



FIRST TO KNOW[®]

Released February 23, 2010

This e-newsletter presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by George A. Helmrach, MD, Chair-Elect, 2009-2010 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Helmrach. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Lp(a) levels and coronary disease

Clarke R, Peden JF, Hopewell JC; for the PROCARDIS Consortium. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;361:2518-2528. **Level of evidence: II-2.**

Abstract copyright © Massachusetts Medical Society. All rights reserved. Used with permission.

BACKGROUND: An increased level of Lp(a) lipoprotein has been identified as a risk factor for coronary artery disease that is highly heritable. The genetic determinants of the Lp(a) lipoprotein level and their relevance for the risk of coronary disease are incompletely understood. **METHODS:** We used a novel gene chip containing 48,742 single-nucleotide polymorphisms (SNPs) in 2100 candidate genes to test for associations in 3145 case subjects with coronary disease and 3352 control subjects. Replication was tested in three independent populations involving 4846 additional case subjects with coronary disease and 4594 control subjects. **RESULTS:** Three chromosomal regions (6q26-27, 9p21, and 1p13) were strongly associated with the risk of coronary disease. The LPA locus on 6q26-27 encoding Lp(a) lipoprotein had the strongest association. We identified a common variant (rs10455872) at the LPA locus with an odds ratio for coronary disease of 1.70 (95% confidence interval [CI],

1.49 to 1.95) and another independent variant (rs3798220) with an odds ratio of 1.92 (95% CI, 1.48 to 2.49). Both variants were strongly associated with an increased level of Lp(a) lipoprotein, a reduced copy number in LPA (which determines the number of kringle IV-type 2 repeats), and a small Lp(a) lipoprotein size. Replication studies confirmed the effects of both variants on the Lp(a) lipoprotein level and the risk of coronary disease. A meta-analysis showed that with a genotype score involving both LPA SNPs, the odds ratios for coronary disease were 1.51 (95% CI, 1.38 to 1.66) for one variant and 2.57 (95% CI, 1.80 to 3.67) for two or more variants. After adjustment for the Lp(a) lipoprotein level, the association between the LPA genotype score and the risk of coronary disease was abolished. **CONCLUSIONS:** We identified two LPA variants that were strongly associated with both an increased level of Lp(a) lipoprotein and an increased risk of coronary disease. Our findings provide support for a causal role of Lp(a) lipoprotein in coronary disease.

Comment. This is a nice update regarding advances in understanding Lp(a) as a genetic risk factor for coronary artery disease (CAD), carotid atherosclerosis, and stroke. New gene chip technology is now able to identify with greater precision where on the short arm of

chromosome 6 the Lp(a) genetic variant is located. These authors associated 16 of 27 SNPs at the Lp(a) locus and their associations with circulating Lp(a) levels. Variants were then associated with new events in both follow-up and case-control clinical studies. The odds for developing CAD were 1.51 times higher for one variant and 2.57 times higher for two or more variants. Interestingly, because of Lp(a) location on the low-density lipoprotein (LDL) circulating molecules, Lp(a) was elevated only when LDL was elevated.

As clinical lipidologists know, lowering LDL is known to reduce risk from Lp(a) at the same time. This study suggests that there is a risk from having this genetic variant regardless of LDL level—however, this was not assessed in the paper. Family history is an important risk factor for cardiovascular disease above and beyond controlling cholesterol, smoking, inactivity, etc. Remember, subjects assessed here were those with known early CAD versus controls; the study was not an assessment of cardiovascular disease risk from the genetic variant in the general population. Lp(a) is known to be race dependent; it would have been interesting to know racial distributions in this study.

This is a fascinating advance in understanding but it does not change screening or intervention practices at this time. We await clarity as to optimum and cost-effective genetic testing for different groups of persons and whether or not it will alter our known strategies for keeping LDL levels on target to reduce atherogenic progression in all persons and in those with this genetic variant.

Robert A. Wild, MD, PhD, MPH, NCMP
 Professor of Reproductive Endocrinology
 Adjunct Professor of Biostatistics and Epidemiology
 Adjunct Professor of Medicine (Cardiology)
 Oklahoma University Health Sciences Center
 Oklahoma City, OK
 Member, NAMS Professional Education Committee

Obesity and smoking effects on life expectancy

Stewart ST, Cutler DM, Rosen AB. Forecasting the effects of obesity and smoking on U.S. life expectancy. *N Engl J Med* 2009;361:2252-2260. **Level of evidence: II-3.**

Abstract copyright © Massachusetts Medical Society. All rights reserved. Used with permission.

