Gender Differences in the Pathogenesis and Management of Heart Disease

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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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Contents

Chapter 1
Atherosclerosis and Gender-Related Differences

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Introduction

Despite years of research and significant advances in our understanding of the pathogenesis of atherosclerotic coronary artery disease, it remains the leading cause of mortality and morbidity worldwide. According to recent World Health Organization report, ischemic heart disease and stroke together account for approximately 15 million deaths annually worldwide [1]. New insights into vascular biology and pathogenesis of atherosclerosis have led to significant advances in the management of the disease. Currently, we know that atherosclerosis is an inflammatory process which involves a complex interplay of dyslipidemia, oxidative stress, and endothelial dysfunction [2–6].

One of the unsolved conundrums in our understanding of atherosclerosis is gender-related differences in the pathogenesis and manifestations of atherosclerotic heart disease. Cardiovascular diseases account for ≈48.3% of inpatient hospital stays for women, accounting for approximately ~$187 billion, in health care costs [7]. Most of these cardiovascular diseases represent atherosclerotic coronary heart disease (CHD).

Gender related differences in atherosclerotic CHD were first recognized in the early 1990s. In the CASS study, a higher operative mortality was observed for women compared with men [8]. Another study Swedish Web System for

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Enhancement of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) showed that women with ST-segment elevation myocardial infarction (STEMI) have a worse prognosis than men and are also less likely to get evidence-based treatment [9]. Multiple studies have shown that women as compared to men have more co-morbidities, advanced symptoms at the time of presentations and worse prognosis after coronary artery bypass surgeries (CABG) [10, 11].

The epidemiological studies corroborate these findings. Incidence of CHD increases by tenfold after menopause in women [12, 13]. Menopause thus plays a decisive role in the increase in CHD risk in women [8]. The Framingham offspring study showed changes in the lipid profile after menopause which may contribute to increased CHD after menopause in women [14, 15].

Importantly, traditional risk factors of CHD are associated with different outcomes in women. For example, smoking and diabetes are much more significant coronary risk factors in women and are associated with a poorer prognosis than in men [16, 17].

Gender Differences in Plaque Morphology

Many studies have found differences in the pattern of atherosclerotic plaque morphology between men and women. Mautner et al. [18] and Burke et al. [19, 20] reported plaque morphology in atherosclerosis to be gender specific. They found that atherosclerotic plaque contains less dense fibrous tissue in women than in men [18]. Plaque erosion with acute thrombus deposition is associated with sudden cardiac death in women [19, 20]. Plaque erosion is a lesion consisting of an intimal layer rich in smooth muscle cells with abundant proteoglycan matrix; necrotic core is thin, ill-defined and not near the luminal thrombus [19, 20]. Plaque rupture is more common in younger women than older women. In women, total serum cholesterol and smoking were more commonly related to plaque rupture, whereas, in men, the ratio of elevated total cholesterol to HDL cholesterol was a better predictor of plaque rupture [19]. Stable plaque and healed infarct were more commonly associated with hypertension and elevated glycosylated hemoglobin in women [19]. Thus, CHD risk factors modify the plaque morphology depending on the gender [19, 20].

Yahagi et al. [21] found that thin cap fibroatheroma/vulnerable plaque is more commonly associated with acute myocardial infarction in men than in women. Although in women plaque erosions were significantly more common than men still plaque rupture was more often related to acute myocardial infarction [21]. Further, plaque erosions in women were also associated with elevated serum myeloperoxidase, activated smooth muscle cells and hyaluronan deposition [22, 23]. Iqbal et al. [24] studied plaque morphology by intravascular ultrasound in women with acute myocardial infarction with nonobstructive disease. They observed that plaque rupture in women was not eccentric, it had more fibrous tissue, and vessels were often angiographically normal. Interestingly, these gender differences in the atherosclerosis

Table 1.1 Atherosclerosis pathophysiology: gender related differences and comparison

Males	Females
• Men have greater atheroma burden, more plaque volume, larger number of non-culprit lesions and more eccentric fibroatheroma than women [26, 27]. • Men have more structural and functional abnormalities in epicardial coronary arteries than women [29]. • Thin cap fibroatheroma/vulnerable plaque is commonly associated with acute myocardial infarction in men [21].	• Women have less dense fibrous tissue in the atherosclerotic plaque [18–20]. • In women, plaque rupture is common. Ruptured plaque is not eccentric and vessels are often angiographically normal [24]. • Women have lower maximal coronary flow reserve than men [26, 29]. • Women have endothelial dysfunction, abnormal cellular metabolism and impaired nitric-oxide (NO)-dependent vasodilation which leads to increase small-vessel tone and causes angina with normal coronary arteries [32, 34–36].

rotic changes are predominantly seen in coronary vasculature and are not observed in the aorta and lower extremity arteries [25].

Men have greater atheroma burden, more plaque volume, more eccentric fibroatheroma, a larger number of non-culprit lesions, and more diffuse epicardial endothelial dysfunction than women [26, 27]. Most recently, Ann et al. [28] studied gender related differences in plaque morphology of patients with STEMI undergoing percutaneous coronary intervention. They found that women in the age group of 66–75 years have a bigger necrotic core and dense calcium deposition in the plaque as compared to men in the same age group. Women also have lower coronary vasodilatory reserve than men, but men have more atheroma burden and structural abnormalities in the coronary arteries than women [26–29] (Table 1.1).

Gender Differences in Atherosclerosis at Cellular Level

The connective tissue and vascular disorders are seen more frequently in women. The female:male ratio of systemic lupus erythematosus is 6–10:1, systemic sclerosis has female to male ratio of 5–14:1 and with Sjogren syndrome, it is about 9:1 [30]. Increased prevalence of connective tissues disorders in females is suggestive of increased vascular reactivity which results in microvascular endothelial dysfunction, microvascular spasm and vasospastic angina [31]. Women also have impaired nitric-oxide (NO)-dependent vasodilation of the coronary microvasculature, increased small-vessel tone and show a predisposition to vasoconstriction in response to various stimuli [6]. All these factors are, at least in part, responsible for angina associated with normal coronary arteries in women [32].

Reis et al. [33] in the WISE (Women's Ischemia Syndrome Evaluation) study explored the role of microvascular dysfunction in female patients in the absence of obstructive coronary artery disease. They found that coronary microvascular endothelial dysfunction is highly prevalent in women with chest pain in the absence of occlusive coronary artery disease. Interestingly, they concluded that microvascular physiology in women is regulated by myocytes present in the media of the coronary microvasculature. They also observed that estrogen in supraphysiologic

concentrations is an in vivo vasodilator that acts on arterial myocytes at the cellular levels. In the coronary microvessels, estrogen mediates vasodilation by myocyte hyperpolarization, inhibiting calcium and endothelin-1-induced, myocyte-mediated arterial vasoconstriction and stimulating prostacyclin production [33].

In the multicentric WISE study, another important observation was the presence of abnormal cellular metabolism in females with non-obstructive coronary disease [34]. In women with chest pain without obstructive CHD an abnormal phosphocreatine/ATP response to exercise stress was identified on nuclear magnetic resonance spectroscopy. This cellular abnormality indicated a shift toward anaerobic metabolism consistent with myocardial ischemia [34, 35]. Importantly, a substantial reduction in phosphocreatine/ATP ratio after exercise stress was a significant predictor of poor cardiovascular outcomes [34, 35]. The role of nuclear magnetic resonance imaging in the evaluation of chest pain and microvascular disease was first explored by Buchthal and colleagues [36]. They found that women with chest pain with no angiographically significant stenosis had a reduction in the phosphocreatine/ATP ratio during exercise that was more than 2 SD below the mean value in the control subjects without chest pain [36].

Recently, Mygind et al. [37] in the iPOWER study conducted in Denmark, described impaired coronary flow velocity reserve, a measure of microvascular dysfunction, in a substantial proportion of women with angina pectoris and no obstructive coronary artery disease. Incidentally, Harder and Coulson first described the effects of estrogen on the vascular smooth muscle [38]. They found that diethyl stilbesterol, an estrogen analog hyperpolarizes the vascular smooth muscle cells. They suggested that changes in K+ conductance could mediate these microvascular effects of estrogen in females through several pathways [35]. Later Sudhir et al. [39], found that estrogen induced coronary vasodilatation is independent of endothelial factors, not mediated by the classical intracellular estrogen receptor but through non-genomic pathways in the epicardial arteries by changes in ATP-sensitive potassium or calcium channels, or both.

These protective effects of estrogen on coronary microvasculature can explain results of studies in experimental animal models of atherosclerosis in which female animals seem to be less prone to develop features of atherosclerosis compared to male animals despite similar high-fat diet [40, 41]. Robins et al. [40] and Wilson et al. [41] found that female hamsters have less fat deposition than male hamsters in the aorta despite similar hypercholesterolemic diet. The female hamsters have better plasma lipoprotein cholesterol profile, larger LDL particle size, and less early aortic atherosclerosis compared to male hamsters [41]. Hayashi et al. [42] found similar results in rabbit model of atherosclerosis.

Role of Estrogens and Androgens in Cardiovascular Health and Disease

The role of estrogens in CHD in women has remained controversial. The incidence of CHD increases after menopause, but hormone replacement therapy with supplemental estrogen to post-menopausal women does not lower the risk of ischemic

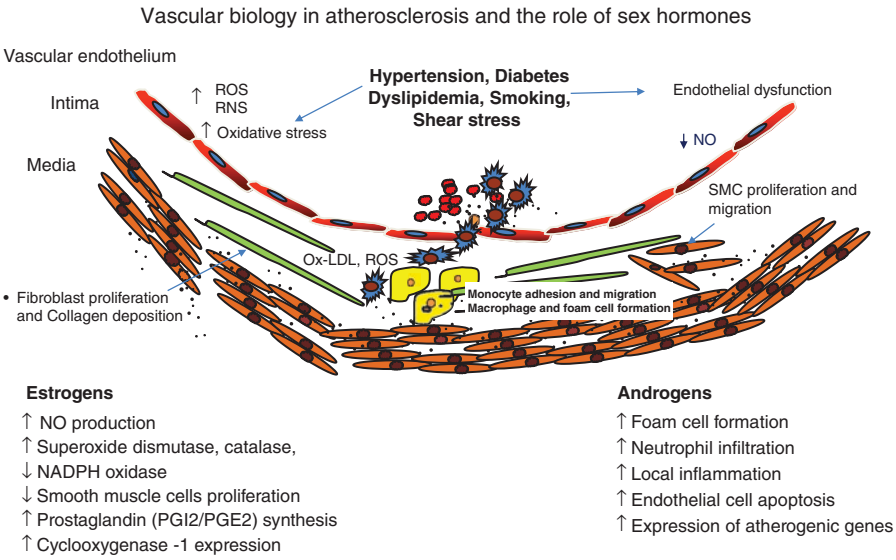

Fig. 1.1 Vascular biology in atherosclerosis and the role of sex hormones

Table 1.2 Estrogens and vascular biology of atherosclerosis

• Estrogen causes potentiation of NO synthesis in the coronary microvasculature and endothelial cells [42].
• Estrogen decreases oxidative stress by accelerating the metabolism of reactive oxygen species by up-regulation of the enzymes superoxide dismutase, catalase, increasing the availability of free NO and down-regulation of NADPH oxidase [47, 48].
• Estrogen augments PGI2/PGE2 synthesis
• Estrogen enhances cyclooxygenase (COX)-1 expression, NO/cGMP-mediated pathways [47] and direct smooth muscle relaxation via endothelium derived hyperpolarizing factor (EDHF) [47, 49]
• Estrogens play an important role in shear stress mediated responses via GPER receptors in the vascular endothelial cells [52–54].

events [43, 44]. These studies suggest that sex hormones play an intricate role in coronary microcirculation and there are still unknown sex-related differences in the atherosclerotic process.

Estrogens have several anti-atherosclerotic properties shown in Fig. 1.1 and Table 1.2. First and foremost, estrogen causes potentiation of NO synthesis, and it is now widely believed that decreased NO synthesis/availability is central to the concept of endothelial injury [42].

The effects of estrogens on the cardiovascular system are either NO mediated or through anti-oxidation pathways. Multiple studies have shown that NO mediated effects are mediated by estrogen receptor (ER) beta [45, 46]. Estrogen decreases oxidative stress by accelerating the metabolism of reactive oxygen species by up-regulation of the enzymes superoxide dismutase, catalase, increasing the availability of free NO and down-regulation of NADPH oxidase [47, 48]. Estrogen also

plays a significant role in myogenic and shear-stress–dependent regulation of arteriolar diameter [47, 49]. These actions are mediated by augmenting the dilator prostaglandins PGI2/PGE2 synthesis, increasing cyclooxygenase-1 expression and NO/cGMP-mediated pathways [47]. Another mechanism by which estrogen may cause smooth muscle relaxation involves endothelium derived hyperpolarizing factor (EDHF), which is considered a metabolite of the cytochrome P450 epoxygenase pathway and its effects are mediated by K+ channels [47, 49].

Estrogens also modulate shear stress mediated responses of the arterioles. Wall shear stress is an important local mediator in the regulation of the arteriolar muscle tone. Vasoactive molecules such as NO, EDHF, and prostaglandins are released through a cascade of chemical/cellular signals, because of the physical stimulus of shear stress in the vascular endothelium [50, 51]. The protective effects of estrogens in shear stress mediated responses are attributed to the presence of G-protein coupled receptor-30 (GPR 30) which is associated with estrogen GPER (G–protein coupled estrogen receptor) receptor family in the vascular endothelial cells [52–54]. GPER induces vasodilation and inhibits vascular smooth muscle proliferation [55]. GPER activation also stimulates human endothelial NO synthase [55, 56]. GPER has been shown to mediate atheroprotective effects of estrogen. It prevents the changes related to diabetes on vascular endothelium and also decreases pulmonary hypertension in some studies [56–58]. Though, more studies are needed to find the role of GPER agonists in the clinical settings.

Androgens also play a significant role in cardiovascular health shown in Fig. 1.1 and Table 1.3. Low free testosterone levels are frequently associated with obesity and diabetes in men [59]. Hak et al. [60] and Corona et al. [61] found that low testosterone levels correlate with increased CHD risk. Rovira-Llopis et al. [62] also showed that low testosterone levels are related to oxidative stress, mitochondrial dysfunction especially in diabetic patients. Multiple studies have found an association between low testosterone levels and CHD [63–65].

However, several investigators point to the deleterious effects of testosterone which may predispose to more CHD in men than women. Ng et al. [66] observed that androgens increase the expression of about 27 genes related to atherosclerosis in male macrophages, but not female macrophages. They concluded that these findings might contribute to higher prevalence of CAD in men than women.

Table 1.3 Testosterone and vascular biology of atherosclerosis

• Several studies have shown low testosterone levels are related to increased cardiovascular risk [59–65].
• Testosterone increases endothelial cell apoptosis, increases gene expression of pro-atherosclerotic genes and increases lipid loading in the male macrophages [66–68].
• Endogenous testosterone is associated with increased local inflammation, neutrophil infiltrates and reduced cardiac function after acute ischemic injury in the animal models [69–72].

This study also explained higher androgen receptor expression and subsequently increased lipid loading in male macrophages described earlier by McCrohon et al. [67]. Ling et al. [68] also observed that testosterone increases endothelial cell apoptosis. Endothelial dysfunction leads to increased adhesiveness of platelets to endothelial surface subsequently leading to thrombus formation. The pro-apoptotic and pro-inflammatory properties of testosterone are especially deleterious after acute ischemic injury. Several others [69, 70] have explored the role of endogenous testosterone in cardiac ischemia. They found that testosterone mediated increased apoptosis and inflammation leads to reduced cardiac function after acute ischemic injury in the males in animal models [69, 70].

Similarly, Cavasin et al. [71] and Crisostomo et al. [72] found that increased testosterone levels after myocardial infarction are related to increased local inflammation, neutrophil infiltrates leading to myocardial dysfunction and cardiac rupture. However, Rettew et al. [73] observed that testosterone also has anti-inflammatory actions by decreasing toll-like receptor 4 (TLR4) expression on human macrophages which may favor early cardiac remodeling. All these studies point to the fact that our understanding of the role of androgens in the pathogenesis of atherosclerosis is still insufficient. More studies are needed for clearly defining the role of androgens in the cardiovascular diseases.

Emerging Risk Factors in Gender and Atherosclerosis

With newer research into the pathogenesis of atherosclerosis, unique risk factors are emerging (Table 1.4). Lipoprotein a [Lp (a)], a novel risk factor for CHD is independently associated with coronary artery calcification in diabetic women. This

Table 1.4 Gender differences in novel risk factors of atherosclerosis

• Nuclear magnetic resonance imaging used in the evaluation of chest pain and microvascular disease showed that women with chest pain with no angiographically significant stenosis had significant reduction in the phosphocreatine/ATP ratio during exercise [34–36]
• Women may have impaired coronary flow velocity reserve, which is a measure of microvascular dysfunction, even with no obstructive coronary artery disease [37].
• Lipoprotein a [Lp (a)] is independently associated with coronary artery calcification in diabetic women [74].
• Women with noncalcified plaques and mixed coronary atherosclerotic plaques have higher serum metalloproteinase-9 levels [75].
• Platelets may be the key to gender related difference between males and females as females have the more pronounced formation of leucocytes platelet aggregates [76] and larger expression of platelet TLRs related to P selectin [77, 78].
• Women as compared to men have lower levels of lipoprotein-associated phospholipase A2 (Lp-PLA2), a novel atherosclerotic marker despite having higher levels of hs CRP [79]

association is independent of the presence of other risk factors such as body mass index, Framingham risk score, hemoglobin A1C, etc. [74]. Gu et al. observed that higher serum metalloproteinase (MMP)-9 levels were associated with noncalcified plaques and mixed coronary atherosclerotic plaques in females but not in males [75]. In in vivo platelet aggregation studies Gremmel et al. [76] showed that women in contrast to men express more leukocyte-platelet aggregates in response to thrombin receptor-activating peptide-6 and adenosine diphosphate. This observation was also reflected in platelet reactivity assays. These results were significant because there was no difference in expression of P-selectin and GPIIb/IIIa in men and women patients.

Toll-like receptors (TLRs), especially on platelets, have an important role in atherosclerotic pathophysiology [77, 78]. Women have greater expression of platelet TLRs which are related to higher P-selectin levels in women whereas in men TLR expression is more likely to be related to inflammatory mediators such as soluble TNF-α receptor 1 and ICAM-1 [77]. In women, TLR expression is related to the body mass index and total cholesterol to high-density lipoprotein ratio; on the other hand, in men it is related to hypertension and lipid profile [77]. Interestingly, only TLR 7 and TLR 8 are located on the X chromosome whereas others (TLR 1–6, TLR 9, 10) are located on the autosomal chromosomes.

Lastly, in the Dallas Heart Study, women as compared to men had lower levels of lipoprotein-associated phospholipase A2 (Lp-PLA2), a novel atherosclerotic marker despite having higher levels of hsCRP [79]. Though some questions remain to be answered regarding these associations, all these studies suggest to gender-related differences in the pathophysiology of atherosclerosis.

Conclusion

Though it is still not conclusively proven that the atherosclerotic process is different in men and women, growing number of studies suggest there is still a lot to learn and discover in our current understanding of atherosclerosis (Table 1.5). Growing knowledge of gender related differences in atherosclerosis will help in improving management of CHD and thereby outcomes in women especially as still many studies have shown worse clinical outcomes in women with comparable risk factors [80, 81]. Description of novel atherosclerotic markers and the gender related differences in the gene expression of these markers are the future avenues for research. Imaging techniques such as intravascular ultrasound and functional nuclear magnetic resonance provide complementary information on coronary artery biology and may play a more important role in understanding plaque morphology and help in the management of atherosclerotic CHD in future.

Table 1.5 Key studies highlighting gender-related differences in atherosclerosis

• Multiple studies [8–11] including the CASS Study [8], SWEDEHEART study [9], Lu et al. [80], Flink et al. [81] showed worse clinical outcomes in women as compared to men with comparable risk factors.
• PROSPECT study [27], Han et al. [26] and Ann et al. [28] described the key differences in plaque morphology in men and women.
• WISE (Women's Ischemia Syndrome Evaluation) study showed that the microvascular dysfunction and abnormal cellular metabolism are the key findings associated with coronary microvasculature abnormalities with non-obstructive coronary artery disease in women [33–35].
• iPOWER study [37] showed that impaired coronary flow velocity reserve, a measure of microvascular dysfunction, is present in women with angina pectoris and no obstructive coronary artery disease.
• Hulley et al. [43] and Women's Health Initiative (WHI) [44] study showed that hormone replacement therapy with supplemental estrogen to post-menopausal women increases the risk of ischemic events.
• Hak et al. [60] in the Rotterdam study and Corona et al. [61] showed that low testosterone levels correlate with increased CVD risk. Multiple studies have identified an association between low testosterone levels and coronary artery disease [63–65].

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Chapter 2
Gender Differences in Metabolic Syndrome

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Introduction

Metabolic syndrome (MetS) represents a cluster of metabolic abnormalities, that include hypertension, central obesity, insulin resistance, atherogenic dyslipidemia, and elevated plasma glucose, which serve as risk factors for the development of atherosclerotic cardiovascular disease (CVD) [1, 2]. The overall prevalence of MetS has been on the rise largely due to the global obesity epidemic, and regional variations in prevalence are influenced by age, sex, genetic factors, geographic location, socioeconomic status, education level, and criteria used for diagnosis [3, 4]. Gender-related differences in the incidence, pathogenesis, clinical presentation and management of CVD are known to exist [5, 6] and similarly MetS also differs between men and women. In this chapter, we aim to review the gender differences in epidemiology and pathophysiology of MetS with emphasis on individual components of MetS, and its implications for CVD in men and women.

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Metabolic Syndrome: Definitions

MetS, a syndrome characterized by a combination of multiple risk factors for CVD and type 2 diabetes mellitus (DM), has a variety of other names including 'insulin resistance syndrome' [7], 'syndrome X' [8], 'hypertriglyceridemic waist' [9], and 'the deadly quartet' [10]. This syndrome was initially described by Reaven in 1988 [7] and since then several health organizations and professional societies have formulated definitions of MetS that can be used to establish a clinical diagnosis (Table 2.1). Insulin resistance plays an important role in the pathophysiology of MetS [7, 11] and has been a key component of all the definitions. MetS has also been found to be associated with development of microalbuminuria, polycystic ovary syndrome, fatty liver, cholesterol gallstones and obstructive sleep apnea, and presence of any of these comorbidities may help corroborate the diagnosis [11].

The first diagnostic criteria for MetS were proposed by World Health Organization (WHO) in 1998, defining MetS as insulin resistance (impaired fasting glucose, impaired glucose tolerance, or DM) in addition to two other risk factors from the ones listed as follows; hypertension (blood pressure ≥160/90 mmHg), high triglycerides, low HDL-cholesterol, central obesity (based on gender-specific waist-hip ratio and/or body mass index), and microalbuminuria [12].

In 1999, European Group for the Study of Insulin Resistance (EGIR) proposed a modification for MetS diagnosis criteria published by WHO to be used only in non-diabetic individuals. EGIR defined MetS in nondiabetic individuals by the presence of insulin resistance or fasting hyperinsulinemia (greater than the 75th percentile of population) and two other criteria, which include from hyperglycemia, hypertension (systolic/diastolic blood pressures ≥140/90 mmHg or treated for hypertension), dyslipidemia, and central obesity (using waist circumference). Hyperglycemia was defined as fasting plasma glucose ≥108 mg/dl or impaired fasting glucose in non-diabetics. Type 2 DM was excluded from this definition, as it was difficult to measure insulin resistance in this group. In contrast to WHO, microalbuminuria was deemed not necessary for the diagnosis of MetS [13].

The National Cholesterol Treatment Adult Treatment Panel III (NCEP-ATP) proposed a more clinically suited definition in 2001. MetS, by these criteria, is diagnosed by the presence of three or more of the following components: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), elevated triglycerides, low HDL, elevated blood pressure, and impaired fasting glucose (fasting glucose ≥110 mg/dl) [14]. American Heart Association/National Heart, Lung, and Blood Institute modified this definition in 2005 by lowering the threshold for impaired fasting glucose from 110 to 100 mg/dl and waist circumference cut point for some populations (especially from South Asia, China, Japan, and other Asian countries) to ≥90 cm in men and ≥80 cm for women, as these populations were predisposed to metabolic syndrome with moderate increase in waist circumference [2].

The International Diabetes Federation (IDF) proposed a revision of ATP III definition in 2004, with abdominal obesity being deemed mandatory for diagnosis. The rationale for this was that abdominal obesity was strongly correlated with the other

Table 2.1 Diagnostic criteria for metabolic syndrome

Criteria	WHO 1998 [12]	EGIR 1999 [13]	NCEP-ATP 2001 [14]	AACE 2003 [83]	IDF 2004 [15]	AHA/NHLBI 2005 [2]	IDF /AHA/ NHLBI 2009 (Harmonized criteria) [16]
Diagnosis	*Glucose intolerance, IGT, or DM and/or insulin resistance + any other 2*	*insulin resistance or fasting hyperinsulinemia + any other 2*	*presence of 3 or more of the criteria*	*at least one component*	*Central obesity + any 2 of others*	*Any 3 of 5*	*Any 3 of 5*
Glucose metabolism	IGT/DM/insulin resistance	IFG in nondiabetic	FPG ≥110 mg/dl	IGT/IFG	IFG or type 2 DM	FPG ≥100 mg/dl	FPG ≥100 mg/dl
Blood pressure	≥160/90	≥140/90 or treated for hypertension	≥135/85 mmHg	>130/85 mmHg	≥135/85 mmHg or on antihypertensive medication	≥130/85 mmHg or on antihypertensive medication	≥130/85 mmHg or on antihypertensive medication
Lipid profile	TG ≥150 mg/dl, HDL <35 mg/dl in men, HDL <39 mg/dl in women	TG ≥150 mg/dl, HDL-C <39 mg/dl, or treated for dyslipidemia	TG ≥150 mg/dl, HDL-C <40 mg/dl in men, <50 mg/dl in women	TG >150 mg/dl, HDL-C <40 mg/dl in men and <50 mg/dl in women	TG >150 mg/dl, HDL-C <40 mg/dl in men and <50 mg/dl in women, or receiving treatment for dyslipidemia	TG ≥150 mg/dl; HDL-C <40 mg/dl in men, <50 mg/dl in women, or on treatment for dyslipidemia	TG ≥150 mg/dl, HDL-C <40 mg/dl in men and <50 mg/dl in women

(continued)

Table 2.1 (continued)

Criteria	WHO 1998 [12]	EGIR 1999 [13]	NCEP-ATP 2001 [14]	AACE 2003 [83]	IDF 2004 [15]	AHA/NHLBI 2005 [2]	IDF /AHA/ NHLBI 2009 (Harmonized criteria) [16]
Obesity	Central obesity (men: waist to hip ratio >0.9; female: waist to hip ratio >0.85) and/or BMI >30 kg/m^2	WC ≥94 cm in men and ≥80 cm in women	WC >102 cm in men, >88 cm in women	N/A	Increased WC (with ethnic specific cut-off)	WC ≥102 cm in men, ≥88 cm in women, lower cut-point for Asian-American population (≥90 cm in men, ≥80 cm in women)	Elevated WC (population and country-specific cut-off)
Other	Microalbuminuria	–	–	Family history of type 2 DM, HTN, CVD; personal history of CVD, PCOS, gestational diabetes, and acanthosis nigricans	–	–	–

WHO World Health Organization, *EGIR* European Group for Study of Insulin Resistance, *ATP* Adult Treatment Panel, *NCEP* National Cholesterol Education Program, *AACE* American Association of Clinical Endocrinologists, *IDF* International Type 2 diabetes Federation, *IGT* impaired glucose tolerance, *FPG* fasting plasma glucose, *IFG* impaired fasting glucose, *TG* triglycerides, *BMI* body mass index, *HDL-C* high density lipoprotein cholesterol, *WC* waist circumference, *CVD* cardiovascular disease, *PCOS* polycystic ovary syndrome, *NHLBI* National Heart, Lung, and Blood Institute, *AHA* American Heart Association, *DM* diabetes mellitus, *HTN* hypertension

MetS components, especially insulin resistance. IDF also proposed different cut-off of abdominal obesity definition depending on ethnic group or country of origin with the aim of creating a definition that could be used worldwide. Apart from obesity, the other criteria for diagnosis of MetS were similar to ATP III [15].

The most updated version of the definition was issued in 2009 as collaborative effort by the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute. In this joint statement, abdominal obesity was not considered to be an obligatory parameter for the diagnosis, but it remained as one of the components along with dyslipidemia, hypertension, elevated fasting glucose. Waist circumference cut-points for abdominal obesity proposed by IDF were maintained in this joint statement [16].

Gender Differences in Epidemiology of MetSyndrome

In the twenty-first century, the global prevalence of MetS has been on the rise. Regional variations are noted due to the interplay of various factors, such as age, race, socioeconomic status, level of physical activity, culture, diet, genetic background, and education levels, that are known to play a role in its epidemiology (Fig. 2.1). Gender plays an integral role in influencing the prevalence and clinical expression of MetS. The gender specific distribution of MetS varies based on geography and definition used for diagnosis. (Table 2.2) The individual components of

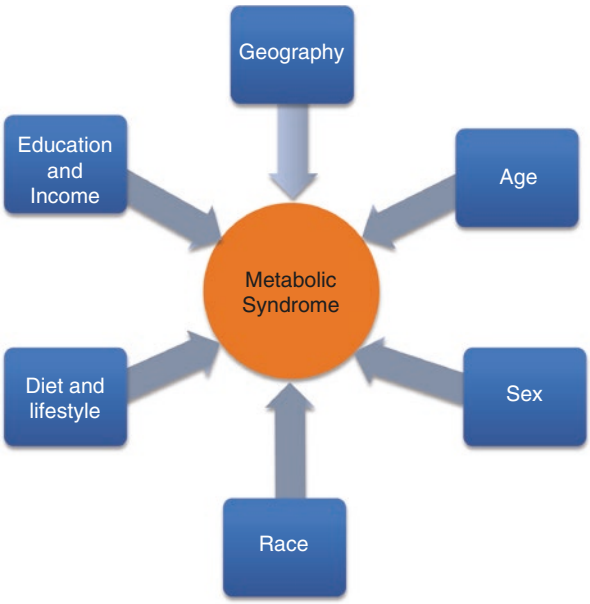

Fig. 2.1 Factors influencing the prevalence of metabolic syndrome

Table 2.2 Prevalence of MetS based on geography, sex and definition

Geography	Investigators/ year of publication	Study population (n)	Prevalence of MetS (%)	Prevalence in Men (%)	Prevalence in Women (%)	Defining criteria
North America						
US	Aguilar et al 2015 [20]	1931	34.7	32.8	36.6	NCEP-ATP III
US	Moore et al 2017 [19]	51,371	34.2	33.4	34.9	Harmonized criteria
US	Beltran-Sanchez et al. 2013 [84]	2034	22.9	23.69	21.80	Harmonized criteria
US	Hari et al. 2012 [85]	6770	33.1	29.23	36.56	NCEP-ATP III
Canada	Riediger et al. 2011 [86]	1800	19.1	20.5	17.8	NCEP-ATP III
US (Hispanics)	Heiss et al. 2014 [87]	16,319	33.7	34	36	Harmonized criteria
US	Ford et al. 2010 [88]	3461	34.3	36.1	32.4	NCEP-ATP III
Canada (Oji-Cree population)	Pollex et al. 2006 [89]	515	29.9	24.6	33.9	NCEP-ATP III
Asia						
Korea	Yang et al. 2014 [90]	14,888	28.4	26.6	21.3	ATP III
Korea	Park et al. 2015 [28]	5760	25	25.3	24	Harmonized criteria
Thailand	Podang et al. 2013 [91]	2544	16.6	18.2	10.3	ATP III
China	Xi et al. 2013 [92]	7488	21.3	20.9	21.7	ATP III
China	Song et al 2015 [93]	15,477	27.4	27.9	26.8	NCEP-ATP III
Philippines	Sy et al 2014 [94]	3072	25.6	26.6	24.8	NCEP-ATP III and IDF
Rural China	Yu et al. 2014 [95]	11,496	39	45.6	31.4	AHA/ NHLBI 2005
Taiwan	Wu et al. 2017 [96]	214,216	–	15.85	9.17	NCEP-ATP III
Macau	Sobko et al. 2014 [97]	1592	–	10.5	3.7	IDF
South India	Deepa et al. 2007 [98]	2350	18.3	17.1	19.4	ATP III

Table 2.2 (continued)

Geography	Investigators/ year of publication	Study population (n)	Prevalence of MetS (%)	Prevalence in Men (%)	Prevalence in Women (%)	Defining criteria
India	Deedwania et al. 2014 [99]	6198		33.3	40.1	Harmonized criteria
Africa and Middle East						
Morocco	El Brini et al. 2014 [100]	820	35.73	18.56	40.12	Harmonized criteria
UAE	Malik et al. 2008 [101]	4097	41.8	37.1	44.3	IDF
Saudi Arabia	Al-Daghri et al. 2014 [102]	9164		47.2	40.3	ATP III
Iran	Azizi et al. 2003 [103]	10,368	30.1	24	42	ATP III
Europe						
France	Vernay et al. 2013 [104]	1856	14.1	14.4	13.7	ATP III
Greece	Athyros et al. 2005 [105]	4153	23.6	24.2	22.8	ATP III
Italy	Maggi et al. 2006 [106]	5632		25.9	55.2	ATP III

US United States, *UAE* United Arab Emirates, *ATP III* Adult Treatment Panel III, *NHLBI* National Heart, Lung, and Blood Institute, *AHA* American Heart Association, *IDF* International Diabetes Federation

MetS may have a gender-specific preponderance (for example, obesity is more common in women and hypertension is more common in men), and while individuals from both sexes may have a diagnosis of MetS, the criteria met for diagnosis may be different [4, 17, 18].

Data from National Health and Nutrition Examination Survey (NHANES) showed that prevalence of MetS has increased by 35% between 1988 and 2012 in the US, and more than a third of US adult population is estimated to have MetS [19]. From 2003–2004 to 2011–2012, overall prevalence of the metabolic syndrome in the United States increased from 32.9% in to 34.7% [20], and was increasing rapidly in young women [21]. Abdominal obesity and dyslipidemia were reported to be common in both sexes, but women had a statistically significant higher prevalence of abdominal obesity compared to men [22, 23]. Men had a higher prevalence of elevated triglycerides level and impaired glucose tolerance. The rates of hypertension were reported to be similar in both women and men [22]. Central obesity as dominant feature of MetS in women has been consistently seen in population studies from India [24], China [25], and the Caribbean Islands [26].

Studies from US population show that with increasing age MetS becomes increasingly more prevalent, partly explained by the increase in sedentary lifestyle and functional disability among the older population. The steep change in the prevalence of MetS with aging seems to be more pronounced in women. A large prospective study in Europe found a fivefold increase of MetS prevalence in women from ages 19–39 years to 60–78 years, as compared to only a twofold increase in men [27]. A national survey conducted in South Korea and cross-sectional study done in Brazil also confirmed this finding. Young and middle-aged men had higher prevalence of MetS as compared to women in that age group, but the pattern was reversed after the age of 60. Abdominal obesity and insulin resistance, which becomes more common in postmenopausal women, could be partially responsible for this phenomenon [28, 29]. Regardless of the ethnicity, hormonal changes related to menopause seemed to affect the gender disparity in MetS expression.

Low education levels and poor socioeconomic status are also independently associated with MetS [19]. The effect of socioeconomic status on the development of metabolic syndrome is also more pronounced in women. A study from Portugal showed that lower educational levels and household income are associated with an increased prevalence of MetS in women, but not in men [30]. Similar trends have been observed in population studies from Sweden [31] and France [32]. Low education levels and poor socioeconomic status might predispose both genders to poor food and lifestyle choices, however men are "protected" possibly due to higher likelihood in having job requiring physical labor with lower education levels, making them more physically-active than women of the same socioeconomic background.

Gender Differences in Components of Metabolic Syndrome

Hypertension

Hypertension, defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, is an important risk factor for CVD, and affects one out of three adults in the US [33]. The overall prevalence of hypertension is similar in both women and men, however, there exists a gender disparity based on age. In adults up to age 64 years, the prevalence of hypertension is higher in men as compared with women, and over age 65, the prevalence in women across all racial groups is higher than in men [34]. In NHANES database from 1999 to 2004, women had higher mean SBP but lower mean DBP than men, and 82% of the women in this group were postmenopausal. Women also tended to have more central obesity, elevated total cholesterol, and low HDL [35].

The pathophysiology behind age-dependent disparity in hypertension between the sexes is poorly understood and hypotheses centered around hormonal influences have been described. Premenopausal women have a lower risk of developing hypertension and CVD compared with age-matched men. This advantage seems to

diminish after menopause, highlighting the importance of sex hormones in the pathophysiology of cardiovascular disease in both men and women [36].

Estrogen has been observed *in vivo* and *in vitro* to cause vasodilation due to a direct effect on endothelial cell, as well as indirectly through nitric oxide release. Estrogen also works at a genomic level, changing vascular-cell gene and protein expression, with resultant improvement of endothelial function and vascular response to injury. Vasculature in women has been described to have a greater number of estrogen receptors as compared to men, but the density of these receptors goes down in postmenopausal women, lowering the vascular protective effects of estrogen [37, 38].

In addition to this, the increased incidence of hypertension post-menopause can be attributed to the activation of the renin-angiotensin system (RAS), along with the development of obesity. The RAS is regulated differently in men and women, and studies show favorable modulation of RAS by estrogen. Endogenous estrogen increases synthesis of angiotensinogen and expression of protective angiotensin type 2 receptor, and suppresses the expression of pro-hypertensive angiotensin type 1 receptor. An increase in dietary sodium intake causes a greater blood elevation in men compared with women due to these estrogen related effects [39, 40]. Obesity and increased visceral fat are associated with androgen dysregulation and chronic inflammatory states, which in turn, cause endothelial dysfunction leading to hypertension in both men and women [41].

In summary, aging itself is an independent risk factor for developing hypertension, but the changes in blood pressure associated with aging are more pronounced in women compared to men.

Insulin Resistance

Insulin resistance, manifesting as either impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or Type 2 DM, is an integral component of MetS and a well known risk factor for development of CVD [12]. Relative risk of mortality from coronary artery disease is 50% higher for women with diabetes than compared to men. Women with diabetes have significantly higher blood pressures and worse lipid profiles than men with diabetes, predisposing them to a more unfavorable cardiovascular risk profile [42]. The gender disparity in CVD outcomes may also, in part, be attributed to differences in management. A study by Wexler et al. showed that while hypoglycemic medication use was equal in men and women, diabetic women are less likely to receive other medications that contribute to lowering CVD mortality or reach recommended therapy goals [43].

Worldwide, the prevalence of diabetes is higher in men than women. In 2013, there were 14 million more men affected with diabetes than women [44]. The differences in glucose metabolism and degree of insulin resistance or sensitivity between men and women result from differences in sex hormones, body composition, and adiposity between the two genders. Men tend to have more lean mass and

central fat distribution (visceral and hepatic adipose tissue), while women tend to have higher peripheral adipose tissue distribution (in limbs and hips) which is highly influenced by estrogen. The higher visceral adiposity in men is associated with elevated postprandial insulin, free fatty acids, triglyceride levels, and insulin resistance. In contrast to that, the peripheral fat distribution typically found in women is associated with higher insulin sensitivity [45, 46]. Women are also found to have higher levels of adiponectin, a hormone secreted exclusively by adipose tissue [47]. that works by lowering glucose production in liver and improves insulin sensitivity in the muscle and liver by increasing free fatty acid oxidation. Lower adiponectin levels have been associated with insulin resistance [48].

Sex hormones are known to have complex metabolic effects. The maintenance of favorable glucose homeostasis in women is partially attributed to the effect of estrogen. Estrogen, in animal models, has been found to reduce hepatic glucose production and enhance glucose transport in muscle tissue. Similarly, androgens have also been reported to have beneficial metabolic effects in men such as lowering body-fat and improving insulin sensitivity. However, hyperandrogenic states in women, such as polycystic ovarian syndrome (PCOS), have the exact opposite effect [45] and have been associated with development of glucose intolerance and insulin resistance in women [46, 49].

Dyslipidemia

Elevated low-density lipoprotein (LDL) cholesterol levels have been associated with greater CVD risk, and lowering LDL cholesterol levels, especially with HMG-CoA reductase inhibitors, reduces CVD events [50]. It has been long recognized that dyslipidemia patterns vary among different races or ethnic groups, and similarly, gender related differences in lipid profiles have also been found. Women have higher high-density lipoprotein (HDL) cholesterol and lower LDL cholesterol, very low-density lipoprotein (VLDL) cholesterol, total plasma triglyceride, and VLDL triglyceride concentrations compared to age-matched men. In women, the circulating size of VLDL particles are smaller and that of HDL particles are larger [51, 52]. Lipoprotein subclasses are known to confer different CVD risk: higher level of large VLDL and small HDL particles are linearly associated with CVD, while larger sized HDL is inversely correlated with CVD [53, 54].

The mechanism behind differences of plasma lipid profiles between men and women is poorly understood. The amount of visceral fat, lipoprotein lipase activity, and hepatic lipase activity might be the contributing factors. Women have increased removal efficiency of VLDL-triglyceride from the circulation, resulting in lower plasma VLDL-triglyceride concentrations compared to men. Lower hepatic secretion of VLDL particles in women also attributed to lower plasma VLDL-apoB-100 concentrations. Women have more triglyceride-rich VLDL compared to men, which facilitates their clearance as increase in triglyceride content of lipoprotein particles enhances the susceptibility to hydrolysis by lipoprotein lipase [52]. Sex differences

in HDL concentration is believed to be due to higher HDL apolipoprotein A-I synthesis rate in women. Apolipoprotein A-I promotes cholesterol efflux from tissues to the liver for excretion, and is a cofactor for lecithin cholesterolacyltransferase (LCAT), an enzyme responsible for the esterification of cholesterol [51]. Studies have also shown that men have approximately twice the hepatic lipase activity of women, which is inversely correlated with the sizes of LDL and HDL particles [55]. In addition to small HDL size, smaller LDL particle size appears to be positively associated with CVD [56].

In summary, there is significant gender dimorphism in lipid profile between men and women, which could account for cardioprotective effect of female sex.

Obesity

Obesity is an established risk factor for increased morbidity and mortality from cardiovascular disease, diabetes, hypertension, stroke, and cancer [57]. Over time, the average body mass index (BMI) for men and women has increased in almost all countries around the world. The proportion of adults with BMI $\geq$25 kg/m^2 has increased from 28.8% to 36.9% in men and from 29.8% to 38% in women over the last three decades. In developed countries, men tend to have higher rates of obesity compared to women, while in developing countries the situation is the reverse, with higher rates of obesity in women [58]. Some potential contributors to this effect, that include increase in caloric intake, change in diet composition, lower levels of physical activity, are thought to play a role in both sexes globally [59]. Interestingly, overweight and obese men have higher CVD mortality risk compared to women with the same BMI, after adjusting for age, smoking status, and leisure-time physical activity. This significant gender difference might be attributed to multiple factors, including difference in lipid and glucose metabolism, sex hormones, body fat distribution, and cytokines [60].

Women in general have approximately 10% higher total body fat compared to men, but the pattern of adipose tissue accumulation differs between men and women, which is apparent after puberty. Premenopausal women tend to develop peripheral adiposity with subcutaneous adipose tissue accumulation in both abdominal (waist) and gluteofemoral area, while men are more prone to central or visceral obesity. Visceral and subcutaneous adipose tissue have different metabolic properties. Visceral adipose tissue is more sensitive to catecholamine-induced lipolysis and less sensitive to the anti-lipolytic effect of insulin compared to subcutaneous fat. Higher lipolytic sensitivity of visceral adipose tissue leads to increased free fatty acid delivery to portal and systemic circulation, resulting in increased glucose and VLDL production [45, 61]. Visceral fat is an important source of free fatty acids and inflammatory mediators (such as, tumor necrosis factor-α, interleukins, and adipokines), which likely contribute to development of hepatic insulin resistance [62]. Multiple epidemiological studies have suggested an association between visceral adipose tissue and development of atherosclerosis [63], type 2 DM, and CVD [64], although the exact mechanism is poorly understood. Menopause in women results

in change in the body fat distribution towards a more central/android pattern, due to increase in visceral adiposity. Decline in testosterone with aging also associated with increased visceral adiposity in men [65].

Apart from biological factors, sociocultural factors also seem to play a role in gender disparity in obesity. In developed countries, women tend to consume foods high with added sugars and energy-dense processed foods such as cookies, chocolate, and ice cream; while men consume greater amount of meat-based produce and alcohol [66, 67]. Immigration and acculturation also plays a role in development of obesity due to adoption of local dietary habits and physical activity patterns. One review found a positive relationship between BMI and duration of residence among US immigrants with sex variation [68]. Hispanic women seem to have higher rates of obesity compared to hispanic men, but hispanic men have higher disease burden due to lower tendency in men to seek medical attention [69]. Local sociocultural beliefs affect body image different in men and women, for example, in Greece and Spain, obesity is associated with social status among men, but with negative image in women, resulting in women spending more time, effort, and money to obtain ideal thinner shape. On the contrary, in middle eastern countries, women are more likely to be overweight and obese due to cultural norms and social acceptance [67].

Gender Differences in Cardiovascular Disease Risk Associated with Metabolic Syndrome

Epidemiologic evidence shows that MetS is associated with increased risk for type 2 DM, CVD, and all-cause mortality [70–73]. A meta-analysis of 21 studies by Galassi et al. [74] showed that MetS was associated with increased risk of mortality from all causes, CVD mortality, CVD, and stroke, more so in patients diagnosed with MetS using WHO criteria compared to NCEP-ATP III criteria. Non-diabetic patients with MetS have a higher risk of developing CVD as compared to the general population, however, their risk is lower than diabetic patients with MetS [74]. A study by Guzder et al. [75] showed that having metabolic syndrome at the time of diagnosis of type 2 diabetes is associated with 2.5-fold increase in CVD risk, and patients who demonstrate all five features of MetS have nearly fivefold increase in their risk compared to individuals with diabetes alone [75]. This leads us to the much debated issue of whether MetS as syndrome confers any additional CVD risk or, the final CVD risk due to MetS is just a sum total of the independent individual risks conferred by each of its components.

The gender differences in the individual components of MetS have been elaborated in literature, but whether or not the differences in metabolic profiles between men and women lead to a differential risk for Type 2 DM, CVD and overall mortality, is not clearly known. While there are studies that support the notion of differential risk based on the combination of MetS components [76], to our knowledge, only a very few sex-specific analyses of CVD and mortality risk in patients with MetS have been described. The relative risk of CVD with MetS is higher in women compared to men, suggesting MetS might be a stronger risk fac-

tor for CVD in women than in men [74]. Multiple prospective studies and meta-analysis have shown that women with diabetes, compared to men with diabetes, have a greater risk of stroke. In the general population, women have a more favorable overall cardiovascular profile compared to men, but this pattern reverses in the presence of insulin resistance [77]. One study found that the most prevalent metabolic syndrome combination in younger men was a cluster of elevated triglycerides, low HDL, and high blood pressure and, in younger women was a cluster of elevated triglycerides, low HDL, and increased waist circumference. The presence of all five components of MetS in younger adults was strongly associated an increased mortality risk. In adults over age 65, the presence of all five components of MetS was the most common combination, but in older women, having elevated glucose or low HDL seemed to be associated with higher mortality risk, regardless of the number of MetS risk factors. However, this association was not observed in older men [78].

Given the current lack of substantial evidence that can be used to guide practice, larger epidemiologic studies focusing on these disparities are needed to assess whether there is gender disparity in the CVD risk contributed by MetS.

Gender Disparity in Treatment of Metabolic Syndrome

Differential CVD risk in men and women with MetS may be influenced by differences in pathophysiology as elucidated above, but other factors such as disparities in management/treatment strategies have also been identified and thought to contribute. Studies show that women are less likely to receive treatment for modifiable cardiovascular risk factors with aspirin or LDL-lowering medications as compared to men with the same comorbidities. Women are also less likely to reach recommended treatment goals in terms of systolic blood pressure, HbA1C, and LDL cholesterol levels as compared to men [43, 79, 80]. In treating metabolic syndrome, dietary changes and increased physical activity are first-line therapy [14]. The beneficial effect of lifestyle intervention is encouraging and effectively reduces the burden of all MetS components. Studies have shown differences in response to lifestyle modification between men and women [4]. The Diabetes Prevention Program Study found that lifestyle intervention was effective compared with placebo in both men and women, but more in men. Metformin compared with placebo was found to be more effective in men than in women with insulin resistance. Lifestyle changes reduced the incidence of all components except HDL cholesterol level, and metformin lowered the incidence of elevated waist circumference and fasting glucose levels [81]. Aerobic training of moderate or high intensity has been shown to have the highest potential to reduce visceral adipose tissue in overweight individuals, with men having more significant amount of reduction compared to women [82].

The differences in response to MetS-targeted interventions in men and women can serve as a guide for clinicians to individualize treatment strategies. There is a need for a larger scale studies to evaluate the impact of sex-based tailored treatment for MetS to reduce the CVD risk.

Conclusions

MetS has been proven to be an important risk factor for CVD and diabetes mellitus. There are important differences in the pathophysiology, clinical presentation, implications on cardiovascular risk of MetS in men and women. The prevalence of MetS is on the rise globally and in order to control this epidemic, we need studies to help develop a deeper understanding the disease process and sex related differences so that we can tailor treatment strategies to men and women to help reduce the risk of CVD.

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Chapter 3
Hypertension in Women

Amier Ahmad and Suzanne Oparil

Introduction

Worldwide, cardiovascular disease (CVD) is the most common cause of death in women and hypertension is the most common modifiable risk factor for CVD in both sexes [1]. Individuals with elevated blood pressure (BP) defined as >140/90 mmHg are more likely to have a shorter life expectancy and have more years lived with CVD compared to their normotensive peers [2]. Globally, 1.39 billion people (694 million women, 694 million men) are estimated to have hypertension [3]. Hypertension is three times more common in low- and middle-income countries compared to high-income countries, and women in middle/low-income countries have higher rates of hypertension than men. The prevalence of hypertension in both middle/low- and high-income countries, including the United States (US), is higher in post-menopausal women compared to younger women and age-matched men. In the US, hypertension is estimated to occur in 85.7 million adults (52% women, 48% men) [2].

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Gender and Racial Inequalities in Hypertension

Worldwide, women are more aware of their diagnosis of hypertension compared to men (72% women vs 62% men in high-income countries, 36% vs 22% men in low-income countries) [3]. Women are more likely to be prescribed antihypertensive medications (52% vs 49% men in high-income countries, 28% vs 23% men in low-income countries). Control (defined as systolic BP (SBP) <140 mmHg and diastolic BP (DBP) <90 mmHg) rates are higher in women than men in both high-income (32% vs 25% men) and middle/low-income (10% vs 5% men) countries. Overall, middle/low-income countries have lower rates of awareness, treatment, and control of BP in both sexes compared to high-income countries. These large differences are likely related to multiple factors, including limited access to healthcare and medications in poorer countries [4]. Gender differences in rates of awareness, treatment, and control of BP are also seen in the US. White women compared to White men have higher rates of awareness (87% vs 83%), treatment (82% vs 74%) and control (59% vs 55%). Among minority women in the US, awareness of hypertension has improved over the past decade, with 85% of Hispanic women, 90% of Black women, and 80% of Asian women aware of their diagnosis, compared to 87% of White women. Similarly, compared to men, rates of antihypertensive treatment are greater in minority women (82% Black women vs 68% men, 77% Hispanic women vs 60% men, 71% Asian women vs 60% men). Minority women also have higher rates of hypertension control compared to men (54% vs 43% for Blacks; 55% vs 41% for Hispanics; 50% vs 40% for Asians) [2, 5, 6].

Obesity and Hypertension

Obesity is associated with a variety of comorbidities, including hypertension [2]. The National Heart, Lung, and Blood Institute (NHLBI) defines the following weight categories based on body mass index (BMI): overweight ($25.0 \leq \text{BMI} \leq 29.9$ kg/m^2), class I obesity (BMI 30–35 kg/m^2), class II obesity (BMI >35 to 39.9 kg/m^2), and class III obesity (BMI $\geq$40 kg/m^2) [7]. The prevalence of obesity has been increasing worldwide and is currently estimated at 603.7 million adults, or 39% of the world population [8]. Worldwide, obesity is more prevalent in women compared to men and rates of obesity peak in women at a later age (60–64 years) compared to men (50–54 years). In the US, obesity is more prevalent in women (40%) compared to men (35%) of all age groups and all racial/ethnic groups (Black women 57% vs men 38%; Hispanic women 46% vs men 39%; Asian women 12% vs men 11%, and White women 36% vs. men 34%) [2].

The burden of obesity in the US is greatest in minority populations, particularly in Blacks (48%) and Hispanics (43%) [2]. Disparities in income, housing, and education have been linked to the disproportionate rates of obesity in minorities [9]. Within the Black population, poverty has been associated with obesity, as less

nutritious and less costly foods tend to be more calorie dense [10]. Twenty-five percent of Black families are categorized as "food insecure" reflecting their inconsistent access to food due to limited resources [11]. Only 8% of Black individuals live in areas with multiple supermarkets, compared to 31% of White individuals. Further, foods with less nutritional value and more calories are more frequently promoted and marketed to Black individuals compared to Whites [12]. The prevalence of billboards advertising low nutrition foods are 13 times higher in predominately Black neighborhoods compared to White neighborhoods. Further, Black children have less access to parks and playgrounds, limiting their physical activity and placing them at increased risk for developing obesity as adults [11]. Similar issues exist within the Hispanic population, who also faces barriers due to language and culture [11]. Health education programs aimed at improving nutrition are often not available in Spanish, and issues arise that limit access to these education programs due to immigration status.

Hypertension and obesity are strongly associated. In particular, excess weight gain and increased visceral adiposity are consistently associated with hypertension [2]. In an effort to understand racial differences related to the sequelae of hypertension, the Southern Community Cohort Study evaluated the prevalence of multiple comorbidities (CVD, diabetes mellitus (DM), increased BMI) in 69,211 individuals (60% women) (aged 40–79 years) with self-reported hypertension or hypertension diagnosed by in-clinic BP readings who were enrolled in community health centers in the southeastern US [13]. There were highly significant associations of self-reported hypertension with morbid obesity (BMI > 40 kg/m^2) in White women (OR, 4.64; 95% CI, 3.97–5.43) and White men (OR, 4.57; 95% CI, 3.43–6.10), as well as between in-clinic diagnosed hypertension (OR, 5.76; 95% CI, 3.98–8.32) or uncontrolled hypertension (OR, 1.90; 95% CI, 1.34–2.71) and morbid obesity. Data have also shown a linear relationship between BMI and SBP and DBP, and weight loss reduces BP in most hypertensive individuals [14, 15]. Further, overweight and obese persons who are normotensive have higher BPs than comparable individuals with normal body weight, and weight loss in these normotensive obese individuals also lowers BP [15].

The metabolic syndrome (MeS) is a constellation of risk factors that includes hypertension, obesity, insulin resistance, and dyslipidemia, and is associated with the development of CVD and DM [16]. Each component of the MeS is an independent risk factor for CVD, and the combination of risk factors increases both the rate and severity of CVD [17]. The clinical criteria for the diagnosis of MeS are outlined in Table 3.1. The estimated prevalence of MeS between 2009 and 2010 in the US general population was 22% in women and 24% in men. The increase in CVD risk associated with MeS is similar but slightly greater in women (HR 1.80, 95% CI 1.02–3.15) compared to men (HR 1.63, 95% CI 1.11–2.39) [18, 19].

The phenotype of the MeS varies by gender. Waist circumference, low HDL, and body weight tend to be the dominant contributors to MeS in women, while men more commonly have hypertension [20, 21]. The prevalence of MeS also varies by age, with a disproportionate number of older women having MeS. The Monica, Risk, Genetics, Archiving and Monograph (MORGAM) project, a population-based

Table 3.1 Clinical criteria for the diagnosis of metabolic syndrome

Measure	Cutoff
Elevated waist circumference	≥88 cm (≥35 in.) in women
	≥102 cm (≥40 in.) in men
Elevated triglycerides[a]	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C[a]	<50 mg/dL (1.3 mmol/L) in women
	<40 mg/dL (1.03 mmol/L) in men
Elevated blood pressure[a]	≥130 mm Hg systolic blood pressure
	≥85 mm Hg diastolic blood pressure
Elevated fasting glucose[a]	≥100 mg/dL

[a]Pre-existing treatment will meet criteria for this measure. Any three of five constitute diagnosis of metabolic syndrome

study of 36 cohorts from ten European countries, showed a fivefold increase in prevalence of MeS between the ages of 60 and 78 years in women. A major driver of MeS in aging women is menopause. The Study of Women's Health Across the Nation (SWAN) followed 949 women without MeS across the peri-menopausal age range for 9 years and demonstrated that women were more likely to develop MeS following menopause than before (OR 1.45, $p < 0.001$) [22]. This shift in prevalence of MeS following menopause was related to decreasing estrogen levels over time. In pre-menopausal women, elevated levels of estrogen are associated with higher levels of HDL and accumulation of subcutaneous fat in the gluteal and hip regions, rather than in visceral regions [23]. The rise in visceral adiposity parallels the decrease in circulating 17ß estradiol levels during the menopausal transition [24].

Mechanisms Relating Hypertension and Obesity

Obesity results in increased renal tubular sodium reabsorption through several proposed mechanisms: [1] renal compression by external fat [15], [2] activation of the renin-angiotensin-aldosterone system (RAAS) [15], and [3] activation of the sympathetic nervous system (SNS) [14]. Increased visceral adiposity is associated with hypertension [25, 26] via mechanisms that include renal compression with resultant reduction in medullary blood flow and increase in tubular sodium reabsorption. Physical compression of the kidneys by visceral adipose tissue results in intra-abdominal pressures as high as 40 mmHg [27]. In a large cohort of the Dallas Heart Study, renal sinus fat was associated with incident hypertension, as well as the number of antihypertensive medications required to control BP [26]. Further, participants in the Framingham Heart Study with high levels of perinephric fat were two times as likely to have hypertension [28]. Renal sinus fat also results in inflammation and renal medullary extracellular matrix expansion by increasing the concentration of hyaluronan, which results in increased interstitial pressure, tissue edema, and eventually inflammation [29].

Left ventricular hypertrophy (LVH) is more common in obese compared to lean hypertensive individuals as a result of both heightened SNS activity and endothelial dysfunction resulting from obesity [30, 31]. The Strong Heart Family Study documented an increase prevalence of LVH in obese compared to normal weight offspring of participants in the cohort [32]. The volume overload resulting from obesity results in the development of concentric LVH, similar to what is seen with valvular disorders [33]. Gender specific analysis of 1851 women and 1068 men with and without hypertension and without antecedent CVD (history of heart failure, stroke, myocardial infarction, valvular abnormalities) enrolled in the Strong Heart Family Study showed that obesity is associated with LVH in both hypertensive women and men. However, after adjusting for the presence of comorbidities (hypertension, age, SBP, DM), LV mass/fat-free mass was 15% higher in women than men ($p < 0.0001$), suggesting that obesity has a greater influence on LV geometry in women than men [34].

Adipocytes play a key role in mediating obesity-induced hypertension. Leptin, a hormone synthesized and released by adipocytes, promotes appetite suppression and stimulates the SNS by inhibiting glutamate receptors and neuropeptide Y [35]. Most studies of the role of leptin and obesity in hypertension have been carried out in rodents, but small studies have examined the issue in humans. Humans with leptin deficiency experience early-onset obesity, but are typically normotensive [36]. Obese individuals are desensitized to the appetite suppressing effects of leptin, but continue to have SNS activation, and thus hypertension [37]. Leptin also stimulates the release of aldosterone, independent of the RAAS, resulting in increased arterial stiffness and promoting the development of hypertension [38].

Large scale population studies have provided evidence that in older adults, a higher BMI is less likely associated with hypertension than in younger individuals [39–42]. The etiology of this age-associated protection is not well understood. One theory suggests a "survival effect" favoring obese older persons, among whom individuals vulnerable to the complications of obesity have already died, leaving behind those resistant to long term adverse outcomes of obesity [43]. The Sardinia Study evaluated the effect of obesity on hypertension in 3056 untreated adults (1532 women, 1524 men) [43]. Older individuals (60 years and above) were more likely to have hypertension (SBP > 140 mmHg or DBP > 90 mmHg) compared to younger individuals (≤39 years of age), but the likelihood of having hypertension was lower for obese (OR 10.45, 95% CI 4.58–23.85) compared to lean persons (OR 33.89, 95% CI 17.94–64.02) in the older age group. No gender differences were identified in this study.

In addition to age, the effects of obesity, assessed by BMI, on BP differ by gender. Kagan et al. examined the effects of BMI on BP by gender using ambulatory blood pressure monitoring (ABPM) in 5950 individuals (2848 women, 3102 men) with suspected hypertension [44]. Participants had a wide range of BMI (15.9–53.2 kg/m^2). Overweight and obese women had lower daytime BP (136–137/80–83 mmHg) than men (138–142/83–85 mmHg). Heart rate was similar in normal weight, overweight, and obese women, while obese men had higher heart rates than normal weight and overweight men. Obesity was associated with higher DBP in men, but not women. These differences persisted when data were age-matched.

Diagnosis

The diagnosis of hypertension has traditionally relied on in-clinic measurements obtained using a manual sphygmomanometer [4]. However, population based studies have shown that up to 30% of individuals diagnosed with hypertension using in-clinic BP readings are incorrectly diagnosed [45, 46]. Conversely, multiple population based studies have shown that ABPM and home blood pressure monitoring (self-monitoring) are superior methods for diagnosing hypertension [47, 48] The United States Preventative Services Task Force recommends ABPM in all patients prior to beginning antihypertensive therapy as a Grade A recommendation [49].

Rates of hypertension control also differ significantly depending on whether in-office BP readings or ABPM is used. Spanish investigators evaluating hypertension control in 29,148 White women and men (48% women) showed similar rates of control (SBP <140/90 mmHg) in women and men using in-office readings (22% vs 23%), but higher control rates in women than men (49% vs 39%) when ABPM was used [50]. Interestingly, a higher rate of hypotension has also been seen in women compared to men. Division-Garrote et al., in a study of 70,997 treated women and men (48% women), showed that women (10%) were more likely than men (7%) to experience hypotension (daytime ABPM <105/65 mmHg, nighttime ABPM <90/50 mmHg, and 24-h ABPM <100/60 mmHg) [51, 52]. This higher rate of hypotension has been postulated to be the result of antihypertensive medication titration based on in-office BP readings, which tend to be higher in women compared to men [4].

Abnormal ABPM Phenotypes

Higher BPs are normally seen during the daytime, with a 10–20% reduction in BP during nighttime [53]. This nocturnal reduction in BP is known as dipping. Non-dippers, those with a diminished nighttime BP fall or a nocturnal BP rise, are at an increased risk for developing CVD and all-cause mortality [54]. Perez-Lloret et al., in a study of 1689 untreated women and men (51% women) showed a lower rate of nighttime BP elevation (nighttime BP > 120/70 mmHg) in women (0%) compared to men (20%) younger than 30 years of age. This trend normalized with age, such that the prevalence of nocturnal BP elevation was similar in women and men above age 70 years [55].

White coat hypertension (WCH) is characterized by normal daytime BP (ABPM <135/85 mmHg), but elevated in-office BP (≥140/90 mmHg) [56]. Higher rates of WCH have been seen in women (43%) compared to men (34%) in the US [45, 46]. Worldwide, a similar trend persists. In a study of 14,143 women and men (49% women) seen in outpatient clinics across five continents, WCH, as measured by in-office BP readings and ABPM, occurred most often in elderly obese women [57]. The increased prevalence of WCH in this patient population has been thought to be due to higher rates of anxiety and MeS [58].

WCH has long been thought to be a benign hypertension phenotype, with multiple studies documenting no increase in CVD morbidity/mortality long term [59–61]. Recently, Franklin et al. challenged this belief in a study of 653 untreated individuals with WCH and 653 normotensive individuals extracted from the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO) database [56]. In a 10.6 year follow-up period, persons with WCH and 0–2 CVD risk factors had CVD outcomes equivalent to those without WCH. Conversely, those with WCH and >3 CVD had twice as many CVD outcomes compared to the control group. This increase in CVD outcomes in age-matched persons with WCH and increased CVD risk was thought by the authors to be the result of isolated systolic hypertension incorrectly diagnosed as WCH. This study is the first to evaluate outcomes of WCH in persons stratified by CVD risk. No comparison by gender was performed. There is evidence that WCH evolves into sustained hypertension over time, raising concern that WCH may not be as benign as once thought [62]. More research is needed to understand the prognosis of persons with WCH and increased CVD risk.

Masked hypertension is defined as elevated daytime BP (mean awake APBM ≥135/85 mmHg) but normal in-office BP [63]. Globally, the estimated prevalence of masked hypertension is 10% overall, and is higher in men [57]. In the US, masked hypertension occurs less frequently in women (7%) compared to men (18%), but the incidence increases in women with increasing BMI and alcohol intake [45]. In contrast to WCH, masked hypertension is clearly associated with increased CVD risk. Despite this, masked hypertension is underdiagnosed due to underutilization of ABPM in outpatient settings [61, 64].

