

Insights From the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study

Part II: Gender Differences in Presentation, Diagnosis, and Outcome With Regard to Gender-Based Pathophysiology of Atherosclerosis and Macrovascular and Microvascular Coronary Disease

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Coronary heart disease is the leading cause of death and disability in the U.S., but recent advances have not led to declines in case fatality rates for women. The current review highlights gender-specific issues in ischemic heart disease (IHD) presentation, evaluation, and outcomes with a special focus on the results derived from the National Institutes of Health-National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. In the second part of this review, we will assess new evidence on gender-based differences in vascular wall or metabolic alterations, atherosclerotic plaque deposition, and functional expression on worsening outcomes of women. Additionally, innovative cardiovascular imaging techniques will be discussed. Finally, we identify critical areas of further inquiry needed to advance this new gender-specific IHD understanding into improved outcomes for women. (J Am Coll Cardiol 2006;47:21S-9S) © 2006 by the American College of Cardiology Foundation

In part II of this review, we will further define gender differences in clinical presentation, disease pathophysiology, and clinical outcome as well as outline important next steps toward improved detection, assessment, and treatment aimed at improving outcomes in women. For this section, we will attempt to further define the complexity of risk-based models that intertwine with our traditional diagnostic assessments with new evidence on gender-based differences in vascular wall or metabolic alterations and atherosclerotic plaque deposition and functional expression on worsening

outcomes of women (1). We will start our discussion by focusing on the role of differential symptoms and coronary disease incidence and prevalence on medical resource utilization patterns between women and men.

GENDER DIFFERENCES IN ISCHEMIC HEART DISEASE (IHD) PRESENTATION, EVALUATION, AND OUTCOMES

Gaps in medical resource utilization have frequently been reported as "gender bias" in diagnosis or treatment, as noted from observational and administrative databases, causing considerable controversy about the adequacy of cardiovascular care for women, in particular for female ethnic minority subsets of the population (2-12). Recent controversy extends prior work, noting not only an underuse of medical services in women but also an overuse or use without adequate clinical indications for male patients (13). These reports have had an impact upon referral patterns, as early reports of procedural underuse in women have resulted in recent trends toward an increasing referral of female populations to surgical revascularization (14).

The gender-specific difference in cardiovascular disease mortality provides additional support for a lack of comparable progress in population-based risk reduction efforts for women. Since 1984, the total number of deaths from cardiovascular disease has been greater for women as compared with men (2). In the year 2000, approximately 60,000 more women than men died from cardiovascular disease. Although recent reports on age-adjusted coronary heart

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Abbreviations and Acronyms

C-IMT	= carotid intima-media thickness
CT	= computed tomography
FMD	= flow-mediated dilation
IHD	= ischemic heart disease
LV	= left ventricular
MI	= myocardial infarction
NRMI	= National Registry of Myocardial Infarction

disease mortality rates noted an approximately 50% decline since peaking in the 1960s, substantively reduced rates of decline were observed in lower socioeconomic, racial, and female subsets of the population (14,15). Moreover, in a recent report from the Olmstead county registry, marked declines in the incidence of myocardial infarction (MI) were noted from 1979 to 1994 in younger men as compared with an increased incidence in older women (16).

Supplementary evidence has observed substantial delays in health care seeking behavior, less intensive resource use patterns, and longer times to diagnosis for women as compared with men (1,2,17-22). Although a reduced intensity of care may be, in part, related to a differential clinical history, symptom profile, and acuity of presentation, underrecognition of disease in women may also be contributory to worsening outcome, especially for women with an established diagnosis of IHD or acute MI (1,2,23-26). Of the 1.1 million hospitalizations for acute MI each year, more men are admitted through varying age groups (721,000 in men vs. 410,000 in women), with differences narrowing in elderly cohorts (2). Despite more male admissions, the one-year death rate and rate of reinfarction is higher in women (2). Notably, black women have a higher rate of first heart attack than white women for those age 45 to 74 years (2). Symptomatic women, furthermore, have persistent, frequently refractory chest pain requiring more hospitalizations than for men but also with lower ratings of general well-being, more frequent reports of anxiety or depressive symptoms associated with their disorder, and significant limitations in their ability to perform activities of daily living (27,28).

