# Gender Differences in the Pathogenesis and Management of Heart Disease

Jawahar L. Mehta • Jean McSweeney
Editors

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# Foreword

Cardiovascular disease is the leading cause of mortality for women, surpassing deaths from all forms of cancer combined. Yet, until recent decades, heart disease was considered a man's disease, despite more women dying annually than their male peers. Beginning in the 1990s, a cadre of researchers began to investigate the unique aspects of cardiovascular disease in women and embrace the evolving concept of sex-/gender-specific medicine. Scientific evidence accrued that guided an improved preventive, diagnostic, and therapeutic approach to cardiovascular disease in women. Translation of new evidence into clinical care provided stunning results; beginning in 2000, cardiovascular mortality declined sharply in women and has continued to do so.

But all is not resolved. Almost one-half of US women remain unaware that cardiovascular disease is their major health threat, and there is a concerning increase in cardiovascular deaths among young women (those aged 35–50 years), reversing the earlier favorable trend. Cardiovascular disease in women remains understudied, underdiagnosed, and undertreated. To sustain the progress and momentum of recent decades, a concerted research and educational undertaking is mandatory.

Regarding the latter, *Gender Differences in the Pathogenesis and Management of Heart Disease*, edited by Drs. Mehta and McSweeney, provides the latest comprehensive and well-referenced resource for clinical practice. Respected clinician and scientist chapter authors review the landscape of cardiovascular disease in women, offering recommendations and citing knowledge gaps.

The contemporary designation of ischemic heart disease is particularly relevant for women, as it identifies myocardial ischemia as the culprit for morbidity and mortality—whether in the setting of an acute coronary syndrome, whether due to obstructive or nonobstructive disease of the epicardial coronary arteries, to spontaneous coronary artery dissection, to microvascular disease, coronary vasospasm, or a combination of these entities. These multiple etiologies for myocardial ischemia and their clinical implications for recognition and management are carefully explored in a series of chapters. This complex spectrum is applicable to diagnostic procedures and myocardial revascularization undertakings as well.

Whereas women and men share multiple cardiovascular risk factors, many disproportionately disadvantage women, and many are unique to or predominant in women. These are addressed in detail.

Gender differences in the recognition and management of cardiac arrhythmias, with particular attention to atrial fibrillation, impact daily clinical practice. The spectrum of cardiomyopathies and heart failure comparably differs by gender, and the chapter on chemotherapy and radiation cardiotoxicities offers contemporary insights, with both clinical and research implications.

Gender differences in cardiovascular drugs remain incompletely investigated. Recent federal regulations (the Research for All Act of 2015) impact examination of female and male cells, tissues, and animals in basic research, requiring disaggregation of results by sex, and stipulate equitable inclusion of women in clinical trials; this offers promise for expansion of our knowledge base. In this regard, clinicians should be aware of ongoing clinical research studies in their vicinity and encourage appropriate women patients to enroll as participants in such trials. Women should become knowledgeable that the evidence base for clinical recommendations can solely be derived from women participants in research studies and that the limitations of guideline-based cardiac recommendations for women reflect their substantial underrepresentation in cardiovascular and other clinical trials. This is pivotal for gender equity in medicine and medical research.

Novel chapters address topics as diverse as the microbiome and the impact of geographic location on cardiac disease in women. Hypertension is epidemic in the burgeoning population of elderly women where this problem remains underrecognized and undertreated, with poorly controlled hypertension across the life cycle impairing life quality and survival owing to the target organ (including cardiac) damage. Psychosocial factors disparately impact cardiovascular disease in women, with much to be learned about effective interventions, but clinical recognition and management, particularly of depression, is an unmet need.

Both in specific chapters and throughout the volume the authors highlight the cardiovascular inhomogeneity among women, with those of racial and ethnic minorities, educationally and financially disadvantaged women, and those with challenges in accessing health care most adversely affected. High-risk subsets have differing needs and resource requirements that require attention in clinical practice. Women's cardiovascular health is not solely a medical issue. There are major economic, environmental, societal, and sociocultural components. The emerging scientific data about cardiovascular disease in women will have applicability only if women have equal access to quality, affordable health care, which in turn requires that policymakers and legislators become aware of how inequities in research, in prevention, and in access to care adversely affect women, their families, their community, and the public health.

