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This e-newsletter presents 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. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS. Disclosures are available on request. Oversight for this e-newsletter is by Robert A. Wild, MD, PhD, MPH, Chair-Elect, 2006-2007 NAMS Professional Education Committee. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Late-breaking news with comments by Howard N. Hodis, MD, and Richard H. Karas, MD, PhD.

Timing of start of hormone therapy may have effect on risk of coronary heart disease

Rossouw JE, Prentice RL, Manson, JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-1477. **Level of evidence: I.**

Women who initiate hormone therapy (HT) closer to menopause tend to have a reduced risk of coronary heart disease compared to women who begin treatment farther from menopause, but researchers did not find that this reduced risk was statistically significant, according to this study.

Studies examining the effects of the use of postmenopausal hormone therapy on coronary heart disease (CHD) have yielded mixed results, depending on the type of study conducted. There may be a number of reasons for the differences, including the timing of initiation of hormone therapy, according to background information in the article.

Rossouw and colleagues conducted a secondary analysis of data from the Women's Health

Initiative (WHI) trial to determine whether the effects of hormone therapy on risk of cardiovascular disease varied by age or years since menopause began. The WHI trial included 10,739 postmenopausal women who had undergone a hysterectomy who were randomized to conjugated estrogens (CE) or placebo and 16,608 postmenopausal women who had not had a hysterectomy who were randomized to CE plus medroxyprogesterone acetate (CE+MPA) or placebo. Women aged 50 to 79 years were recruited to the study from 40 US clinical centers between September 1993 and October 1998.

"Although not statistically significant, these secondary analyses suggest that the effect of hormones on CHD may be modified by years since menopause and by the presence of vasomotor symptoms, with higher risks in women who were 20 or more years since menopause (or aged 70 years or older). CHD tended to be nonsignificantly reduced by HT in younger women or women with less than 10 years since menopause, and the risk of total mortality was reduced in women aged 50 to 59 years," the authors write.

"We did not have adequate statistical power to assess outcomes in the women aged 50 to 54 years or less than 5 years since menopause. As previously reported, CE appeared to be

associated with lower risk of CHD than CE+MPA. Importantly, the risk of stroke was not influenced by years since menopause, the presence of vasomotor symptoms, or drug regimen, although there was no increased risk of stroke in women aged 50 to 59 years.”

“The absence of excess absolute risk of CHD and the suggestion of reduced total mortality in younger women offers some reassurance that hormones remain a reasonable option for the short-term treatment of menopausal symptoms, but does not necessarily imply an absence of harm over prolonged periods of hormone use. In contrast, risk of stroke did not depend on years since menopause or the presence of vasomotor symptoms. The findings are consistent with current recommendations that HT be used in the short-term for relief of moderate or severe vasomotor symptoms, but not in the longer term for prevention of cardiovascular disease,” the authors conclude.

Comment. Immediately following the initial report from the WHI in 2002¹ that daily continuous CE+MPA had no overall effect on CHD, timing of initiation of HT relative to menopause was hypothesized to account for this discordance with observational studies.^{2,3} Pathobiological evidence from nonhuman primate studies strongly supports this hypothesis.⁴

Publication of the fully adjudicated WHI CE+MPA data 1 year later indicated a trend in the reduction of CHD events in women who were randomized within 10 years of menopause relative to those women randomized 10 to 20 years and 20 years since menopause.⁵

In 2004, data published from WHI indicated that CE alone had an overall null effect on CHD but that women younger than 60 years when randomized in WHI had fewer CHD events than women aged 60 to 69 years and older than 70 years.⁶ The fully adjudicated data published from WHI in 2006 showed that certain composite CHD events were significantly reduced in the women younger than 60 years and randomized to CE therapy relative to placebo.⁷

Salpeter et al demonstrated in meta-analyses of approximately 25 clinical trials that HT significantly reduced both CHD and total mortality in women who were within 10 years of menopause or younger than 60 years when initiating HT.^{8,9}

So, what is new about the current report from WHI? Other than emphasizing the dearth of risk and reduction of CHD events and total mortality in women who initiate HT in close proximity to menopause, perhaps the most salient point is the realization that WHI is not the end-all trial concerning HT and CHD prevention but is a step in providing data for hypotheses for the next generation of trials.¹ After all, WHI, along with the cumulated data, supports the findings from observational studies that the women most likely to derive benefit from HT are young healthy women who initiate HT in close proximity to menopause for relief of menopausal symptoms, in particular, hot flashes.¹¹

Although CE alone appears to be a safer and more effective option than CE+MPA for reducing CHD and total mortality in women in close proximity to menopause or younger than 60 years, caution must be exercised in interpreting the data as the WHI trials of CE+MPA and CE alone were parallel designed trials.

