
Roundtable: Estrogen as a Cardioprotective Agent?

Conflicting information from existing studies has left little choice but to await results of several prominent randomized clinical trials examining the effects of estrogen on the cardiovascular system. Will these trials provide needed answers, or is the wait in vain? Three top experts discuss and debate the key issues.

Last July, the American Heart Association (AHA) reversed its previous position by saying HRT should not be prescribed to healthy women solely to prevent future cardiovascular disease. The AHA also now says women should not initiate the therapy if they have a history of myocardial infarction, but it does not go so far as to recommend stopping the therapy for women with existing

disease who are already taking it. This decision came as a surprise to some, but was similar to the position taken in late 2000 by the International Menopause Society.

Compelling data from the Heart and Estrogen/progestin Replacement Study (HERS) trial show a 52% increase in the risk of heart attack in the first year on HRT among women with existing heart disease. A possible decrease in risk was seen only after women had been on the therapy for two years or more.

The results of several large trials are still to come, including the much-anticipated Women's Health Initiative (WHI), which will not be completed until 2005. Some believe that trial will help answer lingering questions about the benefits of HRT on the heart for healthy women, as well as provide better direction for women who want to continue or resume HRT for quality-of-life reasons. Others think the WHI and trials like it will yield few truly insightful answers and are calling for additional trials that include younger populations of women.

It is well understood that this issue is a vital one for women and their physicians. To obtain more insight into the debate, *Menopause Management* asked three experts to respond to questions regarding what is known about the cardioprotective effects of HRT and what the future holds.

Based on the available basic science literature, is there reasonable evidence to suggest a relationship between estrogen and vascular health and function?

Dr. Wenger: There is conflicting information regarding biologically plausible benefits, and because there are both favorable and unfavorable changes documented, we need randomized clinical outcome trial data. Some aspects show benefit and some do not. One of the things we've learned is that biologic plausibility does not mean benefit. Biologic plausibility simply gives you a hypothesis that you must test in a clinical trial, and what we need now are clinical trial data.

Dr. Grodstein: I would say the current evidence is largely positive but does not constitute absolute proof. And there are some negatives, such as estrogen's effect on coagulation factors, as well as on C-reactive protein. Everything else looks positive in terms of vascular reactivity and cholesterol levels. I think the cholesterol studies that have been done to date are beyond definitive in terms of a positive effect [in HERS, LDL was decreased by 11% and HDL was increased by 10% in the group on HRT].

Participants

Nanette K. Wenger, MD

Professor of Medicine (Cardiology), Emory University School of Medicine; Chief of Cardiology, Grady Memorial Hospital; and Consultant, Emory Heart & Vascular Center, Atlanta.

Francine Grodstein, PhD

Assistant Professor of Medicine, Harvard Medical School; Associate Epidemiologist, Department of Medicine, Brigham & Women's Hospital, Boston.

Thomas B. Clarkson, DVM

Professor of Comparative Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

Dr. Clarkson: The answer is absolutely yes, but one must begin to be more thoughtful in terms of how one interprets the available data. For example, we have re-examined data from monkeys showing that if you intervene early—in the late perimenopausal transition and in the early postmenopausal years—there is a very large inhibitory effect on the progression of coronary artery atherosclerosis, the order of magnitude being about 70% inhibition. On the other hand, if you wait until animals have been estrogen deprived for 2 years, which would be comparable to 6 years of patient experience, the inhibitory effect of estrogen replacement therapy then drops to zero. So the robustness, based on the experimental data, depends on early intervention and what we call primary prevention at the vascular level. Our best estimate would be that the most powerful effects of estrogen therapy will be seen starting with the onset of estrogen deprivation in the perimenopausal transition and continuing through age 55 to 60 years.

What are the strengths and weaknesses of the clinical evidence with regard to the relationship between estrogen and vascular health?

