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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 Wen Shen, MD, MPH, Chair-Elect, 2010-2011 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Helmrich. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS website ([www.menopause.org/news.html](http://www.menopause.org/news.html)).

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## cIMT and menopausal status

Johnson BD, Dwyer KM, Stanczyk FZ, et al. The relationship of menopausal status and rapid menopausal transition with carotid intima-media thickness progression in women: a report from the Los Angeles Atherosclerosis Study. *J Clin Endocrinol Metab* 2010;95:4432-4440. **Level of evidence: II-3.**

The Los Angeles Atherosclerosis Study assessed whether the rate of carotid intima-media thickness (cIMT) progression differs according to menopausal status and rapidity of the menopause transition in 203 community-based women ages 45 to 60. Over the 3 years of the study, women who had not been previously diagnosed with cardiovascular disease (CVD) underwent three repeated measurements of cIMT as a measure of preclinical CVD. Menopausal status was ascertained at each visit: 21 women remained premenopausal, 51 transitioned through perimenopause, and 131 were postmenopausal throughout the observation period. Age-adjusted cIMT progression rates among the groups were similar. In the 51 transitioning women, age was not related to rate of cIMT progression but women who transitioned from pre- to postmenopause within the 3-year period had a higher rate of cIMT progression compared with women with a slower transition. Findings were not altered by statistical adjustments for systolic blood pressure, body mass index, race, cigarette smoking, or hormone therapy use.

The researchers concluded that a more rapid menopause transition was associated with a higher rate of preclinical CVD progression among healthy women undergoing repeated cIMT measurement.

**Comment.** In this provocative article, a rapid menopause transition was associated with the highest rate of preclinical CVD progression, as well as higher cIMT overall at baseline. As the authors note in their discussion of study limitations, however, they cannot really distinguish the chicken from the egg—does the rate of the menopause transition reflect or determine the rate of CVD aging? And what determines the rate of the menopause transition? The authors entertain the hypothesis that elevated baseline cIMT in the rapidly transitioning women might reflect a history of ovarian disruptions resulting in compromised estrogen levels during premenopause (think extremes of nutrition, exercise, and stress).

In your practice, should you measure cIMT in women during perimenopause? I would say, only if the information you receive will alter your decision about recommending cardiovascular preventive strategies. The 2010 American College of Cardiology Foundation/American Heart Association guidelines state that “measurement of carotid artery IMT is

reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk.”<sup>1</sup> And, if you do elect to order the test, be certain you have an accredited laboratory expert in technique.

Meanwhile, I encourage other longitudinal studies with careful categorization of stages of the menopause transition and serial cIMT determinations to follow the lead of this new study by Johnson et al and corroborate or refute these intriguing findings.

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Reference:

1. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guidelines for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report from the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2010;122:2748-2764.

## Cardiovascular effects of anacetrapib

Cannon CP, Shah S, Dansky HM, et al, for the DEFINE Investigators. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* 2010;363:2406-2415. **Level of evidence: I.**

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**Background:** Anacetrapib is a cholesteryl ester transfer protein inhibitor that raises high-density lipoprotein (HDL) cholesterol and reduces low-density lipoprotein (LDL) cholesterol. **Methods:** We conducted a randomized, double-blind, placebo-controlled trial to assess the efficacy and safety profile of anacetrapib in patients with coronary heart disease or at high risk for coronary heart disease. Eligible patients who were taking a statin and who had an LDL cholesterol level that was consistent with that recommended in guidelines were assigned to

