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This complimentary e-newsletter from The North American Menopause Society (NAMS) presents clinical questions and cases commonly seen in a menopause specialist's practice. Recognized experts in the field provide their opinions and practical advice. Robert A. Wild, MD, PhD, MPH, the Editor of *Menopause e-Consult*, encourages your suggestions for topics to be addressed in future issues. Note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Wild. Previously published issues may be viewed on the NAMS Web site ([www.menopause.org/econsult.html](http://www.menopause.org/econsult.html)).

**Question**  
Which women should take aspirin for the primary prevention of cardiovascular disease? What factors should be considered in decision making about aspirin?

## Commentary from:



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Only recently have clinicians had rigorous evidence to guide decision making about the use of aspirin in the primary prevention of cardiovascular disease (CVD) in women. Although it is well established that aspirin is effective in the secondary prevention of CVD and in the treatment of acute myocardial infarction (MI) among *both* women and men,<sup>1</sup> there had been sparse data about the benefits and risks of aspirin in primary prevention

among women until results from a large-scale trial, the Women's Health Study (WHS), were reported in 2005.<sup>2</sup> Previously, guidelines had been largely extrapolated from results of clinical trials in men, which had suggested that aspirin reduces the incidence of first MI by 30% to 35% while having little effect on stroke.<sup>3,4</sup>

*Primary prevention results in women, including results stratified by age.* The WHS, the only large primary prevention trial of aspirin in women, suggested a different pattern of cardiovascular outcomes with aspirin in women compared to men. The WHS evaluated the benefits and risks of low-dose aspirin (100 mg on alternate days) in the primary prevention of major cardiovascular events (MI, stroke, and cardiovascular death) among 39,876 initially healthy women age 45 and over, followed for 10 years.<sup>2</sup> Overall, the trial showed a statistically nonsignificant 9% reduction in the primary outcome of major cardiovascular events. In contrast to the significant reduction in MI and neutral effect on stroke observed in the Physicians' Health Study<sup>3</sup> and other primary prevention trials in men,<sup>4</sup> the WHS demonstrated that aspirin significantly lowered the risk of total stroke by 17% (95% confidence interval, 1% to 31%) and the risk of ischemic stroke by 24% (7% to 37%) in women, but did not lower the risk of MI or cardiovascular death. As expected, aspirin increased bleeding risks. Gastrointestinal hemorrhages requiring trans-

fusion were 40% more common with aspirin, and there was also a nonsignificant 24% increase in hemorrhagic stroke risk.

However, age appeared to be a key determinant of a woman's cardiovascular response to aspirin and her benefit/risk ratio with treatment.<sup>2</sup> Among WHS participants over age 65, aspirin was associated with clear evidence of benefit: a statistically significant 26% (8%-41%) reduction in risk of major cardiovascular events, with a significant benefit on both ischemic stroke (relative risk [RR], 0.70) and MI (RR, 0.66). In contrast, for younger participants, aspirin appeared to provide little or no cardiovascular protection (RR of major CVD events, 1.01 in women ages 45-54; 0.98 in women ages 55-64) and MI risk was not reduced in either group (RR, 1.23 and 1.17, respectively). Testing for statistical interaction by age group revealed *P* values for interaction of 0.05 for major CVD events and 0.03 for MI. In a benefit/risk assessment by age group, the 4,097 women who were over age 65 at enrollment experienced 44 fewer major CVD events with aspirin than with placebo (*P* = 0.008) but had 16 more gastrointestinal hemorrhages requiring transfusion (*P* = 0.05). In contrast, women under age 65 had no reduction in major CVD events, while experiencing a similar increase in gastrointestinal bleeding (leading to a net adverse effect and an unfavorable benefit/risk ratio). A woman's age appeared to be a stronger predictor of her benefit/risk ratio with aspirin than her Framingham risk score, but few women in the cohort had high 10-year coronary risks.

*Meta-analyses of aspirin in primary and secondary prevention of CVD.* Meta-analyses confirm that, in the high-risk setting of prevalent CVD or acute MI, both men and women benefit comparably from the use of aspirin.<sup>1</sup> Thus, in the absence of contraindications, aspirin should be used consistently in men and women for the secondary prevention of CVD. However, meta-analyses of aspirin in primary prevention,

heavily weighted by the results of the large-scale Physicians' Health Study and WHS, suggest sex-based differences in effects: aspirin significantly reduces the risk of MI but not stroke in men and significantly reduces the risk of stroke but not MI in women.<sup>2</sup> Age is an important modulator of the effect of aspirin in women. Among women younger than age 65, aspirin does not reduce major CVD events, while women age 65 and older experience reductions in MI, stroke, and composite CVD events with aspirin therapy. Randomized trial data are not available to assess the efficacy or safety of long-term aspirin use for the prevention of other diseases, such as colorectal cancer.

