



Journal News and Commentary

Notes From Cardiology Clinic: Woman, Lost During Follow-up

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The **Heart Estrogen Replacement Study (HERS)** was the first large clinical trial to assess in postmenopausal women whether estrogen with progesterone, or estrogen alone in women without a uterus, reduced cardiovascular (CV) events.¹ HERS was a secondary prevention trial, but it was quickly followed by the **Women's Health Initiative (WHI)**, for primary prevention.² There were those who thought that these studies were unethical, because observational cohort studies had consistently shown that hormone replacement therapy (HRT) not only reduced CV events,³ but also bestowed other benefits, including protection against osteoporosis and dementia.⁴ HRT improved surrogate CV outcomes such as lipoprotein levels and endothelial function.⁵

She was one of the first patients that we recruited into HERS at our site in Hartford, Connecticut. She arrived fashionably but conservatively dressed, self-confident, and outgoing. "I told my cardiologist that he must refer me for your trial. Women have been left out of research studies for too long. I want to do this for my daughter, and my grandchildren too if I ever have any!" She was 67 years old, a senior executive at a major insurance company, and was used to being in charge. In addition to her job she worked as a volunteer at Hands on Hartford, a food bank, and was a fundraiser for the hospital. She had had a coronary angioplasty 3 years before, but had no other relevant history. Her CV risk factors were controlled, she exercised regularly, and she followed a near-vegetarian diet.

When I get to the very end of taking a history from a new patient, after inquiring about work, and how they spend their time, I usually ask "What do you do for fun?" I have found that this question often provides me with useful insight into what makes my patient tick. Often I hear back a rueful "I don't have fun any more!" To which the follow-up question is "What did you used to do for fun?" And then the patient might turn to the spouse and say wistfully "Remember the summer when the kids were in high school and we took them camping in Algonquin Park?" Or something.

I asked her.

"I masturbate," she said, and explained: "My husband died several years ago, and I found that I really miss physical contact. I have a friend now, and we get along quite well, but he doesn't like to be touched. He was hospitalized recently, and I was standing at his bedside. I wanted to reach out and hug him, or at least hold his hand, but I didn't."

The HERS steering committee, consisting of the study leadership and the principal investigator from each of the 20 clinical sites, met at the end of the study for the unveiling of the results. As with any trial, everyone hoped that the treatment would prove to be beneficial. Additionally, many of the steering committee members had spent a significant part of their career studying HRT. Even beyond that, HRT was different from an ordinary drug; along with the trial participants, many believed that this could be a treatment unique to women, perhaps to partially compensate for past neglect. After all, it was called HERS.

The results? Overall HRT had no effect on the primary end point, nonfatal myocardial infarction or coronary heart disease death, despite an 11% lower low-density lipoprotein cholesterol and 10% higher high-density lipoprotein cholesterol in the HRT group. Despite the lack of effect overall, there was a statistically significant *increase* in the primary end point in the HRT group during the first year, and a significant decrease in these CV events during years 4 and 5. Because of this potential late benefit, follow-up was continued, with women who had been taking HRT requested to continue it, and women who had been taking placebo cautioned to avoid it, because of the increased risk during the first year.

I saw my patient for the last time at her 6-year visit. Medically, not much had changed. She had experienced 2 mini-strokes that had left no obvious damage, and she had no recurrence of coronary symptoms. She had retired from her job. She didn't drive much any more, and her daughter accompanied her. She looked different compared with her first visit; she was casually dressed with no make-up, and her hair was now its natural grey colour. She acted differently as well; the vivacity was gone, she moved slowly, and answered questions as if they were a burden. I noticed an antidepressant among her list of medications. I asked about her friend. "He has been sick a lot lately. I don't see him much any more."

The saddest feature of HERS was the downward course that so many women followed. Few had major CV events, and

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hardly any died, but cancers, fractures, and other medical events were common. Many were widowed during follow-up, and others shouldered important caregiver roles as husbands and other family members developed chronic illnesses. Many worked well beyond retirement age because of financial necessity. Grandmothers were conscripted to act as mothers because their children could not. These outcomes had nothing to do with HRT. My patient, cushioned financially and with a supportive family, was far from the worst off.

Even with the robust social safety net available in Canada, the numbers are stacked against older women. Women marry on average men who are 2 years older, and live on average 4.3 years longer (men 79.3, women 83.6 years) (Statistics Canada 2016: <https://www150.statcan.gc.ca/n1/pub/89-503-x/2015001/article/14316-eng.htm>). As a consequence, 62.7% of women are part of a couple in their late 60s, but only 10.4% are by age 85 or older; the corresponding statistics for men are 77.9% and 46.2% (Statistics Canada 2016). Because women earn less during their careers than men, and because they are more likely to leave the workforce to have children, they have accumulated less wealth and are more likely to live in poverty in old age.

Medically, more than one-third of Canadian women aged 65 and older report that they are usually in pain, compared with approximately one-quarter of men (Statistics Canada 2016). Half of the women in this age group suffer from hypertension. Cardiac conditions that are difficult to treat, such as heart failure with preserved systolic function, Takotsubo cardiomyopathy, and spontaneous coronary artery dissection, are far more common in women than in men.

At the end of her last appointment, my patient and her daughter thanked me for having looked after her. I again

expressed my regrets that HRT did not have a benefit for women like her. I shook the daughter's hand. I turned to my patient. I resisted an impulse to reach out and hug her. I shook her hand and said good-bye, knowing that really, she had already departed, gradually, over the years.

Disclosures

The authors have no conflicts of interest to disclose.

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