Treatment

Randomized controlled trials (RCTs) have consistently shown that reducing BP is beneficial for both women and men, without significant gender differences in outcomes. In the BP Lowering Treatment Trialists' Collaboration review of 31 RCTs (87,349 women and 103,268 men), comparison of multiple treatment regimens with placebos and against one another revealed no gender difference in the primary outcome (stroke, myocardial infarction, heart failure, CVD death) [65]. In contrast to the similar efficacy of antihypertensive therapy in both genders, significant gender specific adverse effects are seen. Women more commonly experience adverse effects associated with antihypertensives [66]. Angiotensin converting enzyme inhibitor (ACEI)-induced cough is threefold more likely to occur in women than men, and women more commonly experience peripheral edema and hirsutism with calcium channel blockers and minoxidil, respectively. Low serum levels of sodium and potassium associated with thiazide diuretic therapy are more frequent in women. Men typically experience gout with the use of thiazides, and are also more prone to develop erectile dysfunction with the use of beta-blockers. No class of

antihypertensives has been associated with decreased libido in women. In fact, use of ACEI and angiotensin receptor blockers has been associated with increased sexual function in women [67].

Special Populations

Gender specific forms of hypertension include post-menopausal, oral contraception-related, and pregnancy-related hypertensive disorders.

Hypertension Following Menopause

The prevalence of hypertension increases in women following menopause, likely related to the effects of decreased circulating estrogen [68]. Increased arterial stiffness, decreased nitric oxide production, and up-regulated angiotensin II receptors are all thought to contribute to the rise in BP in menopausal women. Behavioral factors are also thought to play a role in this age specific rise of hypertension: post-menopausal women have higher rates of obesity and depression, and lower levels of physical activity [58, 69].

Oral Contraception-Related Hypertension

First generation oral contraceptive medications (OCP) were associated with increased BP, thought to be due to their high ethinyl estradiol content [70]. Newer generations of OCP have lower estrogen content and less potent effects on BP. In women with a history of controlled hypertension, a trial of a combination OCP (estrogen/progesterone) at the lowest dose is recommended [71]. OCPs containing only progesterone or intrauterine/implantable devices are recommended for women with uncontrolled hypertension [72].

Hypertension in Pregnancy

Multiple forms of hypertension occur during pregnancy (Table 3.2) [4]. Hypertension during pregnancy has been associated with CVD later in life [73]. A recent study that followed women (n = 131) up to 16 years after experiencing pre-eclampsia at or before 34 weeks gestation showed higher rates of hypertension (38%) and metabolic syndrome (18%) compared to women with normotensive pregnancies (14% hypertension, 2% metabolic syndrome) [74]. Non-CVD

Table 3.2 Hypertension in Pregnancy

Type of hypertension	Definition
Pre-eclampsia	New onset hypertension and proteinuria OR hypertension associated with end organ damage, without proteinuria
Eclampsia	Pre-eclampsia with seizures
Chronic hypertension	A diagnoses of hypertension (BP ≥140/90 mmHg) prior to pregnancy, a diagnosis of hypertension made before the 20th week of gestation, or hypertension lasting past 12 weeks postpartum
Gestational hypertension	Hypertension diagnosed after the 20th week of gestation, without evidence of pre-eclampsia

morbidity/morality also appear to be higher in women who experience hypertension during pregnancy. For example, a recent study of 60,580 women who experienced a pregnancy-related hypertensive disorder showed higher rates of mortality from Alzheimer's disease and stroke in these women compared to women with normal pregnancies [75].

Treatment of hypertension during pregnancy is complicated by the fact that all antihypertensive medications cross the placenta [4]. Medications considered safe during pregnancy include methyldopa, labetalol, nifedipine, and hydralazine [76–78]. Clonidine can also be used, but care must be taken to avoid abrupt discontinuation due to the risk of rebound hypertension [79]. Treatment thresholds and goals for hypertension during pregnancy are debated. The American College of Obstetrics and Gynecologists (ACOG) recommends starting antihypertensive treatment in pregnant women with BP ≥160/110 mmHg [73]. It remains unclear whether initiation of antihypertensives for BPs below this threshold provides benefit or harm to the mother and/or fetus [80, 81]. An ongoing study addressing the short and long term risks/benefits of initiating antihypertensive therapy in pregnant women to a BP target <140/90 mmHg is underway (Chronic Hypertension and Pregnancy Project (CHAP), clinicaltrials.gov identifier: NCT02299414).

Conclusion

Hypertension remains a significant cause of CVD in both women and men. The relationship between hypertension and its long term sequelae are complex, but there appear to be gender specific differences in the pathogenesis of the disorder and in responses to treatment that must be taken into consideration. Black women, particularly those who are overweight and obese, have a disproportionate predilection for the development of hypertension, and are at an increased risk for its long term complications. An aggressive approach to lifestyle modification should be taken with this population. Early diagnosis and management of hypertension are essential for CVD prevention, and the use of ABPM should be considered in all individuals to make the diagnosis of hypertension.

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Chapter 4
Sex-Based Differences in Risk Determinants and Management of Heart Failure

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Introduction

There are both sex-based (biologic) and gender-related (sociocultural) differences in heart failure (HF). Differences in occurrence of HF between women and men may be partly due to variable prevalence and pathophysiologic influence of specific cardiovascular disease risk factors. Disparity in prognosis between woman and men with HF may be influenced by varying treatment efficacy and/or management strategy. It was not until 1991 that the National Institutes of Health (NIH) established a policy that all NIH-funded trials must include both women and men in studies of conditions that affect both sexes [1]. Most of the studies on women and cardiovascular disease including HF commenced following this mandate.

Heart Failure in Women

HF affects 5.1 million people in the United States, more than 40% of HF patients are women, and among the elderly the prevalence of HF is greater in women than in men [2]. In 2010, 32,847 deaths in women were due to HF, which accounted for

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more deaths in women than in men (58.2% versus 41.8%) [3]. The prevalence of HF increases with age, with more women than men having HF after 79 years of age. Although the lifetime risk for the development of HF in a 40-year-old individual is not different between both sexes (one in five), the lifetime risk for the development of HF in a 40-year-old individual without a preceding myocardial infarction is one in six for women versus one in nine for men [4, 5].

The risk factors associated with HF and its underlying pathophysiology differ to some extent by sex. Review of data from the Framingham Heart Study indicates that hypertension and diabetes mellitus impose a greater risk of HF in women than in men [6]. Women with HF have more hypertension, valvular heart disease, and thyroid disorders than men do but are less likely to have obstructive coronary artery disease (CAD) [7, 8]. Even though obstructive CAD is less frequent in women, it is a stronger risk factor than hypertension for the development of HF [9].

Unique circumstances for development of HF in women include cardiac toxicity from the chemotherapeutic drugs used for the treatment of breast cancer [10–12] and cardiomyopathy that occurs in the peripartum period [13–15]. Women with acute decompensated HF are twice as likely as men to have preserved left ventricular (LV) systolic function or HF with a preserved ejection fraction (HFpEF) [16]. Even women with an impaired left ventricular ejection fraction (LVEF) will have a higher LVEF than men do [16]. Notably, women with HF have a lower quality of life, lower functional capacity, more hospitalizations for HF, and more frequent depression [17]. Nonetheless, overall survival is better for women than for men with HF, except among HF patients with ischemic cardiomyopathy where prognosis is similar in both sexes.

Clinical Manifestations and Diagnosis of Heart Failure

The Studies of Left Ventricular Dysfunction (SOLVD) demonstrated that women with an impaired LVEF were more likely than men to have edema, elevated jugular venous pulsation, and an S_3 gallop [18]. However, women ($n = 54{,}674$) in the Acute Decompensated Heart Failure National Registry (ADHERE) registry, comprising both impaired and preserved systolic function, did not differ from men ($n = 50{,}713$) with respect to the frequency of HF symptoms and signs. The difference in this study versus others may be related to how ADHERE was specifically examining manifestations of acute decompensated HF rather than chronic symptoms [8].

The level of natriuretic peptides such as brain natriuretic peptide (BNP) and N-terminal pro Atrial Natriuretic Peptide (NT-proANP) levels used to diagnose HF are higher in women than in men [19, 20]. Although elevated levels of BNP and NT-proANP were associated with a greater risk of HF, the association was similar in both women and men [21]. BNP higher than 500 pg/mL appears to be a stronger predictor of death in women with HF than in men [22]. The levels of biomarkers related to inflammation, including C-reactive protein and interleukin-6, were lower in women than in men [23]. In this study, mortality

was also lower in women compared with men, independent of differences in clinical characteristics [23].

Breast Cancer Chemotherapy-Induced Cardiotoxicity

Cardiotoxic effects of chemotherapeutic agents is well known [10–12]. Briefly, in specific relevance to breast cancer treatment, adjuvant therapy with anthracyclines such as doxorubicin has demonstrable survival benefits but at a greater risk of early as well as late-onset myocardial dysfunction in a cumulative dose-dependent manner [24]. Anthracycline-induced cardiotoxicity is mediated by free radical production causing deoxyribonucleic acid (DNA) damage, apoptosis, cardiomyocyte death, and sarcopenia that may result in irreversible HF [12].

Recombinant monoclonal antibodies such as Trastuzumab used in the treatment of human epidermal growth factor receptor 2 (HER2) positive breast cancer also has proven beneficial effects but with a higher risk of severe HF, symptomatic HF, and decline in LVEF [25, 26]. This deleterious effect on the myocardium is thought to be due to inhibition of cardiomyocyte HER2 signaling and its ligand neuregulin-1 rather than because of induction of cell death and hence is potentially reversible [12, 27].

Peripartum Cardiomyopathy

Peripartum cardiomyopathy causes impaired LVEF in the last month of pregnancy or within 5 months postpartum, with no preexisting cardiac disease and no identifiable cause. Its incidence is estimated to be 1 in 4000 pregnancies, and it is associated with risk factors such as advanced maternal age, African descent, high parity, twin pregnancy, use of tocolytics, and poverty [28]. After the diagnosis, LVEF recovers in approximately half of the patients within 6 months, but 20% of patients deteriorate and either die or require heart transplantation. Recovery appears to be related to a less severe decline in LVEF [4]. The risk during subsequent pregnancies is not entirely clear.

Management of Heart Failure

Although women have been included in clinical trials in greater numbers than minorities, they have still been significantly underrepresented. This underrepresentation and the more prevalent HFpEF in women limit our overall understanding of HF management in women. Nonetheless, treatment guidelines for HF therapy provide similar recommendations for women and men [4]. In several major clinical trials including the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program, women were more likely to have preserved LV

function than men (50% versus 35%) [29]. Overall, evidence-based HF therapies are underused in both sexes, and although women are less likely than men to receive them, this disparity did not translate into a higher rate of hospitalizations for HF or mortality. Women are less likely to receive vasoactive agents, but women and men have equal lengths of hospitalization and age-adjusted in-hospital HF mortality rates.

Beta-Blockers

Carvedilol, metoprolol succinate and bisoprolol are proven in multicenter, prospective, randomized trials to reduce mortality and morbidity in HF patients with reduced LV systolic function. In the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS), carvedilol reduced the combined end point of death or hospital stay in the 469 women studied with LVEF ≤25% and severe symptomatic HF [30, 31]. In the European Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), bisoprolol improved survival in the 515 women studied, with New York Heart Association (NYHA) functional class III or IV and LVEF ≤35% (hazard ratio [HR], 0.37; 95% confidence interval [CI], 0.19 to 0.69) [32]. In the Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF) trial, although metoprolol succinate did not confer survival benefit for women (6.9% versus 7.5%, p = not significant) it reduced HF hospital stay by 42% (p = 0.021) in the 898 women studied with LVEF ≤40% who were NYHA functional class II to IV [33]. Meta-analyses of six major β-blocker trials including 2134 women and 7885 men, showed that women and men with symptomatic HF have similar mortality benefit when treated with beta-blockers (Table 4.1) [34].

To date, the use of β-blockers throughout pregnancy has not been associated with teratogenicity. A meta-analysis to determine teratogenicity of β-blockers in early

Table 4.1 Effect of beta-blockers on mortality in men and women with heart failure[a]

	Number of participants			RR (95% CI)		RRR (95% CI)
Trial-names	Total	Women	Men	Women	Men	Women/men
CIBIS-II	2647	515	2132	0.52 (0.30–0.89)	0.71 (0.58–0.87)	0.73 (0.41–1.30)
COPERNICUS	2287	465	1822	0.63 (0.39–1.04)	0.68 (0.54–0.86)	0.93 (0.54–1.59)
MERIT-HF	3991	898	3093	0.93 (0.58–1.49)	0.63 (0.50–0.78)	1.49 (0.88–2.51)
U.S. Carvedilol HF	1094	256	838	0.32 (0.11–0.93)	0.44 (0.24–0.82)	0.73 (0.21–2.51)
Random effects Pooled estimate		2134	7885	0.63 (0.44–0.91)	0.66 (0.59–0.75)	0.99 (0.70–1.41)

RR relative risk, *CI* confidence interval, *RRR* ratio of relative risk, *HF* heart failure, *CIBIS-II* Cardiac Insufficiency Bisoprolol Study, *COPERNICUS* Carvedilol Prospective Randomized Cumulative Survival Study, *MERIT-HF* Metoprolol Extended-release Randomized Intervention Trial in Heart Failure

[a]Adapted with permission from Shekelle et al. [34]

pregnancy was conducted by Yakoob et al. [35]. They found that first-trimester oral β-blocker use showed no increased odds of all or major congenital anomalies (odds ratio [OR], 1.00; 95% CI, 0.91 to 1.10; 5 studies). However, in analyses examining organ-specific malformations, increased odds of cardiovascular defects, cleft lip/palate, and neural tube defects were observed. While they concluded that the strength and causality of this association is difficult to interpret, it has also been suggested that β-blockers be prescribed cautiously later in pregnancy. β-Blockers have been studied most extensively for treatment of non-severe hypertension in pregnancy, and there has been no significant effect on the incidence of small-for-gestational-age infants [36].

Angiotensin Converting Enzyme Inhibitors

Angiotensin Converting Enzyme (ACE) inhibitors are among the most well-studied medications in HF therapy. ACE inhibitors reduce morbidity and mortality in HF with reduced ejection fraction (HFrEF). Randomized controlled trials clearly establish the benefits of ACE inhibition in patients with mild, moderate, or severe symptoms of HF and in patients with or without coronary artery disease [37–42]. However, this benefit may not be similar for women and men. A combined analysis of more than 30 trials demonstrated a 37% decrease in mortality for men, with only a 22% decrease in women [43]. Another pooled analysis has confirmed the finding that there is a tendency toward less benefit for women treated with ACE inhibitors (Table 4.2) [34].

Table 4.2 Effect of ACE inhibitors on mortality in men and women with heart failure

	Number of participants			RR (95% CI)		RRR (95% CI)
Trial-names	Total	Women	Men	Women	Men	Women/men
CONSENSUS	253	74	179	1.14 (0.68–1.90)	0.61 (0.44–0.85)	1.86 (1.01–3.42)
SAVE	2231	390	1841	0.99 (0.67–1.47)	0.80 (0.68–0.95)	1.24 (0.80–1.90)
SMILE	1556	428	1128	0.74 (0.47–1.18)	0.61 (0.39–0.96)	1.22 (0.64–2.32)
SOLVD-Prevention	4228	476	3752	1.15 (0.74–1.78)	0.90 (0.77–1.05)	1.27 (0.80–2.02)
SOLVD-Treatment	2569	504	2065	0.86 (0.67–1.09)	0.89 (0.80–0.99)	0.97 (0.74–1.26)
TRACE	1749	501	1248	0.90 (0.74–1.11)	0.79 (0.68–0.91)	1.15 (0.90–1.48)
Random effects Pooled estimate		2373	10,213	0.92 (0.81–1.04)	0.82 (0.74–0.90)	1.15 (0.99–1.33)

ACE angiotensin-converting enzyme, *RR* relative risk, *CI* confidence interval, *RRR* ratio of relative risk, *CONSENSUS* Cooperative North Scandinavian Enalapril Survival Study, *SAVE* Survival And Ventricular Enlargement, *SMILE* Survival of Myocardial Infarction Long-term Evaluation, *SOLVD* Studies Of Left Ventricular Dysfunction, *TRACE* TRAndolapril Cardiac Evaluation

[a]Adapted with permission from Shekelle et al. [34]

Angiotensin Receptor Blockers

Patients intolerant to ACE inhibitors because of cough or angioedema should be started on ARBs; patients already tolerating ARBs for other indications may be continued on ARBs if they subsequently develop HF [44]. Sex-specific data for ARBs are limited. Pooled data from the CHARM-Alternative and the CHARM-Added trials that included 1188 women with NYHA functional class II-IV HF and LVEF ≤40% showed that candesartan reduced the combined endpoint of cardiovascular death or HF hospitalization in women [45]. In the CHARM-Overall population, reduction in the combined endpoint was similar for women and men [45]. In the Valsartan Heart Failure Trial (Val-HeFT), Valsartan failed to demonstrate mortality benefit in 1003 women with NYHA functional class II to IV and LVEF ≤40% when compared with a placebo, however, it reduced HF hospital stay (HR, 0.74; 95% CI, 0.55 to 0.98) and first morbid event (HR, 0.79; 95% CI, 0.63 to 0.99) [(4, 46)].

Aldosterone Receptor Antagonists

Subgroup analysis of the Randomized Aldactone Evaluation Study (RALES) with spironolactone and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) with eplerenone revealed similar mortality benefits for women and men with systolic HF [34, 47]. The RALES trial included 446 women and studied the effects of spironolactone in ischemic and nonischemic cardiomyopathy patients with NYHA functional class III to IV and LVEF <35% [47]. The EPHESUS trial included 1918 women participants and studied the effects of eplerenone after an acute myocardial infarction in patients with LVEF ≤40% [48].

Angiotensin II-Receptor Blocker and Neprilysin Inhibitor

Angiotensin II-Receptor Blocker and Neprilysin Inhibitor (ARNI) is an ARB combined with an inhibitor of neprilysin, an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides [44, 49]. In a randomized clinical trial that compared valsartan/sacubitril, with enalapril in symptomatic patients with HFrEF tolerating an adequate dose of either ACE inhibitor or ARB, the ARNI reduced the composite endpoint of cardiovascular death or HF hospitalization significantly, by 20% [49]. The benefit was seen to a similar extent for both death and HF hospitalization and was consistent across subgroups. The use of ARNI is associated with the risk of hypotension and renal insufficiency and may lead to angioedema, as well. Drugs that inhibit the RAAS can cause harm to the fetus, and therefore, as with other ACE inhibitors and ARBs, valsartan/sacubitril should not be administered to pregnant women [50].

Hydralazine and Isosorbide Dinitrate

The combination of hydralazine and isosorbide dinitrate is commonly used in the treatment of HF patients who are intolerant to ACEI or ARB. The original data supporting this practice was from Veterans Administration HF trials and was limited to men [51, 52]. There is still no data available for women using hydralazine and isosorbide dinitrate as a substitute for an ACEI or ARB. In the African-American Heart Failure Trial (A-HeFT), combination hydralazine/isosorbide dinitrate was added to ACE inhibitor/ARB and β-blocker therapy in 1050 self-identified African Americans with NYHA functional class III-IV HF (420 women). The trial was prematurely stopped because of the significant survival benefits that were noted for both women (HR, 0.33; 95% CI, 0.16 to 0.71; p = 0.003) and men (HR, 0.79; 95% CI, 0.46 to 1.35; p = 0.385) in addition to fewer hospital stays, with no significant treatment interaction by sex [7].

Digoxin

Digoxin reduces HF hospital stay but has no beneficial effect on survival [53]. A post hoc subgroup analysis of the Digitalis Investigation Group (DIG) trial was concerning for increased mortality in women with reduced systolic function when treated with digoxin compared with placebo (adjusted HR, 1.23; 95% CI, 1.02 to 1.47), whereas in men digoxin had no effect on mortality (adjusted HR, 0.93; 95% CI, 0.85 to 1.02) [53, 54]. The increased mortality was presumed to be due to digoxin toxicity, because the risk of death increased at higher serum drug levels, and a subsequent analysis of the DIG trial data showed that digoxin at serum level of 0.5 to 0.9 ng/mL was safe and effective for both women and men [55].

Implantable Cardioverter-Defibrillator

Guideline recommendations for implantable cardioverter-defibrillator (ICD) implantation to prevent sudden death are based on many multicenter studies, but women have been underrepresented and few studies have provided adequate sex-specific data [56, 57]. Unfortunately, the limited *post hoc* analyses available for women with an ICD do not clearly demonstrate a mortality benefit [56–58]. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which included 382 women (190 randomized to an ICD and 192 to a placebo) with NYHA class II-III HF and LVEF ≤35% (ischemic and nonischemic cardiomyopathy), the benefits of an ICD were not clear, although the trial was not powered to detect sex differences (HR, 0.96; 95% CI, 0.58 to 1.61 in women) [59]. In the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II), which included 192 women (119 randomized to an ICD) with ischemic cardiomyopathy and an LVEF ≤30%, ICD

use was associated with a nonsignificant trend toward lower mortality in women (adjusted HR, 0.57; 95% CI, 0.28 to 1.18; p = 0.132) [60].

ICDs are underused in both sexes, particularly so in women. Eligible women, especially black women, are less likely than men to receive an ICD (26.5% versus 42.4%, $p < 0.0001$). ICD use increased over time, and the racial disparities disappeared by 2009, but the sex disparities have persisted [61]. None of the randomized trials for ICDs enrolled sufficient numbers of women to permit analysis of sex differences, current data are insufficient to support differential use of ICDs by sex.

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is of benefit in both women and men with HF and a wide QRS complex, however, there is some evidence that women may derive greater benefit from CRT compared with men. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study, which included 493 women, women who underwent CRT had a significant reduction in the combined endpoint of total mortality or hospital stay for any cause than did women receiving just medical therapy, and there was no interaction by sex [57]. In the MADIT-CRT trial, which randomized 1367 men and 453 women with an LVEF ≤30% and NYHA class II HF to CRT plus ICD versus ICD alone, CRT was associated with better outcomes and greater degree of reverse remodeling in women compared with men [62]. Although few studies have reported any sex-specific data, these same findings have been confirmed in a retrospective analysis of the Cardiac Resynchronization–Heart Failure (CARE-HF) study that included 215 women [63].

Left Ventricular Assist Devices

Implantable LV assist devices (LVADs) are being placed more frequently for the management of end-stage refractory HF as a bridge to transplant or a destination therapy [64]. Although there are no sex-related differences in the surgical techniques for implanting LVADs, small women had limited options with early devices as they require a minimum body size to fit properly [65]. However, more recent devices including HeartMate II, HeartMate III and the HeartWare, are smaller and more women have been enrolled in clinical trials with similar survival rates compared with men [66, 67]. A review from the Cleveland Clinic concluded that there were no significant sex-based differences in mortality, time to first infection, bleeding, or device malfunction with either pulsatile- or continuous-flow LVADs. However, women had an increased risk of first neurological event [68]. In a recent study comparing outcomes of continuous flow LVAD implantation between 24 women and 24 men as a bridge to transplantation, women had a longer duration of

inotropic support and higher requirement for postoperative mechanical right ventricular support, but similar survival rates compared with men [69].

Cardiac Transplantation

Based on data from the International Society of Heart and Lung Transplantation registry, women received 23.7% of the 17,868 heart transplants performed from January 2006 to June 2011 [70], representing significant increases from 22.3% and 19.3% in the prior 5- and 10-year periods. Overall survival rates are now similar in women and men, although female recipients of a male donor heart may be at higher risk of 1-year mortality than male recipients from a male donor [70].

Heart transplantation occurs far less frequently in women than in men [71] with only 28% of heart transplants in the United States in 2011 occurring in women [70]. Reasons for lower rates of transplantation in women are not clear; this may be partly explained by higher levels of panel reactive antibody in parous women, which makes identifying suitable donors more challenging [72]. There is also a higher acceptance of patients for transplantation with an ischemic cause of cardiomyopathy, regardless of sex, which increases the proportion of men who undergo transplantation compared to women [73]. Women also tend to be older, possibly decreasing candidacy for transplantation [72].

Conclusions

HF remains an important healthcare concern for women in the United States. Generally, HF affects women at a more advanced age with better global LV systolic function, compared with men. Women are more likely to have hypertension, diabetes mellitus and valvular disease as the etiology and less likely to have coronary artery disease. Most large HF trials have under-represented women in their enrollment numbers, and this has narrowed our knowledge of sex-related differences in HF pathophysiology, diagnosis, and treatment.

In general, survival seems to be better for women than for men with HF, with the likely exception of HF patients with ischemic heart disease where prognosis is similar in both sexes. Current treatment guidelines are not sex-specific because sufficient data is not available, however, as the therapeutic options for HF expand, sex-based modifications to HF management may be considered in future revisions.

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Chapter 5
Gender Differences in Cardiomyopathies

Aisha Siraj, Rimsha Hasan, and Sabha Bhatti

Introduction

Cardiomyopathies are a heterogeneous group of heart muscle diseases with identifiable differences in modes of presentation in different genders. Cardiomyopathies are classified into hypertrophic (HCM), dilated (DCM), arrhythmogenic right ventricular (ARVC), restrictive (RCM), and unclassified cardiomyopathies. Each class is further subdivided into inherited (familial) and non-inherited (non-familial) forms.

There is substantial evidence that biological sex is a strong modulator of the clinical manifestations of each cardiomyopathy. Genotypic gender related differences may result in variability in the phenotypic manifestation of these diseases.

For the clinician, it is important to know the sex-specific differences of clinical disease and the hereditary influences underlying the development of cardiomyopathies, as these may aid in diagnosing such diseases in both genders.

'Cardiomyopathy' is defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of an underlying cause such as coronary artery disease, hypertension, valvular disease as well as congenital anomalies sufficient to cause the observed myocardial abnormality. The disease entity is classified into five distinct morphological and functional phenotypes [1]. These include hypertrophic, dilated, arrhythmogenic right ventricular, restrictive, and 'unclassified or miscellaneous'.

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Over time there has grown a deeper understanding of the subtle differences in disease phenotypes that spring of genotypic differences including gender specific ones.

The importance of gender related differences is gaining increasing attention in cardiovascular medicine [1]. Various studies have demonstrated marked differences between males and females in ischemic heart disease. These differences include but are not limited to risk factors, clinical presentation, diagnostic modalities, the use and effectiveness of various therapies, and prognoses [2–4]. Likewise, several studies have revealed gender differences in heart failure [5] and cardiac arrhythmias [6]. This has led to worldwide research and educational initiatives on the specific characteristics of cardiovascular disease in women [7–9]. An increasing body of data indicates that gender plays an important role in various forms of cardiomyopathies, in terms of its prevalence, severity, and prognosis. We present an overview of the literature on gender related differences in cardiomyopathies.

Familial Hypertrophic Cardiomyopathy

This subgroup of cardiomyopathies includes previously called 'true' hypertrophic cardiomyopathy. It also includes inherited cardiomyopathies with LV hypertrophy as a pathological manifestation of metabolic disorders including glycogen storage diseases, lysosomal storage diseases, familial transthyretin-related amyloidosis, carnitine deficiency and mitochondrial cardiomyopathies [10]. No definite gender based differences have been identified for the later two disease spectrums.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorder, with an estimated prevalence of 1:500 [11]. It is characterized by LV hypertrophy, which predominantly affects the inter-ventricular septum. This may occur with or without LV outflow obstruction. It may also affect other parts, most commonly the apical part of the left ventricle [12]. At the histological level, the key findings are myocardial disarray and fibrosis. In the vast majority of cases, HCM is due to a mutation in a gene encoding a component of the cardiac sarcomere [13]. Commonly involved genes are those encoding β-myosin heavy chain (*MYH7*), myosin-binding protein C (*MYBPC3*), and cardiac troponin T (*TNNT2* and *TNNI3*), and these are detectable in ~75% of HCM patients [14, 15]. However, the relative frequencies of the genes or specific mutations involved may differ across populations and the relationship between genotype and phenotype varies [14]. The mode of inheritance is autosomal dominant, which implies that equal numbers of males and females are carriers of the underlying disease-causing mutation [11]. However, there are phenotypic differences between the sexes.

The largest study to date, by Olivotto et al. [16], was in 969 consecutive patients with HCM; they showed a higher prevalence in males than females (3:2). Interestingly, males were more often diagnosed by routine medical examination than females (41% vs. 23%), in whom the diagnosis was mainly established after onset or worsening of cardiac symptoms or occurrence of cardiovascular events. In addition, the average age at diagnosis was significantly lower in males than in females (38 ± 18 years vs. 47 ± 23 years). However, at presentation, females were more symptomatic than males (NYHA class 1.8 ± 0.8 vs. 1.4 ± 0.6) and more frequently showed LV outflow obstruction (37% vs. 23%). Moreover, female sex was independently associated with the risk of symptom progression to NYHA class III/IV or even death from heart failure or stroke. Essentially similar findings were reported in other studies [17–19]. In order to delineate possible underlying mechanisms, Schulz-Menger et al. [20] performed a magnetic resonance imaging (MRI) study, using the LV remodeling index (LV mass/LV end-diastolic volume). This index was comparable in males and females with LV outflow obstruction, but, in patients without obstruction, females had a lower remodeling index compared with males. Although the clinical implications of these findings are currently uncertain, it shows that sex is associated with differences in LV remodeling in HCM [20].

Fabry's Disease

Fabry's disease is a rare disease, caused by storage of glycosphingolipids in various organs and tissues due to a deficiency of the lysosomal enzyme α-galactosidase A (α-Gal A) [21]. The underlying disorder is a mutation in *GLA*, the gene encoding α-Gal A, located on chromosome Xq22. More than 100 mutations have been reported, including missense, nonsense, or splice site mutations, insertions/duplications and deletions. The phenotype of this multisystem disease is usually dominated by renal failure, neurological features (neuropathy), and skin abnormalities (angiokeratoma, anhydrosis). In addition, the heart is often affected; LV hypertrophy may develop due to myocardial deposition of glycosphingolipids, which is indistinguishable on a standard echocardiogram from HCM, including septal hypertrophy and LV outflow tract obstruction. The hypertrophy can be massive, with an LV wall thickness up to 30 mm. Short PR intervals are often seen on ECGs (without pre-excitation).

Fabry's disease is an X-linked disease, affecting predominantly males, with females being carriers. Indeed, the clinical picture is far more pronounced in males. In rare cases females may manifest the phenotype [22], mostly characterized by neurological and cardiac symptoms [23]. In males with a suggestive phenotype, the diagnosis is made by demonstrating low α-Gal A activity in leucocytes or plasma. In females, demonstration of a mutation in *GLA* is required to confirm the diagnosis. Females usually show less severe progression of hypertrophy compared to males [24]. It was recently suggested in an MRI study that replacement fibrosis may be a valid screening tool in females as opposed to males in the early stages of Fabry's disease [25].

Amyloidosis

Familial Transthyretin-Related Amyloidosis

Familial transthyretin-related amyloidosis (ATTR) is a form of amyloidosis caused by mutated transthyretin (or pre-albumin), leading to deposition of amyloid in various tissues and organs [26]. The underlying disorder is a autosomal dominant mutation of *TTR*, the gene encoding transthyretin. The phenotype of ATTR is dominated by neurological alterations (neuropathy), but cardiomyopathy is also a common finding. However, several studies have shown that sex differences are present in both the occurrence of cardiomyopathy and the degree of the hypertrophy. Males with ATTR more often exhibit cardiomyopathy than females and have higher degrees of hypertrophy [27]. It is noteworthy that post-menopausal females with ATTR have more hypertrophy than pre-menopausal females, whereas an analogous age-related association is not present in males, implicating the influence of sex hormones. Indeed, in a mouse model, 5α-dihydrotestosterone was a strong inducer of transthyretin synthesis [27, 28].

Carnitine Deficiency

Carnitine deficiency is a rare, autosomal recessive disorder, caused by mutations in *SLC22A5*, which encodes a sodium-dependent carnitine transporter protein involved in cellular carnitine uptake. Carnitine deficiency leads predominantly to metabolic or cardiac disease manifestations, including cardiomyopathy [29]. Although typically occurring in childhood, the onset of disease may vary and, rarely, the disease may also present in adulthood [30]. The disease is diagnosed preferentially in females, probably because of intensified screening activities in the mothers of infants with the disease [30, 31].

Non-familial Hypertrophic Cardiomyopathy

This subgroup of cardiomyopathies includes non-inherited forms of LV hypertrophy, such as those seen in athlete's heart, obesity, and non-familial amyloidosis. No sex differences have been reported regarding the cardiomyopathies associated with obesity and amyloid light-chain (AL) amyloidosis.

Athlete's Heart

It is well established that athletic training may lead to cardiac remodeling, both electrophysiological and structural. Depending on the training intensity and duration, the size of the cardiac chambers often increases, in particular that of the left

ventricle. However, this remodeling process mainly affects males; at a comparable training intensity and duration, male athletes, on average, develop a higher degree of LV hypertrophy than females [32, 33]. The hypertrophy is occasionally hard to distinguish from pathological hypertrophy caused by HCM. Importantly, in the athlete's heart, the diastolic function usually remains largely intact, yet subtle changes may occur, in particular in male athletes [34]. In addition, recent evidence also suggests that athletic training may lead to adverse right ventricular remodeling, which may resemble a right ventricular cardiomyopathy phenotype [35].

Senile Systemic Amyloidosis

The non-familial form of transthyretin amyloid deposition (wild-type) is referred to as senile systemic amyloidosis (SSA) and nearly exclusively affects the heart of elderly people [26]. Notably, SSA mainly occurs in males, suggesting a role for the sex hormones. Indeed, Goncalves et al. [36] demonstrated the effects of androgens and estrogens on the expression of transthyretin in the liver of mice, which translated into a rise of transthyretin protein levels in the peripheral circulation. Importantly, 5α-dihydrotestosterone appeared to be a stronger inducer of transthyretin than 17β-estradiol.

Familial Dilated Cardiomyopathy

In at least one-third of patients with idiopathic DCM, familial occurrence can be noted, pointing to nature of the inherited disease [37, 38]. Familial DCM mainly comprises autosomal dominant forms, caused by mutations in several different genes coding for the cytoskeleton, sarcomeric protein/Z-band, nuclear membrane, and intercalated disc proteins. In addition, there are a few X-linked forms, some of which are associated with muscular dystrophies, and other forms seen in mitochondriopathies and inherited metabolic disorders. Duchenne (DMD) and Becker muscular dystrophies are the most common forms of myopathies, and they frequently show cardiac involvement [39, 40]. Mutations in *DMD* result in either no functional (Duchenne) or inadequate (Becker) dystrophin production, leading to structural instability of the muscle cell membrane and muscle degeneration. Because of the compensatory function of the second, non-mutated X-chromosome in females, they have a lower chance of disease manifestation, but may also express the disease phenotype [41], probably due to random X-chromosome inactivation or a gene dosage effect [42]. In general, familial DCM primarily affects males, with a reported male/female ratio of up to 1.5:1 [43], despite the usual mode of inheritance, which is autosomal dominant [44]. Herman et al. [45] reported on various mutations in *TTN*, the gene encoding the sarcomeric protein titin, in 312 patients with idiopathic DCM, which underlies the DCM phenotype in ~25% of cases. Interestingly, almost all patients developed DCM after the age of 40 years (full penetrance), and adverse DCM events, such as cardiac transplantation, implantation of an LV assist device,

and cardiac death, occurred significantly earlier in males than in females carrying the *TTN* mutations. Likewise, Van Rijsingen et al. [46] observed gender based differences in 269 patients with DCM due to mutations in the lamin A/C gene (*LMNA*). Males significantly more often developed relevant reduction of LVEF, malignant ventricular arrhythmias, and end-stage heart failure compared with females, and mortality was also higher in males. The molecular mechanism for the sex difference was established by Arimura et al. [47] who proved direct involvement of the androgen receptor and its co-activators in a mouse model, demonstrating testosterone effects on gene/protein expression and morphological disease expression.

Non-familial Dilated Cardiomyopathy

This subgroup comprises of myocarditis, alcohol abuse, peripartum cardiomyopathy, autoimmune diseases, drug toxicity, nutritional deficiencies, and tachycardia (tachycardiomyopathy). For the latter four disorders, no sex differences in the prevalence and severity of cardiomyopathy have been reported so far.

Myocarditis

Myocarditis is a common cause of DCM and may arise from infective, toxic, or immune sources. The pathogenetic pathways are known to be modulated by sex hormones, resulting in differences between the genders in their cardiac response to inflammatory injury [44]. Indeed, mouse models show that myocarditis occurs more frequently in male than in female mice, and also that it is more severe in male mice [48, 49]. These findings are in accordance with observational studies in humans that show a higher prevalence in males [50–53].

Alcohol-Induced Cardiomyopathy

Excessive alcohol consumption is known to be myotoxic and can result in cardiomyopathy [55]. This occurs through several mechanisms [54]. In experimental studies on the effect of alcohol on cardiomyocytes, male animals showed more functional and structural myocardial impairment while the affect on female heart was found to be less severe [56, 57]. Interestingly, in humans, females seem to have a higher sensitivity to the cardiotoxic effects of ethanol than males [58, 59]. Urbano-Márquez et al. [55] demonstrated that there was no difference in the prevalence of DCM between the sexes, but females required a lower total lifetime dose of ethanol to develop the disease.

Peripartum Cardiomyopathy

By its very nature, peripartum cardiomyopathy is a form of DCM confined to females [59]. It typically occurs between the last month before childbirth and the first 5 months thereafter [60]. Although the exact etiology remains to be fully elucidated, Hilfiker-Kleiner et al. have identified a central pathophysiological role for the hormone prolactin in an animal model of peripartum cardiomyopathy, and have introduced bromocriptine, a dopamine D2 receptor agonist, as a potential treatment [61]. More specifically, their findings suggest that peripartum oxidative stress triggers the proteolysis of prolactin into a smaller 16 kDa fragment, which in turn has detrimental proinflammatory, antiangiogenic, and proapoptotic effects [62]. The fact that it can occur in families raises the likelihood that peripartum cardiomyopathy can be an 'unmasked' form of familial DCM [63–65].

Sarcoid Related Cardiomyopathy

Sarcoidosis is a systemic disease that can involve several different organ systems including the heart. Cardiac involvement in sarcoidosis can result in phenotypic manifestations including ventricular arrhythmias, complete heart block, pulmonary venous hypertension, pericarditis/pericardial effusions, cardiomyopathy as well as ventricular aneurysms.

Though the etiology of sarcoidosis remains unknown, but this ultimately results in formation of noncaseating granulomas that comprise of lymphocytes and phagocytes. These can deposit in the myocardium including left ventricular basal septum, free wall and right ventricle [45]. These can also deposit in papillary muscles, left and right atrium.

Echocardiographic manifestations of sarcoid heart disease were studies in 42 patients and it was discovered that septal involvement (thickening as well as thinning of septum) was observed in eight patients, four patients had increased end-diastolic dimension with decline in left ventricular systolic function [46]. This study did not demonstrate any echocardiographic differences amongst different genders. However it is already established that sarcoidosis, an autoimmune disease, is more prevalent in women than men with cardiac involvement in 20–30% of patients [47].

Several factors are implicated in increased incidence of sarcoidosis in women including hormones, genetics, occupational exposure, smoking, medication use, increased vitamin D deficiency as well occupational exposure. Nearly every aspect of cardiac sarcoidosis ranging from epidemiology to phenotypic manifestation, treatment options and prognosis is influenced by gender. The diagnosis occurs earlier while the presentation follows a bimodal distribution in women. Mortality with cardiac sarcoidosis also happens to be higher in women.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by global or regional right ventricular dysfunction, which is caused by progressive right ventricular adipose and fibrous replacement of the myocardium. Besides histological proof of these structural changes, which may also affect the left ventricle, the diagnosis is based on functional abnormalities, including conduction disturbances and arrhythmias, in addition to the presence of right ventricular dysfunction [10]. Inheritance of ARVC is predominantly autosomal dominant, involving various genes encoding intercalated disc proteins, such as plakophilin and other proteins of the cardiac desmosomes [66]. In addition, mutations in genes encoding non-desmosomal proteins can be involved, including transforming growth factor-β3, the cardiac ryanodine receptor, tmem43, titin, α-catenin, desmin, and phospholamban [67]. However, autosomal recessive transmission has also been described related to mutations in genes encoding plakoglobin and desmoplakin [68]. Sex differences in the prevalence, phenotypes, and clinical courses of ARVC have been described. It is more prevalent in males than females, with an approximate ratio of 3:1 [69]. In a group of 171 consecutive ARVC patients, Bauce et al. [70] found more severe disease expression in males than females, as indicated by larger right ventricular volumes, lower right ventricular EF, and more severe LV involvement. Moreover, ECG abnormalities typical for ARVC and late potentials were more common in male than in female patients, which is consistent with more severe disease. Hodgkinson et al. [71] reported on the impact of implantable cardioverter-defibrillator (ICD) therapy in patients with a specific form of familial ARVC (ARVD5). In a group of 48 subjects at 50% *a priori* risk of inheriting ARVC (as defined by clinical, pedigree, and/or haplotype data), more males were classified as high risk, based on clinical events of sudden cardiac death or ventricular tachycardia, and the relative risk of early death was significantly higher in males than in females [71], which is in line with other reports [72, 73]. Bhonsale et al. [74] reported on 215 patients with arrhythmogenic right ventricular cardiomyopathy-associated mutations and found male sex to be an independent predictor of the first arrhythmic event on multivariable analysis. Finally, Merner et al. [75] identified the missense mutation in transmembrane protein 43 (TMEM43 c.1073C>T, p.S358L) as the cause of this fully penetrant, lethal form of ARVC. They also observed far more serious early events, such as heart failure and death, in males, which again clearly indicates an influence of sex.

The cause of these sex differences in ARVC is unknown, but it has been shown that strenuous physical exertion in susceptible mice may elicit ARVC, and differences in physical exercise between males and females might thus play a role [76].

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) refers to cardiomyopathy with the presence of restrictive ventricular physiology at normal or reduced ventricular volumes (systolic and/or diastolic of one or both ventricles), and normal wall thickness [10].

Restrictive cardiomyopathy rarely occurs as a familial disease, but it can result from autosomal dominant, autosomal recessive, or X-linked inheritance. In most cases, transmission is autosomal dominant, involving mutations in *TNNI3* [77] or *DES* [60, 61] encoding troponin I and desmin [78, 79], respectively, the latter also being associated with conduction disorders and skeletal myopathy [80, 81].

Ammash et al. [82] reported on the experience of the Mayo Clinic in a group of 94 patients with idiopathic RCM, of whom 61% were females. Interestingly, despite the higher occurrence in the females, they showed significantly better survival than the males. However, Rivenes et al. [83] described a higher incidence of sudden cardiac death in girls with RCM.

Non-familial Restrictive Cardiomyopathy

Non-familial RCM mainly results from secondary endomyocardial or myocardial effects from various origins. The final common pathway is fibrotic tissue remodelling of the endocardium, such as is typical for endomyocardial fibrosis, hypereosinophilic syndrome, scleroderma, carcinoid heart disease, or anticancer therapies (radiation and cytostatic drugs). However, non-familial (AL/pre-albumin) amyloidosis and metastatic cancer infiltration of the myocardium may also result in RCM. A small, retrospective, single-centre study reported on a sample of 17 patients referred for surgery from 1971 to 1995 for endomyocardial fibrosis, and indicated that endomyocardial fibrosis was more common in females than in males [84]. However, no sex differences are known for hypereosinophilic syndrome, scleroderma, or carcinoid heart disease, nor for AL amyloidosis, in which cardiac involvement seems to be nearly equally distributed in both sexes [27]. Finally, RCM may also be due to radiation to the chest. Although there is substantial exposure bias (radiation to the chest being more common in females because of breast cancer), it is still not known whether RCM due to radiation is more common in females.

Non-compaction Cardiomyopathy

Non-compaction cardiomyopathy is a rare, structural myocardial disorder of acquired or congenital origin, characterized by prominent trabeculations and recesses in the LV walls. Non-compaction cardiomyopathy is often familial, and different genes are involved, in particular *MYH7* and *MYBPC3*, which are also implicated in HCM [10]. In infants, X-linked inheritance may occur; however, an autosomal dominant pattern of inheritance is detectable in most adult non-compaction cardiomyopathy patients [85]. In a retrospective, single-centre study in 100 patients, Stöllberger et al. [86] described a higher prevalence of non-compaction cardiomyopathy in males, whereas females had more extensive disease. The outcomes were, however, comparable between males and females.

Tako-Tsubo Cardiomyopathy

Tako-Tsubo cardiomyopathy (or 'stress cardiomyopathy') is an abrupt, transient, LV apical ballooning syndrome, mimicking myocardial infarction despite normal coronaries on angiography [10]. The pathogenesis of this relatively frequent disorder seems to be catecholamine-driven, transient myocardial dysfunction, and usually has a benign prognosis [87]. Tako-Tsubo cardiomyopathy occurs preferentially in females, in particular post-menopausal females [88, 89]. Although disease presentation has been reported to be similar between the two genders, Tako-Tsubo cardiomyopathy is more often triggered by emotional stressors in females and physical stressors (e.g. severe pain or acute illness) in males [90]. In the case of a physical stressor, clinical disease manifestation is usually more severe, with shock or cardiac arrest [91], which might point to a biologically less well-established physical stress resistance in male than in female hearts [92]. The pathophysiological explanation for the epidemiological and clinical sex differences in Tako-Tsubo cardiomyopathy is unclear, but gender related differences in the response to various kinds of myocardial stress have been well established experimentally and suggest that sex hormones have some influence [93]. Accordingly, Brenner et al. [94] analyzed the levels of sex hormones in post-menopausal women with Tako-Tsubo cardiomyopathy and age-matched females, with and without myocardial infarction, and found significantly higher estrogen levels at hospital admission in Tako-Tsubo cardiomyopathy patients.

Conclusion

The manifestations of many cardiomyopathies are influenced by gender. In the diagnostic work-up of a subject presenting with a possible cardiomyopathy, the clinician should be aware of this issue. In addition, the patient's gender is also relevant for the therapeutic management and prognosis in the case of established disease. However, there are still many unanswered questions, and further research is clearly needed. In particular, the modifying role of sex hormones needs to be fully elucidated.

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Chapter 6
Cardiovascular Risks of Impaired Fertility and Assisted Reproductive Therapy

Ki Park and Carl J. Pepine

Introduction

Over the last several decades, it has become increasingly appreciated that pregnancy history is important in assessing cardiovascular (CV) risk in women. Due to the tremendous changes that occur during pregnancy in regards to hemodynamic and metabolic alterations, pregnancy is often referred to as a *stress test*, potentially unmasking conditions that can increase CV risk in women. These conditions include pre-eclampsia, gestational diabetes, and gestational hypertension, and were recognized for the first time in the 2011 American Heart Association CV risk stratification guidelines for women. However, it should be noted that adverse pregnancy outcomes also include neonatal outcomes that increase maternal CV risk, such as intrauterine growth restriction and preterm birth. These associations indicate that the milieu under which children are carried to term influences not only the child but serves as a risk marker for future maternal health.

Similarly, emerging evidence supports the suggestion that women who have infertility conditions may also have increased maternal CV risk over the long-term. The inability of women to either conceive or successfully carry a pregnancy

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to term can be caused by a multitude of factors. This is particularly true as maternal age advances, with more women waiting to have children until well past traditional childbearing years of prior decades. Although there have been remarkable advances in the management of a variety of infertile conditions, it is increasingly recognized that conditions of infertility not only affect the ability to bear children but may also increase risk for the development of other chronic conditions. Additionally, it has been suggested that therapies to improve fertility may have important adverse CV and metabolic consequences as well. These associations may even extend to the offspring born through the assistance of reproductive technologies. In particular, accumulating evidence regarding the potential long-term CV effects of both infertile conditions themselves, as well as the specific therapies used to assist conception, has been studied. Study and discussion of such topics is particularly important as CV disease remains the leading cause of death in women.

Background

Use of fertility therapies to assist women in achieving pregnancy continues to increase. The causes of infertility can vary widely from anatomic considerations, to hormonal imbalances, to advanced age and premature menopause. In general, infertility includes disorders of ovulation, endocrine conditions such as hyperprolactinemia, and polycystic ovarian syndrome. Fortunately, in recent decades, the ability for women to conceive has dramatically improved and has opened opportunities for women who otherwise may not have been able to achieve pregnancy. As technology has improved, more women than ever are undergoing various types of assisted reproductive technology (ART), with the use of fertility therapy continuing to increase [1]. However, the spectrum of treatment for infertility varies widely, from oral medication therapy such as clomiphene for ovarian stimulation to more invasive therapies such as *in vitro* fertilization with associated hormone therapies. Yet the association of the baseline infertile state, as well as the effects of fertility therapies, on long-term maternal health are unknown [2]. Of most concern is the potential CV impact of these conditions. It has become increasingly recognized that pregnancy serves as a woman's *stress test*—many conditions that may occur during pregnancy and have the potential to lead to adverse fetal outcomes, such as pre-eclampsia, also can portend increased long-term maternal CV risk. In this same light, it is plausible that the infertile state and related treatment may also have long-term consequences. Although many women may have multifactorial etiologies for their infertility, if adverse associations between specific conditions leading to infertility, which then lead to increased long-term CV risk, can be identified, this may serve as a useful marker to help guide preventative therapies. Additionally, considering that children born from ART are conceived via assistance, there is emerging evidence that the offspring of these women may also suffer from lasting CV effects.

Polycystic Ovarian Syndrome

The majority of work focused on assessing conditions of metabolic dysfunction and markers of elevated CV risk in women with infertility has been directed toward polycystic ovarian syndrome (PCOS), the most common endocrine disorder for women of reproductive age, affecting just under 10% of women. It is not uncommon for PCOS to remain clinically unrecognized unless a woman presents for a fertility evaluation. PCOS covers a spectrum of clinical and metabolic abnormalities, which may manifest to different degrees in different women, but generally features abnormal menses; androgen excess, specifically testosterone; and polycystic ovaries with anovulation leading to infertility. It is well established that PCOS significantly increases the risk for metabolic syndrome. Women with PCOS have a twofold increased risk for metabolic syndrome, and at least half of those with PCOS demonstrate some degree of insulin resistance [3, 4]. This association of prediabetes and diabetes risk is even more evident in women with a family history of diabetes. Although women with PCOS are often thought of as being obese, many of the adverse metabolic findings, such as abnormal lipid profiles with high LDL, have been found in both obese and non-obese PCOS patients [5]. Similarly, PCOS has been associated with increased risk of obstructive sleep apnea, which persists even after adjustment for body mass index. The severity of sleep apnea also appears to correlate with the degree of glucose intolerance [6]. PCOS patients, compared with women without PCOS, also have evidence of elevated blood pressure, regardless of race or ethnicity [7]. In addition, several other conditions known to be associated with elevated CV risk have been associated with PCOS, including elevated C-reactive protein levels and evidence of increased intimal medial thickening on carotid imaging [8, 9]. Whether the increase in CV risk factors associated with PCOS, or the condition itself, predisposes to CV events is unclear. Data on long-term CV morbidity and mortality in women with PCOS are suggestive but not conclusive. Considering the prevalence of PCOS, this is an important knowledge gap and warrants additional study.

Premature Ovarian Failure

Premature ovarian failure (POF) is defined as ovarian function failure before the age of 40. Although relatively rare (~1% of women), this condition can also be seen in women under the age of 30. Commonly referred to as *early menopause*, POF is differentiated in that women with POF can still ovulate on occasion, while in true early menopause ovulation does not occur. The cause of POF remains unclear and likely stems from some combination of genetic/epigenetic and chromosomal abnormalities. Early data suggested an association of POF with elevated CV risk [10, 11]. Initial data from the Seventh-Day Adventist study indicated that women with natural menopause at age <40 years had a near doubling of all-cause mortality compared to those with menopause at age >50. The study also suggested a stepwise

relationship so that for every year of early menopause before age 47, there was a ~50% increase in early death [12, 13]. Mechanisms thought to be involved with this risk association include endothelial dysfunction as assessed by flow-mediated dilation [14]. However, subsequent studies in other cohorts, such as National Health and Nutrition Examination Survey, did not support these findings with regard to all-cause mortality risk [15]. Studies assessing CV mortality more specifically have also been suggestive but not definitive. Van der Schouw suggested a 2% decrease in CV mortality for every year menopause was delayed. Another analysis from the American Seventh-Day Adventist cohort found similar findings [11, 16]. Additionally, women with POF are often prescribed hormone replacement therapy (HRT) with estrogen, and the overall CV effects of these therapies are unknown, particularly in the long-term, although data from the Women's Health Initiative showed that estrogen supplementation is not beneficial relative to CV risk reduction and is even potentially harmful when started in older women [17]. Some data suggest that HRT in women with POF beneficially affects mechanisms involved in CV risk, such as lowering blood pressure, improving vasodilation, and reducing renin-angiotensin up-regulation [18]. A dedicated discussion of HRT is beyond the scope of this chapter, but warrants further study in women with POF.

Endometriosis

Endometriosis is defined as the presence of endometrial tissue outside of the uterus, which can lead to infertility and varied gynecologic symptoms including dyspareunia and abdominal pain. The disorder is characterized by a multitude of inflammatory and metabolic effects, many of which overlap with known mechanisms increasing CV risk. Treatment of infertility related to endometriosis is complex and can often require multiple interventions such as surgical removal of endometriosis tissue and *in vitro* fertilization along with ovulation induction. The most notable data assessing endometriosis and CV risk comes from an analysis from the Nurses' Health Study II [19]. The study found a significant association between endometriosis and CV events. Notably, the highest risk appeared in the women younger than age 50 years. Of additional note, in the women with endometriosis, those who underwent hysterectomy had even higher CV risk. Although hysterectomy is recommended as therapy for symptoms of endometriosis and other conditions, this highlights the importance of assessing potential long-term CV risk of these procedures.

Assisted Reproductive Technology

As infertility is a complex disorder, therapy in the form of ART incorporates a wide spectrum of pharmacotherapeutic interventions and invasive techniques to improve ovulation and conception. Primary anovulation is the most common cause of infertility related to PCOS in the setting of otherwise normal gonadotropic function with

normal estrogen. The other most common class is primary gonadal failure, discussed above as premature ovarian failure. Lifestyle modification and weight reduction are the most commonly recommended first-line steps to improve ability to conceive in those with PCOS.

The term ART encompasses a wide range of fertility therapies such as oral therapies for ovarian stimulation to *in vitro* fertilization and intrauterine insemination, which is commonly performed in conjunction with hormonal stimulation. These processes often need to be performed repeatedly, thus exposing the woman to multiple rounds of hormonal fluctuations. These more aggressive therapies for infertility account for nearly 5% of all pregnancies [20, 21]. As the use of ART has increased, so has the concern regarding associated long-term adverse CV events. Observational studies have suggested a near doubling of maternal mortality in women who utilized ART compared with those who conceived without assistance [1, 22, 23]. Some of these correlations may be mediated by increase in conditions noted to be associated with CV risk such as hypertension, which may be related to use of non-donor oocytes [24, 25], endothelial dysfunction, and altered thrombosis secondary to excess estrogen exposure.

Several large population studies published over the last several years, however, have not definitively supported these concerns. A population-based study from Canada, including over one million women who gave birth over a 17-year period, found after nearly 10 years follow-up that women who received ART actually had a lower risk of adverse events including mortality, thromboembolic events, and depression [26]. However, those analyses were based on broad categorizations of fertility therapy and infertile conditions, and more detailed assessment of specific risks associated with particular therapies could not be made. A similar study assessing nearly 100,000 patients also did not find higher rates of CV events [27]. Although these large-scale studies may support the suggestion of safety of ART, more data are needed. Additionally, the individual risks of specific therapies cannot yet be defined. Considering the increasing numbers of women seeking ART and their older age, these are very important knowledge gaps that warrant further study.

ART Risk in Offspring

It is recognized that children who are born to mothers who suffered from an adverse pregnancy condition appear to have evidence of elevated risk of chronic medical conditions, which may increase long-term risk of CV conditions such as HTN and stroke in these offspring. As proposed by the Barker hypothesis, it is conceivable that the effects of maternal health conditions and either factors leading to infertility or the ART themselves may influence the fetus. The environment in which the fetus was conceived could influence organogenesis and vascular development of the fetus and influence long-term CV risk.

One particular concern relates to the changes associated with a condition referred to as ovarian hyper-stimulation syndrome (OHSS). This often feared complication

of ART can lead to large shifts in fluid throughout the body, prompting multi-organ dysfunction and abnormalities of thrombosis [28]. OHSS has been associated with blood pressure abnormalities and vascular dysfunction in adolescent children born through use of ART [29, 30]. This may be due to associations of the Barker hypothesis with in utero remodeling under ART which later manifestations as CV abnormalities [31]. Children born to mothers who experienced OHSS have been noted to have evidence of echocardiographic and other vascular abnormalities including impaired flow-mediated dilation and abnormal left ventricular dimensions [31, 32]. The increased CV risk in offspring may also be related to alterations in placental function in the setting of ART. Both placental and neonatal abnormalities such as preterm birth have been associated with ART [33].

Fertility Therapy Failure

The use of ART has allowed many women who, due to advanced age or other comorbid conditions, would not have been able to conceive and carry successful pregnancies to term. The side effects of ART vary but can include wide variations in hormones and potential OHSS as mentioned above. Additionally, cycles of ART often need to be repeated to achieve a successful pregnancy. Although the short-term side effects are recognized, long-term side effects are unknown. Even so, some women receiving the most advanced therapies remain unable to conceive. Whether inability to conceive, despite ART, is associated with increased CV risk is unknown [34]. To assess these concerns, INFERTILE was conducted as a population-based cohort study in Canada of nearly 30,000 women. The study found that fertility failure was common, and the risk of adverse CV events, mostly for heart failure and neurologic events, was elevated in women with infertility [35]. Even in women who eventually do conceive, subfertility, defined as infertility for at least 1 year, has been associated with increased CV risk that persisted despite adjustment for BMI [36]. However, the mechanisms to explain these associations remain unclear. It has been suggested that alterations in the renin-angiotensin pathway and associated vascular injury in the setting of fertility therapy may contribute to excess CV risk [37–42]. Alternatively, the inherent condition leading to baseline infertility may also increase CV risks through yet-unknown mechanisms. Again, these are important knowledge gaps warranting additional study.

Miscarriage

Related to the inability to conceive, many women experience recurrent miscarriages. The specific causes of such cases often remain unknown but can include anatomic pathologies or chromosomal abnormalities, amongst others.

Small-sample-size observational studies have suggested an increased CV risk with a history of miscarriages. These studies were synthesized in a meta-analysis that included over 500,000 women that suggested a history of miscarriage was associated with increased risk, by nearly 50%, of coronary disease without association with cerebrovascular disease [43]. A subsequent study similarly assessed pregnancy loss, defined as recurrent stillbirth or recurrent miscarriage, in the Women's Health Initiative data and found a significant association between pregnancy loss and risk of development of CV disease in a group of diverse women using CV events which were centrally adjudicated [44].

Parity

There is some evidence that the number of pregnancies (referred to as parity) is associated with maternal CV risk. There is suggestion that extreme ends of the parity spectrum (nulliparous, multiparous) may convey risk [45, 46]. However, whether these associations are physiologic versus secondary to psychosocial risk factors is unknown. A study by Parikh et al. assessed parity and maternal CV risk in a large Swedish population. They found that the association between parity and CV disease occurred in a J-shaped curve with lowest risk association present in women with 2 births, increasing risk with increasing numbers of births, and highest risk at ≥5 births. These results persisted after adjustment for adverse pregnancy outcomes and social and economic status [47]. Another study combining data from Framingham Heart Study and the National Health and Nutrition Examination Survey noted a similar trend with CV disease risk increasing in women having ≥6 pregnancies [46]. It is hypothesized that repeated alterations in lipid metabolism, endothelial function, and renin-angiotensin might play a role in these associations, although there is likely some concurrent socioeconomic contribution as well.

Conclusion

As the population of women of childbearing age grows with concurrent continued increase in the use of ART, the importance of assessing any association between fertility status and CV risk remains crucial. As emerging data suggest, appreciation of elevated CV risk is particularly important among younger women in whom aggressive CV risk modification can be implemented to focus on reduction of lifetime CV risk. Currently available literature raises more questions than answers and warrants further investigation (Table 6.1). Future studies should focus on pathways linking common disorders of infertility and CV alterations secondary to fertility treatments as well as the mechanisms leading to miscarriage.

Table 6.1 Existing knowledge gaps in the area of impaired fertility, ART, and CV risk

Existing knowledge gaps
Is infertility associated with increased CV risk over the long-term?
If so, what mechanisms drive increased CV risk associated with infertility?
What mechanisms drive infertile conditions?
Is ART associated with increased CV risk over the long term?
If so, what mechanisms drive ART and increased CV risk? (Alterations in renin-angiotensin pathway, endothelial function, microvascular function, etc.)
How do we assess for elevated CV risk in offspring born through ART?
Is there an association between failure of ART/recurrent miscarriage and long-term CV risk?
Is there a definitive association between PCOS and long-term CV risk?
If so, what mechanisms drive increased CV risk associated with PCOS?
Does race/ethnicity play a role in association between fertility conditions and CV risk?

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Chapter 7
Gender Differences in the Gut Microbiome and How These Affect Cardiovascular Diseases

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Introduction

This chapter presents a review of the literature describing gender differences in the gut microbiome of humans, and the possible influence of such differences on cardiovascular diseases (CVD). The literature was reviewed with emphasis on reported gender differences, acknowledging that some research may still be biased towards male subjects. We started this project hoping to identify one or more mechanistic explanations behind a gender bias of CVD in which microbiome differences might play a role.

In order to keep this review focused, a number of subjects were excluded that are frequently covered in (metagenomic) human microbiome studies, such as contributions that concentrated on the developing gut microbiome of new-borns and infants/children, or publications concentrating on the role of the microbiome in chronic obstructive pulmonary disease, human immunodeficiency virus infections, or allergic diseases. Likewise, the effect of diabetes or bariatric surgery on the composition

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of the gut microbiome was ignored, even though there may be gender-specific differences occurring in any of these conditions. The role of obesity is briefly addressed. Animal studies are not included in this review.

There Are Marked Differences in Gut Microbiome of Adult Males and Females

It is widely accepted that the microbial diversity of a gut microbiome may vary according to the age, gender, diet, genetic background, ethnicity, geographic location, and health status of the host; moreover, the composition of the microbiome depends on the location within the intestinal tract [1]. But despite many publications in this area, there is no consensus on what would be characteristic and consistent differences between the microbiome of women and men, all other things being equal. Although multiple reports exist that describe gender differences, there remains a big disparity of observations between studies.

The gastrointestinal microbiome in healthy adults contains major fractions of bacteria belonging to the phyla Firmicutes and Bacteroidetes, with lower numbers of members of Proteobacteria, Actinobacteria, Fusobacteria, Verrucomicrobia, and minor fractions of other Bacteria, Archaea and Eukaryotes [1–3]. Several publications have reported that the gut microbiome in women is characterized by a lower abundance of Bacteroidetes in comparison with men [4–6]. The opposite trend was observed in an obese population of men and (post-menopausal) women, resulting from exceptionally low Bacteroidetes levels in obese men [7]. A higher proportion of Firmicutes (e.g. *Clostridia*), in women compared to men has also been reported, together with *Proteobacteria* [5], *Veillonella* [7] or *Blautia* [8]. In Caucasian women, higher amounts of the Spirochete *Treponema* [8], *Bilophila* (Proteobacteria) [7] and methanogen-producing bacteria have been observed [9]. The latter observation was contradicted by a reported lower amount of methanogens such as *Methanobrevibacter* in women compared to men [7].

In an attempt to describe the variable human gut microbiome in more general terms, three "enterotypes" have been defined (based on results obtained from a population of mainly Europeans), depending on which bacterial genus is more prevalent over the others. This resulted in the *Bacteroides* enterotype (also known as enterotype 1), *Prevotella* enterotype 2 and *Ruminococcus* enterotype 3 [10]. Subsequently, in a study involving healthy individuals from Taiwan, an enterotype was recognized in which *Enterobacteriaceae*, rather than *Ruminococcus* was abundant [11]. This study revealed that the prevalence of the *Bacteroides* enterotype (which the authors confusingly called enterotype 2) was more abundant in women, being double that of men [11]. This seemingly contradicts the works cited above that noted lower Bacteroidetes abundance in women. Li and colleagues had reported that three species from *Clostridia*, one from Bacteroidetes and two Proteobacteria were lower in females than in males [5]. But even when *Bacteroides* (the genus) is the most prevalent type in women's microbiomes, it does not necessarily mean

that the phylum Bacteroidetes is the major phylum. The observations by Liang and colleagues are in agreement with a study involving Americans, in which the stool analyzed from female subjects was less prevalent for *Prevotella* and higher in *Bacteroides* than that of men [12]. The gender-specific differences reported by Dominiani and colleagues (abundance of the *Bacteroides/Prevotella* group was lower in females) was only slightly significant (P = 0.036; [4]).

Similarly, gender differences were recorded by Aagaard and coworkers in other body sites than the gut (though still part of the oral-gastro-intestinal tract) such as the tongue dorsum, the hard palate and the buccal mucosa, where these authors reported a higher level of *Corynebacterium* and *Kingella* in the saliva and *Streptococcus* in the tongue dorsum of women compared to men [13].