receive 100 mg of anacetrapib or placebo daily for 18 months. The primary end points were the percent change from baseline in LDL cholesterol at 24 weeks (HDL cholesterol level was a secondary end point) and the safety and side-effect profile of anacetrapib through 76 weeks. Cardiovascular events and deaths were prospectively adjudicated. **Results:** A total of 1623 patients underwent randomization. By 24 weeks, the LDL cholesterol level had been reduced from 81 mg per deciliter (2.1 mmol per liter) to 45 mg per deciliter (1.2 mmol per liter) in the anacetrapib group, as compared with a reduction from 82 mg per deciliter (2.1 mmol per liter) to 77 mg per deciliter (2.0 mmol per liter) in the placebo group ( $P<0.001$ )—a 39.8% reduction with anacetrapib beyond that seen with placebo. In addition, the HDL cholesterol level increased from 41 mg per deciliter (1.0 mmol per liter) to 101 mg per deciliter (2.6 mmol per liter) in the anacetrapib group, as compared with an increase from 40 mg per deciliter (1.0 mmol per liter) to 46 mg per deciliter (1.2 mmol per liter) in the placebo group ( $P<0.001$ ) — a 138.1% increase with anacetrapib beyond that seen with placebo. Through 76 weeks, no changes were noted in blood pressure or electrolyte or aldosterone levels with anacetrapib as compared with placebo. Prespecified adjudicated cardiovascular events occurred in 16 patients treated with anacetrapib (2.0%) and 21 patients receiving placebo (2.6%) ( $P = 0.40$ ). The prespecified Bayesian analysis indicated that this event distribution provided a predictive probability (confidence) of 94% that anacetrapib would not be associated with a 25% increase in cardiovascular events, as seen with torcetrapib. **Conclusions:** Treatment with anacetrapib had robust effects on LDL and HDL cholesterol, had an acceptable side-effect profile, and, within the limits of the power of this study, did not result in the adverse cardiovascular effects observed with torcetrapib.

**Comment.** Cholesteryl ester transfer protein (CETP) is a plasma protein that transports

cholesteryl esters and triglycerides between the lipoproteins. The first-generation CETP inhibitor (CETPi) (torcetrapiba) dramatically raised HDL-C but increased cardiovascular mortality (presumed but not definitively thought to be related to blood pressure and aldosterone abnormalities). Two second-generation CETPi molecules—dalcetrapib and anacetrapib—are in phase III development and the former has already initiated a large outcome study (dal-OUT-COMES). Dalcetrapib has been shown not to affect blood pressure or aldosterone but lowers LDL-C about 6% and raises HDL-C by about 37%. The DEFINE trial data showed that anacetrapib caused dramatic reductions in LDL-C, apolipoprotein B, and lipoprotein(a), along with phenomenal increases in HDL-C (~130%) and had no safety issues; an outcomes trial (REVEAL) is now planned.

In essence, the process by which HDL removes cholesterol from extrahepatic tissues and returns it to the liver is called “reverse cholesterol transport” (RCT). Once in the liver, the cholesteryl esters are converted to cholesterol and enter the general pool. Then the liver can eliminate cholesterol from the body in the stool by secreting unesterified cholesterol into the bile or by converting cholesterol to bile acids. Measuring fecal sterols is used as an assay of the RCT process. Since CETP is an integral part of the indirect RCT process, one might ask if CETPi could conceivably reduce RCT. With respect to lipid/lipoprotein modulation as well as RCT, dalcetrapib (unlike torcetrapib and anacetrapib) does increase fecal sterols and does not diminish creation of the very small crucial pre- $\beta$ -HDL species.<sup>1</sup> One could speculate that CETPi molecules such as torcetrapib and anacetrapib, which significantly raise HDL-C but do not increase fecal sterols or reduce pre- $\beta$ -HDL species, are creating very large HDL particles that no longer are being delipidated and may not be helping or perhaps even be diminishing RCT. Dalcetrapib, now called a CETP “modulator” instead of inhibitor, does not raise HDL-C as much as the other CETPi molecules, but does increase fecal sterols and pre- $\beta$ -HDL; it seems as

if the large HDLs are being delipidated and retransformed into pre- $\beta$ -HDL.

The most important lesson is to recognize that what a drug does to serum HDL-C often has no relationship to what that drug may be doing to cholesterol homeostasis, to the cardiovascular system, and most importantly how it will affect cardiovascular outcomes. Those of us in the menopausal world should have already learned this lesson with estrogen.

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#### References:

1. Niesor EJ, Magg C, Ogawa N, et al. Modulating cholesteryl ester transfer protein activity maintains efficient pre- $\beta$ -HDL formation and increases reverse cholesterol transport. *J Lipid Res* 2010;51:3443-3454.

Disclosures: Dr. Dayspring reports: Consultant—Merck, Roche/Genentech.

## Protein and glycemic index content in diet for weight loss

Larsen TM, Dalskov SM, van Baak M, et al, for the Diet, Obesity, and Genes (Diogenes) Project. Diets with high or low protein content and glycemic index for weight-loss maintenance. *N Engl J Med* 2010;363:2102-2113.