Dr. Wenger: The data are conflicting, and we hope trials now under way will give us better information. A large primary prevention trial, The Women's Health Initiative in the United States, and a comparable trial in the U.K., called WISDOM, are under way. Those two trials should hopefully give us the clinical trial information we need, but at present we are still waiting for those data. To date, the totality of clinical trial evidence does not show cardiac or stroke benefit, but potential increased risk.

Dr. Grodstein: With regard to the overall picture, it really depends on whether you're talking about primary prevention or secondary prevention. The existing primary prevention data at this

point, in terms of clinical endpoints, are purely observational, and those all indicate a decreased risk of heart disease, a modest increase in the risk of stroke and an important increase in the risk of deep vein thrombosis.

The clinical trials and the observational studies, in terms of clinical endpoints of secondary prevention, are also quite consistent in indicating a short-term increase in the risk of recurrent heart disease, as well as a longer-term decrease.

The secondary prevention studies of stroke don't indicate any benefits. The clinical trials indicate a modest increase overall in the risk of stroke and an increase in pulmonary embolism.

Dr. Clarkson: To a vascular biologist, primary prevention is inhibition of the progression of coronary artery atherosclerosis by preventing minimal-sized plaques in younger women from becoming larger plaques. That's what estrogen seems to do exquisitely well, based on all the available evidence. Cardiologists use the term "primary prevention" to refer to preventing progression in women who are 65 years of age or older and who have complicated plaques in the coronary arteries. The literature is pretty solid as far as showing that if you start with these older women who have complicated lesions and who haven't had ERT, it is likely that instituting ERT will have a deleterious effect.

We all believe, based on observational data and based on animal data, however, that estrogen will have this powerful primary prevention effect if initiated early. For that, we have no clinical trial data. I believe we are waiting on those data mistakenly. In the Women's Health Initiative, for example, the average age is 64 years. That trial is going to provide some evidence about primary prevention as defined by cardiologists, but it is not going to provide any useful information about primary prevention as vascular biologists define it. There is an urgent need

for trials that initiate some form of estrogen replacement, such as the birth-control pill, during the perimenopausal transition. These women would then immediately switch over to HRT as part of what is commonly referred to these days as the "hormone continuum." It's absolutely urgent that we plan and undertake such trials if we are ever going to get the answers we really need.

Is there reasonable evidence that estrogen can potentially prevent the development of heart disease?

Dr. Wenger: At this time, no. We hope the clinical trials will provide us with this, but at this time there is no "evidence" to suggest that estrogen is a reasonable agent to give to prevent coronary disease or stroke, or a recurrent clinical event.

Dr. Grodstein: The data that exist and have been published are quite consistent with regard to decreases in major coronary heart disease events with estrogen use. We'll have to wait a few more years to see the results of additional studies, such as the Women's Health Initiative in the United States and WISDOM in the U.K.

Dr. Clarkson: The answer is yes, if initiated early. I think physicians should make every effort to educate their patients about the benefit of early initiation and endeavor to make it happen as often as possible.

When confronted with women who are 65 and older, I think we need to let them know there is no evidence that it will be beneficial and there is evidence that it may even be deleterious.

Is there reasonable evidence that a mechanism exists whereby estrogen may play a role in reversing existing coronary heart disease?

Dr. Wenger: The recommendations

are that we not start hormones for women with existing coronary disease because of the potential early risk. It is inappropriate to tell women that if they survive the first years they'll do better in the long run on HRT, because the data don't support that idea. We need more precise data about the presence and/or magnitude of the early risk.

Dr. Grodstein: I don't think there is substantial evidence. Five years ago we would have said women at high risk of an event, which clearly are the women who have already had one event, are the best candidates. But that was never based on any data. It was based on what made sense at the time.

Dr. Clarkson: The answer to that is no. There are mechanistic explanations whereby estrogen may worsen existing disease, so I would say there is no good evidence that it is worth trying, and very good evidence, based on the available data, that it should not be tried.