One of the most influential factors in the microbiome composition is the diet of the host [14, 15], and it can be assumed that gender differences in dietary intake exist; nevertheless, publications in which gender-related differences in diet were related to microbiome composition were not identified. It has been studied, however, how particular dietary components affect the microbiome. For instance, an association was observed between the consumption of yogurt and the composition of the gut microbiota of Japanese students, and interestingly, the extent of this association varied according to gender [16]. Thus, more frequent yogurt consumption correlated to a higher abundance of *Lactobacillus sakei* in females, but it had a negative association with *L. sakei*, *Enterobacteriaceae* and *Staphylococcus* in males. These are not dominant gut bacteria, as they typically are present in low numbers ($<10^5$ cells/g feces) but are considered a regular and indispensable component of a healthy gut microbiota [16]. The study further reported that stools from women contained higher loads of bacteria, with fewer organic acids present and a higher pH value, than stools from men. In particular, *Bifidobacterium*, formic and succinic acid were reported at higher levels in men, producing a significant positive relationship between the succinic acid and *L. casei* [16].

In 2012, the consortium of the Microbiome Human Project concluded that although commonly investigated variables such as the host gender can shape microbiome changes in healthy Western individuals, there should be other relevant and under-investigated factors that may have a bigger influence to these changes [17]. The enterotypes were considered by some as not sex-related [3, 11] and their existence was attributed to other factors such as functional properties or host immune modulation [10]. For instance, lower levels in the aspartate biosynthesis modules were detected in women in comparison with those of men [10].

Other authors supported the view that the influence of gender on the composition of a gut microbiota is limited, and when present, it was less influential than the geographical origin [18] or the genetic background [14] of the individual. Likewise, no significant differences were found between the microbial composition of Japanese women and men when fecal samples from healthy subjects were analyzed by metagenomics [19] or in patients suffering from Myalgic Encephalomyelitis or Chronic Fatigue, by quantification of viable counts [20].

From the available literature, we conclude that the variability of the gut microbiome between individuals is less shaped by their gender than by other factors.

The Gut Microbiome Affects Risk and Outcome of Cardiovascular Disease: the Role of Obesity

The literature is more uniform about the conclusion that the gut microbiome plays a significant role in CVD [21–24]. There are various mechanistic explanations for such a role, including microbial production of biologically active products that interact with crucial host pathways [24]. Before dealing with these mechanisms in detail, the role of the microbiota in obesity is briefly discussed.

The etiology of obesity is clearly multifactorial, with dietary, genetic, and lifestyle factors being recognized, to which the gut microbiome can be added as a possible cause as well as a mediator [25]. A strong correlation exists between diet, microbiota, and obesity [26]. The composition of the microbiota is in part shaped by diet, while obesity is also correlated to dietary quantitative intake and composition. Particular gut bacteria are most likely also (partly) responsible for the body mass index (BMI), as they can increase the metabolic availability of food [27]. It is easy to imagine how the fraction of saccharolytic organisms in the microbiome determines the level of metabolized dietary oligo- and polysaccharides that then become available to the host. However, that is only one mechanistic explanation how gut bacteria can contribute to obesity. Others are reviewed elsewhere [26]. Again, gender differences have become apparent. It was observed that in obese men, but not in obese women, reduced peripheral insulin sensitivity (a sign of developing Type II diabetes) correlated with a higher ratio of Bacteroidetes/Firmicutes [28]. This ratio was also higher in the male than in the female subjects. The authors concluded that women might be less sensitive to gut microbiota-induced metabolic aberrations than men [28]. Obesity increases the risk for CVD in various ways, as it may cause elevated triglycerides, high LDL-cholesterol, low HDL-cholesterol, high blood pressure, and elevated blood glucose and insulin levels; the gut microbiota may affect any or all of these factors [25]. Gender-specific differences in the gut microbiota can then be expected to cause differences in CVD risk.

The effect of a dysbiosis, i.e. an alteration in the microbiome composition with negative health consequences, may have pathological consequences, including hypertension, atherosclerosis or heart failure [22]. For instance, the microbiota can be responsible for the variation in blood lipid levels (*e.g.* triglycerides and high density lipoproteins, HDL) [27]. It has been demonstrated that individuals with a higher BMI have higher levels of *Christensenellaceae, Rikenellaceae*, *Mollicutes*, *Dehalobacterium* and Archaea remain at low levels and *Bacteroidales* and *Clostridiales*, which are involved in the metabolism of bile acid and short chain fatty acids, have a negative association with BMI and triglycerides [27]. Similarly, the role of the microbiota is evident from its correlation with hypertension through the production of short chain fatty acids, which may increase blood pressure, a condition that is typically present in aged populations [29].

Regarding the type of bacteria that are associated with CVD, an increase in Firmicutes and fewer members of Bacteroidetes have been detected in hospitalized patients in comparison with healthy controls (differences among sexes were not reported with CVD or assessed) [30]. In other studies in patients with CVD,

Lactobacillales were significantly increased while levels of Bacteroidetes were reduced [31, 32].

Although a more diverse gut microbiome is generally regarded as healthier and more robust than a less diverse gut community, one publication hints at a less favorable consequence of a diverse microbiome. Individuals of the long-running Bogalusa study were divided according to their highest and lowest lifetime burdens of CVD risk factors; the gut microbiome of these two study groups were then compared, which resulted in a strong correlation of high gut diversity with high CVD risk factors, independent on the model used to calculate associations [33]. However, evenness did not play a role. This suggests that the abundance of distinct microbial taxa may be more important than their relative frequency in determining CVD risk. Six bacterial taxa were consistently found associated with increased or decreased risk, by all models tested, but gender differences were not reported. Interestingly, some Firmicute members (*Tyzzerella*) were associated with high risk while others (*Catenibacterium*) were found in lower abundance in the high-risk group [33].

Microbiome, Cardiac Diseases, TMAO and Gender

An important pathway by which the gut microbiota affects the cardiovascular health of the host is via trimethylamine (TMA) and its N-oxidized form, TMAO, which is formed in the liver. We would like to point out gender-related observations that may be (in part) related to differences in the microbiome. Although earlier studies reported conflicting results on the role of TMAO (*e.g.* see [34, 35]), it is now mostly accepted that TMAO produced by gut microbes contributes to atherogenesis [36, 37]. Nevertheless, the mechanistic link that explains how TMAO might (directly or indirectly) promote CVD remains to be determined [38]. TMAO is a metabolic product from substrates such as L-carnitine, which is abundant in meat-rich diets [39]. A diet rich in eggs also raises TMAO levels [40] and intake of fish has an even stronger effect than beef or eggs, though this was only tested in men [41]. TMAO levels in blood plasma has predictive value for peripheral artery disease [42–44], heart failure [45], major adverse cardiac events [46], and long-term mortality for CVD patients [47–49] and correlate to infarcts in patients undergoing cardiovascular surgery [47]. TMAO enhances platelet reactivity [50] and women have more TLR transcripts in their platelets, which may make them more sensitive to TMAO [51]. A direct role of TMAO in heart failure was shown in mice studies [52]. Interestingly, in mice and rats, TMAO levels in urine are higher in females than in males, and since estrogen regulates the gene responsible for TMA oxidation, gender differences in humans can also be expected [36]. In conclusion, studies that are conducted to determine the role of TMAO in CVD should not only correct for age differences, but should also report on differences between the genders, as there may be clinical and therapeutic consequences that are otherwise overseen. If dietary or microbial (probiotic) intervention studies are performed, male and female patient populations should be analyzed separately.

There Is a Paucity in Gender-Related Other Causes of Microbiome and CVD

The gut microbiome can be considered to function as an endocrine organ, and in this function, production of TMAO is not the only way in which it affects CVD. Other important products are branch-chain and short chain fatty acids and unsaturated lipids [24, 53]. However, we were unable to identify reports on gender differences in the microbial production of these bioactive compounds and unsaturated lipids. Likewise, interactions between the microbiota and bile acid production have been established [24, 54] but so far the only gender-related observations reported were an increase of fecal bile acids in patients of irritable bowel disease (IBS) [55]. For this condition, which coincides with a dysbiosis of the gut microbiome, women have a 2.2 times higher risk than men [56]. Patients with inflammatory bowel diseases also appear to have a higher risk for CVD, despite a lower prevalence of 'classical' risk factors [57]. Since IBS is more common in women, one would expect a gender disparity for IBS-related CVD as well. This would provide one of the few examples where a microbiome dysbiosis is found in unequal proportion between the sexes, with consequences for cardiovascular diseases.

Bacterial translocation (the penetration of deeper tissue by enteric bacteria due to impaired intestinal barrier function) has long been recognized as associated with occurrence of CVD, possibly as a result of prolonged low-level inflammation [24, 58], but gender differences have not specifically been addressed to our knowledge. Bacterial translocation could be responsible for endotoxemia, and circulating bacterial-derived lipopolysaccharides is strongly associated with cardio-metabolic disorders [59]. A high-fat diet raises these levels, presumably by inducing changes in the gut microbiota [60]. In view of the (inconsistent) differences between the gut microbiota of women and men, it would be interesting to see how gender affects the association between endotoxemia and CVD risk. At least in rats, acute septic shock resulting in cardiac arrest as a result of high endotoxemic levels can be treated with mesenchymal stem cells, and this treatment is more effective in female than in male animals [61].

The presence of enteric pathogens has also been linked to CVD. For instance, patients suffering from chronic heart disease have far higher levels of particular pathogens in their stools, in particular *Campylobacter* species (a cause of diarrhea) that were found more frequently and at levels 85 times higher in patients than in controls [62]. Notably, the study group contained five times more men than women, which may in part explain the high incidence of *Campylobacter*, as this pathogen is known to cause more often infections in men than in women [63]. This and other enteric pathogens can (temporarily) increase gut permeability, thus contributing to endotoxemia and bacterial translocation.

A link also exists between endotoxemia, CVD and periodontitis, as subgingival microbiota contributes to endotoxemia [64], Likewise specific oral pathogens, in particular *Aggregatibacter actinomycetemcomitans*, have been implicated as a risk factor for CVD [65]. Notably, women suffer more often from these conditions than

men [60], but the contribution of gender differences in the oral microbiota and their link to CVD has not yet been assessed.

The role of infections, for example by *Chlamydophila pneumoniae*, *Helicobacter pylori* or cytomegalovirus and CVD has been heavily discussed in the past, whereby both a correlation with progression of the disease [66] and lack of such a correlation [67] have been reported. Persistent *C. pneumoniae* infection has been observed to be associated with overweight and obesity in women [68], so if the infection plays a role in CVD, these women may have an increased risk. *H. pylori* infection, on the other hand, is more often found in male than female individuals [69]. With over 90% of the world's population having acquired a cytomegalovirus infection at some point, there seems to be little gender bias in its prevalence.

Conclusions

We tried to summarize from the literature whether consistent gender differences exist in the gut microbiome and, if so, how these affect cardiovascular diseases. Although a number of disparities were identified between male and female microbiomes, few observations were reported consistently when different populations were studied. Nevertheless, the differences that have been observed could, at least in theory, result in different risk factors for CVD. We extended this review to search for other associations how bacteria living in the gut affect the health of the cardiovascular system, bearing in mind where gender differences in the microbiome could play a role. To this, we added effects described by oral microbiota as well as (enteric) pathogens.

We conclude that over the years multiple microbial factors have been identified that can play a role in the development and progress of CVD that display some kind of gender bias. Either men or women can be at a disadvantage, depending on the type of interaction. Although most studies report the gender of their patient groups under study, little research has been conducted to specifically look at gender differences that relate to the microbiome.

Since a gut microbiome is constantly adjusting to variation, responding to factors from the environment (food intake) and the host, and since men and women can have notable behavioral differences, the known risk factors for CVD may, at least in part, be reflected by changes in the microbiome. It may be that the gut microbiome enhances certain effects in one gender more than in the other. However, all other things being equal, there is no overall positive or negative generally applicable effect of a microbiome being 'female' or 'male' in terms of its effect on CVD.

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Chapter 8
Angina and Ischemia in Women with No Obstructive Coronary Artery Disease

Suegene K. Lee, Jay Khambhati, and Puja K. Mehta

Introduction

Cardiovascular disease (CVD) continues to be the leading cause of death in women, regardless of race or ethnicity [1]. Among CVD, ischemic heart disease (IHD) is a major contributor to death, and while IHD death rate has declined in older women over the past several years, the death rates appear to be increasing in young women [1]. IHD mortality in women has not fully been explained by ischemia from significant obstructive coronary artery disease (CAD) [2]. In fact, data indicate that women are more likely than men to have the finding of no obstructive CAD on coronary angiography in the settings of unstable angina/acute coronary syndromes as well as in stable ischemic heart disease (SIHD) [3]. Women with IHD experience a greater symptom burden, greater disability, have more IHD risk factors, and more psychosocial risk factors such as depression, anxiety, and post-traumatic stress disorder compared to men [4–6]. Previously it was considered a benign finding when a women is found to have no obstructive CAD despite signs and symptoms of ischemia, although mounting evidence from the past two decades indicates that coronary microvascular dysfunction (CMD) may be an explanation in at least half of these cases, and CMD is associated with an elevated cardiovascular risk, which

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includes myocardial infarction, stroke, and congestive heart failure [7–11]. CMD occurs due to endothelial dependent and endothelial-independent mechanisms. In addition to CMD, etiologies such as prolonged coronary vasospasm, spontaneous coronary artery dissection (SCAD), stress cardiomyopathy (Takotsubo cardiomyopathy), plaque erosion and thrombi, and myocarditis should also be considered in the differential when no obstructive CAD is found in the setting of acute coronary syndrome (Table 8.1). This chapter focuses on CMD diagnosis and treatment in symptomatic women with ischemia and no obstructive CAD.

Table 8.1 Differential diagnoses in myocardial infarction with non-obstructive coronary artery disease

Diagnostic considerations in the evaluation of myocardial infarction with non-obstructive coronary arteries (MINOCA)	
Clinical disorder	Diagnostic investigation
Non-cardiac disorders	
Renal impairment	Serum creatinine
Pulmonary embolism	CTPA or ventilation/perfusion imaging
Cardiac disorders	
Myocardial disorders	
Cardiomyopathy (Takotsubo, dilated, hypertrophic)	Left ventriculography, Echo, CMR
Myocarditis	CRP, CMR, EMB
Myocardial trauma or injury	History (trauma, chemotherapy), CMR
Tachyarrhythmia-induced infarct	Arrhythmia monitoring
Coronary disorders	
Concealed coronary dissection (aortic dissection involving valve, spontaneous coronary dissection)	Echo, CT angiogram
Sympathomimetic-induced spasm	Drug screen (eg, cocaine)
Epicardial coronary spasm	ACh provocation testing
Microvascular spasm	ACh provocation testing
Microvascular dysfunction	Coronary flow reserve
Coronary slow-flow phenomenon	TIMI frame count
Plaque disruption/coronary thrombus	Intravascular ultrasound
Coronary emboli	Echo (left ventricular or valvular thrombus)
Thrombotic disorders	
Factor V Leiden	Thrombophilia disorder screen
Protein C & S deficiency	

Pasupathy, S., Tavella, R., Beltrame, J.F. The What, When, Who, Why, How and Where of Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) *Circ J* 2016; 80:11-16
ACh acetylcholine, *CMR* cardiac magnetic resonance imaging, *CRP* C-reactive protein, *CT* computed tomography, *CTPA* computed tomographic pulmonary angiogram, *Echo* echocardiography, *EMB* endomyocardial biopsy, *TIMI* thrombolysis in myocardial infarction

Definition and Classification

Previously, women with chest pain in the absence of obstructive CAD were labeled with an ill-defined term, "cardiac syndrome X (CSX)", which is now considered an outdated term; improved diagnostic methods have shown us that at least half of these CSX patients may have CMD [3, 12]. The coronary microvasculature contributes greater than 70% of resistance to coronary blood flow; microvascular dysfunction can occur due to structural, functional, and extravascular alterations, and results in impaired coronary blood flow reserve (CFR) [13]. Plaque erosions, distal luminal obstruction from micro-embolization, arterial remodeling with smooth muscle cell hypertrophy, and capillary rarefaction contribute to CMD [13, 14]. Myocardial structural abnormalities caused by etiologies including aortic stenosis, hypertrophic or infiltrative cardiomyopathy can also lead to a reduction in myocardial blood flow reserve [13]. Given that CMD is a heterogeneous disorder with many underlying pathophysiologic mechanisms, four main classifications of CMD are proposed that take into consideration primary CMD vs. secondary causes: (1) CMD in the absence of obstructive CAD and myocardial diseases; (2) CMD in the presence of structural myocardial diseases (such as hypertrophic or dilated cardiomyopathy); (3) CMD in the presence of obstructive CAD; (4) iatrogenic CMD such as in the setting of post-percutaneous coronary intervention [7, 13].

The microvasculature cannot be visually assessed on coronary angiography, but the response of the microvasculature to vasoactive substances can be detected by invasive Doppler flow and resistance measurements; advanced non-invasive cardiac imaging can also quantify myocardial flow reserve and diagnose CMD. While coronary endothelial dysfunction and CMD are important contributors in the pathophysiology of IHD in women, recent reports demonstrate that CMD is highly prevalent in both men and women [15]. Contemporary registries are also documenting a high prevalence of non-obstructive CAD during angiographic evaluation in men. Given the emerging epidemic of non-obstructive CAD, systematic sex-specific studies of CMD prevalence, risk, and evidence based treatment are needed [2, 16, 17]. An important issue in the diagnosis and management of CMD is the confusion in the literature to describe this group of patients, and lack of consistent terminology and standardized diagnostic criteria. To address this problem and to improve CMD research and patient care, the Coronary Vasomotion Disorders International Study Group (COVADIS) investigators have proposed international standards for the diagnostic criteria of coronary vasomotor disorders [18, 19].

Pathophysiology

The vascular endothelium is a monolayer of cells that line the inside surface of arteries, veins, and capillaries. It functions as a barrier and a dynamic organ responsive to stimuli and responsible for the production of a number of regulatory factors

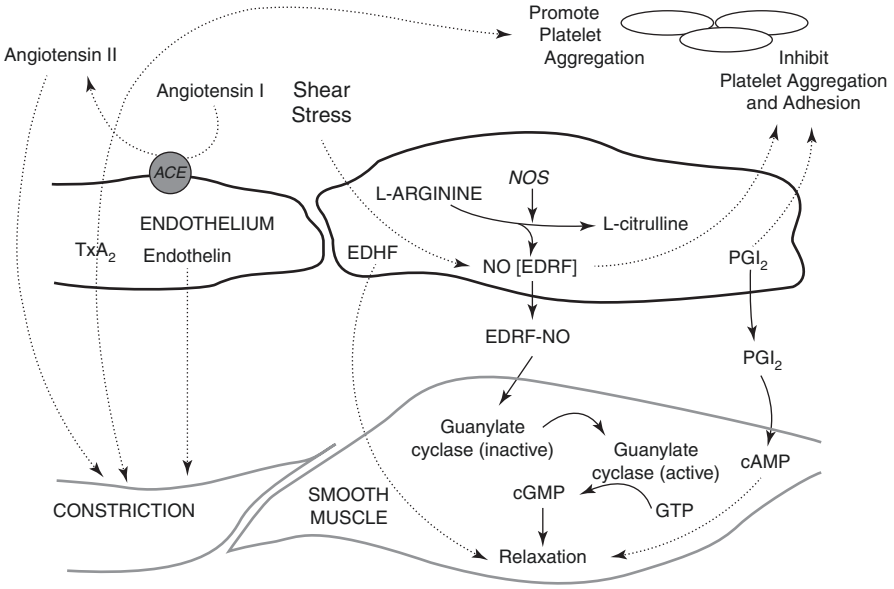

Fig. 8.1 Diagram of endothelial function. Endothelium-derived dilating and constricting factors. *ACE* angiotensin converting enzyme, *cAMP* cyclic adenosine monophosphate, *cGMP* cyclic guanosine monophosphate, *EDHF* endothelium-derived hyperpolarizing factor, *EDRF* endothelium-derived relaxing factor, *GTP* guanosine triphosphate, *NO* nitric oxide, *NOS* nitric oxide synthase, PGI_2 prostacyclin, TxA_2 thromboxane A_2. (Reprinted with permission from Elsevier) [21]. (Quyyumi AA. Endothelial function in health and disease: new insights into the genesis of cardiovascular disease. *Am J Med*. 1998; 105(1A): 32s-39s)

[20]. Through stimulation via shear stress, temperature changes, and factors such as bradykinin and acetylcholine, the endothelium mediates vasomotor tone, effectively altering the diameter of the lumen, changing vascular resistance and, consequently, modifying blood flow (Fig. 8.1) [21, 22]. The endothelium also mediates hematologic effects, including the inhibition of clotting factors, platelet aggregation, and inflammatory cell adhesion [23]. Furthermore, the endothelium engages in vascular regeneration through endothelial progenitor cells as mediators capable of vascular repair [22].

Endothelial dysfunction (ED) occurs when homeostatic mechanisms are altered, resulting in the loss of several key regulatory functions [20, 21]. ED plays a fundamental role in early atherosclerosis and plaque formation; peripheral as well as coronary endothelial dysfunction are both associated with adverse cardiovascular outcomes [24, 25]. The hallmark of endothelial dysfunction pertains to oxidative stress, causing upregulation of renin-angiotensin system, release of pro-inflammatory cytokines, and consequently, a reduction of NO [20, 21]. Lower NO bioavailability results in a pro-thrombotic, pro-inflammatory environment, paving the way to the development of atherosclerotic plaque lesions [21, 23]. Gender may also play a significant role in the development of ED as certain single nucleotide polymorphisms (SNPs) associated with a higher risk of coronary ED have been found to be sex specific [26].

ED is associated with cardiovascular risk factors, including aging, a sedentary lifestyle, obesity, hypertension, hypercholesterolemia, diabetes mellitus, and tobacco use, although CMD is not effectively reflected by traditional CVD risk factors [25, 27–32]. Impaired microvascular vasodilation and/or abnormal vasoconstriction which result in failure to auto-regulate blood flow implicates autonomic nervous system dysfunction as an important mechanistic pathway in CMD. Women with CMD also tend to have angina at low cardiac workloads and mental stress-related angina, which likely involves autonomic regulation [33–38]. Myocardial ischemia due to mental stress is independent of CAD severity [39], and the normal increase in coronary diameter to mental stress is blunted in those with endothelial dysfunction [40–42]. Psychosocial risk factors such as depression and anxiety are highly prevalent in women, are associated with adverse outcomes and may mediate the link between mental stress and CMD [43–46]. Normally, epicardial coronary arteries contribute less than 10% of vascular resistance, whereas the microcirculation accounts for the majority of resistance and thus regulates blood flow according to the myocardial oxygen demand [13, 47]. In addition to metabolic and local autoregulatory mechanisms that control coronary blood flow, the ANS, via the sympathetic and the parasympathetic (vagal) systems, plays a critical role in vasomotor regulation [33–36, 48]. Previous studies conducted in CSX have observed impaired parasympathetic tone as well as sympathetic predominance [49–51]. In CSX patients, abnormal cardiac adrenergic nerve function detected by using the sympathetic nuclear imaging isotope, ^{123}I-*meta*-iodobenzylguanidine (*m*IBG), has been reported previously [52]; no associations have been found between a low measured coronary flow reserve and abnormal cardiac sympathetic function [53].

Pathophysiologic links between CMD and progression to heart failure with preserved ejection fraction (HFpEF) have been proposed and are being investigated [29–31]. It has been hypothesized that in patients with CMD, repetitive bouts of microvascular ischemia may lead to microinfarctions, fibrosis, and diastolic dysfunction, and progressive heart failure. In the Women's Ischemia Syndrome Evaluation (WISE) study, those suspected of ischemia who had no obstructive CAD, one third were found to have an elevated left ventricular end diastolic pressures. In WISE, those women with signs and symptoms of ischemia who had no obstructive CAD and were followed for 6-years, heart failure hospitalization was predominately due to preserved ejection fraction [54]. In another WISE cohort, an elevated interleukin-6 level predicted heart failure hospitalization and all-cause mortality, suggesting that inflammation may be a mediator in CMD-associated HFpEF [55]. Recently, acetylcholine-induced coronary microvascular spasm was shown to be associated with diastolic dysfunction in patients with no obstructive CAD [56].

Other Etiologies of Angina, Ischemia, and No Obstructive CAD

In addition to CMD, when a woman presents with signs and symptoms of ischemia in the setting of no obstructive CAD, etiologies such as coronary artery spasm, spontaneous coronary artery dissection, and stress cardiomyopathy should be in the differential and are briefly discussed here.

Coronary Artery Spasm

Coronary artery spasm can occur in the presence of significant atheroma or in the absence of angiographic lesions, and prolonged vasospasm can progress to myocardial ischemia and infarction. While vasospastic angina can occur in both the epicardial vessels and the microvasculature, the underlying cause of coronary artery vasospasm remains unclear [57]. Several mechanisms, including autonomic nervous system activation by stimuli, endothelial dysfunction, smooth muscle hypercontractility, inflammation, and oxidative stress have been implicated [58]. Medications such as sympathomimetics, non-selective beta-blockers, and ergot alkaloids can also precipitate vasospasm [58]. In a porcine model, both adventitial inflammation and endothelial dysfunction have been directly implicated in the pathogenesis of coronary artery spasm [59]. While driven by a number of stimuli, the primary mechanism driving spasm is from vascular smooth muscle hyperreactivity [19]. In women with chest pain and normal coronary arteries angiographically, there is increased prevalence of both epicardial and microvascular coronary constriction [57]. A classic entity attributed to coronary artery spasm, Prinzmetal's angina is a variant angina with preserved exercise capacity and chest pain associated with transient ST elevations [57]. The Coronary Vasomotion Disorders International Study Group has proposed diagnostic criteria to define vasospastic angina which includes the presence of nitrate-responsive angina, transient ischemic EKG changes (ST elevation, ST depression, negative U waves) and coronary artery spasm in response to a provocative stimulus [18].

Spontaneous Coronary Artery Dissection (SCAD)

Predominantly occurring in young women, spontaneous dissections in the coronary arteries occur when a separation of the arterial wall results in hemorrhage (Fig. 8.2), subsequently causing myocardial infarction. The mechanisms that precipitate SCAD are not well understood, and SCAD is not associated with CAD risk factors. Given

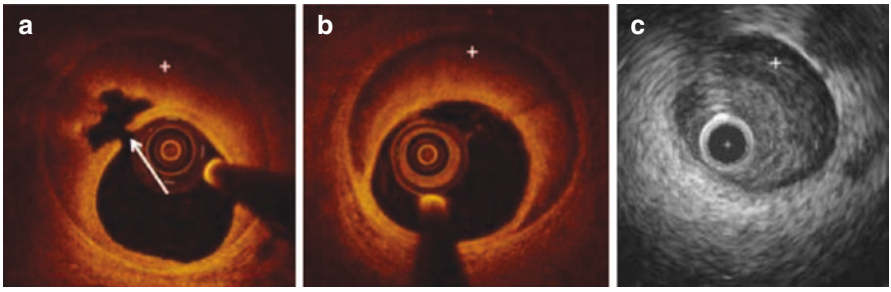

Fig. 8.2 Intracoronary Imaging of SCAD (**a**) False lumen with intramural hematoma (plus sign) and intimal rupture (arrow). (**b**) False lumen with intramural hematoma (plus sign). (**c**) False lumen with intramural hematoma (plus sign) (Saw J, Mancini GBJ, Humphries KH. Contemporary review on spontaneous coronary artery dissection. *J Am Coll Cardiol*. 2016; 68(3):297-312)

the predominance in young women and in peripartum females, hormonal changes may potentially contribute to the development of SCAD [60]. SCAD can be either due to an intimal tear or dissecting medial hematoma, possibly from rupture from the vaso vasorum, and can occur in vessels with and without atherosclerosis. In fact, optical coherence tomography has distinguished two distinct subtypes of SCAD: (1) a false lumen between the adventitia and media associated with an intimal tear and (2) separation of the media and adventitia with an intramural hematoma with or without an intimal tear [61]. Adventitial vaso vasorum proliferation has also been linked with SCAD, but no causal relationship has been established [62]. In the absence of atherosclerosis, fibromuscular dysplasia (FMD), connective tissue disorders, the peripartum state, extreme exertion, inflammatory disorders, and coronary artery vasospasm have all been implicated as potential underlying etiologies [60, 63]. Furthermore, coronary tortuosity and extracoronary vascular abnormalities such as aneurysms and aortic tortuosity in the neck, abdomen, and pelvis often coincide with SCAD [60].

Stress Cardiomyopathy

Takotsubo cardiomyopathy is typically comprised of a transient, apical left ventricular dysfunction typically induced by strong emotional or physical stimuli (Fig. 8.3) [64]. Patients present with signs of myocardial infarction with symptoms, EKG

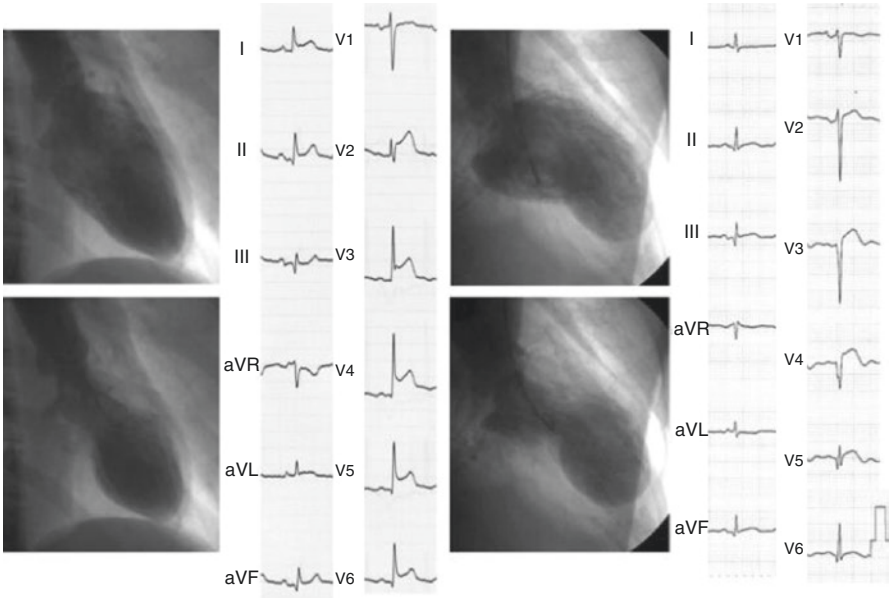

Fig. 8.3 Left ventriculogram and electrocardiogram in Takotsubo cardiomyopathy on left panel; anterior acute myocardial infarction on right panel (Kurisu S, Kihara Y. Tako-tsubo cardiomyopathy: clinical presentation and underlying mechanism. *J Cardiol.* 2012;60(6):429-437)

changes, and cardiac biomarker elevations but are found to have no obstructive CAD on angiography; mortality in the acute phase is comparable to acute myocardial infarction due to obstructive CAD [65]. In addition to the apical-sparing variant, there are other ventricular patterns that have been described including biventricular pattern [64]. Most cases of Takotsubo cardiomyopathy involve post-menopausal women, have normal coronary arteries, and is not associated with acute plaque rupture from underlying atherosclerosis [64]. The underlying mechanisms are unclear, but prolonged coronary spasm and CMD have been implicated in the setting of a catecholamine surge [64]. Given the rare occurrence of coronary spasm, CMD is more likely; however, the determination of CMD as the cause or a consequence has been difficult [64]. It remains unclear why a majority of cases present in women [66, 67]. A possible mechanism for post-menopausal female prevalence may include the age-specific decrease in vagal tone and baroreflex sensitivity from reduced estrogen levels, thereby augmenting the catecholamine-mediated stress response. Recently, increased SNS activity and impaired BRS has been shown in women with takotsubo syndrome compared to women with chronic heart failure [68].

Clinical Presentation

Compared to acute myocardial infarction in men, stable angina is the most common initial presentation of IHD in women [69]. The non-obstructive pattern of CAD, as opposed to the detectable flow-limiting atherosclerotic disease, oftentimes delay recognition of IHD in women, since routine diagnostic testing currently focuses on obstructive CAD. Although both women and men have typical and atypical symptoms of angina, women are more likely to present atypically, including dyspnea, upper back pain, nausea/vomiting, indigestion, palpitations, or unusual fatigue [70]. Women also verbalize symptoms more than men and have greater somatic awareness [71]. In a recently published study of 155 women with no obstructive CAD who had CMD, 30% were found to have typical angina (defined as substernal chest pain precipitated by physical or emotional stress and relieved with rest or nitroglycerin); and those with typical angina had worse endothelial dysfunction and quality of life [72].

Risk Factors

A comprehensive discussion on traditional and novel IHD risk factors in women [5] is not the focus of this chapter, but we highlight some unique risk factors below to point out that current IHD risk assessment tools (i.e. the Framingham Risk Score, the Reynold's Risk Score [73], and the atherosclerotic cardiovascular disease (ASCVD) risk score) do not take into account unique IHD risk factors that may contribute to CMD [74, 75]. IHD in women is associated with traditional risk

factors, such as age, hypertension, diabetes, cigarette smoking, dyslipidemia, obesity, and physical inactivity. Patients with CMD are more likely to have these risk factors compared to the general population; however, in the WISE study, cardiac risk factors were modestly related to CMD (diagnosed by invasive coronary reactivity testing or perfusion index by cardiac magnetic resonance imaging). In women suspected of IHD with no obstructive CAD and with IVUS measured atherosclerosis, waist circumference and systolic blood pressure were independently associated with plaque severity (even after adjustment of factors such as age, diabetes, hyperlipidemia, hormone replacement, and tobacco smoking); thus, authors concluded that metabolic syndrome by itself is not an independent IHD predictor in women [76].

There are unique ASCVD risk factors for women that should also be considered, such as gestational hypertension, pre-eclampsia, gestational-diabetes, and pre-term labor. Pre-eclampsia affects 3–7% of all pregnancies and has been shown to result from vascular dysfunction—increased vascular resistance and vasoconstriction occurs in vasculature of the mother [77]. A large meta-analysis showed that after pre-eclampsia, women had an increased risk for ischemic heart disease after 11.7 years (RR: 2.16, 95% CI: 1.86–2.52), stroke after 10.4 years (RR: 1.81, 95% CI: 1.45–2.27), and overall mortality after 14.5 years (RR: 1.49, 95% CI: 1.05–2.14) [78]. The shared pathway of vascular dysfunction may explain the association of pre-eclampsia and development of ASCVD and adverse cardiovascular events that occur years later [77].

Autoimmune disorders, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and depression are conditions that disproportionately affect women and are also recognized risk factors for IHD, and were added to the Women's Heart Disease Prevention guidelines in 2011 [79, 80]. SLE patients who present with chest pain are often thought to have pericarditis even though there are often no objective EKG findings and the physical exam does not point to pericarditis. It may be possible that some of these patients are having angina due to CMD [81–84]. Ishimori et al. found that 44% of women with SLE with typical and atypical chest pain without obstructive CAD had visual perfusion defects on stress cardiac magnetic resonance, compared to 0% in 10 asymptomatic reference control subjects ($p = 0.014$). The presence of SLE was a significant predictor of an abnormal myocardial perfusion reserve index (MPRI) [82]. Carotid plaque determined by carotid ultrasonography was found to be more prevalent in patients with SLE than in the matched controls (37.1% vs. 15.2% respectively, $p < 0.001$) [85]. The diagnosis of RA was also associated with a 50% increased risk of ASCVD death in a meta-analysis of 111,758 patients (meta-standardized mortality ratio 1.59, 95% CI: 1.39–1.61) [86].

The American Heart Association (AHA) recognizes depression as a risk factor for adverse outcomes in patients with acute coronary syndrome [87]. Women generally have higher contributions of psychosocial risk factors (45.2% versus 28.8% in men) to MI [88]. Depressive symptoms also predicted the presence of CAD in women 55 years-old or younger (OR: 1.07, 95% CI: 1.02–1.13) and increased the risk of death in this group of women (adjusted HR 1.07; 95% CI: 1.02–1.14) [89]. In 514 women suspected of IHD, the WISE study reported that anxiety predicted cardiac symptom severity and healthcare utilization in women [45]. Anxiety in this study was

measured by the Spielberger Trait Anxiety Inventory (STAI), anxiolytic use, and anxiety disorder treatment history. The use of anxiolytics predicted hospitalizations for chest pain and catheterizations (HR: 2.0, 95% CI: 1.1–4.7), as well as symptoms of nighttime angina and nitroglycerine use. STAI scores and anxiety treatment history correlated with nighttime angina, angina frequency and shortness of breath. Furthermore, anxiolytic use and a higher STAI value (using a median of 18) predicted greater costs, including medications and hospitalizations, regardless of severity of CAD [45].

Assessment

Non-invasive Assessment

Exercise Treadmill Testing

One of the most widely available and relatively inexpensive forms of stress testing, exercise treadmill testing (ETT), is recommended as the first step for evaluation of women with suspected IHD, per the 2014 AHA consensus statement on stress testing in women [90]. This test is appropriate for women who are able to physically achieve adequate levels of exercise, defined as 4–5 metabolic equivalents (METs) and for those with a normal resting electrocardiogram (ECG). Significant ST-segment depression with exercise is considered diagnostic for ischemia, either from obstructive CAD or from non-obstructive CAD; ETT is unable to accurately distinguish between ischemia due to obstructive CAD vs. non-obstructive CAD [3, 91]. Reproduction of symptoms, heart rate and blood pressure responses, as well as heart rate recovery should also be considered when assessing a women for IHD [92, 93]. ETT has been considered to be less accurate in women because of a higher false positive rate; it should be noted that the gold standard in these cases was evaluation with angiography for detection of obstructive CAD, which is an anatomic assessment (and not a physiologic assessment of impaired myocardial blood flow). Given that women with IHD often present with no obstructive CAD, the ST segment depressions may represent ischemia due to CMD. Furthermore, mental stress induced angina is more prevalent in women [40], and ETT may not be as accurate in detection of ST segment changes due to mental stress [39, 40, 94, 95]. Despite limitations of ETT, it is an excellent first-line test for detection of IHD, and functional capacity measured by METs is an important prognostic indicator in both men and women [92].

Stress Echocardiography

Although not commonly used in the clinical setting, Doppler echocardiography is a noninvasive means to measure CFR, which is the ratio of hyperemic to resting coronary blood flow. CFR of the left anterior descending artery (LAD) in 1660 patients (906 women and 754 men) with chest pain of unknown origin was measured by

Doppler in response to dipyridamole. A CFR ≤2 was independently associated with an adverse prognosis in women (hazard ratio [HR] 16.48, 95% confidence interval [CI] 7.17–37.85, $p < 0.0001$) [96]. Patients with diabetes, obesity, hypertension, were found to have a low CFR of the LAD on dobutamine stress echocardiography [97]. Furthermore, the degree of impairment of CFR was exaggerated as the number of risk factors increased. Contrast echocardiography is another technique where microbubbles can be used to generate time-acoustic intensity curves to calculate blood flow velocity; this can detect myocardial perfusion abnormalities and quantify coronary blood flow, however, is not routinely used in most clinical centers [98–100].

Cardiac Positron Emission Tomography (PET) Imaging

Rest/stress myocardial positron emission tomography (PET) is a well-validated and reliable method for quantification of myocardial flow reserve and is used to diagnose CMD [101–108]. Stress agents include dipyridamole, dobutamine, adenosine, or regadenoson, while commonly used nuclear tracers include N-13 ammonia or rubidium-82. PET is also the preferred imaging choice for patients with a body mass index (BMI) >40, with large breasts or breast implants, or chest wall deformities [109]. It can provide reproducible measurements of regional myocardial blood flow in milliliters per minute per gram of tissue, which is a functional parameter used to assess coronary microcirculation [110]. Normal CFR ranges from 2 to 4, i.e. myocardial blood flow increases 2–4 times during peak hyperemia induced by vasodilators such as adenosine [111, 112]. It should be noted that CFR is dependent on rate pressure product, and thus blood pressure changes can impact CFR. A reduction in CFR can be due to obstructive epicardial stenosis or due to microvascular dysfunction in a setting of non-obstructive CAD. A low CFR is associated with a worse prognosis, and a preserved CFR has a very high negative predictive value for excluding ischemia [15, 96, 113–117].

Given its high diagnostic accuracy, reproducibility, short tracer half-life, and fast acquisition protocols that minimize radiation exposure, PET is an essential nuclear testing modality to non-invasively diagnose CMD. One of the limitations of cardiac PET is that it is not available at many centers and is often not covered by medical insurance, which makes it challenging to diagnose a low coronary flow reserve non-invasively at some centers. At centers where cardiac PET, CMR or invasive coronary reactivity testing is not available, we recommend empiric symptom management with anti-anginal medications based on symptoms, risk factor profile, and ETT results. Women with persistent symptoms can also be referred to centers of excellence that have the ability to diagnose CMD for a definitive diagnosis and a therapeutic plan.

Cardiac Magnetic Resonance (CMR) Imaging

CMR imaging is an emerging technique that has numerous advantages, including high spatial resolution and evaluation of ventricular function, perfusion, viability and scar assessment as well as myocardial tissue characterization in a single exam.

A large, prospective trial compared CMR to single-photon emission computed tomography (SPECT) in 752 patients with suspected CAD undergoing coronary angiography. CMR consisted of rest and adenosine stress perfusion, cine imaging, and late gadolinium enhancement. Its sensitivity and negative predictive value was significantly superior, compared to SPECT ($p < 0.0001$ for both) [118]. CMR can detect segmental as well as global ischemia and is being used as a technique to detect CMD in some centers [119, 120]. In the WISE study, semi-quantitative myocardial perfusion reserve index (MPRI) was determined from CMR in symptomatic women with no obstructive CAD who were diagnosed by CMD by invasive coronary reactivity testing (CRT). Women with symptoms had lower pharmacologic stress MPRI compared to controls, and lower MPRI predicted one or more abnormal CRT variables. The sensitivity and specificity of an MPRI threshold of 1.84 predicting CRT abnormality were 73% and 74%, respectively [121]. Although a promising field of imaging, further studies assessing the diagnostic and prognostic abilities of CMR are needed.

Biomarkers

Oxidative stress and inflammation are implicated in the pathogenesis of endothelial dysfunction and IHD [122–125]. Glutathione maintains thiol groups of biomolecules in their reduced states and prevents peroxidation of membrane lipids [126]. It also transports nitric oxide (NO), the major endogenous vasodilator, from larger epicardial coronaries to the distal smaller vessels and microcirculation [127]. Studies have shown an association between glutathione levels and CFR, indicating that lower glutathione levels reflect higher amounts of oxidative stress and endothelial dysfunction [128, 129]. Markers of oxidative stress, such as aminothiols and asymmetric dimethylarginine (ADMA) have been studied in endothelial injury and dysfunction. Asymmetric ADMA is a byproduct of the metabolism of L-arginine, the substrate for NO production, that has been found to be elevated in patients with hypertension, dyslipidemia and atherosclerosis [130–133]. ADMA acts as a competitive inhibitor to endothelial nitric oxide synthase, leading to decreased NO production and bioavailability [130]. Plasma ADMA levels have correlated with endothelial dysfunction [131] and subclinical atherosclerosis [134].

Markers of inflammation have also been studied as possible diagnostic or prognostic tools. Highly sensitive-C reactive protein (hs-CRP) is a nonspecific marker of inflammation that has been studied in the prediction of cardiovascular risk in women [135]. Most notably, the Reynolds Risk Score used hs-CRP in addition to traditional risk factors, to estimate the 10-year risk of major adverse cardiac events from studying 24,558 initially healthy women for a median of 10.2 years [73]. However, hs-CRP can fluctuate with infections, inflammatory conditions, and even throughout the day and reflects metabolic changes of many pathways [136]. While hs-CRP has been linked to atherosclerosis, a study of women undergoing angiography for suspected ischemia found that hs-CRP was not associated with angiography

CAD, but was predictive of adverse CV outcomes [137]. In another WISE study of women with ischemia and no obstructive CAD with preserved ejection fraction, interleukin-6 levels predicted heart failure hospitalization and all-cause mortality [55].

Progenitor cells (PC) are essential to endothelial cell regeneration and can be measured peripherally. In 123 women with non-obstructive CAD enrolled in WISE study, lower CFR was associated with higher levels of circulating PCs [138], implying that PCs are mobilized in response to the CMD and resultant chronic myocardial ischemia.

Invasive Assessment

Coronary Reactivity Testing

Coronary reactivity testing (CRT) may be used in patients with angina and evidence of myocardial ischemia to definitively diagnose coronary endothelial and microvascular dysfunction. CRT can help clarify the etiology of symptoms and guide management in those with persistent symptoms and objective evidence of ischemia. CRT involves intra-arterial infusions of non-endothelium-dependent vasodilators, such as adenosine, or nitroglycerin, or endothelium-dependent vasodilators, such as acetylcholine, bradykinin, or substance P (Fig. 8.4), although the latter two are not commonly used. A Doppler flow wire, placed in the epicardial vessel, measures the coronary flow velocity in response to vasoactive agents. Quantitative coronary

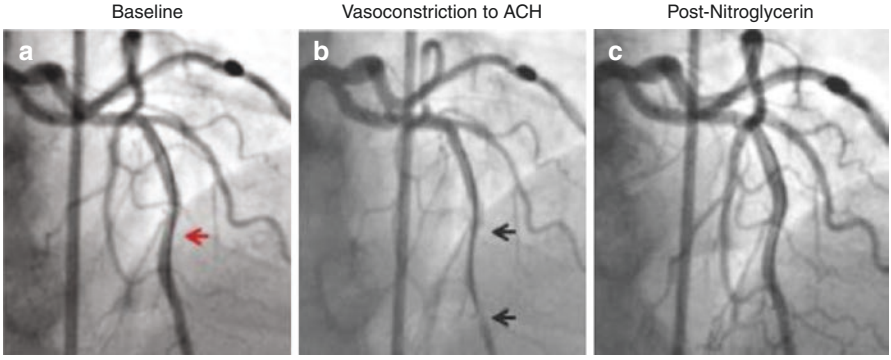

Fig. 8.4 Coronary Angiogram and coronary reactivity testing. (**a**) The figure shows Doppler flow wire in the left anterior descending artery (red arrow). (**b**) In response to acetylcholine infusion, there is abnormal coronary artery vasoconstriction (black arrows), indicating endothelial dysfunction. (**c**) Resolution by intracoronary nitroglycerin (Wei, Mehta, Johnson, et al. Safety of coronary reactivity testing in women with no obstructive coronary artery disease. Results from the NHLBI-sponsored WISE study. *JACC: Cardiovascular Interventions*. 2012. 5(6): 646-652)

angiographic response of epicardial diameter changes is also measured during CRT. Coronary blood flow can then be calculated by the product of average peak velocity and vessel diameter.

To test endothelial-dependent response of coronaries, acetylcholine is injected into the coronary artery in increasing concentrations, and the diameter and velocity changes are measured. Acetylcholine activates the endothelial muscarinic receptors that metabolize L-arginine, stimulate NO synthase and thus generate NO [139], which then activates cyclic GMP and mediates vascular smooth muscle cell relaxation. In normal or preserved endothelial function, coronary epicardial vessels dilate in response to acetylcholine. However, with an impaired endothelial function, acetylcholine's direct smooth muscle constrictor effects on epicardial vessels overcome the dilator effects of endothelium-dependent NO release [140]. The ratio between coronary blood flow during maximal dilation with adenosine compared to baseline is defined as the coronary flow reserve (CFR) [141]. CFR represents the coronary circulation's capacity to respond to an increase in oxygen demand with an appropriate increase in blood flow, where an appropriate CFR is over 3 in healthy adults and CFR <2 is considered impaired. It should be noted that CFR varies by factors such as age, sex, and rate-pressure product [142]. There are multiple studies have reported on the prognostic value of CFR, in those with and without obstructive CAD [143]. A CFR of less than 2.3 in a WISE study in women with no obstructive CAD was prognostic of adverse outcomes, including death, nonfatal MI, nonfatal stroke, hospitalization for congestive heart failure, angina and other vascular events (event rate 26.7% vs. event rate 12.2% for CFR $\geq$2.3; $p = 0.01$) [115].

Patients in the lowest tertile of CFR had the largest number of adverse events, when compared to those in the highest tertile [144]. Suwaidi et al. categorized patients with insignificant CAD into normal endothelial function, mild and severe endothelial dysfunction according to their response in coronary blood flow to acetylcholine. Fourteen percent with severe endothelial dysfunction had a total of ten cardiac events, whereas those with normal function and mild endothelial dysfunction had none ($p < 0.05$) [145]. The Women's Ischemia Syndrome Evaluation (WISE) study also found that an abnormal response to acetylcholine predicted cardiac events in a median follow-up of approximately 4 years [146]. Approximately half of patients with acute coronary syndrome with no obstructive CAD were found to have coronary vasospasm on intracoronary acetylcholine provocation testing in the Coronary Artery Spasm as a Frequent Cause for Acute Coronary Syndrome (CASPAR) study [147].

Currently there are no standardized protocols assessing coronary microvascular function and each institution performs these tests according to their own protocols. The doses of the vasoactive agents used in the WISE study were 18 mcg and 64 mcg for intracoronary adenosine, graded infusions of 0.364 and 36.4 mcg over 3 min for acetylcholine and 200 mcg of nitroglycerin in the left coronary artery [148]. No reactivity-testing related deaths were found in the 293 women in the WISE study, and two serious adverse events (0.7%) occurred (one dissection and one MI resulting from spasm) [148].

Management

Lifestyle Modifications

Women with IHD should all be counseled on a Mediterranean diet, physical activity, and tobacco cessation. The AHA and American College of Sports Medicine recommend at least 30 min of moderate-intensity physical activity for at least 5 days of the week, or 20 min of vigorous aerobic exercise 3 days a week, or a combination of the two [149], and for those with metabolic syndrome, regular exercise is crucial [150]. Exercise has been shown to improve endothelial function, independently of its reduction in cardiovascular risk factors [151]. Twelve weeks of aerobic interval training and a low-calorie diet of 800–1000 kcal per day increased the CFR of 70 obese, non-diabetic patients with CAD and a baseline CFR below 2.5: CFR increased by 0.26 (95% CI: 0.04–0.48) in the aerobic interval training group and by 0.39 (95% CI: 0.13–0.65) in the low-calorie diet group. Another study found a 29% increase in CFR in patients with coronary endothelial dysfunction, diagnosed on CRT, after only 4 weeks of exercise, compared to those in the control group [152]. Smoking is also a well-known and most important modifiable risk factor for ASCVD, and the proposed mechanisms are thought to be secondary to smoking increasing adherence of platelets and macrophages to the vessel wall, developing a procoagulant and inflammatory environment [153]. Smoking cessation, for only 2 weeks, has been found to reduce platelet aggregations, and thus, decrease oxidative stress [154], a major culprit in endothelial dysfunction.

Pharmacotherapy

While some medications have been shown to improve endothelial function and cardiovascular outcomes in patients without obstructive CAD (Fig. 8.5), others have been shown to improve symptoms. Here we discuss a variety of pharmacotherapies that may be used in women with angina and IHD, although large outcomes based clinical trials in those with CMD are needed. Our current strategy is to use anti-ischemic, anti-anginal, and anti-atherosclerosis medications in those with signs and symptoms of ischemia who have been diagnosed with CMD.

Statins

There are no large randomized controlled outcome trials of statins in subjects with no obstructive CAD who have CMD. However, there are intermediate trials demonstrating benefit of statins on endothelial function, and thus the current ACC/AHA recommendations for statin therapy [155] can be followed for patients with CMD,

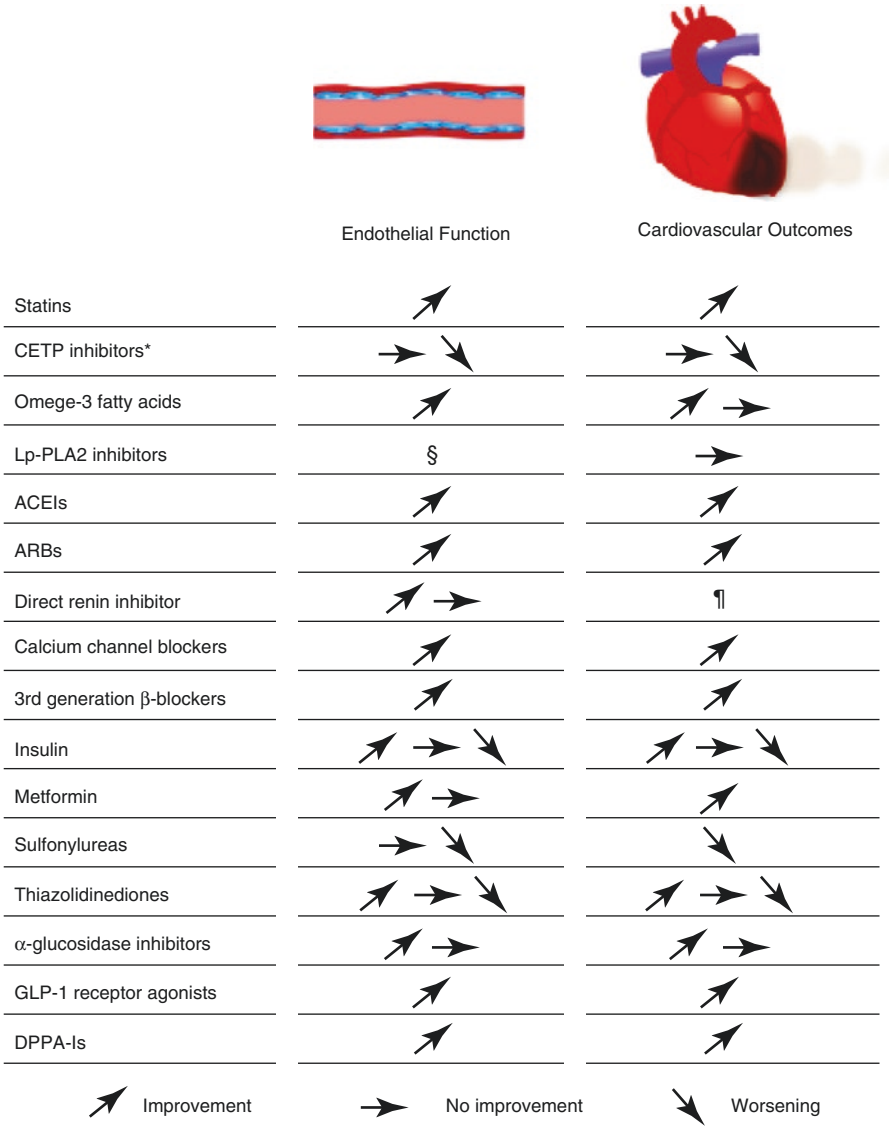

Fig. 8.5 Summary on the effects of each drug on endothelial function and cardiovascular outcomes (Lerman et al. *Prog Cardiovasc Dis.* 2015;57(5):431-42) *Torcetrapib and dalcetrapib

especially given the high prevalence of subclinical coronary atherosclerosis. Patients with CSX with dyslipidemia on simvastatin were found to have significant improvement in endothelial function, measured by brachial artery flow-mediated dilatation, as well as a decrease in LDL levels [156]. Studies have also shown that atorvastatin improved CFR as early as 2 months [157]. Interestingly, independent of its effects

on LDL cholesterol, statins have been shown to improve endothelial dysfunction, by increasing the bioavailability of NO [158, 159] and by reducing circulating levels of adhesion molecules P-selectin and ICAM-1 [160]. Statins have also been shown to improve exercise tolerance and reduce angina [161].

Antiplatelet Agents

Although they may not have significant obstructive plaque burden, patients with CMD have been shown to have coronary atherosclerosis by intravascular ultrasound in the WISE study [76, 162]. In symptomatic patients with demonstrable ischemia, aspirin can be used as recommended in ACC/AHA stable angina guidelines [163], even if without obstructive CAD. There are no clinical trials of dual anti-platelet therapy in women with no obstructive CAD, and thus a decision of adding clopidogrel or another anti-platelet agent in addition to aspirin in women with no obstructive CAD should be made on an individual basis and clinical history.

Symptom Management

Beta-blockers

Beta-blockers reduce the frequency and severity of angina symptoms [163], and specifically carvedilol and nebivolol are preferred in patients with non-obstructive coronary disease with their anti-oxidant properties by stimulating the release of endothelial NO [164]. In one study, four months of carvedilol improved flow-mediated, endothelial-dependent dilatation in patients with CAD, while placebo and 2 h after carvedilol had no significant effect on endothelial dysfunction [165]. Intracoronary administration of nebivolol also increased CFR, in a dose-dependent response, in patients with CAD in another study [166].

Interestingly, in 24 men and women with angina and non-obstructive CAD, nebivolol did not improve endothelial function. However, it did lead to plaque progression and constrictive remodeling assessed by intravascular ultrasound in 1 year, likely from the higher number of low shear stress segments in those who received nebivolol [167].

Angiotensin Converting Enzyme Inhibitors (ACE-I)

ACE-Is have also been shown to improve CFR and exercise capacity in patients with CSX [168]. CFR improved in women with CMD (defined as CFR <3 after intracoronary adenosine) and lower baseline CFR values who were assigned to quinapril, as opposed to placebo. Those who received the ACE-I also reported improved angina measured by the Seattle Angina Questionnaire [169]. The

combination of atorvastatin and ramipril was used in a randomized trial of patients with angina, normal coronary angiograms, and ischemia during stress testing. This combination therapy improved both Seattle Angina Questionnaire scores and exercise duration, compared to placebo. Increased brachial artery flow-mediated dilation and decreased extracellular superoxide dismutase were found in these patients on both a statin and an ACE-I [170]. After treatment with an angiotensin receptor blocker, significant improvements in MBF in response to adenosine were noted in patients with hypertension and CAD before a reduction in blood pressure was seen, suggesting improvement on microvascular function [171]. Sixteen weeks of treatment with pioglitazone, an insulin sensitizer thiazolidinedione, in 26 nondiabetic patients also improved MBF in response to adenosine, as well as myocardial glucose use—again suggesting a beneficial effect on coronary microvascular function [172].

Calcium Channel Blockers (CCBs)

CCBs improve angina and exercise tolerance in patients with CMD [173, 174]. However, several trials comparing beta-blockers, nitrates and CCBs have shown that beta-blockade may be more effective compared to CCBs. Atenolol and propranolol were superior in improving angina, compared to amlodipine and verapamil, respectively [175, 176]. However, in those who are suspected of coronary vasospastic angina, CCBs are first line therapy in addition to nitrates [177]. Several trials have shown that diltiazem, verapamil, and nifedipine reduce episodes of Prinzmetal's angina [178–180].

L-Arginine

L-Arginine is the substrate for endothelial NOS to produce NO. Thus, increasing levels of the substrate and thus increasing NO production could possibly treat endothelial dysfunction. Indeed, L-arginine treatment for 6 months improved endothelial function in patients with non-obstructive CAD [181]. Randomized trials assessing L-arginine's role in management of CMD are needed.

Nitrates

Nitrates upregulate cGMP which leads to relaxation of vascular smooth muscle cells and causes a vasodilatory effect. While there are no randomized trials, an observational study of 99 patients with CSX showed that in 40–50% of the patients nitrates were effective anti-anginals agent [182]. Physicians must advise patients to take a nitrate-free interval of at least 12 h daily, as nitrate tolerance may develop after continued use.

Ranolazine

Ranolazine reduces calcium overload in myocytes by altering the sodium current and is used as an anti-angina medication [183]. It has been specifically tested in subjects with CMD and non-obstructive CAD. A randomized, placebo-controlled pilot study in 20 women with CMD demonstrated improvement in angina by Seattle Angina Questionnaire measures [184]. A subsequent larger RWISE trial in 128 patients (96% women) with CMD found that ranolazine improved angina and CMR determined myocardial perfusion reserve index in those with more severe coronary microvascular dysfunction (CFR <2.5), but did not significantly improve the severity or frequency of angina or CFR in the overall cohort [185].

Estrogen

The risk of IHD increases after menopause, along with the development of ASCVD risk factors, such as hypertension, diabetes, and dyslipidemia. Thus, estrogen has been implicated in the pathophysiology of CMD, especially as the mean age of diagnosis of CSX patient was 48.5 years and 62% of the women were postmenopausal [182]. Estrogen has been hypothesized to have a beneficial effect on vascular reactivity, as well as lipid profiles [186]. Transdermal estrogen improved angina as well as endothelium-dependent coronary vasomotion in 15 postmenopausal women with normal coronary angiograms: in 24 h, there was no vasoconstriction with acetylcholine with a mean diameter change significantly different from the pre-estrogen diameter reduction that was observed ($p = 0.003$) [186].

However, the results of Women's Health Initiative (WHI) and the Heart and Estrogen/Progestin Replacement Study (HERS) led to the U.S. Preventive Services Task Force (USPSTF) recommendations against the use of combined estrogen and progestin or estrogen alone for prevention of ASCVD in menopausal women. There was no difference in incidence of CHD events between the estrogen-progestin and placebo group in the HERS trial, despite a decrease in low-density lipoprotein (LDL) and an increase in high-density lipoprotein (HDL) in the experimental group [187]. The combined estrogen-progestin therapy group of the WHI was at increased risk for total ASCVD, including CHD (HR: 1.29; 95% CI 1.02–1.63), stroke (HR: 1.41; 95% CI 1.07–1.85), and total cardiovascular disease (HR: 1.22; 95% CI 1.09–1.36) over an average follow up of 5.2 years [188]. The use of unopposed estrogen increased the risk of stroke (HR: 1.39; 95% CI 1.10–1.77) and total cardiovascular disease (HR: 1.12; 95% CI 1.01–1.24) [189]. Women in the more recent Kronos Early Estrogen Prevention Study (KEEPS) experienced improvement in menopausal vasomotor symptoms with hormonal therapy, but again there was no improvement in subclinical markers of atherosclerosis, measured by carotid intima-media thickness or coronary artery calcifications [190].

Ivabradine

Ivabradine reduces heart rate by selectively inhibiting the funny channels (I_f) in the sino-atrial node [191–193] and was recently approved for treatment of chronic stable angina in patients with normal sinus rhythm in the U.S. It was non-inferior to atenolol at all doses in a randomized double-blind trial in 939 patients with stable angina [194], and found to improve CFR in patients with stable CAD [195]. However, another study showed no effect on CMD, but an improvement of symptoms [196].

Other Medical Therapies

Low-dose tricyclic antidepressants (TCA) have also been studied, as impaired cardiac nociception is thought to play a role in CMD. Imipramine has been studied and reported to reduce the frequency of pain [197, 198]. TCAs may modulate the effects of norepinephrine uptake and anticholinergic effect that lead to analgesia.

Nicorandil, an adenosine triphosphate sensitive nitrate-potassium channel agonist used in Europe, was found to improve peak exercise capacity in patients with cardiac syndrome X and angina, but failed to significantly improve exercise-induced ST changes [199, 200]. Fasudil, a rho kinase inhibitor currently available in Japan, inhibits smooth muscle vasoconstriction and has been shown to increase ischemic threshold and exercise duration in patients with stable angina [201–204]. Trimetazidine inhibits cardiomyocyte free fatty acid beta-oxidation and promotes glucose oxidation, which leads to decreased acidosis and preservation of energy by the ischemic cell [205]. While its role in patients with CMD is not yet clear [206–208], it has shown benefit in chronic stable angina as anti-ischemic and anti-anginal therapy [209, 210]. Compared to placebo, trimetazidine reduced the number of weekly angina attacks, weekly nitroglycerin tablet consumption and improved exercise time to 1 mm segment depression [210].

Non-pharmacologic Treatments

Enhanced External Counterpulsation (EECP)

EECP is a non-invasive, FDA approved treatment for management of refractory angina. It has been shown to improve functional capacity, anginal class, and time to ST-segment depression during exercise stress testing in patients with CAD [211–213], with its benefit lasting as long as 3 years [214]. Proposed mechanisms include

improved collateral blood flow and endothelial function from the diastolic augmentation of myocardial perfusion via inflation of pneumatic cuffs on the lower extremities during EECP [215–217].

Stem Cell Therapy

Bone-marrow stem-cell transplantation has improved exercise capacity, myocardial perfusion, and cardiac function in patients with MI [218]. However, stem cell therapy remains experimental and has not been studied in patients with angina and no obstructive CAD. Microvascular rarefaction, a reduced number of arterioles and capillaries [219] has been speculated to play a role in coronary microvascular angina [220], and restoring impaired microvascular function has been a focus of preclinical stem cell therapy studies [221].

Cognitive Behavioral Therapy and Group Support

An 8-week program of the cognitive behavioral therapy improved angina frequency and severity in women with ischemia and non-obstructive CAD [222]. In a study of 49 women with CSX, 12 monthly group support meetings helped reduce health-care demands and maintained social support for these individuals [223]. A multidisciplinary team approach of including psychiatrist/psychologist, a chronic pain specialist, along with cardiologist is needed to provide comprehensive care to women who have persistent symptoms of chest pain.

Conclusion

Women have a lower prevalence of obstructive CAD compared to men, yet have high rates of myocardial ischemia and subsequent mortality. CMD is highly prevalent in women with signs and symptoms of ischemia, and CMD should be considered in the differential when no obstructive CAD is found. CMD can be definitively diagnosed by invasive coronary reactivity testing, which assess endothelial and non-endothelial dependent mechanisms. Non-invasive imaging with cardiac PET can provide CFR and diagnose CMD, which is a diagnosis associated with adverse cardiovascular prognosis. In addition to IHD lifestyle modifications, CMD treatment revolves around anti-anginal, anti-ischemic, and anti-atherosclerotic medications, as well as non-pharmacologic strategies to improve symptoms and quality of life. Larger clinical trials are needed in this population to determine therapeutic algorithms and to improve CMD outcomes in women.