#### Level of evidence: I.

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**Background:** Studies of weight-control diets that are high in protein or low in glycemic index have reached varied conclusions, probably owing to the fact that the studies had insufficient power. **Methods:** We enrolled overweight adults from eight European countries who had lost at least 8% of their initial body weight with a 3.3-MJ (800-kcal) low-calorie diet. Participants were randomly assigned, in a two-by-two factorial design, to one of five ad libitum diets to prevent weight regain over a 26-week period: a low-protein and low-glycemic-index diet, a low-protein and high-glycemic-index diet, a high-protein and

lowglycemic-index diet, a high-protein and high-glycemic-index diet, or a control diet. *Results:* A total of 1209 adults were screened (mean age, 41 years; body-mass index [the weight in kilograms divided by the square of the height in meters], 34), of whom 938 entered the low-calorie-diet phase of the study. A total of 773 participants who completed that phase were randomly assigned to one of the five maintenance diets; 548 completed the intervention (71%). Fewer participants in the high-protein and the lowglycemic-index groups than in the low-protein–high-glycemic-index group dropped out of the study (26.4% and 25.6%, respectively, vs. 37.4%;  $P = 0.02$  and  $P = 0.01$  for the respective comparisons). The mean initial weight loss with the low-calorie diet was 11.0 kg. In the analysis of participants who completed the study, only the low-protein–high-glycemic-index diet was associated with subsequent significant weight regain (1.67 kg; 95% confidence interval [CI], 0.48 to 2.87). In an intention-to-treat analysis, the weight regain was 0.93 kg less (95% CI, 0.31 to 1.55) in the groups assigned to a high-protein diet than in those assigned to a low-protein diet ( $P = 0.003$ ) and 0.95 kg less (95% CI, 0.33 to 1.57) in the groups assigned to a low-glycemic-index diet than in those assigned to a high-glycemic-index diet ( $P = 0.003$ ). The analysis involving participants who completed the intervention produced similar results. The groups did not differ significantly with respect to diet-related adverse events. *Conclusions:* In this large European study, a modest increase in protein content and a modest reduction in the glycemic index led to an improvement in study completion and maintenance of weight loss.

**Comment.** Maintenance after intentional weight loss is a key factor in treating obesity. From this large international study, it appears that diets moderately higher in protein content with slightly lower glycemic index are most effective for weight maintenance. However, as the authors note, only 5.4 percentage points of dietary protein separated the protein groups, and only 5 glycemic index units separated the glycemic index groups. There was no difference in satiety

between the groups. Before the 26-week weight maintenance phase of the study began, all participants consumed between 800 to 1,000 kilocalories per day through Modifast products and vegetables for 8 weeks. Even in this highly motivated group, only 71% completed the study phase.

Interestingly, this study included only participants with children between 5 and 17 years of age. The dropout rate was higher than expected. Still, research that recognizes the role of the family unit in weight control also addresses the importance of parents sharing healthy lifestyle habits with their children.

This study reinforces that weight loss is only the beginning of the solution to obesity. Increasing the protein and lowering the glycemic index in the diet may assist weight maintenance, but more investigation into the factors influencing obesity, loss, and maintenance is needed.

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## Sexual dysfunction rates in an inner-city menopause clinic

Schnatz PF, Whitehurst SK, O'Sullivan DM. Sexual dysfunction, depression, and anxiety among patients of an inner-city menopause clinic. *J Womens Health (Larchmt)* 2010;19:1843-1849. **Level of evidence: II-2.**

Schnatz et al examined the prevalence of female sexual dysfunction (FSD) in a sample of 102 women at the Women's Life Center at Hartford Hospital (2004-2008) in Connecticut. Women were age  $52.9 \pm 6.8$ , 80.0% Hispanic, and 47.8% were unemployed. A total of 92.8% earned less than \$25,000, and 95.8% did not have a college degree. Researchers defined FSD as: decreased sexual desire, dyspareunia, or vaginal dryness, depression, and anxiety.

FSD was identified in 75.6% of participants; prevalence of depression was 80.9% in women with a decrease in sexual desire versus 52.8% ( $P = 0.01$ ) in those without; anxiety was identified in 76.6% of women with a decrease in sexual desire versus 45.7% ( $P = 0.01$ ) in those without.

