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Hormone Replacement Therapy and Cardiac Prevention

To the Editor:

The consensus statement by Mosca et al1 that was recently published in Circulation should be applauded because it shows that researchers finally realize that women have unique cardiovascular needs. Despite this praise, I do have concerns regarding their overgeneralization of the Heart and Estrogen/Progesterone Replacement Study (HERS) trial2 and their stance on hormone replacement therapy (HRT) for the prevention of coronary disease. I was disappointed that the position on HRT was not stronger.

After a critical review of the literature, there are several reasons why I think this should be the case. First, one must delineate primary versus secondary prevention when addressing the HRT issue because the pathophysiology is likely different. In women with established coronary disease, events occur from antecedent atherosclerotic plaque rupture and thrombus formation. In those without established coronary disease, however, the turning point in disease progression is the development (rather than the rupture, or thrombosis) of the atherosclerotic plaque. This plaque development is multifactorial and partially related to endothelial dysfunction and the establishment of lipids within the arterial wall. Although the data are nonrandomized, much exists3 that suggests a benefit of HRT in women without established coronary disease via a reduction in cardiac events and death due to coronary heart disease (enough to support a class B recommendation according to the Canadian Task Force on Preventative Health Care grading system).

Additionally, one must be cautious when extrapolating results from the HERS trial to all women with established coronary disease. Although the authors were correct in stating the cohort was undertreated with respect to lipid-lowering4 (which is a major problem in itself in treating female cardiac patients), >80% of the HERS study group had revascularization within 6 months of entry into the trial. This high rate of revascularization is likely reflected in the low event rate in both the placebo and treatment arms of the HERS trial. The majority of female patients with established coronary disease (at least in a conservative country such as Canada) are not treated with revascularization. Unfortunately, the role of HRT in the female patient will remain contentious. I hope that doctors do not dismiss the role of HRT in the secondary prevention of coronary disease. Until further data are available, I think HRT should be recommended for primary prevention.

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Response

We agree with Dr Abramson that the results of the Heart and Estrogen/Progesterone Replacement Study (HERS) should not be overgeneralized. However, we do not agree that current data support a stronger recommendation for the use of hormone replacement therapy (HRT) for either the primary or secondary prevention of cardiovascular disease (CVD). We acknowledged in our consensus statement that the results of HERS may not apply to women without vascular disease or who are on other hormone regimens (such as progestins other than medroxyprogesterone acetate or unopposed estrogen). Although the rate of coronary revascularization is substantially higher in the United States compared with Canada, this has not been associated with improved 1-year survival. Moreover, it is unknown if revascularization would modify the relation between HRT and coronary events.

The potential for HRT to reduce CVD in some women exists; however, there is also potential for harm. As we pointed out, although there was an overall null result at the conclusion of the study, there was a significant increase in CVD events in women treated with combination HRT in year 1 of HERS. Currently, there are no definitive criteria to determine which women may be susceptible to early adverse effects associated with HRT. Therefore, we stated that, at present, the initiation of HRT in the setting of secondary prevention is not clearly indicated (but it can be continued if a women has done well with ongoing therapy).

Although we acknowledge that the pathophysiology of CVD is likely different in the setting of primary versus secondary prevention, we submit that this categorization is an oversimplification because many older women have unrecognized CVD, making the distinction difficult. The basis for not making a stronger recommendation in primary prevention is the absence of available data from randomized clinical trials to test the benefits and risks of HRT in this population. The role of HRT in primary prevention is supported by observational epidemiologic studies; however, until data from rigorously designed studies such as the Women’s Health Initiative5 and the European Women’s International Study of Long Duration Oestrogen After Menopause (WISDOM)4 are available, we think that it would be inappropriate to make a strong recommendation for or against the use of HRT for primary prevention. In the interim, because HRT has other benefits and side effects, we think the recommendation to individualize the decision is justified.

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