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Chapter 9
Microvascular Angina as a Cause of Ischemia: An Update

Edina Cenko, Peter Louis Amaduzzi, and Raffaele Bugiardini

Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndromes
AHA	American Heart Association
CAD	Coronary artery disease
CASS	Coronary Artery Surgery Study
CCB	Calcium channel blockers
CCTA	Coronary computed tomography angiography
CFR	Coronary flow reserve
CMD	Coronary microvascular dysfunction
CMRI	Cardiac magnetic resonance imaging
CVD	Coronary vascular dysfunction
ECG	Electrocardiogram
EECP	Enhanced external counterpulsation
EMMACE-2	Evaluation of Methods and Management of Acute Coronary Events
ESC	European Society of Cardiology
FFR	Fractional flow reserve
GRACE	Global Registry of Acute Coronary Events
HDL	High-density lipoprotein

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HOPE	Heart Outcome Prevention Evaluation
IMR	Index of microvascular resistance
IVUS	Intravascular ultrasound
LDL	Low-density lipoprotein
MVA	Microvascular angina
PET	Positron emission tomography
RCT	Randomized clinical trials
SAQ	Seattle Angina Questionnaire
SPECT	single photon emission computed tomography
TIMI	Thrombolysis in Myocardial Infarction
TTDE	Transthoracic doppler echocardiography
VINTAGE-MI	Vascular Interaction With Age in Myocardial Infarction
WISE	Women's Ischemia Syndrome Evaluation

Introduction

Microvascular angina (MVA) is suspected in patients presenting with angina or angina-like chest pain with "*normal*" appearing coronary arteries. "*Normal*" is defined as no visible epicardial coronary artery disease (CAD) or lumen irregularities (<50%) as judged visually at coronary angiography. This finding is five times more common in women than in men [1]. Among patients with chest pain and normal coronary angiography an unknown number are suffering from cardiac pain of ischemic origin. Uncertainty is often difficult to allay, for medical attendants as well as for patients, resulting in perpetuation of symptoms, difficulties in management and establishment of risk of subsequent coronary events [2, 3]. There is, therefore, a need for improvement of the diagnosis of chest pain with an ischemic etiology and for evaluation of the impact of MVA on clinical outcomes.

Epidemiology: The Magnitude of the Problem

Several published reports, including the National Heart, Lung, and Blood Institute-sponsored Coronary Artery Surgery Study (CASS) and the Women's Ischemia Syndrome Evaluation (WISE) study, have reported that up to half of patients with chest pain undergoing coronary angiography are found to have "normal" or non-obstructed epicardial coronary arteries [4, 5]. Patients with angina and "normal" or near normal coronary arteries are predominantly women [6, 7]. Of interest, the prevalence of non-obstructive disease varies depending upon gender, ethnicity and clinical setting; while the percent of obstructive CAD is higher for men than women in every ethnic subset, black men and women have the highest rate of non-obstructive CAD as seen by angiography [8]. On this note, it has been shown that at least one half of women with suspected angina have non-obstructive CAD at coronary angiography [4, 9]. The prevalence is lower in the setting of more specific clinical

symptoms. Post-hoc analyses of large clinical trials demonstrates that 10–25% of women presenting with acute coronary syndromes (ACS) have "normal" or non-obstructive CAD, compared to 6–10% in men [2, 8, 10–14]. This finding raises the possibility that women are being inappropriately referred for coronary angiography; a point contradicted by studies documenting underutilization of cardiac catheterization in women [15]. Coronary computed tomography angiography (CCTA) may be useful in acquiring a more accurate identification and risk stratification based on more precise evaluations of CAD anatomy [16, 17].

Are Risk Factors Shared with Obstructive Disease?

Traditional risk factors have long been identified for their pathogenetic role in CAD, however, the inter-gender variability of their prevalence and effects have emerged more recently [18]. Global risk scores, such as the Framingham Risk Score, tend to predict a lower risk of lifetime CAD in women compared to men and may therefore underestimate the true risk in the female population [19]. Women, who are predominantly affected by non-obstructive CAD, have been shown to develop similar rates of incidence of CAD events as men but with a delay of around 10 years [18]. Therefore, age plays a distinct role in terms of incidence and outcome in women compared to men. Hypertension has been observed to have different proatherogenic effects in women, possibly due to the protective effect of estrogens, a notion reinforced by the association between conditions tied to the female gender, such as hypertensive disorders in pregnancy and polycystic ovarian syndrome, and a greater lifetime risk of hypertension and ischemic heart disease [20].

Although high-density lipoprotein (HDL) values are usually lower in men, the risk of CAD derived from low-density lipoprotein (LDL) and total cholesterol seem to be similar in men and women, and therefore may contribute equally to obstructive and non-obstructive CAD [18]. Hypertriglyceridemia, on the other hand, seems to be a stronger risk factor for women than men, and the same can be said about diabetes [21–24]. Pathological coronary flow reserve (CFR), a measurement of coronary microvascular function, has been shown to correlate with risk factors such as age, hypertension, smoking, elevated heart rate, obesity and LDL levels, although these conditions do not fully explain the pathological reduction of CFR [25, 26].

Novel risk markers, such as high-sensitivity C-reactive protein, have been observed to more accurately predict risk of CAD in women and correlate with signs and symptoms of ischemia even in patients with non-obstructive CAD [26–28].

Definitions

Classification is critically dependent on the underlying pathogenetic model of the disease, which, in turn, determines selection of therapy. Regrettably, the pathophysiology of myocardial ischemia despite "normal" or near normal coronary angiograms is still rudimentary. Over the past 10 years, many terms have been

proposed to label such patients, including cardiac syndrome X [29], microvascular angina [30], vasotonic angina [31], and non-atherosclerotic myocardial ischemia [32]. More recently, a new classification of coronary microvascular dysfunction (CMD), based upon the clinical setting in which the disease take place, was introduced. This categorization distinguishes CMD in obstructive CAD, in the context of cardiomyopathies, and CMD in the absence of these former clinical conditions [33]. A second method of classification, on the basis of clinical presentation, has been suggested. This designation identifies stable or chronic MVA and unstable or acute MVA [34]. Another distinction may be made between primary and secondary MVA, with the latter occurring in the context of specific conditions [34].

However, the evidence supporting these "new" classifications is still lacking. Therefore, in order to make this overview more readable, we will describe MVA in the context of previously accepted terminology.

MVA in Syndrome X

The term syndrome X was introduced for the first time by Kemp [35] in an editorial published in 1973. The term "syndrome X" was used in this editorial to denote the uncertainty of chest pain etiology in these patients, a term subsequently used by other investigators, but often with different criteria for its definition. Most studies included patients with CAD ranging from minimal irregularities to stenoses up to 50% of luminal diameter at visual angiographic analysis [36, 37], while others included patients with smooth coronary angiograms as assessed by quantitative coronary angiography [2].

MVA and Abnormalities in Coronary Blood Flow

Despite differences of definition, most groups have reported that patients with chest pain and angiographically normal coronary arteries have abnormalities in coronary flow and metabolic responses to stress [38–42]. These findings are believed to be consistent with a microvascular etiology, as based on the observation of normal coronary angiograms. However, this extrapolation is an assumption, as conventional angiography cannot reliably identify functional disorder the epicardial vessels, which may impair blood flow as well. We believe that the term MVA may have outlived its usefulness, because these patients often exhibit a disorder not only of the coronary microcirculation, but also of the entire coronary artery and peripheral circulation [31, 41]. The authors of the current review propose the term "coronary vascular dysfunction" (CVD) as the most appropriate description of patients having chest pain despite "normal" or near normal coronary artery at angiography.

MVA in Acute Coronary Syndromes

MVA in ACS can be suspected in patients with new or worsening episodes of angina, usually associated with minimal efforts or present at rest, despite evidence of normal or near normal coronary arteries as assessed by angiography [33, 35].

Vasospastic and Vasotonic Angina Are Synonymous with MVA?

Focal or diffused coronary spasm, also known as vasotonic angina, is a distinct nosological entity, caused by an increased reactivity of vascular smooth muscle cells and or endothelial dysfunction, that requires differential diagnosis with MVA [31, 43, 44]. When the coronary spasm is focal, a condition known as variant or Prinzmetal's angina, patients typically present transient ST-elevation [45]. Diffuse coronary spasm, instead usually involves the distal portion of coronary arteries, and is more commonly characterized by ST-segment depression. Under these circumstances a disorder of the entire coronary arterial three may be suspected [31, 44].

Pathophysiology

The idea that some forms of ischemic heart disease may be caused by abnormalities of the microcirculatory vessels is not new. It was proposed 16 years ago as a cause of angina pectoris [30]. Other studies, however, have questioned an ischemic cause for symptoms, even in patients selected for abnormal noninvasive testing [30, 42, 46–48]. More recently, studies incorporating assessment of endothelial function indicate that subsets of patients may be at higher risk of serious cardiovascular events [2, 9, 49–52].

Reduced Coronary Flow Reserve and Myocardial Ischemia

A reduced CFR can be seen in 20–50% of patients with chest pain and normal angiography [30, 31, 42, 53–55]. Buchthal et al. [56] from the WISE study group reported that 7 of 35 women with chest pain and normal angiograms had findings compatible with myocardial ischemia during hand-grip exercise, as assessed by cardiac nuclear magnetic resonance imaging (CMRI). Panting et al. [55] performed CMRI in 20 patients (16 women) with chest pain, normal angiograms and ischemic-appearing ECG responses to exercise stress. During adenosine infusion, 19 of 20 patients experienced chest pain. Disappointingly, none of these patients showed

reversible perfusion abnormalities following stress to suggest inducible myocardial ischemia. These data further symbolize the uncertainty of chest pain etiology in many patients presenting with chest pain and normal angiograms.

Coronary Vascular Dysfunction

Abnormality of both endothelium-dependent and -independent vasodilatation due to early atheroma may be a cause of vascular dysfunction [41, 49, 53, 57–60]. The relationship between vascular dysfunction and myocardial ischemia in patients with chest pain and normal angiograms can be summarized as follows: submaximal increase in myocardial blood flow during effort could often be inadequate to match changes in oxygen demand and, therefore, may be a cause of angina. This simplified hypothesis, however, is at variance with the clinical presentations of these patients. Indeed, many of them experience angina at rest, which implies a primary reduction of coronary blood flow and oxygen supply. The issue of how to explain persistent chest pain despite normal angiograms, especially in women, is still unsettled.

Endothelial Dysfunction

Studies incorporating assessment of endothelial function in patients with vascular dysfunction indicate that subsets of patients may be at higher risk of serious cardiovascular events [2, 9, 49–52]. A normally functioning vascular endothelium is required for appropriate dilatation of arteries during exercise [61]. Endothelial dysfunction could underlie a nonspecific enhancement of the response to a variety of vasoconstrictor stimuli [62–64].

Coronary vascular dysfunction due to abnormal endothelium-dependent coronary vasodilatation is predictive of adverse outcomes [41, 49, 65–67]. Conversely, impaired endothelial-independent vasodilatation predicts favorable outcomes [41, 65, 66]. The reason of this discrepancy is not known. Endothelial dysfunction leads to the initiation of atherosclerosis and is linked to many risk factors that predispose individuals to atherosclerosis. On the contrary a blunted response to exogenous nitric oxide donors (coronary endothelial-independent vasodilatation) might simply reflect the presence of atherosclerosis, revealing only an increased stiffness of the vessel wall [68]. Endothelial dysfunction and atherosclerosis, although causally related, are distinct problems. Recent studies indicate that endothelial dysfunction and early atherosclerosis, as detected by optical coherence tomography (OCT), although associated in many coronary segments, may exist separately [69, 70]. Functional alterations of the coronary arteries can be identified at a stage when atherosclerotic lesions are not detectable by any imaging technique.

Hidden Atherosclerosis

Recent pathophysiological studies demonstrate that the current concept of myocardial ischemia induced by epicardial coronary functional or fixed luminal narrowing should be renewed. Acute coronary syndromes often result from disruption of modestly stenotic plaques, not detectable by angiography, but only by intravascular ultrasound [71–73]. Plaque rupture and erosion often lead to thrombotic complications [71], or occasionally plaques may rupture and debris may be washed downstream leading to peripheral coronary microembolization often associated with rhythm abnormalities [74–77]. Disturbed microvascular integrity could therefore be due to "hidden" epicardial atherosclerosis.

Diagnosis of Coronary Vascular and Microvascular Dysfunction

The diagnosis of CVD and CMD requires the exclusion of cardiac and non-cardiac conditions that could be alternative explanations for chest pain. Diagnosis of CVD and CMD involves the demonstration of ischemia despite "normal" or near normal coronary arteries.

The Price of Misdiagnosis

Epidemiological studies demonstrate that undiagnosed angina is costly in terms of mortality, morbidity, and healthcare utilization [78, 79]. Sixty-five percent of patients reported angina during an 11-year follow-up and remained without a diagnosis. Among those with an abnormal ECG the absolute risk of non-fatal myocardial infarction was similar between patients with and without a diagnosis (16% versus 15%). Also, compared with apparently healthy subjects, those with undiagnosed and diagnosed angina had a 2.4 and 3.2 times greater risk, respectively, of impaired physical functioning [80]. These findings underscore the importance of identifying the cause of angina in patients with chest pain and normal angiography.

Symptoms

Chest pain is the most common symptom of coronary atherosclerosis prompting subjects to seek medical attention. Patients may present with stable or unstable symptoms. Interpretation of early symptoms plays a key role in the recognition of patients with normal coronary arteries at angiography, but at risk of future

development of atherosclerosis and coronary events [49, 51, 81]. At one extreme are patients in whom angina develops every time the workload of the heart is increased beyond a fairly fixed threshold; at the other extreme are patients who are not necessarily restricted in their physical activity by angina, but suffer rest pain without an obvious cause. Effort that provokes angina on one day may be performed without angina on another day. Both women and men most commonly (80%) report typical angina [49]. A number of women report pain as more intense and long lasting [49, 51, 81]. Women use more emotional words to describe chest pain [49, 51]. Moreover, their pain is less frequently judged by cardiologists to be typical of angina of cardiac origin [49, 51, 82]. Chest pain persisting for many years is associated with future development of coronary atherosclerosis [49, 51] and adverse outcomes [51, 82]. In clinical practice, symptoms in most of these patients are often indistinguishable from those with obstructive CAD. More information and additional testing is needed. It is each time important to find whether or not myocardial ischemia exists.

Poor Quality of Life

Along with severe and often unpredictable symptoms, chest pain is often associated with increased psychological morbidity, debilitating symptoms and a poor quality of life [83–85]. Women with chest pain and normal and near normal coronary arteries at angiography have higher levels of anxiety and depression than their CAD counterparts and healthy age-matched subjects. Depression is related to social support and recent traumatic life events [51, 83, 86]. Patients whose chest pain failed to improve or increased in frequency in the 12 months following angiography had significantly higher psychiatric morbidity at the baseline assessment than patients whose chest pain frequency and severity had abated [87, 88].

Non-invasive Testing

Considering that there are no imaging techniques that allow direct visualization of the microcirculation, hemodynamic evaluation of the microvascular bed can be done through functional assessment. CMD should be evaluated through functional studies, by assessing both vasodilator and vasoconstrictor function of the coronary circulation.

ECG Exercise Testing

The majority of patients presenting with chest pain do not undergo invasive investigation immediately, and the cardiologist, following history, physical examination, and imaging or non-imaging exercise stress test, usually makes a diagnosis of

the pain as cardiac or non-cardiac. Non-imaging exercise testing is less sensitive in women than in men, possibly due to a greater functional reduction in aging women [89]. The lower prevalence of severe CAD and the fact that more women than men fail to reach maximum aerobic capacity during exercise may account for this difference in sensitivity [89]. Moreover, the overall prognostic value of non-imaging exercise testing is under debate. If an exercise test is performed only up to a low level of workload then it may be normal in a proportion of patients who will experience subsequent coronary events [90]. Conversely, positive tests showing ST-segment depression may not correspond to any underlying coronary lesion and these "falsely positive" tests are more common in women [91]. Mechanisms that may contribute to gender difference remain unclear and may be related to differential effects of estrogens on the ST-segment [92] or differences in vascular reactivity [93].

Single Photon Emission Computed Tomography (SPECT) and Cardiac Magnetic Resonance Imaging (CMRI)

Use of imaging rather than non-imaging stress testing may be helpful in the identification of microvascular flow obstruction. CMRI and SPECT show a substantial overlap in detection of adequate or inadequate flow reserve patterns [55, 94]. In patients with a normal resting ECG, exercise stress myocardial perfusion SPECT yields additional prognostic value over clinical, historical, and exercise treadmill test data for the prediction of coronary events [95]. SPECT abnormality is predictive of both cardiac death and myocardial infarction in patients with obstructive and non-obstructive CAD [96, 97]. Perfusion imaging, unlike angiography, closely correlates with CFR and reflects function of the epicardial conduit arteries as well as normal capacity of the resistance vessels [95]. A growing number of centers offer sophisticated cardiac diagnostic tests to aid diagnosis and management of patients with ischemic heart disease. CMRI allows assessment of either subendocardial and myocardial perfusion, myocardial fibrosis as well as evaluation of left ventricular ejection fraction. As a consequence, use of CMRI instead of SPECT for initial diagnostic imaging of patients who have chest pain has become more common [55, 94].

Cardiovascular Computed Tomographic Angiography

CCTA is a noninvasive technology, which produces an anatomical rather than functional evaluation of the coronary circulation, and is able to identify and prognosticate CAD and its outcome [98, 99]. CCTA can accurately evaluate the burden of atherosclerosis and plaque morphology, with results comparable to those of intravascular ultrasound (IVUS). CCTA studies in patients with non-obstructive CAD have shown that the presence of noncalcified and mixed coronary plaques was associated with worse long-term clinical outcomes compared to those with calcified plaques [100]. Noncalcified and mixed coronary plaques were associated with

worse clinical outcomes in women [101]. Furthermore, death rates have been shown to increase with the number of diseased coronary arteries, in both obstructive and non-obstructive CAD [16, 102]. Recent studies have shown that CCTA has a greater prognostic value in women and patients with stable chest pain and a low burden of obstructive disease, as compared to functional testing [103, 104]. A substudy of the Women's Ischemia Syndrome Evaluation (WISE) reported that presence of non-obstructive CAD in women was associated with a fivefold higher rate of cardiovascular events compared to normal cohorts [105]. However, men were excluded by this study. In a more recent work, noncalcified followed by mixed coronary plaques were more prevalent in both genders aged <55 years as well as in women aged ≥55 years [106]. In summary, the presence of noncalcified and mixed plaque in symptomatic subjects with non-obstructive CAD as detected by CCTA adds incremental prognostic value over traditional risk factor assessment and the number of diseased coronary arteries in both genders.

Transthoracic Doppler Echocardiography (TTDE)

There are methods that have a potential role in evaluating CFR. TTDE may be used to assess vasodilator reserve by measuring CFR, defined as the ratio between peak vasodilatory velocity and baseline velocity. Ratios <2.5 are usually indicative of CMD, however values between 2.5 and 3.5 may warrant further investigation [107]. Measurements of CFR by TTDE have been shown to be reproducible with those observed by positron emission tomography (PET) and invasive techniques [108]. TTDE is a cost-effective, non-invasive and rapid examination which can be also be executed in an ambulatory setting. However, limitations of TTDE are the presence of a good echocardiographic window and the fact that measurements of CFR are made in the distal left anterior descending artery and is therefore an incomplete measure of global CFR [109, 110]. An alternative to TTDE may be transthoracic myocardial contrast echocardiography, which used intravenous injection of microbubbles and has been found to produce similar measurements of coronary blood flow as TTDE and PET [111, 112]. Transesophageal echocardiography with Doppler imaging has become a further fascinating and appealing tool for diagnosis [113, 114]. However, studies have shown a high inter-operator variability of all of these echocardiographic derived techniques [115].

Non-invasive Assessment of Endothelial Function

Peripheral endothelial function testing through measurements of flow-mediated dilatation (FMD) is attractive because it is non-invasive and allows repeated measurements [116]. Upper-arm occlusion for 5 min results in reactive hyperemia after the release of the cuff; the increase in shear stress results in endothelium-dependent flow-mediated vasodilation. The degree of dilatation of the studied vessel from baseline to peak hyperemia reflects the degree of endothelial function. A recent

publication has recommended standardization of this methodology [117]. Peripheral vascular endothelial function can be also assessed by strain-gauge venous impedance plethysmography. This technique examines the change in forearm blood flow in response to direct administration of agonists into the brachial artery [118]. A new, more objective method of measuring 'global' endothelial function has been developed utilizing waveform analysis and beta-2 stimulation of the endothelium using inhaled salbutamol [118]. This technique is fully mobile, uses a laptop computer and applanation tonometry and is ideal for assessing endothelial function in large numbers of subjects [119]. However, several large noninvasive studies are still needed to determine the predictive value of brachial ultrasound testing as a potential predictor of coronary dysfunction.

Invasive testing

Coronary Angiography

Slightly more than half of patients who have an imaging stress test subsequently undergo coronary angiography and nearly half of those who had angiography later undergo coronary revascularization [120]. These data reflect underlying uncertainties about when to test for CAD. These observations also demonstrate that identification of non-obstructive CAD is a frequent clinical finding. Data analysis of patients undergoing their first coronary angiography over a 3-year period showed that 32% had entirely normal coronary angiograms and an additional 15% had <50% stenosis in any of the major vessels [121]. The frequency of non-obstructive CAD is higher in black patients and in women [2, 121]. Chronic stable angina is the most common clinical presentation in patients without obstructive CAD [121]. Many of these patients do not have angiographically visible plaques, but they have coronary disease. The heterogeneity of this patient population may complicate patient selection for appropriate medical management.

Coronary Flow and Pressure Measurements

Sensor-tipped guide wires have enabled cardiologists to identify physiological measures as absolute CFR, relative coronary flow reserve, index of microvascular resistance (IMR) and pressure-derived fractional flow reserve (FFR), the most frequently used being absolute CFR and FFR [122]. CFR is commonly expressed as the ratio between maximal myocardial blood flow after abolition of arteriolar tone and resting baseline flow. Threshold values <2–3 are often associated with diagnosis of microvascular dysfunction [53, 97]. Coronary flow reserve measurements can however be misleading. A ratio <2–3 can be due either to an increased resting flow or reduced maximal flow, or both. High perfusion pressure due to hypertension is a cause of increased baseline flow and may be a source of significant error [97, 122].

FFR is easily measured during routine coronary angiography by using a pressure wire to calculate the ratio between coronary pressure distal to a coronary artery stenosis and aortic pressure under conditions of maximum myocardial hyperemia [123]. The use of FFR measurement provides the cardiologist with a straightforward, readily available, quantitative technique for evaluating the physiologic significance of a coronary stenosis. A clinical FFR threshold of >0.8 is used to exclude the presence of a functionally significative stenosis [124]. IMR, is a simple guidewire-based quantitative measure of the coronary microcirculation. IMR is calculated by multiplying the distal coronary pressure by the mean transit time of a 3 mL bolus of room temperature saline during maximal coronary hyperemia induced by intravenous adenosine. Threshold values of >25 are considered indicative of CMD [125]. In patients with normal or near normal coronary arteries, an impaired CFR, FFR values >0.8, and an increased IMR generally indicates the presence of CMD [123]. Thus, coronary blood flow measurements by Doppler can be used to identify vascular dysfunction in patients with normal or near normal coronary angiograms.

Intracoronary Ultrasound (IVUS)

In the early stages of atherosclerosis, compensatory enlargement of arterial diameter is an important mechanism for preserving luminal size despite plaque growth [126]. The adaptive arterial remodeling response to plaque accumulation is limited and appears to be exhausted when plaque size exceeds a cross-sectional area of 45% or of an increase of 60% of the vessel size circumference [126]. IVUS is a relatively new modality for assessment of atherosclerotic disease burden. IVUS demonstrated that atherosclerotic disease is diffuse and involves the entire arterial tree, including multiple plaques that are not associated with vessel narrowing [71, 127–130]. Early atherosclerosis, as assessed by IVUS does not necessarily correlate with impairment of coronary blood flow as documented by intracoronary Doppler ultrasound. In a series of 44 patients with normal coronary angiograms more than 50% had signs of early atherosclerosis with IVUS, but only 20% had a reduced coronary flow reserve [129]. Thus, early signs of atherosclerosis can be detected by IVUS. This may have implications for detecting the causes of vascular dysfunction [130].

Invasive Coronary Endothelial Function Testing

Endothelial function of the coronary microvasculature can be assessed with intracoronary Doppler techniques to measure coronary blood flow in response to acetylcholine. Vasomotor response to acetylcholine is also assessed. Reduced vasodilatory response of the coronary microcirculation or paradoxical vasoconstriction of the epicardial vessels is a sign of coronary endothelial dysfunction [41, 49, 65–67]. A number of studies addressed the long-term prognostic value of coronary endothelial function testing in patients with non-obstructive (20–40% stenosis) CAD.

Suwaidi et al. examined 157 patients and reported that there were significantly more cardiovascular events over a 2-year follow-up in patients with endothelial dysfunction [66]. Schachinger et al. and von Mering et al. noted similar findings over a 7- and 4-year follow-up, respectively [65, 67]. Recent investigations addressed this issue in patients with completely normal coronary angiography and demonstrated that 30% of women with chest pain and severe endothelial dysfunction, as assessed by intra-coronary acetylcholine testing, developed angiographically visible atherosclerosis during a 10-year follow-up [49]. Halcox et al. evaluated 176 patients with normal coronary angiography for a mean follow-up of 46 months [41]. Outcomes of this analysis were cardiovascular death, acute myocardial infarction, unstable angina pectoris, and acute ischemic stroke. Acute vascular events occurred in 4.5% of patients. When patients were divided into two groups with either normal or abnormal endothelial function, the event rate of patients with endothelial dysfunction increased up to 14%. Patients with relatively preserved endothelial function have low event rates irrespective of the degree of visible atherosclerosis [68].

Prognosis

Prognosis of patients with chest pain and normal or near normal coronary arteries at angiography is not as benign as reported by preliminary cohort studies [5, 131–133] Although prognosis is better than patients with obstructive CAD and/or culprit coronary artery lesions, patients with MVA are at increased risk of major cardiovascular events such as cardiac death, myocardial infarction, stroke, heart failure and coronary revascularization when compared to the baseline population [2, 9, 50, 52].

In over 4000 patients with stable angina pectoris, non-obstructive CAD and normal left ventricular function, enrolled in the CASS registry, 7-year mortality rates were 4% in patients with completely normal coronary angiography and 8% in those with mild disease (<50% stenosis in at least one coronary artery segment) [5]. Likewise, a recent study reported that among over 8000 patients with non-obstructive-CAD undergoing elective coronary angiography for stable CAD indications, enrolled in the Veterans Affairs health care system, non-obstructive CAD was associated with higher rates of 1-year nonfatal myocardial infarction and mortality, after the index angiography as compared with no-CAD patients [134]. Outcome data from the WISE study have shown that women with persisting symptoms of chest pain, non-obstructive CAD and evidence of myocardial ischemia, such as MVA, have a poorer prognosis than their counterparts without evidence of myocardial ischemia [51, 107, 135]. The combined risk of death, myocardial infarction, stroke, and heart failure is >2% per year in women with functional CAD and a history of chronic chest pain symptoms, such as MVA, persisting more than 1 year [51, 107, 135]. Numerous studies have assessed the prognostic importance of microvascular dysfunction as determined by CFR values. In women with chest pain and non-obstructive CAD, CFR <2.32 threshold was reported to associated with a 27% increased risk for major cardiovascular events such as death, nonfatal myocardial

infarction, nonfatal stroke, or hospitalization for congestive heart failure, as compared to an outcome rate of 12% in patients having an CFR ≥2.32 during a median follow-up of over 5-years [52]. Similarly, among diabetic patients without known CAD and impaired CFR, the annual cardiac mortality rate was similar to that of non-diabetic patients with obstructive CAD but preserved CFR (annual cardiac mortality rate: 2.8%/year versus 2.0%/year respectively) [136]. Moreover, studies have shown that patients with impaired CFR or positive acetylcholine testing, show evidence of progression of atherosclerosis within the next decade [49, 50, 66, 137, 138].

Outcomes of patients (men and women) with ACS and non-obstructive CAD include 2% chance of death and myocardial infarction just after 1-year follow-up [2, 10, 134]. The risk is not invariably high and the TIMI Risk Score and GRACE risk score help to estimate risk [10]. The rate of death or non-fatal myocardial infarction ranges from 0.6% in patients with a TIMI score of 1, to 4.1% in those with a score of 4 or more.

Among patients with non-obstructive CAD and non-ST-segment elevation ACS enrolled in the In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, 30-day rates of death or nonfatal myocardial infarction were 2% in patients with no-CAD (no stenosis identified) and 6% in those with mild CAD (any stenosis ≤50%) [139].

Management of Vascular Dysfunction and Microvascular Angina

Managing patients with non-obstructive CAD and vascular dysfunction, such as MVA, can be frustrating for both patients and physicians, as no randomized clinical trials (RTCs) comparing therapeutic management have been conducted in these populations. Therefore, there is a lack of information regarding optimal treatment options. Indications are not dependent on the presence of obstructive or non-obstructive CAD at the time of angiography [124]. Moreover, one more limitation concerns the small cohort studies used for this special population as the lower is the incidence of adverse events the greater is the number of the patients needed to generate solid evidence [2, 43, 140]. Recommendations from international guidelines state that antiplatelet agents, statins, and beta-blockers and/or calcium channel blockers (CCB) are indicated for secondary prevention and symptom relief as a first line treatment for all patients unless contraindicated, whereas angiotensin-converting enzyme inhibitors (ACE-inhibitors) may be continued indefinitely for those patients with left ventricular dysfunction, hypertension, or diabetes mellitus and are reasonable in the absence of these co-morbidities or in patients with refractory symptoms [124, 141]. Furthermore, many patients with MVA have multiple cardiovascular risk factors. Yet, the treatment of MVA should begin with optimal cardiovascular risk factors control. Therefore, collaboration between physicians and patients on lifestyle changes and modifiable risk

factors control along with secondary prevention therapy play a crucial role in patient's quality of life and prognosis.

Lifestyle Modifications

Lifestyle changes, risk factor management and physical training should be considered essential components of any therapeutic approach [142]. Lifestyle interventions that can be encouraged include, smoking cessation, weight management, and a healthy diet (increased consumption of fruits, vegetables, seafood, legume, nuts fiber, whole grains; decreased consumption of salt, added sugar, saturated fatty acids, and red and processed meats) [143]. Physical training increases coronary blood flow rates which in turn maintain maximal myocardial perfusion [138]. Physical training improves endothelial function and quality of life in patients with CAD [144]. In studies of women with MVA, 8-weeks of regular physical training of 30 min, three times/week was associated with over 30% increase in exercise capacity, 26% increase in peak oxygen uptake and reduced angina frequency [145, 146]. Although, the evidence is limited to small studies, cognitive behavior therapy such as autogenic training, and relaxation therapy have shown some benefits as well in term of psychological morbidity and quality of life in women with MVA [145–147].

Enhancement of Event-Free Survival

There is fair or good evidence that antiplatelet agents, statins, and ACE-inhibitors, reduce the risk for cardiovascular events in patients with known heart disease [124, 141, 142]. Despite this evidence, it is still unsolved if patients with non-obstructive CAD and/or vascular dysfunction derive benefit from use of conventional guideline-recommended therapies.

Antiplatelet Agents

Low-dose aspirin remains the cornerstone antiplatelet therapy for event prevention in patients with CAD. While there are no studies that have assessed the benefits of aspirin treatment in patients with MVA, it should be noted that these patients are at increased risk for future major adverse cardiovascular events when compared to the general population. Therefore, it is rational to recommend low-dose aspirin therapy in patients with MVA. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines do not address the issue of prevention therapy in patients with non-obstructive CAD [141]. On the opposite, the 2013 European Society of Cardiology (ESC) guidelines on the management of stable CAD state

that all patients with non-obstructive CAD merit secondary prevention with aspirin as a first line therapy. As such we believe that the ACC/AHA approach is much more restrictive than that of the ESC [124].

Statins

The beneficial effect of statins on coronary microcirculation and myocardial perfusion have been established in clinical studies [40, 148, 149]. Statins may counteract the oxidative stress and improve endothelial function in patients with CMD [40]. Secondly, many patients with MVA in addition to impaired CFR, show early signs of atherosclerosis as assessed by IVUS or provocative studies and progression of atherosclerosis at long-term follow-up [49, 50, 129, 130]. Statins seems to be important in this population due to their antiatherosclerotic effect. In MVA patients with LDL-cholesterol levels <160 mg/dL (4.0 mmol/L), 3-months statins treatment improved endothelial function, exercise tolerance and time to 1 mm-ST segment depression [149]. Further studies showed that 6-months treatment with statins and ACE-inhibitors significantly improved endothelial function, exercise tolerance, angina threshold, and reduced markers of oxidative stress, when compared with placebo [40]. Other studies have shown that statins treatment was associated with improved CFR and myocardial perfusion [148, 150, 151].

ACE-Inhibitors

The HOPE (Heart Outcome Prevention Evaluation) trial assessed the role of ACE-inhibitors in patients who were at high risk for cardiovascular events but who did not have left ventricular dysfunction. ACE-inhibitors significantly reduced the rate of death, myocardial infarction and stroke in a broad range of patients thus suggesting that the use of ACE-inhibitors may prevent the progression of initially clinically silent atherosclerosis [152]. ACE-inhibitors may improve microvascular function and coronary microvascular resting tone, by controlling the vasoconstrictor effects of angiotensin-II and, may reduce oxidative stress by counteracting the effects of angiotensin-II in increasing NADPH activity and nitric oxide production in the microvascular smooth muscle [138, 153]. In addition, 6-months treatment with ACE-inhibitors (ramipril) and statins (atorvastatin) resulted in an improvement of oxidative stress as measured by superoxide dismutase activity, endothelial function and quality of life defined by exercise capacity and score with Seattle Angina Questionnaire (SAQ) [40]. In a recent WISE sub-study, in women with MVA and CFR ≤2.5, 4-months treatment with ACE-inhibitors (quinapril) improved anginal episode frequency as well as increased CFR by 16% (+0.55 change from baseline) [154]. A meta-analysis of 19 trials including over 1100 patients, showed that treatment with ACE-inhibitors improved endothelial function at a range from 1 month to 4 years of follow-up [155]. Data from the Evaluation of Methods and Management of Acute Coronary Events (EMMACE-2) registry provided evidence that

ACE-inhibitor therapy was associated with reduced 6-month all-cause mortality in patients presenting with ACS but without obstructive CAD [156].

Anti-ischemic Therapy

Symptoms represent a major burden for health care providers and for patients themselves. Patients complain that their physicians fail to grasp how life-altering and life-limiting this condition is. The optimal treatment for patients who have severe symptoms is still under scrutiny. CCBs, nitrates and hormone replacement therapy seem to have little effect in preventing chest pain during daily life [64, 157–161]. Beta-adrenergic blockers appear to be highly effective, especially for patients with exertional angina [64, 157, 124].

Beta-blockers decrease oxygen consumption, reduce sympathetic activation, improve diastolic perfusion time and endothelium-dependent vasodilation, and therefore reduce angina frequency and severity [64, 157, 124]. In other studies beta-blockers (propranolol and atenolol) were shown to be highly effective as compared to CCBs (verapamil and amlodipine) [64, 157]. One study showed that the number of ischemic episodes, measured during continuous 48-h electrocardiographic Holter monitoring was significantly reduced with beta-blocker therapy but not with CCBs [64]. In earlier studies, CCBs such as diltiazem failed to improve CFR in patients with MVA [161]. Accordingly, it is reasonable that beta-blockers represent the first line of treatment. Yet, CCBs should be considered if patients are intolerant to beta-blocker therapy or in patients with significant effort angina, despite beta-blocker therapy suggesting significant coronary microvascular spasm in this population [124].

Nitrates reduce coronary microvascular tone and induce arterial and venous vasodilation. However, studies have failed to show a clear benefit of nitrates on symptom relief in patients with MVA [157, 160, 162]. One study showed worsening of angina and reduced coronary blood flow after nitrates administration [160]. Moreover, the chronic efficacy of nitrates is blunted by the development of the phenomena of tolerance, which may also contribute to a rebound effect that is: worsening of anginal symptoms after cessation of nitrate therapy [163, 164].

Non-traditional anti-ischemic therapies such as ivabradine, ranolazine, xanthine derivatives and phosphodiesterase-5 inhibitors have shown inconsistent evidence of clinical benefit and symptoms relief.

Supplementation of L-arginine, may counteract oxidative stress, improve endothelial function, and reduce symptoms [165] The Vascular Interaction With Age in Myocardial Infarction (VINTAGE-MI) trial raised concerns regarding L-arginine supplementation safety in post-myocardial infarction patients [166]. Thus, caution is needed before recommending L-arginine supplementation in post-myocardial infarction patients with MVA.

Emerging therapy with phosphodiesterase-5 inhibitors was evaluated in 23 women from the WISE study. Administration of one single dose of 100 mg of oral

sildenafil resulted in improvement of CFR in women with MVA and CFR ≤2.5. This study did not evaluate symptoms [167].

Ranolazine and ivabradine are two new anti-ischemic agents. Ranolazine, a specific inhibitor of late sodium current, reduces intracellular calcium levels leading to improved myocardial relaxation and improvement of anginal symptoms [168]. A recent systematic review showed uncertain effects of ranolazine monotherapy on cardiovascular outcomes in patients with stable CAD [169]. Ranolazine was assessed in a few studies in patients with MVA with conflicting results regarding quality of life and other myocardial perfusion [170–172]. Ivabradine reduces heart rate through selective inhibition of sinus node I_f *(funny current)* channel [173]. A recent meta-analysis of over 36,000 stable CAD patients found no effects of ivabradine therapy in reducing cardiovascular-related morbidity and mortality [174]. In one study of patients with MVA, 4-weeks ivabradine therapy improved symptoms but without effects on coronary microvascular function [175].

Low dose tricyclic anti-depressants such as imipramine improve symptoms possibly through a visceral analgesic effect [176, 177]. Imipramine has been shown to improve exercise capacity and decrease anginal symptoms in patients with MVA and abnormal cardiac pain perception [177].

Non-pharmacological treatments such as spinal cord stimulation and enhanced external counterpulsation (EECP) has been examined in patients with CMD and refractory angina. An earlier study showed no improvement in coronary microvascular tone during sympathetic activation by cold-pressor test following transcutaneous spinal cord stimulations. However, this study did not evaluate symptoms [178]. More recent studies showed contradictory results. In these studies, transcutaneous spinal cord stimulations improved symptoms, exercise tolerance and myocardial perfusion in patients with MVA refractory to optimal medical therapy [179–182]. EECP is believed to improve endothelial function, inflammation and CFR in patients with CMD [183]. In one small study, EECP improved symptoms in 87% of 30 patients at 1-year follow-up [184]. In another small case-control study EECP improved symptoms, coronary flow and inflammation at 6-months follow-up [185]. Unfortunately, these studies were small and further evidence is needed to confirm the usefulness of these therapeutic approaches.

Clinical Decision Making

As the medical community becomes increasingly aware that atherosclerosis poses a serious health risk even in its mild form, it is important for the broad internal medicine community to understand that the presence of non-obstructive coronary artery disease at coronary angiography is NOT normal. Aspirin should be certainly given to all of these patients. Today there is evidence that ACE-inhibitor therapy is associated with reduced mortality from circulatory diseases in patients presenting with ACS but without obstructive CAD. Conversely, there are no data to “prove” that other prevention medications, such as beta-blockers or statins improve long-term

cardiovascular prognosis in patients with chest pain and normal or near normal angiography. Nonetheless, these prevention therapies should be recommended on an indefinite basis. Patients are confronted with the possibility that the risk of correcting risk by the indefinite use of some drugs might be greater than the uncorrected risk [186]. Whether and to what extent aggressive anti-atherosclerotic therapies should be prescribed to these patients remains an issue to be further clarified.

Perspectives

Development of large-scale collaborative clinical trials and post hoc analyses are recommended. Large numbers of patients will need to be studied, as relatively low-risk patients will be included. These studies require considerable communication among all parties: researchers, physicians, hospital administrators and policy planners. This can only be realized by close collaboration between important scientific institutions playing a prominent role in research funding and program development.

Conflict of Interest Statement We declare that we have no conflict of interest.

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Chapter 10
Gender and Racial/Ethnic Differences in CVD Risk: Behavioral and Psychosocial Risk and Resilience

John M. Ruiz, Caroline Y. Doyle, Melissa A. Flores, and Sarah N. Price

Overview

Cardiovascular disease (CVD) burden varies significantly by a myriad of demographic factors, notably sex/gender, race/ethnicity, and socioeconomic status (SES). Identifying variations by these categories is useful in risk surveillance and prevention efforts. Perhaps more important is understanding that these groups represent variations in risk and resilience factors. Increasing evidence supports not only constitutional/biological risk but the critical role of psychosocial and behavioral factors. These factors may exert direct effects as well as interact with traditional risk factors to negatively, and positively, influence outcomes.

In this chapter we begin by complementing the epidemiological reviews provided elsewhere in this book by extending the focus to racial/ethnic and socioeconomic disparities in CVD. We then move on to the heart of the chapter by reviewing behavioral and psychosocial pathways with an emphasis on sex, race/ethnicity, and SES. We conclude with a review of emerging psychosocial resilience factors and recommendations for care. Sex and gender are used interchangeably and the discussion of race/ethnicity is largely focused on non-Hispanic (NH) Whites, Blacks, and Hispanics who constitute a majority of the available data.

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Sex, Sociodemographic Factors and CVD

A review of sex/gender differences including broad epidemiology, specific pathways, contributing diseases, interventions, and ancillary outcomes, is available throughout this book. Briefly, women experience similar incidence for most CVD although generally 7–10 years later than men [1]. Despite improvements in care, women continue to experience significant disparities in preventive cardiology including routine diagnostics, secondary prevention pharmacotherapies, management of complementary disease moderators, and treatment of acute events including diagnosis, interventions, rehabilitation, and long-term management strategies [1]. Perhaps as a result of these treatment disparities, women experience significantly lower post-myocardial infarction (MI) longevity then men [2]. These sex differences are exacerbated by two key factors: race/ethnicity and SES.

Race and Ethnicity

A considerable literature documents racial/ethnic disparities in CVD prevalence, treatment and outcomes. This work largely reflects comparisons between Blacks/African Americans and White/Europeans Americans and has contributed to a generalized notion of minority health [3].

Robust data document the disproportionate CVD burden experienced by NH Blacks relative to NH Whites in the United States [1, 4–8]. Although NH Whites and Blacks experience similar rates of coronary heart disease (CHD) the disease appears to advance more quickly among NH Blacks leading to outcome disparities including higher rates of stroke (4.0% vs. 2.3%) and myocardial infarction (MI) at younger ages as well as a 30% higher age-adjusted mortality [1]. Moreover, compared to all other racial/ethnic groups, Blacks are at the highest risk of developing heart failure (HF) including incident HF not preceded by MI [9]. In addition to constitutional and risk factor differences, the National Academy of Medicine (NAM; formerly the Institute of Medicine) highlights deficiencies in access to quality care as a key contributor to observed disparities including disease progression [10]. For example, Blacks are less likely to be aware of their high blood pressure and among those with diagnosed hypertension, less likely to have their blood pressure controlled [11–13]. Similar data document racial differences in the prescription of statins and other cardio-protective medications including at post-acute event discharge [14, 15]. Complementing these trends, prospective data demonstrate faster progression of subclinical disease among Blacks relative to Whites [16, 17]. In the context of acute events, Blacks are more likely to experience treatment delays and less likely to receive revascularization procedures and pharmacotherapies at discharge [1, 7]. They are also more likely to experience post-discharge complications, be rehospitalized, experience subsequent events, and premature post-MI mortality. In sum, persistent and pervasive Black-White disparities in all aspects of CVD burden remain despite longstanding awareness.

In contrast to NH Black-White disparities, Hispanics/Latinos experience better health and greater life expectancy than NH Whites; an epidemiological phenomenon commonly referred to as the *Hispanic Health Paradox* given the discrepancy between risk factors and outcomes [18–20]. This ethnic health advantage is evident in most major disease domains including CVD [21]. For example, the most recent AHA statistical tabulations report the age-adjusted overall heart disease prevalence is lower for Hispanics (7.8%) than either NH Whites or NH Blacks (11.1% and 10.3%, respectively) [1]. Disaggregating the data reveals that compared to NH Whites, Hispanics experience similar or lower rates of hypertension, CHD, incident MI, and stroke [1] and three recent meta-analyses document a 30% survival advantage over non-Hispanics among persons with CVD [20, 22, 23]. Although Hispanics tend to have higher rates of diabetes, dyslipidemia, metabolic conditions, and a range of SES challenges similar to NH Blacks and they experience similar treatment disparities, these risks appear to either not carry the same predictive validity for Hispanics or are offset by unknown resilience factors [19, 21].

Interactions between race/ethnicity and sex contribute to a mixed picture for racial/ethnic minority women. These interaction are illustrated for age-adjusted mortality in Fig. 10.1 with data from the 2017 AHA Statistical Update [1] which reports similar prevalence trends for CHD, incident MI, and stroke. The data illustrate gender differences as well as race/ethnicity differences within gender.

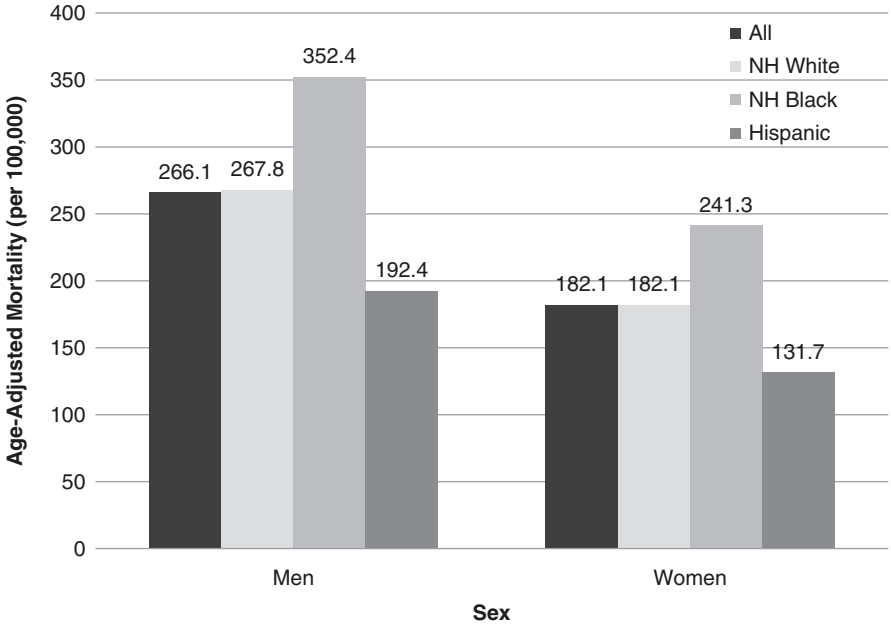

Fig. 10.1 Sex and racial/ethnic differences in age-adjusted deaths attributable to cardiovascular causes as reported in the 2017 American Heart Association Statistical Update (adapted using data from [1])

Although these outcomes data are somewhat expected, they belie disparities in disease management. For example, Black and Hispanic women are more likely than White women and men of any race to experience significant disparities in health literacy, access to specialty care, treatment delays, initiation of secondary prevention pharmacotherapies, hospital admission for acute MI symptoms, use of revascularization procedures, and rehabilitation [24, 25]. Notably, these gender by race/ethnicity treatment disparities often exist despite control for socioeconomic factors including income, insurance, and healthcare access and mirror trends in other disease domains [10, 16].

Socioeconomic Status

Along with sex and age, SES is amongst the most robust and consistent predictors of mental and physical health risk and outcomes. Socioeconomic status reflects an individual or group's position or standing in a hierarchical social structure. It is often operationalized as financial (income, wealth) or education attainment but also includes relative social status measures including occupation, neighborhood, and social status position (e.g., leadership, honors, etc.). Although the relationship between SES and health is generally characterized as graded, the true slope of effect appears non-linear with stronger effects at the lower relative to the higher end of the SES continuum.

In addition to its main effects, SES is a critical health mediator for women and racial/ethnic minorities who are overrepresented at the lower end of the SES spectrum. For example, in 2013, 14.2% of women 18–64 years of age lived below the federal poverty level compared to 10.5% of men [26]. Among racial/ethnic groups, one in four Hispanics and NH Blacks live below the poverty line. Further, these factors interact such that racial/ethnic minority women are particularly vulnerable to poverty. Recent data show that women are 4–8 percentage points more likely to be in poverty compared to men in all racial/ethnic groupings measured in the American Community Survey [26, 27]. Wage disparities are an important contributor to these SES differences. For example, the current gender wage gap is 20%, meaning that women regardless of race/ethnicity earn 80 cents on the dollar compared to men [28]. Likewise, there is considerable racial/ethnic variation in income with Asian Americans having the highest median full time wage followed by NH Whites, NH Blacks, and Hispanics [27]. Notably, these gender and racial/ethnic wage disparities remain even within specific jobs and controlling for seniority. Moreover, there are important buying power differences between racial/ethnic groups meaning that racial/ethnic minorities often must pay higher prices for the same daily goods (food, medications, fuel, etc.) based on neighborhood segregation and geographic distribution [29, 30]. Hence, women and particularly minority women often earn less and must pay premium costs for daily goods. These trends have led renowned disparities researcher David R. Williams to note that the minority poor are more poor than the White poor [30].

A large body of research documents the inverse relationship between SES and heart disease risk, particularly CHD [31–34]. In addition to its association with prevalence, lower SES is associated with greater risk of experiencing an MI [35, 36]. For example, an analysis of data from the Behavioral Risk Factor Surveillance System (BRFSS) found that individuals with less than a high school education were 1.5–3.0 times more likely to experience an MI compared to those with a college degree [37]. In addition, lower individual and neighborhood SES are predictive of greater post-MI mortality risk [38–41] as well as complications following surgical interventions such as coronary artery bypass grafting [42–45]. Importantly, SES markers may work synergistically to increase risk [46]. That is, clustering of SES risks such as low education attainment, low status work, and lower income are observed to interact to heighten risk above what single constructs might connote.

The effects of SES on cardiovascular incidence, morbidity, and mortality may vary by sex. A recent meta-analysis of 116 diverse cohorts representing over 22 million participants examined sex differences in the impact of SES on CVD risk. [47]. Age-adjusted relative risk (RR) comparing the lowest to highest levels of education for men and women was derived for each outcome and women-to-men ratios of RRs (RRRs) were used to directly compare sex differences in risk. Results indicate that graded effect of SES on CHD and CVD was significantly stronger for women. Specifically, the impact of SES on CHD was 24% greater and for CVD was 18% greater for women relative to men. These findings underscore the point that women are both overrepresented at the low end of the SES continuum and that the impact of that status is relatively greater than for men.

Summary

Sex, race/ethnicity, and SES are powerful determinants of cardiovascular risk and outcomes. Much of the associated risk is evident in treatment disparities with downstream implications for disease incidence, management, and outcomes. Importantly, these sociodemographic factors are observed to interact synergistically to increase risk. Next, we consider the role of behavioral factors in CVD risk and how these sociodemographic factors contribute to disparities in those behaviors.

Health Behaviors

Cardiovascular disease risk is determined by a confluence of non-modifiable and modifiable factors [1, 48]. The AHA increasingly recognizes the critical role of behavioral factors as lifelong influences on the development, course, and outcomes of CVD. An example of this behavioral emphasis is the AHA's Health Campaign for Life's Simple 7 which unequivocally supports the role of behavioral factors

including smoking, physical activity (PA), diet, and weight as key determinants of cardiovascular risk [49, 50]. The remaining factors—blood pressure, glucose, and cholesterol are directly influenced by the four behavioral factors. In this section we review the most salient health behaviors, including emerging behavioral risks, as well as clusters of factors (e.g., ideal cardiovascular health markers) with an emphasis of moderation by sex, race/ethnicity, and SES. Importantly, these are all modifiable risks with a multitude of effective pharmacological and non-pharmacological interventions available.

Smoking

Smoking is perhaps the most recognized behavioral risk factor for disease. In its report, *The Health Consequences of Smoking—50 Years of Progress*, the U.S. Surgeon General concludes, "Since the first Surgeon General's report in 1964 more than 20 million premature deaths in the U.S. can be attributed to cigarette smoking" [51]. The AHA estimates that from 2005 to 2009 over 480,000 premature deaths in the U.S. were due to smoking with nearly one third of those resulting from secondhand smoke exposure [1]. Put another way, smoking is responsible for approximately 5.5 million years of potential life lost annually in the U.S. with an estimated economic cost in excess of $300 billion [51].

Adult smoking rates have steadily declined over the last 50 years from 42.4% in 1965 to 15.1% in 2015 with considerable variation in current prevalence by sex, race/ethnicity, and SES (see Fig. 2; [51, 52]). Conclusive evidence documents the deleterious causal effects of smoking on CVD [1, 51]. Meta-analytic data of prospective cohorts report a smoking-attributed two- to threefold increase in CVD risk and a two- to fourfold risk of stroke and other ischemic events [53]. This relationship is non-linear with low levels of exposure (primary, secondhand) dramatically increasing risk [1]. Importantly, the effects of smoking on CVD morbidity and mortality vary by sex with the impact appearing to be greater for women than men. For example, a meta-analysis of 75 cohort studies representing over 2.4 million participants reported the smoking attributable risk on CHD to be 25% greater in women than men [54]. Likewise, a meta-analysis of 81 cohort studies representing nearly 4 million individuals found that Western women were at a 10% greater risk of stroke and other ischemic conditions relative to men [53].

Despite these risks, smoking cessation has critical risk reduction benefits at all stages of disease [51, 55–57]. Population level interventions including limiting opportunities to smoke, increasing pricing, etc. have continued to reduce the rate of smoking [51] and appear to motivate current smokers to engage in individual-level interventions. Individual interventions range from pharmacological strategies including medications and nicotine replacement therapies to psychological interventions including cognitive behavioral therapies, hypnosis, a wide variety of other treatments. All intervention methods show modest effects with the average number of quit attempts approaching 30(!) before expected success [58].

Importantly, cessation success is contingent on patient readiness, treatment preference, and dosage. Motivational interviewing [59] is an effective counseling technique used to harness intrinsic motivation among individuals who are considering a behavior change such as smoking cessation [60]. In clinical settings, motivational interviewing may be conceptualized as a way to *improve* readiness to change and should be complemented by prescription of an intervention that matches the patient's preference [61]. In addition, emerging research suggest that cultural tailoring of interventions may also improve cessation success particularly among racial/ethnic minorities [62, 63].

Physical Inactivity, Diet, and Weight

Body weight, diet, and physical activity (PA) are reciprocally related components of cardiovascular health. While diet and PA obviously impact weight, body weight and size can hinder ability to participate in PA [64, 65]. Body mass index (BMI) is a key metric for assessing obesity with implications for CVD risk [65]. The Centers for Disease Control (CDC) estimates that 70.7% of adults age 20 years and over are overweight with 37.9% of all adults meeting criteria for BMI-base obesity [66]. Obesity rates vary by sex, race/ethnicity (see Fig. 10.2) with prevalence inversely associated with SES within groups.

National physical activity guidelines for adults prescribe at least 150 min of moderate-intensity aerobic physical activity or 75 min of vigorous-intensity aerobic activity per week along with 2 days of resistance activity [67]. Data from the 2012

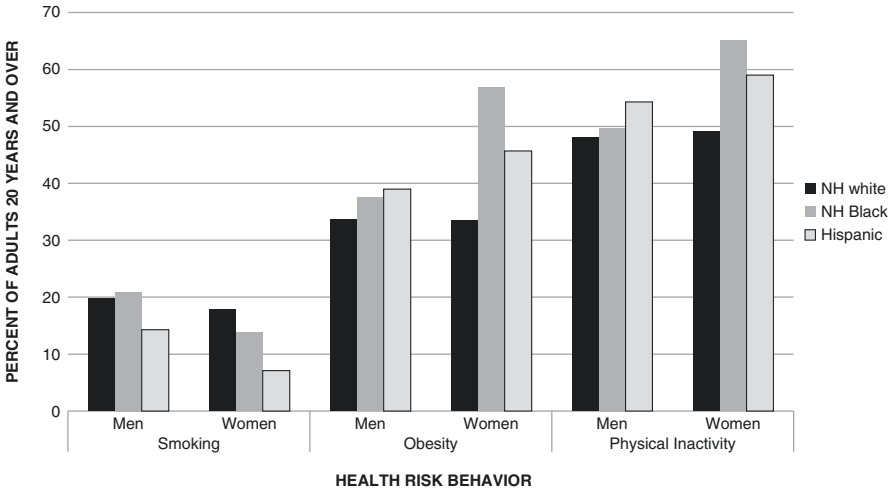

Fig. 10.2 Sex and racial/ethnic differences in age-adjusted health behaviors as reported in the 2017 American Heart Association Statistical Update (adapted using data from [1])

National Health and Nutrition Examination Survey (NHANES) showed 44.0% of adults met these criteria with significant differences by sex and race/ethnicity. Combined data from NHANES and from the National Health Interview Survey (NHIS) indicate that girls and women are more likely to be physically inactive than boys and men with the gap increasing with age [1]. In addition, NH Blacks and Hispanics were more likely to report leisure-time physical inactivity compared to NH Whites. Importantly, these data focus on "leisure-time" activity and do not account for work-related or transportation-related physical activity. Occupational physical activity may be more important among Hispanics, NH Blacks, and all lower SES persons who may be more likely to work in physically-demanding blue-collar versus white-collar jobs [68].

American Heart Association dietary guidelines stress both caloric consumption cutoffs and specific nutrition food types (e.g. whole grains, fruit, nonstarchy vegetables, etc.). These metrics are scored to create a multidimensional measure of dietary nutrition. Current data document extremely poor dietary compliance in the U.S. population. For example, data from 33,932 participants participating in seven cycles of NHANES between 1999 and 2012 document prevalence of an ideal dietary score (>80 of expected guideline compliance) as ranging from 0.6% in children to 1.5% in adults meaning that 98.5% of the adult population are not meeting the ideal guidelines ([69]). In contrast, the prevalence of poor dietary nutrition (<40% adherence, lowest category) for adults was 45.6%.

Poor dietary adherence varied significantly by sex, race/ethnicity, and SES. The prevalence of poor dietary adherence was greater among men than women (49.3% vs. 42.2%, respectively) and among NH Black and Hispanics (58.8% and 57.7%, respectively) compared to NH Whites (42.8%) [69]. Consistent with other SES findings, prevalence of poor dietary adherence was greatest amongst those in the lowest quartiles of income and education.

Ideal Cardiovascular Health metrics

The AHA has set a goal of reducing CVD by 20% by the year 2020 [50]. To achieve this goal, the AHA has identified targets for "seven factors and behaviors that increase the chance of living free of cardiovascular diseases and stroke" [50]. The behaviors are the four reviewed previously including not smoking, adhering to diet and physical activity recommendations, and maintaining a healthy weight. In addition, maintaining ideal levels of three factors—cholesterol, blood pressure, blood glucose—are part of the clustered strategy [50, 70]. Note that the three factors are directly influenced by the behaviors. The AHA program, *Life's Simple 7*, argues that adhering to the entire cluster rather than to individual metrics is a critical primary prevention strategy. To this point, emerging data demonstrate the predictive validity of the cluster of these "ideal cardiovascular health" [71–75]. For example,

a meta-analysis of nine prospective cohort studies involving 12,878 participants found that maintaining ideal cardiovascular health was associated with a 69% lower risk of stroke and an 80% lower risk of CVD, including a 75% lower risk of cardiovascular mortality [76].

Unfortunately, overall adherence in the U.S. adult population is poor with the AHA commenting that "virtually 0%" of the population are achieving guidelines on all 7 metrics [1]. A two-thirds majority of the adult population are achieving adherence to no more than 4 metrics with an estimated 13% achieving adherence to 5. Just 5% are achieving 6. Adherence varies by age with younger adults performing better. In addition, women at all ages are performing better than men. Finally, NH Blacks and Hispanics are observed to meet fewer metrics than other racial/ethnic groups.

Sleep

Before leaving this section, it's important to discuss emerging behavioral influences on CVD. Perhaps the most salient of these emerging factors is sleep. Most people give sleep little thought, particularly when they feel generally satiated. However, a growing body of literature supports the notion that sleep is a behavioral risk factor for health [77–80]. For example, a meta-analysis of 72 studies found that chronic sleep deprivation was associated with greater inflammation levels [81]. Other studies document relationships between sleep disturbance and incidence of diseases including obesity, diabetes, and all manner of CVD [82–84]. Finally, a recent meta-analysis of 27 prospective cohort studies representing 1,382,999 participants found that both short and long sleep are predictive of all-cause mortality [85].

According to the American Sleep Association, the average adult needs between 7 and 9 h of sleep. With this statistic as a baseline, the CDC estimates that more than one in three Americans suffer from chronic perturbations in sleep [86]. Current CDC estimates are that men and women generally have similar sleep duration behaviors. However, among older persons, the impact of sleep duration, particularly long sleep (>9 h per 24 h cycle) varies considerably by sex with women at nearly a twofold greater risk of mortality than men [87]. Among women, long-sleep is associated with a 42% greater risk of early mortality relative to those sleep 7 h [80]. At the same time, prospective evidence controlling for age and key behavioral factors suggest that women who get too little sleep (>7 h per 24 h cycle) may be a significantly greater risk of CHD development [78].

The NAM as well as the CDC and that National Institutes of Health have all identified sleep as an emerging public health challenge. Although the mechanisms of action are yet to be clearly determined, screening and treatment are warranted. A range of pharmacological and non-pharmacological treatments are available as is the availability of clinicians with expertise in sleep medicine [88, 89].

Summary

There is little debate about the causal role of behavior in CVD incidence and outcomes. Despite this recognition, the prevalence of ideal behavioral adherence is extremely low in the U.S. adult population with important variations by sex, race/ethnicity, and SES. Given these challenges, a national culture change with respect to ideal cardiovascular health may be necessary to improve disease prevention and management particularly in light of the AHA's 2020 goal to reduce disease incidence by 20%. However, behavior does not exist in a vacuum. In the next section we discuss the role of psychosocial factors as moderators of disease risk, often through behavioral pathways.

Psychosocial Influences on CVD

Psychosocial factors are broadly recognized as influences on CVD risk from disease incidence to acute morbidity and mortality [48, 90, 91]. Increasingly well-designed prospective studies and meta-analyses support psychological stress, acute emotional experiences, clinical syndromes such as depression, as well as social environments and deficits of social resources as predictive of disease risk, progression, and outcomes. As illustrated in the biopsychosocial model [92], these factors reciprocally interact with biology to influence disease risk. Importantly, sex, racial/ethnic and SES factors moderate exposure and impact of psychosocial factors on disease risk [3].

Psychological Stress

From its folklore beginnings to the contemporary science, psychological stress has long been hypothesized to influence health outcomes [93, 94]. The American Psychological Association's annual *Stress in America* survey [95] finds that the mean stress level in the U.S. in 2017 was 5.1 on a scale of 1 (little or no stress) to 10 (a great deal of stress). Importantly, women have consistently reported more stress than men over the last two decades (5.0 vs. 4.6 in 2016). These differences may be rooted in gender differences in daily sources of stress. For example, in 2016 women reported being more stressed about finances and family responsibilities than men. In addition, lower SES and racial/ethnic minority populations experience significantly higher daily stress stemming from their economic and social status challenges [96, 97].

Substantial evidence documents the deleterious and causal effects of psychological stress on all aspects of CVD. For example, prospective evidence demonstrates a relationship between stress and CVD risk factors [98, 99], CHD incidence [100, 101], atherosclerotic progression [102, 103], incident MI [104], and CVD-specific and all-cause mortality [105, 106]. To put these relationships into perspective, data

from the global INTERHEART study of MI predictors in 52 countries found that the magnitude of effect for psychological stress was comparable to the effects of smoking and far greater than traditional risk factors such as obesity, physical activity, and diet [107].

Stress influences disease risk through direct and indirect pathogenic pathways. For example, well-controlled non-human primate and human laboratory studies along with ambulatory/daily experience studies document direct stress effects on acute emotions and downstream physiological reactions across multiple systems [108–110]. Prospective cohort evidence supports this direct physiological pathway as a predictor of disease development and atherogenic progression I humans [111–113]. In addition, acute negative affectivity such as experiences of anger are well-documented to precede acute coronary events [114, 115]. Finally, extreme stress-related emotional experiences such as reactions to earthquakes, terrorist events, and relationship loss are known to precede cardiac events in persons with no history of disease [116–118].

In addition to these direct effects, stress impacts disease risk through indirect pathways such as effects on health behaviors. For example, perceived stress is associated with greater likelihood of smoking and smoking frequency, physical inactivity, poor diet, and weight gain [119–122]. Greater perceived stress is also associated with poor treatment adherence which may undermine secondary and tertiary intervention efforts [123]. Again, the association between stress and these intermediate factors tends to be stronger for women [124, 125].

Anxiety and CVD in Women and Minorities

In addition to general stress levels, specific stress-related psychological syndromes such as anxiety and depression may further exacerbate risk. Anxiety disorders are the most prevalent type of mental disorder in the US, with 58 million Americans (18.1%) experiencing an anxiety disorder within a 12-month period [126, 127]. Anxiety disorders are characterized by excessive worry, apprehension, and fear that interferes with the activities of everyday life. Overall, women are 60% more likely to experience anxiety disorders, when compared to men, and minority individuals are less likely to experience anxiety in their lifetime. Non-Hispanic Blacks (NHBs) are 20% less likely to experience an anxiety disorder when compared to non-Hispanic Whites (NHWs), and Hispanics are 30% less likely to experience them when compared to NHWs [128].