Does any of the epidemiologic evidence suggest a role for estrogen in the primary prevention of coronary heart disease?

Dr. Wenger: No, but remember, we have so much evidence for other interventions for preventing coronary disease, and certainly those should be applied: smoking cessation, weight control, healthy diet, physical activity and pharmacologic control of lipids and blood pressure, if needed. The coming trials will, we hope, answer the question, "Is HRT a component of preventive benefits?" HRT doesn't obviate all the other approaches that have been suggested. In women already taking statins, for example, we don't know what the preventive benefit of estrogen might be. We have to examine the balance of benefits versus risks. That's the information we are ultimately after.

Dr. Grodstein: I've always felt that

the most important thing we should address is lifestyle modification. We did an analysis in the Nurses' Health Study, where we looked at women who solely practiced a moderate lifestyle. They maintained a relatively good diet, didn't smoke cigarettes, walked for half an hour a day and drank an average of one glass of alcohol per day. We found that if we could get all women to do those very basic, very simple lifestyle practices and not even think about hormone therapy, we could eliminate 80 to 90% of heart disease.

Those exact same practices are good for your bones. They're good for everything, so I would much rather see women improve their lifestyle, even in the most moderate way, and maintain their health that way without having to worry about "Is estrogen good for me?" or "Is estrogen bad for me?" There are a lot of risks and benefits to be weighed.

Dr. Clarkson: All of the observational data would support a role for estrogen. These data are all consistent, and there is probably no better source of information than the Nurses' Health Study. Diet and exercise are certainly wonderful lifestyle changes to have people make, as is stopping smoking. However, our monkey data suggest that women need a reasonable plasma estradiol concentration. We don't know for sure what that is, but it's somewhere around 40 to 50 pg/mL of estradiol in order for good lifestyle changes to even be able to express themselves in a favorable way. For women who are down around 5 to 10 pg/mL of estradiol, our data would suggest that they will not see benefit to their heart from lifestyle changes alone without getting that estradiol concentration up a little higher.

The Nurses' Health Study estimate of an 80 to 90% reduction in heart disease from lifestyle changes alone is a mathematical estimation, based on their data, that is not well supported by our understanding of experimental pathology. Carefully done primate studies do not support that contention.

Would you recommend that a postmenopausal woman who is already taking HRT and has no established disease, but does have a recognized risk factor, continue HRT primarily for protection against a coronary event?

Dr. Wenger: For the woman who is already on HRT, patient preference and noncardiovascular benefits and risks should be weighed in that decision. We do not have the answers to be able to tell a woman that she should or should not continue HRT primarily for the cardiovascular benefit.

Dr. Grodstein: It really does depend on many other things, including whether the woman likes taking estrogen. You have to consider whether she is having side effects and maybe has been sticking with it only because she thinks it will prevent heart disease. Even if she makes the decision to continue based only on a desire to prevent future coronary disease, she might be putting herself at risk of breast cancer in the long term.

For each individual woman there are so many different things that factor into this decision. And again, I would think this is a situation where it can't hurt to talk to her about lifestyle modification. I'd much rather see her choosing this option rather than choosing estrogen primarily for prevention. If you can get her to start exercising, this is something that is going to have great benefits on her heart and her bones.

Dr. Clarkson: All the experimental evidence would support that she should continue, but it would depend on her other risk factors and preferences.

The other thing to keep in mind is that for women at high risk who are already taking statins, the evidence is clear that statin drugs have favorable interactions with HRT, so it makes sense to stay on the hormones. For surrogate risk factors, the published evidence is abundantly clear

in showing beneficial effects of combining the two. As far as outcome data, David Herrington has published on a subset of women in the HERS trial who were taking statins. According to those published data, statin therapy negated any adverse effects of HRT.

I think most everyone agrees with that line of thinking, and if we could then get those same women to make positive lifestyle changes in addition to taking statins and HRT, I think that would be a very positive thing. ■

Suggested Reading

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