The absolute event data for CE alone relative to placebo for women younger than 60 years appear quite favorable: 10 fewer CHD events, 2 fewer strokes, and 10 fewer total deaths (all per 10,000 women per year of CE therapy). In addition, WHI showed approximately 8 fewer breast cancers per 10,000 women per year of CE therapy in women younger than 60 years who were randomized to CE alone relative to placebo.¹²

The statistically significant reduction in total mortality in women younger than 60 years with the combination of CE+MPA and the CE-alone data may be the most significant finding from the current WHI report since this is the case even with all of the putative risks considered and as other potential primary prevention therapies,

including lipid-lowering therapy, do not significantly reduce total mortality in women.¹³

It is important to consider HT in perspective to other primary prevention therapies used for CHD prevention in women as the cumulated data indicate that HT used in women in close proximity to menopause or younger than 60 years is as effective and as safe as other primary prevention therapies such as lipid-lowering therapy and aspirin.¹⁴

The long-term risks of HT cannot be determined from the WHI and the supposition made by the authors of the current report that initiating HT in young women in close proximity to menopause could result in increased risk as women age is completely unsubstantiated and, in fact, contradicts the literature. For example, even though we understand that atherosclerosis may continue to progress even with lipid-lowering therapy, there is no evidence that continued lipid-lowering therapy increases events while patients age, which the authors assume may occur with HT. In fact, all available evidence indicates, and the paradigm used in prevention dictates, quite the opposite, that the earlier a prevention is initiated, the greater the long-term benefit. The WHI as well as other trials demonstrate significant trends in the reduction of CHD events with time, indicating benefit but not risk with duration of therapy.^{10,11} However, it must be recognized that HT is a different form of prevention than lipid-lowering therapy and all possibilities must be considered. This is precisely why the WHI, along with previously completed clinical trials of HT and prevention, is not the end-all study but can be used to guide the next generation of trials to address the remaining important questions concerning HT in the primary prevention of CHD and total mortality in postmenopausal women.

This was the case with design of the Early Versus Late Intervention Trial with Estradiol (ELITE) soon after WHI in 2002. Funded by the National Institute on Aging, ELITE was designed to study the effect of HT on cognition and the progression of atherosclerosis in postmenopausal women according to the timing of initiation of HT

relative to menopause.¹⁵ Another study, the Kronos Early Estrogen Prevention Study (KEEPS), will provide additional data in regards to different delivery modes of low-dose HT in young postmenopausal women. If indeed HT reduces the progression of atherosclerosis in young postmenopausal women in close proximity to menopause, larger event-driven randomized controlled trials will be mandated.

Until shown otherwise, women and practitioners alike can feel comfortable that the cumulated data indicate that HT, in particular estrogen alone, is safe and effective in reducing CHD events, stroke, and total mortality in women younger than 60 years and in close proximity to menopause.

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Comment. This most recent report from the WHI presents a reanalysis of the findings of the two WHI HT trials examining the effects of CE-alone or in combination with MPA on age, the number of years following menopause at the time of randomization, CHD events, stroke, total mortality, and a “Global Index” of health outcomes. The WHI studies were conducted to provide clinical trial evidence to further test the hypothesis, based on an array of observational data as well as animal and basic science data, that postmenopausal HT would reduce the risk of cardiovascular disease (CVD). Considerable controversy and confusion ensued when the results of the CE+MPA trial, and subsequently the CE-alone trial, did not demonstrate reductions in CVD risk and in some instances demonstrated increases in events.¹⁻³

A great deal of effort has gone into trying to develop a sufficient understanding of these apparently discrepant findings. An issue of intense focus in this discussion has become whether the timing of initiation of HT, in relation to age and/or the duration of time since menopause, alters the CVD effects of the therapy.⁴⁻⁶ Simply put, this “timing of initiation”

hypothesis states that HT may have beneficial effects early on in the atherosclerotic process but then either loses these protective effects or is associated with frank harm when HT is initiated in women with more advanced atherosclerosis. This hypothesis was based largely on animal-based experiments and on basic science data supporting potential mechanisms that could mediate these differential effects.