Compounding the challenge of female patients with a lower quality of life and greater symptom burden is the frequent reporting that women presenting for the diagnostic evaluation of chest pain symptoms have "excellent survival" (29-31). Of this symptomatic cohort, they more often have insignificant or non-obstructive coronary disease or less subclinical disease (22-37). As recently reported in the American College of Cardiology's National Cardiovascular Data registry in 375,886 patients referred for diagnostic left heart catheterization (45% women), the prevalence of obstructive coronary disease was less in women across all age (<50 to \geq 80 years) groups (35). From this registry, the prevalence of significant obstructive coronary artery disease (i.e., stenosis \geq 50%) ranged from 27% to 64% for women and 45% to 87% of men ages <50 to \geq 80 years of age,

respectively ($p < 0.0001$ for all age subsets). Similar findings are reported for coronary angiography performed for acute coronary syndromes (38), and, thus, women are less likely to benefit from clinical risk reduction algorithms focusing on coronary revascularization strategies (39,40).

GENDER-SPECIFIC ISSUES RELATED TO ARTERIAL SIZE AND ATHEROSCLEROTIC DISEASE BURDEN

Recent innovations in cardiovascular imaging have revealed a differential event-free survival in women with vascular imaging abnormalities by computed tomography (CT), magnetic resonance, or retinal photography (41,42). Although the prevalence of atherosclerosis measured by these imaging abnormalities for women lags behind that in men (similar to IHD rates), evidence that the combination of smaller arterial size, potentially more prominent positive remodeling, and a greater role of the microvasculature (as noted by evidence using carotid artery intima-media thickness [C-IMT], retinal artery narrowing, or coronary calcification) carry a greater prognostic weight in women as compared with men (41-48); more details on the role of the microvasculature will be discussed in part III of this review. For example, any given extent of coronary calcification using the Agatston score is associated with worsening mortality in women as compared with men (41). This score does not consider arterial size but only coronary calcium extent and is associated with relatively greater mortality rates for women compared with men. Smaller arterial size contributes to lower rates of success with revascularization strategies and more frequent angina (49,50).

PROGNOSIS IN ENDOTHELIAL DYSFUNCTION

The prognostic value on coronary and peripheral endothelial function testing is compiled in Figure 1. In synthesizing the 15 published reports on coronary and peripheral testing for endothelial dysfunction, the overall relative risk ratio for abnormal findings is elevated nearly 10-fold (95% confidence interval [CI] 7.8 to 12.8) (51-65). Recent evidence suggests that the relationship between endothelial dysfunction and outcome may be mediated by other factors such as the extent of atherosclerotic disease burden (66,67). Of women who are at highest risk, preliminary evidence suggests that chronic hyperglycemia results in markedly reduced endothelium-dependent and -independent coronary vasodilator function (68).

These results are important because restoration of endothelial function is associated with improved outcomes (69,70). In a recent clinical study of 400 hypertensive, postmenopausal women, improvement in flow-mediated dilation (FMD) ($>10\%$ relative to baseline) of the brachial artery, using high-resolution ultrasound, was associated with a 7.3-fold lower rate of cardiovascular events when compared with women with $\leq 10\%$ improvement in FMD (69). A recent report also noted no significant improvement