BACKGROUND: Although increases in obesity over the past 30 years have adversely affected the health of the U.S. population, there have been concomitant improvements in health because of reductions in smoking. Having a better understanding of the joint effects of these trends on longevity and quality of life will facilitate more efficient targeting of health care resources. **METHODS:** For each year from 2005 through 2020, we forecasted life expectancy and quality-adjusted life expectancy for a representative 18-year-old, assuming a continuation of past trends in smoking (based on data from the National Health Interview Survey for 1978 through 1979, 1990 through 1991, 1999 through 2001, and 2004 through 2006) and past trends in body-mass index (BMI) (based on data from the National Health and Nutrition Examination Survey for 1971 through 1975, 1988 through 1994, 1999 through 2002, and 2003 through 2006). The 2003 Medical Expenditure Panel Survey was used to examine the effects of smoking and BMI on health-related quality of life. **RESULTS:** The negative effects of increasing BMI overwhelmed the positive effects of declines in smoking in multiple scenarios. In the base case, increases in the remaining life expectancy of a typical 18-year-old are held back by 0.71 years or 0.91 quality-adjusted years between 2005 and 2020. If all U.S. adults became nonsmokers of normal weight by 2020, we forecast that the life expectancy of an 18-year-old would increase by 3.76 life-years or 5.16 quality-adjusted

years. **CONCLUSIONS:** If past obesity trends continue unchecked, the negative effects on the health of the U.S. population will increasingly outweigh the positive effects gained from declining smoking rates. Failure to address continued increases in obesity could result in an erosion of the pattern of steady gains in health observed since early in the 20th century.

Comment. This article uses complex epidemiologic modeling to predict the effect of trends in smoking and obesity on American public health. Evaluating the study methodology is beyond the scope of this commentary. However, the conclusions of this paper deserve consideration by all healthcare providers including (and perhaps especially) menopause clinicians. The good news is that considerable gains have been made for the health of the United States with respect to smoking, and clinicians have made a difference! Many excellent materials are available to help continue this effort.¹ Keep in mind that for every year beyond the age of 40 that someone smokes, they lose 3 months of life expectancy.

The bad news is that Stewart et al's work suggests that the obesity epidemic has negated the positive effects of smoking cessation on mortality and quality of life. Other studies have shown this trend to be worse for women than men, especially for black women. Although it is preferable to institute weight management strategies many years before menopause (as the Institute of Medicine's recent change in recommendation for weight gain in pregnancy reminds us²), midlife women do tend to gain weight. Menopause clinicians have an opportunity to provide anticipatory guidance to these women^{3,4} and educate them about advantages of and strategies for weight loss.⁵ This paper adds more evidence supporting the need for this effort.

Marcie K. Richardson, MD, NCMP
 Director
 Harvard Vanguard Menopause Consultation Service
 Boston, MA
 Member, NAMS Consumer Education Committee

References:

1. Aveyard P, West R. Managing smoking cessation. *BMJ* 2007;335:37-41.
2. Institute of Medicine. Weight gain during pregnancy: reexamining the guidelines. Available at: <http://www.iom.edu/Reports/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines.aspx>. Accessed February 9, 2010.
3. Mastorakos G, Valsamakis G, Paltoglou G, Creatas G. Management of obesity in menopause: Diet, exercise, pharmacotherapy and bariatric surgery. *Maturitas* 2009 Dec 29. [Epub ahead of print]
4. Eckel RH. Nonsurgical management of obesity in adults. *N Engl J Med* 2008;58:1941-1950.
5. U.S. Department of Health and Human Services. Weight-control Information Network. Available at: <http://win.niddk.nih.gov/publications/understanding.htm>. Accessed February 9, 2010.

Tamoxifen timing in postmenopausal breast cancer patients

Albain KS, Barlow WE, Ravdin PM, et al, for the Breast Cancer Intergroup of North America. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009;374:2055-2063. **Level of evidence: I.**

Abstract copyright © Elsevier. All rights reserved. Used with permission.