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# Heart Disease in Women: Preface

There has been a dramatic increase in lifespan over the last five decades. According to the Centers for Disease Control and Prevention, life expectancy in the United States as of 2015 was at an all-time high of 78.8 years [1]. Women born in 2015 were expected to live 81.2 years and men 76.3 years. The increase in lifespan is seen in all ethnic groups. Lifespan prolongation has also occurred in other parts of the world, with relatively greater increase in developing and underdeveloped countries than in the developed countries. Lifespan is expected to increase even further in the decades to come.

Women live on an average 5–7 years more than men in almost all parts of the world. Coronary heart disease (CHD) and cancers are the major causes of death in the developed world and will soon become the major causes of death among men and women, especially those over the age of 65, all over the world as deaths from communicable diseases decline.

The differential in lifespan between men and women will result in a sharp increase in elderly female population. This change in demographics will result in very large number of women being seen for CHD in the outpatient setting as well as in the hospital setting by healthcare providers—who at the moment are not trained to recognize and treat special aspects of CHD in women.

Prevalence of CHD is a particular burden in certain racial groups—namely African-Americans, Hispanics, and Native Americans [2]. This may relate to their relatively poor socioeconomic status compared with White women. Relatively low level education and poverty among African-American and Hispanic women delay access to medical care and treatment. Therapies, both medical and nonmedical, as we know, are provided less often to minority women and, when prescribed, are utilized less often by patients in lower socioeconomic status for a variety of reasons [3]. Notably, both ARIC and REGARDS showed almost 33% higher age-adjusted risk for nonfatal CHD in African-American women compared with Caucasian women.

It is generally recognized that the deaths from CHD exceed all other causes of death in women, and the incidence of CHD increases significantly in the postmenopausal years. The risk factors for CHD such as smoking, hypertension, diabetes, and

dyslipidemia are generally same in women as in men. In addition, there are some unique risk factors for CHD in women. This issue has been addressed in detail by Dr. Brewer and colleagues in this book [3]. Poverty also seems to affect women as a risk factor for CHD; thus we see higher prevalence of CHD in women in rural areas than in urban areas [4]. In keeping with this concept, CHD in women is an important but unrecognized burden in poor areas of the world [5].

The presentation of CHD is significantly different in women than in men. These variations in presentation are generally not recognized by many general physicians and specialists. This leads to a significant delay in the diagnosis and treatment of heart disease in women, contributing to worse outcomes in women.

There are major differences in hypertension awareness and treatment of hypertension in women and men. Luckily, hypertension awareness and control rates are on the upswing. Hypertension and obesity are strongly associated, and obesity predisposes to development of hypertension particularly in the elderly women. The mechanism of this association and its clinical relevance are discussed by Drs. Ahmad and Oparil [6].

As mentioned above, there is a marked delay in instituting therapy in women. Even simple medical therapies such as aspirin and statins are prescribed less often to women with CHD than men. Modern-day aggressive therapies such as percutaneous and surgical coronary interventions are recommended less often to women than men. Although the precise basis for differences in outcome after percutaneous and surgical coronary interventions in women and men is not clear, it may relate to more extensive disease as well as small size of the coronary arteries in women which may be the basis of restenosis after bypass surgery or percutaneous coronary stenting [7]. All this leads to poor outcome in women as compared with that in men.

Current therapy of CHD is based on extensive clinical trials with large sample sizes. These trials have resulted in institution of accepted strategies such as control of elevated blood pressure and diabetes, use of statins, aspirin, and other antiplatelet drugs, renin-angiotensin-aldosterone system inhibitors, and lastly percutaneous and surgical coronary revascularization strategies. All these trials have resulted in evidence-based treatment options. Indeed, this approach has led to a dramatic and sustained decrease in CHD morbidity and mortality over the last five decades. Sadly, the number of women in these trials has been relatively small. Therefore, there is ongoing question if the so-called evidence-based medicine is as effective in women as in men. This mandates additional trials be conducted, including sufficient numbers of racially diverse women to determine efficacy of treatments.

With aging of the population, we see a host of cardiac arrhythmias in both men and women. These arrhythmias arise as a result of myocardial ischemia, sustained hypertension, and other types of heart disease. We are beginning to understand the differences in different types of arrhythmias in men and women [8]. Once the differences and their basis are defined, differences in therapy may be elucidated.

These differences in patterns of heart disease in men and women over the last 3 decades have led to large-scale studies of different modes of diagnosis and treatment. These studies are still ongoing and will hopefully include sufficient numbers of women and lead to delineation of vagaries of disease pattern and efficacious therapies unique to women.

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