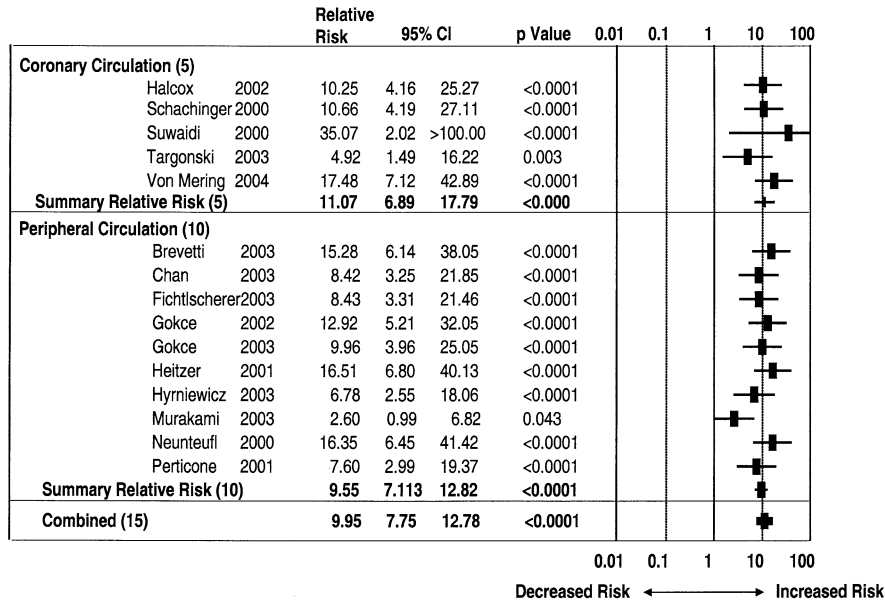


Figure 1. Forest plot of the summary relative risk for major adverse cardiac events in women with coronary or peripheral endothelial dysfunction. The summary relative risk ratio is elevated 11.1- and 10.0-fold for evidence of coronary and peripheral endothelial dysfunction. CI = confidence interval.

in FMD with selective estrogen receptor modulation with raloxifene in postmenopausal women (71).

Gender-specific differences in the process of risk factor injury and atherosclerotic responses may explain the frequency and significance of chest pain symptoms in women. While the etiology and genesis of chest pain symptoms in women is currently not well understood, a number of hypotheses are suggested. We postulate that decades of relatively higher levels of inflammation, coupled with a clustering of risk factors that occurs with a loss of estrogen during menopause, may be associated with more frequent endothelial dysfunction, a loss of arterial compliance, and dysfunction in the microvasculature, resulting in myocardial flow heterogeneity more frequently in women. Evidence from intravascular ultrasound and autopsy data support the role of sex-hormone-mediated positive remodeling in women whereby greater atherosclerotic storage may be promoted minimizing luminal intrusion of plaque (72-76); a similar phenomenon has been reported after cardiac transplantation (77). Although described simplistically here, it is possible that there are multiple types of atherosclerotic diseases with varying pathophysiologic pathways, one of which is particular for our female patients.

DIAGNOSTIC VERSUS PROGNOSTIC RISK ASSESSMENT

The longstanding patient management approach for IHD has been to utilize an array of diagnostic tools that estimate the likelihood of “culprit” obstructive coronary lesions as the etiology for provoking ischemia and patient symptoms. This strategy is expected to be less effective in women with a greater prevalence of non-obstructive coronary disease and a higher frequency of myocardial ischemia, and indeed it is. An alternative strategy would rely upon the estimation of

the “culprit patient” or prognosis, and, thus, any test that provides independent prognostication in women might be used. Therefore, a shift in reliance upon prognostic risk versus diagnostic obstructive lesion detection may be particularly helpful in women, especially in minimizing the role of disease-based terminology such as “false positive” test results. A synthesis of evidence suggests that accurate risk assessment is possible with conventional testing including measures of functional capacity, plaque burden, extent and severity of perfusion abnormalities, global ventricular function measurements, as well as with inflammatory markers. For example, as based upon the current evidence, the prognostic value of either stress echocardiography or single-photon emission computed tomography imaging reveals that a high risk scan is associated with a ~10-fold increased risk of cardiac death or MI (78). An optimal non-invasive risk model may include, in addition to the use of a global risk score that includes traditional risk markers, measures of: 1) ventricular function; 2) regional flow or perfusion; 3) metabolism or energy requirements (e.g., ³¹P-magnetic resonance spectroscopy or positron emission tomography estimates of aerobic metabolism); and/or 4) vessel wall abnormalities (e.g., C-IMT, electron beam tomography, or retinogram) and markers of inflammation (41-44,79). Predictive models may also be improved by the addition of markers of left ventricular (LV) hypertrophy because the attributable mortality risk is greater in women than men (80).

