Hormone Replacement Therapy and Cardiovascular Disease: A Statement for Healthcare Professionals From the American Heart Association

To the Editor:

I was personally disturbed by the American Heart Association (AHA) statement on hormone therapy and cardiovascular disease that recently was published in Circulation.1 Two different medical journals, Climacteric2 and Maturitas,3 recently published a position paper from the Workshop on Controversial Issues in Climacteric Medicine: Hormone Replacement Therapy (HRT) and Cardiovascular Diseases, which was organized in October 2000 by the International Menopause Society (IMS). All persons interested in the health care of postmenopausal women should read it. Menopause experts, including internists and cardiologists, see the cardiovascular issue from a perspective different from that of American cardiologists, although they are interpreting the same database and research articles and, ultimately, are reaching similar conclusions. The authors of the AHA statement report that the biological basis of estrogen benefits the cardiovascular apparatus and mention epidemiological data showing a 35% reduction of cardiovascular events in normal women using hormones after menopause. However, their conclusions and final messages are different, referring mainly to the secondary prevention trial named the Heart and Estrogen Progestin Replacement Study (HERS). The term HRT, as it is used in the article, includes treatment with estrogen alone or in combination with different progestins and using different schedules of administration. At the end of the article, the authors say that their conclusions are based primarily on a fixed dose of oral conjugated estrogens combined with medroxyprogesterone acetate. In the past, we used to recommend a “gold-standard” dose for all women and all indications. Today, we recognize that even healthy menopausal women in their fifties need individualized therapies (in terms of substances, doses, and schedules), given the heterogeneous nature of disorders related to menopause.

In the HERS study, elderly and obese women affected by heart disease were treated with doses of hormones that were studied and intended for healthier women who were at least 15 years younger. For this and other reasons, HERS cannot be seen as a landmark study, as reviewed by an European Expert Panel.4 Younger. For this and other reasons, HERS cannot be seen as a landmark study, as reviewed by an European Expert Panel.4

I object to the conclusions of the editorial by Mosca et al.1 My main objection is the tendency to lump together all forms of hormone replacement therapy (HRT) as if they all had the same effects on the female body.

I have used cyclic-sequential HRT (specifically, Premarin 1.25 mg daily for days 1 to 25 of the month and Provera 10 mg daily for days 13 to 25 of the month) since the early 1980s in management of the dyslipidemia of the menopause. I never have prescribed continuous combined HRT (eg, Prempro) because I consider it unphysiological. One of my patients was prescribed Prempro by her local physician’s medical assistants, and she developed a massive stroke within 9 months.2 She had none of the standard risk factors for stroke. Indeed, in my HRT clinic, only one woman developed a (minor) stroke while taking cyclic-sequential HRT, and she was smoking cigarettes at the time. She since has quit smoking and continues to take HRT without sequelae. Cyclic-sequential and continuous combined HRT are vastly different regimens, at least as far as procoagulant activity is concerned.

I would also point out that the effect of HRT on lipids is dose dependent. The regimen I have used has much greater effects on LDL-cholesterol lowering, and although HDL-cholesterol rises only a bit, at least it does not fall. The continuous combined regimen used in the Hormone Estrogen/Progestin Replacement Study and the Estrogen Replacement and Atherosclerosis Study would never be expected to duplicate the effect of the cyclic-sequential HRT regimen I use. This point is not insignificant because failure to achieve a desired result would not be unusual when an inadequate dose of medication is used.

Dr Genazzani raises questions about the process for the American Heart Association (AHA) Advisory on Hormone Replacement Therapy (HRT). The AHA Scientific Statement1 included a rigorous process of nomination of a panel of experts by 3 distinct AHA scientific committees and required expert peer review with written responses to comments. The revised manuscript was reviewed by the AHA Science Advisory and Coordinating Committee and received a unanimous vote of approval. This process ensured that the paper was balanced and reflective of the position of the organization rather than of individuals. We are surprised that Dr Genazzani concludes that we have interpreted data differently than the International Menopause Society (IMS) summary workshop paper. Some authors of the AHA

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Response

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Advisory also participated in the IMS workshop, and the conclusions generally are consistent. We disagree that no new relevant information became available after the IMS workshop in 2000. We cite 2 important randomized, controlled clinical trials, the results of which became available in 2001. One showed no effect of 17-β estradiol on the progression of carotid intimal-medial thickness with or without a progestin. Another showed that among women with coronary heart disease (CHD), 17-β estradiol with or without a progestin was not effective for preventing stroke or death and was associated with a 61% nonsignificant increase in fatal strokes. These data were also considered when writing the AHA Advisory. Subsequently, the Women’s Health Initiative announced that there was a nonsignificant excess of cardiovascular events in the hormone-treated groups compared with placebo after 3 years, and the trial is ongoing.

We agree with both Drs Feeman and Genazzani that all forms of HRT should not be lumped together. Thus, we included a footnote to the Advisory acknowledging that the majority of data available for clinical recommendations are based on standard dosing of conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA). We defined hormone replacement therapy (HRT) and estrogen replacement therapy (ERT) in the opening paragraph and used the terms in the appropriate context throughout the text, with the caveat above. Despite the considerable clinical experience of both Drs Feeman and Genazzani, clinical trial evidence remains insufficient to assert that other HRT regimens have a more favorable impact on cardiovascular disease. If such data become available, the AHA will update its recommendations.

We remain hopeful that ERT/HRT will prove beneficial for the primary prevention of CHD. However, as stated in a recent editorial, “Until better evidence is available, the cautious stance taken [by the AHA] seems eminently reasonable.”

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