Ischemic Heart Disease in Women
Many Questions, Few Facts

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After at least 2 decades of growing awareness on coronary heart disease in women, we are left with many questions, few answers, and plenty of opinions. Review articles, books, sessions at scientific meetings, and commentaries regarding various aspects of heart disease in women have proliferated. These reports have highlighted important sex differences in the pathophysiology, presentation, and treatment of ischemic heart disease and have denounced pervasive sex-related disparities in referral and treatment for heart disease as a major reason for outcome differences between the sexes. Such activities have been useful in driving attention to heart disease in women, an area largely ignored by the scientific community and the public just 15 to 20 years ago. However, we must recognize that to date, limited data substantiate many of these statements; such recognition is important to guide future research efforts. A careful look at recently published literature reveals only modest advancements toward clarifying sex-based differences in the pathophysiology of ischemic heart disease and sex-based differences in outcome. At the same time, key questions concerning strategies for prevention and treatment of heart disease in women remain unanswered, and cardiovascular clinical trials continue to include fewer women than men.[1]

Is the Pathophysiology of Ischemic Heart Disease Different in Women Than in Men?

A fundamental question is whether the mechanisms underlying ischemic heart disease in women differ from those in men. This is an important question because if pathophysiology differs in women, such differences can inform strategies for prevention, detection, and treatment that would be most effective for women. That pathophysiology may differ in women compared with men is suggested by several factors. First, despite having more symptoms and physical limitations,[2,3] women have less obstructive coronary heart disease than men along the entire spectrum of acute coronary syndromes[4] and when referred for revascularization.[5,6] Second, the syndrome of chest pain without obstructive coronary artery disease (CAD) is distinctly more common in women than in men.[7] Third, among women, chest pain symptoms and disability do not correlate with severity of coronary stenoses.[8] Fourth, women, particularly those who are young or middle-aged (whom one would expect to be most advantaged for coronary disease risk compared with men), show higher rates of adverse outcomes after acute myocardial infarction (MI) than men of similar age, despite less severe coronary narrowing, smaller infarcts, and more preserved systolic function.[9] To explain these observations, a number of abnormalities in coronary vascular structure and function have been proposed that could lead to symptoms, disability, and other adverse outcomes in the absence of critical coronary stenosis.[10–12] These include positive remodeling (compensatory vessel enlargement), diffuse atherosclerosis (versus plaque), coronary endothelial dysfunction leading to vasoconstriction, and microvascular disease. Coronary microvascular disease, in particular, is put forward as a major etiologic factor for ischemic heart disease in women and a prevalent determinant of chest pain, ischemia, and disability in women ("microvascular angina").[12] Consequently, the identification of nonobstructive atheroma has been put forth as a potentially helpful strategy for the risk stratification of women.[12]

Although this is a compelling theory, to date there is little evidence to suggest that vascular abnormalities in the absence of obstructive atheroma are more commonly implicated in the pathogenesis of ischemia among women than men. Recent studies have evaluated sex differences in coronary structure and function using intravascular ultrasound and other types of vascular testing. In a sample of 978 patients with established CAD, Nicholls et al[13] found no sex difference in arterial remodeling; in this study, women were as likely as men to undergo either positive or negative remodeling. In a study of 142 patients referred for coronary evaluation and found to be free of obstructive CAD, women did not show worse endothelial function than men.[14] Women actually had less epicardial coronary endothelial dysfunction than men (shorter coronary artery segments affected), even after correction for body size. The few studies that have compared endothelium-independent vasodilatory reserve in response to adenosine (an index of microvascular function) have reported similar values in women and men referred for coronary angiography[14,15]; in one study it was lower in women, but this difference was largely explained by the women's older age and smaller body size.[14] All intravascular ultrasound studies have found that women had less atheroma volume than men, including both luminal plaque and atheroma within the media, despite older age and more risk factors, and even after accounting for body surface area and vessel size.[13,14,16] After adjusting for body size, women also have smaller coronary vessels.[16]

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Although these studies confirmed the known clinical observation that women with established or suspected CAD have lower plaque burden than men, they were unable to identify other vascular abnormalities that might explain sex differences in clinical presentation. If anything, women showed better endothelial function than men; this result parallels the known finding from community samples that women have better peripheral endothelial function than men (measured as flow-mediated vasodilation percent from baseline) until about age 70 and at all levels of risk factors.[17–19] Similarly, asymptomatic women compared with asymptomatic men have higher coronary perfusion reserve measured with MRI, a measure of global coronary vasoreactivity,[20] although this difference is in part explained by differences in risk factors. This does not mean that coronary vascular dysfunction, when present, is not prognostically important in women; however, even in this respect, data are limited. The Women's Ischemia Syndrome Evaluation (WISE) study has provided substantial information on this topic. Unfortunately, many of these reports are limited by the characteristics of the sample selection, the small number of "hard" end points, and the lack of a male comparison group. In a sample of 163 women enrolled in WISE, all referred for clinically indicated coronary angiography and assessed for coronary reactivity, those with impaired vasodilation to intracoronary acetylcholine had a higher rate of subsequent coronary events than those without.[21] In this small sample, however, the results were driven by hospitalizations for angina and percutaneous interventions (36 of 58 events). WISE investigators also studied 35 women who were hospitalized for chest pain but who had no angiographically significant coronary artery obstructions and compared them with 12 age- and weight-matched control women with no evidence of heart disease. Phosphorus-31 nuclear magnetic resonance spectroscopy was done before and after isometric handgrip exercise. Seven (20%) of the 35 women with chest pain and no angiographically significant stenosis had decreases in the phosphocreatine:ATP ratio (a metabolic marker of ischemia) during exercise that were >2 SDs below the mean value in the control subjects without chest pain, suggesting that a subgroup of women presenting with chest pain and normal angiograms may have ischemia due to microvascular coronary disease.[22] A follow-up of these women within the WISE study showed a higher event rate compared with those with normal nuclear magnetic resonance spectroscopy and an event rate similar to that of the women with obstructive CAD.[23] Again, however, the higher event rate was due to hospitalizations for angina and repeat angiography: No deaths or MI events were documented in this group.