GENDER-SPECIFIC ISSUES IN OBSTRUCTIVE CORONARY DISEASE

In approximately 60% of cases, the initial presentation of IHD in women is acute MI or sudden cardiac death (2,81-84). For the women initially presenting with a fatal

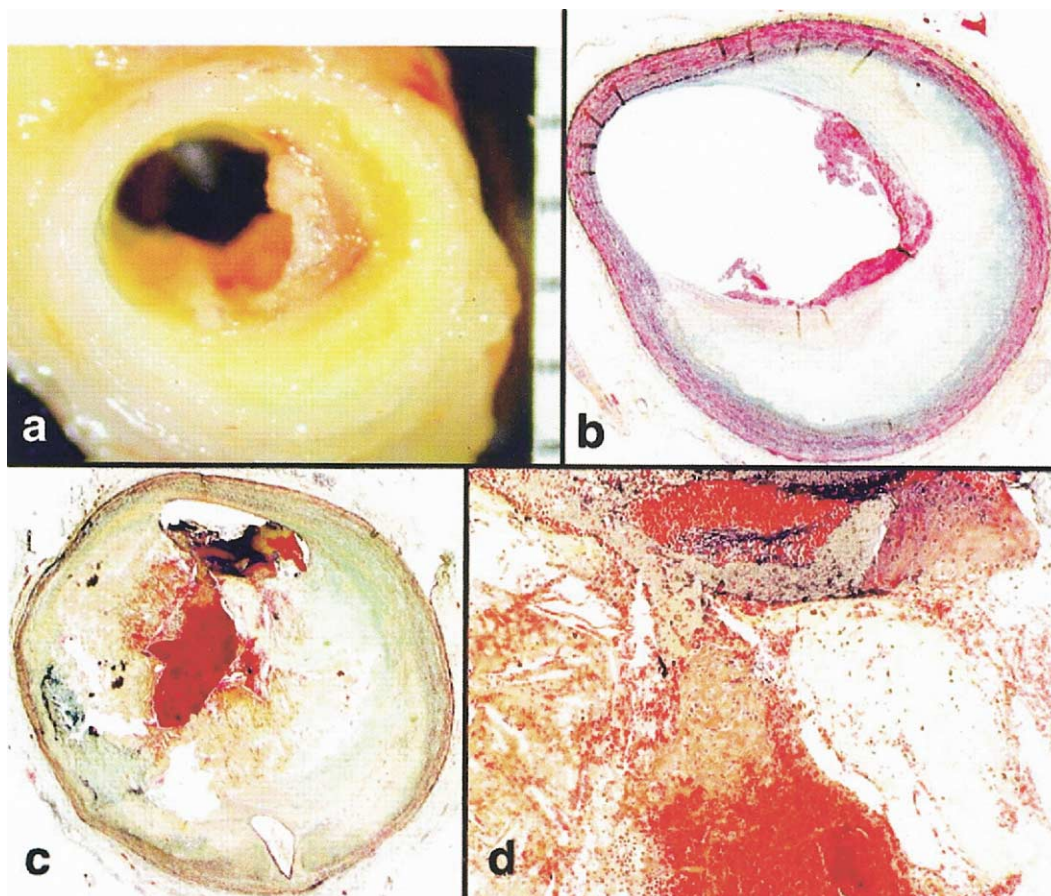


Figure 2. An example of plaque erosion, the typical presentation for sudden cardiac death in younger women. This example reveals an eccentric plaque with subocclusive thrombus in multiple views and sections (a to d) in a 58-year-old female smoker. Reproduced with permission (75).

ischemic event, there are morphologic differences in the etiology for sudden cardiac death by age and gender (72–76). Plaque rupture found as sudden cardiac death post-mortem typically occurs with a large necrotic core and disrupted fibrous cap infiltrated by macrophages and lymphocytes in men and older women. By comparison, younger women have a greater tendency toward plaque erosion where a fibrous cap is absent at the plaque erosion site and the exposed intima consists predominantly of smooth muscle and proteoglycans (Fig. 2). In a recent autopsy series, women also had a greater frequency of distal microvascular embolization in the setting of a fatal epicardial thrombosis as compared to men (76). This greater rate of embolization was independent of type of thrombus or the presence of necrosis.

