

Cardiovascular Health in Women: Current Trends, New Findings

Women experience coronary artery disease (CAD) approximately 10 years later than men, but the gender advantage ends there. By a number of parameters, women tend to have poorer outcomes, speakers said at several sessions devoted to women and CAD.

Women with stable coronary disease have better survival than men. In contrast, outcomes after an acute myocardial infarction (MI) are worse in women, with higher mortality rates during hospitalization at 30 days and at 1 year and more nonfatal complications including recurrent MIs, said Leslee Shaw, MD, Emory University, Atlanta, GA.

Poorer outcomes in acute coronary syndromes (ACS) may be the result of differences in characteristics at presentation, underlying biology, and treatment bias. On average, women tend to be older at the onset of ACS; have more diabetes and hypertension; present with more atypical symptoms, thus delaying therapeutic interventions; and are more likely to have nonspecific or nontraditional biomarker patterns (more frequent T wave inversions and normal troponin levels, but higher levels of brain natriuretic peptide and C-reactive protein). On angiography, women typically have more nonobstructive CAD and less severe and less extensive obstructive disease. They also tend to have smaller and less severe infarcts, and preserved systolic function, yet more heart failure, Dr. Shaw said.

Carl Pepine, MD, University of Florida, Gainesville, FL, described how traditional risk factors and also conditions unique to women may contribute to their risks (Table 1).

Table 1. Preclinical Conditions Leading to More Severe or Different Forms of Vascular Disease.

<ul style="list-style-type: none"> • Traditional RFs (among women vs men) <ul style="list-style-type: none"> • More • More clustering • Greater magnitude • Conditions Unique to women <ul style="list-style-type: none"> • Age of menopause, HRT • Polycystic ovary syndrome (PCOS) • Hypoestrogenemia of hypothalamic origin • Hypertensive disorders of pregnancy • Gestational diabetes • Peripartum coronary or aortic root dissection • Delivering a “thin baby” etc. <p style="text-align: right; font-size: small;">Pepine et al. JACC Feb 2006.</p>
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Dr. Pepine maintained that vascular biology of atherosclerosis may be affected by gender-related (eg, hormone-mediated) issues, leading to differences in clinical presentation and outcomes (Table 2). “A host of features support a hypercoagulable and prothrombotic state in women,” he said.

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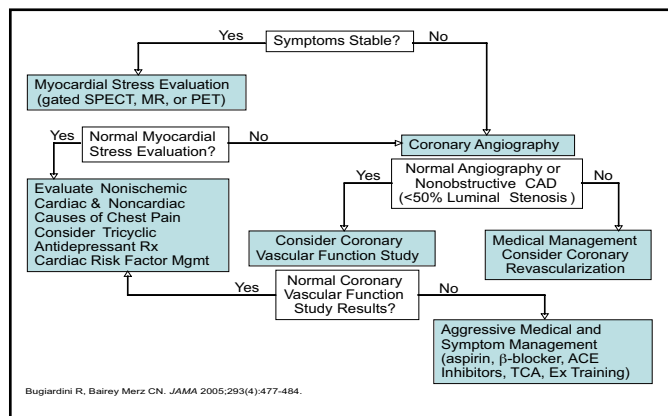
Table 2. Coronary Vascular Conditions Leading to More Severe or Different Forms of Vascular Disease.

<p>•Structural findings (among women vs men)</p> <ul style="list-style-type: none"> •Macro- and Microvessels <ul style="list-style-type: none"> •Smaller size •Increased stiffness (fibrosis, remodeling, etc) •More diffuse disease, erosion >rupture •Rarefaction (drop out), disarray, microemboli, etc •Microvessels of atheroma and myocardium <p>•Functional findings</p> <ul style="list-style-type: none"> •Macro- and Microvessels <ul style="list-style-type: none"> •Endothelial dysfunction •Smooth muscle dysfunction (Raynaud's, migraine, CAS) •Vasculitis (Takayasu's, rheumatoid, SLE, CNSV, giant cell, etc) •Immune disorders (myasthenia, etc) <p style="text-align: right;">Pepine et al. JACC Feb 2006.</p>

The tendency for women to have normal or nonobstructive coronary disease in ACS contributes to the lack of perception of risk after the acute event. In an analysis of patients with nonobstructive CAD in three major trials (Bugiardini R et al. *Arch Int Med* 2006;166:1391-1395), patients with non-ST-segment elevation ACS had a 12% risk for a cardiac event through 1 year. Patients with mild disease versus those with normal angiographic findings had worse outcomes. The combined endpoint of death, MI, revascularization, or unstable angina was reached by 15.1% in the mild disease group versus 9.4% in patients with normal coronaries (p=0.05), she noted.

Women with nonobstructive disease, therefore, should be carefully assessed for the extent of atherosclerosis and coronary vascular function so that their true cardiovascular risk can be defined and the disease intensively managed, Dr. Shaw said (Figure 1).

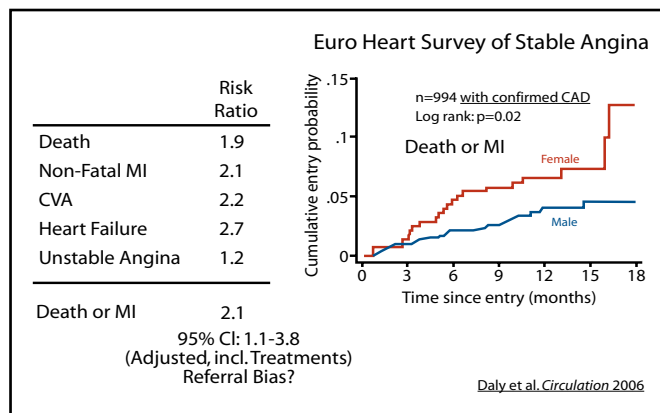
Figure 1. Management of Patients with Nonobstructive CAD.



