

## STATE-OF-THE-ART PAPERS

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

## Part I: Gender Differences in Traditional and Novel Risk Factors, Symptom Evaluation, and Gender-Optimized Diagnostic Strategies

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Despite a dramatic decline in mortality over the past three decades, coronary heart disease is the leading cause of death and disability in the U.S. Importantly, recent advances in the field of cardiovascular medicine have not led to significant declines in case fatality rates for women when compared to the dramatic declines realized for men. The current review highlights gender-specific issues in ischemic heart disease presentation, evaluation, and outcomes with a special focus on the results published from the National Institutes of Health-National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. We will present recent evidence on traditional and novel risk markers (e.g., high sensitivity C-reactive protein) as well as gender-specific differences in symptoms and diagnostic approaches. An overview of currently available diagnostic test evidence (including exercise electrocardiography and stress echocardiography and single-photon emission computed tomographic imaging) in symptomatic women will be presented as well as data using innovative imaging techniques such as magnetic resonance subendocardial perfusion, and spectroscopic imaging will also be discussed. (J Am Coll Cardiol 2006;47:4S-20S) © 2006 by the American College of Cardiology Foundation

Ischemic heart disease (IHD) remains the leading killer in the U.S. and is the dominant contributor to the nation's morbidity and healthcare expenditures (1-3). While advances in the treatment of IHD have reduced case fatality rates, subsequent heart disease survivors contribute to increasing disease prevalence as a result of a growing popula-

tion of post-myocardial infarction, post-revascularization, and heart failure survivors that require substantive ongoing healthcare (4,5). Rising rates of cigarette smoking, physical inactivity, obesity, hypertension, and the metabolic syndrome also contribute to the rising IHD incidence rates among younger women and men (5). While it seemed clear in prior decades that we were "winning the war" on IHD, the recent U.S. national trend data reveal a continuing, yet alarming, growth in the IHD epidemic that our overburdened healthcare system is poorly equipped to handle (6-21).

For the sizeable proportion of women presenting for coronary artery disease (CAD) evaluation, our traditional disease management approaches that focus on detection of a critical stenosis often fail to identify those women critically at-risk. More than a quarter of a million women die each year in the U.S. from IHD and its related conditions, and current projections indicate that this number will continue to rise with our aging population (1,2,5). Recent estimates from the Centers for Disease Control (CDC) reveal that 38% of all deaths in women are related to coronary heart disease as compared with 22% resulting from cancer (5). Indeed, since 1984, more women than men have died annually from IHD (2), refuting the notion that this is a

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**Abbreviations and Acronyms**

CAD	= coronary artery disease
CDC	= Centers for Disease Control
CI	= confidence interval
DASI	= Duke Activity Status Index
FRS	= Framingham risk score
HDL	= high-density lipoprotein
hsCRP	= high sensitivity C-reactive protein
IHD	= ischemic heart disease
LDL	= low-density lipoprotein
METS	= metabolic equivalents
MR	= magnetic resonance
PCr/ATP	= phosphocreatine/adenosine triphosphate
SPECT	= single-photon emission computed tomography
WISE	= Women's Ischemia Syndrome Evaluation

“man’s disease” and suggesting that it might be relabeled a “woman’s affliction” (Fig. 1).

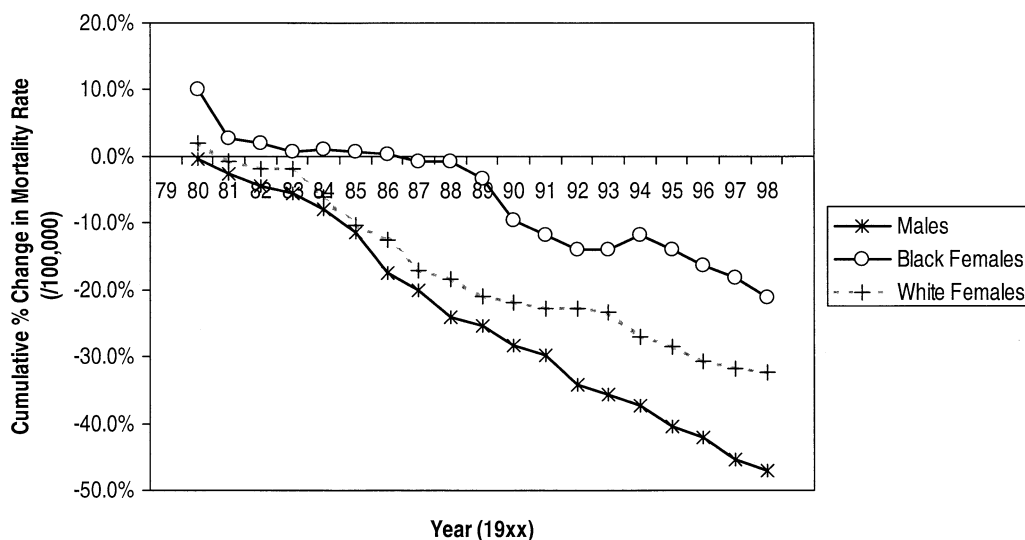
Notably, the dominance of disease attributable to women is not simply due to aged women’s longevity as compared with men. Ischemic heart disease is the leading killer of women at *all* ages with annual mortality rates that affect more women under the ages of 35, 45, and 55 years than breast cancer (2,5,22). Recent data from the CDC on 729,000 heart disease deaths reported in the U.S. noted that sudden death rates increased significantly from 38% in 1989 to 47% in 1999 and that women were more likely to die of a cardiac arrest before hospital arrival (52%) as contrasted with 42% for men. Although the total number of sudden cardiac deaths is higher in men (23), this latter statistic of an increasing pre-hospital sudden death rate in women is noteworthy as it represents a significant change from prior decades (5,23,24).

The evaluation of IHD in women presents a unique and sometimes difficult challenge for clinicians, due to their

greater symptom burden, higher rate of functional disability, and a lower prevalence of obstructive CAD by coronary angiography as compared to men. Notably, women with IHD have more adverse outcomes as compared with men (2,25,26) despite the repeatedly documented lower angiographic disease burden and more often preserved left ventricular function as compared to men (27).

The compendium of coronary heart disease data indicate that current research and strategy development must focus on gender-specific issues in order to address the societal burden and costs related to these demographic shifts in IHD that place women in the majority of those impacted. This significant burden of the disease in women places unique diagnostic, treatment, and financial encumbrances on our society that are only further intensified by a lack of public awareness about the disease on the part of patients and clinicians alike. This societal burden of the disease is, in part, related to our poor understanding of gender-specific pathophysiologic differences in the presentation and prognosis of IHD and the paucity of diagnostic and treatment guidelines tailored to phenotypic differences in women.

Our understanding of gender-specific differences in the initial presentation, pathophysiology, treatment effectiveness, resource utilization patterns, and clinical outcomes have changed dramatically over the past decade (8,9,11-13,28). Historically, research in the area of IHD has consistently reported that CAD is manifested earlier in the lives of men, with much of the prior research focusing exclusively on men and/or disproportionately enrolling male patients. The more frequent evaluation of men has promoted a perception that IHD was a “man’s disease,” and the ensuing knowledge gap on the part of physicians and patients alike created inequities in healthcare access and processes of care that resulted in suboptimal care for at-risk women (1-26,29-35). Inequities in access are further exac-



**Figure 1.** Cumulative % change in coronary heart disease mortality in black and white women as compared with men in the U.S. from 1979 to 1998. Based upon recent estimates, there has been greater declines in coronary heart disease mortality in men as compared with black or white women. Adapted from Benjamin EJ, et al. (20).

erated by socioeconomic gaps between women and men (36–38). It is increasingly appreciated that socioeconomic disparities and psychosocial issues in varying ethnic female subsets compound the challenges in assessing at-risk women resulting in underutilization, underdiagnosis, and under-treatment patterns of care (1–3,6,12,16,17,39–41).