In summary, the data are simply not there to indicate a major role of coronary endothelial dysfunction and microvascular disease in the etiology and prognosis of ischemic heart disease in women. Even less evidence is available about the role of coronary vessel remodeling. It is not that these hypotheses are incorrect; it is mainly that research has been too limited. We do not know how prevalent these conditions are among women who have ischemic heart disease or are at risk for the disease. We do not know if these mechanisms are more prevalent in women than in men, which would help explain sex differences in presentation and outcome of ischemic heart disease. Finally, we do not know if they are associated with adverse events such as acute MI or death. Presently, we are far from being able to conclude, or even suggest, that these hypothesized abnormalities play a larger etiologic or prognostic role for ischemic heart disease among women than among men.

Do Women Fare Worse Than Men After Acute Coronary Syndromes?

A general pattern of higher mortality and complication rates in women after acute coronary syndromes (ACS) compared with men has been described for many years. But what should be recognized is that sex differences in mortality after ACS do not occur across the board but only in specific patient subgroups. The first is the group of patients with ST-segment–elevation MI (STEMI).[4,24,25] In contrast to these patients with STEMI, no sex differences are usually found among the patients with non–ST-segment–elevation MI after adjustment for risk factors and among patients with unstable angina; women actually do significantly better than men after correction for age and risk factors.[4,24] The second group in which sex differences in outcome are found comprises the younger patients with MI, as reported by many population-based and registry studies.[9,24,26–30] Among older patients, there are no differences or even a tendency for women to do better. This effect modification due to age is less apparent in data sets from randomized clinical trials,[4,31] probably due to the selection characteristics and possible differential enrollment by sex in these trials.

Little is known about why women face higher risks than men in these patient groups. Differences by MI type may be due to the pathophysiology underlying these events. For example, acute occlusion caused by thrombus superimposed on a ruptured or eroded atherosclerotic plaque is believed to play a larger role in transmural infarctions than other types of ACS.[32] Thus, it is possible that sex differences in vessel size and collateralization put women at greater risk than men after STEMI but not after other types of ACS.

It is also unclear why sex differences in the outcome of MI are seen in young and middle-aged patients but not older patients. One would expect that women younger than 50 years of age, the majority of whom are premenopausal, should be more advantaged rather than less advantaged compared with men of similar age in terms of survival. On the other hand, for coronary disease to occur in younger women, it must be aggressive, driven by multiple risk factors, or caused by secondary or unknown causes. That is, the delayed onset of coronary disease in women could in part drive sex differences in the risk profile on presentation and paradoxically also drive their poorer outcomes. Indeed, younger women with MI compared with men have a higher rate of risk factors and comorbidities such as diabetes, history of heart failure, and stroke, although these factors do not entirely explain sex differences in outcome.[9,33] It is possible that unaccounted comorbidities and risk factors are responsible for the residual outcome differences seen in comparison with men. Alternatively, other unknown factors may be involved; among these, social and psychological factors have rarely

been considered. A recent study, for example, documented a remarkable decrease in mortality in women with coronary heart disease randomly assigned to a stress-reduction intervention specifically tailored to women.[34] Although we do not have a full explanation for the excess mortality risk in younger women with MI compared with men, this excess risk is narrowing,[33] reflecting a sharper mortality decline among women than men in recent years. This trend suggests that environmental or behavioral causes of sex differences in outcomes may be more important than biological ones.

The declining mortality rate among post-MI women for cardiovascular mortality is consistent with a decreasing trend in cardiovascular mortality in the entire population of women since the mid-1960s, which is similar to men.[35] Yet, countless studies have denounced an absence of decline or even an increase in cardiovascular mortality rates among women despite a concurrent decrease in men.[12,36–38] These assertions may result from a misinterpretation of mortality statistics that have plotted the number of deaths caused by cardiovascular disease.[39] The total number of deaths (not the death rate) caused by cardiovascular disease has slightly increased in women, while decreasing in men, until the year 2000. This increase probably reflects the aging US population and the fact that women live longer than men, because age-standardized rates show a similar decline in women and men over the past several decades in the United States and many other countries in the world.[35,40,41] After the year 2000, in the United States, even the number of cardiovascular deaths has shown a similar if not steeper downward trend in women compared with men.

