disease and cancer, investigators collected data on 15,632 initially healthy women (mean age at baseline, 54.4 years) followed for a mean of 7.6 years. Data analyzed included total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, non-HDL-C, apolipoproteins (apo) A-I and B_{100}, and high-sensitivity C-reactive protein (CRP) in relation to cardiovascular events. Only the first CV event for a participant was used in the analyses.

Adjusted analyses of hazard ratios (HR) showed that women with the highest levels for each measured parameter (quintile 5) had the greatest risk of future cardiovascular events, when compared with the lowest quintile. For total cholesterol, the HR was 2.08 (95% CI, 1.45-2.97) for levels above 242 mg/dL; levels of 217 to 242 mg/dL were also significant at 1.71 HR (95% CI, 1.19-2.48). For LDL-C, only levels above 153.9 mg/dL were significant (HR, 1.62; 95% CI, 1.17-2.25). For non-HDL-C levels, the HR was 2.51 (95% CI, 1.69-3.72) for levels above 191.0 mg/dL. Levels of 145.0 to 165.5 and 165.6 to 191.0 also had significantly higher HRs. For apo B_{100}, the HR was 2.50 (95% CI, 1.68-3.72) for levels above 126.2 mg/dL. For high-sensitivity CRP, all levels above the 0.50 mg/L of the first quintile were significant. The HR was 2.98 (95% CI, 1.90-4.67) for levels above 4.19 mg/L, the highest quintile. Only HDL-C and apo A-I did not have significantly increased HRs. Results were also significantly increased for all lipid ratios: total cholesterol to HDL-C, LDL-C to HDL-C, apo B_{100} to apo A-I, and apo B_{100} to HDL-C.

Tsimikas S, Brilakis ES, Miller ER, et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. *N Engl J Med* 2005;353:46-57. **Evidence level: II-2.**

Circulating levels of oxidized low-density lipoproteins (LDL) are strongly associated with coronary artery disease, particularly in patients younger than 60 years of age, according to this observational cohort study. Oxidized LDL and Lp(a) lipoprotein levels were measured in 504 patients (mean age, 60.1 years; 38% female) immediately before undergoing coronary angiography.

Overall, the ratio of oxidized phospholipids to apo B_{100} as well as the Lp(a) lipoprotein levels were significantly associated with a graded increase in the extent of coronary artery disease (CAD)(P <0.001). CAD was defined as stenosis of more than 50% of the luminal diameter. Among patients younger than 60 years, those in the highest quartiles for these two measures had significantly higher risk for CAD than those older than 60 years (P <0.001). Overall, the association of oxidized phospholipids to apo B_{100} ratio to CAD was independent of all clinical and lipid measures except for Lp(a) lipoprotein. However, for those younger than 60 years, the ratio remained an independent predictor of CAD.

Comment. While abundant evidence, including results from these two papers, supports a relationship of atherosclerotic cardiovascular disease to LDL-C levels, this measurement does not reflect the full range of lipoprotein species known to promote atherosclerosis. The results of Ridker et al are consistent with previous observations that other lipid-related measurements, notably those that assess triglyceride-rich lipoproteins, are strongly related to cardiovascular disease risk. Among the individual measurements in this study (which did not, however, include plasma triglycerides), levels of non-HDL-C and apo B, as well as the inflammatory marker CRP, were the strongest risk predictors. Non-HDL-C provides a measure of triglyceride-rich lipoproteins, while apo B is an index of the total number of atherogenic lipoprotein particles, including the small, dense LDL subspecies that are not adequately assessed by the LDL-C value.

It is recognized that lipoprotein oxidation in the artery wall is a critical step in the development of atherosclerosis and in promoting inflammatory responses that can trigger acute cardiovascular events. Previous studies, however, have not demonstrated a clear and consistent relationship between oxidized lipids in plasma and cardiovascular disease. Using a specific assay for oxidized phospholipids, Tsimikas et al have shown that these are strongly and independently associated with angiographically demonstrated CAD, and that they may be particularly important in contributing to the well-established cardiovascular disease risk conferred by Lp(a) lipoprotein particles.

While the assay of Tsimikas et al is not yet appropriate for clinical application, their results, like those of Ridker et al, add to the growing recognition that cardiovascular risk markers beyond the standard tests can be used to sharpen risk assessment and thereby improve identification of candidates for preventive treatment.

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Comment. Conventional lipid measures in the Women's Health Study* [Ridker *JAMA* 2005] equally or better predicted future cardiovascular events than the less widely available and more costly apolipoprotein analyses. The added prognostic information of high-sensitivity CRP, beyond that conveyed by all lipid measures, as reported by Ridker et al in this large prospective cohort of apparently healthy middle-aged women, buttresses the construct that both inflammation and dyslipidemia contribute to atherosclerotic risk. This testing may particularly benefit intermediate-risk women in guiding the intensity of recommended interventions. It is important that statin use at enrollment and during the study was exceedingly low, likely reflecting both the years of enrollment (1992-1995) and the low-risk status of the participating women.

By contrast, the Tsimikas et al study of oxidized phospholipids, Lp(a) lipoprotein and coronary artery disease examined the presence and extent of obstructive coronary artery disease at angiography rather than the end point of clinical cardiovascular events (as in the Women's Health Study). Furthermore, they used a cohort of patients undergoing diagnostic coronary arteriography rather than a healthy population.

Although data are reported separately for the cohorts aged 60 years or younger and those older than 60 years, sex-specific analyses are lacking for the 38% of enrolled women. Only male sex appears in the list of risk factors predictive of obstructive coronary artery disease of both age cohorts with odds ratios of 4.40 and 5.05, respectively, the most highly significant risk factor. Oxidized phospholipid:apo B_{100} ratio and Lp(a) lipoprotein levels were both strongly associated with a graded increase in the extent of coronary artery disease in the total study cohort, with relationships stronger for patients aged 60 years and younger. Given the lack of sex-specific data, we cannot ascertain whether data regarding the risk of this proinflammatory milieu apply equally to women. And, of course, the extent of angiographic coronary artery disease is but one component of the risk of coronary events.

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*Note: Dr. Wenger asked that this comment indicate that she served as Chair of the Data Safety and Monitoring Board of the Women's Health Study.

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 U.S. Preventive Services Task Force.

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.
Level III	Meta-analyses; reports from expert committees; case reports.

Easy-Read Booklets Now Available in Three Languages

To meet an increasing demand, NAMS has reintroduced its consumer education booklet, *Menopause: A New Beginning,* which is written for women with low literacy skills. Updated with the most current information, this booklet offers basics about menopause in an easy-to-read format. The material is illustrated with light-hearted cartoon art that invites readership. The entire content has been tested to ensure that it is appropriate for the intended audience.

In answer to healthcare provider's requests, the booklet is now being offered in three languages: English, Spanish, and French. This project represents the first time that NAMS has offered educational material in French — demonstrating its commitment as The North American Menopause Society to serve French-speaking women in Canada.

To make the materials available to the widest possible audience, the three versions of the booklet are posted on the NAMS Web site (www.menopause.org) as PDF files. Healthcare providers are invited to download the template for a small fee ($45 for NAMS members, $65 for nonmembers, for each language), then print as many copies as are needed.