BACKGROUND: Tamoxifen is standard adjuvant treatment for postmenopausal women with hormone-receptor-positive breast cancer. We assessed the benefit of adding chemotherapy to adjuvant tamoxifen and whether tamoxifen should be given concurrently or after chemotherapy. **METHODS:** We undertook a phase 3, parallel, randomised trial (SWOG-8814, INT-0100) in postmenopausal women with hormone-receptor-positive, node-positive breast cancer to test two major objectives: whether the primary outcome, disease-free survival, was longer with cyclophosphamide, doxorubicin, and fluorouracil (CAF) given every 4 weeks for six cycles plus 5 years of daily tamoxifen than with tamoxifen alone; and whether disease-free survival was longer with CAF followed by tamoxifen (CAF-T) than with CAF plus concurrent tamoxifen (CAFT). Overall survival

and toxicity were predefined, important secondary outcomes for each objective. Patients in this open-label trial were randomly assigned by a computer algorithm in a 2:3:3 ratio (tamoxifen:CAF-T:CAFT) and analysis was by intention to treat of eligible patients. Groups were compared by stratified log-rank tests, followed by Cox regression analyses adjusted for significant prognostic factors. This trial is registered with ClinicalTrials.gov, number NCT00929591. FINDINGS: Of 1558 randomised women, 1477 (95%) were eligible for inclusion in the analysis. After a maximum of 13 years of follow-up (median 8.94 years), 637 women had a disease-free survival event (tamoxifen, 179 events in 361 patients; CAF-T, 216 events in 566 patients; CAFT, 242 events in 550 patients). For the first objective, therapy with the CAF plus tamoxifen groups combined (CAFT or CAF-T) was superior to tamoxifen alone for the primary endpoint of disease-free survival (adjusted Cox regression hazard ratio [HR] 0.76, 95% CI 0.64-0.91; $p=0.002$) but only marginally for the secondary endpoint of overall survival (HR 0.83, 0.68-1.01; $p=0.057$). For the second objective, the adjusted HRs favoured CAF-T over CAFT but did not reach significance for disease-free survival (HR 0.84, 0.70-1.01; $p=0.061$) or overall survival (HR 0.90, 0.73-1.10; $p=0.30$). Neutropenia, stomatitis, thromboembolism, congestive heart failure, and leukaemia were more frequent in the combined CAF plus tamoxifen groups than in the tamoxifen-alone group. INTERPRETATION: Chemotherapy with CAF plus tamoxifen given sequentially is more effective adjuvant therapy for postmenopausal patients with endocrine-responsive, node-positive breast cancer than is tamoxifen alone. However, it might be possible to identify some subgroups that do not benefit from anthracycline-based chemotherapy despite positive nodes. FUNDING: National Cancer Institute (US National Institutes of Health).

Comment. Antiestrogen therapy and chemotherapy are both effective modalities for the treatment of breast cancer. Thus, combining antiestrogen therapy with chemotherapy was a

logical step in the 1970s and 1980s. In fact, many clinical trials were performed with the use of chemo-antiestrogen combinations, which was common practice at the time. However, as clinical evidence accumulated, no significant benefit was observed in early trials when antiestrogen therapy was added concurrently to chemotherapy. In addition, experimental evidence at the time was suggestive of possible antagonistic effects of antiestrogen agents (eg, tamoxifen) with chemotherapy. The prevailing hypothesis was that antiestrogen therapy alters the cell kinetics of breast cancer cells, making them less susceptible to the effects of chemotherapy.

The three-arm SWOG-8814 trial was designed, in part, to help define the timing of adjuvant antiestrogen therapy in relation to CAF chemotherapy. In one arm, patients received tamoxifen alone; in the other two arms, patients received either sequential (CAF-T) or concurrent (CAFT) chemotherapy and tamoxifen. The study began enrollment in 1989 and early results were first presented at the 1997 American Society of Clinical Oncology annual meeting. In 2002, the comparison of the sequential (CAF-T) versus the concurrent (CAFT) arms was reported, showing superiority for the sequential approach of chemotherapy followed by adjuvant tamoxifen. This article by Albain et al is an update of the original study, confirming a strong trend toward improved progression-free survival for the sequential approach.

For all practical purposes, the current publication represents “old news” to the practicing medical oncologist. Largely based on the early results of this study, and for many years now, adjuvant tamoxifen has been given only after adjuvant chemotherapy has been completed. The final results of the trial are a confirmation that the sequential approach, practiced over the last decade, is correct. Despite the comparison not reaching statistical significance, the lack of any perceived benefit for concurrent administration of chemotherapy

and tamoxifen, in addition to the possible harm of the approach as suggested by the current as well as previous publications of the same work, make the sequential approach the standard of care.