The higher frequency of plaque erosion in women as compared to more plaque explosion in men may contribute to the higher mortality noted for younger women when compared with age-matched men (18,19), although this relationship may be confounded when considering the etiology of pre-hospital deaths. Other data sets demonstrate that among patients undergoing urgent coronary angiography for acute coronary syndromes, women have a higher prevalence of non-obstructive coronary arteries resulting in diagnostic uncertainty and therapeutic indecision and delays

(27,38). Additionally, the relatively higher IHD mortality in women may also be related to a relatively greater burden of atherosclerosis in relation to the degree of positive arterial remodeling, possibly due to sex-hormone-modulated atherosclerotic storage.

The prevalence of the obstructive coronary disease is relatively low in premenopausal women with disease prevalence of approximately 5% for those <35 years of age. The prevalence of obstructive coronary disease increases dramatically for a woman after age 50 and ranges from 14%, 29%, 48%, 65%, and 79% for women ages 35 to 44, 45 to 54, 55 to 64, 65 to 74, and ≥ 75 years, respectively (2,81). A major covariate for obstructive coronary disease prevalence is the presence of symptoms where non-anginal, atypical, and typical angina increase with the prevalence of obstructive coronary disease from 6% to 57% (2,81–84). After sudden cardiac death, the most common presentation of obstructive coronary disease for women is atypical symptoms including fatigue, shortness of breath, and atypical chest pain (3,19,36,44,85). Despite a moderately strong relationship in this ranking, the correlation of symptoms with obstructive coronary disease is less accurate and less precise in women than for men (85).

In the setting of acute or chronic obstructive coronary disease, women have an overall worse prognosis than men

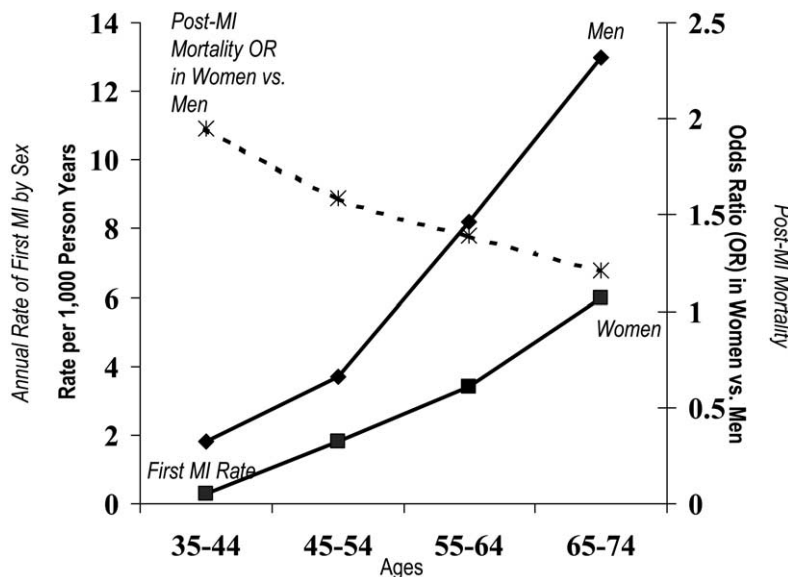


Figure 3. This graph shows the annual rate of first myocardial infarction (MI) by gender noting the significantly higher rate across all age groups in men as compared with women. Despite the differences in the rate of myocardial infarction by gender, post-infarction mortality is elevated significantly in younger women. In an adaptation of the result from Vaccarino et al. (18), the odds ratio was elevated approximately two-fold for women in the 35-to-44-year range and elevated ~1.6-fold for women in the 45-to-54-year range.

(2,18,19,21,22,83,84,86-94). In particular, near-term prognosis for women appears to be driven by the acuity of presentation and the degree of comorbidity (94). Younger women presenting with acute MI are also at particularly high risk of death, as recently reported in the National Registry of Myocardial Infarction-2 (NRM1-2) database, in part due to comorbidity, infarct severity, and medical management differences (Fig. 3) (18). In this NRM1-2 database of 384,878 (40% women) patients, the odds ratio of death was increased 11% for every five-year *decrement* in age in the women. When outcomes were adjusted for comorbidity, infarct severity, and medical management differences, only one-third of the variability in worsening outcome could be explained among the women. This notion of a high-risk younger female cohort further demonstrates our lack of understanding of gender-related differences in outcome (18).