Anxiety disorders are a significant risk factor for CVD including CHD, HF, stroke, and sudden cardiac death [129–131]. In a recent meta-analysis including 249,846 individuals, anxious persons are significantly (26%) more likely than non-anxious individuals to develop CHD [131]. Anxiety is also associated with the progression of cardiovascular disease and the incidence of cardiac related events [130, 132]. In persons that have experienced a cardiac event, anxiety can impede recovery [133], and increase the risk for future cardiac events [134, 135], CVD related mortality [136] and hasten all-cause mortality [137].

In addition to being at greater risk, women with anxiety are more likely to report cardiovascular symptoms [138] and are more likely to develop anxiety disorders following an MI [139, 140]. Further, women with anxiety/CVD comorbidity are at greater risk for incident CHD and all-cause mortality [138]. Similarly, in racial/ethnic minority patients with chronic heart disease, NHBs are more likely to exhibit anxiety and depression than their non-minority counterparts which may contribute to observed disparities [141].

Depression and CVD in Women and Minorities

Depression is perhaps the most salient psychological syndrome investigated as a determinant of CVD. More than 300 million people suffer from depression, and it is a leading cause of disability worldwide [142]. Depression is typically measured as a continuous variable (depressive symptoms) through various self-report measures rather than as a dichotomous, clinical diagnosis although such work is done particularly in intervention research [143]. Overall, women are twice as likely to experience depressive symptoms and clinical depression compared to men [144]. Although data regarding racial/ethnic differences in depression among women are mixed, there is some evidence that Hispanic and NH Black women have higher odds of significant depressive symptoms compared to NH White and Asian American women [144, 145]. In addition, the prevalence rate is 2.5 time greater among persons living below the poverty line compared to those at or above it.

It should be noted that the assessment of depressive symptoms is subjective and gender and cultural differences in symptom reporting may impact the data. Moreover, gender differences in the experience of depression may contribute to an underestimation among men where symptoms may include frustration and anger vs. the typical sadness associated with the syndrome. Nevertheless, women experience significant rates of depression which may contribute to CVD risk [146].

The relationship between depression and CVD is well-documented with key professional bodies such as the AHA issuing advisory statements [147, 148]. Meta-analytic data of prospective data support the independent causal role of depression on CHD risk, on incident MI, and its role in post-MI morbidity and mortality [149–151]. Depressive symptoms predict incident CHD among otherwise initially healthy women [152] and women with comorbid CHD and depressive symptoms are at increased risk for recurrent adverse cardiovascular events, poor post-MI prognosis, and all-cause or CHD-associated mortality [152, 153]. Furthermore, among women with comorbid CVD and depression, more severe and chronic depressive symptoms have a larger impact on prognosis [154].

Unfortunately, interventions to reduce CHD risk through depression remediation have achieved limited success [155, 156]. In the largest of these trials, the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial, MI patients with depression were randomized to either usual care or cognitive behavioral therapy plus optional antidepressant medication. Although depressive symptoms improved in all interven-

tion groups, only White men showed improved cardiovascular outcomes, and minority women in the intervention arm actually had higher mortality rates than control participants [157]. Although the small differences in depression outcomes between treatment and control groups limit the ability to detect an effect of treatment on morbidity and mortality, secondary analysis reveals that prognosis does improve along with depression [158]. More work must be done to understand these group-specific pathways linking depression to CVD with the goal of remediating both conditions.

Summary

Behavioral and psychosocial factors are intrinsic, robust, and unique determinants of all aspects of CVD risk. The pathways and impact of these factors on disease appears to vary as a function of sex, race/ethnicity, and SES. Notably, women and some racial/ethnic minorities experience lower rates of disease or onset at relatively later in life than might otherwise be expected by their risk profiles. This seemingly paradoxical outcomes may be due to unaccounted offsetting resilience factors.

Psychosocial Resilience

Resilience generally refers to overcoming, adapting, and potentially thriving in the context of adversity [159]. Examples of health resilience include the Hispanic mortality paradox [19, 160], the residents of Limone sul Garda, Italy with their high cholesterol and absence of CHD [161], long-lived smokers [162], and those who survive and thrive after a natural disaster [163], to centenarians [164]. Observation is complemented by a burgeoning science investigating the mechanism of health resilience ranging from genetic variations to psychosocial contributions. Amongst the myriad of psychosocial candidates, dispositional optimism and social integration have emerged as robust determinants of outcome advantages with known sex and cultural variations.

Dispositional Optimism

Dispositional optimism refers to individual differences (i.e., personality trait) in the generalized expectation of positive future outcomes as well as a tendency to focus on positive aspects "silver linings" in negative contexts [165, 166]. A robust literature supports the relationship between dispositional optimism and mental and physical health, particularly CVD [165, 167]. Greater dispositional optimism is associated with lower incidence, slower progression, lower incident MI, better outcomes following revascularization, and lower disease specific and all-cause

mortality [168, 169]. Conversely, high pessimism, the expectation of negative outcomes, is associated with CVD risk factors including higher levels of inflammation [170] and longitudinally associated with higher CVD incidence and disease-specific and all-cause mortality [171].

There is little evidence of sex or race/ethnicity-specific effects of optimism on health although a few studies suggest that the influence of optimism and pessimism on CVD outcomes may be stronger for men than women [168, 172]. Optimism is believed to facilitate health resilience through its effects on motivation. For example, optimists are more likely to stay engaged in healthy lifestyle changes, demonstrate better treatment adherence, and actively cope with challenges which may facilitate engagement in rehabilitation following an acute event [173]. As an ancillary benefit, optimists tend to have larger social networks and report greater social support which can buffer stress and coping in times of need [174].

Social Integration and Support

The size and strength of one's social network is a well-established moderator of health [175–177]. For example, a meta-analysis of 148 prospective studies including 308,849 participants found that greater social integration was associated with a 50% increased likelihood of survival over the course of the study period [178]. These are not trivial or "second-class" effects as the benchmarked effect size of social integration on mortality was significantly greater than smoking, physical activity, diet, and BMI—all of which are integral metrics of AHA's Ideal Cardiovascular Health. Moreover, these effects are broad, robust, and replicated across health conditions and all aspects of cardiovascular health.

Although men tend to have broader social networks, women are more likely to seek out, provide, and be open to the provision of social support [179–181]. Laboratory research demonstrates that the provision of social support, particularly from women, more strongly attenuates stress-related physiological reactivity [182–185]. Cohort data documents stronger buffering effects of social support on stress, depression symptoms, and objective CVD biormarkers and disease outcomes in women relative to men [186–190].

Cultural variations in social networks and support may also contribute to ethnic advantages in CVD. As noted earlier, Hispanics have significantly lower CVD incidence and survive longer in the context of CHD than non-Hispanics despite significantly greater risk. A leading hypothesis to explain this paradoxical phenomenon is that cultural values for collectivism and interpersonal harmony facilitate the building of strong social network bonds with implications for health [19]. Indeed, moderators of cultural values such as foreign-born nativity, earlier generational status, lower U.S. acculturation, and living in a more Hispanic ethnicity-dense neighborhood are all associated with greater support and lower disease [19, 191, 192].

Resilience Interventions

Given its demonstrated impact on objective health outcomes, interest has grown in social support-based interventions [193]. Unfortunately, the few interventions tested have had mixed results with women. For example, interventions randomizing post-MI men with high distress to receive a telephone-delivered social support intervention effectively reduced cardiac morbidity and mortality [194, 195]. However, when the work was extended to include women, the intervention produced iatrogenic results [155].

Despite this outcome, social support interventions remain a pathway of interest. There are two important lines of work to consider and these may provide a roadmap for resilience interventions going forward. First, the match between the person's treatment preference and the treatment itself may be critical. In an elegant program of research in end stage renal disease, Christiansen and colleagues demonstrated that adherence and objective health outcomes were strongly influenced by the match between patient coping style (active vs. passive) and the nature of the treatment [196, 197]. A second consideration is the method of delivery. Telehealth and mHealth interventions using text messages and phone calls are showing promising results for improving health behaviors, adherence, motivation, and objective outcomes [198, 199]. These interventions tend to be non-invasive, cost effective and sustainable. With current U.S. cell phone ownership at 77% in 2016 and 88% online [200], these technology-based interventions may represent the future delivery pathway for psychosocial resilience building interventions.

Conclusions

Behavioral and psychosocial factors very considerably by demographic factors with documented implications on CVD risk/resilience. Surveillance efforts across the healthcare spectrum should incorporate these factors to identify higher risk groups and individuals for targeted interventions. Treatment should consider not only evidence-based best practice but also person by treatment fit in order to facilitate adherence. Finally, emerging research documenting disease resilience reminds us that CVD is multiply determined and highlight the road ahead as we strive to mitigate risk for all.

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Chapter 11
Sex-Specific Differences in Acute Myocardial Infarction

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Epidemiology

Ischemic heart disease remains the number one cause of death in men and women across the United States and the developed world, more than stroke, lung, colorectal cancer, and breast cancer [1]. Among the 1.4 million patients hospitalized for ischemic heart disease in the United States annually, 810,000 are due to acute myocardial infarction (AMI) [2]. Approximately 610,000 people die from AMI annually in the United States, equaling a rate of one in four deaths [3].

Since the 1980s, there has been a decline in mortality rate from AMI in both men and women in developed countries [4]. In the United States, from 1980 to 2002, mortality rates from AMI declined by 52% in men and 49% in women [4]. In Europe, mortality rates of AMI have seen similar decline over the past three decades in most Northern and Western European countries but increasing in some Central and Eastern European countries [1]. The reduction in mortality rate is attributable to a decline in in-hospital mortality rates from AMI in both sexes [1, 5]. This decline in mortality from AMI may be due to greater awareness and better in-hospital management from AMI patients as a result of advancement in diagnosis, coronary revascularization strategies, medical therapy, and coronary care over time.

While there has been a steady decline in mortality rates, this trend is not reflected equally across various demographic groups. In England, data from 1984 to 2004 showed that mortality rates among men aged 35–44 have been increasing since

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2002 [6]. Similar trends are seen in the United States, with the decline in mortality rates from AMI slowing in both men and women aged 45–54 [7]. These discordant trends in mortality rates from AMI are even more pronounced among young women (aged <55) [4, 7]. In the past decade, mortality rates from AMI among young women (aged <55) have declined at a much lower rate compared to men and women aged >65 [4]. Young adults (<55 years old) make up 22% of the hospital admissions each year for AMI, and 25% of these are women under the age of 55 [8]. Young women have higher comorbidities, longer length of hospital stay, and higher in-hospital mortality rates compared to men of the same age [3, 4, 8].

The causes for these disproportionate trends in morbidity and mortality decline from AMI between men and women are multifactorial and may be attributable to differences in pathophysiology, risk factors, clinical presentation, diagnosis, and management which will be discussed in this chapter.

Pathophysiologic Differences

AMI is defined by ischemic symptoms, ECG findings, and elevated biomarkers and includes ST elevation myocardial infarction (STEMI) and non-ST elevation MI (NSTEMI). Clinical and epidemiologic data indicate that there are differences in pathophysiology of AMI between men and women that in turn affect variation in clinical presentation, diagnosis, and outcomes post AMI [2, 9–11].

One of the major pathophysiologic pathways that can ultimately lead to AMI starts with the development of atherosclerotic plaque in the vascular wall. Injury to the coronary endothelium due to various risk factors and exposures such as hypertension, smoking, hyperlipidemia, and diabetes leads to plaque formation under conditions of abnormal shear stress, oxidative stress and inflammation [2, 12, 13]. Once the endothelium is injured, a cascade of events occurs where pro-inflammatory, pro-thrombotic, and pro-fibrotic milieu promotes the development of atherosclerotic plaque. Activated macrophages oxidize low-density lipoprotein, release chemo attractants and cytokines, and recruit macrophages to form lipid plaque at the site of the damaged endothelium [14]. Dysfunctional endothelium leads to decreased production of nitric oxide in comparison to constrictive factors such as endothelin-1 [12, 13]. Excess endothelin-1 leads to increased expression of adhesion molecules such as selectins, which promote plaque formation [12, 13, 15]. The delicate interplay among various factors including endothelial function, plaque stability, the size of the plaque rupture, the degree of inflammation at the site of rupture, and thrombotic factors determines whether a plaque disruption will result in an acute ischemic event [12, 13, 15–17].

Plaque rupture or erosion can trigger an acute ischemic event. Plaque rupture is the most common cause of AMI, and causes 76% of fatal myocardial infarctions in men and 55% in women [18]. Ruptured plaques have a large necrotic core and a thin fibrous cap that can be infiltrated by foamy macrophages, T cells, and matrix metalloproteinases; once the fibrous cap is disrupted, a coagulation cascade is activated

resulting in an occlusive thrombus [19]. Plaque erosions on the other hand, lead to coronary obstruction by a slower process which can trigger thrombi development directly on the dysfunctional endothelium and cause more downstream micro-embolization leading to focal myocardial necrosis [20].

The incidence of plaque rupture in AMI is more prevalent in men compared to women (16.6% vs 6.6% in one study) [21]. Women on the other hand have more plaque erosions, and more distal thrombi which can cause microvascular occlusion. The intravascular (IVUS) sub-study of the Relationship between Intravascular Ultrasound Guidance and Clinical Outcomes After Drug Eluding Stents (ADAPT-DES) also found a lower prevalence of thin cap fibroatheroma (TCFA) in women with acute coronary syndrome (ACS) [20, 22]. TCFAs can abruptly rupture whereas the development of thrombi over eroded plaque may result in more distal emboli and may take longer for the appearance of ischemic symptoms [20, 22].

Compared to men, women with AMI are less likely to have obstructive coronary atherosclerosis in the epicardial vessels [21, 23]. Women tend to have more non-obstructive coronary artery disease (CAD) (15%) in the setting of AMI compared to men (8%) based on data pooled from 11 ACS trials and more predominantly have single vessel disease compared to multi-vessel disease in men [24]. The recent Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study confirmed this by finding less extensive CAD in women with AMI via coronary angiography and intravascular ultrasound [21]. A combination of endothelial, microvascular dysfunction, micro-embolism, and sex differences in arterial remodeling may be the mechanisms for AMI in women with no obstructive CAD. In a study looking at atheroma burden and endothelial function in patients with non-obstructive CAD, the researchers found that men had longer segments of the coronary arteries with endothelial dysfunction, while women had lower maximal coronary flow reserve (CFR) suggesting greater microvascular dysfunction in women [25]. Coronary microvascular dysfunction (CMD) may be an early stage of coronary heart disease and is predominant in women based on results from the Women's Ischemia Syndrome Evaluation (WISE) study [26]. These results were reproduced in a recent study, which found a lower burden of atheroma in the left main artery and left anterior descending artery and lower maximal CFR in women [27]. The WISE study did not include men, but patients who present with ischemia and no obstructive CAD are increasingly identified and more research to better understand sex-differences in this clinical problem is needed [28].

Acute plaque rupture with thrombotic occlusion of the artery resulting in AMI and progressive narrowing of the lumen due to atherosclerosis leading to unstable angina can occur in both men and women. However, studies indicate that women are more likely to have the finding of no obstructive CAD on coronary angiography in the settings of unstable angina and acute myocardial infarction [29]. The pathophysiology of ischemic heart disease is complex in women, and in the setting of conditions such as hypoestrogenemia and autoimmune disorders, women may have vascular dysfunction which can lead to ischemic events even if there is no obstructive CAD identified (Fig. 11.1). In women, etiologies such as spontaneous coronary artery dissection, CMD, plaque ulceration and erosion, coronary artery spasm, as

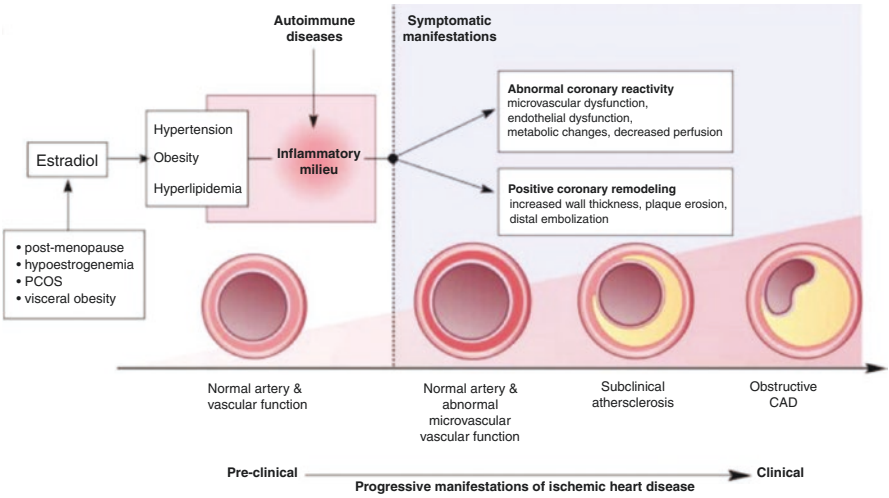

Fig. 11.1 Overarching Working Model of Ischemic Heart Disease Pathophysiology in Women. Risk factor conditions such as obesity, hypoestrogenemia, inflammation, and exposure to traditional CAD risk factors leads to subclinical atheroma formation with progressive decline in coronary flow reserve, and over time ultimately leads to obstructive atherosclerosis. Shaw et al. Women and Ischemic Heart Disease. J Am Coll Cardiol. 2009;54(17):1561-1575. Reprinted with permissions

well as distal embolization of thrombi should also be considered in the differential when obstructive CAD is not found on angiography. In particular, CMD due to endothelial and/or non-endothelial dependent dysfunction has been implicated in the setting of no obstructive CAD as an explanation of persistent symptoms in women and is discussed in another chapter in this textbook [30].

Pathophysiological differences in the development AMI between male and female can also be explained through variations in sex hormones and their effects on endothelial function, especially the role of estrogen. Stimulation of estrogen, androgen, and progesterone receptors activate transcription of hormone sensitive genes such as nitric oxide synthases seen cardiac myocytes, which promote vasodilation and antihypertrophic responses [31, 32]. Estrogen also plays a protective role in cardiac remodeling after MI through the activation of myocardial mitochondrial K ATP channels, resulting in decreased left ventricular dilation while testosterone accelerates early cardiac remodeling, leading to more rupture [33, 34]. In multiple studies of cardiac remodeling in mice, male mice with absent estrogen receptor α have more severe ischemia-reperfusion injury while female mice with absent estrogen receptor β have increased markers of heart failure and increased mortality after MI [35, 36]. A model of the various signaling pathways of estrogen and its effect on the cardiac cell is shown in Fig. 11.2.

Endogenous estrogen exerts positive effects by increasing nitric oxide synthesis, which improves endothelial-mediated vasodilation, inhibits growth of vascular smooth muscle cells, reduces leukocyte adhesion molecules, and increases synthesis

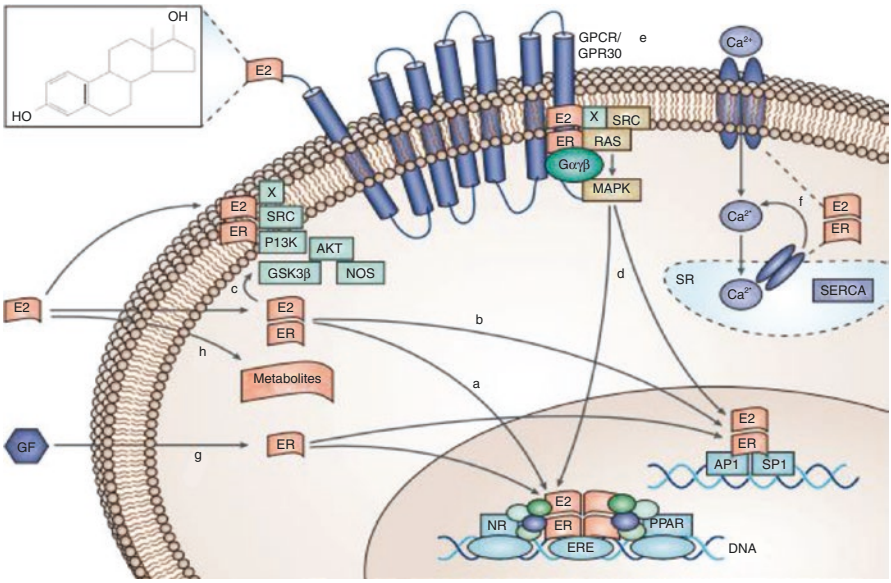

Fig. 11.2 Multiple signaling pathways of estrogen in cardiovascular cells. Estrogen (E2) can activate a cytosolic protein-bound estrogen receptor (ER) that then shuttles into the nucleus and activates gene transcription (a). ERs can also control gene transcription by modulating the activity of other transcription factors 53, 55 (b). In addition, estrogen can induce membrane association of an ER (c), which subsequently stimulates SRC, phosphatidylinositol 3-kinase (PI3K), AKT and glycogen synthase kinase-β (GSK3β), which, in turn, leads to activation of nitric oxide synthase (NOS) and subsequent production of nitric oxide. Estrogen can also modulate calcium influx at the L-type calcium channel or calcium handling at the sarcoplasmatic reticulum (f). Regitz-Zagrosek V. Therapeutic implications of the gender specific aspects of cardiovascular disease. Nat Rev Drug Discov. 2006 May;5(5):425-38. Review. Reprinted with permissions

of vascular endothelial growth factor to promote angiogenesis and re-endothelization after MI [37–39]. Defects in the estrogen receptor α gene have been found to result in a higher rate of myocardial infarction, especially in men and maybe women as well, although this study [40] did not have enough women with events to be studied separately [40]. These cardioprotective effects of estrogen on vascular function may help explain the lower incidence of AMI in pre-menopausal women.

Risk Factor Differences

Traditional Risk Factors

Traditional risk factors for ACS include age, sex, smoking, hypertension, hyperlipidemia, and diabetes, as identified in the Framingham Heart Study and are incorporated into the Framingham risk score. The INTERHEART study, a global

case-control study of risk factors for AMI in 14,000 patients with AMI and 16,000 matched controls from 52 countries, further expanded information on these traditional risk factors to include nine modifiable risk factors: smoking, diabetes, hypertension, diet, physical inactivity, abdominal obesity, alcohol consumption, hyperlipidemia, and psychosocial factors [41]. These nine modifiable risk factors account for 90% of the population attributable risk of ACS in men and 94% in women [41]. Using traditional risk factors alone, the Framingham Risk Score tends to underestimate the risk of heart disease in women; however, newer risk stratifying methods such as the Reynolds Risk Score and the GRACE score incorporate some of these novel risk factors to help improve detection of heart disease risk in women [42–46].

These risk factors affect men and women differently, with greater prevalence of certain risk factors and stronger associations with AMI among women with diabetes, metabolic syndrome, and depression [47, 48]. While the prevalence for diabetes is higher in men [49], women with diabetes have a higher risk of ischemic heart disease compared to men with diabetes [50–52]. In the INTERHEART study, risk of developing AMI in women with diabetes is twice that of men, OR 4.26 (95% CI: 3.68, 4.94) compared to 2.67 (95% CI: 2.43–2.94) [53]. Mortality from AMI for women with diabetes is higher compared to diabetic men, with 154% excess risk of AMI related deaths among women with type I diabetes [54].

Metabolic syndrome refers to a clustering of risk factors, which includes abdominal obesity, hypertension, dyslipidemia (with high triglycerides and low HDL), and glucose intolerance. Metabolic syndrome is more prevalent after menopause and is strongly associated with increased risk of AMI in women compared to men [55–57]. Total cholesterol levels are also higher in women than men after the fifth decade of life [58, 59]. More specifically, hypertriglyceridemia has a stronger association with ACS in women compared to men [60]. Physical activity and moderate alcohol consumption however, appeared to be more protective in women compared to men [41].

Smoking is another extremely strong risk factor for ACS development in both women and men. The INTERHEART study found a three to eightfold increased risk of ACS among smokers compared to nonsmokers [53]. While the prevalence of smoking is higher among men, women, especially young women smokers have the highest risk of developing AMI, with the relative risk of MI 50% higher in female smokers as found in the Copenhagen study [61]. The reasons for the strong association with smoking and myocardial infarction among younger women are unclear, but studies have found higher relative risk for AMI among women who smoke and who are also obese, but these women also had hyperlipidemia and prolonged exposure to oral contraceptives use [61, 62].

Psychosocial factors such as emotional stress, depression, childhood adversities, post-traumatic stress disorder (PTSD) tend to be more prevalent among women and have been shown to have strong associations with the development of AMI [48, 63–65]. The INTERHEART study also found a higher risk of ACS in women compared to men with psychosocial stressors including depression, perceived stress levels, recent major life events, with a 3.5 increased odds in women compared to 2.6 in men [41]. Among patients with cardiovascular disease, depression rates are more

prevalent in females compared to males and especially more common in young women who have experienced AMI [66, 67]. The risk of AMI doubles in women with depression [68]. Childhood adversities such as physical and sexual abuse/neglect are stronger predictors of AMI in women compared to men [69]. Similarly, the risk of ACS is increased threefold in women with PTSD [70]. Mental stress-induced myocardial ischemia has been recently found to be 2–3 times more prevalent in young women with recent myocardial infarction in comparison to men [66, 71, 72].

Nontraditional and Emerging Risk Factors

In addition to traditional risk factors, novel risk factors unique to women are increasingly being recognized for their differential impact on the development of ischemic heart disease in women compared to men. The Women Ischemia Syndrome Evaluation (WISE) identified several unique risk factors for myocardial ischemia in women. These factors include inflammatory biomarkers and conditions such as high-sensitivity C-reactive protein (hsCRP), pregnancy related conditions, ovulatory dysfunction [26, 59, 73]. hsCRP levels have been found to be higher in women compared to men and may be associated with a greater risk of myocardial injury [74, 75]. Elevated CRP levels are also more prominent in autoimmune conditions such as systemic lupus erythematosus, mixed connective tissue disorder, and other rheumatologic disorders which are also risk factors for ischemic heart disease in women.

Pregnancy related conditions such as gestational hypertension, preeclampsia, and gestational diabetes (GDM) have been identified as risk factors for the development of ischemic heart disease in women [76–79]. Women with preeclampsia during pregnancy have a twofold risk of developing ischemic heart disease (RR 2.16, 95% CI: 1.86–2.52) later in life [77]. Perhaps due to the higher risk of developing type 2 diabetes in women with gestational diabetes (GDM), they also have a greater risk of developing ischemic heart disease compared to women without a history of GDM [78, 79].

While ischemic heart disease lags behind by approximately 10 years in women compared to men, the risk of developing AMI increases significantly after menopause. Post-menopausal state occurs as a result of cessation of ovulation stripping away the cardio-protective effects of endogenous estrogen, which may be responsible for the increase risk of AMI in women of older age [26]. Perhaps also due to the benefits of endogenous estrogen on endothelial function, functional hypothalamic amenorrhea, a subset of ovarian dysfunction which causes decreased estrogen production has been shown to increase risk of premature coronary atherosclerosis in younger women [80]. Several studies have found that early menopause before age 45 to be highly associated with increased risk of AMI, as high as 50% in one study compared to women with later onset of menopause [81, 82]. The etiology for the increased incidence of AMI in post-menopausal or peri-menopausal women may be

related to the decline in estrogen levels. While estrogen may have several biologic effects on vascular function such as endothelium dependent vasodilation and cardiac remodeling as previously mentioned, these cardio-protective benefits of endogenous estrogen may be more indirect, as a recent study found no relationship between estrogen exposure duration and prevalence of angiographic coronary artery disease [83].

Clinical Presentation of AMI

Perhaps due to the pathophysiological differences of ischemic heart disease between men and women, the clinical presentation of AMI also vary across gender based on results from multiple studies looking at common symptoms reported at the initial presentation to the emergency room. A meta-analysis of 74 studies on clinical presentation of AMI found that women have a similar or sometimes even higher prevalence of angina compared to men [84]. Similarly, the GRACE registry reported comparable prevalence of angina in men (94%) vs women (92%), with more atypical symptoms including jaw pain and nausea in women compared to men [85]. In contrast, another meta-analysis of 69 studies of AMI symptoms found women having fewer typical symptoms compared to men [86]. Patients from the National Registry of Myocardial Infarctions admitted with AMI also reported less chest pain in women compared to men [87]. Greater vagal activation in females during acute MI may help to explain the higher prevalence of atypical symptoms such as nausea and dizziness [88, 89]. In a recently published study looking gender differences in symptom presentation in a patient population with AMI requiring percutaneous coronary intervention, women were found to more likely report jaw, throat, or neck pain on initial presentation compared to men, odds ratio 2.91, 95% CI 1.58–5.37, while no sex differences were found in rates of reported chest or typical discomfort [90]. As a result of the greater influence of vagal stimulation in women and the linkage of these physical areas to the vagal nerve, women with acute myocardial infarction tend to report more diverse atypical symptoms including nausea, cranio-facial pain, diaphoresis, dizziness, pleuritic/burning chest pain, fatigue, indigestion, and palpitations [10].

More women than men present with NSTEMI and non-obstructive CAD [91]. However, in those women with non-obstructive CAD, greater than 50% will continue to have clinical signs and symptoms of ischemia, most commonly angina, requiring repeated testing and hospitalizations [92]. In the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO), young women with—AMI have more cardiovascular risk factors and comorbidities and higher clinical risk scores at baseline compared to men. However, men had higher cardiac biomarkers levels and more classic ECG findings on presentation [93]. Women also tend to wait longer between symptom onset and presentation to the emergency room compared to men as found in one study, 63 min, compared to 43 min for males, $p < 0.0001$ [94].

Diagnosis of AMI

The diagnosis and detection of AMI requires using clinical history, findings on an ECG and serum cardiac biomarker values. While a history of chest pain is the most common symptom in both men and women presenting with AMI, there is disagreement with regards to whether women are more likely to present primarily with atypical symptoms [95–97]. As discussed above, women are more likely to have nonspecific atypical symptoms including back and jaw pain with more nausea, vomiting, dyspnea, palpitations and indigestion during an acute ischemic event, which can make triaging and diagnosis more difficult for healthcare providers. In general however, the majority of women presenting with AMI present with typical symptoms of left sided chest pain associated with shortness of breath and or diaphoresis [98].

ECG changes of AMI vary from ST segment elevations, ST depressions, t-wave changes, Q-waves, rhythm changes, or to more non-specific findings. Gender does not seem to affect ECG based diagnosis of AMI; however delays related to time from presentation to initial ECG have been reported [99]. Cardiac biomarkers, more specifically troponin assays, are necessary for the diagnosis of AMI. In general, troponin levels are lower in women compared to men [100, 101]. High sensitivity assays with sex specific thresholds can help to increase the diagnostic capability of AMI in women and identify those at higher risk [102]. Better understanding of the clinical relevance of these differences may be warranted before sex specific thresholds can be applied in clinical practice.

There are several tools available to guide risk stratification among patient presenting with AMI which use clinical variables to predict short and long term outcomes. The Thrombolysis in Myocardial Infarction (TIMI) and the GRACE score have been well validated in large cohort based populations [103, 104]. These risk scores vary in their accuracy in prediction of post AMI prognosis when evaluated specifically by sex. The TIMI risk score was shown to be better at predicting in-hospital mortality in men compared to women among patients who presented with STEMI in a Belgian cohort [105]. Similarly, in a recent Spanish cohort study with STEMI, the discriminative capacity of the GRACE score at predicting in-hospital and 6-month mortality was found to be lower in women compared to men [42]. To date, there are no sex specific risk scores which help prognosticate gender specific risk among patients with AMI.

Management Disparities

There are several striking gender differences in the management of AMI between men and women. First, despite advances in medical and revascularization therapies, women presenting with AMI are less likely to undergo timely reperfusion, including PCI, at the time of admission [106–109]. Women are more likely to be managed with a conservative approach and less likely to undergo invasive evaluation and/or treatment

[110–112]. On the other hand, women have been shown to benefit from a more aggressive approach with percutaneous revascularization; however, women are also at higher risk for procedure related complications such as bleeding [113]. Balancing the associated risks with the known benefits of a more invasive approach is necessary when evaluating women with AMI. For example, use of specific bleeding minimization strategies such as trans-radial approach stands to benefit women more than men. With respect to specific treatments, there does appear to be a higher risk of bleeding and mortality among women treated with thrombolytic therapy compared to primary PCI [10]. This may make primary PCI a more suitable treatment strategy among women.

Second, while numerous trials have demonstrated improved outcomes related to optimal medical therapy including anti-platelet agents, beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and statins, women are less likely to be discharged on guideline directed therapies post-AMI [85, 109, 112, 114]. Reasons for this remain unclear and represent an opportunity to address barriers to treatment.

Third, even with increased awareness of the prevalence and symptoms of AMI in women, women themselves tend to often delay seeking care, with greater time from symptom onset to presentation to a healthcare facility [115]. Evaluation of more than 150,000 patients from the 'Can Rapid Risk Stratification of unstable Angina Patients *S*uppress Adverse Outcomes with e*arl*y Implementation' (CRUSADE) and the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network–Get with the Guidelines (NCDR ACTION Registry–GWTG) of the impact of awareness campaigns showed no effect on the difference in delay seen between men and women even after awareness campaigns were instituted [116]. This delay in seeking care most likely contributes to the differences seen in management and eventual outcomes. In a separate study looking at sex differences in time to hospital presentation and outcomes, females were found to be more likely to wait longer before seeking treatment and in turn were less likely to be admitted to the coronary care or intensive care unit (CCU/ICU) compared to men who presented with similar symptoms of AMI [94]. This study also found that females admitted to the medical wards were 89% more likely to suffer in-hospital mortality than their male counterparts, with no gender difference in mortality rate for those admitted to the CCU or ICU [94].

Overall, optimal diagnosis and treatment of AMI in men and women depends on prompt symptom recognition, triaging strategies, and patients' timely presentation to a healthcare facility. The extent to which these various modifiable and non-modifiable factors contribute to the disparities in the management of patients with AMI remains to be clearly elucidated.

Outcomes Post AMI

Whether female gender itself predicts worst outcomes among patients with AMI remains controversial. Depending on the outcomes being measured and the type of AMI being evaluated, there is considerable heterogeneity in the published data

[117–119]. It is clear that there is a complex relationship between age, gender and type of AMI and the specific outcome being measured. For example, data from several large randomized control trials were analyzed to investigate the relationship between gender and 30 day mortality related to AMI. Over 136,000 patients were evaluated and women were noted to have a relative 90% excess risk of mortality compared to men. However, after adjusting for baseline clinical differences and angiographic severity of disease, there was no significant gender difference in outcome post MI noted [24]. Less is known about gender differences in long term AMI related mortality.

Interestingly, more recent analyses have highlighted another trend which warrants discussion. Although there has been a steady decline in AMI-related mortality over the past three decades, this favorable change has been less evident in younger patients, especially in younger women [3, 4, 7, 8]. Several studies have found a lower survival rate among younger women presenting with AMI compared to men of similar age [4, 7, 8]. Data from the National Registry of Myocardial Infarction (NRMI) showed that younger women (age <50 years) had the highest mortality compared to younger men (6.1% vs 2.9%) while no gender difference in AMI related mortality was found between older women and men of similar age [120]. A recent Canadian study looking at trends in 70,628 patients with AMI found similar trends with greater number of comorbidities such as diabetes and metabolic syndrome in women with AMI and higher incidence of AMI hospitalizations among young women age <55 years [121]. This study found that women had higher in-hospital mortality rate post AMI compared to men and that this trend is even more pronounced in young women aged <55 years. Results from the study showed that from 2000 to 2009, the odds of 30-day mortality was 45% higher in young women aged 20–55 years compared with young men (OR 1.45; 95% CI: 1.15, 1.83). This excess risk of mortality in women was also observed among the age groups 56–64, 65–74 [OR 1.27 (95% CI 1.06, 1.52) and 1.26 (1.13, 1.41), respectively]. Overall, women age <55 years had consistently significant higher odds of 30-day mortality post AMI compared with their male counterparts [121].

Another high risk group with decreased survival rate post-AMI is young diabetic women. In a register linkage study using data from the Estonian Myocardial Infarction Registry, primary outcomes including nonfatal myocardial infarction, revascularization rates, and all-cause mortality were compared between diabetics and nondiabetics and stratified by sex [122]. Among 2330 patients who underwent PCI for acute myocardial infarction in the study, diabetics had higher rates of cardiovascular risk factors, co-morbidities, and 3–4 vessel disease and worse outcomes compare to nondiabetics; these findings are even more pronounced among women with diabetes [122]. This Estonian linkage registry found that women with diabetes were younger and had longer delay times to first medical contact; they also were less likely to receive aspirin and reperfusion for STEMI [122]. Over a 2-year follow up, women with diabetes, especially younger women, had higher revascularization and all-cause mortality rate (Fig. 11.3) compared to men with diabetes in a multivariate analysis; these results were mainly due to the high in-hospital mortality rates (12%) among diabetic women [122]. Similarly, in an analysis of the National Inpatient Sample of diabetic patients with AMI, there was an overall

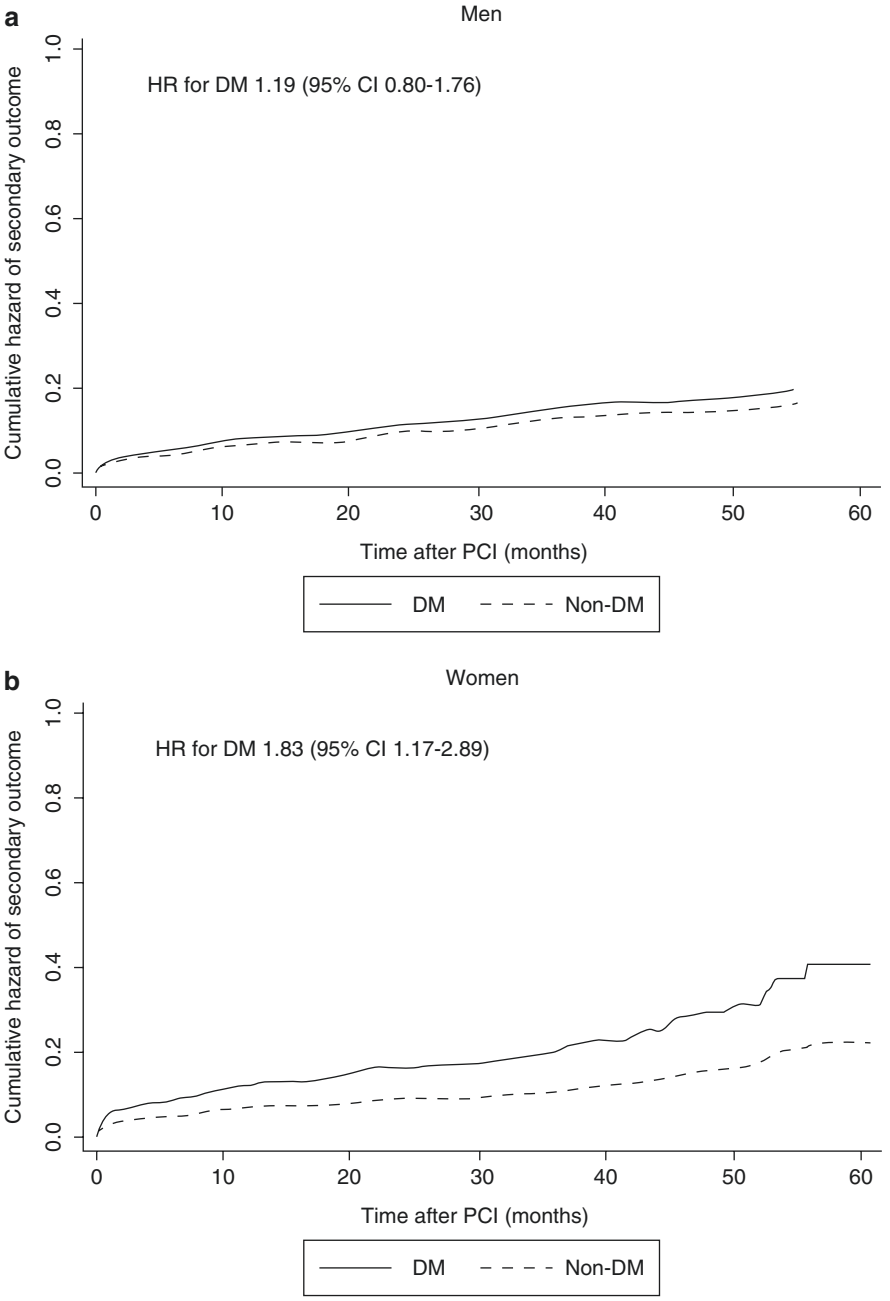

Fig. 11.3 Hazard ratio of all-cause mortality in men and women with and without diabetes following percutaneous coronary intervention during follow up. *CI* confidence interval, *DM* diabetes, *HR* hazard ratio, *PCI* percutaneous coronary intervention. Blondal M, Ainla T, Marandi T, Baburin A, and Eha J. Sex-specific outcomes of diabetic patient with acute myocardial infarction who have undergone percutaneous coronary intervention: a register linkage study. Cardiovasc Diabetol. 2012 Aug 11;11:96. Reprinted with permission

decline in mortality rate over a 10 year study period [123]. Diabetic women, however, remained at a higher risk for in-hospital mortality. Furthermore, younger patients, especially women saw minimal change in their overall risk over time, with in-hospital mortality post AMI remaining stagnant [123]. The disproportionate survival rate post PCI in young women suggest a need to risk stratify and intensify treatment modalities to improve outcome in younger women post AMI, especially among those with diabetes.

When evaluating the outcome of PCI procedure related bleeding, female gender continues to play a significant role [124, 125]. Despite advances in procedural safety and an overall reduction in bleeding risk, female gender continue to predict a twofold higher risk of bleeding post PCI. Analysis from the Northern New England PCI registry of >13,000 women undergoing PCI compared with 30,000 men showed an overall improvement in bleeding events over time, however female sex remained a strong independent predictor of bleeding and vascular complications over a 6-year period [126]. Figure 11.4 compares the adjusted risk of female sex predicting bleeding and vascular complications over a 6-year period. Similarly, the Cath PCI Registry studied 570,777 patients between 2008 and 2011, and observed that women had a near twofold increased risk of bleeding compared with men [126].

Sex specific mechanisms including body mass index, access vessel anatomy, platelet biology and function and PCI related pharmacology all may play a role in mortality outcome post AMI. For example, in a meta-analysis of six clinical trials of glycoprotein inhibitors (GPI) vs. heparin, there was a 20% reduction in death and myocardial infarction rates in men; women receiving glycoprotein inhibitors on

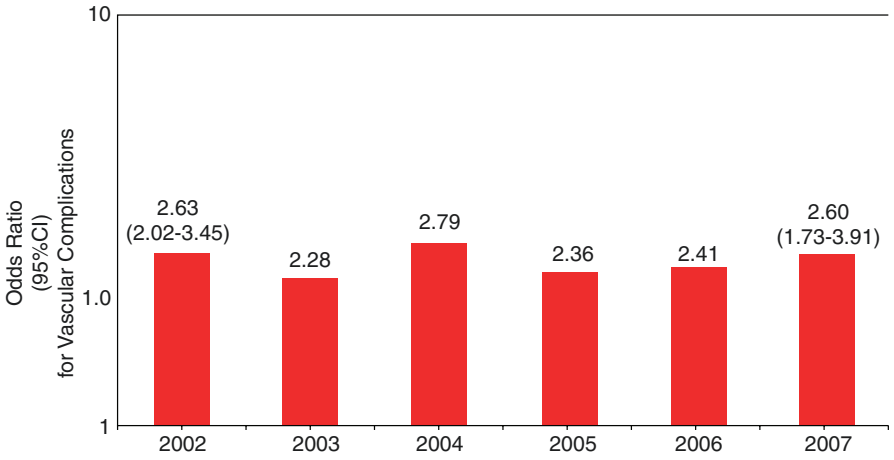

Fig. 11.4 Adjusted risk of female sex predicting bleeding and vascular complications over a 6-year period. Despite improvement in overall bleeding event rates, female sex persists to carry a 2.6-fold increased risk of bleeding with no change appreciable from 2002 (odds ratio, 2.63 [95% confidence interval {CI}, 2.02–3.45) to 2007 (odds ratio, 2.60 [95% CI, 1.73–3.91]). Ahmed, Bina, and Harold L. Dauerman. "Women, bleeding, and coronary intervention." *Circulation* 127.5 (2013): 641-649. Reprinted with permission

the other hand had a 15% higher risk of death and MI compared to men [127]. This finding of lower efficacy of antithrombotic therapy in women may be related to significantly higher bleeding event rates seen in women as compared with men treated with GPI therapy. Bleeding avoidance strategies such as use of radial approach and safer antithrombotic therapies may have the most benefit in women who are at the highest risk of bleeding based on known risk factors.

Disparities in Research

Historically women have been underrepresented in cardiovascular research trials [128–130]. An analysis of 156 randomized controlled trials cited by the 2007 American Heart Association guidelines showed that while the proportion of women in these studies increased significantly over time, from 9% in 1970 to 41% in 2006, it remains low relative to women's overall prevalence of ischemic heart disease in the population. When looking at trials that enrolled both men and women, women represented only 34% of the participants by 2006 [130]. Indeed the FDA excluded women of childbearing age from drug studies in 1977. It was not until 1993 with the National Institute of Health Revitalization Act & the FDA's *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* that guidelines were established for the inclusion of women and minorities in clinical research. While these regulations will likely lead to an increase in overall number of women included in research studies, the proportion of women in mixed gender studies even after 1993 remained unchanged at around 27% according to two separate analyses of cardiovascular randomized controlled trials, one by Cochrane and one National Heart, Lung, and Blood Institute-sponsored [129, 131].

It has been shown that due to biological differences in body mass, volume of distribution, liver metabolism, and kidney function, pharmacokinetic response to cardiovascular drugs differs by gender. However, only 22% of participants in safety trials to assess appropriate dosing for subsequent larger trials were women according to a 2001 report [129]. This has clinical implications as women suffer increased adverse effects from cardiovascular medications such as increased drug-induced torsades de pointes and fibrinolytic-associated bleeding in setting of PCI [132, 133]. Further clinical implications of these sex-based differences remain under investigated and poorly understood. Without adequate female participants, studies cannot be powered to detect sex-based differences. A meta-analysis by Berger et al. of the benefits of aspirin for primary prevention of cardiovascular disease illustrates the importance of including large numbers of women. They found the protective effects of aspirin differ greatly by mechanism and degree when stratified by gender. Aspirin reduced the risk of MI by 32% in men, but by 17% in women [134]. Gender based analysis is essential to fully understand protective, ineffective, or potentially harmful effects of therapeutic interventions. The implication of the under-representation

of women in trials is considerable, as we continue to create and implement practice guidelines based on incomplete research and evidence.

There is still much to be learned about women and AMI given the disparities in past research, including many questions regarding the relative influence of biological, pathophysiological, and psychosocial factors in the development and progression of ischemic heart disease, the etiology for mechanical complications post AMI in women and effective strategies to reduce these complications, and finally modifiable factors contributing to sex disparities in applying evidence-based guidelines in the treatment of AMI [10].

Conclusions

Cardiovascular disease has traditionally been viewed as a "man's disease" despite being the leading cause of death irrespective of sex or gender. This has led to bias both in terms of diagnosing and managing clinical disease but even in basic scientific understanding of the pathophysiological process of ischemia in women. Patient's sex influences baseline risk factors, clinical presentation, provider assessment, and diagnostic decisions. As we continue to learn more about gender differences in acute myocardial infarction, nontraditional risk factors that disproportionately affect women emerge. It appears that certain mechanisms underlying ischemic heart disease in women are distinct from that of men, and need to be further investigated and treated as such. More importantly, the relationship between coronary microvascular dysfunction and AMI needs to be further studied. Despite increased awareness and advancement in women's cardiovascular health, there still remain major gaps in our understanding of the complex array of differences between men and women with AMI. The spectrum spans from inherent biologic differences in disease pathology to disparities in delivery of care due to patient and provider perception. Women continue to die at disproportionately higher rates as compared to men, and suffer increased morbidity post-AMI. Although older age and increased co-morbidities at the time of presentation may influence outcomes in women presenting with AMI, there is evidence of higher morbidity and mortality in women, especially younger women. Identifying better methods for timely diagnosis and tailoring treatment based on gender-specific risk, may be necessary to further improve AMI care in women.

More research, executed with dedication to include large numbers of women, is needed to better understand the differences in the pathophysiology of ischemic heart disease in women. Educational campaigns aimed at correcting this health inequality must target not only medical providers, but also patients and the public to prevent delays in women seeking care and enable women to be their own cardiovascular advocates. To close the gender gap in ischemic heart disease outcomes, greater investment in further research, provider education, and public awareness is essential.

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Chapter 12
The Prevention, Diagnosis and Treatment of Ischemic Heart Disease in Women

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Abbreviations

ACC	American College of Cardiology
ACEI	ACE inhibitors
ACS	Acute coronary syndromes
AHA	American Heart Association
ARB	Angiotensin receptor blockers
ARIC	Atherosclerosis Risk in Communities
ASCVD	Atherosclerotic cardiovascular disease
ATP	Adult Treatment Panel
CABG	Coronary artery bypass grafting
CAC	Coronary artery calcium
CAD	Coronary artery disease
CASS	Coronary Artery Surgery Study
CCTA	Coronary computed tomographic angiography
CMR	Cardiac magnetic resonance imaging
CONFIRM	Coronary CT Angiography Evaluation for Clinical Outcomes

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CVD	Cardiovascular disease
CT	Computed tomography
ECG	Electrocardiogram
ELITE	Early versus Late Intervention Trial with Estradiol
ETT	Exercise treadmill test
FRS	Framingham risk score
HERS	Heart and Estrogen/Progestin Replacement Study
hsCRP	High-sensitivity C-reactive protein
IHD	Ischemic heart disease
IOM	Institute of Medicine
ISCHEMIA	International Study of Comparative Health Effectiveness and Invasive Approaches
KEEPS	Kronos Early Estrogen Prevention Study
MACE	Major adverse cardiac events
MHT	Menopausal hormone therapy
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
MVD	Microvascular disease
NCDR	National Cardiovascular Data Registry
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart Lung and Blood Institute
PCE	Pooled Cohort Equation
PCI	Percutaneous coronary intervention
PCOS	Polycystic ovarian syndrome
PET	Positron emission tomography
PRHI	Peripheral reactive hyperemia index
PROMISE	Prospective Multicenter Imaging Study for Evaluation of Chest Pain
ROMICAT	Rule Out Myocardial Infarction using Computer Assisted Tomography
SCORE	Systematic Coronary Risk Evaluation
SPECT	Single-photon emission computed tomography
WHI	Women's Health Initiative
WISE	Women's Ischemia Syndrome Evaluation
WOMEN	What is the Optimal Method for Ischemia Evaluation in Women

Introduction: The Current State of Ischemic Heart Disease in Women

The number of men and women who are affected by and die from cardiovascular disease (CVD) outnumber all other conditions including all forms of cancer in the US [1, 2]. In 2014, CVD in women resulted in one death every 79 seconds, approximately the same number of women's lives that were claimed by cancer, chronic lower respiratory disease, and diabetes mellitus combined. Several studies have

demonstrated diagnostic and management dilemmas in women due to distinct differences in the experience of CAD among women in comparison to men, including: lower prevalence of angiographically obstructive CAD, greater symptom burden and higher rate of functional disability [3]. These discrepancies have called for a more inclusive term, "ischemic heart disease" (IHD), in women to capture a wider spectrum and definition of a sex-specific pattern of CAD in women [4]. There is consistent evidence that adverse outcomes in women with IHD may be fueled by underestimation of cardiovascular disease (CVD) risk, leading to under diagnosis and under treatment. The reasons for these gender disparities are complex and multifaceted; therefore it is crucial to elucidate the interplay of key clinical, pathophysiological and psychosocial determinants in the evolution of IHD. Continuation of ongoing efforts to increase awareness of the burden of CVD as the leading cause of death among women is necessary given the persistent knowledge gap of CVD as their greatest health threat and that a woman's heart can differ from a man's [5].

The high profile report by the Institute of Medicine (IOM) in 2001 on the biological contributions of sex to human health concluded that sex-specific differences occur at a cellular level and are crucial to our understanding of the natural evolution of disease, thus should be taken into consideration in research [6]. Similar sentiments were once again highlighted in 2010 in the IOM publication "Women's Health Research: Progress, Pitfalls, and Promise" [7]. The persistent paucity of trials with adequate sex and gender differences in the study design and analysis, and limited reporting of outcomes data with sex and gender differences has hindered identification of potentially important sex differences and slowed progress in women's health research and its translation to clinical practice [2, 7, 8].

Unfortunately, most of our current knowledge and guidelines directing the prevention, management and treatment of IHD and its risk factors are based on data from randomized clinical trials with only small proportions of women. This underrepresentation was confirmed by a retrospective review of females in clinical trials from 1997 to 2006 which was estimated at only 27% [9]. Furthermore, the substantial heterogeneity across studies and lack of consideration of sex-specific factors in study design and implementation, limit the ability to draw more conclusive inferences [10]. In addition, there are a disproportionately small number of studies addressing CVD in women, but studies have instead overwhelmingly targeted reproductive concerns, termed "bikini medicine" [2, 11]. Thus, there remains uncertainty in the management of IHD in women as many algorithms that we use today are derived from predominantly male populations [12]. Further complicating this issue is the fact that the majority of physicians feel ill-equipped to assess women's CVD risk and report limited use of available guidelines [5].

This review outlines the current challenges in primary and secondary prevention, diagnosis and management of IHD in women. We present a comprehensive selection of key evidence highlighting the epidemiology, risk factors, screening, diagnosis and treatment of IHD in women. We also identify gaps in knowledge of IHD in women which in turn may spur further sex-specific research and interventions towards the improvement of cardiac care and outcomes in women.

Epidemiology of Ischemic Heart Disease

Incidence and Prevalence

The view of CAD as a "man's disease" is gradually dissipating as its recognition as a major cause of morbidity and mortality amongst women continues to grow. Among Americans aged 20 years or older, 16.5 million have CAD (6.3% US adults) [1]. The prevalence among men is 7.4% and 5.3% in women [2]. Overall, the prevalence of CAD is lower in middle-aged women than in men according to the most recent iteration for the National Heart Lung and Blood Institute (NHLBI) National Health and Nutrition Examination Survey (NHANES); however there exists an overall upward trend in women [13], especially younger women. This data is likely an underestimation as it only accounts for obstructive CAD (angiographically-determined stenosis >50%) and does not include other forms of IHD [14].

As women age, the incidence of all initial coronary events including myocardial infarction (MI), angina pectoris, unstable coronary syndromes and coronary deaths) increases and eventually approaches that of men by age 60 [15–17]. There is a lag time period of about 10 years in the incidence of all coronary events in women behind men which increases to about 20 years for critical events such as MI and sudden death [2, 12]. Notably, the incidence of total coronary events triples in women over age 65 compared to younger women [18]. There is evidence of a racial disparity as black women aged 45–64 within the Atherosclerosis Risk in Communities (ARIC) study were significantly more likely than their white counterparts to experience CVD death as a first event [19]. Discouragingly, recent statistics indicate that although the overall CVD mortality is decreasing for both men and women, it is accelerating in younger women, especially those in mid-life [2, 20–22].

Clinical Presentation

The initial assessment of women with symptoms concerning for IHD can be confounded by our conventional views of "typical" angina symptoms primarily seen in predominantly male study cohorts. Interestingly, effort angina is of increased prevalence among women in comparison to their male counterparts [23, 24]. Yet, a wide range of "atypical" symptoms occur more frequently in women including nausea, fatigue, dyspnea, weakness as well as unconventional descriptors, triggers and locations of chest-related symptoms [25, 26]. Some have suggested that lack of existence of a female-specific characterization of IHD symptoms has resulted in suboptimal care and outcomes among women as an emphasis has been placed on identifying non-cardiac etiologies to chest pain that is not "typical" [26]. Strikingly, women are more likely not to report anginal symptomatology as a disconnect appears to exist between perception of symptoms and health status [20]. Unfortunately, the presence

of symptoms alone, whether "typical" or "atypical" places women at a greater risk of future cardiovascular events [27].

Obstructive Versus Non-obstructive CAD

Despite having more symptomatology and debility than men, women have less anatomical obstructive CAD [28, 29]. Several studies have confirmed the clinical observation that women have a lower plaque burden than men, including atheroma within the media and luminal plaque. The NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study sought to better elucidate the complexity of IHD in women. Of over 800 women in the cohort who underwent clinically indicated angiograms, 62% were found to have non-obstructive CAD at catheterization [30]. These findings were further corroborated within the American College of Cardiology (ACC)-National Cardiovascular Data Registry (NCDR), as 51% of women with stable angina referred for coronary angiography had non-obstructive disease compared with 32% of men [31]. The issue remains whether women experience myocardial ischemia by a different pathophysiology than men, as they more commonly do not have obstructive CAD. The underlying mechanism for ischemia in patients with non-obstructive CAD presents a diagnostic challenge and recent data suggest that these patients are vulnerable to major adverse cardiovascular events similar to individual with an obstructive pattern of injury [2, 24, 32].

Cardiovascular Mortality

Although there has been a decline in overall cardiovascular mortality in men and women from 2000 to 2014, the leading cause of death among women remains CAD [2]. Despite advances in diagnostic and medical therapies, increased public awareness efforts and improved access to care, greater than 250,000 women in the US still die annually from CHD-related deaths fivefold higher than women with breast cancer [2, 3, 33]. Women are more likely to die after their first MI whereas men have four times more coronary events than women [1]. There is an even greater disparity among middle-aged black women as they have a 2.5 times higher mortality from CAD than similarly-aged white women [3, 33, 34].

The vast majority of studies have reported higher mortality rates for women compared with men after an acute MI [10], but this trend may be explained by age, higher prevalence of cardiac risk factors, poorer clinical presentation and treatment differences [10]. There is also evidence suggesting worse mortality rates in younger women following an acute MI [10, 35–39]. Fortunately, differences in mortality risk following percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) appear to be narrowing between men and women [10, 35]. This has been attributed to advances in revascularization techniques and therapies and improved guideline adherence.

Healthcare Cost Burden

Between 2013 and 2014, CVD constitutes 14% of the national health expenditures, with the annual direct and indirect costs of care for women at an estimated $199.6 billion [1]. Much of these costs are associated with the diagnosis and management of persistent angina in women without obstructive CAD. An annual excess expenditure of $280 million has resulted from the over half a million coronary angiograms completed in women which in only half of the cases are revealing of actual flow-limiting stenosis [40]. This estimate does not account for the incurred continued longitudinal medical assessments including increased office visits, procedures and hospitalizations for women with persistent chest pain [40]. The average lifetime cost estimate is approximately $770,000 and ranges from $1.0 to $1.1 million for women with non-obstructive CAD which approaches that of women with obstructive CAD [30]. This presents an enormous challenge to clinicians in treating these women with a greater symptom burden but no evidence of the classically described male pattern of obstructive CAD (>50% stenosis).

Quality of Life

Despite similar lifestyle and pharmacologic management strategies, women with angina have been shown to have inferior functional status scores than men even after adjustment for confounders such as CAD severity and comorbid conditions [41]. Women with IHD are likely to have higher rates of depression, anxiety and inadequate social support which may have a detrimental effect on mental and physical functioning [41–45]. Clearly, the implications of this disparity in psychosocial well-being are substantial and deserve further attention in the clinical care of women with IHD.

Risk Factors for IHD in Women

Traditional Risk Factors

Validated traditional risk factors for CVD—family history of premature CAD, age, smoking, hypertension, diabetes, dyslipidemia, obesity and physical inactivity are well-described in the etiology of IHD in women. “Traditional” CVD risk factors assessed within the Framingham risk score (FRS) underestimate IHD risk in women and are associated with proportionally greater risk for unsuitable outcomes [4]. Female relatives with premature CAD confer a more potent risk to family members than male relatives with premature CAD [46]. Diabetic women have a threefold higher risk for CAD in comparison to nondiabetic women and have significantly

greater IHD mortality rate than diabetic men. Previous evidence has shown that lipid profiles in women worsen in post-menopausal phase of life, with reductions in "good" (HDL) and increases in "bad" (LDL) cholesterol [47–49]. Also studies suggest that higher triglyceride levels are a more prevalent and potent, independent risk factor for IHD in women than in men [50–52]. However, a recent large population-based cohort study of women and men showed contrasting trends in lipid profiles as menopause was associated with upward shifts in most lipid parameters [53]. Moreover, smoking has been identified as a stronger risk factor for IHD among middle-aged women in comparison to men, conferring approximately twice the risk for IHD [54, 55].

Women experience a more exponential increase in IHD after age 60, whereas men have a more linear increase [55]. Despite the clear evidence that both men and women with optimal risk factor profiles have lower risks of IHD compared to those with suboptimal profiles, less than 2% of the US population in NHANES (75% women) actually met the seven simple ideal cardiovascular health metrics [54, 56]. Although women are increasingly aware of CVD as the "number one killer of women" there remain significant disconnects between this awareness and perceived individual risk [57] which is especially significant for women who are younger and of diverse ethnicity [58].

Unique and Emerging Risk Factors

As our knowledge of the complex interplay of sex-unique gene expression and function increases, we have come to identify new and emerging risk factors for IHD in women [2]. While the underlying mechanisms surrounding these new risk factors have not been fully elucidated, these discoveries are promising for identifying future areas to focus research and new discoveries. Metabolic syndrome—a clustering of cardiometabolic risk factors [glucose intolerance, central obesity, hypertension, dyslipidemia (low HDL, high triglycerides)] is more common after menopause, and has been associated with hormonal alterations, a markedly higher risk of IHD and cardiac events [59]. High-sensitivity C-reactive protein has also been shown to consistently be higher in women than in men after puberty and there is clear variation with estrogen levels in postmenopausal women [53, 60]. In some studies, high-sensitivity C-reactive protein (hsCRP) may improve risk stratification for IHD in women, particularly those with metabolic syndrome [61–63]. Autoimmune diseases such as systemic lupus erythematosus, scleroderma and rheumatoid arthritis, which are more common in women, have also been associated with an increased risk of IHD [64].

Hormonal fluxes over a woman's lifespan may also influence IHD risk, and provide unique risk factors, seen only in women. In particular, the length of a woman's reproductive span appears to inversely relate to CVD risk [65, 66]. It has been observed that early menarche (<12 years at onset) increases subsequent risk of cardiac events and both CVD and overall mortality [67]. Entities causing ovarian

dysfunction, such as functional hypothalamic amenorrhea, have been associated with premature coronary atherosclerosis and associated CVD events [68]. Moreover, polycystic ovarian syndrome (PCOS) is coupled with risk factor clustering including diabetes, obesity and the metabolic syndrome, thus leading to heightened IHD risk [4]. Furthermore, pregnancy appears to be a natural stress test given its identification of women at higher risk for CVD [2]. Pregnancy-related factors such as pre-term delivery, hypertensive pregnancy disorders, and gestational diabetes are a few of the new areas of emerging data associated with increased CVD risk in women [2, 69]. The recent effectiveness-based prevention guidelines for women have identified pre-eclampsia and gestational diabetes as "at risk" categories for IHD [61] and there is further supportive evidence linking these entities to a twofold increased CVD risk [70, 71].

Microvascular and Endothelial Dysfunction

The prevalence of "normal" or "near-normal" epicardial arteries in women with chest pain, suggests alternative pathophysiological mechanisms from the classic demand-supply mismatch of flow-limiting coronary artery stenosis. Possible explanations for this chest pain syndrome, often termed "non-obstructive CAD", include abnormal coronary reactivity, plaque erosion/distal micro embolization and microvascular or endothelial dysfunction [29]. These mechanisms are characterized by impairment in vasomotor tone and vascular homeostasis which lead to characteristic ischemic symptoms [41, 72]. Close to one half of the women presenting with chest pain in the presence of non-obstructive CAD within the WISE study had coronary microvascular dysfunction as determined by invasive [73] and noninvasive methods such as magnetic resonance imaging [74, 75]. Further evidence suggests the clinical and prognostic importance of impaired coronary vasomotion, as its detection was associated with adverse cardiovascular outcomes irrespective of CAD severity in the same cohort of women [76].

Traditional cardiovascular risk factors of increased prevalence and impact in women have been implicated in the development of endothelial dysfunction [41]. These conditions, whether alone or in conglomerate, lead to vascular endothelial injury and increased oxidative stress which further promotes coronary atherogenesis [15]. There is also evidence of a higher risk of progression to atherosclerotic CAD in patients with endothelial dysfunction [77].

Risk Assessment for Ischemic Heart Disease Prevention

Over 80% of middle-aged women have more than one traditional cardiac risk factor for atherosclerotic cardiovascular disease (ASCVD) risk [3]. The high burden of cardiac risk factors in women has fueled our efforts in primary and secondary

prevention of IHD through more precise risk stratification and assessment models. The classic FRS has historically been the most prominent and widely used tool for estimating 10-year cardiovascular risk. The strength of the FRS lies in its ability to risk stratify populations, however it has been shown to underestimate individual patient risk, particularly in women. Among women sustaining their first MI, the majority were classified in the low risk category by FRS score (95%), with the remaining in the intermediate category (5%) [78, 79]. Given the FRS shortcomings, a number of other global risk score calculators have debuted from different study cohorts including the Systematic Coronary Risk Evaluation (SCORE) [80], the QRISK algorithm [81], the Adult Treatment Panel (ATP) III guidelines (FRS-based) [82] and the Reynold's risk score [83]. Ideally, scoring systems have the highest accuracy in the population from which they were developed [78]. This presents substantial room for inaccuracies in women and ethnic groups whom are disproportionately understudied. The Reynold's risk score, which includes hsCRP, was derived from and validated in women cohorts and in comparison with the FRS resulted in improved risk prediction with reclassification in 15% of intermediate-risk FRS women to high risk [83, 84].