Our current understanding and treatment of IHD pathophysiology in women is based on “critical stenosis” diagnostic approaches. New findings support the concept of a multifactorial model where sex hormones interact with traditional and conditional risk markers leading to an increase in the functional expression of atherosclerotic plaque deposition or vascular or metabolic alterations resulting in worsening outcomes for women (1). The current review provides a synopsis of available evidence on gender-based differences in IHD and outlines important next steps toward enhancing detection aimed at improving outcomes for women. Part I of the review focuses on developing an understanding of gender-specific differences in traditional and novel risk factors as well as gender differences in the diagnosis of CAD (42–47).

### GENDER-SPECIFIC DIFFERENCES IN IHD PREVALENCE AND RISK FACTORS

Despite being the leading killer of women at all ages, the prevalence of obstructive CAD in women is relatively low before menopause (average age ~51 years) (4,48–52), only approaching equal prevalence rates for men and women in their seventh decade of life (2,5,52,53). In general, comparable incidence rates are achieved for women who are ~10 years older, such that the CAD rates of 55-year-old men are similar to that of 65-year-old women (4). The delayed onset of the disease results in a relatively lower likelihood of obstructive CAD for most of the women we evaluate including those in their fourth through seventh decades of life.

When risk factors are compiled in the form of global risk scores (e.g., Framingham risk score [FRS], calculated by summing point scores [or by adding risk equivalents] given to age, blood pressure, cholesterol, diabetes, and cigarette smoking), 4%, 13%, and 47% of women ages 50 to 59, 60 to 69, and 70 to 79 years, respectively, are at intermediate-high risk of coronary heart disease death or non-fatal myocardial infarction, respectively (54). For a 40-year-old woman, her lifetime risk of CAD, as based upon the FRS, is 0% to 2.3% for those with a low, intermediate, to high FRS as compared to rates ranging up to 11.6% for 40-year-old men (55). Although a family history of premature CAD is missing from the Framingham risk equation, individuals with at least one parent with premature CAD (onset age <55 years in a father, <65 years in a mother) have a greater risk for CAD events with age-adjusted odds ratios of 2.6-fold (95% confidence interval [CI] 1.7 to 4.1) higher for men and 2.3-fold (95% CI 1.3 to 4.3) higher for women (56).

**Table 1.** A Comparison of Gender Differences in Traditional Cardiac Risk Factors Including Differences in Varying Age Thresholds, Mean Population, Prevalence, and Outcome Differences

	Men	Women
Risk factor threshold values		
Age threshold for ↑ disease risk	≥45 yrs	≥55 yrs
Family history of premature CHD	<55 yrs	<65 yrs
HDL cholesterol		<50 mg/dl
Population average values		
Lipids		
Total cholesterol	↑	↑ For women after age ~50 yrs
HDL cholesterol		↑
Prevalence rates		
Hypertension*	↑	
Smoking†	↑	
Coronary disease or outcome risk		
Triglycerides		↑
Diabetes mellitus		↑
Obesity (e.g., BMI ≥30 kg/m <sup>2</sup> )‡	↑	↑
Central obesity (>35 kg/m <sup>2</sup> *)		↑

Gaps narrow: \*in elderly, †women lag in declining rates of smoking and noted increased prevalence of young female smokers; ‡obesity increasing in the last decade such that ~25% of women are now obese with a body mass index (BMI) ≥30 kg/m<sup>2</sup>. Additionally, women generally engage in less leisure-time physical activity and exhibit a greater functional decline in their postmenopausal years.

CHD = coronary heart disease; HDL = high-density lipoprotein.

There is also substantial gender-related variability in the prevalence and outcome associated with traditional cardiac risk factors (Table 1). That is, although overall rates of hypertension and smoking are higher in men, elderly hypertensive women and young female smokers are prominent at-risk subsets (2,5,57,58). Cigarette smoking is noted to increase inflammation, thrombosis, and oxidation of low-density lipoprotein (LDL) cholesterol supporting the hypothesis that there is a dose-response relationship between smoking and increased oxidative stress as a potential link to CAD (59). However, for women smokers, coronary heart disease mortality risk from cigarettes is equivalent to the risk associated with weighing ~42 kg more than her non-smoker counterpart (60).

Population studies have noted that total cholesterol measurements are higher in men until the fifth decade of life but, beyond this age, women have greater values (57,58). Furthermore, gender differences in high-density lipoprotein (HDL) values diminish with advancing age. High-density lipoprotein cholesterol values decline in men at the time of puberty and are generally lower than those of women at all ages. Women typically experience a relatively mild decline in HDL cholesterol at the time of menopause (2,4,5). In a comprehensive review of 25 population studies, Manolio et al. (61) reported that HDL cholesterol inversely predicted coronary heart disease in younger women and men as well as older (≥65 years) women. However, HDL cholesterol was not predictive of fatal coronary heart disease in older men (61). Thus, for all but HDL cholesterol, the relative risks for IHD in women and men as related to total and LDL

cholesterol are similar (2,4,5). When examining lipoprotein subclasses, women do have less atherogenic subclass profiles than men (62). Recent evidence from the Framingham Offspring study, however, reported that women have a two-fold higher concentration of large HDL particles when compared with men (8 vs. 4 mmol/l) (62). Hypertriglyceridemia is also a more potent independent risk factor for IHD in women as compared with men (4). A recent meta-analysis of 17 studies (n = 46,413 men and 10,864 women) revealed that the coronary heart disease relative risk for hypertriglyceridemia was elevated 32% in men and 76% for women (63).

Although younger-aged diabetic women (i.e., <45 years) have an equally low prevalence of atherosclerosis (64), numerous studies have reported a significantly higher cardiovascular mortality for diabetic women as compared with diabetic men (65–67). Notably, the age-adjusted prevalence of cardiovascular disease is nearly two-fold higher in diabetic versus non-diabetic women (57), with the highest risk being reported in non-Hispanic blacks. Thus, it appears that diabetes eliminates the “female advantage” of a predominately lower CAD prevalence and outcome risk that is realized for the majority of women (66). While some of the gender-related differences in mortality for diabetic women appear to be related to older age, more frequent hypertension, hyperlipidemia, poor glycemic control, and higher smoking rates, much of the relatively greater risk for IHD associated with diabetes in women remains unanswered (65,68).

As women progress through the approximately one-third of their life in menopause, there appears to be a greater loss in physical functioning when compared with their male counterparts (69). This greater loss in functional capabilities contributes to greater weight gain, insulin resistance, and hypertension (70–72). Furthermore, a loss in ovarian estrogen during menopause is associated with an androidal shape and deposition of abdominal fat, a body habitus profile that is more often associated with an increased CAD risk in women (72). In women, body mass index is more closely associated with computed-tomographic-determined anthropometric measurements of visceral adipose tissue (73). With an increasing prevalence of obesity in U.S. women (from 12.2% in 1991 to 20.8% in 2001), the accompanying rising frequency of insulin resistance, dyslipidemia, diabetes, and hypertension will likely contribute to increasing rates of IHD (70–72,74). Some have posited that poor childhood nutrition and lower socioeconomic status may precipitate insulin resistance and obesity, thus increasing a woman's risk of CAD (75).