*Conclusion.* Recent randomized trials have informed decision making about the use of aspirin in the prevention of CVD in women. Aspirin should be used consistently in the secondary prevention setting in both men and women for prevention of recurrent events, in the absence of contraindications (eg, a history of serious gastrointestinal bleeding or aspirin allergy). In the primary prevention setting, the WHS findings indicate that women age 65 and older are likely to experience a net benefit from preventive low-dose aspirin therapy and should be considered for such therapy unless contraindicated. Most experts would recommend a dose of 81 mg to 100 mg daily, although higher doses may be required for patients with diabetes or established CVD. For most women below age 65, the WHS suggests that the risks of aspirin may outweigh the benefits. It is not known, however, whether subgroups of younger women at elevated CVD risk may benefit from aspirin or whether higher doses are needed for heart protection. The available evidence does not support the routine use of aspirin in women younger than age 65 for coronary protection unless they are at elevated risk by virtue of a high coronary risk score (high 10-year risk by the Framingham or Reynold's Risk Score) or the presence of diabetes, a position also taken by the American

Heart Association.<sup>5</sup>

**Disclosure:** Dr. Manson reports no conflicts.

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**C**ase  
A very physically active and mentally alert 70-year-old woman was recently referred to our office for persistent, severe postmenopausal symptoms. She was having hourly hot flashes as well as bothersome night sweats, which affected the quality of her sleep. The poor sleep quality was negatively influencing her quality of life. The woman has been taking hormone therapy (HT) intermittently since she was 60 years old but discontinued in 2002 after the initial information from the Women's Health Initiative came out. After starting and stopping twice more, she was prescribed a lower dose of HT in 2003, which she continued until 2006. Still suffering from severe symptoms in 2008, she wished to discuss restarting therapy. Her present medical history was being well controlled for hypothyroidism (levothyroxine), hypertension (valsartan and metoprolol), and depression (venlafaxine). Among the medications she is taking for other medical conditions are a daily dose of baby aspirin for her heart and 600 mg gabapentin for restless leg syndrome (RLS). Should she restart HT?

## Management Issues by:



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In 2005, the National Institutes of Health published a consensus statement on the lack of information regarding duration of menopausal symptoms, since most studies do not follow women beyond the first 2 years postmenopause. Politi et al<sup>1</sup> conducted a literature review and identified 10 eligible longitudinal and cross-sectional studies with 35,445 participants for meta-analysis. They found the median duration of symptoms was 4 years, and 10% of all participants were still symptomatic 12 years after the final menstrual period (FMP). Specifically, the symptoms peaked 1 year after FMP, and did not return to premenopausal levels until 8 years after FMP. The age of these participants ranged from 39 to 65 at inception of study to a maximum of age 75 at conclusion. The prolonged duration of significant vasomotor symptoms in 10% of women requires a review of treatment recommendations on an individual basis, based on a woman's risk/benefit profile.

*Sleep disturbances.* It has been postulated that vasomotor symptoms are a cause of sleep disturbance in peri- and postmenopause. Other causes include mood disorders, primary insomnia, sleep-disordered breathing, and RLS. Incidence of insomnia in peri- and postmenopause is significantly higher than in premenopause. Recent studies suggest that spontaneous awakenings in postmenopausal women are associated with luteinizing hormone pulses and elevated core body temperature.<sup>2</sup>

In the past, studies noted improved sleep in women using HT.<sup>2</sup> However, more recent studies have conflicting findings on the effect of HT on nighttime hot flashes as well as sleep disturbance.<sup>2</sup>

*Mood disorders.* Similarly, the data on HT in mood and anxiety have been conflicting. Some studies suggest that estrogen improves depression, but that the addition of progesterone worsens depression. Menopause is a risk factor for sleep-disordered breathing, possibly due to the decrease in progesterone and the redistribution of body fat in postmenopausal women.<sup>3</sup>

*RLS.* This syndrome has been associated with increased incidence of night sweats in perimenopause. In a study of 5,000 women in Sweden, the prevalence of RLS increased with age. RLS was also associated more often with disturbed sleep, depression, and heart disease.<sup>4</sup>

*Side effects from medications.* With all her health conditions and the medications this woman is taking, the side effects should be reviewed continuously when managing this postmenopausal woman with severe menopausal symptoms. For instance, both the valsartan for hypertension and the venlafaxine for anxiety

and/or depression can potentially cause insomnia. Metoprolol can increase sweating. It is interesting to note that the woman in this case is already taking venlafaxine and gabapentin, two of the more effective alternatives to HT for vasomotor symptoms.

*Conclusion.* Until further clinical trials can shed more light on the risks and benefits of initiating different forms of HT in older women, this patient was counseled not to restart HT due to her numerous risk factors. This case exemplifies the lack of knowledge about caring for older postmenopausal women. The resulting impact on her quality of life has been substantial.

**Disclosure:** Dr. Shen reports no conflicts.

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### 2009 Call for Abstracts

Don't miss the opportunity to submit your research abstracts to NAMS for presentation at the 20th Annual Meeting (September 30-October 3, 2009) in San Diego, CA.

- Submit your abstracts through the NAMS Web site:  
[www.menopause.org](http://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, 2009
- The abstract submission deadline is April 30, 2009
- 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

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