

## LEADERSHIP PAGE



# Cardiovascular Disease

## A Focus on Women's Health

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Improving the cardiovascular health and quality of health care for women requires recognition and understanding of the differences across the woman's life span, from pathophysiology of coronary artery disease involving sex-specific risk factors to disease presentation of valvular disease and heart failure, to increased long-term major adverse cardiovascular events (MACE) from pregnancy complications. Reducing cardiovascular morbidity and mortality in women and closing the knowledge gap of sex-specific diagnostic and therapeutic strategies are scientific and public health priorities. This issue of *JACC: Case Reports* highlights the importance of understanding women's cardiovascular disease and health.

### CARDIOVASCULAR DISEASE AND RISK FACTORS

Cardiovascular disease (CVD) remains the leading cause of death in women in the United States and Europe (1,2). Although there has been a significant decline in CVD mortality over the past 40 to 50 years, the mortality in younger women has plateaued in the past decade, and the annual mortality rate remains greater for women than for men (1). The overall improved survival of and decrease in the prevalence of coronary artery disease have been ascribed to both therapeutic advances and primary and secondary risk factor modifications. Furthermore, the prevalence of CVD in women >75 years of age is greater than that of men of the same age, and mortality after myocardial infarction is higher in women (2).

Sex differences in CVD pathophysiology, diagnosis, and outcomes are increasingly being recognized and

characterized. Atherosclerosis is qualitatively and quantitatively different between the sexes. Myocardial ischemia in women may have a higher proportion of nonobstructive coronary disease and microvascular dysfunction, and acute myocardial infarction may have a higher proportion of plaque erosion and spontaneous coronary artery dissection (3). Women also have a greater risk of thrombosis and more anticoagulation and device-related bleeding complications, all of which present diagnostic and therapeutic challenges for clinicians. Furthermore, there are variations in prevalence and risks among women of different racial and ethnic groups, and the intersection of sex, race, and epigenetics must be considered.

Primary risk factors for women are similar to those of men with a few notable additions. Gynecologic and obstetric histories are unique to women and, recently, have been shown to predict long-term cardiovascular risk (4). Pregnancy-related complications such as preeclampsia and gestational diabetes confer 2- to 4-fold increased risk of future hypertension and diabetes as well as independently predicting an increase in MACE (4). This presents a window of opportunity to identify and educate women at increased CVD risk and target early intervention and prevention strategies. A multidisciplinary approach, including obstetrics, primary care, and cardiology, is required to reach women and implement prevention strategies.

The postmenopausal state is an independent risk factor and should be assigned a weight equivalent to that in males in American College of Cardiology/American Heart Association guidelines and risk models. Early age of menopause onset, either surgically or naturally, increases CVD risk and mortality. Although hormonal shifts have been shown to directly lead to detrimental changes in lipid profile, endothelial function, and insulin sensitivity,

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exogenous hormone replacement therapy has not been shown to safely reverse the negative pathophysiology (2). Premenopausal polycystic ovary syndrome has been shown to increase the risk of MACE above that of the inherent negative risk profile of the syndrome.

### VALVULAR HEART DISEASE IN WOMEN

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Valvular heart disease and heart failure remain significant causes of CVD in women. Rheumatic heart disease affects women more than men, predominantly in their young reproductive and productive lives and remains a major cause of morbidity and mortality worldwide. In the United States, degenerative mitral regurgitation is the primary cause of valvular heart disease. Women tend to present to surgery with more comorbidities including heart failure and advanced age. Although it is an unadjusted factor, short-term mortality after isolated mitral valve surgery is greater in women; this was not significant when the increases in comorbidities are considered (5).

Degenerative aortic stenosis occurs equally in men and in women, yet significant sex differences create challenges in women. Women have greater degrees of aortic stenosis for similar levels of valve calcification and also have been shown to have different patterns of myocardial remodeling and heart failure than men. Women had been less frequently referred to surgical aortic valve replacement (SAVR), presumably due to the higher in-hospital mortality. Today, one-half of patients undergoing transcatheter aortic valve replacement (TAVR) are women; and although women have higher rates of vascular and bleeding complications, they have been shown to have superior survival after TAVR than after SAVR. This finding has not been demonstrated in men (5).

### CARDIOVASCULAR DISEASE AND PREGNANCY

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Cardiovascular disorders are the leading cause of maternal mortality worldwide. Today, in emerging economies, rheumatic valvular disease remains a significant cause of maternal mortality; this is a disorder of poverty and access to care. Conversely, in developed countries, CAD has become the leading cause of maternal mortality and morbidity but causes differ, with congenital heart disease, heart failure, and hypertensive disorders predominating. Understanding the hemodynamic and physiologic changes

of normal gestation and its effects on pregnancy complicated by heart disease is central to safely counsel and care for these women. Women at high risk for complications and adverse outcomes, those with modified World Health Organization classifications II to IV, require pre-conception, intra-partum, and postpartum coordinated care. Multidisciplinary teams including maternal fetal medicine specialists, anesthesiologists, and neonatologists at centers of excellence are needed for improving the outcomes of women with heart disease and their offspring (6). Access must be made available to effective and safe birth control tailored to the underlying cardiovascular phenotype, as well as access to high-quality, safe pregnancy termination for those women in whom pregnancy is contraindicated. For example, conditions such as pulmonary arterial hypertension, severe left ventricular dysfunction, and severe aortic dilation in Marfan disorder confer prohibitively high maternal mortality risk of 40% to 100% (6).

### CHALLENGES AND SOLUTIONS

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Because there are differences in pathogenesis, physiology, and presentation of cardiovascular disease between men and women, a sex-specific approach to assessing risk factors and underlying mechanism is needed. Clinical trials have historically unrepresented women due to overt exclusion during reproductive years and ongoing challenges in recruitment. Medication dosages, treatment effect of devices, and interventional and surgical instrumentation remain unresolved challenges. The U.S. National Institutes of Health Office of Research in Women's Health has a mandate for inclusion of women in research studies, which extends to include female animals and cells in basic research to address sex as a biological variable and better understanding of disease mechanisms. Characterizing the knowledge gaps in prognostic, diagnostic, and therapeutic strategies as well as identifying the scientific, structural, and cultural barriers to the incorporation of sex differences in scientific discovery and research are needed.

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