Menopause Care Updates 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 and healthy aging. Each review has commentary from a recognized expert that addresses its clinical relevance. Oversight for this e-newsletter was by Nancy Jasper, MD, FACOG, NCMP, Chair-elect of the 2015 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or by Dr. Jasper.

Introducing Menopause Care Updates

As promised, NAMS is proud to launch its latest educational product, Menopause Care Updates, a benefit to all NAMS members. This new publication takes the place formerly held by First to Know. First to Know will continue to publish in its originally intended format—delivering breaking scientific news and analysis whenever it happens.

Planned to publish bimonthly for the remainder of 2015, Menopause Care Updates will become a monthly publication next year under the Editorship of the Chair-elect of the NAMS Professional Education Committee, currently Dr. Nancy Jasper.

Menopause Care Updates will present a summary and in-depth commentary on several recently published articles, chosen because they may influence changes in thinking or in clinical menopause practice. In addition, brief summaries of two to three other clinically relevant articles will be presented, and Dr. Isaac Schiff will continue to offer his Editor Picks from the current issue of Menopause.

We hope that these changes will allow us to dedicate more analysis and discussion of major papers and offer our membership a more robust publication of value to their clinical practices.

As always, NAMS invites your comments and suggestions.

Wulf H. Utian, MD, PhD DSc(Med)
NAMS Executive Director

Cardiovascular risk in statin users treated with hormone therapy


Summary. Swedish women aged 40 to 74 years who were statin users were studied to find the effects of hormone therapy (HT) on their risk of cardiovascular disease (CVD) and all-cause mortality. Study participants (N=40,958) who had used statins in the previous 12 months were divided into 2 cohorts: those who used HT (n=2,862) and nonusers (n=38,096). Population-based national health registers provided information on dispensed drugs, comorbidity, CVD outcomes, and all-cause mortality. The women were followed for a mean of 4 years. Seventy percent of the women used statins as primary prevention.
The data showed 5 cardiovascular deaths per 10,000 person-years in HT users and 18 in nonusers (hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.12-1.19). All-cause mortality rates were 33 and 87, respectively (HR, 0.53; 95% CI, 0.34-0.81). Researchers concluded that there was no association between HT use and cardiovascular events and that HT is associated with a reduced risk of all-cause mortality in women treated with statins.

Commentary by

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In addition to reducing cholesterol levels through inhibition of a key enzyme in cholesterol synthesis, statins have beneficial cardiovascular (CVD) effects, such as nitric oxide production, improving endothelial function, and modifying immune-inflammatory responses. It has therefore been suggested that combining statin therapy with hormone therapy (HT) may counteract some potentially adverse effects of HT on inflammation and CVD risk.

The present study by Berglind and colleagues, a registry-based observational cohort study, supports this counteraction hypothesis, yet has several limitations that warrant further discussion.

An important consideration in this study is that the definition of HT included estradiol (with and without progestogen) menopausal HT and selective estrogen receptor modulators (SERMs).

It is not stated what percentage of women were on SERMs, which traditionally are used for bone health and breast cancer treatment and prevention. The discussion of this paper focused around the possible beneficial effects of estradiol over synthetic estrogens, the Women’s Health Initiative (WHI), and the Heart and Estrogen/progestin Replacement Study.

The authors did not mention studies about CVD and SERMs. SERMS have not been shown to increase CVD risk and, in a subset of higher-risk women, reduce CVD risk. Although this study found no overall increased risk of CVD and a reduced risk of all-cause mortality, the results do not adjust for SERMs, which is a limitation.

Further methodologic issues of concern include that only 7% of the total statin users were on HT, leading to wide confidence intervals (CIs) indicative of low power.

Other important limitations include the unknown duration of HT use, route of HT, and the timing of HT initiation, which is now believed to be an important determinant of risk versus benefit for vascular health. It is also unclear what percentage of women was using estrogen alone versus estrogen plus progestin therapy.

Biomarkers and risk factors play an important role in how we as clinicians determine which women are appropriate or not appropriate candidates for HT. In the WHI, in women with a baseline low-density lipoprotein cholesterol of 130 mg/dL or higher, HT increased CVD risk by more than 40% (odds ratio, 1.46; 95% CI, 1.02-2.10).

The NAMS algorithm and mobile app MenoPro for menopause symptom management was developed to help clinicians personalize HT versus nonhormonal decisions based on risk factors and symptoms.