Are Women With Heart Disease Treated Less Aggressively Than Men, and Does Differential Treatment Contribute to Outcome Differences?

A less aggressive clinical treatment of women with coronary heart disease relative to men has been documented for years, with a tendency to refer to it as sex bias in health care delivery. Most of this literature has been conducted in hospitalized patients with ACS. Although it is indisputable that variations in clinical care occur by demographic groups, it should also be recognized that such variations are complex and may be due to a variety of factors other than sex. For example, women with MI are older, have lower levels of biomarkers of cardiac necrosis, and have less severe obstructive CAD. Furthermore, in recent studies, reported differences in treatment by sex were small. In the Get With the Guidelines–Coronary Artery Disease (GWTG-CAD) database, differences in receipt of aspirin and β-blockers between women and men were only 2 percentage points; for example, 93% of the men and 91% of the women received aspirin within 24 hours. Yet, such small differences were presented as evidence of treatment disparities.[25] Similar results were obtained in other large contemporary databases, including CRUSADE,[38] GRACE,[42] NRMI,[43] the CURE trial,[44] and the Medicare database.[45] The tendency to overstate treatment differences by sex may derive from an excessive reliance on *P* values. As the size of cardiovascular databases available for research continues to grow, we must be wary that highly significant *P* values may not always denote clinically meaningful differences.

Although sex differences in evidence-based medications are small in almost any recent study, some studies have reported larger differences for reperfusion therapy in patients with STEMI, although results vary.[25,43,45] These gaps may in part derive from bleeding concerns among women rather than sex per se. Consistently larger treatment differences are seen for less evidence-based procedures, such as coronary catheterization and revascularization procedures.[38,43–45] Even for these interventions, however, it is unclear whether differences reflect true disparities. Women's lower prevalence of obstructive CAD at catheterization explains the lower use of revascularization,[38,44] suggesting that on average, underuse of these procedures in women is not necessarily inappropriate.

Another indication that underuse of treatments and procedures in women with ACS compared with men may not be clinically significant is that it does not seem to account for mortality differences between women and men with ACS, if any are found.[38,42,44,45] Even in this context there is a tendency to overstate any differences found. In a French MI database, lower use of percutaneous interventions explained less than a half of a percentage point of the mortality difference between women and men; still, the authors concluded that one quarter of the gender gap in mortality was related to differential use of percutaneous coronary intervention.[46] That conclusion derived from the fact that the age-adjusted difference in mortality was $<2\%$ in this population.

In a population-based database of patients with MI, Alter et al[47] clearly demonstrated that differences in care have little to no role in explaining sex differences in post-MI mortality. Whereas care became progressively less aggressive among older women relative to men, survival advantage tracked in the opposite direction, with older women clearly favored. These findings suggest that factors other than treatments should be explored as determinants of survival differences after MI between women and men.

It should be noted that most of the data on sex differences in the clinical management of coronary disease derive from studies of patients with ACS. A large knowledge gap involves angina pectoris. Little is known about sex differences in the management of angina, despite its being the most common manifestation of CAD in women and therefore, for many women, representing the starting point for their cardiovascular care delivery. Recent data from Europe suggest that women with angina are less likely to be referred for coronary revascularization and to receive preventive treatments[48,49] even after adjusting for clinical factors including presence of perfusion defects.[48] Older data from the United States suggested similar disparities,[50–53] but no contemporary data are available to determine whether such differences in referral are still present.

Conclusion

After at least a decade of renewed interest in women's cardiovascular health, we are left with more questions than answers. Fundamental questions about the pathophysiology of ischemic heart disease in women remain unanswered. We have gained few clues about the basis for sex differences in

coronary heart disease and what is unique about the female vascular system. As a result, we are yet unable to explain sex differences in the epidemiology, presentation, and outcome of coronary heart disease. Key questions remain about why women are protected from cardiovascular disease, why this protection is restricted to the coronary system,[54] and why this protection ends when women have diabetes or an acute MI. We lack studies that compare biological mechanisms of disease between women and men to better define vascular processes that are unique to women. We lack sufficiently large follow-up studies to link such processes to cardiac end points. After decades of focusing on estrogen, other pathways should now be considered; among these are the factors underlying the vascular physiology of pregnancy and menstruation, such as vascular regeneration and repair, hormonal factors other than estrogen (such as testosterone), autonomic function, and the immune system. Furthermore, the role of nonbiological factors should be evaluated in more detail. Do psychological and behavioral risk factors such as depression, family/work stress, socioeconomic deprivation, and early life adversities play a larger role in women than in men in increasing their risk for adverse cardiac events? These factors are more prevalent in women but have rarely been evaluated in terms of explaining sex differences in cardiovascular outcomes. Finally, are there true differences in referral rates for diagnostic testing and treatments between women and men with suspected heart disease in the current era, and, if so, how can referral rates be increased when appropriate? How can we increase the inclusion of women in cardiovascular clinical trials? Without an answer to these questions, little can be done to improve the prevention and the treatment of coronary heart disease in women.

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