A point raised by the authors in their discussion is that the current results cannot necessarily be extrapolated to the use of aromatase inhibitors because, at the time the study was conducted, tamoxifen was the only adjuvant antiestrogen therapy available. Aromatase inhibitors have a different mechanism of action than tamoxifen and the results may not be generalizable. However, given the lack of direct clinical evidence supporting concurrent administration of aromatase inhibitors with chemotherapy, the standard of care today is to initiate adjuvant aromatase inhibitor hormonal therapy after the completion of chemotherapy.

Kostandinos Sideras, MD
Department of Medical Oncology
Mayo Clinic Rochester
Rochester, MN

Effect of eszopiclone on insomnia, depression, and anxiety

Joffe H, Petrillo L, Viguera A, et al. Eszopiclone improves insomnia and depressive and anxious symptoms in perimenopausal and postmenopausal women with hot flashes: a randomized, double-blinded, placebo-controlled crossover trial. *Am J Obstet Gynecol* 2010;202:171.e1-171.e11. **Level of evidence: I.**

Abstract copyright © Elsevier. All rights reserved. Used with permission.

OBJECTIVE: Menopause-associated insomnia is commonly associated with other symptoms (hot flashes, depression, anxiety). Given frequent symptom cooccurrence, therapies targeting sleep may provide an important approach to treatment during midlife. **STUDY DESIGN:** Peri/postmenopausal women (40-65 years old) with sleep-onset and/or sleep-maintenance insomnia cooccurring with hot flashes and depressive and/or anxiety symptoms were randomized to eszopiclone 3 mg orally or placebo in a double-blinded, crossover 11 week

trial. Changes in the Insomnia Severity Index (ISI) scale and secondary outcomes (diary-based sleep parameters, depression/anxiety, hot flashes, quality of life) were analyzed using repeated-measure linear models. **RESULTS:** Of 59 women, 46 (78%) completed the study. Eszopiclone reduced ISI scores by 8.7 + or - 1.4 more points than placebo ($P < .0001$). Eszopiclone improved ($P < .05$) all sleep parameters, depressive symptoms, anxiety symptoms, quality of life, and nighttime but not daytime hot flashes. **CONCLUSION:** Eszopiclone treats insomnia and cooccurring menopause-related symptoms. Our results provide evidence that hypnotic therapies may improve multiple domains of well-being during midlife.

Comment. This report demonstrates that central nervous system medication (in this case, a nonbenzodiazepine hypnotic) can significantly improve insomnia in perimenopausal women. Interestingly, associated nocturnal hot flashes and anxiety and depressive symptoms associated with insomnia were also significantly improved by the medication, as was women's quality of life. Thus, eszopiclone offers an alternative strategy for women who suffer from perimenopausal symptoms of nocturnal hot flashes and mood problems not meeting criteria for psychiatric diagnoses.

Other pharmacological therapies for these symptoms currently include hormone therapy (HT) or antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). The psychotropic medications have been of particular benefit for women who have contraindications to HT use, such as women who are breast cancer survivors or women who have a history of other hormone-dependent cancers.

Eszopiclone may also be of use for women who seek nonhormonal strategies for their symptoms for other reasons. It would be interesting to see a comparison of this

medication with current HT regimes, and with SNRI or SSRI regimes. Both the efficacy of the medications on symptoms and their side effects should be compared.

Lorraine Dennerstein AO, MBBS, PhD, DPM, FRANZCP
 Professorial Fellow
 The University of Melbourne
 Department of Psychiatry
 National Ageing Research Institute
 Melbourne, Australia

The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

- | | |
|------------|---|
| Level I | Properly randomized, controlled trial. |
| Level II-1 | Well-designed controlled trial but without randomization. |
| Level II-2 | Well-designed cohort or case-control analytic study. |
| Level II-3 | Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies). |
| Level III | Meta-analyses; reports from expert committees; descriptive studies and case reports. |

2010 Call for Abstracts

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

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

First to Know® is a registered trademark of The North American Menopause Society

Copyright © 2010 The North American Menopause Society

All rights reserved

5900 Landerbrook Drive, Suite 390

Mayfield Heights, OH 44124, USA

Tel 440/442-7550 • Fax 440/442-2660 • info@menopause.org • www.menopause.org