The guidelines on treatment of cholesterol to reduce ASCVD risk by the ACC and American Heart Association (AHA) generated much controversy though its aim was to provide clinicians a more straightforward, evidence-based tool [85]. The 2013 ACC/AHA Pooled Cohort Equation (PCE) predicts the 10-year risk for development of a first ASCVD event in adults aged 40–79 years old. This instrument eliminates the use of a target cholesterol level, recommends a fixed statin intensity based on classified risk group, includes stroke as an endpoint and allows for estimates by sex and race. The guideline's pooled cohort equation was originated and validated in men and women within geographically and racially representative populations including blacks [86]. Critics suggest that this novel score calculator overestimates risk by 75–150% in at least seven external validation cohorts which could lead to excessive statin therapy [87, 88]. Nevertheless, the outstanding issue remains intermediate to high risk groups, including women, are in dire need of lifestyle and risk factor optimization for CVD risk reduction, and refined IHD detection to ideally prevent, or treat adverse CVD events.

Diagnosis of Ischemic Heart Disease

The diagnosis of IHD in women is more challenging and is often delayed as women present later and more frequently with atypical symptoms. Women are usually evaluated for CAD about 10–20 years later than men. Although the majority of women present with the same symptoms of CAD as men, a significant number also experience atypical symptoms. For example, in a large study of patients diagnosed with myocardial infarction, 58% of women compared to 69% of men described chest pain as their presenting symptom [89]. Moreover, when women with acute coronary syndromes (ACS) undergo cardiac catheterization, at least twice as many women as

compared to men, will have no significant obstructive CAD, yet their prognosis is worse than that of both men and women who do not have chest pain syndromes [90]. This makes the diagnosis of IHD in women more challenging. Even more complex are those women who present with manifestations of coronary disease that are very poorly understood, but far more common in women; these include stress-induced cardiomyopathy(apical ballooning syndrome), spontaneous coronary artery dissection, coronary vasospasm and coronary embolism. These entities once considered "rare" are increasingly being diagnosed in women. Additional imaging techniques, including MRI with late gadolinium enhancement [91]; echocardiography with ultrasound enhanced cardiac perfusion [92]; intravascular ultrasound and optical coherence tomography [93, 94] are useful in establishing the diagnosis and providing a framework to better understand the pathophysiology of these less common acute cardiovascular entities. These diagnostic tools provide guidance to determine the most appropriate therapy.

Unfortunately, current guidelines on the management of acute and stable cardiac ischemic syndromes do not include a sex-based diagnostic approach. It is important to underscore that the majority of available multicenter clinical studies and trials used to support current guidelines are based on predominantly male cohorts. Within these limitations, we will review the current noninvasive and invasive approaches to the diagnosis of IHD in women, including functional testing (stress testing), anatomic imaging (coronary computed tomography (CT), and endothelial function assessments.

Noninvasive Testing

The 2014 AHA Consensus Statement on the "Role of Noninvasive Testing in the Clinical Evaluation of Women with Suspected Ischemic Heart Disease," provides evidence-based guidelines on diagnosis of IHD in symptomatic women by non-invasive testing [95]. The choices of non-invasive testing are similar in both sexes, however women are more likely to have "false positive" results, and due to a lack of confidence in accuracy, these non-invasive diagnostic tests are often improperly utilized [95]. Pretest probability must be taken into account when determining the need for and choice of testing for ASCVD. Initial pretest assessment of exercise capacity is important to ascertain whether a woman can exercise to an adequate level at which ischemia may be detected. In women unable to perform activities of daily living or perform adequately on ETT, a pharmacological stress test is preferred. Stress imaging tests provide information about wall motion abnormalities or perfusion, and provide assessment of ventricular function.

Functional Testing

Functional tests include ETT with electrocardiogram (ECG), exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single-photon emission computed tomography (SPECT) or positron emission tomography

(PET), pharmacologic stress cardiac magnetic resonance imaging (CMR), CT perfusion and CT or Doppler ultrasound-derived flow reserve measurements.

ETT is the most common method of diagnosing CAD in women despite a higher false-positive rate compared to men. ETT is recommended as the diagnostic test of choice in symptomatic, low-intermediate risk women who are able to exercise and have an interpretable resting ECG. Exercise stress testing provides valuable information about exercise capacity, and hemodynamic response to exercise and recovery, all markers of cardiovascular risk [96]. Women who are unable to exercise beyond stage 1 of a standard Bruce protocol, achieving <4–5 metabolic equivalents, are at the highest risk of cardiovascular events and this portends worse clinical outcome [97]. This is contrary to women achieving exercise workloads of >10 metabolic equivalents which predicts a very low risk of inducible ischemia [98]. Lack of appropriate blood pressure and heart rate increase with exercise, or a drop of blood pressure with exertion, are concerning for IHD in both men and women [99]. Regardless of gender, high risk patients identified by ETT demonstrate symptom limited angina and marked ST segment changes of ≥2 mm or downsloping ST segments in multiple leads. This threshold is however less accurate for detection of ischemia in women. Lower sensitivity and specificity of ST-segment responses with exercise have been documented [100]. Exercise capacity is further reflected by Duke Treadmill Score, calculated as exercise time − (5 × ST segment changes in mm) − (4 × angina index). This scoring tool not only identifies high risk patients for CAD, but also provides prognostic information [101].

A frequent reason for performing ETT in women is the high negative predictive value. In order to explore whether myocardial perfusion imaging (MPI) with SPECT could provide incremental information for diagnosis in symptomatic women at low to intermediate pretest probability over ETT alone, the "What is the Optimal Method for Ischemia Evaluation in Women" (WOMEN) trial was performed [26, 96]. Similar 2-year clinical outcomes were observed, with no difference in major adverse cardiac events (MACE) (<3%). Overall, the cumulative diagnostic cost savings was 48% for ETT compared with exercise MPI. Thus, for symptomatic women with low to intermediate risk who are capable of exercising, ETT is the recommended initial test of choice to provide diagnostic and prognostic information.

It is well known that the burden of non-obstructive CAD disproportionately affects women with prevalence of up to 50% at angiography [14]. The pretest probability of CAD is lower in women, and more false positive results for stress imaging have been reported. In women, the accuracy of stress echocardiography and its diagnostic sensitivity and specificity in detecting CAD is higher compared to exercise ECG [102–104]. In comparison, exercise echocardiography has higher sensitivity in men [105]. Despite these differences, the prognostic value of exercise echocardiography is comparable between men and women [106]. Women with low-risk stress imaging findings, have <1% risk of CAD. Women with moderate to severe wall motion or perfusion abnormalities are at higher risk, and may have annual CAD event rates as high as 5–10% per year, depending on the vascular territory and the choice of stress imaging used [106, 107]. Additionally, reaching a workload of >6 metabolic equivalents during exercise echocardiography was associated with decreased risk of cardiac events and cardiac death in both men and women [106].

Challenges in interpretation of stress imaging tests in women are technique-dependent. Nuclear stress testing challenges can occur due to breast tissue attenuation and smaller left ventricular size in women which limits the detection of small perfusion abnormalities. New techniques however are currently used to overcome the frequency of attenuation artifacts. Questions about radiation safety associated with radionuclide stress tests have been raised [108], and tests utilizing ionizing radiation are frequently avoided or used cautiously in young women due to increased lifetime risk of cancer.

Anatomic Testing

In the last decade, the evidence regarding the utility of cardiac CT has grown exponentially. Coronary computed tomographic angiography (CCTA) and coronary artery calcium (CAC) score provide additional tools in the diagnosis and prognosis of patients with CAD. CCTA can risk-stratify patients with acute chest pain and intermediate likelihood of ACS. A unique strength of CCTA is the ability to rapidly and non-invasively visualize, quantify, and characterize atherosclerotic plaque components. CCTA shows the extent of both calcified and non-calcified plaque, obstructive and non-obstructive atherosclerosis, with lower radiation exposure and improved image quality. Data from the "Coronary CT Angiography Evaluation for Clinical Outcomes" (CONFIRM) trial showed that the presence of multi-vessel CAD in women by CCTA predicted a 3–4-fold higher risk of death [109]. The "Rule Out Myocardial Infarction using Computer Assisted Tomography" trial (ROMICAT), comprised of 40% women, demonstrated that half of patients with acute chest pain at low to intermediate likelihood of ACS had no CAD by CCTA, with very high negative predictive value [110]. Two-year follow up of the ROMICAT study cohort revealed that CCTA predicts MACE and has incremental prognostic value in patients with acute chest pain. The probability of MACE within 2 years increased in parallel with increased burden of coronary disease (plaque, stenosis, left ventricular wall motion abnormalities) [111]. The subsequent ROMICAT II trial sought to examine gender differences in outcomes and found that women undergoing CCTA compared to standard cardiac evaluation had fewer hospital admissions, shorter length of hospital stay and lower total radiation dose compared with men. Thus, CCTA is a viable alternative for women undergoing assessment of CAD. CAC increases with age and is more substantial in men [112]. Women tend to have less severe burden of atherosclerosis, with very low prevalence in premenopausal women. CAC scoring was shown to have similar predictive value for arteriographic CAD in men and women. The sensitivity of CAC for detection of obstructive disease is >95% in women, and specificity of the test is significantly higher in women compared to men [113]. Therefore, CAC scoring also adds value in assessment of CAD in women, with minimal radiation exposure.

The "Prospective Multicenter Imaging Study for Evaluation of Chest Pain" (PROMISE) trial compared functional to anatomic assessment. The study enrolled a large, community-based population of symptomatic patients of which more than half were women (with intermediate level of risk) undergoing evaluation for suspected CAD. Anatomical testing as compared with use of functional testing did not reduce the incidence of events over a median follow-up of 25 months [114]. The "Randomized Evaluation of Patients with Stable Angina" (RESCUE) trial also compared CCTA

with SPECT MPI [12]. This study is currently in follow up and participant outcomes will be assessed by age, sex, comorbidity, and angina classification class at presentation. The NHLBI-sponsored "International Study of Comparative Health Effectiveness and Invasive Approaches" (ISCHEMIA) trial is another comparative effectiveness study with plans to randomize patients with chronic IHD with moderate to severe ischemia on stress imaging to therapy with invasive angiography or medical management [115]. These studies will further expand our understanding of the diagnosis and treatment of suspected IHD in both men and women.

Microvascular Testing

Coronary microvascular disease (MVD), defined as limited coronary flow reserve and/or coronary endothelial dysfunction are the presumed mechanisms of ischemia in women with persistent angina, variable evidence of ischemia on stress testing, and no evidence of obstructive CAD on angiography. MVD is characterized by a decrease in the size of epicardial vessels and microvasculature, increased arterial stiffness, increased fibrosis, altered remodeling, more diffuse atherosclerotic disease, and the presence of endothelial or smooth muscle dysfunction [116]. MVD portends a worse prognosis in women with an estimated 2.5% annual MACE rate in women [117]. In the last few decades, non-invasive and invasive techniques have evolved to adequately assess coronary physiology.

Noninvasive techniques such as PET, CMR and transthoracic echocardiography Doppler allow for the assessment of myocardial blood flow and coronary flow reserve. Decreased flow reserve in women is associated with worse outcomes, with increased rate of cardiac death, stroke or heart failure [27, 118]. Early detection of endothelial dysfunction, measured by brachial artery flow mediated vasodilation, has also been associated with a 1.3 to 4.4-fold increase in IHD in women [119]. Additional simpler noninvasive techniques have emerged, with specially-designed fingertip probes to measure the peripheral reactive hyperemia index (PRHI), a measure thought to reflect endothelial function [120] and has been shown to be significantly reduced in the setting of persistent chest pain syndromes associated with non-obstructive CAD in women [121].

Invasive Testing

In individuals with a high pretest probability of CAD, coronary angiography remains the gold standard for diagnosis and permits catheter-based intervention when indicated. Evidence from the NCDR and the WISE study, indicate that over 50% of women with chest pain referred for coronary angiography do not have significant obstructive CAD [3]. In these patients, strong consideration of coronary physiologic testing should be done, to evaluate for MVD and endothelial dysfunction. Although noninvasive techniques are evolving, the gold standard remains catheter-based [122]. Pharmacologic assessment of coronary blood flow and flow reserve by cardiac catheterization, permits evaluation of both

endothelium-dependent and endothelium independent mechanisms [123]. Women with impaired coronary flow reserve had a significantly increased risk for adverse cardiovascular events, despite their low burden of obstructive CAD on invasive coronary angiography [124]. Although coronary physiologic testing does have potential risks and limitations, the evaluation for coronary vascular dysregulation, either invasively, or noninvasively, is recommended in women with persistent chest pain syndromes without obstructive CAD for proper diagnosis and effective treatment.

Treatment of Ischemic Heart Disease

Although our understanding of IHD in women points to a differing pathophysiology than men, the recommended treatment of CVD in women is similar to men, with respect to both primary and secondary prevention, and ACS. According to the current ACC/AHA guidelines for management of ACS, indications for non-invasive/invasive diagnostic procedures and the treatment strategies should be implemented similarly for both men and women with the overarching goal to improve quality of life and outcomes [125]. However, despite these recommendations and goals of care, women continue to be treated less aggressively than men, with less intensive use of evidence-based medical and procedural therapy, less enrollment in cardiac rehabilitation, and less intensive therapeutic lifestyle counseling [126–129]. In a large international prospective study of over 30,000 men and women (22.6%) with stable CAD, it was found that although risk profiles of men and women differed substantially, their 1 year outcomes were similar, although fewer women underwent revascularization [130]. Further research is needed to better understand gender determinants of outcome and devise strategies to minimize bias in the management and treatment of women.

Therapeutic Lifestyle Intervention

Lifestyle modification, risk factor control and overall CVD prevention is paramount in women. Smoking cessation, moderate intensity physical activity most days of the week, heart healthy diet, weight reduction and maintenance, and treatment of underlying depression-if present are some of the interventions important to reduce poor outcomes. Major risk factor interventions include optimization of blood pressure, lipids, and glycemic control, as well as weight management through lifestyle changes, medical therapy and/or interventions.

Medical Anti-ischemic Therapy

Anti-ischemic medical therapy including aspirin, the angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), beta blockers, aldosterone inhibitors and statins are frequently delayed in women due to delay in symptom

presentation and are less intensively used, despite their beneficial effects. These treatment differences in gender are possibly attributed to lower prevalence of obstructive CAD in women. Aspirin is recommended as part of management of ACS in both men and women and has been shown to be equally beneficial for secondary prevention, it is less consistently used for primary prevention of CVD in women [131]. With regards to primary prevention, it has been shown that aspirin prevents stroke in women older than 45 years old, and prevents MI in those over age 65 years [132]. The Euro Heart Survey showed that women were significantly less likely to receive aspirin and statin for treatment of stable angina [127]. After hospital discharge for non-ST-elevation MI, women received about 3% less aspirin and beta blockers and about 13% less statin therapy compared to men [126]. These are concerning findings, considering that statins and ACEI were shown to improve endothelial dysfunction, which is so prevalent in women.

Therapies for Acute Coronary Syndromes

The 2014 ACC/AHA guidelines for management of ACS, recommended that women be treated in a similar manner to men with the same indications for noninvasive and invasive testing. Large scale observation from the CRUSADE initiative showed that despite these recommendations, women are treated less aggressively, with less cardiac catheterizations, PCIs, fibrinolysis procedures or CABG, which may contribute to different clinical outcomes [126]. A meta-analysis comparing early invasive versus conservative treatment in men and women with unstable angina showed similar reductions of death, MI or recurrent ACS using invasive therapy in men and women [133]. However, the risk of composite end-point was lower in biomarker (creatinine kinase-MB or troponin) positive women. Regarding potential risks associated with these invasive procedures, women have been shown to have more bleeding complications [134]. In addition, a recent analysis of post-MI patients treated with PCI showed that women (especially blacks) have worse outcomes than men as demonstrated by their persistent angina and unplanned rehospitalization 1-year following their cardiac event [14]. This could potentially be explained by the lower referral rates of women to cardiac rehabilitation after an ACS, despite the clear benefits on overall well-being and reduction of future cardiac events [135, 136].

Therapies for Specific Conditions in Women

Treatment of microvascular angina in women starts with risk factor modification and therapeutic lifestyle changes. Exercise training and cardiac rehabilitation is often recommended. Statins are especially beneficial in improving endothelial function. Traditional anti-ischemic drugs, including nitrates, beta blockers, ACEI and calcium channels blockers are first line therapy. L-arginine, precursor of nitric oxide,

improves angina and improves small vessel endothelial function in non-obstructive CAD [137], although its long term use in certain situations is being questioned. The efficacy data on non-traditional anti-ischemic medications including ranolazine (an anti-anginal agent) or xanthine derivatives such as aminophylline are mixed. Xanthines and tricyclics are effective on abnormal cardiac pain perception [138]. Isolated reports of the use of cGMP phosphodiesterase inhibitors have emerged, but no consistent studies have been done.

Strategies for long-term management of coronary microvascular dysfunction in women are not well established. Most women who initially achieve good response with medications over time develop symptoms refractory to prior therapy. Some of these challenges in management are partially due to our still incomplete understanding of the pathophysiology of MVD. Large, randomized outcome clinical trials testing the efficacy of currently available medical therapies or novel therapies in women with refractory symptoms are lacking. Further research is needed to evaluate the best long term treatment strategy and to provide treatment guidelines.

Data on the safety and efficacy of menopausal hormone therapy (MHT) in primary prevention of CAD is insufficient to recommend its use [139, 140] for the prevention (primary or secondary) of CAD. The Heart and Estrogen/Progestin Replacement Study (HERS) showed no evidence of cardiovascular benefit in women with established obstructive CAD [141, 142]. In postmenopausal women without prior CVD events, the KEEPS) [143] and "Early versus Late Intervention Trial with Estradiol" (ELITE) [144] trials randomized participants to MHT or placebo and used surrogate markers of atherosclerosis (CCTA and CAC scoring) to determine MHT effects on the progression of atherosclerosis. Both trials attempted to answer questions raised by the WHI of optimal timing of MHT in postmenopausal women. The results of both trials were mixed. In KEEPS, MHT did not affect atherosclerosis progression by arterial imaging (by CIMT). However in the ELITE study, there was a lower rate of subclinical atherosclerosis progression by CIMT (but not CAC score) in postmenopausal women treated earlier with MHT. While both studies renew the discussion of the role of MHT in women, the data presented to date do not support the use of MHT in primary prevention of CAD.

Conclusion

Although we have made great strides in the reduction of CVD mortality in women through advances in diagnostic and therapeutic approaches, gaps remain in our knowledge of the full impact of CAD in women. Variables unique to women, the pathophysiology for IHD in women, and the prevalence of non-obstructive CAD and MVD are a few of the challenges we face in bridging the knowledge gap and improving outcomes [3]. Our review provides a synthesis of key evidence highlighting gender disparities in the epidemiology, presentation, risk assessment, mortality and clinical diagnosis and management of women with IHD. Women have an increase in incidence of CVD events with age, although there is an

emergence of events in younger women. Our current diagnostic strategies are inherently tailored towards identification of "classical" obstructive CAD, with subsequent catheter-based or surgical interventions. Although some women do fit into this "accepted" algorithm, we do not yet have a clear understanding of what to do with the patients, the majority of whom are women, who do not fit neatly into this standard algorithm, yet have persistent symptoms, and increased morbidity and mortality.

These disparities provide a framework for clinicians and researchers to "refashion" and reassess our current practices in the evaluation of women with IHD with the overarching goal of providing efficient and cost-effective healthcare for improved clinical outcomes. The fundamental hurdle remains to build credible sex-specific evidence on CVD mechanisms through better representation of women in cardiovascular clinical trials. In this era of health care reform, future guidelines for the assessment of IHD in women must include gender-specific risk assessment models as well as diagnostic and therapeutic algorithms for obstructive and non-obstructive CAD.

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Chapter 13
Gender Differences in Outcome After Coronary Revascularization

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Since the introduction of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), coronary revascularization played an important role in reducing cardiovascular mortality over 40–50 years, especially in patients presenting ST-segment elevation myocardial infarction (STEMI). While the benefit of coronary revascularization has been shown both in men and women, cumulating evidences regarding prevalence of coronary artery diseases and clinical outcomes after coronary revascularization revealed apparent sex differences. Women were associated with greater unadjusted peri-procedural mortality following PCI or CABG [1–8], suggesting the older age and presence of comorbidities in women. In terms of long-term outcomes, women as compared with men were associated with lower adjusted 10-year risks for all-cause death after PCI, [9] while long-term mortalities following CABG were similar between men and women [10]. While lower coronary disease burden, lower prevalence of epicardial endothelial dysfunction, and differences in the clinical management following coronary revascularization might possibly explain the observed differences in clinical outcomes between men and women, underlying pathophysiological sex differences on coronary revascularization remains largely unclear.

It is well-known that women are generally 10 years older than men when presenting with coronary artery disease [11–13], because of the protective effects of estrogen until their menopause. This concept has been indirectly supported by observations young women with hypoestrogenemia [14]. In the nation-wide registries of coronary artery disease, despite older age and greater prevalence of traditional risk factors such as hypertension and diabetes, women less likely to have

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Table 13.1 Baseline patient characteristics between men and women in large-scale registries

	GWTG-CAD [1]		German Society of Cardiology [2]		BWGIC registry [3]	
	Men	Women	Men	Women	Men	Women
No of patients	47,556	30,698	65,972	24,262	95,030	35,955
Age	64.7 ± 14.1	72.6 ± 14.2	68 (60–74)	72 (65–78)	64.8 ± 11.6	70.3 ± 11.3
Diabetes	28.0%	32.8%	25.0%	29.8%	20.3%	26.8%
Hypertension	57.7%	67.8%			52.9%	63.3%
Hyperlipidemia	36.1%	33.0%			58.4%	58.9%
Smoking	32.8%	21.6%			30.8%	19.8%
Heart failure	12.8%	20.0%				
Previous MI	21.2%	18.3%			17.9%	12.3%
Previous PCI			51.6%	42.9%	29.9%	25.4%
Previous CABG			16.5%	10.1%	10.8%	7.4%
Poor LV function			13.4%	8.9%		
Renal insufficiency	9.5%	10.9%	16.7%	16.5%	3.1%	3.6%

Data were derived from [1–3]

Baseline characteristics between men and women in GWTG-CAD, German Society of cardiology, and BWGIC registry. Women were generally older and had a greater prevalence of traditional risk factors, while women were less likely to have previous history of coronary artery disease. *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *LV* left ventricular

previous history of coronary artery disease, have a lower extent of coronary artery disease (i.e. lower number of diseased vessels) and present less often with STEMI (Table 13.1) [1–3].

In the sub-analysis of PROSPECT study evaluating serial assessments of three-vessel coronary arteries by virtual histology intravascular ultrasound, young women (<65 years old, N = 88) had a fewer number of fibroatheromas (2.0 vs. 3.0, p = 0.007) and non-culprit lesions per patient (4.0 vs. 5.0, p = 0.004) with smaller plaque volumes (46.8% vs. 47.7%, p = 0.04), and more fibrotic plaques (4.4% vs. 2.2%, p = 0.03) than men in the same age group (N = 398) [15]. ADAPT-DES study also showed lower prevalence of plaque rupture and thin-cap fibroatheroma in young women (<65 years old) as compared with young men [16]. Although Bharadwaj et al. based on optical coherence tomography and near infrared spectroscopy (NIRS) failed to show sex-specific differences in plaque characteristics [17], Haaf et al. reported a tendency towards lower NIRS-derived lipid core burden index (LCBI) in women as compared with men [18]. Men as compared with women also seem to have more diffuse epicardial endothelial dysfunction, which is a known precursor of atherosclerosis [19]. Pathophysiological mechanisms of smaller disease burden in women are largely unknown. We may speculate that not only the absence of protective effect of estrogen but also more smoking may be associated with endothelial dysfunction and the subsequent higher prevalence of atherosclerosis in men as compared with women.

The FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study demonstrated that functional flow reserve (FFR)-guided PCI improved outcomes compared with an angiography-guided PCI [20]. In a subanalysis of this study, the benefit of FFR-guided PCI was observed in both men and women [21]. It is noteworthy that FFR values in the similar degree of stenosis were significantly higher in women than in men (0.75 ± 0.18 vs. 0.71 ± 0.17, P = 0.001). While microvascular dysfunction and/or smaller myocardial mass could be a possible explanations of this finding, several studies have been conducted to elucidate the difference in microvascular dysfunction between men versus women. Coronary flow reserve (CFR), which was regarded as an indicator for coronary microvascular dysfunction, showed a linear association with adverse outcomes [22]. Maximal CFR was significantly lower in women than men (2.80 vs. 3.30, P < 0.001) [19, 23], suggesting greater prevalence of microvascular dysfunction in women. On the other hand, Kobayashi et al. measured the index of microcirculatory resistance (direct measurements of coronary microvasculature), which was similar between men and women, suggesting larger resting coronary flow with no significant difference in microvascular dysfunction [23]. Further studies are needed to elucidate the difference in coronary physiology between men versus women.

In addition to the clinical presentation, women and men differ substantially in diagnostic evaluation and their management. Women seem to derive more prognostic information from an anatomical assessments such as cardiac computed tomography, whereas men tend to derive similar prognostic value from both anatomical assessments and stress testing such as exercise electrocardiography, stress echocardiography, and stress nuclear [24]. Recently, high-sensitivity assays for measurements of cardiac troponins emerged as a clinical decision making tool to detect chronic myocardial injury [25]. While high-sensitivity troponin T was an independent predictor for all-cause mortality in both sex (Men: HR 6.45, 95%CI 4.68–8.87, P < 0.001, Women: HR 4.29, 95%CI 2.36–9.03, P < 0.001), difference between high and normal high-sensitivity troponin T values appeared to be more marked in men [26]. It remains unclear whether there are sex-specific differences in the clinical phenotype of coronary artery disease, or in sex-specific bias of diagnostic testing, or both. In the outpatient setting among patients with suspected coronary disease, women undergo coronary revascularization less frequently than men [27, 28]. Since sex-specific difference in clinical presentation, diagnostic evaluation and management may widely varied among different cultures and countries, world-wide survey is warranted to characterize those differences.

Although women represented >30% of patients undergoing PCI, only a small proportion of women are enrolled in randomized clinical trials comparing stent type. To clarify safety and efficacy between stent types, several meta-analyses have been conducted and showed no significant interaction between gender and stent type: between first generation DES (sirolimus eluting stent or paclitaxel-eluting stent) versus bare-metal stent (BMS); [29–31] and between second generation DES (everolimus-eluting stent) versus first generation DES (paclitaxel-eluting stent) [32]. In a large-scale patient-level pooled analysis including a total of 11,557 women, newer-generation DES are associated with an improved safety profile

compared with early generation DES and BMS [33]. A nation-wide analysis of the CathPCI registry also showed favorable risk reductions for major adverse cardiac events following DES implantation as compared with BMS in both men and women without significant interaction [34]. Given these observations, women should be treated using newer-generation DES.

Diagnosis of STEMI is associated with high risk of major adverse cardiac events. In a large-scale Get With the Guidelines-Coronary Artery Disease (GWTG-CAD) registry, there were no significant adjusted risks for in-hospital mortality rates between women and men in the overall acute myocardial infarction cohort (adjusted OR 1.04, 95%CI 0.99–1.10), while there was a significant difference in the STEMI cohort (10.2% vs. 5.5%, P < 0.001, adjusted OR 1.12, 95%CI 1.02–1.23) [1]. The underuse of evidence-based treatments and delayed reperfusion among women were reported to be possible explanations for the greater risks of adverse events following STEMI in women [1]. More recently, in a large scale German PCI registry (N = 185,312), female sex was shown to be associated with 20% increase risks of in-hospital death (adjusted OR 1.19, 95%CI 1.06–1.33) and major adverse cardiac events (adjusted OR 1.19, 95%CI 1.07–1.34), while there was no difference among patients undergoing PCI for stable coronary artery disease, or non-ST-segment acute coronary syndrome [2]. While gender difference may be a possible explanations for these findings, large-scale prospective imaging studies are warranted.

Duration of dual antiplatelet therapy (DAPT) is determined based on ischemic events versus bleeding risks [35]. While female sex was regarded as a predictor of bleeding events following DAPT [36], a pre-specified sub-analysis of PRODIGY study showed no significant interaction between sex and duration of DAPT (6-month vs. 24-month) on both ischemic and bleeding endpoints [37]. It is of note that neither DAPT score [38], PARIS score [39], nor PRECISE-DAPT score [40] included sex as a potential confounder.

As relatively small number of women were included in the clinical trials, differences in the benefit of PCI in a specific subset have not been well investigated so far. In patients with unprotected left main stenting, adjusted 2-year risks of death (HR 1.12, 95%CI 0.80–1.56), cardiac death (HR 1.05, 95%CI 0.70–1.57) or death/myocardial infarction (HR 0.53, 95%CI 0.19–1.47) were not significant between men (N = 1048) and women (N = 404) [41]. Further studies are needed to confirm these observation.

Sex differences in patients undergoing CABG has not been well investigated so far. In the BARI 2D trial comparing PCI versus CABG in patients with type 2 diabetes, no sex differences were observed in clinical outcomes after adjustment for difference in baseline variables throughout 5 years, while number of patients were limited (Men: N = 1666, Women: N = 702) [42]. In large-scale single center studies (N >10,000), female sex was independently associated with an increased risk of short-term mortality after CABG surgery [7, 8], but it was no longer an independent risk factor for all-cause mortality in the long-term outcomes following CABG [10].

In conclusion, female sex is associated with greater short-term mortality following coronary revascularization, mainly driven by older age and greater prevalence of

comorbidities, while long-term outcomes after coronary revascularization is similar between men and women, or even better in women as compared with men. Sex difference in coronary disease burden, coronary physiology, response to diagnostic testing, and clinical management may play an important role in the observed difference in clinical outcomes between men and women. Further studies are needed to elucidate role of gender in determining short-term and long-term outcome following coronary revascularization.

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Chapter 14
Sex Differences in Cardiac Arrhythmias

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Introduction

The knowledge of pathophysiology, diagnosis and treatment of cardiac arrhythmias has evolved and grown significantly over the past seven decades [1]. However, the recognition and understanding of sex differences in cardiac arrhythmias has not kept pace with these major developments. This is likely attributable to the somewhat complex and heterogenous nature of cardiac arrhythmias, and a significant need for more sex-based studies of specific cardiac arrhythmias. For example, atrial fibrillation (AF) remains one of the most commonly encountered arrhythmias in clinical practice, however men and women are affected differently and likely require different treatment. Landmark randomized control trials promoting primary prevention implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT) were almost exclusively performed in men. Contemporary studies and retrospective analysis of older trials have suggested that outcomes with cardiac electronic implantable devices are different in men and women. Understanding the mechanisms leading to these sex difference is a complex task and requires further investigation. This chapter provides a contemporary review of sex differences for each category of cardiac arrhythmias, with the goal of providing a framework for clinical practice.

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Sex Differences in the Normal Electrocardiogram (EKG)

Electrocardiography is an essential clinical tool for diagnosis and treatment of arrhythmias. Women have more robust sinus node function with higher sinus heart rates and shorter sinus node recovery times compared to men [2]. They also exhibit shorter PR intervals and QRS durations on the surface ECG. Men have longer P wave durations compared to women after adjusting for heart rate [3]. The differences in these basic electrophysiological properties may also persist into older age [2]. Sex differences are also observed in ventricular repolarization, which manifests as the QT interval. Women are more likely to have longer corrected QT intervals (QTc) independent of autonomic tone and menstrual cycle variability [2, 4]. Although men have longer QRS durations than women, shorter QT intervals in men may be explained by shorter durations of the early part of repolarization. Men are also more likely to demonstrate early repolarization on the ECG as compared to women [5], potentially explained by differential hormonal effects on the cardiac ion channels responsible for the early repolarization phase [6].

Supraventricular Tachycardia (SVT)

Atrial Fibrillation and Atrial Flutter

Epidemiology

Atrial fibrillation (AF) and atrial flutter (AFL) are the most common arrhythmias observed in clinical practice. Stroke, hospitalization, and loss of productivity are the major consequences of AF [7, 8]. The incidence of AF (per 1000 person-years) is reported to be between 1.6 and 2.7 in women and 3.8–4.7 in men [9, 10]. Accordingly, the lifetime risk of AF from the Framingham Heart Study at age 40 was higher in men (26.0% for men vs. 23.0% for women) [11]. The prevalence of AF continues to rise among both men and women. In a study investigating the global burden of disease from 1980 to 2010, there was not only an increase in overall burden, incidence, and prevalence of AF, but most importantly an increase in AF-associated mortality in both men and women (Fig. 14.1a) [12]. The estimated number of individuals with AF globally in 2010 was 33.5 million. The age-adjusted mortality for women was consistently higher as compared to men from 1990 to 2010 (Fig. 14.1b) [12], and it was almost entirely attributed to higher mortality among women diagnosed with AF in low and middle income (LMIC) countries. There are likely to be a variety of factors that could explain this disturbing trend, which needs urgent investigation. As mortality from communicable diseases is reduced in the LMIC nations, rates of non-communicable conditions such as cardiovascular disease are likely to rise further, with major implications for sex-specific AF burden.

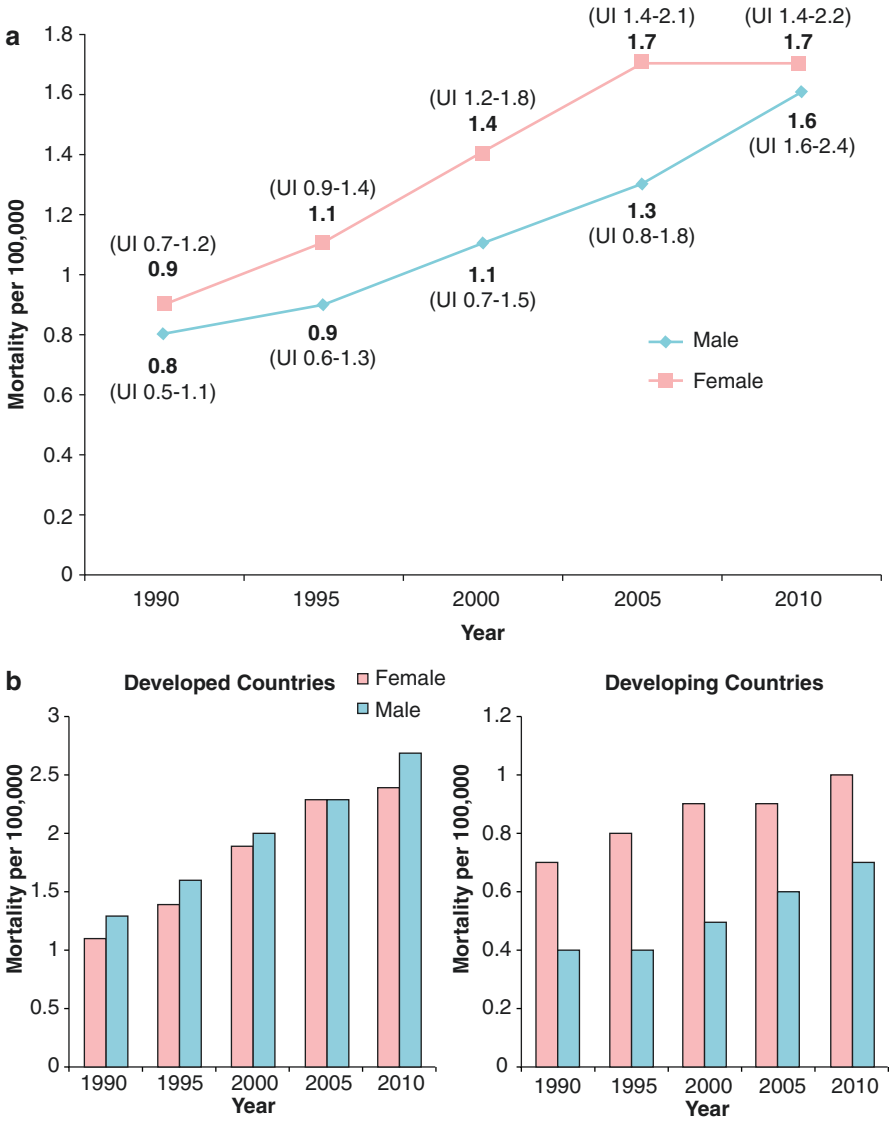

Fig. 14.1 Sex differences in mortality associated with atrial fibrillation (AF). (**a**) Male and female estimated age-adjusted mortality (per 100,000 population) associated with atrial fibrillation from 1990 to 2010. UI indicates uncertainty interval. (**b**) Mortality associated with AF stratified by sex and type of region (developed vs. developing). (Reprinted from Chugh et al. *Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 Study*) [12]

Presentation and Pathophysiology

There is a wide variety of symptoms reported by patients with AF/AFL that include palpitations, shortness of breath, exertional intolerance, chest pain, lightheadedness, syncope, anxiety/unease or fatigue. Women often present differently than men. In a European study by Lip et al., women with AF were more likely to present with palpitations and anxiety and more likely to be treated with a rate-control strategy as compared to men. Heart failure with preserved ejection fraction (EF), hypertension, valvular heart disease, lower quality-of-life scores, and older age were also more likely in women than in men presenting with AF [13]. Coronary artery disease and chronic obstructive lung disease may be more prevalent in men than in women with AF [14]. For reasons that may be related to cultural or sex bias, women with AF are diagnosed later in their disease course than in men, and they may be referred less frequently to specialized centers or clinics for the management of their arrhythmia [15].

Differences in left atrial and pulmonary vein size and function as well as levels of sex hormones may potentially contribute to the sex differences observed in AF. Left atrial enlargement (LAE) is associated with incident and recurrent AF [16]. In an analysis of over 2500 patients from the AFFIRM trial, increased left atrial diameter was more frequently observed in women and was an independent predictor of death in women as compared to men [17]. From these studies, it is difficult to ascertain whether LAE precedes or is a consequence of AF. Sex hormones may play a role in the pathogenesis of AF via modulation of left atrial physiology [18]. In a review of the Framingham Heart Study cohort of men with AF, there was a significant association between testosterone and estradiol levels, and incident AF [19]. The potential mechanisms may include detrimental alterations of metabolic status, potentiation of atherosclerosis, and atrial remodeling in addition to the molecular pathways mentioned above. However, the hormonal milieu as it pertains to arrhythmogenesis may be more complex.

Management and Outcomes

Thromboembolic stroke is the most devastating complication of AF, and has been implicated in at least 25–30% of all ischemic strokes [20]. Retrospective analyses have consistently demonstrated that female sex, especially in the setting of other risk factors, is associated with a higher risk of thromboembolic events as compared with male sex [21, 22]. For this reason, the current United States and European guidelines advocate for the use of the CHA_2DS_2-VASc risk scoring system to assess thromboembolic risk in patients with AF with inclusion of sex as a risk factor [23, 24]. Although the guidelines recommend anticoagulation for women in the setting of at least one other risk factor, rates of anticoagulant prescriptions appear to be lower in women. In the Canadian Registry of AF (CARAF) study, elderly women with new-onset AF were less likely to be prescribed anticoagulation than elderly men and this difference was not explained by differences in stroke risk [25]. In fact, elderly women have been identified as a high-risk group in this context [21, 26]. A meta-analysis of randomized trials with the newer oral anticoagulants demonstrated similar efficacy between men and women [27].

Currently utilized risk scores for bleeding complications associated with anticoagulants, have not included sex as a risk factor [28]. Bleeding rates among women who are on anticoagulants may be similar or possibly lower as compared to men. In a study of over 13,000 patients, the risk of major bleeding while on warfarin therapy for AF was comparable between males and females [21]. In another study, women treated with warfarin therapy for AF had lower rates of major bleeding as compared to men. There was no difference in the time in therapeutic range for warfarin between the two sexes [29]. Bleeding rates with administration of the newer oral anticoagulants appears to be similar among men and women [27].

Percutaneous left atrial appendage occlusion devices lower stroke risk in patients with AF who are intolerant to oral anticoagulation. However, comparisons of outcomes between men and women are sparse. In a recent meta-analysis of the Watchman™ device, there was a trend (not statistically significant) toward a lower hazard ratio (favoring the device) for men in comparison to women [30].

Managing patients with AF requires a strategy of rhythm or rate control. Overall, women are less likely to receive rhythm control compared to men [13]. Also, electrical cardioversion is used more frequently in men than women [31]. When a rhythm control strategy is employed, women who are prescribed antiarrhythmic drugs may be at higher risk for pro-arrhythmia than men. Female sex is associated with a significantly increased risk of polymorphic ventricular tachycardia in the setting of a prolonged QT interval (*torsades de pointes*) with the use of the class III antiarrhythmic sotalol [32]. Studies of the other class III antiarrhythmic drugs dofetilide and ibutilide demonstrate similar findings [33, 34]. Women constitute a majority of the cases of acquired long QT syndrome and *torsades de pointes* independent of other comorbidities [35]. It is possible that the longer intrinsic QT interval in women compared to men, predisposes women to a higher incidence of pro-arrhythmia from QT-prolonging drugs. Interestingly, the hormonal milieu during different time periods in the menstrual cycle may alter the risk of pro-arrhythmia in women treated with class III antiarrhythmic drugs, and cyclical variations in the QT interval in women may have implications for treatment and research in this area [36].

For patients with symptomatic paroxysmal AF refractory to at least one antiarrhythmic medication, catheter ablation for AF as a rhythm control strategy, is a class I recommendation [23]. Women with AF may be referred for catheter ablation later than men, [15, 37]. Success rates of catheter ablation for AF may also vary between the sexes. It has been well documented that catheter ablation for paroxysmal AF provides better long-term arrhythmia-free survival as compared to ablation for persistent or long-standing persistent AF. There may be an association between delayed referrals and a preponderance of later stage (persistent or long-standing persistent) AF amongst women undergoing ablation; however, this remains to be confirmed. Studies comparing AF catheter ablation outcomes between men and women show mixed results. Catheter ablation of AF in 221 consecutive patients did not show a significant difference in acute or long-term success rates in women as compared to men [37]. More contemporary data suggests the opposite. Female sex was associated with higher long-term recurrence rates after both radiofrequency and cryoballoon catheter ablation of AF [38, 39]. The largest randomized clinical trial comparing radiofrequency ablation to cryoballoon ablation for paroxysmal AF included 39%

women. There was no difference in long-term outcomes between the two techniques amongst all patients; however, stratification based on sex was not performed [40].

Complication rates associated with catheter ablation of AF/AFL may also be different between men and women. In a study evaluating outcomes of catheter ablation of AFL in 985 patients over 12 years, women had a significantly higher incidence of major and minor complications as compared with men [41, 37]. Overall, female sex is associated with a higher incidence of complications with catheter ablation of AF and is a predictor of complications in both univariate and multivariate analyses [42]. Recent studies demonstrate that women undergoing first time catheter ablation using either radiofrequency ablation or the cryoballoon technique had a higher incidence of in-hospital complications, especially access site bleeding and hematoma [38, 39]. The cryoballoon technique was used in about 20% of men and women in this study [40]. Women are consistently under-represented in AF catheter ablation trials and this needs to be addressed in future studies.

Another option for the symptomatic patient refractory to medical or catheter ablation therapy, is surgical ablation. In a study by Shah et al., women undergoing surgical ablation were generally older and had more heart failure than men but were similar to men in their rates of stroke, survival, and success over an 8-year follow-up period [43].

Clinical Implications

Treatment of AF/AFL requires a comprehensive and individualized approach to the patient. Men and women with AF/AFL differ in their symptoms, referral patterns, comorbidities, response to treatments, and outcomes. The contemporary approach to management of AF should therefore reflect the sex differences mentioned above (Table 14.1).

Atrioventricular Nodal Re-Entry Tachycardia

Atrioventricular nodal re-entry tachycardia (AVNRT) is the most common form of non-AF/AFL SVT, accounting for about 50% of all SVT cases [44]. Women are affected twice as often as men and exhibit a bimodal distribution, with women presenting at an earlier age than men [45, 46]. Sex differences in the basic electrophysiologic properties of the normal AV node provide clues to the mechanisms by which these differences arise [47]. Hormonal changes during the menstrual cycle in premenopausal women may impact the frequency of this condition [48, 49].

Although the success rates of catheter ablation for AVNRT have not been shown to be different between men and women, symptoms after catheter ablation may be quite different. Women may experience more symptoms (e.g., ‘heart skipping’) after ablation as compared to men, and are prescribed antiarrhythmic medications more frequently than men [50].

Table 14.1 Sex differences in atrial fibrillation (AF): clinical management

Clinical variable (the 5 R's)	Sex difference in women as compared to men	Management strategy
Recognition	More likely to be diagnosed later in the disease course. Less likely to be referred to a specialty clinic/center.	Extended-day Holter monitoring for diagnosis, burden, and rate assessment of AF if symptoms are suggestive of arrhythmia. Early referral to a specialized center or clinic once AF is diagnosed.
Rhythm control	Less likely to be considered for a rhythm control strategy. Less likely to be considered for electrical cardioversion. More likely to have pro-arrhythmia due to AADs.	Early consideration for electrical cardioversionInitiation of AAD while in sinus rhythm to assess baseline ECG parameters (including sinus heart rate and QT interval). Preference for use of class I AAD. Detailed medication and supplement reconciliation to avoid pro-arrhythmia from drug-drug interaction or non-cardiac QT prolonging medications. Consider initiation and titration of class III AAD (other than amiodarone) during the first half of the menstrual cycle for pre-menopausal women, under continuous cardiac monitoring.
Rate control	No significant differences.	Routine use of atrioventricular nodal blockade with beta-blockers and calcium channel blockers as first line therapy.
Reduction of stroke and bleeding risk	Higher risk of stroke. Possible lower risk of bleeding.	Counseling on stroke risk as it pertains to women with one additional risk factor. Assessment of stroke and bleeding risk with risk scores especially for elderly women. Appropriate dosing of anticoagulants. Consideration for left atrial appendage occlusion device implantation in appropriate candidates.
Referral for catheter ablation	Less likely to be referred for catheter ablation. More likely to have complications from catheter ablation.	Early referral to a specialized clinic/center, especially if refractory to AAD. Careful peri-operative management of vascular access sites and anticoagulation dosing regimens. Early referral for catheter ablation of atrial flutter.

AAD anti-arrhythmic drugs

Wolf-Parkinson-White Syndrome (WPW) and Atrioventricular Reentry Tachycardia (AVRT)

Tachycardias related to WPW syndrome and accessory pathways (AP) occur more frequently in men than in women [51, 45]. Interestingly, the location of accessory pathways may be different among men and women. In a study by Hsu et al. investigating AP location by age and sex in 282 consecutive patients, significantly more women than men had a tricuspid annular AP [52]. Liu et al. studied manifest AP conduction (presence of pre-excitation/delta wave) and concealed AP conduction

(absence of pre-excitation/delta wave) in 567 patients undergoing electrophysiology study. Manifest AP conduction was seen more often in men; however, there was equal distribution of concealed APs among men and women [53].

Atrial Tachycardia (AT)

Atrial tachycardia, the least common of all SVTs, has a female preponderance [54]. The largest study of sex differences in focal ATs demonstrated that men were more likely to be older, have more cardiovascular comorbidities, and have a lower incidence of other SVTs than women. The anatomic origin of AT and acute and long term success rates after catheter ablation were no different among men and women [55].

Clinical Implications

Approaches to the treatment of SVT in men and women should be tailored to the sex differences observed. A detailed history and review of triggers for SVT should be obtained especially in pre-menopausal women who may have a cyclical trend of tachycardia throughout the ovarian cycle. If electrophysiology study and catheter ablation is pursued, a strategy of scheduling the patient during a period of the ovarian cycle where SVT occurs more frequently may be useful. AVNRT will be the most common cause of SVT in women and a discussion of risk and benefits of catheter ablation should be tailored to include the risks of ablation for AVNRT (i.e., risk of AV block) more so than other arrhythmias. In line with sex differences in SVT, post-ablation counseling should include the possibility of recurrent symptoms that may not be related to SVT, and which may require extended monitoring to characterize the heart rhythm during symptoms.

Ventricular Arrhythmias (VA)

Ventricular Tachycardia in Structurally Normal Hearts

Monomorphic ventricular tachycardia (MMVT) and frequent ventricular premature beats (VPBs) in the absence of ventricular myocardial pathology constitutes the group of idiopathic ventricular arrhythmias. Overall, they represent about 10% of ventricular arrhythmias in clinical practice [56]. These arrhythmias may originate in the right and left ventricular outflow tracts, tricuspid and mitral annuli, mid-myocardial or sub-epicardial areas, or be of fascicular or papillary muscle origin. Tanaka et al. studied 625 consecutive patients with idiopathic VAs with equal numbers of male and female patients. Right ventricular outflow tract (RVOT) VAs occurred more frequently in women than in men. Men had a higher incidence of left ventricular outflow tract (LVOT), tricuspid and mitral annular, ventricular septal, and non-outflow tract VAs as compared to women. The preponderance of women with RVOT VAs was also observed in an analysis of the site of origin of VAs in

structurally normal hearts in over 700 patients [57]. In a survey of men and women with RVOT VAs, triggers for VAs were more likely associated with states of hormonal flux (pre-menstrual and peri-menopausal) rather than states of catecholamine access (exercise or stress) [58].

Fascicular ventricular tachycardia (FVT) is an idiopathic VA that involves the His-Purkinje system. Studies of FVT have been done almost exclusively in male patients, suggesting a much higher incidence of this type of idiopathic re-entrant VA in men as compared to women [59–61]. Conceptually, there is considerable overlap in the mechanisms of re-entry between FVT and AVNRT. Why re-entry in the AV node would be more likely in women and re-entry in the His-Purkinje system more likely in men requires further exploration. These findings provide an opportunity to investigate the role of sex and possibly sex hormones on normal His-Purkinje system function and the substrate for re-entrant arrhythmias.

There is a paucity of data comparing symptoms, burden, or treatment outcomes among men and women with idiopathic VAs. Catheter ablation remains the treatment of choice for patients with symptomatic or high burden VAs who are intolerant, refractory to, or defer medical therapy. One complication of frequent idiopathic VPBs, VPB-induced cardiomyopathy (CM), has been studied extensively over the years. Although the frequency, location of origin, lack of symptoms, and QRS duration of VPBs have all been implicated in VPB-induced CM, sex differences have not been described with this phenomenon [62].

The mechanisms of sex differences in idiopathic VAs are not well understood. At a cellular level, sex hormones may regulate ion channel expression, distribution, and function leading to differences in arrhythmogenesis [48, 63–65]. Whether autonomic nervous system differences play a role in the sex differences in idiopathic VAs is another area that requires further research.

Ventricular Arrhythmias in Structural Heart Disease

Ischemic Heart Disease

There are a limited number of studies that have investigated sex differences in sustained ventricular arrhythmias in patients with structural heart disease. By far the most common cause of structural heart disease globally is ischemic heart disease [66]. Overall, data from clinical trials evaluating outcomes with ICD therapy (either as primary or secondary prevention) are mainly driven by data from male cohorts. A comparison of men and women from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) showed that among the 1232 patients enrolled, less than 20% were women. Compared to men, women had a similar cumulative mortality at 2 years; however, the risk of appropriate ICD therapy for VT/VF was lower in women as compared to men [67]. In an analysis of sex differences in the Multicenter UnSustained Tachycardia Trial (MUSTT) a minority of women were included in the trial (14%) and they were less likely to have inducible sustained ventricular arrhythmias. Women were more likely to be older, have more heart failure, and have more recent infarcts as compared to men [68]. The sex differences in

the rate of appropriate ICD therapy may be greatest in those patients presenting with sustained monomorphic VT and those with inducible VT at electrophysiology study [69]. This suggests that arrhythmogenesis in ischemic cardiomyopathy may be different in men and women and warrants further exploration.

Women were also under-represented in the majority of catheter ablation trials of ventricular tachycardia related to structural heart disease. In an international registry of over 2000 patients referred for VT ablation with structural heart disease, women comprised only 13% of the patients [70]. A study by Baldinger et al. of patients referred for catheter ablation of VT over the past decade showed that women were on average younger than men at the time of referral and few women had structural heart disease. Of those with structural heart disease, a higher proportion of women was observed in the non-ischemic as compared to the ischemic group [71]. It is difficult to determine whether the sex differences identified are due to referral patterns or truly reflect a lower incidence of VT and ICD therapies in women due to physiologic differences in arrhythmogenesis among men and women with structural heart disease.

Non-Ischemic Dilated Cardiomyopathy (NIDCM)

This large subset of cardiomyopathies can be inherited or acquired. Lamin A/C gene mutations are one of the most common causes of familial dilated cardiomyopathy. An analysis of a multicenter cohort of 269 patients with Lamin A/C gene mutations supported a higher incidence of malignant ventricular arrhythmias in men as compared to women [72]. It is unclear if the trend toward a higher incidence of VT and ICD therapies in men is consistent across all non-ischemic cardiomyopathies. In a study of patients in Japan with NIDCM with ICD therapy, women and men had similar rates of appropriate ICD therapy and electrical storm during an average follow-up period of 33 ± 28 months [73]. As with ischemic CM, studies on catheter ablation for NIDCM have predominantly been done in men. In a recent analysis of long term outcomes from catheter ablation of NIDCM, the proportion of women was 20% [74]. Male sex was possibly associated with higher VT recurrence as compared to female sex but this was not statistically significant.

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D)

ARVC/D is an inherited disease characterized by progressive fibro-fatty replacement of ventricular myocardium [75]. A common complication and presentation of ARVC/D is ventricular arrhythmia or sudden cardiac death. The incidence of VAs in ARVC/D may be higher in men than in women. An analysis and follow-up of 301 patients with confirmed ARVC/D (58% male) showed that male sex was a risk factor for ventricular arrhythmias at a follow-up period of up to 5.8 years [76]. Strenuous exercise has also been associated with higher arrhythmic risk and it is possible that the sex differences seen are partly due to higher prevalence of strenuous or athletic activity in young men as compared to young women [77]. It is interesting to note in this cohort that no subject had an arrhythmic event before the age

of 16 years, which may potentially implicate sex hormones in the pathogenesis of life threatening ventricular arrhythmias in ARVC/D.

Sarcoid Cardiomyopathy

Up to 25% of patients with systemic sarcoidosis can also have cardiac involvement. Globally, the highest prevalence of disease is in middle-aged Northern European and African American women. Familial clustering is not uncommon and suggests a genetic component in certain cases [78]. VAs may be the first presenting sign of systemic disease with cardiac involvement or isolated cardiac sarcoidosis. Although sex differences are apparent in the epidemiology of sarcoidosis, differences in the incidence and outcomes of VAs in males and females have not been described. Interestingly, although there is a higher prevalence of disease among women, studies of catheter ablation of VAs due to cardiac sarcoid mostly report findings in male subjects [79, 80]. Whether female sex protects against scar-related arrhythmogenesis in this progressive disease is an area that would require further research in large multi-center analyses.

Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy is the most common of all the inherited cardiomyopathies and is characterized by myocardial hypertrophy and disarray of the fibers, as well as myocardial fibrosis. Men and women are equally affected [81]. VAs in HCM are usually due to polymorphic ventricular tachycardia or VF and less likely to be MMVT. HCM is the most common cause of SCD in the young, especially male athletes. It appears that once HCM is diagnosed, the risk of SCD is similar among men and women. In a study of 969 consecutive HCM patients from Italy and the U.S., female patients were noted to be on average older, have more outflow tract obstruction, and have more symptoms than men. Women had a poorer prognosis with more rapid progression toward death from heart failure or stroke. SCD and mortality was similar among men and women with HCM in this group [82].

Familial Arrhythmia Syndromes

Long QT Syndrome (LQTS)

Long QT syndromes are inherited genetic disorders caused by mutations in genes encoding ion channels in cardiac myocytes, and manifest more commonly in women. As in the overall population, women with long QT syndrome (especially LQTS1 and LQTS2) have on average longer QT intervals than their male counterparts [83]. There is a significant association between longer QT interval duration and risk for cardiac events in patients with LQTS, that may explain the difference in cardiac events between adult men and women with this disorder. One of the largest studies

of the familial long QT syndrome supports an age-related difference in the risk of cardiac events among men and women that hints at a possible role of sex hormones in arrhythmic risk. Pre-pubertal boys have a higher risk of cardiac events than girls, but the reverse is true in adulthood, with women showing a higher risk of cardiac events after puberty. Interestingly, this was seen in all cohorts including probands, phenotype and genotype positive family members, and LQT1 gene carriers [84]. Changes in the hormonal milieu after puberty can possibly reduce the relative QT interval in men and may mitigate arrhythmic risk. On the other hand, hormonal changes in women may not affect or may prolong the relative QT interval after puberty. Moreover, the bradycardic effect on prolongation of the QT interval is attenuated in men as compared to women [85]. The complex interplay of sex hormones with repolarization currents on a molecular level, and the relevance to clinical outcomes in men and women with LQTS are areas that require further investigation.

A strategy toward a more aggressive preventative approach for pre-pubertal boys with LQTS may be warranted in clinical practice. Pharmacotherapy may be de-escalated later in life given that arrhythmic risk may be reduced in adult males. However, the same may not be true of women who may have a higher lifetime risk of cardiac events than men, in part due to less QT interval shortening after puberty, and more hormonal effects on QT prolongation during the ovarian cycle. In addition, with advancing age, there may be increased use of over-the-counter or prescription QT-prolonging medications that disproportionately increase the arrhythmic risk in women compared to men. The sex differences observed in the arrhythmic risk of LQTS patients may have a significant clinical impact in the evaluation and treatment of this patient population.

Brugada Syndrome (BrS)

An experience of over 300 patients with BrS reported a preponderance of male subjects with certain clinical characteristics that are different from women. A greater rate of spontaneous type-1 Brugada-pattern electrocardiograms is seen in men as compared to women. It also appears that men experience syncope, aborted sudden death, and documented ventricular fibrillation (VF) more frequently than women with BrS [86]. The exact mechanism of the differences observed in men and women with BrS is unclear. The genetics of BrS have not been shown to be a factor in sex differences, with no difference in the distribution of specific gene mutations between men and women. Ion channel density and sex-related hormonal effects may play a role [87, 65].

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

CPVT is characterized by ventricular arrhythmias arising during high catecholamine states in the context of a normal baseline ECG and structurally normal heart. It is caused by mutations in genes encoding proteins that affect calcium handling

in the cardiac myocyte [88, 89]. Limited data exist to suggest sex differences among patients with CPVT. Young men with cardiac ryanodine receptor (RYR2) mutations were shown to have a higher risk of cardiac events than young women in one study [90]. A study on the genotypic and phenotypic heterogeneity among referrals for CPVT suggested that men, as compared to women, were more likely to be positive for the RYR2 mutation. Since the majority of the RYR2 mutation-negative patients were women, research focused on sex-specific gene discovery has the potential to improve clinical management [91].

Short QT Syndrome (SQTS)

SQTS is a rare familial arrhythmia syndrome characterized by accelerated repolarization, with most patients having a corrected QT interval of ≤340 milliseconds (ms) [92]. The prevalence of a short QT interval in over 18,000 subjects 14–35 years of age (using a threshold of ≤330 ms) was 0.2% [93]. The true prevalence of the SQTS is unknown. To date, gene mutations in five different genes have been associated with SQTS, with most of these reported in a familial setting. Sex differences in the duration of the QT interval and repolarization are discussed in other arrhythmic syndromes mentioned above. The possibility of a protective effect of longer baseline QT interval duration in women with SQTS is an interesting hypothesis. However, it is likely that if, in fact, sex differences exist among patients with SQTS, the rarity of this disorder would make it difficult to study this aspect.

Early Repolarization Syndrome (ERS)

ERS is characterized by J-point and ST-segment elevation in at least two contiguous ECG leads in the setting of a clinical event such as VF or sudden death. The ECG pattern of early repolarization (global, lateral, or inferior lead involvement) may change the cardiac risk profile for the individual asymptomatic patient [94]. Male sex is strongly associated with the ER ECG pattern and this pattern is less prevalent with increasing age [95, 96, 94, 97]. There may be some overlap with BrS; hence, both genetic arrhythmia syndromes have a male preponderance, especially in the rates of cardiac events.

Implantable Cardioverter-Defibrillator Therapy Utilization and Outcomes

There has been considerable research into the sex differences among recipients of primary or secondary prevention ICDs. Sex disparities have been described in the utilization of ICD therapy in those patients with structural heart disease that are at

risk for or have had VAs or SCD. Curtis et al. analyzed ICD utilization in a Medicare population and demonstrated that men were more likely to receive an ICD than women [98]. Mortality was no different among men and women with primary or secondary prevention ICDs. As mentioned, the major primary prevention ICD trials were not adequately powered to detect sex-related differences in outcomes. Meta-analyses of primary prevention ICD trials have shown mixed results. In a meta-analysis of five major primary prevention ICD trials with over 3000 men and 900 women, a statistically significant reduction in mortality was reported in men with heart failure and reduced LV ejection fraction (LVEF) (hazard ratio [HR] 0.78) but not in women (HR 1.01) [99]. Another meta-analysis with a larger proportion of women and inclusion of a cardiac resynchronization trial (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure—COMPANION) demonstrated similar mortality rates among men and women with ICDs; however, there was less appropriate ICD therapy in women as compared to men [100]. This suggests that mortality in women with heart failure and reduced LVEF may be driven more by non-arrhythmic death. The relative contributions from arrhythmic and non-arrhythmic death in overall mortality in women with heart failure may also change based on the disease substrate. A recent randomized controlled trial in patients with non-ischemic cardiomyopathy, heart failure, and LVEF ≤35% showed no significant overall mortality benefit with prophylactic ICD implantation, especially in older patients [101]. Women comprised about 30% of the control and treatment groups and all patients were on guideline-directed medical therapy. Sex differences were not observed in this study, but the study was likely underpowered for this analysis. It is likely that multiple factors contribute to sex differences in utilization and outcomes of ICD implantation in structural heart disease. These may include differential effects of sex hormones on the underlying substrate, co-morbid associations, clinical referral patterns and the net clinical gain of ICD implantation beyond guideline-directed therapy in women vs. men. Future studies should incorporate a larger proportion of women to address this issue.

Sudden Cardiac Arrest (SCA)

The burden of SCA in men vs. women to have changed over time. In older analyses, men appeared to be three times more likely to experience SCA than women [102]. Contemporary data suggests that the sex gap has narrowed [103, 104, 102]. One possible explanation may lie in the declining proportion of SCA patients presenting with VF observed in the past two decades [105, 106] with a relative increase in the subgroup presenting with pulseless electrical activity (PEA), a manifestation that is more common in women. A report from the ongoing prospective Oregon Sudden Unexpected Death Study (Oregon-SUDS) confirmed that female sex is independently associated with PEA [107]. Conversely, the lower proportion of VF vs. PEA in contemporary studies may be explained by lower rates of mortality from coronary artery disease, and higher mean LVEF in women with OHCA as compared to

men [108]. However, women who present with a shockable rhythm like VF may have improved resuscitation and survival rates compared to men [109], resulting in equivalent survival rates despite a higher proportion of PEA in women [110].

SCA-related sex differences may also vary by age. A nationwide study of young patients (1–35 years-of-age) with sudden cardiac arrest in Denmark suggests that the incidence of SCA in young men is twice that of young women. There was no difference in the rates of explained and unexplained SCA, arrhythmic death, and death during sleep. In the 35–44 year age group, women had higher rates of unexplained SCA compared to men [111]. In the 35–65 year age group, women were just as likely to experience warning symptoms that preceded SCA compared to men [112]. Older age may diminish the sex differences regarding traditional CAD risk factors and underlying coronary disease [113]. Furthermore, non-coronary, structural causes of SCA due to VF may be more prevalent in women and these may include valvular heart disease, non-familial dilated cardiomyopathy, inflammatory cardiomyopathies, and myocarditis. Overall, women were significantly less likely than men to have a diagnosis of LV dysfunction or coronary artery disease before SCA [114]. Improvements of SCA risk stratification for prevention of SCA may have even higher importance for women.

Conduction System Disease

Sex differences have been described in various bradyarrhythmias requiring permanent pacing. In retrospective and prospective analyses, women have a higher incidence of sinus node dysfunction and men a higher incidence of AV node dysfunction [115]. Women are more likely to receive single chamber pacemaker systems. The differences in selection of dual vs. single chamber pacemakers may not be completely explained by a higher incidence of sinus node dysfunction in women. A retrospective analysis of over 30,000 patients implanted with a permanent pacemaker demonstrated that women on average presented at an older age than men [116]. A more recent detailed study by Nowak et al. also showed similar trends with regard to indications for permanent pacing and type of system used [117]. It remains unclear whether physician bias toward single chamber systems in the elderly plays a role in these observed differences.