Viola Vaccarino, MD, PhD, Emory University, Atlanta, GA, reiterated that because risk is perceived to be lower in women, a “higher risk burden” is required for diagnosis and therapy. “This leads to referral bias; to patients being sicker when diagnosed, hospitalized, and treated; and to less preventive treatment,” she said.

While MI is the most common initial manifestation of CAD in men, for women it is uncomplicated angina. Lower utilization of noninvasive diagnostic tests for angina in women can translate to delayed or absent treatment, disease progression, and worse outcomes. In the European Heart Survey of Stable Angina (Daly C et al. *Circulation* 2006;113:490-98), women were 14% less likely to be referred for angiography, 30% less likely to undergo revascularization, and significantly less likely to be put on antiplatelet therapy, statins, and beta blockers (p<0.001). This less aggressive therapy resulted in poorer outcomes and an increased risk of death or MI (p=0.02; Figure 2).

Figure 2. Clinical Course of Angina with Confirmed CAD, Women vs Men.



Effect of Estrogen

Estrogen is thought to be cardioprotective, based largely on the fact that women develop ischemic heart disease predominantly after menopause, but there are several biological reasons as well, according to Dr. Pepine. Estrogen interacts at the endothelial cell level to reduce reactive oxygen species, increase nitric oxide, relax vascular smooth muscle, suppress inflammation, and inhibit vascular smooth muscle cell proliferation.

The cardioprotective benefits of estrogen replacement therapy, however, have been difficult to prove. Jacques E. Rossouw, MD, National Heart, Lung, and Blood Institute (NHLBI), Bethesda, MD, reviewed current concepts about hormone therapy (HT) and CAD, concluding that “the most realistic way to view HT is

that it has a narrow therapeutic range compared to other prevention strategies.” Maximum benefit (and least harm) is likely to occur with short-term use of HT for vasomotor symptoms immediately following menopause, with the long-term focus being on proven methods for CAD prevention, he said.

The randomized Women’s Health Initiative (WHI) study (Writing Group for the WHI Investigators. *JAMA* 2002;288:321-333) concluded that estrogen plus progestin increased coronary heart disease in the first few years of use, and also increased stroke, blood clots, breast cancer, and dementia. Estrogen alone increased stroke, blood clots, and dementia but had no effect on heart disease or cancer. WHI investigators combined the randomized trial and observational datasets of the WHI and found less risk when HT was initiated within 10 years of menopause, versus more distantly (Table 3; Rossouw JE et al. *JAMA* 2007;297:1465-1477).

Table 3. Risk of CHD with Hormone Therapy Stratified by Timing of Initiation of Treatment.

Hazard Ratio vs Placebo in WHI Hormone Trials		
Years since menopause	E+P	E alone
<10	0.88 (0.45-1.43)	0.48 (0.20-1.17)
10-19	1.23 (0.85-1.77)	0.96 (0.64-1.44)
20+	1.66 (1.14-2.41)	1.12 (0.86-1.46)
p for trend	0.05	0.15

The lack of cardioprotection seen in the WHI study was in conflict with protective effects found in the observational Nurses Health Study (NHS), in which women may have initiated HT earlier (at menopause), before CAD develops. “Estrogen does not reduce existing atherosclerosis. In fact, it may destabilize vulnerable plaques and precipitate thrombosis,” he suggested. In the NHS, when time of onset of HT was considered, protection from HT was diminished in patients treated later after menopause.

Similar results emerged from the Women’s Ischemia Syndrome Evaluation (WISE) study, reported at the AHA by George Sopko, MD, of the NHLBI. Among 654 postmenopausal women, the incidence of angiographically proven CAD was approximately 10% among women who started HT before age 45, compared with 25% of those starting HT after age 45 and over 40% for those never taking hormones.

Atherosclerotic Risk with Oral Contraceptives

Oral contraceptives, which contain more estrogen than HT, have been less studied. Investigators from Belgium reported that oral contraceptives may raise the risk for atherosclerosis 3,040% for every decade of use. In a study of 1,301 women, 81% of whom used oral contraceptives for an average of 13 years, the prevalence of carotid as well as femoral artery plaque (observed on ultrasonography) rose significantly for each decade of exposure, reported Ernst Rietzschel, MD, Ghent University, Ghent, Belgium.

“In the light of widespread and usually prolonged oral contraceptive use, oral contraceptives could be an important factor in the global atherosclerotic burden,” Dr. Rietzschel said, suggesting that clinicians closely monitor and control the classic risk factors.

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In addition to their blood-pressure-lowering effects, beta blockers provide other cardioprotective benefits in select patient subgroups. For example, a meta-analysis of four intravascular ultrasonography trials showed that beta-blockers slow the progression of coronary atherosclerosis in patients with known coronary artery disease (n=1,515) [Sipahi I et al. *Ann Intern Med* 2007]. Therefore, beta-blockers may play an important role in overall cardiovascular risk reduction.

Antihypertensive research is rapidly evolving, and Prof. Dahlöf acknowledged that the focus of research in blood pressure control is moving beyond traditional agents. Given the results of LIFE and other recent trials that have demonstrated the superiority of newer agents over atenolol, atenolol is no longer an appropriate reference drug for future trials of cardiovascular risk in hypertension, he said. However, he argued that beta-blockers should be judged on an individual molecular basis, adding that newer beta-blockers still have a role in hypertension research.

“Although beta-blockers are no longer the preferred first-line agents in the treatment of uncomplicated hypertension, these agents still have a place in the therapeutic armamentarium,” Prof. Dahlöf concluded. “Beta-blockers are needed in patients with special conditions and indications.”