Recent evidence from the Women's Ischemia Syndrome Evaluation (WISE) study reported that overweight women were more likely than normal weight women to have CAD risk factors. Interestingly, neither body mass index nor abdominal obesity measures were significantly associated with obstructive CAD or adverse cardiovascular events after adjusting for other risk factors ( $p = 0.05$  to  $0.88$ ) (76).

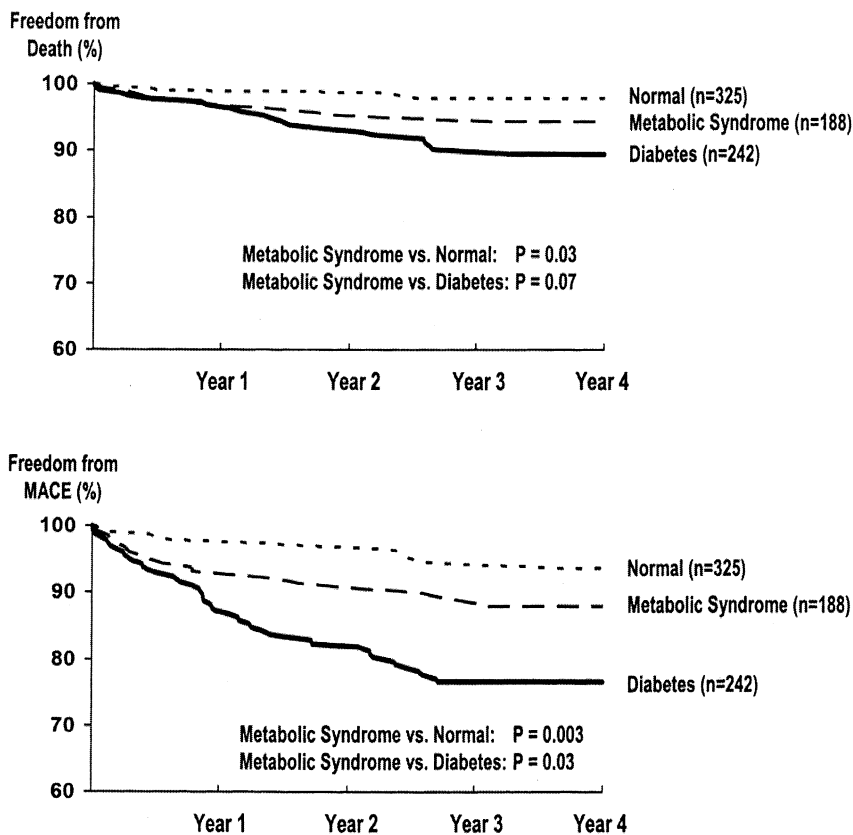
Thus, it appears that the metabolic alterations associated with obesity are key factors in placing a woman at risk for CAD and cardiac events.

A clustering of risk factors is common in postmenopausal women, notably obesity, hypertension, and dyslipidemia (2,5,57,58,66,77–85), possibly related to gender-specific metabolic differences exacerbated by hormonal imbalances. The metabolic syndrome represents a clustering of risk conditions including insulin resistance (with or without glucose intolerance), dyslipidemia (elevated triglycerides, small LDL particles, or low HDL cholesterol), hypertension, and abdominal obesity. Recently, the National Cholesterol Education Program Adult Treatment Panel-III simplified the definition as that occurring in the presence of three or more of the following (for women): 1) waist circumference >35 inches; 2) fasting triglycerides >150 mg/dl; 3) HDL cholesterol <50 mg/dl; 4) hypertension (systolic blood pressure  $\geq 130$  mm Hg, diastolic blood pressure  $\geq 85$  mm Hg, or use of antihypertensive drug therapy); or 5) a fasting glucose measurement  $\geq 110$  mg/dl (83,84). Recent evidence suggests that obesity itself is not an independent predictor of disease but that the metabolic syndrome is one link between obesity and cardiovascular disease (86).

Women with the metabolic syndrome have an increased prevalence of subclinical disease, and they are at an intermediate cardiovascular disease mortality risk when compared to those with normal glucose levels or frank diabetes (85–90). In a recent report by Marroquin et al. (90), the four-year relative risk of cardiac events was increased approximately two-fold for women in the WISE study with the metabolic syndrome as compared to those with a normal metabolic status (Fig. 2). Larger waist circumferences in women with the metabolic syndrome may play a role in worsening cardiac risk factor profiles leading to an increased risk of CAD. For example, women with larger waist circumference measurements walk on average 1,000 fewer steps per day and are, thus, less active (91) minimizing the beneficial effects of a healthier lifestyle on lipids, blood pressure, and glucose measurements. Women with a history of polycystic ovary syndrome have a greater frequency of multiple risk factors including central obesity, insulin resistance, and a greater prevalence of the metabolic syndrome and diabetes, although studies linking this with an increase in IHD are inconsistent (92).

Interestingly, there is a strong relationship between the metabolic syndrome and depression, a relationship that may be particularly relevant given the 70% higher prevalence of depression in women (93). In the WISE study, approximately one in four women reported prior treatment for depressive symptoms (39). Lett et al. (94) recently put forth several possible mechanisms for the link between depression and the metabolic syndrome including poor treatment adherence, lifestyle factors, traditional risk factors, platelet activation, and inflammation but also dysfunction of the





**Figure 2.** From the National Institutes of Health-National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation (WISE) study, event-free survival by metabolic status was recently reported in women. These results reveal that women with the metabolic syndrome are at intermediate risk for major adverse cardiac events (MACE) (death, non-fatal myocardial infarction, stroke, or congestive heart failure). Reprinted from Marroquin OC, et al. (90).

autonomic nervous system and hypothalamic pituitary adrenal axis.

### SEX HORMONES AS RISK FACTORS FOR IHD

In the premenopausal woman with normal ovulation, endogenous sex hormones including estrogen are hypothesized as the primary reason for their low incidence of IHD as compared with age-matched men. During menopause, a woman's estrogen levels are approximately one-tenth of that during her premenopausal years (95). Estradiol is the predominant source of estrogen in the premenopausal years while estrone, produced by peripheral conversion of androgens in the adipose tissue, is the main source during a woman's postmenopausal years. Thus, not only is the overall level of estrogen lower postmenopausally but the predominant estrogen type varies from a woman's pre- to postmenopausal years. It is reasonable, therefore, to hypothesize that the endogenous estrogen type might provide relative protection from IHD premenopausally because of the many animal studies that have demonstrated the antiatherosclerotic effects of estrogen (95-98). Additionally, basic science work shows that estrogen reduces cellular hypertrophy, enhances vessel wall elasticity, and has antioxidative and anti-inflammatory properties (95-98).

