EDITORIAL

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Keeping an Open Mind on HRT

This month, I'm going to wade headfirst into a dangerous and controversial area of medicine: Whether or not hormone replacement therapy (HRT) might be a reasonable, long-term option for postmenopausal women. Many of you are probably wondering whether I've completely lost it, because you're thinking that this issue has already been definitively, irrevocably settled by the landmark Women's Health Initiative (WHI) trial. I'll admit upfront that I can't give you any definitive answers, but I'm hoping that I may be able to persuade you that things are not nearly as cut-and-dried as you may have been led to believe.

As a self-styled (and overly opinionated) cardiovascular endocrinologist, I'm especially interested in the question of whether or not postmenopausal HRT might actually have a beneficial role in retarding the progression of atherosclerotic cardiovascular disease in older women. This, after all, is a pretty relevant question, because the numero uno cause of death in American women today is cardiovascular disease, notwithstanding the huge amount of attention and money that the breast cancer lobby has been able to attract.

Let's go back a few decades and review the standard medical practices of the 1990s, before the estrogen waters became very, very muddied. Postmenopausal estrogens were routinely prescribed in that blessedly naive era, both to treat disconcerting symptoms such as hot flushes and mood fluctuations, and also for their purported benefits to reduce the progression of cardiovascular disease. After all, a large number of observational studies, upward of 30, had all demonstrated rather convincingly that there is a very strong correlation between the use of postmenopausal HRT and a lower incidence of adverse cardiovascular events.

This made very good sense, because estrogens are very potent vasodilators, and they also increase high-density lipoprotein (Lp) cholesterol levels quite smartly (and reduce Lp(a) levels to boot). But the fundamental problem here is that these were strictly observational studies with the inherent selection biases that are part and parcel of such studies. It seems probable in retrospect that the women who were taking postmenopausal estrogens were a rather select group of health-conscious patients who were less likely to develop heart disease than were those women not on estrogens, simply because the former group was living a much healthier lifestyle with better diet, more exercise, and better medical care.

Then along came the era of controlled randomized trials in this area. The Heart and Estrogen/progestin Replacement Study (HERS) trial in the late 1990s was the first to begin to shake our faith in the value of postmenopausal HRT. This trial seemed to show that women had an increased incidence of heart attacks and other thrombotic events in the first few years after initiating HRT, compared with their counterparts who were randomized to placebo therapy. But those who looked closely at the data noted that this apparent negative effect waned dramatically in the fourth and fifth years of the study, suggesting that perhaps there was an unfortunate early effect to promote thrombotic events by revving up the coagulation machinery, but which was then followed by a counter-balancing beneficial effect of estrogens on the rate of progression of cardiovascular disease over time.

But the HERS trial was completely overshadowed several years later by WHI, a huge NIH-funded trial that aimed to provide final answers as to whether or not postmenopausal women should take HRT. The WHI was actually 2 separate studies, one of combined estrogen/progestin replacement therapy, and one of estrogen therapy alone in women who previously had a hysterectomy and, hence, had no need of the cancer protection that progestins offer in women with intact uteruses.

The combined therapy study included nearly 16,000 postmenopausal women with an average age of 63 years. Those randomized to active therapy received conjugated estrogens in a dose of 0.625 mg, along with medroxyprogesterone acetate 2.5 mg, for the planned study duration of 5 years. But the combined study was terminated early because of a modestly increased occurrence of breast cancer in the treated group. Most relevant here is that the early reports of the WHI results suggested a hazard ratio for coronary heart disease (nonfatal myocardial infarction or death due to coronary artery disease) in the treated cohort of 1.24 (24% more events than in the placebo group), a number that is not very impressive at all in the grand scheme of things.

Subsequently, more detailed analyses of the data suggested that any increase in cardiovascular risk was confined to the older (aged ≥ late 60s) women of the combined-therapy cohort.

The estrogen-only wing of the WHI continued for a while longer. Its results were not very concerning at all when it came to cardiovascular events. The hazard ratio for cardiovascular events in the treatment group was only 0.95, hardly a concerning number, since it actually hinted ever so gently at a beneficial effect of HRT on cardiovascular events. And there was a stronger suggestion of such a possible cardioprotective effect in the subset of younger women enrolled in the estrogen-only trial, those aged 50 to 59 years when they entered the study. Might it be that estrogens are actually beneficial in slowing the rapid acceleration in atherosclerosis that occurs in the early postmenopausal years, particularly in the absence of progestins, if only one can avoid the exceptionally bad luck of an early estrogen-induced thrombotic event?

Those questions are still largely unanswered, but a very interesting trial published recently aimed to reopen the question of the true effects of HRT on cardiovascular outcomes in postmenopausal women. The findings of the Kronos Early Estrogen Prevention Study (KEEPS) came out recently.[1] The lead author and lead investigator Dr. S. Mitchell Harman is a close friend of mine who served recently as my Chief of Endocrinology at the Phoenix VA and then became my interim successor as Chief of Medicine when I moved to the Greater Los Angeles VAMC because of my wife's Sjogren's-driven need for a more humid climate.

The KEEPS trial was a 4-year, randomized, double-blind, placebo-controlled trial in 727 women aged 45 to 54 years who were all newly menopausal, so that the effects of HRT could be assessed right after the onset of menopause. The KEEPS investigators hoped to demonstrate a favorable effect on cardiovascular outcomes with the administration of HRT so early on, but the trial was unfortunately too small to come up with those results. However, the trial went for its full planned duration, because there were absolutely no harmful effects seen with either oral conjugated estrogen therapy or with transdermal estrogen therapy, each of which was given together with oral progesterone.

There was a trend toward a slower increase in coronary artery calcium (CAC) scores in the minority of women who had elevated scores to begin with. But overall there was no difference in the rate of progression of either CAC scores or of carotid intima-media thickness as measured by ultrasound; the latter is a standard research measure used to detect subtle differences in the rate of progression of cardiovascular disease. A pessimist would observe quite correctly that estrogens did not show a protective effect on cardiovascular outcomes, apart from the hint of a slower rate of progression of CAC scores in those with elevated levels at the onset. But an optimist would say that these results demonstrate the cardiovascular safety of early postmenopausal HRT, since there was no signal at all of a harmful effect.

So where does this leave us now? Unfortunately, we are completely bereft of definitive answers, and we are unlikely to get meaningful new data anytime soon, as there is currently zero enthusiasm at the NIH for devoting scarce resources to a re-examination of these same issues.

The bottom line is that we can agree that cardiovascular worries need to be put into proper perspective and that they have been overblown, at least in the lay press. I further believe that younger postmenopausal women who have solid indications for such therapy, be they hot flushes or advanced osteoporosis, should not be denied the benefits of HRT because of cardiovascular concerns.

I would be willing to consider long-term open-ended therapy in at least some of these patients. And let's also not forget that estrogens clearly reduce the incidence of colon cancer and may well reduce the prevalence of the much-dreaded Alzheimer disease that awaits many older women.

I'll be the first to acknowledge that this editorial is ending with not a bang, but a whimper. But that's about the best I can come up with given the extremely severe limitations of the data available to us. I'll consider this editorial a success if it encourages you to at least keep an open mind on the issue of the cardiovascular effects of estrogens and to accept my premise that we still lack so much of the data we truly need to reach definitive conclusions. ●

Author disclosures

The author reports no actual or potential conflicts of interest with regard to this article.

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REFERENCE

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