For women without CVD, the 10-year atherosclerotic cardiovascular (ASCVD) risk score and time since menopause onset determines whether a woman is an appropriate
candidate for HT. For women with ASCVD risk between 5% and 10% and within 10 years of menopause, transdermal rather than oral HT is recommended. However, in women who are more than 10 years since menopause, HT is not recommended.

Research on the interaction between statin therapy and HT is scant. However, this study exemplifies the rationale that observational studies should be used for hypothesis generation for future controlled trials. More research is needed before adopting statin therapy to counteract HT adverse CVD effects. Meanwhile, HT should not be used alone or in combination with statins for the prevention of CVD, and effective tools such as MenoPro can help guide clinicians regarding personalized treatment decision-making.

References

Disclosure: Dr. Shufelt reports no relevant conflicts of interest.

Timing of osteoporotic fracture in younger postmenopausal women

Summary. Participants aged 50 to 64 years without hip or vertebral fracture or receiving antifracture treatment at baseline from the Women’s Health Initiative bone mineral density (BMD) cohort study were examined as part of a study designed to estimate the time between first BMD tests and incidence of a first major fracture.

BMD tests were performed between October 1993 and April 2005, with fracture follow-up through 2012. Outcomes were time for 1% of the women to sustain a hip or vertebral fracture and 3% of the women to sustain a major osteoporotic fracture before beginning treatment.

Over a maximum follow-up time of 11.2 years, the time for 1% of women aged 50 to 54 years without baseline osteoporosis to have a hip or vertebral fracture was 12.8 years (95% confidence interval [CI], 8.0-20.4); for women aged 60 to 64 years, 7.6 years (95% CI, 4.8-12.1); and for all the women aged 50 to 64 years, 3.0 years (95% CI, 1.3-7.1). Time to a major osteoporotic fracture results were similar.

Researchers concluded that the results show that women aged 50 to 64 years without osteoporosis on their first BMD test are unlikely to benefit from frequent rescreening before age 65.

Commentary by
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Given that the risk of hip and spine fractures in healthy women aged 50 to 64 years with average bone mineral density (BMD) T-score values of more than −1 is so low (1.7% over about 14 years, or about 0.1% per year), it is no surprise that the time interval for 1% of these patients to experience such a fracture is very long. It is difficult for me to appreciate the clinical relevance of these results or how the results of this study can be translated into recommendations about the frequency of follow-up bone density testing. The purpose of repeating a bone density test is not to determine when a fracture will occur but rather to identify those patients whose bone density is low enough, when combined with other risk factors, to warrant treatment to reduce fracture risk.

Large observational studies are valuable resources with which many important questions can be evaluated. Unfortunately, the analyses of most large observational studies, as is true in the Gourlay paper, provide the average results for large groups of patients rather than individual patient data.

As aptly stated by Dr. Gallagher in an editorial accompanying the Gourlay paper, clinicians do not see groups of patients. Clinicians see individual people with various combinations of concerns and risk factors such as age and BMD, fall frequency, personal and family history of fracture, and years since menopause. There are very few “average” patients because, except in Lake Woebegone, about half of people are above normal and an equal number below.

For example, the rate of bone loss in healthy women aged 50 years and older is strongly related to the recency of menopause—more rapid in the first few years and very slow thereafter. It is highly likely that a thin 52-year-old woman just entering menopause whose lumbar spine bone density T-score value is −2.2 will have osteoporosis by bone density criteria and be a clear candidate for treatment within 2 to 3 years. She would not be well served by a recommendation for follow-up testing based on the evidence that, in women her age, the interval to develop a hip or spine fracture is more than 12 years.

Rather than this paper being useful for clinicians, it more likely that these “average” results will be used by health authorities and payers to forge restrictive clinical guidelines.

The take-home message from the paper is in the abstract—that women aged 50 to 64 years are unlikely to benefit from frequent rescreening before age 65. Comments found in the Discussion and Conclusion sections of the paper that “these results should not be interpreted to suggest that no postmenopausal woman younger than 65 should have a DXA [dual energy x-ray absorptiometry] test” and that “screening frequency should be based on age and baseline T-score values” will go unnoticed. The analyses here are reminiscent of the results in older postmenopausal women published by Dr. Gourlay with statements about the appropriate (very long) interval of follow-up bone density testing.

Unfortunately, although those results showed the average changes, the Washington State Health Care Authority used those recommendations to limit the interval of repeat bone density testing for all women, depriving physicians and patients from individualizing clinical decisions.