The WISE study results suggest that endogenous estrogen deficiency in young women may be a potent risk factor for IHD (99). We observed in premenopausal women that a stress-induced central disruption in ovulatory cycling with resulting hypoestrogenemia was associated with a 7.4-fold (95% CI 1.7 to 33.3) increased risk of obstructive CAD (measured at coronary angiography) in women with suspected ischemia (99). In this report, hypoestrogenemia of hypothalamic origin (defined as measurements of estradiol <184 pmol/l [50 pg/ml], follicle stimulating hormone <10 IU/l, and luteinizing hormone <10 IU/l) was the most powerful predictor of angiographic CAD. Further work in the WISE study has also documented a protective effect of prior oral contraceptive use for later-onset postmenopausal atherosclerosis (100). The WISE study findings, supported by other publications, suggest that premenopausal estrogen deficiency due to a central disruption of ovarian function may be a potent risk factor for IHD. Premenopausal estrogen deficiency could explain the more adverse prognosis experienced by younger post-myocardial infarction women when compared to age-matched men (26,27). And, finally, although this discussion has focused on estrogen, androgens have been shown to express atherosclerotic-related genes in men but not in women, perhaps contributing to the gender-related differences in CAD prevalence (101).

## OTHER NOVEL RISK FACTORS FOR IHD IN WOMEN

A review of evidence reveals that the compilation of traditional risk factors underestimate risk in women (54–55,102–104). This pattern of underrecognition in women has prompted additional research to assess the value of novel risk markers (e.g., inflammatory markers, retinal artery narrowing, coronary calcification) that may provide improved accuracy for the detection of CAD in women (54,55,102–104). Accordingly, evaluation of the role of novel risk markers, such as inflammation (e.g., high sensitivity C-reactive protein [hsCRP]) (105–107), suggests an improved predictive accuracy above and beyond traditional risk factors in estimating cardiovascular disease risk in women. Recently, a number of reports have introduced a variety of laboratory and imaging risk markers that uniquely and/or differentially predict cardiovascular disease risk in women (104–112).

Evidence to support the utility of novel risk markers are the data revealing a lack of correlation between novel and traditional risk factors, such as a poor correlation between hsCRP and LDL cholesterol measurements (113). Additionally, recent reports have also noted that hsCRP measurements provide added prognostic value (over and above traditional risk factors) in estimating important cardiovascular events in large epidemiologic cohorts of women (104,106,107,112,113). For example, in the Women's Health study, a prospective cohort of approximately 30,000 middle-aged, predominantly postmenopausal apparently healthy women, the relative risk of future vascular events increased as the level of hsCRP went from low-normal to high-normal (106). This was true for all cardiovascular events as well as for the specific combined end point of myocardial infarction or stroke.

High sensitivity C-reactive protein also acts synergistically with other risk factors in estimating prognosis where the presence of both LDL cholesterol and being a current smoker raised the relative risk of cardiovascular death and other events in women (106,107,114,115). Of note, hsCRP has also been related to other markers of cardiovascular risk including the metabolic syndrome, type 2 diabetes, and congestive heart failure (114–116). For women with the metabolic syndrome and high levels of hsCRP, their risk of cardiovascular events was similar to that of diabetic women (89,90). This illustrates a potentially productive approach for improving risk assessment in women such that, although women are generally at lower risk when compared with men, the combination (i.e., clustering) of risk markers acts additively and/or multiplicatively to increase risk and therefore improve risk assessment for female cohorts.

Other inflammatory markers, like fibrinogen, have been evaluated; however, it appears that hsCRP and interleukin-6, both acute phase reactants, may play a role in risk evaluation due to their ease of evaluation, standardization of methods, repeatability, and low cost (116).

The predictive value of novel risk markers may provide us with additional insight into gender-specific differences in the pathophysiology of IHD; hsCRP measurements correlate with signs and symptoms of myocardial ischemia and may be related to the pathogenesis of angina in women, in particular for those with non-obstructive CAD (117). Interestingly, data from the Third National Health and Nutrition Examination Survey demonstrate that women, in general, have higher mean C-reactive protein values compared with men, with the difference becoming apparent at the time of puberty (118). A relatively high C-reactive protein  $\geq 1$  mg/dl was observed in 13% of women as compared with only 6% of men in this population survey (118); hsCRP measurements not only vary by gender but also by ethnicity. From the Women's Health study, median C-reactive protein levels were, on average, significantly higher among black women (2.96 mg/l) than among white (2.02 mg/l), Hispanic (2.06 mg/l), or Asian (1.12 mg/l) women (119).

Recent data support hypotheses of an autoimmune precursor for atherosclerotic disease in women. Notably, gender-specific differences in C-reactive protein, as an inflammatory marker, are consistent with the observed 2- to 50-fold greater frequency of inflammatory-mediated autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, etc. in women as compared to men (120). This work suggests that inflammation may play a gender-specific role in atherosclerotic disease for women, although this reasoning is currently speculative (121). In a recent matched case-control study of 394 patients (>90% women), evidence of atherosclerotic plaque (as measured by carotid ultrasonography) was present nearly five times more often in those with systemic lupus erythematosus when compared to age- and gender-matched healthy controls (122). In another matched case-control series of patients with systemic lupus erythematosus (>85% women of 134 patients), the prevalence of coronary calcification, a measure of atherosclerotic plaque burden, increased dramatically after age 50 years (123). Thus, it may be a combination of aging and/or the exposure duration of the autoimmune disease on the cardiovascular system that may impact on the atherosclerotic plaque process. We await further work on the relationship between atherosclerotic disease and rheumatoid arthritis, a more common condition in women, to further support this hypothesis of an autoimmune precursor for cardiovascular disease.

Anemia has also recently been linked to worsening outcomes in women. Anemia in patients presenting with acute myocardial infarction or heart failure has frequently been associated with adverse outcomes. The WISE study group recently reported on the prognostic significance of hemoglobin values in women with suspected ischemia. In this report, anemic women had a higher risk of all-cause death (10% vs. 5%;  $p = 0.02$ ) and major adverse cardiovascular outcomes (26% vs. 16%;  $p < 0.01$ ) when compared with non-anemic women. Additionally, in a risk-adjusted Cox model, decreasing

hemoglobin values were associated with a higher risk of adverse outcomes (hazard ratio = 1.20,  $p = 0.002$ ). Anemic women also had a shorter survival time free of adverse outcomes ( $p < 0.001$ ). These findings extend previous reports noting an inverse relationship between lower hemoglobin values and higher risk of adverse cardiovascular outcomes to those women with chest pain symptoms (124).

## ASSESSMENT OF MYOCARDIAL ISCHEMIA AND OBSTRUCTIVE CORONARY DISEASE IN WOMEN

**Symptom assessment.** The evaluation of chest pain symptoms in women has been hampered by attempts to apply a “typical” angina definition derived from predominantly male populations to female cohorts, as there are substantial differences between women and men in the type, frequency, and quality of symptoms noted during their presentation (125). For women, prodromal symptoms are often unusual including fatigue, sleep disturbance, and shortness of breath. Despite the reported gender differences, typical symptoms are significantly associated with acute coronary syndromes in women (126). In a recent report, there were no observed gender differences in the accuracy of typical symptoms, defined as chest pain or discomfort, dyspnea, diaphoresis, and arm or shoulder pain, in diagnosing acute coronary syndromes (126). Of these features, chest pain or discomfort and diaphoresis were characteristics mostly associated with acute coronary syndromes in women. Additionally, women, in general, report more acute than prodromal symptoms, and up to half of women presenting with an acute myocardial infarction report no prior chest pain symptoms (127). In some reports, women present less often than men with exertional chest pain symptoms that may be defined as “typical” angina (2,49,50). However, women present more frequently than men for the evaluation of and are hospitalized more often for chest pain (4.0 million visits for women vs. 2.4 million visits for men) (2).