Initial subgroup analyses from the WHI studies were interpreted largely as not supporting the timing of initiation hypothesis. In the CE+MPA trial, no relationship between age of initiation of CE+MPA and CHD events was observed, and a trend toward a relationship between time since menopause and CHD events was reported as non-significant ($P = 0.33$).⁷ Interestingly, a report from the Nurses Health Study stated that a reanalysis of the results of the CE+MPA trial in the WHI did demonstrate a significant relationship between time since menopause and CHD ($P = 0.03$),⁸ although the details of this discrepancy were not made clear. Earlier reports from the CE-alone trial demonstrated a nonsignificant trend for an association between age and CHD effects of CE ($P = 0.06$).² Time since menopause was difficult to assess in this trial, so measures related to timing of surgical intervention in these women were analyzed, but no clear relationships were found.

The current investigation was performed to increase the power of these analyses by combining these two data sets, and to examine these relationships in more detail. The main finding from these analyses is that there were trends toward a reduced risk for CHD and total mortality in women who initiated HT at a younger age or closer to the time of menopause and an increased risk in older women and those with long-delayed onset of therapy. These trends, however, did not achieve statistical significance as defined for these analyses. The previously reported increase in risk of stroke with HT was found not to be affected by age or time since menopause.

These findings are important and contribute significantly to ongoing discussions central to our

evolving understanding regarding the effects of HT on CVD risk. The major impact of the current findings should be to help dispel some of the fear that has arisen in younger women considering use of HT for alleviation of menopausal symptoms. A very complicated dynamic developed following the publication of the results of the CE+MPA arm of the WHI. The WHI studied mainly older women, and the events recorded in the WHI were overwhelmingly representative of events in older women. Thus, in this regard, the subjects in the WHI were not very representative of younger women in clinical practice in their 50s who are initiating HT around the time of menopause. Despite this, the WHI results were generalized to these women, too, and thus the number of women in the United States using HT fell precipitously. The current findings impact directly on this situation because they support the idea that fears of cardiovascular harm in women aged 50 to 59 years were grossly overestimated. In fact, in the current analysis, there were no significant increases in risk for any of the outcomes evaluated in the women aged 50 to 59 years at randomization. This was true in the hazard ratios analysis and in the absolute risk assessment. In fact, there was a statistically significant decrease in total mortality for this cohort aged 50 to 59 years (hazard ratio [HR], 0.70; confidence interval [CI], 0.51-0.96). These findings should be very reassuring to women in this age bracket who are considering use of HT.

The subgroup analyses regarding the impact of moderate or severe menopausal symptoms are also interesting and informative. The current analysis demonstrates that there were no interactions between age or time since menopause and the cardiovascular effects of HT in women without moderate or severe menopausal symptoms. The main group demonstrating an increased risk of CHD with HT was women aged 70 to 79 years who also had moderate to severe menopausal symptoms. This observation clearly suggests that women in this category are unlikely to be candidates for HT. This observation also raises many interesting questions as to what underlying differences so strongly influence the effects of HT on CHD risk in this subgroup. But, most importantly, it is also

very reassuring for a lack of harm in the much more relevant group of younger women seeking relief from menopause-related symptoms.

While the current findings are interesting and informative, there are some important limitations of the approach that deserve comment. First, the authors have combined the results of the CE-alone and CE+MPA studies despite the fact that the populations of women studied were clearly different and had different patterns of cardiac risk. And, the interventions are also importantly different, as supported by the differences in patterns of effects on CHD, breast cancer, and other outcomes of the trials. The authors have carefully applied sophisticated statistical methods to allow them to make these comparisons, but interpretation of these results in terms of their clinical implications are difficult. Considerations for initiation of CE versus CE+MPA should not be lumped together, and each regimen should be considered on its own specific characteristics. In addition, the difficulties in assessing time since menopause in both studies is worthy of mention. As in the initial series of publications from the CE-alone arm, appropriately designating the time of menopause in a population of women who have undergone hysterectomy but have various patterns of oophorectomy, hormone use, etc, is quite difficult. Similarly, assessing the time of menopause by recall in a population of older women with or without hysterectomy also has its difficulties. Given these considerations, the associations examined between time since menopause and outcomes seem less strong than those between age and outcomes.

In summary, the current analyses demonstrate no apparent increase in risks with use of HT for any of the outcomes examined in women aged 50 to 59 years at the time of initiation of therapy. Indeed, a nonsignificant 30% reduction of all cause mortality in this age bracket is encouraging. The risks widely associated with HT appear confined to older women at the time of therapy initiation and in particular to older women with moderate to severe menopause-related symptoms—an observation worthy of further study. Overall, these findings should help reassure younger women who are considering use

of HT for appropriate indications that such use does not include an increased risk of CVD.

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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. 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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