Conclusions

It is important for the practicing clinician to recognize the existence, as well as specific nature of sex differences that are described for individual types of cardiac arrhythmias. A summary of the sex differences reported in the various cardiac arrhythmias is shown in Fig. 14.2. Future clinical trials should be powered to detect sex differences in treatments and outcomes of cardiac arrhythmias and device-based

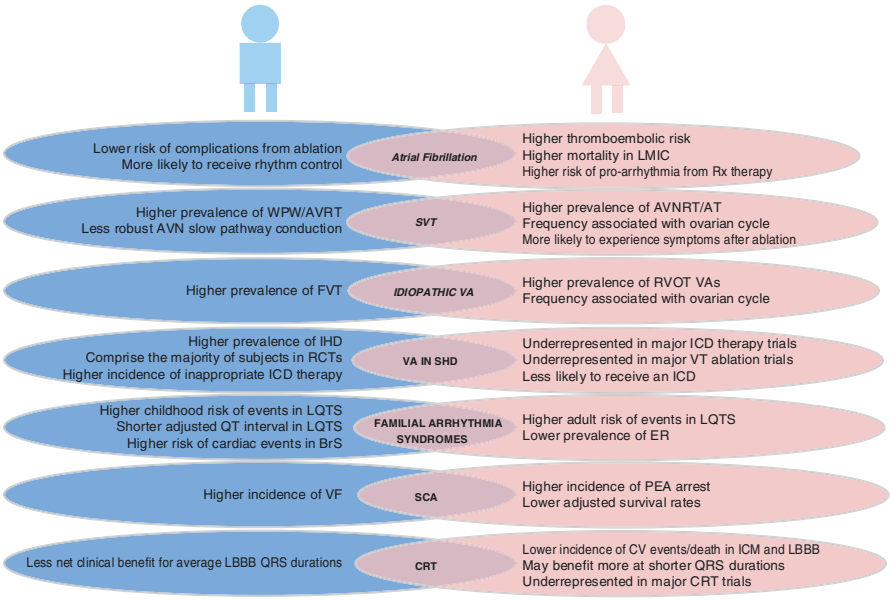

Fig. 14.2 Sex differences in cardiac arrhythmias - Overview. *VA* Ventricular arrhythmia, *LMIC* lower and middle income countries, *AVNR*T AV node re-entrant tachycardia, *SVT* supraventricular tachycardia, *AT* atrial tachycardia, *RVOT* right ventricular outflow tract, *VA* ventricular arrhythmia, *ICD* implantable cardioverter defibrillator, *VT* ventricular tachycardia, *LQTS* long QT syndrome, *ER* early repolarization, *PEA* pulseless electrical activity, *SCA* sudden cardiac arrest, *CV* cardiovascular, *ICM* ischemic cardiomyopathy, *LBBB* left bundle branch block, *CRT* cardiac resynchronization therapy, *WPW* Wolf-Parkinson-White, *AVRT* atrioventricular re-entrant tachycardia, *FVT* fascicular ventricular tachycardia, *SHD* structural heart disease, *IHD* ischemic heart disease, *BrS* Brugada syndrome, *VF* ventricular fibrillation

therapies, especially those involving catheter ablation for VAs and implantation of the primary prevention ICD. Women and men presenting with cardiac arrhythmias warrant an individualized, sex-specific approach to evaluation and treatment.

Disclosures None.

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Chapter 15
Gender Differences in Atrial Fibrillation: Incidence, Mechanistic Basis of the Differences and Treatment Options

Naga Venkata K.C. Pothineni and Srikanth Vallurupalli

Introduction

Atrial fibrillation (AF) is a common arrhythmia affecting more than 33 million people worldwide [1]. Atrial fibrillation occurs when atrial electrical remodeling (pulmonary vein triggers, multiple wavelets or rotors) initiates abnormal atrial impulses, these impulses become sustained in the face of atrial remodeling (atrial fibrosis due to factors such as hypertension, coronary artery disease, heart failure, mitral valve disease and obstructive sleep apnea) [2]. Its prevalence continues to increase, reflecting an aging population as well as an increase in risk factors known to cause AF. A wealth of evidence has improved our ability to diagnose and effectively treat AF. An intriguing aspect of this common disease - gender based differences is well recognized but poorly understood. We will explore the accumulating evidence suggests that significant differences exist in incidence, pathogenesis and response to treatment between men and women in this chapter.

Differences in Atrial Electrophysiology in Normal Men and Women

Gender based differences in normal cardiac electrophysiology have long been recognized and influence susceptibility to arrhythmias [3]. Women have higher resting sinus heart rates likely secondary to differences in physical conditioning,

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autonomic and hormonal influence [4]. Women also have enhanced AV node conduction and shorter AV node refractory periods compared with men [5]. In response to rapid atrial pacing, the degree of shortening of atrial effective refractory period was significantly less in premenopausal women compared to post-menopausal women and age matched men [6]. Women have narrower QRS complexes and longer QT and corrected QT (QTc) intervals than men which is probably related to differences in estrogen and testosterone levels [3]. Differences in cardiac ion channel expression exist between men and women. Ambrosi et al. investigated the mRNA expression of 89 ion channel subunits, calcium handling proteins, and transcription factors important in cardiac conduction and arrhythmogenesis in the left atria and ventricles of failing and non-failing human hearts of both genders [7]. In the left atrium, gender-specific analysis showed lower expression levels in transcripts encoding for Kv4.3, KChIP2, Kv1.5, and Kir3.1 in both non-failing and the failing female heart compared with the male heart. Gender differences in autonomic control of the cardiovascular system have been described as well. Women tend to have higher degree of parasympathetic activation compared with men who have a higher sympathetic tone [8]. Differences in electrophysiological properties also translate into epidemiological differences in arrhythmias. It is well known that men are more susceptible to the development of atrial fibrillation (AF), whereas women have higher incidence of long-QT syndrome and drug-induced torsades de pointes [9].

As a result of these differences, some arrhythmias are more common in women than men. For example AV nodal reentrant tachycardia is far more common in women while atrial fibrillation and atrioventricular reentrant tachycardia is more common in men [3].

Mechanisms of Gender Differences in Incidence of Atrial Fibrillation

AF results from abnormal electrical impulses that are sustained in the presence of an abnormal atrial substrate. Though many different pathophysiological mechanisms of AF have been described, the most common initiator appears to be abnormal electrical impulses from pulmonary vein muscle sleeves [2]. In animal studies, spontaneous beating rates were much higher in pulmonary vein sleeves of male rabbits compared to female rabbits [10]. Similarly, delayed after depolarizations were significantly higher after exposure to isoproterenol in male rabbits. In human subjects, gender based differences in atrial electrical substrate were investigated in two studies with varying results. In a large study of patients with paroxysmal atrial fibrillation referred for ablation, women appeared to have a higher number of non-pulmonary vein triggers [11]. However, in this study women had a much higher incidence of mitral valve disease. This along with other confounders suggest that left atrial remodeling was far more advanced in women in this study compared to men. In a smaller but better matched study, there were no differences in pulmonary vein or atrial substrate electrophysiology in men and women [12].

Men develop AF at a younger age than women. Though this may reflect a higher incidence of risk factors such as coronary artery disease, protective effect of hormones such as estrogen in pre-menopausal women play an important role [13]. Estrogen has important anti-inflammatory and vascular protective factors. Indeed the decrease in estrogen after menopause may explain why women develop AF on an average of 10 years after men.

While studies have shown a significant increase in AF in individuals with a family history of AF, the effect of sex on this predisposition is unknown. Most studies on familial risk of AF found no significant gender based difference except a large Swedish registry that found the odds of AF in mothers with patients with AF were much higher than the odds in their fathers [14, 15].

Of the genetic variants studied, the 97 T polymorphism in KCNE5 gene located on the X chromosome has been found to be protective against AF [15]. Since women have two X chromosomes, this has been postulated to explain the higher incidence of AF in men.

Gender Differences in Incidence and Clinical Presentation of AF

In the Global Health Burden study, atrial fibrillation was almost twice more common in men than in women (prevalence 570 vs. 360/100,000) [1]. Between 1990 and 2010, this disparity has persisted in both prevalence and incidence [16]. However, since women live significantly longer than men, the total number of women alive with AF outnumbers the number of men among those above 65 years of age.

Clinical Presentation

Significant differences in clinical symptomatology of AF and baseline characteristics exist between men and women. In the large prospective ORBIT- AF (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry, women with AF experienced more symptoms, more functional impairment, and worse quality of life in comparison with men [17]. Women reported a higher frequency of AF related symptoms such as palpitations, exertional dyspnea, effort intolerance, lightheadedness, dyspnea at rest, fatigue, and chest discomfort. Women with AF were older (77 vs. 73 years; $p < 0.001$) and had lower prevalence of coronary disease and sleep apnea compared with men. Similarly, in the Euro Observational Research Program on Atrial Fibrillation, women experienced a significantly higher rate of palpitations (80.2% vs. 68.5%, $P < 0.0001$) and fear and anxiety (14.6% vs. 10.5%, $P = 0.0007$), compared with men [18]. Women also experienced more dyspnea and general non–well-being than men, although these

differences were not statistically significant. Health status scores were significantly lower for women overall, specifically for the psychological and physical domains. In both these studies, women with AF had a higher prevalence of heart failure with preserved ejection fraction. Similar patterns of AF related symptoms were reported in the PREFER (Prevention of thromboembolic events European Registry in AF) as well. In this analysis of 7243 patients, 95% of women with AF were symptomatic compared to 90% of men [19]. Most common symptoms were fatigue, dyspnea and palpitations; these were more frequently reported by women. Among patients seeking emergency medical care, women are more likely to present with atypical symptoms such as weakness and fatigue, have longer duration of symptoms and are more likely to be hospitalized for AF management [20]. The reasons why women develop more symptoms with AF are unknown. A possible explanation could be the presence of more advanced atrial fibrosis and dysfunction at the time of onset of AF (both by virtue of increased age and increased incidence of hypertension). The loss of atrial contribution to cardiac output in AF may result in worse symptoms.

Gender Differences in Treatment of AF

Management of AF includes measures to resolve symptoms (either by controlling ventricular rate or achieving sinus rhythm), prevent adverse cardiac remodeling and reduce the risk of stroke.

Management of AF (Fig. 15.1)

Management of AF can be broadly classified into a rate control and rhythm control strategy. Multiple randomized trials over the past decade have demonstrated no significant difference between rate control and rhythm control strategies for AF [21–24].

Gender Differences in Rate Control of AF

Important gender based differences in rate control have been recognized with rate control more commonly used in women than in men. In the EORP-AF registry, women with symptomatic AF were more likely to receive rate control therapy compared to men (33.1% vs. 26.0%, p = 0.002) [18]. Use of digoxin as a rate control agent was significantly higher in women (25% vs. 19.8%, p = 0.005) while there was no difference in prescription rates of beta blockers or calcium channel blockers. In the ORBIT-AF registry, women were less likely to be receiving

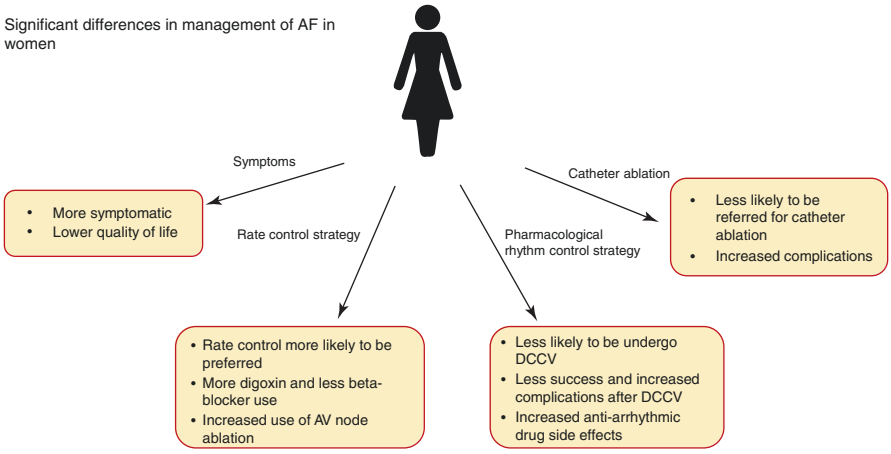

Fig. 15.1 Currently used management strategies appear to be more harmful in women reflecting the need for studies that focus on the pathophysiology behind these gender based differences. *DCCV* direct current cardioversion; *AV node* atrioventricular node

β-blocker therapy (62.0% vs. 65.5%, $p < 0.001$) and were more likely to receive digoxin (24.6% vs. 22.6%, $p = 0.02$) [17]. The increased use of digoxin in women has raised concerns since previous studies have demonstrated worse cardiovascular outcomes with long-term use of digoxin in patients with AF. For example, in the ROCKET-AF trial, digoxin was used in 42% of female patients compared to 38% of males and its use was associated with increased all-cause mortality (HR 1.17; 95% CI 1.04–1.32), vascular death (HR 1.19; 1.03–1.39) and sudden death (HR 1.36; 1.08–1.70) [25].

The reasons for this difference in treatment strategies is unknown. The increased incidence of atypical symptoms such as fatigue and dyspnea in women may play a role. In the EuroHeart survey of greater than 5000 patients with AF, there was no gender based difference in choice of rate versus rhythm control in those with typical AF symptoms [26]. However, in patients with atypical symptoms, women received rhythm control less frequently (39% vs. 51%, $p < 0.001$).

Gender-specific differences in the pharmacodynamics and pharmacokinetics of cardiovascular drugs exist. Women have higher plasma concentrations of beta blockers [27] and verapamil [28] compared with men. Thus, an excess initial dose of medication may result in side effects and these drugs may be discontinued and substituted with digoxin. However, these differences have not been systematically studied. This intolerance to rate control medication is indirectly supported by the increased use of invasive and non-pharmacological rate control measures in women. In the contemporary ORBIT-AF registry, women had significantly higher rates of AV nodal ablation and pacemaker implantation (adjusted HR 1.97, 1.30–2.97) compared with men [17].

Gender Differences in Rhythm Control of AF

Gender based differences in rhythm control strategies (anti-arrhythmic medications, cardioversion and ablation) also exist.

Cardioversion and Anti-Arrhythmic Drug Use

Electrical cardioversion is less often used in women and when used is complicated by less success and higher risk of complications. In the EORP-AF survey, rates of electrical cardioversion were 18.9% in women compared to 25% in men [18]. In the PREFER observational cohort of greater than 6000 patients with AF, women were more likely to receive pharmacological cardioversion while men had higher rates of electrical cardioversion [19]. In a nationwide analysis of inpatient cardioversions performed in the United States, electrical cardioversion use for AF was significantly higher in men compared to women (58.4% vs. 48.6%) [29]. When electrical cardioversion is used, rate of AF recurrence appears to be higher in women [30].

Women are more prone to bradycardic complications of electrical cardioversion. In the FinCV study, female sex was an independent risk factor for bradycardic complications after cardioversion for acute atrial fibrillation (OR 2.5; 95% CI 1.4–4.8, P = 0.004) [31]. While the cause of this is unknown, there are two possible explanations: (a) Higher plasma concentrations of AV nodal blocking agents at the time of conversion to sinus rhythm which may cause sinus bradycardia and (b) Worse sinus node function due to increased age, co-morbidities and atrial fibrosis. In a small study of patients who required pacemaker implantation after AF ablation, female sex correlated with a longer corrected sinus node recovery time (CSNRT) though sex was no longer a determinant in the multivariate analysis [32]. Women tend to have more adverse events related to anti-arrhythmic medications compared with men [3]. The most important adverse event is the occurrence of proarrhythmic side effects such as torsades de pointes which can result in sudden death. Women appear to have a higher risk of proarrhythmia with cardiovascular drugs [33].While women have longer QTc interval than men, that alone may not explain their increased risk of torsades. Due to unknown reasons, women appear to develop torsades at a QTc interval that does not cause arrhythmia in men [34]. Similar to rate control medications, bradycardia remains a significant complication of rhythm control medications. In the Fibrillation Registry Assessing Costs, Therapies, Adverse events, and Lifestyle (FRACTAL) registry, female sex was an independent risk factor for pacemaker implantation among patients taking amiodarone for AF [35].

Catheter Ablation

Catheter ablation has emerged as an important therapeutic strategy in the management of AF refractory to pharmacological therapy and has been shown to decrease morbidity and improve quality of life. Major societal guidelines recommend

ablation as a class I indication for paroxysmal AF and class IIa indication for persistent AF [36, 37]. The totality of available evidence suggests that women are referred late and less frequently for catheter ablation of AF compared with men. Among US Medicare beneficiaries, women are significantly less likely to be referred for catheter ablation than men (HR 0.65; 95% CI 0.63–0.68) even after adjusting for multiple confounding variables [38]. Women are also underrepresented in randomized trials of AF ablation, constituting about one-fifth of the study population [39]. When referred, women are older and have larger left atrial dimensions indexed to body surface area suggesting already advanced atrial substrate remodeling [11]. This advanced fibrosis may translate into a lower success rate of AF ablation though the evidence is inconclusive with some studies reporting similar success rates and others worse chance of success in women [11, 40–42].

Multiple studies have reported higher complication rates of AF catheter ablation in women. In a multicenter cohort of 3265 female patients, women more often had persistent AF, higher proportion of non-pulmonary vein triggers, lower ablation success rates and significantly higher complication rates, driven primarily by vascular complications [40]. In a nationwide analysis of AF ablation complications (close to 90,000 procedures), women suffered higher in-hospital complication rates than men (7.51% vs. 5.49%, $P < 0.001$) [43]. A more recent administrative database analysis of 7460 women undergoing AF ablation confirmed increased risk of complications, including vascular complications (2.7% vs. 2.0%; $P < 0.001$), hemorrhage (2.3% vs. 1.6%; $P < 0.001$), and cardiac perforation or tamponade (3.8% vs. 2.9%; $P < 0.001$) in the 30 days following ablation [41]. Overall, women had a trend towards increased risk for all-cause hospitalization compared with men (9.4% vs. 8.6%; $P = 0.07$).

The reasons for higher complication rates in women are unknown. Women tend to have smaller vessel diameters compared to men which may increase the risk of vascular injury from large caliber sheaths placed during ablation. Gender differences in pharmacokinetics of anticoagulants such as heparin used during ablation also exist [44]. During AF catheter ablation, women have higher activated partial thromboplastin times compared to men even when lower doses of heparin are administered [45, 46].

AF and Thromboembolism: Men Vs. Women

AF is a well-recognized risk factor for stroke. Significant gender differences in AF induced stroke risk have been described [45–47]. In the prospective Swedish atrial fibrillation cohort study of 182,678 patients with AF, female gender was an independent risk factor for stroke [HR 1.17; 95%CI 1.11–1.22] even after adjusting for multiple confounding variables [45, 46]. This increased risk in women is reflected in the inclusion of gender in the widely used CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled]-Vascular disease, Age 65–74, and Sex category [female]) for stroke risk prediction. Several factors including differences in baseline risk factors, differences in cardiac remodeling and coagulation patterns likely influence this increased risk [48].

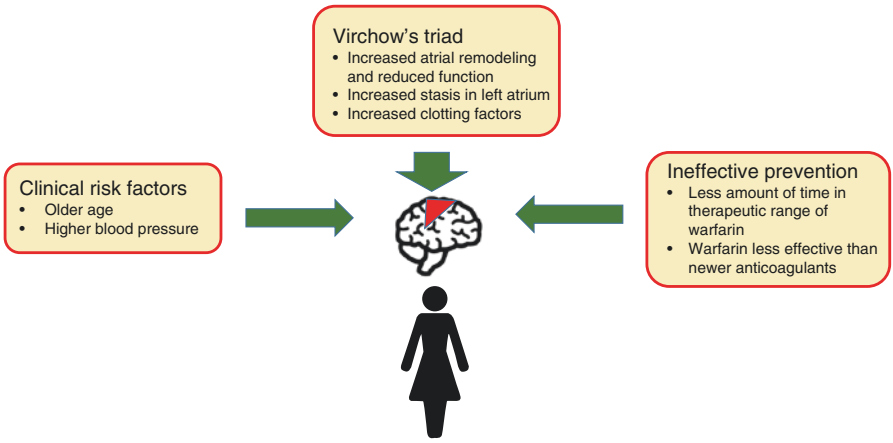

Fig. 15.2 Possible mechanisms behind increased risk of ischemic stroke in women with atrial fibrillation

Mechanism of Gender Based Differences in Stroke

Thrombus formation in the left atrium, mostly in the left atrial appendage is the predominant mechanism for AF related stroke. Propensity to thrombus formation in the body often reflects a combination of factors—abnormalities in vessel wall, increase in procoagulant factors and stasis of blood (the Virchow's triad) (Fig. 15.2). Limited evidence suggests that women with AF appear to develop a substrate that predisposes to stroke.

Increased Atrial Remodeling in Women

Limited available data suggests that women with AF have far greater atrial remodeling than men. Li et al. analyzed atrial tissue from men and women with long standing persistent valvular AF and showed that women have a significantly higher degree of fibrotic remodeling. This morphological difference was driven by differential expression of various fibrosis- related genes and proteins such as TGFβ, which were up-regulated in women [49]. In a sub analysis of the AFFIRM trial, female sex was significantly associated with increased left atrial remodeling [50]. Whether this is related to later age of onset of AF or gender related differences in atrial remodeling is unknown. Interestingly, Cochet et al. showed that only female gender and presence of long standing AF were related to increased atrial fibrosis assessed by delayed gadolinium enhancement on cardiac magnetic resonance imaging [51]. The higher degree of atrial remodeling may explain both worse symptoms (by virtue of increased left atrial pressure) and higher stroke risk (worse stasis of blood) in women.

The molecular mechanisms behind increased atrial remodeling in women are poorly understood. While several mechanisms for fibrosis exists, gender differences in two important mechanisms**- C reactive protein and fibroblast growth factor 23** have been recognized [14]. C-reactive protein is a common inflammatory marker which is expressed in response to pro-inflammatory cytokines [52]. Higher levels of C reactive protein have been linked to worse cardiovascular outcomes and an increased risk of AF. C-reactive protein increases cardiac fibrosis both by itself and by accentuating angiotensin mediated remodeling [53]. Interestingly, **women have higher levels of CRP** compared with men even after correcting for baseline differences [52].

Another molecular mechanism that has recently gained interest is the role of fibroblast growth factor 23 (FGF 23). FGF 23 plays an important role in phosphate metabolism and Vitamin D homeostasis and is a powerful mediator of cardiac and vascular hypertrophy [54, 55]. Higher levels of FGF23 have been associated with increased risk of AF [56]. **Women have higher mean levels of FGF 23 than men** which may explain a more profound atrial remodeling response and thus, increased risk of atrial fibrillation [56].

When gender differences are discussed in any disease, the role of sex hormones such as estrogen and testosterone are emphasized. It is important to recognize that since AF is a disease of post menopausal women (with lower levels of estrogen), gender differences between men and women cannot be readily explained by virtue of sex hormones alone.

Increased Pro-Coagulant Factors

Though gender based differences in expression of procoagulant factors in AF are unknown, data from coronary artery disease literature suggest that they do exist. Women have higher levels of vonWillebrand factor, fibrinogen, C reactive protein and factor VII than men [57]. Whether these mediate the increased risk of stroke in AF is unknown.

Increased Stasis

Increased atrial remodeling predisposes to atrial muscle dysfunction which in turn, promotes stasis of blood. Among patients referred for AF ablation with a CHADS VASC score > 2, **women had more advanced left atrial remodeling** (increased LA volumes, reduced LA endocardial voltage which signifies worse fibrosis) **and poorer left atrial appendage function** than men [58].This combination may result in increased blood stasis and predispose to thrombus formation.

Vascular Factors

While most of the stroke risk from AF is related to cardioembolism, the risk of ischemic non-embolic stroke in this population cannot be underestimated. In epidemiological studies of risk of stroke from AF, all ischemic stroke is assumed to be

related to embolism itself. However, it is well known that noncardioembolic stroke is relatively common in patients with atrial fibrillation. In an analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) I-III trials, 52% of ischemic strokes were cardioembolic, 24% of strokes were non-cardio embolic while 24% could not be classified [59]. By virtue of older age and increased blood pressure, women with AF may be at higher risk of non-cardioembolic stroke, a risk that may not be mitigated by treatment with anticoagulation.

Women with AF appear to have more severe functional consequences of stroke men [60]. In this study, women with AF had more disabling strokes than men (median National Institutes of Health Stroke Scale score [interquartile range] = 9 [4–17] vs. 6 [3–13]; $P < 0.001$).

Anticoagulation in Women with AF

Oral anticoagulants significantly reduce stroke risk in AF. Large registry data have demonstrated similar prescription rates of oral anticoagulants in women and men with AF, although a few studies reported significant disparities. In the Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) registry of 17,000 newly diagnosed non valvular AF patients, there was underuse of anticoagulation in all patients with no differences between men and women [61]. The EORP-AF investigators reported higher rates of anticoagulation (95.3%) in women compared to men (76.2%) with a CHADS2VaSC score of >2 [18]. Similar rates of anticoagulant prescription have been noted in the outpatient ORBIT-AF registry [17]. While these large registries reported similar prescription rates, an analysis of the American College of Cardiology PINNACLE (Practice Innovation and Clinical Excellence) registry showed that men were more likely to receive oral anticoagulants than women [62, 63].Whether this represents as true disparity or reflects increased co-morbidities that lead clinicians to avoid anticoagulation in women is not well understood.

Efficacy of Anticoagulants

Vitamin K antagnosits(warfarin): For many decades, vitamin K antagonists were the only oral anticoagulant available for stroke prophylaxis in AF. Women appear to have an increased residual risk of stroke while receiving warfarin for anticoagulation. In a meta-analysis, women with AF had a significantly higher residual risk of stroke and systemic thromboembolism than men while on warfarin (OR 1.28, 95% CI 1.11–1.47) [64]). There are two possible explanations for this phenomenon, (a) Inability to achieve therapeutic anticoagulation in women with warfarin or (b) Vitamin K antagonists may not be as efficacious in women. In a post-hoc analysis of the AFFIRM trial, women were at greater risk of ischemic stroke than men despite similar anticoagulation patterns [47]. A higher proportion of women

however were outside the therapeutic range for warfarin. Time in therapeutic range (TTR) is recognized as a major factor determining stroke risk in AF patients on warfarin. Female sex has been associated with lower TTR in various studies leading to an addition of female sex as a component of the SAMe-TT2R2 score (female sex, age <60 years, medical history [>2 comorbidities], treatment [interacting drugs], tobacco [doubled], race [doubled]), which has been validated as a predictor of poor TTR in patients on warfarin [65]. However, in the post-hoc analysis of the AFFIRM trial, even in group of patients with a satisfactory TTR of >66% (considered adequate anticoagulation), women had a significantly higher residual risk of stroke (log rank p test, p = 0.009) [47]. There are no known gender differences in genetic polymorphisms that effect warfarin metabolism.

Non vitamin K antagonist Oral AntiCoagulants (NOACs): Compared with warfarin, gender differences in stroke risk did not appear in the large randomized controlled trials of NOACs. A meta-analysis of 71,683 participants included in four major trials revealed no gender based differences in stroke risk or bleeding risk among patients assigned to DOACs [66]. In contrast to warfarin, there was no gender bias in the residual risk ischemic stroke among patients assigned to DOACs [65].While it is premature to suggest use of NOACs in all women, a score such as SAMe-TT2R2 should be used to choose the appropriate anticoagulant,

Gender Differences in Cardiovascular and All-Cause Mortality from AF

While the difference stroke risk is well known and widely accepted, differences in other cardiovascular outcomes and mortality are less well understood. A meta-analysis of 30 studies from 1996 to 2015 including more than four million participants found that female sex is an independent risk factor for all cause and cardiovascular mortality and incident heart failure in patients with AF [67]. However, in an analysis of the ORBIT-AF registry (a more contemporary cohort) showed than men with AF have worse prognosis [17]. Since mortality depends as much on the predisposing factors than AF itself, it is possible that outcomes would be different based on the characteristics of patients enrolled in each study.

Conclusion

In summary, several gender based differences in atrial fibrillation have been described. Women appear to have more symptoms and a higher stroke risk from AF while suffering from more complications from treatments (rate control, cardioversion, anti-arrhythmic drugs and catheter ablation) used for AF. While the introduction of NOACs appears to have been a major step in reducing stroke risk in women, the underlying mechanism remains poorly understood. Gender differences should

be studied at both molecular and clinical fronts to reduce the significant health burden posed by AF in women.

Disclosures None.

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Chapter 16
Gender Differences in Cardiovascular Drugs

Amanda J. Stolarz and Nancy J. Rusch

Introduction

Women take more medications per capita than men, but women also are less adherent to medication regimens compared to men. The reduced adherence may partially relate to the 1.5 to 1.7-fold higher risk of adverse drug events in women [1–3]. Cardiovascular therapy in women also is less likely to follow evidence-based guidelines [1, 4]. For example, the use of aspirin and statins as primary and secondary prevention against cardiovascular events is less common in women compared to men across all races and ethnicities [5]. Moreover, current evidence-based guidelines may not be appropriate for the female patient population due to the underrepresentation of women in clinical trials. The same factor likely contributes to the limited recognition of gender-based differences in responses to cardiovascular therapies. Another consideration is pregnancy as a condition unique to women, which not only limits drug choice due to teratogenicity concerns, but also can alter the pharmacokinetics and pharmacodynamics of medications. The topic of cardiovascular medications during pregnancy was reviewed recently [6] and will not be included in this chapter. Instead, this chapter focuses more globally on the emerging evidence for unique gender-related differences in pharmacokinetics and pharmacodynamics of several important categories of cardiovascular medications [7–9]. These categories of drugs include the statins, antiplatelet and antithrombotic agents, digoxin, β-adrenergic receptor blockers (β-blockers), calcium channel blockers, isosorbide mononitrate, aldosterone antagonists, and drugs that can induce long QT syndrome.

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Pharmacokinetics

Before discussing gender-related differences for individual cardiovascular drugs, it is important to recognize there are global pharmacokinetic differences between women and men, including altered patterns of absorption, distribution, metabolism, and excretion (Table 16.1). For example, absorption in women is slower than in men. Women have reduced gastric acid secretion and slower gastrointestinal motility, which can result in diminished or delayed absorption of enteric-coated formulations, especially following meals [7–12]. Therefore, to ensure adequate bioavailability, women should take enteric-coated medications and medications recommended to be taken on an empty stomach prior to the first meal of the day. Similarly, women should wait longer than prescribed after eating a meal if the medication is taken more than once daily [7]. Enteric-coated cardiovascular medications reported to show delayed or reduced bioavailability in women due to slowed or attenuated absorption include verapamil, captopril, felodipine, and aspirin [7–12].

Volume of distribution for drugs also may be less in women compared to men due to lower body weight and smaller intravascular, organ, and muscle volumes [7–9]. Thus, loading doses or intravenous boluses of cardiovascular drugs with narrow therapeutic indexes may require adjustment to prevent adverse events in women. For example, weight-based dose adjustments are routinely recommended for class I and class III antiarrhythmic agents, digoxin, heparin and other cardiovascular drugs [7–9]. However, the volume of distribution for lipophilic drugs in women may be higher when normalized to body weight, because women generally have a higher percent of body fat despite having a lower body weight [7].

Several metabolic enzymes including CYP1A2, CYP2E1, and certain glucuronyltransferase and sulfotransferase isoforms, as well as P-glycoprotein (drug efflux pump), are reported to have higher activity in men compared to women [8]. On the other hand, CYP2D6 and CYP3A are reported to have slightly higher activity in women of childbearing years [8, 13, 14]. No specific gender differences have been reported for CYP2C9 or CYP2C19 [8, 13, 14]. The significance of these gender-based

Table 16.1 Gender differences in pharmacokinetics

	Women	Men	Refs
Absorption	↓ Gastric acid secretion ↑ GI transit time		[7–12]
Distribution	↓ Body weight ↓ Intravascular volume ↓ Organ volume ↓ Muscle volume ↑ Adipose tissue		[7–9]
Metabolism	↑ CYP2D6 ↑ CYP3A	↑ CYP1A activity ↑ CYP2E1 activity ↑ P-gp activity	[8, 13, 14]
Excretion	↓ GFR		[7–9, 15]

↑ increased, ↓ decreased

metabolic differences on the availability and half-lives of cardiovascular drugs is poorly understood. Additionally, glomerular filtration rate in women is 10–25% slower than in men even after adjusting for body size [7–9]. Thus, cardiovascular medications that primarily undergo renal elimination, such as digoxin, will be cleared more slowly [7, 8, 15].

Statins

Elevated serum low density lipoprotein cholesterol (LDL-C) is associated with an increased incidence of cardiovascular events [16, 17]. Statins reduce circulating LDL-C levels by directly inhibiting 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, a key enzyme for cholesterol synthesis in the liver [17]. The cardiovascular benefits derived from statin use are attributed to the combination of the reduction in LDL-C and additional pleiotropic effects linked to decreased inflammation, improved endothelial function, and enhanced atherosclerotic plaque stability [17–21]. However, meta-analyses have provided inconsistent data related to the ability of statins to prevent primary cardiovascular disease in women without overt clinical cardiovascular dysfunction [17]. The discrepancies may be related to ill-defined risk stratification or under-utilization of guidelines in women compared to men. The American College of Cardiology/American Heart Association (ACCF/AHA) recently issued guidelines for initiating and maintaining statin therapy [17]; however, these guidelines do not distinguish risk stratification between women and men despite the general recognition of gender-specific differences in the pathogenesis and symptoms of cardiovascular disease [17, 22]. In addition, some reports suggest that the risk of adverse drug events, such as statin-induced myalgia and diabetes, is higher in women compared to men, due to the reduced metabolism, smaller muscle mass, and lower body weight of women; these factors may be exaggerated in older, frailer women [9, 23, 24]. However, healthcare providers should determine individual risk versus benefit for the use of statins in primary prevention of cardiovascular events in women and encourage adherence to a statin regimen for women with a clear medical indication by avoiding over-emphasis of possible adverse effects. Meanwhile, the use of intensive statin therapy for secondary prevention of cardiovascular events in women already manifesting cardiovascular disease has been demonstrated to significantly decrease myocardial infarction, unstable angina, heart failure and death, and therefore, is routinely recommended [16–25].

Antiplatelet Agents: Aspirin

Platelets are critical players in the etiology of atherosclerosis, and their role in the pathogenesis of cardiovascular disease has been established by studies showing the clinical benefits of antiplatelet agents, such as aspirin and clopidogrel [26].

Aspirin inactivates the enzyme cyclooxygenase (COX)-1, which in turn inhibits platelet function and aggregation as a result of reduced synthesis of pro-thrombotic prostaglandins and thromboxane A_2 [27]. Aspirin significantly reduces the risk of myocardial infarction in men with minimal effect on the risk of stroke [9, 28]. Conversely, aspirin was not effective for primary prevention of myocardial infarction in women [26, 28], but significantly reduced the risk of stroke [26, 28, 29]. Several possible reasons exist for the gender disparities observed in the cardiovascular benefits of aspirin therapy. First, the pharmacokinetics of uncoated aspirin is altered in women compared to men. In women, uncoated aspirin has faster absorption, a larger volume of distribution, and more rapid hydrolysis [30], potentially diminishing its beneficial effects. Alternatively, the gender disparity in aspirin's cardiovascular benefit may relate to heterogeneous platelet functions and disease pathogenesis between men and women. For example, a recent study identified gender-specific responses to stress in patients with stable ischemic heart disease [31]. This study reported that after induction of stress, either mentally, or pharmacologically using serotonin or epinephrine, women were more likely to respond with higher platelet aggregation, whereas men were more likely to respond to these stressors by increasing blood pressure [31].

Additionally genetic polymorphisms in platelet glycoproteins (Gp) have been linked to increased cardiovascular events. However, the gender distribution of these polymorphisms has not been defined [26]. Some evidence suggests that female carriers of at least one Gp Ib-alpha5C allele have a higher risk of cardiovascular events compared to females homozygous for the Gp Ib-alpha5T allele [32]. However, the risk for cardiovascular events in female carriers of at least one Gp Ib-alpha5C allele was reduced with hormone replacement therapy when compared to females homozygous for the Gp Ib-alpha5T allele [32]. This finding agrees with other reports that estrogen decreases platelet reactivity in women [33, 34]. Future studies are needed to determine gender-specific regulation and mechanisms of platelet function and potential differences in therapeutic outcomes for antiplatelet agents. Given the current evidence, aspirin is routinely recommended for the primary prevention of cardiovascular events in men and secondary prevention of cardiovascular events in men and women [26, 28, 35].

Antithrombotics

Atherothrombosis is the leading cause of unstable angina, myocardial infarction and cardiovascular death [36]. Anticoagulation and fibrinolytics are two pharmacologic strategies available to prevent or decrease thrombosis in patients. Anticoagulants prevent thrombosis by inhibiting clot formation, whereas fibrinolytics degrade clots that have already formed [35]. Both categories of medications demonstrate comparable reductions in myocardial infarction and cardiovascular death in women and men [37]. However, antithrombotic therapy is associated with an increased risk of bleeding in women [37]. Specifically, women treated with the anticoagulant heparin

for acute myocardial infarction measured higher activated partial thromboplastin times (aPTT) than men, which are associated with increased risk of bleeding [38]. Two randomized controlled clinical trials demonstrated that women have a higher risk for nonfatal and fatal complications compared to men when treated with thrombolytic therapy after acute myocardial infarction, including the combination of heparin with either streptokinase and/or alteplase [39, 40]. In other studies, the female gender was an independent risk factor for increased bleeding rates following fibrinolytic treatment for acute myocardial infarction [41, 42].

Digoxin

Digoxin may be administered for the treatment of heart failure and to slow conduction through the atrioventricular node because of its positive inotropic and parasympathetic effects, respectively [43]. As previously mentioned, digoxin has a smaller volume of distribution and slower renal clearance in women compared to men, which may partially explain the increased mortality risk for women treated with digoxin for heart failure [7–9]. A post-hoc analysis of the 1997 Digitalis Investigation Group study determined that female patients with heart failure using digoxin not only had a significantly higher mortality risk compared to women taking placebo, but also showed a 5.8% higher mortality rate compared to men treated with digoxin [44, 45]. A trend emerged linking higher serum digoxin concentrations to all-cause mortality in women; however, the small sample size of women in this trial limited statistical significance of these findings [9]. Despite limited data, recent ACC/AHA guidelines recommend lowering the therapeutic serum concentration range of digoxin from 0.8–2 to 0.5–0.9 ng/mL to reduce mortality in heart failure patients regardless of gender, and clinicians are encouraged to adopt this lower serum digoxin concentration range of 0.5–0.9 ng/mL, especially when treating female patients [46].

Beta Blockers

The β-adrenergic receptor blockers (β-blockers) are used extensively in the treatment of multiple cardiovascular pathologies including hypertension, heart failure, angina, arrhythmias, and post-myocardial infarction. These drugs bind to β-adrenergic receptors located in the heart, kidney, smooth muscle, and other sites and prevent the binding of endogenous catecholamines (epinephrine and norepinephrine) released from the sympathetic nervous system [47]. The three isoforms (β1, β2, β3) of the β receptor exhibit tissue –specific expression and actions, and the β1 receptor serves as the primary target of β-blockers in the treatment of cardiovascular diseases. Activation of β1 receptors in the heart increase heart rate and force of contraction, and in the kidney, β1 receptors are responsible for renin secretion,

and ultimately the circulating levels of angiotensin II. Therefore, β1-receptor blockers decrease heart rate and force of contraction, and attenuate renin secretion; collectively these events lead to a reduction in blood pressure [47]. Studies suggest β-blockers exhibit gender-specific pharmacokinetics and may provide different survival benefits to men and women. In a study of normal healthy volunteers, women receiving oral metoprolol twice daily showed a greater reduction in heart rate and systolic blood pressure during exercise as compared to men; however, elimination half-life remained the same between the two sexes [48]. The authors attributed these enhanced cardiovascular effects to a presumably higher serum drug concentration facilitated by increased absorption of metoprolol in women [48]. Despite these presumed higher serum drug concentrations, metoprolol has not demonstrated enhanced anti-ischemic effects in women with chronic stable angina compared to men [49]. Moreover, inadequate representation of women in large clinical trials has led to inconsistent data related to the survival benefits of β-blockers in women diagnosed with heart failure after myocardial infarction [9]. Both the Metoprolol CR/XL study and the COPERNICUS trial failed to show decreased mortality associated with the use of β-blockers in female patients with heart failure [50, 51]. Conversely, when gender-specific analysis was applied to data in the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) trial, the β-blocker bisoprolol significantly decreased mortality in women compared to men with heart failure [52, 53]. The pooled mortality data from these three trials showed survival benefits associated with β-blocker use in both men and women with heart failure [53, 54]. These results further emphasize the importance of adequate inclusion of women in clinical trials to provide evidence-based medication use that relies on the outcome of female as well as male subjects.

Drug-Induced Long QT Syndrome

The QT interval of the electrocardiogram represents the duration in the cardiac cycle of electrical activity associated with ventricular depolarization (and concomitant cardiomyocyte contraction) and ventricular repolarization (that mediates cardiomyocyte relaxation). Slowed ventricular repolarization leads to prolongation of the QT interval (long QT syndrome), which results in a predisposition for arrhythmias, in particular Torsades de Pointes (TdP), a rare but often fatal polymorphic ventricular arrhythmia [55, 56]. Women have longer QT intervals at baseline compared to men even after correction for heart rate [57, 58]. This difference is most pronounced at the onset of puberty, but then it gradually declines with age such that by age 50, no significant difference in QT intervals is apparent between genders [59]. This longer QT interval in women may partially explain the fact that the female gender has been identified as an independent risk factor for QT prolongation and TdP [60, 61].

For this reason, several studies have sought to determine the influence of sex hormones and the menstrual cycle on QT interval [59, 62–65]. Several studies have

demonstrated that endogenous testosterone shortens the cardiac action potential, and thus shortens the QT interval [62–65], which may partially account for the baseline difference in QT interval between men and women [62]. Endogenous progesterone also shortens the duration of the cardiac action potential [62–65]. However, since progesterone levels fluctuate throughout the menstrual cycle, with the highest levels occurring during the luteal phase and much lower levels during the follicular phase, the effects on cardiac action potential shortening also may be cyclical. This assertion is supported by a study conducted in healthy Japanese women, who were monitored by electrocardiogram continuously for 24 h during the luteal and follicular phases of their menstrual cycle. The results revealed shorter QT intervals and higher serum concentrations of progesterone during the luteal phase of the menstrual cycle [63].

In addition to the underlying physiological difference in QT interval length between genders, many common cardiovascular medications can lengthen the QT interval and lead to TdP [65]. Women accounted for 64–75% of cardiovascular drug -induced TdP in a meta-analysis of 93 publications with at least one identified case of TdP associated with the use of Class IA or Class III anti-arrhythmic or anti-anginal agents (quinidine, procainamide, disopyramide, amiodarone, sotalol, bepridil, or prenylamine) [59]. A subsequent meta-analysis of 22 clinical trials including a total of 3135 patients treated with D,L-sotalol showed that women had a three-fold higher risk of developing TdP even after adjusting for additional risk factors (ventricular arrhythmias, congestive heart failure, and D,L-sotalol dose >320 mg/day) [60]. Higher serum drug concentrations due to lower body weight and decreased volume of distribution may partially account for the increased risk of drug-induced long QT interval after administration of anti-arrhythmic and anti-anginal agents to women compared to men. However, lower body weight and less volume of distribution cannot be the only factors contributing to an increased incidence of long QT syndrome in women given that there is no defined relationship between serum drug concentration and QT prolongation with certain anti-arrhythmic agents, including quinidine and sotalol [7, 66]. A recent open-label non-randomized trial in healthy young adults demonstrated that even across similar serum drug concentrations, women had an increased risk of sotalol-induced prolonged QT interval compared to men [67].

Additional studies focused on gender-related differences in autonomic nervous system activity showed that β-blockers significantly prolonged the QT interval in healthy women compared to men [68]. Moreover women with $LQTS_1$, a mutation in the KCNQ1 potassium channel gene associated with increased QT interval length, who were administered β-blocker agents, exhibited significant QT prolongation compared to men with $LQTS_1$ [69]. Thus, mechanisms underlying the gender-related difference related to risk of prolonged QT and TdP cannot be fully explained by higher serum drug concentrations or differences in autonomic tone, and may vary depending on levels of endogenous sex hormones and menstrual cycle phase. Future studies should account for these factors to more accurately determine the gender-specific arrhythmogenic potential of commonly used medications.

Calcium Channel Blockers

Calcium channel blockers (CCBs) inhibit the calcium-dependent contractile tone of vascular smooth muscle, resulting in vasodilation; some of these drugs also decrease heart rate and force of contraction, making CCBs ideal candidates for the treatment of cardiovascular diseases, particularly hypertension and angina. Gender-differences in pharmacokinetics have been described for verapamil and amlodipine, two widely used CCBs [70, 71]. Women exhibit faster elimination rates for oral verapamil and achieve higher plasma concentrations of amlodipine compared to men. These differences may be partially attributed to lower body weight, increased activity of CYP3A4 and decreased activity of P-gp as compared to men [70, 71]. In an 18-week, open-labeled prospective study across all age groups, hypertensive women treated with the CCB, amlodipine, showed a greater reduction in blood pressure compared to hypertensive men [72, 73]. However, the accentuated antihypertensive effect of amlodipine was accompanied by an increased incidence of peripheral edema in women compared to men [72, 73]. This adverse effect potentially could reduce adherence of women to CCB therapy, and even its discontinuation, negating the beneficial effects on blood pressure observed in female patients.

Isosorbide Mononitrate

Isosorbide mononitrate is a nitric oxide donor that directly dilates blood vessels and is administered to relieve anginal pain. In a pharmacokinetic study, the plasma concentrations of two different extended release formulations of isosorbide mononitrate were significantly higher in women compared to men, which was attributed solely to the lower body weight in the female subjects [74]. Although the clinical significance of these findings has yet to be determined, this study suggests that doses of extended release isosorbide mononitrate should be weight-based rather than fixed.

Diuretics and RAAS Inhibitors

No gender differences in pharmacokinetics or pharmacodynamics are described for diuretic medications, or attributed to inhibitors of the renin-angiotensin-aldosterone system (RAAS). The latter category of drugs includes angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and the renin inhibitor, aliskiren [75, 76]. However gender appears to play a role in prescribing practices for these medications [77, 78]. After controlling for age and comorbidities, studies show that hypertensive men are more likely to be prescribed RAAS inhibitors, while hypertensive women are more often treated with a diuretic [77, 78]. This gender-related difference could be due to the potential teratogenic and

abortive effects of RAAS inhibitors in women of child-bearing years, and reluctance by health care providers to prescribe such agents without assurances of adequate birth control [79–82]. Women also have an increased risk of adverse events caused by RAAS inhibitors compared to men, including an increased incidence of ACE inhibitor -induced cough [83] and increased incidence of hyponatremia attributed to thiazide diuretics [84]. Thus, women should be monitored carefully for these off-target effects.

Aldosterone Antagonists

Although women generally experience more adverse reactions to cardiovascular drugs, single drug classes are associated with gender-related adverse effects in men. One example is the aldosterone antagonists. Aldosterone antagonists bind the mineralocorticoid receptor in the kidney, colon, and sweat glands to inhibit sodium and water reabsorption and inhibit potassium excretion. These agents are used in the treatment of hypertension and heart failure, because they reduce morbidity and mortality in both sexes [85–88]. However, it is well documented that spironolactone, a nonselective aldosterone antagonist, increases the incidence of gynecomastia in men, which is the enlargement of breast tissue. In a large retrospective trial of 699 hypertensive patients treated with spironolactone, the incidence of gynecomastia in male subjects was 6.9% at doses $\leq$50 mg per day and 52.2% at doses $\geq$150 mg per day [89]. The dose-dependent incidence of gynecomastia caused by spironolactone is likely related to the structural similarity of spironolactone to progesterone and its ability to bind to sex-steroid receptors. In a small study of 16 patients, the six patients treated with spironolactone all developed gynecomastia concomitant with lower blood levels of testosterone and higher blood levels of estradiol compared to the ten patients not treated with spironolactone [90]. Selective aldosterone antagonists, like epleronone, which selectively bind to and inhibit the aldosterone receptor, reduce the incidence of gynecomastia [87].

Implications in the Treatment of Transgender Patients

The cornerstone of treatment for the transitioning of transgender patients is hormone replacement therapy, where opposing sex hormones are administered to alter the balance of testosterone, estrogen, and progesterone to match the patient's gender identity [91]. As mentioned in previous sections, endogenous testosterone and progesterone appear to protect against certain arrhythmias and QT prolongation [59, 62–65], while endogenous estrogen has been shown to be protective against myocardial infarction and heart failure [92]. However, administration of exogenous estrogen increases clotting factors and decreases anti-thrombin activity [92–94], leading to increased risks of deep vein thrombosis, pulmonary embolus, and myocardial infarction [92–96]. Therefore, hormone replacement therapy with estrogen carries an inherent risk of

increasing cardiovascular events and should be a consideration when treating transgender patients [92–96]. However, not all gender differences in cardiovascular management are fully explained by differences in adult sex hormones. It is possible some gender-based differences including a higher enzyme activity of CYP1A2, CYP2E1, and certain glucuronyltransferase and sulfotransferase isoforms, as well as increased P-glycoprotein activity in men [8], or decreased glomerular filtration rate in women [7–9], are derived from sex hormone driven *in utero* programming or may be genetically linked to the X- or Y- chromosome as a fundamental biological difference. Under these circumstances, differences in drug pharmacokinetics and efficacy still would exist irrespective of transgender status. Regardless, it is important to be cognizant of a patient's biological sex at birth to plan the best treatment options.

Summary

Clinical manifestations of cardiovascular disease present differently in women and men due to gender-specific differences in physiology. Accordingly, cardiovascular drugs exhibit different pharmacological and pharmacokinetic profiles between women and men, and it is inappropriate to extrapolate data from clinical trials that include predominantly male patients to a female patient population. This chapter not only highlights the importance of adequate inclusion of both genders in drug safety and efficacy trials, but also underscores the significance of remaining cognizant of a patient's biological sex at birth. Table 16.2 summarizes some of the cardiovascular drugs with

Table 16.2 Cardiovascular drugs with gender-specific therapeutic and adverse effects

Drug	Gender-specific effects	Refs
Statins	Increased side effects in older women with low body weight	[9, 23, 24]
Antiplatelet agents	Ineffective primary prevention of heart attack in women Decreased stroke prevention in men	[9, 26, 28]
Antithrombotic agents	Increased risk of bleeding	[37–42]
Digoxin	Increased mortality in women	[44, 45]
β-blockers	Enhanced antihypertensive effect and heart rate reduction in exercising women	[48]
Antiarrhythmic agents	Increased risk of prolonged QT and TdP in women	[59, 60]
Calcium channel blockers	Enhanced antihypertensive effect in women Increased incidence of edema	[72, 73]
Isosorbide mononitrate	Increased plasma concentrations in women	[74]
ACE inhibitors	Increased incidence of cough in women	[83]
Diuretics	Increased risk of hyponatremia in women	[84]
Aldosterone antagonists	Risk of gynecomastia in men	[87–90]

TdP Torsades de Pointes

gender-specific therapeutic and adverse effects. Gender-related differences in drug profiles are now recognized in the package inserts for a growing number of cardiovascular drugs, including simvastatin, atorvastatin, lovastatin, heparin, enoxaparin, and sotalol, thereby recognizing the need to adjust loading or maintenance doses for female patients. As the results of more studies improve our ability to weigh the risk/benefit ratio of cardiovascular drugs in women and men, gender may emerge as an important factor in choosing drug categories and recommending medication doses.

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Chapter 17
Cardiovascular Side Effects of Breast Cancer Therapy

Marjan Boerma

Introduction

In 2012, there were more than 1.6 million breast cancer cases worldwide [1]. This year alone, the United States will see an estimate of more than 252,000 new breast cancer cases, about 15% of all new cancer cases [2]. Most breast cancer patients will undergo surgery to remove the tumor(s), and possibly nearby lymph nodes and/or surrounding tissue. In addition, based on the stage of the cancer, cancer cell expression levels of estrogen and progesterone receptors, and the presence of certain high-risk mutations such as BRCA1/2, surgery is combined with radiation therapy, chemotherapy, and/or hormonal therapy [3–6]. More recently, targeted agents have been developed that are aimed at inhibiting cancer cell proliferation or inducing cancer cell death via targeting intracellular signaling such as of the growth factor receptor pathways. For instance, if tumor cells are positive for the human epidermal growth factor type 2 receptor (HER2/neu), the treatment plan may include small molecule inhibitors of the HER2 signaling pathway, or anti-HER2 antibodies such as trastuzumab.

While breast cancer therapy has greatly improved over the decades and is leading to ever increasing cancer cure rates, side effects of breast cancer therapy are also common. Side effects vary from skin erythema, fatigue, hair loss, peripheral neuropathy and various other systemic sequelae of chemotherapy. This chapter is focused on adverse cardiovascular effects of common chemotherapeutic agents, targeted therapies, and radiation therapy modalities. These side effects may be aggravated by pre-existing cardiovascular risk factors such as hypertension, dyslipidemia and diabetes. Many clinical and pre-clinical research studies have been performed to understand mechanisms of cardiovascular toxicity of breast cancer treatments, to identify biomarkers that may aid in early detection of cardiovascular

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side effects, and develop potential intervention strategies to limit them. While a lot of questions are still unanswered, progress has been made in each of these areas.

Cardiovascular Side Effects of Systemic Chemotherapy

Common chemotherapeutic treatments of breast cancer patients include anthracyclines and alkylating agents such as cyclophosphamide. While many of these agents have long been known to cause regular and sometimes severe acute and late cardiovascular side effects, including cardiac dysfunction, cardiomyopathy, pericarditis, and conduction abnormalities [7–9], anthracycline cardiotoxicity is best known and studied most extensively. Although anthracycline use in breast cancer treatment in the United States has declined in the last two decades, this chemotherapeutic strategy is still a helpful treatment option in breast cancer cases with a high risk of recurrence [10].

Research into Mechanisms by Which Anthracyclines Injure the Heart

In the heart, anthracyclines are thought to act via the induction of the reactive oxygen species, mitochondrial dysfunction, changes in calcium homeostasis and contractile function, and cardiomyocyte cell death. We refer the reader to some of the many excellent review articles in this area [11–13]. In addition to mechanisms above, adverse effects of the anthracycline doxorubicin are mediated at least in part via inhibition of topoisomerase IIβ in the heart [14]. Topoisomerase IIβ is involved in p53 activation, antioxidant enzyme expression, and regulation of peroxisome proliferator activator receptor (PPAR) pathways [15].

Pre-Clinical and Clinical Development of Strategies to Reduce Cardiac Side Effects of Anthracyclines

In light of known molecular mechanisms of cardiovascular toxicity of anthracyclines, various pharmacological strategies to interfere in these pathologies have been designed and tested.

One of the strategies to reduce cardiovascular toxicity of anthracyclines is to encapsulate the chemotherapeutic agents in liposomes. Liposomal anthracyclines are thought to exit more easily out of the permeable tumor vasculature compared to the vasculature in the heart, leading to a more favorable distribution of the chemotherapeutic agent in the tumor versus the heart. While some liposomal forms of anthracyclines are clinically available, their use is not widespread and further research is required to determine safety, pharmacokinetics, and efficacy [16–18].

Aerobic exercise has been shown to significantly reduce both short-term and long-term cardiac side effects of cancer therapy including anthracyclines, by reducing oxidative stress, improving endothelial dysfunction, and improving myocardial metabolism [19, 20].

In addition, pharmacological modifiers of adverse effects may be given, before, during and/or after cancer treatment. Especially when administered before or during therapy, one of the main requirements is that the pharmacological modifier does not interfere with the effects of therapy on the cancer cells. The only US Food and Drug Administration (FDA)-approved pharmacological intervention in anthracycline-induced cardiotoxicity is dexrazoxane, an iron chelator that is thought to act by minimizing the harmful iron complex formations by anthracyclines in the heart [21–23]. As for liposomal anthracyclines, the clinical use of dexrazoxane is not widespread.

Angiotensin II (Ang II) type 2 (AT2) receptor inhibition has shown cardioprotective properties in breast cancer patients treated with anthracyclines [24]. Beta-blockade and statins may also be beneficial [25–28]. Noteworthy pre-clinical research in this area involves natural compounds that induce the erythroid 2 [NF-E2]-related factor 2 (Nrf2) pathway, thereby inducing the expression of antioxidant enzymes in normal tissues such as the heart [29, 30]. Some of these compounds, such as sulforaphane, have the potential of simultaneously protecting the heart from the harmful effects of anthracyclines while enhancing cancer cell kill by anthracyclines, as shown in cell culture studies [31–33]. Clinical studies with Nrf2 inducing compounds, including some in cancer therapy, have begun.

Cardiovascular Side Effects of Hormonal Therapy

Patients with estrogen or progesterone positive breast cancer can be prescribed various forms of hormonal therapy such as tamoxifen. More recently, aromatase inhibitors have been developed that block the synthesis of estrogen [34]. Some cardiovascular side effects of aromatase inhibitors have been described [35–37], and hence care must be taken in follow-up, especially when other cardiovascular risk factors are present.

Cardiovascular Side Effects of Breast Cancer Radiation Therapy

Radiation Therapy Regimens in Breast Cancer Therapy

For many years, breast cancer was treated with tangential radiation therapy, in which radiation fields are directed at an angle to the whole or large part of the breast. While this technique has been replaced with other radiation therapy modalities in many

institutions in developed countries, it is still commonly used in other parts of the world. Recent developments in breast cancer radiation therapy include brachytherapy, intensity modulated radiation therapy (IMRT) and proton therapy, with the purpose of delivering a homogeneous radiation dose to the tumor(s) while simultaneously sparing normal tissues [38–40]. Interestingly, while the mean radiation dose to the heart is expected to be low in breast cancer proton therapy, extensive clinical evidence of the rate of cardiovascular side effects of this technique has yet to be obtained [41]. Alternatively, radiation can be delivered while the patients exercises a deep inspiratory breath-hold. The aim of this technique is to reduce radiation dose to heart and lung by increasing the distance between these normal tissues and the breast. This technique has become widespread and does reduce normal tissue radiation exposure [42, 43].

Since many breast cancer patients have been treated with tangential radiation therapy over the years, the cardiac side effects of this radiation therapy technique have been studied extensively. Because of the anatomical location of the heart, tangential radiation therapy of the whole breast, especially in left-sided breast cancer, can lead to a significant dose of radiation to part of the heart [44–46], and these doses to the heart are associated with an increased rate of cardiovascular disease [47, 48]. Most manifestations of cardiac radiation toxicity become apparent a decade or more after exposure and include accelerated atherosclerosis, ischemic heart disease, and adverse myocardial remodeling.

Because of recent developments in radiation therapy in some countries, cardiac radiation toxicity is not of major concern in most breast cancer patients treated there today. However, because most manifestations of radiation-induced heart disease become apparent a decade or more after exposure, cancer survivors who have had significant doses to the heart in past treatments, or breast cancer patients treated in parts of the world where sophisticated and expensive radiation therapies are not available, may still be at risk. Methods for early detection and intervention in radiation-induced heart disease are not available, but pre-clinical research in this area is ongoing.

Pre-Clinical Research into Mechanisms by Which Radiation Injures the Heart

Most pre-clinical research into radiation-induced heart disease has been performed with local heart irradiation in various rodent models, and several decades ago large animal models were also common [49–51]. Before we discuss some of the recent pre-clinical research into mechanisms by which local irradiation adversely impacts cardiac and vascular tissue structure and function, we would like to make the reader aware that most of these studies have been performed in (young) adult male animal models. Since males and females are known to differ in cardiovascular disease risk, additional research into how local heart irradiation modifies cardiac function and structure in females is required.

Pre-clinical research has provided evidence for a role of microvascular alterations, growth factor signaling pathways, and inflammation in radiation-induced adverse myocardial remodeling, as reviewed elsewhere [52–55]. Different mechanisms are likely at play in accelerated atherosclerosis. Because of the low rate of spontaneous atherosclerosis in wild-type mouse and rat strains, radiation-induced accelerated atherosclerosis is difficult to reproduce in these animal models. Apolipoprotein E (ApoE) knockout (KO) mice, on the other hand, have presented with macrophage-rich atherosclerotic plaques upon local irradiation of the carotid artery, and damage in the myocardial microvasculature and atherosclerotic lesions in the coronary arteries in the irradiated heart [56–60]. Radiation-induced accelerated atherosclerosis has also been studied in rabbits that are administered a diet high in lipids [61]. Inflammation, oxidative stress, and endothelial dysfunction are thought to play a role in the disease process [62]. However, exact mechanisms by which radiation injures the myocardium and induces accelerated atherosclerosis are not yet fully known.

Pre-Clinical Research into Potential Pharmacological Interventions in Adverse Cardiovascular Effects of Radiation Exposure

Several pharmacological interventions have been tested in animal models of localized heart irradiation. For instance, since radiation-induced heart disease in animal models is associated with chronic oxidative stress [63], some agents that act via anti-oxidant mechanisms have been tested [64–67]. However, a single anti-oxidant that significantly alters cardiac radiation injury has yet to be found. While statins partly reduced adverse remodeling in rodent models of local heart irradiation [68, 69], radiation-induced accelerated atherosclerosis in the carotid artery of ApoE KO mice was not affected [70]. The angiotensin converting enzyme (ACE) inhibitor captopril has shown to reduce cardiac radiation injury in the rat [71, 72]. It is not yet clear whether these beneficial effects were due to ACE inhibition alone or whether any of the pleiotropic properties of captopril played a role.

Cardiovascular Side Effects of Targeted Therapies

The last decade has seen the emergence of therapies aimed at inhibiting cancer cell growth or inducing cell death via targeting intracellular signaling pathways. Trastuzumab, an anti-HER2 monoclonal antibody and lapatinib, a tyrosine kinase inhibitor that targets the HER2 and epidermal growth factor receptor signaling pathways, are now commonly used in the treatment of HER2-positive breast cancer. These and other targeted anti-cancer agents are associated with cardiovascular side

effects in a small but significant subset of patients that range from asymptomatic decreases in left ventricular ejection fraction (LVEF) to congestive heart failure [73–76]. Advanced age and pre-existing cardiovascular disease can increase the risk [77]. While some of the severe side effects can be life-threatening, in the majority of cases of decreased LVEF, this decline seems reversible upon termination of the treatment [78–80].

Mechanisms of and Intervention in Cardiotoxicity of Targeted Therapies

Mechanisms by which anti-HER2 and other targeted therapies may cause cardiac function loss and adverse remodeling are still not well understood. Pathophysiological mechanisms are thought to involve oxidative stress, inflammation, and inhibition of survival pathways in cardiomyocytes [81, 82]. Work on potential intervention has focused on angiotensin pathway modulation. While some clinical studies have shown beneficial effects of ACE or AT2 receptor inhibition on the decline in LVEF in response to cancer treatments involving anthracyclines [24, 83], a recent trial with the AT2 receptor inhibitor candesartan administered during and 26 weeks after trastuzumab treatment could not show a significant benefit on LVEF [84]. Additional clinical trials have been designed to assess whether ACE inhibition and beta-blockade during trastuzumab therapy of breast cancer can positively affect cardiac function [85].

How Do Breast Cancer Treatments Interact in Their Effects on the Heart When Administered in Combination?

Since breast cancer therapy involves a combination of treatments, and several of these adversely affect the cardiovascular system, there is concern about potential additive or synergistic effects [86].

Research in animal models has shown that radiation, anthracyclines, and tyrosine kinase inhibitors may enhance each other's effects on cardiac mitochondrial function and morphology. However, no enhanced adverse cardiac remodeling was observed [87, 88]. In addition, cardiac radiation toxicity in a rat model was not enhanced by concomitant administration of tamoxifen, endocrine therapy, or aromatase inhibitors [89].

While several clinical studies found no additive or synergistic cardiotoxic effects of combined HER2-targeted therapies [90, 91], or of targeted therapies combined with anthracyclines [92, 93], other retrospective studies do indicate an increased risk of cardiovascular toxicity when targeted therapies were administered with anthracyclines [94–96]. Addition of radiation therapy to systemic breast cancer

treatment containing trastuzumab did not significantly increase early cardiotoxicity [97, 98]. However, potential late complications of combined cancer treatment have not yet been assessed because long follow-up is required. Further pre-clinical and clinical research is being performed to identify the risks of current combined cancer therapies [99].

Early Detection of Cardiovascular Toxicity of Cancer Treatment

An early detection of cardiovascular toxicity of cancer treatment will aid in the selection of patients who could benefit from intervention. Some studies have shown that echocardiography, specifically strain analysis, can detect anthracycline-, targeted therapy-, and radiation-induced loss of cardiac function at a relatively early stage in cancer patients [100–103] and pre-clinical animal models [104]. Other imaging modalities that provide a sensitive measure of cardiac function, such as cardiac magnetic resonance imaging, or standard screening of coronary artery disease can also be useful [105]. While experts in this area have provided guidelines for clinical implementation of cardiac assessment in cancer patients and survivors at risk [106–108], standard clinical protocols are not yet common.

Early detection of cardiovascular side effects of cancer therapy may be optimal when imaging is combined with sensitive biomarkers [109]. However, biomarkers that specifically indicate cardiac toxicity of cancer therapy have not yet been identified. Common biomarkers of cardiac injury, on the other hand, have been tested extensively. For instance, increased levels of cardiac troponin I are observed within months after treatment in some, but not all breast cancer patients treated with anthracyclines [110–112]. Since biomarkers such as cardiac troponins are released into the circulation during acute cardiac injury, they are likely not sensitive indicators of chronic adverse cardiac remodeling such as after radiation treatment. Also, biomarkers need to distinguish cardiac complications of cancer treatment from heart disease due to other causes. Here, −omics technologies or other molecular assessments such as of circulating microRNAs may prove useful [113–115].