Thus, it appears from reviewing this evidence that the qualifying symptom characteristic that discerns women and men is an exertional component to the defining of typical angina. It does appear that as defined by the Yale group that typical angina that includes chest pain or discomfort, dyspnea, diaphoresis, and arm or shoulder pain is accurate at detection of unstable angina but that, in many reports, the inclusion of exertional components often renders dramatic gender-related differences in symptom predictive accuracy.

There does appear to be an interaction effect of symptom presentation with age, in that older women often present similarly to men. This would include the fact that older women have more frequent typical angina. However, women <65 years are also 50% more likely than younger men to be discharged with a diagnosis of unstable angina. There is no gender difference in the rate of acute coronary syndromes in older patients hospitalized for chest pain syndromes (age interaction  $p < 0.0001$ ) (128). Additionally, younger women are also less likely to present with ST-

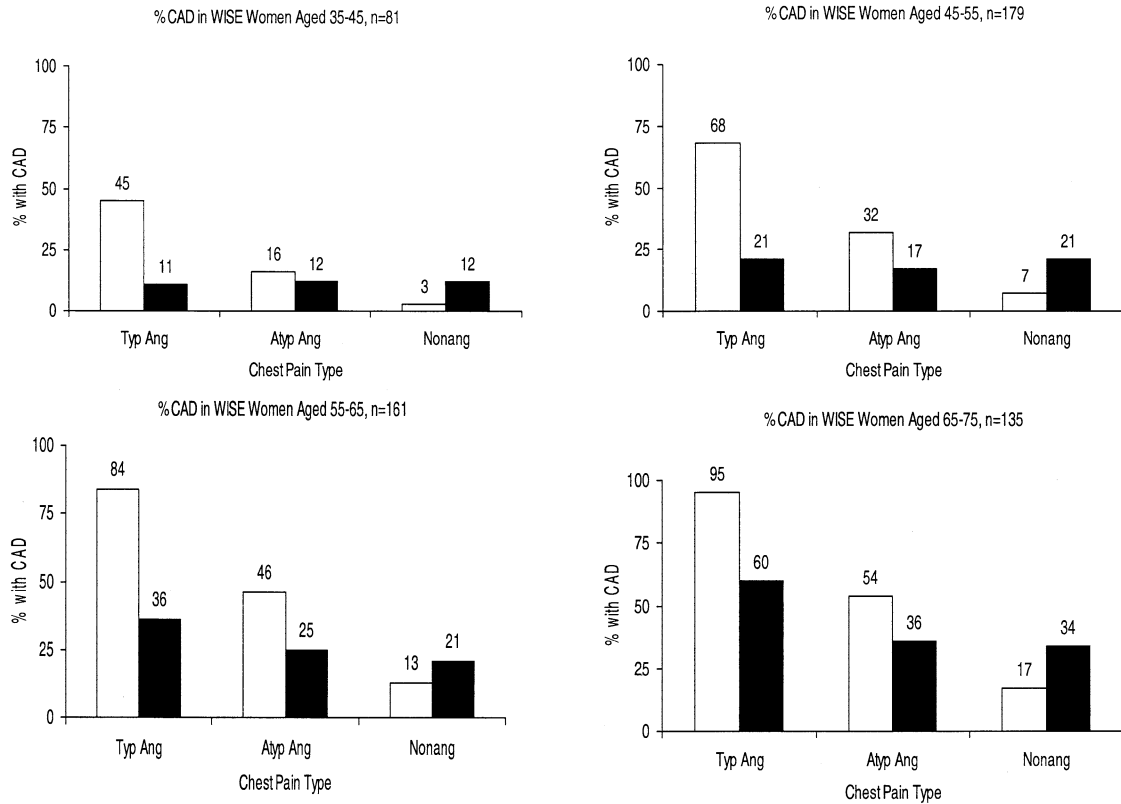
segment elevation, a factor that may protract their time to diagnosis, the ensuing intensity of management, and result in worsening outcomes.

When evaluated for symptoms suggestive of myocardial ischemia, women have lower rates of obstructive CAD at angiography (Fig. 3) (48–50,104). This lower CAD likelihood by gender was initially suggested, by Diamond and Forrester (129), nearly two decades ago. From their early work, women with typical or atypical chest pain symptoms have calculated obstructive CAD probabilities substantially less than that of men. For example, typical exertional angina in a 55-year-old man has a probability of obstructive CAD of approximately 90% as compared with a wide range from 55% to 90% for a 55-year-old woman. This observation that chest pain symptoms are less accurate and less precise predictors of obstructive CAD in women continues to be noted in contemporary data series (130,131).

In particular for diabetic patients, symptoms are generally not as effective guides to CAD risk as compared with objective evidence of ischemia (132). In part, a woman’s description of symptoms may be a guiding force in determining the likelihood of CAD (133). For patients with stable, intermittent chest pain, their description of pain is the most important predictor of CAD and may be a factor contributing to less intensive management for female patients (133). Today, however, we face several critically important questions for evaluating symptoms in women: can current symptom evaluation tools be improved for more accurate detection of obstructive CAD in women? Do symptom differences suggest a gender-specific pathophysiology such that gender-specific new tools should be developed for assessment of IHD in women (134–137)? However, as yet, evidence is not available to definitively answer these questions.

A majority of women without obstructive CAD at coronary angiography continue to have symptoms that contribute to a poor quality of life and consumption of large amounts of health care resources due to repeated evaluations and hospitalizations (39,104,138–140). In many cases, physicians rely upon cardiac imaging to differentiate cardiac from non-cardiac symptoms in women (141). However, this approach leaves unanswered the question of how to detect and manage myocardial ischemia in the absence of significant obstructive CAD.

**Exercise electrocardiographic (ECG) evaluation.** The exercise ECG is the most frequently performed diagnostic test. Its use and indications for women are limited to those with a relatively normal 12-lead ECG and capabilities of performing moderate-to-high levels of exercise. These prerequisites are increasingly found in only a minority of women referred for IHD assessment (142). The exercise ECG, using a threshold for abnormality of  $\geq 1.0$  mm of ST-segment depression, has a lower diagnostic accuracy (sensitivity and specificity for significant coronary artery obstruction ~60% to 70%) in women as compared to men (with diagnostic sensitivity and specificity measures ~80%) (143–146) (Table 2).



**Figure 3.** From the National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation (WISE), the Diamond probability of coronary artery disease (CAD) as compared with observed coronary disease prevalence in symptomatic women ages 35 to 45, 46 to 55, 56 to 65, and 66 to 75 years. These results note that probability estimates based upon data series of several decades ago overestimate the likelihood of coronary disease in women; as based upon a comparison of a contemporary series of women referred to coronary angiography. Atyp Ang = atypical angina; Nonang = non-angina; Typ Ang = typical angina. **Solid bars** = WISE prevalence; **open bars** = Diamond probability.

This diminished accuracy in women is related, in part, to their lower CAD prevalence as well as greater comorbidity and functional impairment that preclude women from achieving maximal levels of exercise when compared with (generally) more active men (Table 3). Women undergoing exercise testing are often incapable of performing >5 metabolic equivalents (METs) of treadmill exercise leading to inadequate heart rate responses (147). In sedentary women, an early hyperexaggerated heart rate response, excessive dyspnea, and premature fatigue can be seen within the first few minutes of exercise, in particular with the aggressive Bruce protocol where stage I requires 4.7 METs of work. Women performing submaximal levels of exercise with no inducible ischemia typically remain without diagnostic confirmation and explanation for their symptoms,

thus raising anxiety and depression about the basis for their chest pain (39).