There are clear differences in outcomes for women admitted with acute coronary syndromes as compared to those evaluated with stable chest pain symptoms. For women with stable chest pain symptoms, overall cardiac survival is superior to men (29-31). In those women presenting with acute MI, however, the one-year death and reinfarction rates are higher in women (2,81). Variability in outcome is related to comorbidity, infarct severity, and management intensity; however, the majority of the gender gap is currently unexplained (18-20). Women presenting with unstable symptoms are more frequently found to have non-obstructive coronary arteries and non-Q-wave MIs, such that aggressive revascularization management strategies have not been found to be effective, compared to a clear benefit among the men. Indeed, with revascularization, women paradoxically have similar long-term adverse out-

come rates to the men, despite having less extensive and severe obstructive coronary disease, better LV function, and higher rates of "normal" coronary arteries, all of which should portend a relatively better outcome (22).

With and without obstructive coronary disease, women are more frequently admitted for congestive heart failure symptoms with preserved LV function as compared to men, although recent reports note a probable decreasing incidence in women but not men (91,95,96). In the Framingham study, Levy et al. (95) note a decreasing incidence that may be related to a reduction in diastolic dysfunction and improved hypertension detection and management in women (especially in the postmenopause) (96).

Paradoxically, while women are more likely to be admitted for congestive heart failure with preserved LV function than men, they are more likely to die (2), suggesting a potential misunderstanding of disease heart failure pathophysiology and treatment in women. Notably, this is also true both with and without obstructive coronary disease. After coronary bypass surgery, operative mortality is higher for women (n = 441,542 patients enrolled in the Society for Thoracic Surgery database [28% women]; operative mortality = 4.0% for women and 3.2% for men, p < 0.0001) (97), in part due to excessive rates of congestive heart failure (38,97-99). Similar findings are observed in angioplasty registry data (86-88). Additionally, of those with heart failure symptoms, women are more likely to have a lower quality of life with more frequent depression when compared with men (100).

After medical stabilization and a pathway that includes "gender-neutral" aggressive intervention, the long-term outcome after percutaneous coronary interventions and coronary bypass surgery appears similar by gender (86,88,89,97-

99). Of concern, however, women receive relatively less symptom relief with revascularization procedures compared to men, in terms of persistent symptoms, evidence of ischemia, and reduced functional capacity (12,82). However, women have a more difficult recovery after coronary bypass surgery (101). As compared with men, women start with and exhibit a greater decline in physical functioning and depressive symptoms. In this recent report by Vaccarino et al. (101), the more difficult recovery was not explained by baseline illness severity, health status, or other clinical factors.

SUMMARY POINTS FOR IHD IN WOMEN

The data reviewed here lead to a number of summary points with regard to IHD in women:

1. Traditional diagnostic tests that focus on identifying obstructive disease do not work as well in women compared to men. Indirect evidence reviewed here suggests that prognostic risk assessment (e.g., detection of the culprit patient) may work relatively better than diagnostic obstructive coronary disease assessment (e.g., detection of the culprit stenosis) for women. Future investigation should be aimed at testing this strategy.
2. The “typical” female presentation of signs and symptoms of IHD is more complex and multifactorial than that of men. Evidence reviewed here suggests that additional risk assessment (blood inflammatory markers, evidence of plaque burden, and evidence of ischemia) may be of relatively greater importance in women due to this diagnostic uncertainty. Future efforts should be directed at exploring new risk assessment paradigms in women.
3. Although men and women face relatively similar traditional cardiac risk factor loads, there may be gender-specific differences in response to this atherosclerotic risk burden. In particular, differences in inflammatory response, possibly mediated by reproductive hormones, and specifically estrogen deficiency in premenopausal women, may be etiologic in subsequently observed differences in IHD presentation, pathophysiology, and responses to treatment. Greater understanding of these gender-specific pathophysiological processes in women is needed.
4. Persistent signs and symptoms of IHD in the setting of non-obstructive coronary disease is a significant health problem for women, and appears to be related to vascular dysfunction. Data now demonstrate that the magnitude of this problem rivals the prevalence and cost of female-specific cancers, and that it is associated with a diminished event-free survival. Little is known regarding diagnostic and therapeutic approaches. Investigation furthering our understanding of the disease pathophysiology, diagnosis, and therapeutic strategies is needed.
5. Estrogen deficiency due to anovulatory menstrual cycling appears to be prevalent in premenopausal women with signs and symptoms of ischemia and is adversely associated with obstructive coronary disease, and may be etiologic for obstructive coronary disease during the postmenopausal years. Indirect evidence reviewed here suggests the hypothesis that estrogen deficiency may be a contributor to the observed more adverse outcomes in premenopausal women compared to age-matched men with IHD. Future investigation should be aimed at understanding both the premenopausal etiologic antecedents of IHD observed later in the postmenopausal years, and the relatively more adverse outcomes observed in these younger women, such that therapeutic strategies can be developed.