Cardio-Oncology: Cardiovascular Surveillance and Treatment of Breast Cancer Patients and Cancer Survivors

Because of the well-known cardiovascular side effects of cancer therapy, a close involvement of cardiologists in the treatment plan and follow-up of cancer patients is warranted. Hence, the development of the cardio-oncology field is now part of a widespread discussion to improve patient care [116, 117]. Within the last decade, more integrated cardio-oncology clinical teams have been developed in institutions

throughout the world [118, 119], and importantly there is an increasing role for primary care physicians in the follow-up of cancer patients [120]. Future development of sensitive biomarkers and safe intervention strategies will allow individualized treatments that reduce or eliminate cardiovascular toxicity of cancer treatment [121].

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Chapter 18
Burden of Cardiovascular Diseases in Women and Reduction Strategies in India

Meenakshi Sharma and N.K. Ganguly

The journey towards providing universal healthcare in India has been a challenging one. The country has some remarkable achievements including increase in life expectancy from 32 years in 1948 to 68.3 years in 2015 [1], 'small pox eradication' in 1980, 'guinea worm disease free country' in 2000 and 'polio free India' in 2014. The female life expectancy, which was below that of males in the middle of twentieth century, increased to 70 years in 2015 as compared to 66.9 years in males [1]. This was mainly due to decline in maternal mortality rate by 50% from 1990 to 2015 [2, 3]. The country still has the highest number of maternal deaths worldwide (50,000 in 2013). Infant mortality rates declined by 58% from 1990 to 2015 (37.9 deaths per 1000 live births) with an immunization coverage rate increasing from 43% in 2005–06 to 62% in 2015–16 [4–6]. Mortality rates for those under 5 years of age are higher among females than males, partly because of preference for a male child [5, 6]. Continuing and strengthening efforts to reduce maternal mortality rate and under 5 year age mortality rates will help India in reducing its disease burden. India also continues to have the highest TB burden with an estimated incidence of 2.2 million of the cases of the global 9.6 million [7]. A vast majority of Indian population has latent TB. Though deaths due to HIV/AIDS and TB have declined in all age groups in India, a 10.7% increase was observed in females in the age group 15–49 years in 2015 as compared to 1990 [8].

In this backdrop of still very high burden of maternal and infant mortality and TB related deaths, the country underwent an epidemiological transition brought about by economic development, rapid urbanization and lifestyle changes. Females continue to bear the maximum brunt due to continuing high maternal and child mortality rates, and infectious diseases coupled with additional burden of non-communicable diseases (NCDs). NCDs accounted for 60% of the 4.5 million deaths in females in India [9].

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We present here the current status of cardiovascular diseases (CVD) and its risk factors in females in India and discuss strategies to reduce the burden.

Epidemiology of Cardiovascular Diseases (CVD)

The office of the Registrar General of India reported that 62.3% of the medically certified deaths in India were of males and 37.7% were of females in 2015 [10]. Males had more access to hospital care at the end of life stage as compared to females. Access to hospital care is more in urban areas as most of the data on medically certified deaths are from urban areas [10]. As a result, there are huge gaps in understanding of CVD burden, especially in female and rural populations.

Diseases of the circulatory system/CVDs increased from 19.9% in 2004–06 to 33.2% in 2015; from 21.52 to 32.8% in males and 17.8 to 33.9% in females [10, 11]. Female deaths attributed to CVD almost doubled during the 10 year period. Around 12.1% of the CVD deaths occurred in premenopausal women (age group 15–44 years) and 84.2% in post-menopausal women. The distribution of major cause of CVD deaths as reported by MCCD 2015 is provided in Fig. 18.1 [11]. However, MCCD 2015 does not provide age wise distribution of major causes of CVDs. Rural areas continued to have lower CVD related mortality rates (<10%) as compared to urban areas (>35%) [12]. Geographical distribution of mortalities due to CVDs in India in 2015 indicates that different regions in the country are at different levels of epidemiological transition. The highest mortality rates due to CVD

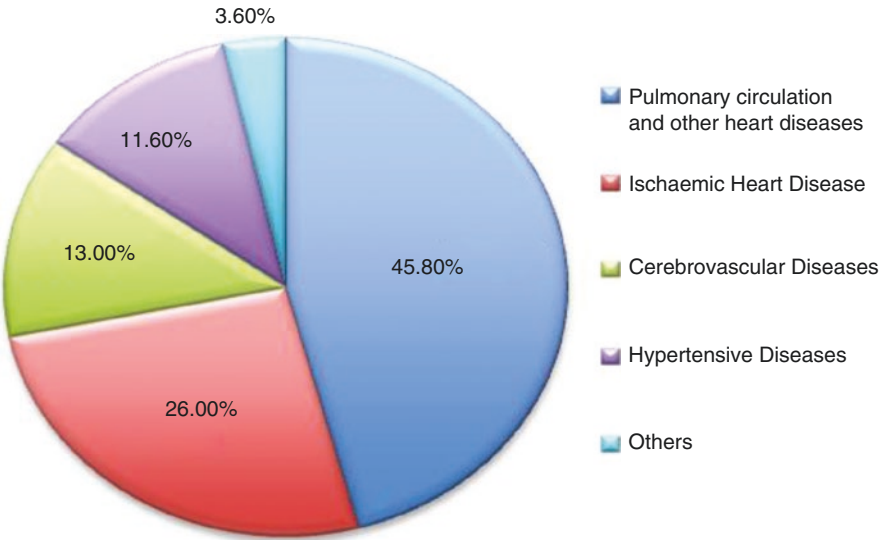

Fig. 18.1 Distribution of major cause of deaths among diseases of circulatory system under MCCD-2015 in females [11]

were seen in Southern States of Telengana (53%) and Tamil Nadu (50%), the lowest was in the North East State of Assam (6.9%) [10].

The Global Burden of Disease (GBD) study reports mortalities and morbidities due to CVDs, ischaemic heart disease, stroke and hypertensive diseases. Age standardized death rates for CVD in India have increased from 172.5 in 1990 to 212 per 100,000 population in 2015 as compared to global increase from 237.4 in 1990 to 243 per 100,000 population in 2015 [8]. CVD related deaths in all age groups increased by 2.41% globally as compared to 23% increase in India from 1990 to 2015 (Fig. 18.2) [9]. Although female deaths related to CVDs were reduced by 4.44% globally during this period; India witnessed an increase in CVD deaths in females by 13.16% [9]. Even in females in reproductive age group (15–49 years), there was 5.63% increase in CVD deaths and in 50 years and above, CVDs were the topmost cause of death in 2015. CVDs are now responsible for 1.15 million (42.6%) of the NCD related deaths in females in India with 43.5% of deaths occurring below 70 years of age (Fig. 18.2) [9]. However, disability adjusted life years (DALYs) showed a decline by 5.13% in all age groups and 30.68% in 15–49 years age group in females [9]. Years lived with disability increased by 17.05% in all age groups but decreased by 11.49% in females 15–49 years old [9].

Very few longitudinal studies have evaluated mortality rates due to CVDs in India. These findings of these studies are given in Table 18.1 [13–15].

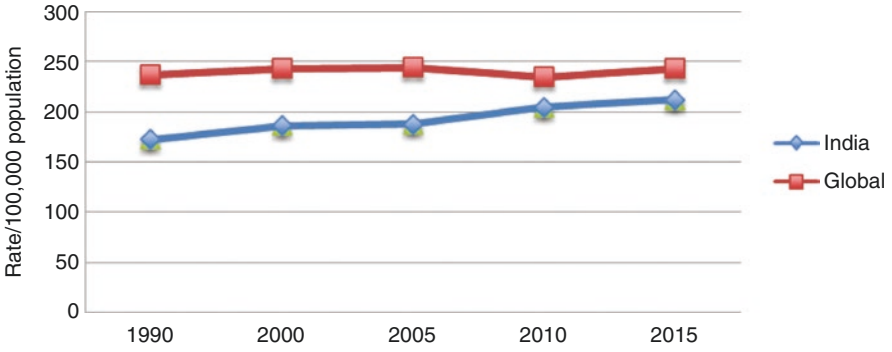

Fig. 18.2 Trends in age standardized death rates due to CVDs

Table 18.1 Mortality rates due to CVDs in India in longitudinal studies

Study	Study duration	Population studied	CVD mortality rates/100,000	
			Men	Women
Andhra Pradesh Rural Health Initiative (APRHI) [13]	2 years	180,162 (rural)	255	225
Kerala Based Population Registry of Lifestyle Diseases (PROLIFE) [14]	7 years	161,942	490	231
Mumbai Cohort Study (MCS) [15]	5 years	148,713	525	299

The Prospective Urban and Rural Epidemiological (PURE) Study (n = 156,424) in 17 countries had participation from four Low Middle Income (LMI) countries (India, Pakistan, Bangladesh and Zimbabwe; n = 33,834) [16]. The study had a follow up period of 4.1 years. India had the largest representation from LMI countries with a sample size of 29,258. Though the INTERHEART risk score was lowest in LMI countries, the annual incidence of CVD in LMI countries was 6.43/1000 as compared to 4/1000 in High Income countries; case fatality rates were 17.3% in LMI countries versus 6.5% in High Income countries [16]. This disparity was also observed among urban and rural areas of LMI countries. Rural areas had higher mortality rates as compared to urban areas, though the burden of risk factor was lower in rural areas [16]. The rural population suffers more because of poor access to healthcare and treatment. Women in these populations perform worse due to social disparities.

We present here a review of burden of important CVDs in females in India and the associated risk factors.

Rheumatic Heart Disease (RHD)

In India, Wig in 1935 provided the first clinical evidence of Rheumatic Fever (RF) in Punjab [17]. This was followed by large number of hospital based studies which by the mid 1950s established that RF/RHD was the most common cause of structural heart valve damage in the paediatric population [18].

RHD has been known to contribute to 30% of the cardiac admissions in secondary care hospitals [19]. As early as 1935, RHD was known to account for 40% of cases in males and 52% in females [20]. A house-to-house survey in an urban population of Chandigarh showed the prevalence of chronic RHD and RF to be 2.07/1000 among female subjects and 1.23/1000 among males [21]. Three large multi-center school based surveys were conducted by the Indian Council of Medical Research (ICMR) in children in the age group of 5–14 years between 1970 and 2010 [22]. The prevalence of RHD in the 2000–2010 study was 0.1–1.2 per 1000 of school children population and appears to be on the decline (Table 18.2) [22]. Registries

Table 18.2 Prevalence rates of RHD in children aged 5–14 years in ICMR studies from 1970 to 2010 [22]

Study	Number of Centres	Population size	Prevalence rate/1000 population (average)
ICMR study (1972–1975)	Five (Agra, Alleppy, Bombay, Delhi and Hyderabad)	1,33,000	0.8–11 (5.3)
ICMR study (1984–1987)	Three (Delhi, Varanasi and Vellore)	53,786	1.0–5.6 (2.9)
ICMR study (2000–2010)	Ten (Shimla, Jammu, Chandigarh, Jodhpur, Indore, Kochi, Wayanad, Mumbai, Vellore and Dibrugarh)	1,76,904	0.1–1.2 (1.1)

were set up at ten study sites under ICMR's 2000–2010 project in the same district where school survey was done. The surveillance by most of the registries under this project was using government healthcare facilities. The study was coordinated by us from ICMR Hqrs. Prevalence of RF/RHD was 84 (median) per 100,000 population with a range of around zero per 100,000 in Kochi, Kerala, South India to 161 per 100,000 population in Vellore, Tamil Nadu, South India [22]. Though RHD prevalence was similar among boys and girls in school surveys in this study, a greater number of RHD cases were registered among females 20 years and older [22]. In our own school based survey in Roopnagar district, Punjab, North India (2002–2009), the prevalence rate of RHD was 1.0 per 1000 school children with majority of cases (63%) occurring in females in age group of 5–14 years [23].A study from rural Himachal Pradesh in North India noted a prevalence rate of 5.8 per 1000 rural population with ten times higher prevalence in females than males [24]. Though the exact reasons for higher percentage of RHD cases in females is not clear, the data collected by the above studies may be biased because of inclusion of public sector healthcare facilities in the survey. It is likely that more females seek treatment from public sector healthcare facilities as compared to males who take more expensive treatment at private sector. Another possibility is that females with RHD were picked up during antenatal check-up as pregnancy related changes are known to increase the severity of RHD [25]. Women are also more likely to stay in the home environment and are therefore exposed more to over-crowding, a known risk factor for RHD. Detailed studies will be required to understand the reasons of RHD preponderance in females in India.

More recent studies using echocardiography indicate a 10–20 times higher prevalence of subclinical RHD in school children [23]. Revising Jones Criteria for acute RF diagnosis, American Heart Association in 2015 recommended use of Doppler echocardiography for diagnosing cardiac involvement [26]. In India, screening through portable echocardiography in community settings is difficult as it involves use of ultrasound machine which has been brought under the Pre-Conception and Pre-Natal Diagnostic Techniques Act for the purpose of prohibition of sex selection. As registration of echocardiography machine under this Act is a cumbersome process, this handy and cheap technology for detection of heart disease is not available to the general population because of social reasons.

The mortalities and morbidities due to RHD in India are considerably high as large majority of 2–2.5 million RHD patients in India are not able to afford expensive imported artificial valve replacements [18, 27]. The Randomized Evaluation of Long Term Anticoagulant therapy (RE-LY) registry indicated that RHD contributes to 33% of the atrial fibrillation burden in adults in India [18]. Recently Indian Heart Rhythm Society-Atrial Fibrillation (IHRS-AF) registry reported that 47.6% of Atrial Fibrillation patients have RHD [28]. The Atrial Fibrillation patients in India are younger (average age of 54.7 years) with a marginally greater number of females as compared to males (51.5% and 48.5% respectively) [28]. It is likely that this higher percentage of female Atrial Fibrillation patients is because of higher prevalence of RHD in females in India.

Ischemic Heart Disease (IHD) and Stroke

The cross sectional studies in different regions of the country used multiple criteria, (clinical history and/or ECG waves) to diagnose IHD. Based on these studies, prevalence of IHD has varied from 2% in urban area in 1960 and 1.7% in rural areas in 1970 and to 7.4% in rural areas and 14% in urban by 2013 [29, 30]. Females, in general, have lower prevalence rates of IHD than males. However, the time trends from two cross sectional surveys in Vellore (South India) in age group of 30–64 years in 1991–1994 and 2010–12 suggests that age adjusted prevalence rates of IHD have tripled in rural (7.6% in 2012) and doubled in urban (13.4% in 2012) areas for women [31]. In men, there was very little change. This increase in prevalence in women was seen in both pre- and post-menopausal women. Females had lower levels of previously diagnosed IHD, but had higher symptoms of angina and ECG evidence of ischaemia in the 2012 survey [31]. The risk factors found to be associated with IHD were female sex, urban residence, lower education, past history of smoking, low daily intake of fruits and vegetables, family history of premature heart disease, and diabetes mellitus. It will be important to undertake large scale studies in women in different parts of country to understand the exact trends.

The lifetime risk of stroke is known to be higher in women (1 in 5) as compared to men (1 in 6) [32]. The age adjusted prevalence rates of stroke in India range from 84–262/100,000 in rural and 334–424/100,000 in urban India [33]. The incidence of stroke is between 119–145/100,000. Case fatality rates have been reported to be as high as 42% in the city of Kolkata, State of West Bengal [33]. Age standardized stroke incidence rate from our recent population based urban stroke registry in Punjab, North India was 130 per 100,000 populations [34]. Age standardized mortality rates were reported to be 192/100,000 population in a rural population from North India in 2015 indicating that stroke is an emerging problem in rural India [35]. Data from north India cannot be extrapolated to the rest of the country as there are wide cultural variations resulting in very different dietary habits. Females have a higher age adjusted stroke prevalence rates (564/100,000 in females versus 196/100,000 in males) and incidence rates (204/100,000 in females versus 196/100,000 in males) [33]. Premenopausal women also had higher prevalence rates than men [33]. Ischemic stroke are more common in most of the regions of the country except for east and north east regions where hemorrhagic strokes are seen more.

Lack of nationally representative surveillance data hampers understanding of true burden of IHD and stroke in India. In MCCD 2015, both IHD and cerebrovascular diseases accounted for 39% of CVD deaths in females and 41.7% in males [11]. Government of India's Macroeconomic Commission of Health report estimates 62 million IHD patients in 2015 as compared to 36 million in 2005 [36].

Other Heart Diseases

Data on other heart diseases are scarce in the country. India's first heart failure registry observed that heart failure patients in India are younger (average age of 61 years) with higher mortalities in females (9.9%) as compared to males (7.4%)

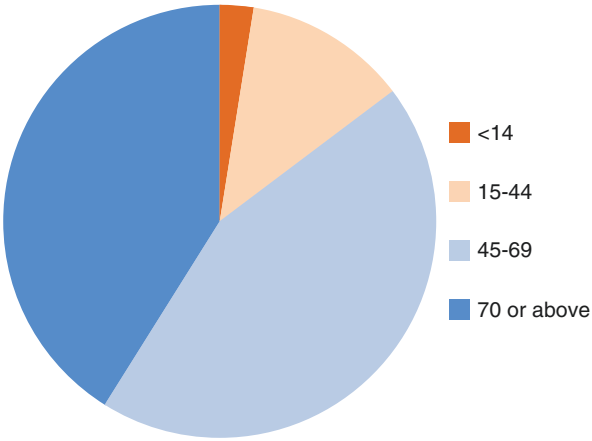

Fig. 18.3 Proportion of deaths in females due to CVDs in different age group [11]

[34]. Cumulative mortality at 90 days was 18.6% in heart failure patients [37]. Deaths due to hypertensive heart disease constituted 10.8% of deaths due to circulatory system/CVD deaths in MCCD 2015 [10]. Cerebro-vascular and hypertensive diseases constituted 13.0 and 11.6% deaths in females as compared to 10.3% in males [10] (Fig. 18.3).

CVD Risk Factors in Women

The National Family Health Survey 2015–16 (NFHS-4), the fourth in the NFHS series, provides information on population, health and nutrition for India and it's States / Union territories [5]. The survey collected data on various NCD risk factors like BMI, blood pressure, blood sugar and smoking. Significantly, the number of women in NFHS-4 survey in the age group 15–49 years who were anaemic was 53% (Fig. 18.4).

Around 21% of women were overweight or obese in NFHS-4 survey (2015–16) [5]. Urban women were more (31.3%) obese/overweight as compared to rural (15%) women. High blood pressure and diabetes were more prevalent in urban areas than in rural areas. Around 28–33% of the women tried to quit smoking in the given year, indicating higher prevalence of smoking in women than the reported 6.8% when asked 'Do you use any kind of tobacco?' [5] National Family Health Survey (NFHS-3; 2005–06) reported a very low consumption of fruits and vegetables (zero to 1 serving of fruit in a week) in both males and females [38].

Several surveys and cross sectional studies have shown that the burden of both behavioural and physiological risk factors in Indians is very high. As per Global Adult Tobacco Survey), there are 275 million tobacco consumers (164 million use smokeless forms of tobacco) ≥15 years, one million annual tobacco attributable deaths and quit ratios of lower than 20% makes it difficult to undertake prevention activities [39]. India, with 100 million smokers, is the second largest tobacco market in the world [40]. Of the males 15 years and older, 24.3% (99.9 million) use tobacco in some form. Use of tobacco in females is 2.9% (11.3 million), which is lower than

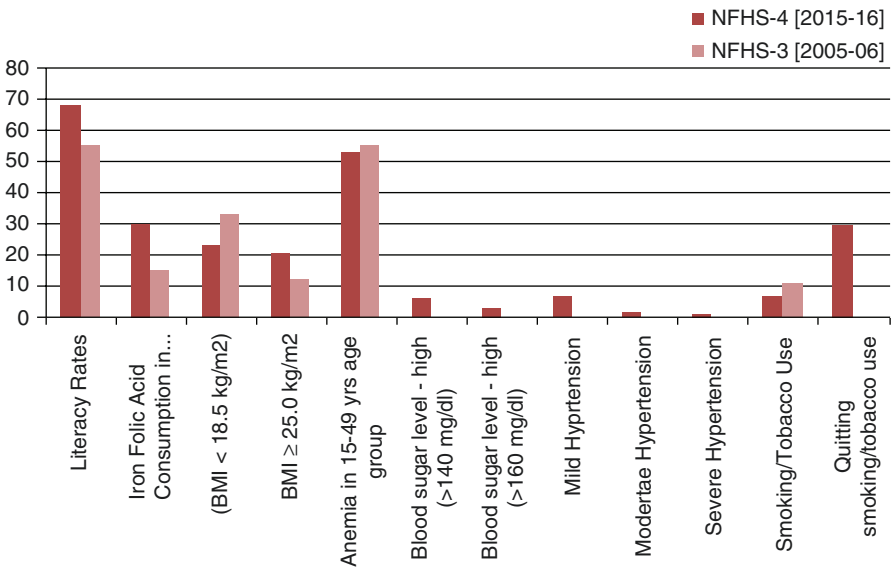

Fig. 18.4 Change in distribution of risk factors of CVD in females in India as per NFHS-4 survey [5]. Note: Datasets on blood sugar levels, blood pressure and quitting of smoking/tobacco use were measured only in NFHS-4

in males [40]. However, data from five nationally representative surveys indicate that smoking rates in females have doubled from 1.4 to 2.9% from 2005 to 2010 [41]. Smoking rates were higher (12.4 to 19%) in women of lower socio-economic status, making them more vulnerable to CVDs. Smokeless tobacco and bidis are commonly used by smokers in India. Women in India start smoking at a later age than their male counterparts [40]. Quit ratios are <20%, which is very low. The International Tobacco Control Project, India, surveyed individuals 15 years and older to find whether other users have an influence on use of smoked or smokeless tobacco [42]. The study suggested that besides the influence of close friends, the female smokers were nine times more likely to smoke if their mother smoked [42]. Thus tobacco cessation strategies in females will need to address the influence of family members in females.

Women in India are also more exposed to indoor air pollution. The main types of cooking fuel used by Indian households are firewood (49%), cow dung cake (8.9%), coal (1.5%), kerosene (2.9%), cooking gas (28.6%); electricity (0.1%), biogas (0.4%) and other means (0.5%) [43]. The use of biomass fuel during cooking increases concentration of particulate matter, carbon monoxide and aromatic. The household air pollution due to burning of these biomass fuels is responsible for around 40% of deaths due to chronic bronchitis and TB in women and 12% of stillbirths in India [43]. There are studies from other countries which indicate that indoor air pollution increases CVD mortality. A study from Iran, enrolled >50,000 adults mainly from rural areas between 2004–08 and followed

them up through 2012 [44]. The study observed that use of kerosene/diesel for home cooking increased the risk of CVD mortality by 10% for 10 years of its use. This could be reduced by 6% by using a cleaner fuel like gas [44]. Though women had lower baseline risk for CVD due to lower rates of smoking, the effect of indoor pollution due to cooking fuel was higher in this population. The Global Alliance for Clean Cook stoves is collaborating with many countries to reduce indoor pollution [44]. In order to reduce indoor pollution, Government of India announced Pradhan Mantri Ujjwala Yojana Scheme in 2016. Under this Scheme, free cooking gas connections will be provided to women/50 million families under below-poverty-line in next three years.

ICMR-India Diabetes Study suggests that one out of every two Indians are physically inactive, 77 million Indians are pre-diabetic and 80% have abnormal lipid levels [8, 45, 46]. World Health Organization on World Health Day 2016 stated that 8.7% of India's population (69.2 million) is diabetic. The prevalence of diabetes is between 4.6% and 14% in urban areas and 1.7% and 13.2% in rural areas [47]. Women with gestational diabetes mellitus have higher risk of developing diabetes. At any given point of time, 4 million women in India have gestational diabetes mellitus [47]. Prevalence of gestational diabetes mellitus in States of Punjab and UP has been reported to be 35% and 41%, whereas that in Kashmir is 3.2% and in Tamil Nadu state is 17.9% [47].

Prevalence of hypertension is around 30% in the adult population ≥ 18 years and that of diabetes is 17% in urban and 9% in rural India [45, 46]. Prevalence of physical inactivity was greater in urban areas (65%) than in rural (50%) and in females (63%) as compared to men (45.7%) [46]. Hypertension caused 1,638,050 deaths due to poor control of blood pressure in India surpassed only by China [8]. In India, 931,524 of hypertension related deaths were in males and 706,526 in females [8]. High rates of hypertension prevalence have been reported in populations taking high salt tea. Hypertension prevalence rate of 37% have been observed in high altitude Ladakh (Himachal Pradesh) population consuming salted tea and 43% in migrants settled in Leh [48]. Importantly, hypertension prevalence in the Indian population continues to escalate.Two cross sectional surveys in adults aged 35–64 years were conducted by ICMR between 1991–94 and 2010–12 in urban and rural National Capital Region and Vellore [28, 45, unpublished data with ICMR]. The prevalence of hypertension increased from 23.0 to 42.2% and 11.2 to 28.9% in urban and rural NCR of Delhi and from 18.2 to 25.7% in urban and 7.5 to 15.3% in rural areas of Vellore between the two surveys. The rise in prevalence of hypertension was more in men in rural areas (191% in rural NCR and 127% in Kanayambadi block near Vellore) than in females. Significantly, the proportion of subjects with optimal blood pressure (BP<120/80 mmHg) in survey 2 decreased to 34% as compared to 52.5% in survey 1. The prevalence of alcohol use, obesity, abdominal obesity and diabetes increased significantly among those with hypertension in survey 2 compared with survey 1 in both regions of the country.

There was no change in the overall awareness, treatment and control rates of hypertension between the two surveys in the NCR [49]. The overall awareness (46.4% vs. 26.8%), treatment (40.0% vs. 20.4%) and control rates (15.9% vs. 8.0%)

in rural areas remained much lower than in urban NCR areas. Women in both urban and rural NCR areas had higher health seeking behaviour. However, all hypertensive subjects performed poorly as far as lifestyle modifications were concerned. There was an increase in physical activity in only 22% of rural and 27% of urban hypertensive subjects. Females performed worse. The dietary modifications were there in 55% in rural and 70% in urban areas.

The implications of rise in high blood pressure and poor health seeking behavior in Indians are gruesome. As per GBD 2015 report, hypertension accounts for 67% of 313,000 chronic kidney disease deaths and around 50% of the 24million strokes and coronary heart disease (CHD) deaths in India [8]. In ICMR's urban Punjab stroke registry and Management of Acute Coronary Event (MACE) registry running at 27 centres around the country (unpublished data), hypertension was the most common risk factor in stroke (81%) [34] and heart attack (47%) cases. Chances of stroke are known to be higher in females with hypertension. Females presenting with heart attack in MACE registry had higher prevalence of hypertension (60%) as compared to males (43%). Smoking, overweight/obesity and diabetes were found to be present in 29%, 25.1% and 53% of heart attack patients with hypertension [MACE registry; unpublished data].

Strategies for Reducing CVDs in Women

The cardiovascular health is known to decrease with age, from adolescence to adulthood. Starting as early as possible in the course of life is being advocated as the best approach to prevent or delay CVD and other chronic diseases. Intervening at the stage of conception or better at pre conception stage may set an individual on a healthy life trajectory. The importance of 'Suprajanan', science related with preparing the process of childbirth in advance, has been mentioned in Ayurveda. The Vedic culture in India promoted 'Garbha sanskaar'(Garbha: foetus; sanskaar: ritual) so that preparation of childbirth becomes an experience for creation of a healthy individual. The Garbha sanskaar has three stages (1) Preconception (beej sanskaar); (2) Duration of pregnancy (Garbha sanskaar) and (3) Post-delivery (Bal sanskaar). These three stages can be addressed through maternal nutrition and keeping her mental, physical, emotional and spiritual state healthy. This strategy is what has been referred to as primordial prevention of CVDs. The adolescent to adulthood stage can be tackled through primary prevention models targeting risk factors. The last strategy is secondary prevention through provision of access to healthcare.

In India, this can be done through:

1. Targeting maternal nutrition for primordial prevention
2. Targeting primary prevention through the National Program
3. Targeting secondary prevention through management of acute coronary syndrome (ACS) cases.

Targeting Maternal Nutrition as a Primordial Prevention Strategy

Barker's hypothesis that low birth weight contributes to diabetes, cognitive dysfunction and other NCDs has been confirmed by studies in Indian birth cohorts. Forty two percent of pre-pregnant women in India are underweight and a large percentage of pregnant women are not healthy [50]. As per NFHS-4 (2015–16), only 30% of the pregnant women consume iron folic acid for 100 days or more [5] (Fig. 18.4). A staggering 50% of women in reproductive age group of 15–40 years are anaemic [5] (Fig. 18.4). These factors are likely to translate into high rates of neonatal mortality and low birth weight babies. In a cohort of low birth children born to rural undernourished women, the babies were found to be small, had reduced abdominal viscera and muscle mass, continued depositing fat and had insulin resistance at age of 4 years [51]. This 'thin –fat insulin resistant' phenotype in South Asians is now widely accepted. The importance of maternal nutrition on developing foetus's epigenome is also known [51]. Improvements in maternal nutrition are thus likely to be a cost effective strategy in preventing development of CVDs in later life. The inclusion of adolescents in the Program "A Strategic Approach to Reproductive, Maternal, Newborn, Child, and Adolescent Health (RMNCH+A) in India", launched in 2013, can have marked influence on cardiac health of the next generation, if properly implemented [52].

Primary Prevention of CVDs Through National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS)

India launched NPCDCS in 2010 in 100 districts with an aim to build national capacity and strengthen infrastructure for promotion of health, early diagnosis, referral and management of cases. The funds for this program are provided to States under the NCD Flexi Pool. By March 2017, all 36 States/Union Territories in India had State NCD Cells, whereas District NCD Cell could be established in 390 of 707 districts under this Program [53]. Number of District NCD clinics was 388. Of the 4883 CHCs, 2115 had CHC NCD Clinics. Also, 133 cardiac care units have been established for management of cardiac emergencies [53]. In the last 3 years, 22.4 million persons attended NCD clinics of which 9.7% had diabetes, 12.09% had hypertension and 0.55% had CVDs [53]. The absolute number of people with CVDs was 123,200. Outreach activities in primary healthcare facilities and health camps in 2016–17 covered 16.8 million people. Recently, a population based strategy for screening of diabetes, hypertension, cervical and oral cancer has been initiated by National Health Mission in 100 districts. Also a pilot project "Integration of AYUSH with NPCDCS" has been initiated in six districts. This program is intended to harness the benefits of alternate medicine in prevention and control of CVDs. Government of India has also recently launched a pilot program in three districts for prevention and control of RF and RHD (Fig. 18.5).

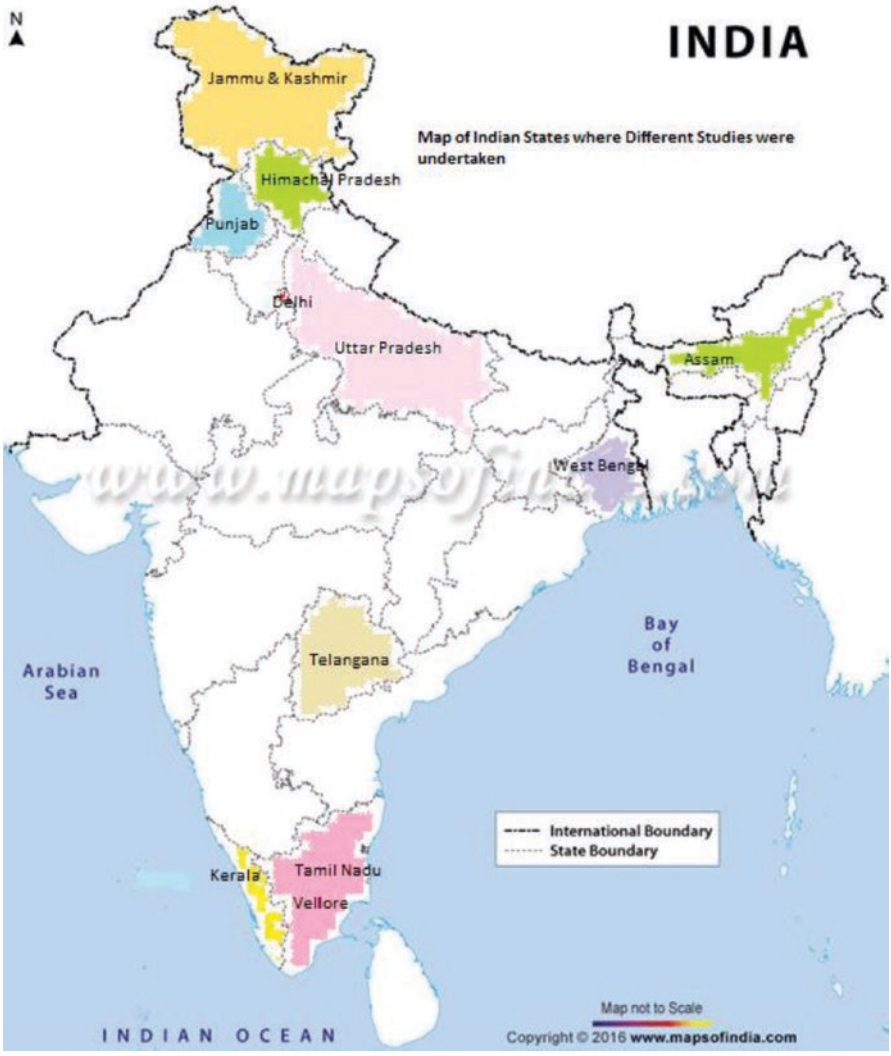

Fig. 18.5 Map of India showing the regions in which different studies mentioned in the chapter were undertaken

Secondary Prevention Through Management of ACS in Females: The STEMI Challenge

ICMR's ongoing Management of Acute Coronary Event (MACE) registry observed that 21.8% of admitted Acute Coronary Syndrome (ACS) and 18.9% of ST elevated myocardial infarction cases (STEMI), a severe form of heart attack, admitted in hospitals were females (unpublished data). CREATE registry from India collected

data between 2002–05 and had similar findings (23.6% and 18.5% of females with ACS and STEMI respectively) [54]. Around 7% of the ACS cases among females in MACE registry were in the age group of 18 to 44 years and 40% of these had STEMI (unpublished data). Prospective Rural and Epidemiological (PURE) study, CREATE registry, Kerala ACS registry and unpublished data of ICMR's Management of Acute Coronary Event (MACE) Registry indicate that symptom to door time to hospital in ACS cases is abysmally high in Indian patients. As a result, mortality rates are higher in lower SES (8.2%) than in higher SES (5.5%) [54–56]. In STEMI cases, a median time of 300 min was observed when ACS patients were able to reach directly Cath lab enabled facilities. However, if the first medical contact was other than Cath lab enabled facility, the symptom to door time is much higher. Females with STEMI in the age group 18–44 years reached hospital very late (720 min) (MACE unpublished data). This may be because females may experience ACS/STEMI differently and exhibit different symptoms as compared to males. Females are less likely to present with chest pain [57]. Moreover, females and lower socio-economic patients are lesser educated and are more likely to be less aware of symptoms of acute coronary event (ACE) as well as its risk factors. The delay in presentation can be major cause of lost opportunity for thrombolytic treatment in STEMI cases resulting in poor outcomes in females.

Opportunities in STEMI Management

As per WHO, the density of physicians per 1000 population in India was mere 0.725 in year 2014. The number of cardiologists is even far lower. Therefore, mere setting up of Cardiac Care Units under the National program (NPCDCS) does not assure provision of care facilities to cardiac emergency patients.

The main challenge in India remains management of emergency cases at various levels of the healthcare system. ST elevated Myocardial Infarction (STEMI) requires very prompt recognition, triage and reperfusion. Educating females regarding symptoms of STEMI and other heart attacks is needed to reduce the time from symptom to hospital door. The major challenge for India in management of STEMI in peripheral settings is shortage of physicians, availability of cheap drugs, and out of pocket expenditure. A hub and spoke model using pharmaco-invasive therapy, ambulance facility, chief minister insurance scheme and a novel technology (STEMI kit) for ECG transmission has been successfully deployed in a district of Tamil Nadu [58]. Few states are in the process of scaling up of this model.

The next challenge is provision of reperfusion therapy to STEMI cases at a low cost. The universal healthcare coverage planned by Government of India is definitely going to be a big step in this direction. Reduction in costs of treatment will be beneficial to the county at large. The major breakthroughs in STEMI care globally are fibrinolytic therapy and primary percutaneous intervention. Bacterial streptokinase has been used as a clot buster since 1970, but is non specific and can cause of haemorrhagic complications. Genentech recombinant human tissue plasminogen

activator (tPA) introduced in 1990s, gets activated only in presence of fibrin. However, the prohibitively high cost of tPA ($460 per dose) as against streptokinase ($ 30 to $ 40) makes its access difficult to Indian population in general and female patients in particular given the huge gender disparities [59, 60]. Only recently, CSIR-IMTECH has developed a third generation Clot Specific Streptokinase (CSSK) in collaboration with Nostrum Inc., US. The drug has received permission for phase II clinical trials (CTRI/2014/03/004442) by Drug Controller General of India (DCGI) in 2017 and if found effective, will provide cheaper alternatives. Similarly, the overpricing of coronary stents hampered access to percutaneous intervention to emergency care by poor patients in India. The National Pharmaceutical Pricing Authority (NPPA) has early this year capped the price of bare metal ($112) and drug eluting cardiac stents (DES; $463) [61]. This has brought a major relief to the patient population. The country has also developed indigenous technology for the stents which needs to be tested against imported stents for quality [62, 63]. Though, it appears logical to conclude that these cost reduction strategies will increase access to healthcare in female patients, further studies will be required to assess the exact impact.

Conclusions

There are gaps in our understanding of the magnitude of the problem in women. The current data available in the country indicate higher prevalence of CVDs in females in India. The most prominent risk factors in women are hypertension, diabetes, obesity, physical inactivity, low consumption of fruits and vegetables. Though smoking rates are low in Indian females, the exposure to indoor pollution makes them highly prone to cardiovascular diseases. The higher malnourishment in females makes them highly susceptible to metabolic diseases. India will need to build models to improve maternal nutrition, educate women regarding CVDs and their risk factors and develop primary and secondary prevention models under the NPCDCS.

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Chapter 19
Regional Differences in HD in Women

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Geographic and Racial CVD Disparities in Women

Introduction

Cardiovascular disease (CVD) is the number one cause of death throughout the world, accounting for 17.5 million deaths in 2012. Of this number, 7.4 million deaths were attributed to coronary heart disease (CHD) while 6.7 million deaths were attributed to stroke [1]. Eighty-two percent of non-communicable disease deaths occur in low-to-middle-income countries; 37% of which are caused by CVD [1]. Notably, CVD rates, which continue to escalate, are a growing health concern with staggering economic effects throughout the world. Globally, low-to-middle-income countries are disproportionally impacted by CVD with the poorest people being most affected, further contributing to poverty due to catastrophic health spending [1]. Thus, at the macro-economic level, these countries' economies bear a heavy burden associated with CVD [1]. CVD accounts for nearly one out of every three deaths in the United States (U.S.) [2]. Approximately 2200 Americans die each day from CVD, an average of one death every 40 seconds [2]. Costs associated with CVD in the U.S. currently are approximately $316 billion annually, including both health expenditures and lost productivity [2].

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Geographic and Gender Differences in CVD Burden

CVD is the leading cause of death in women worldwide although it is often still viewed as a disease that primarily affects males [1, 3]. Women have higher CVD mortality rates than men in rural and urban areas but the highest mortality rates are among women in rural areas, especially in women of color [2]. Because women typically live longer than men, worldwide, 54% of adults over age 60 are women [3]. In this age group, CVD is the leading cause of death regardless of the status of the country (developed or developing), accounting for 46% of deaths as compared to 14% due to cancer [3]. Long-standing behavioral choices of women contribute to high CVD mortality rates. For instance, rates of tobacco use in adolescent girls are increasing overall worldwide and are approaching those among adolescent boys [3]. Additionally, longstanding unhealthy diets and lack of physical activity contribute to women's risk factors for CVD [1]. Depression is also often linked both as a contributor to and outcome of CVD [4]. According to the World Health Organization (WHO), depression is the major cause of disease burden in women, such as CVD, regardless of women's income status and frequently leads to suicidal ideation and completion [3]. Women in geographically rural areas in China have a higher number of suicide attempts and completion rates than men residing in rural areas [3]. Additionally, women throughout the world have higher disability rates than men, especially women residing in poverty and who have low education levels; this further contributes to depression and compounds disease burden [3]. Women are more likely to be disabled after a CVD event than men, which may contribute to depression rates [5, 6].

Women in the U.S. have many risk factors for developing CVD, similar to women worldwide [2, 6]. However, women's risk factor burden varies by geographic location, race/ethnicity, and socioeconomic status [2]. There is wide variation in CVD mortality rates by region, state, and county [7]. Indeed, CVD mortality rates may differ substantially within the same city or county, most likely reflecting the overall impact of social determinants of health [7, 8]. According to Dr. Gary Gibbons of the National Institutes of Health, understanding these state-based, county-level variations should provide the foundation for developing multi-sector interventions tailored to the needs of specific locations, assist in determining required doses of interventions, and inform policy decisions [8]. Women in the U.S., especially minority women, disproportionality reside in poorer neighborhoods and experience the negative impact of social determinants of health, increasing the disparity in CVD mortality rates by geographic location [2]. Therefore, gender/geographic disparity in CVD mortality rates may be partially due to women's increased risk factors as compared with men, especially in those residing in rural areas.

Therefore, this chapter will explore: rural/urban differences in CVD incidence/prevalence, risk factors, treatment and outcomes for women with an emphasis on disparities by race/ethnicity within geographic areas. The authors conducted a search of PubMed, CINAHL, and Medline using the keywords of cardiovascular disease, rural, urban, African American, Hispanics, neighborhood and women.to identify pertinent articles related to women's CVD geographic and racial/ethnic

disparities. Research in this area is very sparse so the authors will discuss: (1) gender differences in the U.S. in rates, symptoms, awareness of risk factors, treatments, followed by (2) rural/urban differences for women overall and by race/ethnicity, followed by (3) relevant literature on rural/urban differences for women (not by race/ethnicity) and differences for women by race/ethnicity (not by rural/urban).

Geographic Location and Outcomes

It is important to evaluate CVD outcomes by geographic locations such as rural vs. urban due to the noted widening disparities [9, 10]. According to research, CVD mortality rates in the U.S. rural population are significantly higher than among their urban counterparts ($p < 0.001$) [9]. Additionally, the highest rates are found among rural Blacks [9, 10]. Some of the disparity in CVD mortality may be explained by the greater prevalence of CHD (OR = 1.09, $p = 0.011$) and of the important risk factors of diabetes mellitus and hypertension [11]. Residents of rural areas often have more socioeconomic and health risk factors for CVD including poverty ($p < 0.001$), obesity ($p < 0.001$), and tobacco use ($p < 0.001$) [11]. In fact, one study found that people who lived in rural areas from childhood to mid-adulthood were at increased risk of being overweight or obese later in life (0.29 kg/m^2 increase in body mass index per time point in a rural area) [12]. Additionally, rural populations in the U.S. are more likely to have less access to primary care providers and to the financial resources needed to seek medical care, resulting in both lower rates of primary and secondary preventive measures and to increased mortality and disability rates [11].

However, definitions of rurality used in the research literature and across different government agencies vary widely. A single, generally accepted geographic classification scheme for the rural/urban continuum (and thus a common definition of geographic rurality) remains elusive. These rural definitions vary in description according to population density, isolation or distance to nearest town, agricultural landscapes, and size of community [13]. The variation in definitions used makes it difficult to compare CVD outcomes across studies because each researcher chooses a definition that is most relevant to their study purpose [13]. Therefore, we have included any studies regardless of definition that examined geographic CVD disparities in this review.

Rural VS. Urban Populations

The U.S. all-cause mortality rate is higher in rural areas than in urban ones. CHD mortality rates have decreased for women, but this reduction has not been equitable across geographic region or racial/ethnic groups [9, 11, 14]. Kulshreshtha et al. [14] reported a 40% decline in overall age-adjusted CHD mortality rates; despite similar proportionate declines in rates for Blacks and Whites, Blacks had consistently higher CHD mortality rates than Whites [14]. Changes in CHD mortality rates also

varied across the geographic spectrum. From 1999 to 2009, CHD mortality declined 42% in large metropolitan areas, by 40% in medium metropolitan areas, and by only 35% in rural areas. By 2009, CHD mortality rates were higher in rural than in urban areas. Blacks had higher CHD mortality than Whites across all urbanization levels in every region of the country throughout the study period. In fact, race/ethnicity and rurality were found to be independent predictors of CHD mortality. Notably, rates of early-onset CHD mortality (before age 65) were consistently higher in rural than urban areas from 1999 to 2009 and declined more slowly in rural areas (22% vs. 35%, respectively), widening that gap even further [14].

In a separate study, O'Connor et al. found that crude prevalence of CHD was 38.8% higher in rural than urban areas [11]. The authors compared risk factors for both genders of rural and urban residents, and found that tobacco use, obesity, and age were all higher while income was lower in rural than in urban areas ($p < 0.001$ for all) [11]. Interestingly, after controlling for CHD risk factors including gender, age, weight, ethnicity, tobacco use, and income, people living in rural areas were still more likely to have CHD than those living in urban areas (OR = 1.09, $p = 0.011$) [11]. This suggests that the increased CHD prevalence in rural areas may be due to factors such as more limited access to health care and healthy food. These studies demonstrate that while CHD prevalence and mortality may have been higher in urban areas in the past, they are now higher in rural areas, in part, due to slower rates of decline in rural areas. This may indicate that urban areas have benefitted from increased education and to reduced risk of CVD and CHD, but rural areas have not received such benefit.

A nationwide study that examined the impact of a 'rural penalty' for Black and White residents, found that both Blacks and Whites had higher mortality rates in rural than in urban areas and Blacks had higher mortality rates than Whites in both rural and urban areas [15]. A recent study (N = 67,047) examined data from patients who had been evaluated by emergency services and found that a higher percentage of rural patients died shortly after injury (90% of rural deaths occurred within 24 hours compared to 64% of urban deaths) [16]. Mortality was also higher among rural patients who had been transported to a hospital in the first 24 hours (rural 0.65%; 95% CI 0.17%–1.13% vs. urban, 0.13%; 95% CI 0.09%–0.16%), although there were no significant differences in mortality when compared across the entire hospital stay [16]. Another nationwide study found that rural residents received lower levels of health care screenings such as cholesterol screening; this varied by race/ethnicity with the lowest screening rates experienced by Blacks [17]. Women are even less likely than men to receive CVD-related screenings regardless of where they live [18]. This puts rural minority women at the greatest risk of not receiving preventative screenings and not receiving timely care when experiencing an acute stroke or CHD event.

Neighborhood Characteristics

Health outcomes also vary by neighborhood characteristics, whether in rural or urban areas. Sociocultural attributes, such as economic conditions, social conditions, walkability, traffic rates and patterns, number of store fronts, and concentration of fast

food restaurants, influence the health status of residents and may contribute to development of CVD risk factors. For instance, Adams et al. [19] reported that neighborhood characteristics such as street connectivity, lack of parks, and high crime rates have significant detrimental effects on the health of senior citizens (aged 66–97) who often live on fixed incomes and walk in their neighborhoods for physical activity [19]. Since CVDs are more prevalent among senior citizens and increased physical activity is a primary intervention to combat obesity, diabetes, and hypertension, all potent CVD risk factors, such neighborhood characteristics may partially explain differences in health outcomes for those living in poor and unsafe neighborhoods compared to those living in more affluent and safer neighborhoods. A study by Li et al. [20] supports the idea that neighborhood characteristics impact health [20]. They reported a statistically significant association between decreased systolic and diastolic blood pressure for those living in highly walkable vs. less walkable neighborhoods ($p < 0.001$). Traffic density and proximity to major roads, attributes that contribute to less walkable neighborhoods, were associated with increased incidence of CHD in residents aged 45–64 [21]. Many rural areas in the U.S. have gravel two-lane roads with no walking paths, making walking unsafe. Since many women with lower socioeconomic status live in rural areas, not being able to walk in a safe environment makes it difficult for them to engage in the physical activity needed to decrease major risk factors like obesity, hypertension, and diabetes.

In rural areas, access to nutritious food such as fresh fruits and vegetables is also a challenge. Research indicates nutritious food items generally cost less in urban areas, but cost is highest in rural areas where there are large concentrations of Black residents as compared to those with White residents [22, 23]. Supermarkets and grocery stores are not the only avenue to obtain fresh nutritious food [24]. Nontraditional food stores such as discount stores are becoming more prevalent and are carrying a greater variety of nutritious foods, including fruits and vegetables [24, 25]. However, some nontraditional stores identify neighborhood crime as a barrier to opening/sustaining their businesses, thus limiting healthier food options for those in unsafe neighborhoods [26].

Many residents in rural areas report traveling great distances (up to 80 miles) to shop for high quality food [27]. One study in rural Texas found the average distance to a supermarket for rural residents to be 9.9 miles vs. 4.5–4.7 miles to a nontraditional store with fresh and processed fruits and vegetables [24]. Limited distance to a food store is linked with increased consumption of fruits and vegetables, necessary dietary changes as recommended by the American Heart Association to decrease CVD risk factors [24]. This is especially important for rural dwelling women who often have difficulty obtaining transportation to supermarkets. However, food affordability is also an important factor [28]. Supermarkets and grocery stores usually have a greater variety of healthy foods at a lower price than convenience stores [29]. Drewnowski et al. [28] found an inverse relationship between the price of food in a supermarket and obesity rates. Shoppers at higher cost supermarkets had lower obesity rates than shoppers at the lower cost supermarkets, perhaps because they are of higher socioeconomic levels and more weight conscious [28].

Diabetes is a well-documented risk factor for CVD and CHD [2]. Although O'Connor et al. found that unadjusted diabetes prevalence rates are higher in rural than urban populations, this association is non-significant after adjustment for poverty, obesity, and tobacco use [11]. However, according to another study, residents of most rural areas (62%) do not have access to diabetes self-management education (DSME) programs which focus on managing and preventing complications of diseases such as CVD [30]. Rural areas without a DSME program were less affluent, had a higher proportion of Black and Hispanic residents, and had a higher prevalence and incidence of diabetes [30]. Blackmon et al. [31] found diabetic medications are frequently under used in the rural Black population and reported financial limitations as a major barrier to medication adherence in this population. Medication adherence in this study was associated with being insured ($r = 0.594$; $p = 0.001$) and employed ($r = 0.440$, $p = 0.05$) [31]. Strict management of diabetes is critical to preventing the development or worsening of CVD. However, rural populations, especially Black and Hispanic rural populations, have fewer resources to manage diabetes [30].

Another important characteristic of neighborhoods that may contribute to developing CVD is the type and availability of restaurants. In adults aged 50–74, the greater density of fast food restaurants is positively associated with obesity [32]. Additionally, a systematic review of studies of the impact of the built environment in multiple countries found that body mass index, blood pressure, diabetes mellitus, and metabolic syndrome rates were associated with the density of fast food restaurants, supermarkets/grocery stores, and highly walkable environments [33]. Sixteen percent of the studies reviewed ($n = 18$) specifically focused on CVD outcomes and neighborhood attributes [33], all of which reported an association between neighborhood attributes and CVD outcomes (myocardial infarction [MI], CHD, congestive heart failure, angina, and stroke) [33]. Barber et al. [34] examined neighborhood disadvantage, social conditions, and CVD incidence in Blacks in the Jackson, Mississippi area. They found neighborhood disadvantage to be associated with a 25% increase in CVD risk for Black women compared to Black men after covariate adjustment (HR = 1.25; 95% CI = 1.05, 1.49) [34].

Minorities in the U.S.

Hispanics comprise the fastest growing ethnic group in the U.S. In 2014, they made up 17.3% of the U.S. population [35]. Twenty percent (11.1 million) of Hispanics were undocumented immigrants with limited or no access to health insurance, and thus little access to health care except in emergency situations [35]. Access to health care in the U.S. is largely driven by health insurance. In every industry, Hispanics are less likely than Whites to have employer-sponsored health insurance; 63% of Whites vs. 38% Hispanics had employer sponsored health insurance in 2014 [36]. The actual rate of health insurance coverage for Hispanics is likely to be less than 38%, because the estimates do not include undocumented Hispanics [37]. Furthermore, at the present time, access to medical care varies enormously from

state to state. In some states, undocumented immigrants are eligible for Emergency Medicaid for catastrophic illnesses such as cancer; other states cover initial visits only and do not cover ongoing care.

In the 1990s, an influx of new immigrants started to settle in the primarily rural and socioeconomically depressed areas of the U.S. Midwest and South, e.g., in Alabama, Arkansas, Georgia, North and South Carolina, and Tennessee, areas with limited access to health care. Undocumented immigrants are often fearful of seeking health care even when it is available, speak little or no English, and have low educational and socioeconomic levels [35, 36]. These adverse social determinants of health put them at increased risk for developing multiple risk factors for CVD and CHD. Providing preventive health services to this population prior to the development of chronic illnesses such as CVD or CHD would be more cost effective than treating them in emergency settings after, for example, an MI [37].

In contrast, most Blacks are U.S. citizens and speak English. The largest concentrations of Blacks are also found in the southern U.S., and they share many of the same health challenges as Hispanics such as living in rural areas with limited health care services, poor access to nutritious food and safe places to exercise.

Neighborhood Segregation

There are inconsistencies in findings regarding segregation and health outcomes among minority groups but there is substantial literature revealing that residential segregation is deleterious to the health of Blacks [34, 38–42]. Blacks are the most residentially segregated group in the U.S. and the group at highest risk for CVD and its consequences [43]. Residential segregation, whether in rural or urban areas, increases health disparities through many avenues including fewer employment opportunities resulting in inadequate income and lack of health insurance, poor access to health care, fewer stores that offer fresh fruits and vegetables, lack of parks and other safe places to exercise, and increased air pollution, noise, and violence [43]. Many studies indicate that Blacks living in highly segregated neighborhoods have higher mortality rates from CVD, higher incidence of hypertension and poorer control of their hypertension compared to Whites and Hispanics [39, 41, 42, 44].

The relationship between residential segregation and health among Hispanics is more complex. Some research shows that Hispanics living in segregated neighborhoods tend to have worse health outcomes than Whites, especially for infectious diseases [45]. However, the bulk of research suggests that segregated neighborhoods for Hispanics may be beneficial and protective to their health. This benefit has been demonstrated in studies of mortality, disease prevalence, and CVD risk factors [46, 47]. Other authors identify the “Hispanic paradox”; the tendency for Hispanics to have better health and lower mortality than other groups of similar socioeconomic status despite presence of risk factors [48, 49]. This paradox wanes as the population becomes more acculturated. Others theorize that the “Hispanic paradox” does not exist, but that lower mortality rates in this population are merely due to inaccurate reporting of Hispanic deaths. This is possible since most of the studies to date primarily focus on Hispanics who speak English, have access to health care, and

have access to a telephone, most likely omitting the most vulnerable immigrants. However, one systematic review and meta-analysis investigated the possibility of a Hispanic mortality advantage and concluded that the Hispanic population has a 17% lower risk of mortality compared with other racial groups [50]. Hispanic ethnicity was also associated with a 25% reduced mortality advantage among individuals with CVD in the U.S [50].

Awareness of CHD in Women

Despite public awareness campaigns to improve women's knowledge about CHD, women continue to have less timely treatment, poorer outcomes of care, and higher mortality rates compared with men [51, 52]. Minority women (Blacks, Hispanics, Native Americans, and immigrant women in rural America) are more likely to suffer from CHD, but less likely to be aware of their cardiac risk than White women [11, 53]. Factors that contribute to increase CHD rates in minority women include decreased health care coverage, lack of access to health services, cultural and social attitudes, and dietary habits [54].

Since 1997, awareness of heart disease as the leading cause of death in women has improved, but awareness among minority women continues to lag [51, 52]. Black women persistently have lower levels of heart disease awareness than other races/ethnicities. In 2012, awareness of heart disease among Black women was similar to that of White women in 1997, indicating that awareness campaigns have not reached this high risk group of women [51]. Studies conducted by the American Heart Association targeted women who were English speaking, were willing to complete a telephone interview or online survey, and were relatively educated. These criteria excluded a large portion of the Black and Hispanic women; therefore, actual levels of awareness may be lower than reported in these populations. Similarly data show that Hispanic women have lower levels of heart disease awareness than White women and are not aware that men and women may have different presenting symptoms for an MI [53]. In awareness studies, women reported they most commonly accessed health information including information about heart disease from media sources such as magazines and television. It is unclear whether the information from these sources was available in languages other than English and/or were written at an appropriate literacy level. This is especially important for Hispanic women, many of whom do not speak or read English.

Stroke Awareness

Just as with CHD, knowledge of stroke warning signs is low among women of all races/ethnicities. According to a national telephone survey of women ≥25 years old in the U.S. (N = 1205), only 51% of women recognized sudden unilateral weakness

or numbness of the face or limb as warning signs for stroke and this did not differ significantly by race or ethnicity [55]. The significance of difficulty speaking or understanding speech was recognized by 44% of women overall; recognition was lowest for Hispanic women (White: 48%, Black: 44%, Hispanic: 36%) [55]. Fewer than 25% of women knew that sudden severe headache, unexplained dizziness, or change in vision were stroke warning signs. The majority of women (84%) knew to call 911 if they thought they were having a stroke and this did not vary among White, Black, or Hispanic women. The survey was conducted in English, which may affect the data regarding Hispanic women, and was conducted by telephone which limits participation to those with telephones. It is possible that those with lower educational levels and socioeconomic status may not have participated. Therefore, these statistics may be over-estimates of recognition of stroke symptoms.

Ennen and Zerwic [56] compared rural (defined as areas with fewer than 2500 people) and non-rural residents' knowledge of stroke symptoms through mailed surveys (N = 566; 42% female; 50% rural). Younger participants (≤65 years of age) had higher stroke symptom knowledge than older participants (>65 years of age) ($t = 2.67$; $p < 0.01$); however, there were no statistically significant differences in stroke knowledge scores by gender. Interestingly, those in rural settings had higher stroke symptom knowledge than those in non-rural settings ($t = 2.18$; $p < 0.03$). However, it should be noted that 99% of rural participants were White as compared with 89% in the non-rural sample. The majority of participants had at least a high school education (95% for rural and 93% for non-rural). Stroke risk factor knowledge was also examined. Although there were no significant differences by location or gender, younger participants were more likely to correctly identify stroke risk factors than older participants [56].

Treatment Delay in Women

Women in the U.S. have higher rates of lengthy delay (>12 h) in hospitalization for MI than men [57]. Many factors have been found to increase women's delay in seeking medical attention for CHD including absence of chest pain as a primary symptom, older age, and the presence of diabetes [58, 59]. A study in Sweden examined pre-hospital delay in people with a first MI (N = 265; 33% women) [60]. Those in rural areas reported a longer delay in transport time (0.78 hour in urban communities vs. 1.65 hours in rural communities; $p < 0.001$). However, there were no statistically significant differences in total pre-hospital delay between rural and urban communities.

Living in a rural area with less access to hospitals and to ambulance services detrimentally impacts outcomes of acute CVD. The American Heart Association published recommendations for pre-hospital care for suspected stroke that emphasizes reducing time-to-treatment [61]. Stroke patients should be transported to the closest certified primary stroke center or comprehensive stroke center or the closest institution that provides appropriate emergency stroke care. Most of the medical

centers that meet these criteria are located in urban areas and stroke victims living in rural areas are at a time to treatment disadvantage [61].

Results of a recent meta-analysis (N = 5 trials including 1287 patients; 47% women) reported the importance of timely stroke treatment [62]. Endovascular treatment that began within 7 hours and 18 min of symptom onset resulted in the best outcome, with earlier times demonstrating the optimal outcomes. In fact, for every 9 min delay in symptom onset to reperfusion time and for every 4 min delay in emergency department door to reperfusion time, 1 out of 100 endovascular-treated stroke patients had worse disability outcomes [62]. These researchers did not report analysis by gender or race.

The American Heart Association has also published guidelines for treatment of ST-elevated MI which includes recommendations for communities to help ensure rapid treatment for patients who are eligible for reperfusion therapy [63]. Ideally, all eligible patients should receive reperfusion therapy within 12 hours of symptom onset. Patients should be transported directly to a primary percutaneous coronary intervention (PCI) capable hospital by emergency personnel with a goal of receiving PCI within 90 min of first medical contact and fibrinolytic therapy should be administered within 30 min of hospital arrival when it is selected as the primary reperfusion method [63]. Again, distance to comprehensive medical centers puts rural residents at a disadvantage for timely treatment. Women living in rural areas are even at greater risk than men because diagnosing CHD in women is challenging for many reasons including: atypical symptom presentation, unreliable electrocardiogram findings, more likely to be present with non-obstructive CHD, and lack of recognition of symptoms by both the patient and the health care provider [51, 64–67]. Many women still underestimate their risk of CHD and fail to seek treatment in a timely manner often unaware of women's typical symptoms, thus contributing to their delay in seeking treatment [51, 68, 69].

Treatment Differences by Ethnicity

Since the early 1980s, there has been documentation that minority groups are less likely to receive appropriate cardiac diagnostic evaluation and to receive the appropriate invasive cardiac treatment even when presenting with similar signs and symptoms as Whites [70–72]. Studies have shown that White males consistently are more likely to get a coronary artery bypass graft (CABG) than women, 70.6% vs. 49.4% respectively [70, 72]. Blacks receive less aggressive cardiac workup than Whites [71, 72]. In fact, Black women have the highest risk of not receiving reperfusion therapy and coronary angiography of any group [72]. Partially due to this, even after controlling for low socioeconomic status, education, lack of insurance and lack of access, Black women are more likely to die from CHD than any other racial group.

The reasons for differences in treatments and procedures by gender and race/ethnicity are unclear. One possibility is that minority group members are more likely to live in poor neighborhoods, and may be treated by physicians with lower qualifications and have less access to subspecialty care and the most current diagnostic imaging.

Disparate CVD Outcomes in Rural and Urban Women

Health care providers often underestimate risk of CHD in women, especially younger women, and delay ordering appropriate diagnostic and screening tests [69, 73]. Therefore, women are more likely to have worse outcomes after the development of CHD than men [69, 74–79]. Persons living in rural areas, especially women, are less likely to receive recommended cardiovascular medications. A systematic review and meta-analysis of 51 studies examined cardiovascular medication utilization and adherence in rural vs. urban men and women (N = 51 studies) [80]. Those in rural areas were 12% less likely to receive evidence-based cardiovascular medication therapy than urban residents in unadjusted analysis. However, pooled analysis revealed that in the studies that adjusted for potential confounders such as age, gender, and socioeconomic status, there were no statistically significant differences between rural and urban residents in use of cardiovascular medications. There was significant heterogeneity between studies in measures of medication adherence, drug class examined, and patient and practitioner characteristics. Most studies adjusted for some potential confounders, but not for potential socioeconomic confounders. In fact, only 14 studies adjusted for health insurance status, which has been shown to contribute to medication adherence rates.

Residents living in rural areas also have less access to recommended stroke treatment than those living in urban areas. Researchers recently examined the largest publically available database of acute ischemic stroke hospital discharges (N = 914,500; 2.3% received thrombolysis) and found that rural residents were much less likely to receive thrombolysis than urban residents ($p < 0.0001$) [81]. Thrombolysis rates in urban hospitals increased yearly from 2001 to 2010 (from 1.17 to 4.87%); however, thrombolysis rates in rural hospitals increased much more slowly from 2001 to 2010 (0.87–1.59%). Adjusted logistic regression revealed that thrombolysis for acute ischemic stroke was twice as likely to occur in urban hospitals as compared with rural ones (adjusted odds ratio 2.11; 1.97–2.27). Women were also less likely to receive thrombolysis than men in this nation-wide sample of stroke patients ($p = 0.0009$). In other words, the rural thrombolysis treatment disparity for women with acute stroke is not improving despite education and intervention efforts to increase compliance of thrombolysis treatment for eligible patients [81].

Conclusions

Few research studies compare CVD/CHD outcomes in rural vs. urban populations and we found no studies that compared women's CVD or CHD outcomes by both race/ethnicity and by geographic location. However, research clearly indicates that women have higher rates of CVD than men in rural and urban areas with the greatest disparity for rural women, especially minority women [2]. Further, women have

increased risk factors for CVD compared with men such as depression, lack of physical activity, and increasing tobacco use [1]. Health disparities among minority groups persist despite massive educational campaigns to improve CVD and CHD outcomes in minority women. The existing literature demonstrates that minority women such as Hispanics and Blacks have higher mortality rates from CVD/CHD, have higher incidence of diabetes, stroke, hypertension, increase obesity, and are less aware about the risk factors for CHD and other CVD [82]. Social determinants of health including increased poverty, decreased education, lack of access to health care and unsafe neighborhoods further burdens these women [83]. Thus, the disparity in CVD outcomes for women in rural areas and women of color may be partially due to their number of risk factors, but further research is recommended to fully elucidate the causes of this disparity and identify interventions to eliminate them. To improve their health, it is imperative to develop strategies that are tailored for these populations. Developing community level interventions are important to improve social determinants of health to improve CVD outcomes for rural minority women [66]. Research is needed to develop and test interventions that are culturally appropriate and to address CVD disparities in women of all races and ethnicities in both urban and rural locales.

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Erratum to: Microvascular Angina as a Cause of Ischemia: An Update

Edina Cenko, Peter Louis Amaduzzi, and Raffaele Bugiardini

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This book was inadvertently published with an incorrect spelling in the first name of the author of Chapter 9. This has now been updated as Dr. Raffaele Bugiardini.

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