Other reasons posited for a diminished accuracy of the ECG in women include a lower QRS voltage and hormonal factors. A digoxin-like effect of endogenous estrogen can possibly promote higher false positive rates in premenopausal women. Hormone replacement therapy, with its ensuing vasodilatory properties, may result in false negative test results (148-158) (Table 3). For the premenopausal woman, chest pain and the inducibility of ST-segment abnormalities can vary by the menstrual cycle with lower mid-cycle estradiol levels being associated with a greater frequency, intensity, and severity of ECG-based ischemia (148-159). All of these reasons may play a role in the diminished accuracy of chest pain and ST-segment changes in women (43).

**Table 2.** A Compilation of Published Meta-Analyses on the Diagnostic Accuracy of Exercise Electrocardiography, Stress Echocardiography, and Stress SPECT Imaging in Women

Author, Year (Ref.)	Exercise Electrocardiography		Stress Echocardiography		Stress SPECT	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Fleischmann et al., 1998 (143)	—	—	85%	77%	87%	64%
Kwok et al., 1999 (146)	61%	70%	86%	79%	78%	64%
Beattie et al., 2003 (143)	—	—	81%	73%	77%	69%
Average	61%	70%	84%	76%	81%	66%

SPECT = single-photon emission computed tomography.



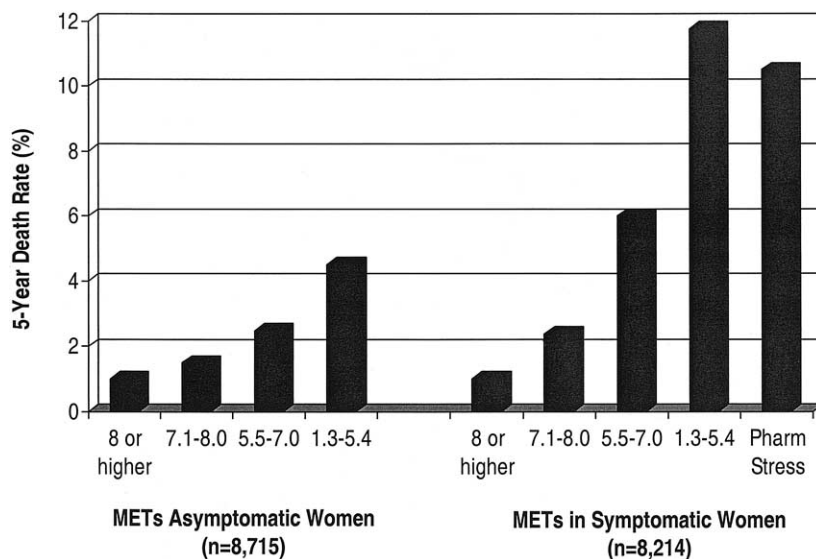
**Table 3.** Factors Affecting the Accuracy of Diagnostic Testing in Women

1) Menopausal status
<p>Premenopausal women: endogenous estrogen may elicit a digoxin-like effect and provoke ST-segment changes resulting in a false positive exercise electrocardiogram.</p> <p>In the premenopausal woman, angina and ischemia have been shown to vary by the menstrual cycle. In the luteal/menstrual phase, where estradiol levels are low, a greater prevalence of ischemia and reduced time to ischemia onset has been noted.</p> <p>Postmenopausal women: the prevalence of coronary disease is increased resulting in a higher predictive accuracy.</p> <p>Menopausal symptom therapy (previously called hormone replacement therapy): these agents promote peripheral vasoreactivity with evidence noting an increase in exercise time, a decrease in myocardial ischemia in postmenopausal women with coronary disease (note: there has been a decrease in the prevalence of electrocardiographic (but not perfusion) ischemia.</p>
2) Functional capacity
<p>There is a diminished ability to elicit ischemia if adequate heart rate and estimated metabolic equivalents (METs) have not been achieved. Women incapable of performing 5 METs on exercising testing should be re-tested with pharmacologic stress imaging.</p>
3) Disease prevalence
<p>In women with a lower prevalence of disease and a greater prevalence of single-vessel disease, the overall predictive accuracy of stress testing with or without imaging is diminished when compared to a male population.</p>
4) Electrocardiographic changes
<p>Resting ST-T-wave changes: the presence of significant resting ST-T-wave changes on a 12-lead electrocardiogram diminishes the accuracy of identifying peak exertional changes. Current American College of Cardiology/American Heart Association guidelines recommend cardiac imaging in women and men with significant ST-T-wave changes on their resting electrocardiogram.</p> <p>Lower electrocardiogram voltage: population-based studies have noted a lower QRS voltage that may affect the test's diagnostic accuracy in women.</p>

These data reveal that relying on the exercise ECG alone for IHD detection may be imprecise and more precarious in women than in men. However, exercise stress test risk scores (e.g., Duke treadmill score) have been shown to improve prognostication in women but, of all the factors noted during testing, the strongest predictive parameter from the treadmill test is exercise duration (43,159-163). Of note, women have generally worse functional capacity, engage less often in physical exercise programs, and have more functional decline during their menopausal years as compared to age-matched men (69). Women who achieve <5 METs are at increased risk of cardiac events (Fig. 4) (142,147,161-163). For women, information as to their capabilities when performing activities of daily living may be a useful guide to approximate peak MET levels (147). Specifically, routine household activities require about ~4 METs of work.

Recently, the 12-item Duke Activity Status Index (DASI) questionnaire has been shown to risk stratify women (76,147,164-166). Using self-reported activities of daily living, women achieving <4.7 METs of work had a 3.7-fold increased risk of death or non-fatal myocardial infarction when compared to those women reporting higher functional abilities (147). From this recent report by Shaw et al. (147), two-thirds of the cardiac events in the WISE women occurred in those with an estimated capacity of <4.7 DASI METs. In the WISE study, women with evidence of lower DASI scores were also significantly more likely to have risk factors and obstructive CAD (44% vs. 26%;  $p < 0.001$ ) and each 1-MET increase in the DASI score was independently associated with an 8% (hazard ratio, 0.92; 95% CI 0.85 to 0.99;  $p = 0.02$ ) decrease in risk of major adverse cardiovascular events during follow-up (76).

Peak and recovery heart rate measures also improve risk assessment and diagnostic accuracy for IHD in women (167-



**Figure 4.** Prognostic value of functional capacity in asymptomatic (n = 8,715) and symptomatic (n = 8,214) women as synthesized from published reports. This figure illustrates five-year mortality for asymptomatic and symptomatic women. METs = achieved metabolic equivalents during exercise testing; Pharm stress = women referred for adenosine or dipyridamole single-photon emission computed tomography or dobutamine stress echocardiography.

173). Recent reports emphasize the importance of tracking heart rate responses in the recovery phase of exercise. Deconditioning may manifest elevated sympathetic nervous system activity and a delayed restoration of cardiac vagal tone post-stress (168–173), reflected by persistently elevated heart rates post-exercise. By subtracting 2-min recovery from the peak heart rate value, a decrease of less than 44 beats is inversely related to all-cause mortality in women (169). This measurement of heart rate recovery may be particularly important for deconditioned women who have a rapid heart rate increase within the first few minutes of the onset of exercise that remains elevated during recovery.