NEW HYPOTHESES IN THE PATHOPHYSIOLOGY OF IHD IN WOMEN

Recent lines of evidence indicate that sex hormones play a role in the development of IHD in women. Endogenous and exogenous sex hormones influence fat distribution/deposition, insulin resistance, lipid metabolism, coagulation factors, and inflammation measured by high sensitivity C-reactive protein. We propose that vascular dysfunction, in the absence of obstructive disease, is generally more prevalent in women as compared to men, due to these sex hormone differences, and is manifest by more frequent symptoms and evidence of provocative ischemia or altered metabolism. Because of this gender-specific link, we also hypothesize that vascular dysfunction is more frequently present in women with obstructive coronary disease, and may, therefore, contribute to the higher adverse outcomes also experienced by this group as compared with men.

In this expanding definition of the “typical female” IHD pathophysiology, vascular dysfunction plays a central role as the genesis of symptoms and ischemia as well as a global estimator of outcome (including “soft” symptom-based events). We further postulate that ischemia in the setting of vascular dysfunction places a woman at relatively higher risk than her male counterparts for any amount of obstructive coronary disease. These women with ischemia consistently have less symptom relief with current therapies primarily because the pathophysiology is not well understood. This latter point further supports the role of ischemia due to vascular dysfunction as a source for symptoms and being the primary determinant of outcome. We propose that symptoms occur in stressful settings due to impaired flow reserve and endothelial dysfunction among vessels with a relatively smaller arterial lumen, which results in myocardial ischemia. This latter point may be further exacerbated in the setting of insulin resistance, the metabolic syndrome, or hypertensives with diastolic dysfunction,

potentiating the declining functional capacity in postmenopausal women.

DEVELOPING INVESTIGATIVE STRATEGIES FOR IMPROVED IHD RISK ASSESSMENT AND THERAPEUTIC INTERVENTIONS FOR WOMEN

From multiple lines of evidence reviewed herein, it appears that ischemia due to vascular dysfunction plays an important role in the genesis of IHD in women, placing the culprit lesion strategy as incomplete for diagnosis, estimation of prognosis, and treatment of female patients. Piecing together the unfolding observational evidence on women with suspected IHD has been the focus of several researchers but most prominently that of the National Institutes of Health-National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Critical areas of investigation for improving IHD detection and treatment include:

1. Study of a wider berth of symptoms, functional disability, and quality-of-life indicators that are abnormal but do not clearly define a "typical" presentation
2. Additional symptom assessment combined with traditional and novel risk factors as well as stress-induced cardiac imaging ischemic markers to provide an improved risk assessment in women
3. Further inquiry as to whether women with diminished functional capacity, evidence of myocardial ischemia, or vascular dysfunction should be considered "at-risk" even in the absence of obstructive coronary disease
4. New imaging techniques that may more clearly document the diagnosis of ischemia due to vascular dysfunction, and facilitate the development of new treatment approaches
5. Inquiry assessing the role gender-specific reproductive hormones play in IHD etiology, pathophysiology, diagnostic and prognostic assessment, and therapeutic response

In summary, this review puts forth an alternative, yet more complex, hypothesis for IHD in women that considers both novel and traditional risk factors, as well as new opportunities in cardiovascular imaging. This new paradigm for the evaluation of women requires additional research to assure its further development and validation. Through testing of these new hypotheses, we hope that new treatment paradigms may be designed to improve outcomes for women with IHD.

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