Prevalence of depression was 83.3% among women reporting dyspareunia versus 55.9% ( $P = 0.03$ ) among those who did not. Anxiety was identified in 76.7% among those reporting dyspareunia versus 52.9% ( $P = 0.07$ ) among those who did not. The only variable associated with a statistically higher likelihood of FSD were sleep problems (odds ratio, 5.57, 95% confidence interval, 1.22-25.33,  $P = 0.03$ ) and no significant differences were seen when comparing FSD between Hispanics and non-Hispanics.

**Comment.** Schnatz et al demonstrate an association between poor sleep, anxiety, depression, and FSD in Hispanic women with low socioeconomic status. As the report states, establishing cause and effect in this type of study is not possible.

Instead, the researchers suggest that clinicians address causes of insomnia to assist their patients who sleep poorly and have sexual dysfunction. A higher prevalence of sleep apnea was also found in these middle-aged, perimenopausal women.<sup>1,2</sup> If poor sleep quality persists after a woman has reduced her caffeine and alcohol consumption and improved her sleep regimen, clinicians may consider recommending a sleep study to detect sleep apnea, particularly if there is no relief with lifestyle modifications or medications. Were additional follow-up possible, it would be interesting to determine if those women diagnosed and treated for sleep apnea had a lower prevalence of anxiety, depression, and sexual dysfunction.

References:

1. Bixler EO, Vgontzas AN, Lin H-M, et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med.* 2001;163:608-613.

2. Young T, Finn L, Austin D, et al. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med.* 2003;167:1181-1185.

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## Editor's picks from January *Menopause*

NAMS spotlights the most recent issue of the Society's official journal, *Menopause*, selected by its Editor-in-Chief, Dr. Isaac Schiff.

Goldstein SR, MD, Neven P, Cummings S, et al. Postmenopausal evaluation and risk reduction with lasofoxifene (PEARL) trial: 5-year gynecological outcomes. *Menopause* 2011;18:17-22.

In a randomized trial, postmenopausal women with osteoporosis received 5 years of treatment with lasofoxifene or placebo. Treatment with lasofoxifene resulted in benign endometrial changes that did not seem to increase the risk for endometrial cancer or hyperplasia in postmenopausal women.



Kurtz EG, Ridker PM, Rose LM, et al. Oral postmenopausal hormone therapy, C-reactive protein, and cardiovascular outcomes. *Menopause* 2011;18:23-29.

C-reactive protein predicts cardiovascular event among women in the Women's Health Study in a log-linear relationship among both hormone therapy users and nonusers. C-reactive protein of 3 mg/L or greater seems to indicate higher cardiovascular risk in both hormone therapy users and nonusers.



Labrie F, Martel C, Balser J. Wide distribution of the serum dehydroepiandrosterone and sex steroid levels in postmenopausal women: role of the ovary? *Menopause* 2011;18:30-43.

Measurement of 11 metabolites of dehydroepiandrosterone in intact and oophorectomized women further indicates that the postmenopausal ovary does not secrete significant amounts of estradiol or testosterone but that it secretes about

20% of total circulating dehydroepiandrosterone, with 80% being of adrenal origin in that age group.



Bea JW, Zhao Q, Cauley JA, et al. Effect of hormone therapy on lean body mass, falls, and fractures: 6-year results from the Women's Health Initiative hormone trials. *Menopause* 2011;18:44-52.

An evaluation of 6 years of hormone therapy in postmenopausal women enrolled in the Women's Health Initiative demonstrated that lean body mass preservation up to 3 years does not persist through 6 years of hormone therapy. Falling and fracture rates were not altered by this early lean body mass preservation.



Davis SR, Kirby C, Weekes A, Lanzafame A, Piterman L. Simplifying screening for osteoporosis in Australian primary care: the Prospective Screening for Osteoporosis;

Australian Primary Care Evaluation of Clinical Tests (PROSPECT) study. *Menopause* 2011;18:53-59.

The PROSPECT tool was developed to facilitate targeted screening and hence reducing the need for unnecessary radiology tests at the primary care level.



Wiacek M, Hagner W, Zubrzycki IZ. Measures of menopause driven differences in levels of blood lipids, follicle-stimulating hormone, and luteinizing hormone in women aged 35 to 60 years: National Health and Nutrition Examination Survey III and National Health and Nutrition Examination Survey 1999-2002 study. *Menopause* 2011;18:60-66.

Most lipid changes are a combination of menopause and aging.

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.                                  |

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