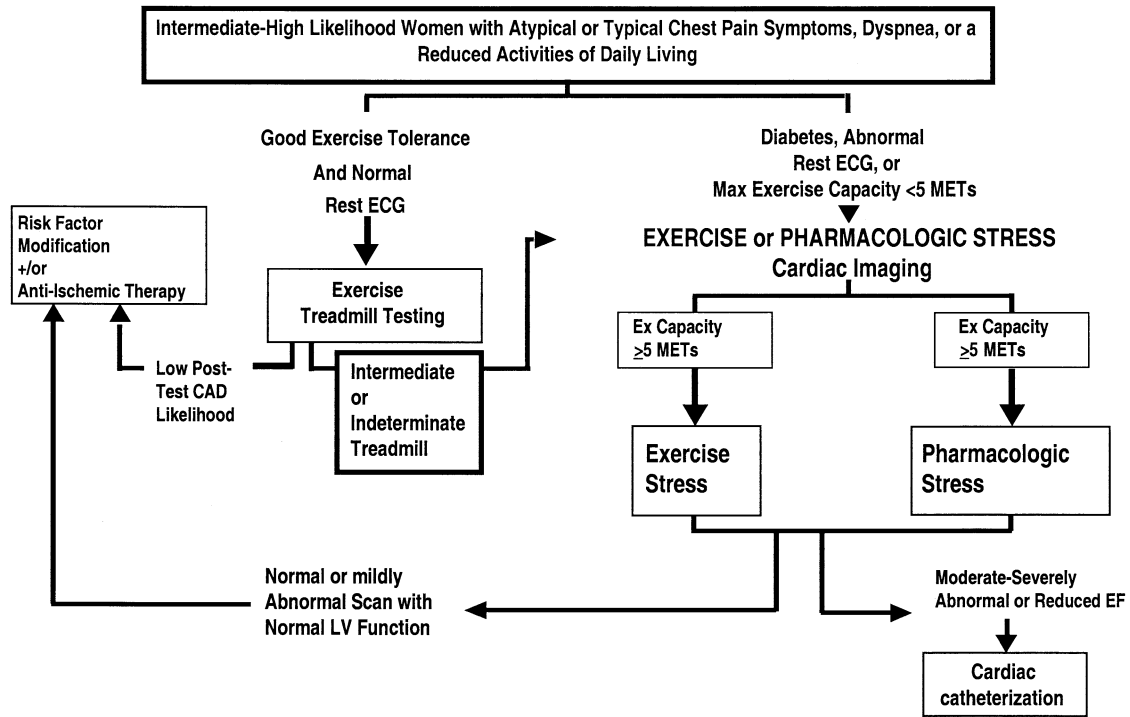
**Stress-induced perfusion abnormality assessment.** In the time course of the ischemic cascade, reductions in myocardial perfusion occur earlier than either ECG or ventricular wall motion abnormalities and may provide a more precise (or sensitive) measure for estimating IHD risk. Although many other techniques can be applied, myocardial perfusion single-photon emission computed tomography (SPECT) is a nuclear-based technique that is most commonly used for the evaluation of women presenting with chest pain symptoms (174). Generally, the literature supports the fact that SPECT imaging is highly sensitive for the detection of CAD in both women and men (174). The accuracy of SPECT techniques is diminished in women with a limited exercise capacity and, for that reason, pharmacologic stress testing (commonly performed with adenosine or dipyridamole) is recommended by the American College of Cardiology/American Heart Association and American Society of Nuclear Cardiology guidelines (174–176). Diagnostic specificity, however, can be influenced by both breast tissue and obesity that can interfere with image quality and cause false positive test results, especially in the anterior and lateral regions of the heart. For this reason, the higher energy Tc-99m radioisotopes are preferred in women due to a reduction in soft tissue attenuation artifacts (174–176). From the recent American Society of Nuclear Cardiology statement on women and based upon randomized trial evidence, use of Tc-99m agents improves diagnostic specificity in women (174,175). In general, however, the interpretation of regional perfusion deficits is challenging in women as one must first exclude technical limitations with either attenuation correction or prone imaging techniques. Further reductions in false positives (i.e., improvements in diagnostic specificity) can be aided by integrating global or regional left ventricular wall motion and function as well as wall thickness as a guide to discerning true positive reductions in regional myocardial perfusion. For example, a stress-induced perfusion artifact may be called in the setting of normal contraction and thickening of the left ventricle.

The improvements in image quality with Tc-99m-based agents and computer capabilities (including attenuation correction) for SPECT imaging has resulted in dramatic improvements in diagnostic accuracy for women (Table 2). As a result, large observational series have noted similar abilities to risk stratify women and men with chest pain symptoms (174–182). From a multicenter registry of 3,402

women with stable chest pain symptoms when stratified by the number of vascular territories with ischemia, three-year survival was similar and ranged from 98.5% to 85% for 0 to 3 coronary artery territories (181). Diabetic women, in particular those requiring insulin treatment, have the worst event-free survival with inducible ischemia (177,182,183). From a summary meta-analysis, the relative risk of cardiac death or non-fatal myocardial infarction with a high-risk perfusion scan was elevated 9.0-fold (95% CI 6.9 to 11.7) and was similar to recent prognostic evidence with stress echocardiography (182). A revision of the recent consensus statement from the American Society of Nuclear Cardiology's work-up algorithm for non-invasive imaging in women is depicted in Figure 5 (174).

For SPECT perfusion techniques, deficits are identified based upon differences in regional distribution of blood flow that is comparatively assessed (i.e., normalized) across the myocardium. It is therefore possible that in the setting of global coronary vascular dysfunction (endothelial or microvascular dysfunction), the SPECT study could show no regional differences in the distribution of flow and appear normal. Additionally, global reductions in flow or impaired vasodilatory responses to stress may reflect balanced reduction in flow, although this is more often noted in the setting of severe, multivessel CAD. Thus, the use of both positron emission tomography and magnetic resonance (MR) techniques may provide unique advantages over SPECT; however, this has yet to be established in the published literature. An additional challenge with the use of nuclear imaging techniques is the fact that women have smaller hearts with the possibility that smaller myocardial areas of reduced perfusion may be missed as a result of limitations in spatial resolution with SPECT cameras. Although these small abnormalities may not be prognostically important (i.e., for major cardiac events), they may explain persistent chest pain syndromes in women, particularly for those with non-obstructive CAD.

**Stress-induced wall motion abnormality assessment.** As wall motion abnormalities appear after perfusion abnormalities, evaluation of this marker has been associated with a higher diagnostic specificity (104,142–144,146). Stress echocardiography, the most commonly applied test for wall motion assessment, has advantages due to its lower cost, absent radiation exposure, and ability to image both cardiac structures as well as ventricular function. Despite these advantages, echocardiographic techniques can also be suboptimal in women due to obesity or lung disease limiting acoustic windows and reducing exercise tolerance. Use of intravenous contrast enhancement has been shown to improve left ventricular opacification for those with an initially suboptimal acoustic window. Women who are incapable of maximal exercise are commonly referred to dobutamine (in the U.S.) or dipyridamole (in Europe) pharmacologic stress echocardiography (184). An important factor that affects the acquisition of peak stress wall motion changes is the experience of both the sonographer and clinician to rapidly obtain multiple echocardiographic views at peak heart rates.