Epidemiologists with access to large cohorts can perform many analyses for which the study was never planned without having to recruit additional patients or to even see the ones who are or were in the study. It is no surprise, and in my opinion unfortunate, that such studies now dominate publication in the field of osteoporosis.

Although there is much we can learn from epidemiologic data, we are more in need of studies that address the management of individual patients. From the database available to Dr. Gourlay, it would be helpful to address such practical questions as 1) what
characteristics other than age and BMD were associated with fracture risk in these younger postmenopausal women? or 2) what was the distribution of patient-specific intervals of time, stratified by age and baseline BMD, for women to transition to BMD-defined osteoporosis when pharmacologic treatment might be considered?

References


Disclosure: Dr. McClung reports no relevant conflicts of interest.

In Other News

NAMS presents summaries of other recently published articles for your review

Hysterectomy and sexual performance


Researchers in Turkey studied 121 women who underwent surgical menopause and 122 women who had undergone natural menopause to see whether surgical menopause affects sexual performance differently than natural menopause. The women were aged between 45 and 65 years, and all had been postmenopausal for at least 1 year. A 6-question survey was used to rate performance parameters of sexual desire, coital frequency, arousal, orgasm frequency, dyspareunia, and vaginal lubrication. Survey answers were compared between the 2 groups, and in all areas except vaginal lubrication, which was lower in the surgical menopause group, there was no statistical difference in sexual performance parameters between them.

Vaccine prevention for herpes zoster in older adults


A phase 3 study of a herpes zoster subunit vaccine was conducted in 15,411 participants to evaluate safety and efficacy in older adults. Participants were stratified by age group (50-59 y; 60-69 y; and ≥70 y) and received 2 intramuscular doses of the vaccine (n=7,698) or placebo (n=7,713) 2 months apart. Over a mean follow-up of 3.2 years, herpes zoster was confirmed in 6 participants in the vaccine group and 210 participants in the placebo group. Vaccine efficacy ranged between 97.2% and 97.9% in all age groups, and efficacy in the group aged 70 years and older was similar to the other age groups. Injection-site and systemic reactions were more frequent in the vaccine group, and the proportion of participants who had serious adverse events or potential immune-mediated disease or who died was similar in the two groups.

Association between fruit and vegetable intake and hip fracture risk


A Swedish cohort study of 34,947 women and 40,644 men free of cardiovascular disease and cancer investigated whether a dose-response effect could be found between fruit and vegetable intake and subsequent hip fracture.
Participants answered lifestyle questionnaires in 1997 when they were aged 45 to 83 years and were followed for a mean of 14.2 years. Rates of fruit and vegetable intake ranged from one-third of participants reporting an intake of more than 5 servings per day down to 6% reporting 1 or fewer servings per day. Researchers observed 3,644 hip fractures during 1,037,645 person-years. Participants reporting zero consumption had an 88% higher rate of hip fracture compared with those reporting 5 servings per day (adjusted hazard ratio, 1.88; 95% confidence interval, 1.53-2.32). Consumption of more than 5 servings per day, however, did not confer additionally lower rates. Researchers concluded that fruit and vegetable intake of fewer than 5 servings per day results in higher rates of hip fracture.

**Menopause Editor’s picks for July 2015**

NAMS spotlights selections from the most recent issue of the Society’s official journal, *Menopause*, chosen by its editor in chief, Isaac Schiff, MD.

**Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60 to 65 years**
Pragya Gartoula, MSc; Roisin Worsley, MBBS, FRACP; Robin J. Bell, MBBS, PhD; and Susan R. Davis, MBBS, FRACP, PhD

**Exploratory comparison of vaginal glycogen and Lactobacillus levels in premenopausal and postmenopausal women**
Paria Mirmonsef, PhD; Sharada Modur, PhD; Derick Burgard, BS; Douglas Gilbert, BS; Elizabeth T. Golub, PhD, MPH; Audrey L. French, MD; Kerrie McCotter, BS; Alan L. Landay, PhD; and Greg T. Spear, PhD

**An actigraphy study of sleep and pain in midlife women: the Study of Women’s Health Across the Nation Sleep Study**

**Poor sleep in relation to natural menopause: a population-based 14-year follow-up of midlife women**
Ellen W. Freeman, PhD; Mary D. Sammel, ScD; Stephanie A. Gross, MS; and Grace W. Pien, MD