

Heart Disease in Women Where do we stand?

Thomas Dayspring MD, FACP

Atherothrombotic disease is the number one cause of morbidity and mortality in American women. Real progress in both our understanding and making therapeutic progress in women began in the mid 1990s, as randomized clinical trial data started to emerge. Many of our previous beliefs and paradigms based on men's data or observational trials of women have had to undergo radical rethinking.

Prior to 1998, estrogen was a standard part of prevention regimens. However, current guidelines from the American Heart Association, American College of Cardiology and the National Cholesterol Education Program have refocused our efforts on how to accurately assess risk and to prevent and treat atherosclerosis with evidence based therapies. All of the organizations have removed estrogen from the list of therapeutic modalities which should be used for cardioprotection.

There is now data available from multiple large and small randomized controlled trials looking at CV outcomes and plaque prevention or stabilization and estrogen (unopposed) has been successful in only one carotid plaque study. These trials included both secondary and primary prevention settings. Data from the giant Women's Health Initiative, looking at over 27,000 postmenopausal women has failed to detect any cardioprotection and has identified a small trend towards adversity in the EPT group. In contrast other therapies such as statins, fibrinolytics, ACE inhibitors, platelet drugs have all demonstrated an ability to improve CV outcomes and/or plaque in women.

It is now recognized that atherothrombosis is a chronic inflammatory disease of the arteries that begins very early in life and causes clinical events in adulthood. It is rupture of nonocclusive plaques, which generates an arterial thrombus that causes most of the morbidity and mortality of CVD. Therapies that stabilize the plaque have been successful in improving outcomes. There are many abnormalities that lead to endothelial dysfunction or inflammation, including lipoprotein, coagulation, renin-angiotensin, homocysteine as well as other disorders. The high sensitivity C-reactive protein has emerged as the most readily available and reproducible diagnostic tool to indicate the presence of endothelial inflammation and to help assess CV risk is present. Researchers have identified therapies that reduce C-reactive protein and also identified oral estrogen as an agent capable of aggravating CRP levels.

New insights into lipid biology have identified lipoproteins, which transport the lipids (cholesterol and TG) as the major players in plaque etiology and inflammation. The concentrations and sizes of VLDL, IDL, LDL and HDL are culprits in initiating and worsening arterial plaque. Removing atherogenic lipoproteins or modifying them into non-atherogenic particles is emerging as a very effective strategy. Triglycerides and HDL-C, through their influence on lipoprotein concentrations, particle composition, particle size, and relationship to insulin resistance have emerged as significant predictors of risk in women.

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Understanding coagulation, inflammation, genetics, and lipoprotein biology also is providing insights into both the efficacy of combination standard lipid drug therapies as well as the complexities of estrogens' or selective estrogen receptor modulators (SERMs) effect on the vasculature. Such insights also provide plausible mechanisms as to why different estrogens, progestogens and SERMs and their routes of administration may have widely varying CV effects and safety. The timing of estrogen therapy with respect to earlier versus later in menopause is emerging as critical to vascular response.

If we are to begin to make real progress in the battle against CVD in women, we must identify risk using our new diagnostic tools, much earlier in life and become extremely aggressive in our therapies including lifestyle and pharmacologic strategies. We also need to fine tune who estrogen will or will not benefit.