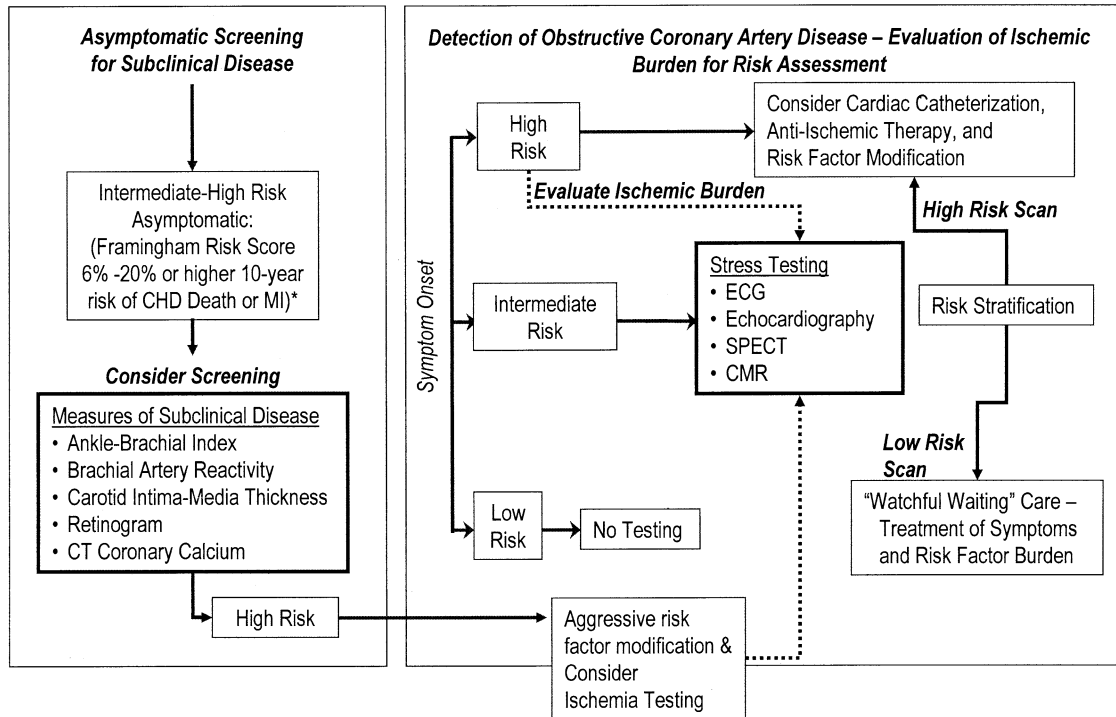
**Figure 5.** A revision of the recent consensus statement from the American Society of Nuclear Cardiology's (ASNC) work-up algorithm for non-invasive testing in women. The revision includes the application of ASNC's guidelines to all cardiac imaging modalities. Adapted from Mieres JH, et al. (174). CAD = coronary artery disease; ECG = electrocardiogram; EF = ejection fraction; Ex = exercise; LV = left ventricular; METs = metabolic equivalents.

Thus, similar to SPECT imaging, there are limitations to the use of echocardiography in women that may challenge the test's interpretation.

Despite these limitations, the diagnostic accuracy data, based upon several decades of experience and nicely summarized in a recent report from the Agency for Health-Related Quality, reveal that exercise echocardiography is highly accurate at detecting CAD in women (i.e., Table 2, sensitivity ~84% and specificity ~76%). Additionally, more recent evidence also supports the use of stress echocardiographic techniques for the estimation of prognosis in women (44,146,185–187). In a recent report in 4,234 women, the extent of ischemic wall motion abnormalities was highly predictive of cardiac death (185). For women undergoing exercise echocardiography, five-year survival ranged from 99.4%, 97.6%, and 95% for those with no, single, and multivessel ischemia, respectively ( $p < 0.0001$ ). Significantly higher cardiac death rates were noted for those women undergoing dobutamine stress echocardiography with annualized death rates ranging from ~1% to ~3% for zero- to three-vessel ischemia ( $p < 0.0001$ ) (185).

**Cardiovascular MR assessment.** Cardiovascular MR imaging may also provide unique clinical utility for the evaluation of subendocardial ischemia, improved precision for the assessment of left ventricular function and mass, and a detailed anatomic evaluation of both the myocardium as well as the imaging the peripheral vasculature (188–194). Magnetic resonance spectroscopy can also detect alterations in myocardial metabolism with changes in high-energy

phosphates (193,194). There are specific advantages to the use of MR imaging that may lend itself to the evaluation of women including excellent soft tissue characterization and contrast, three-dimensionality, an absolute quantitation of blood flow, and overall superior temporal and spatial resolution to image vascular and myocardial abnormalities (188–194). Although not in common practice, MR techniques have been applied for the evaluation of suspected myocardial ischemia in female patients with chest pain symptoms and to lower risk cohorts (188–194). From one recent small series, MR perfusion was reported to be highly accurate to the detection of single-vessel obstructive CAD (191). Due to superior spatial resolution, MR delineates subendocardial perfusion (an initial manifestation of myocardial ischemia) from epicardial perfusion and may provide corollary evidence as to the etiology of chest pain symptoms in women, particularly in the absence of obstructive CAD (189). Panting et al. (189) utilized this feature of MR perfusion imaging to support the concept that subendocardial ischemia may be responsible for chest pain in women with angina but without obstructive CAD. From this report, they demonstrated reduced subendocardial perfusion in response to vasodilator stress using adenosine. Additionally,  $^{31}\text{P}$  MR spectroscopy identifies alterations in high-energy phosphates (i.e., reduction in phosphocreatine/adenosine triphosphate [PCr/ATP] ratio) providing a direct assessment of metabolic myocardial ischemia (193,194). A recent report noted worsening event-free survival (predominately chest pain hospitalizations) for



**Figure 6.** Proposed paradigm for testing of asymptomatic and symptomatic women including detection of subclinical and obstructive coronary disease. \*6% to 20% for intermediate Framingham risk scores and >20% for high Framingham risk scores. CHD = coronary heart disease; CMR = cardiovascular magnetic resonance imaging; CT = computed tomography; ECG = electrocardiogram; MI = myocardial infarction; SPECT = single-photon emission computed tomography.

those women with a reduced PCr/ATP ratio  $\leq 20\%$  and non-obstructive coronary arteries. This recent prognostic finding from the WISE study raises the significance of the  $^{31}\text{P}$  MR evidence of myocardial ischemia as an explanation for the frequent hospitalization of women with non-obstructive coronary arteries who have persistent and often refractory symptoms warranting hospitalization while consuming large amounts of healthcare resources. Furthermore, evidence of metabolic ischemia offers an insight into the pathophysiology and potential target for the treatment of syndrome X, as testing and treatment strategies are not currently defined (194). These results coincide with a similar report on cardiac syndrome X noting that hsCRP values were in the intermediate range between healthy controls and those with CAD (195). Thus, this evidence from small patient cohorts suggests that chest pain in the setting of non-obstructive CAD, a prevalent condition, may be less benign than previously considered (to be discussed in greater detail in part II of this review). However, MR has its own limitations with a closed bore magnet causing claustrophobia in certain patients.

## CONCLUSIONS

In this review, we have synthesized a large body of evidence on gender-related differences in cardiovascular epidemiology with notable differences in disease prevalence and associated clinical outcomes for women. Variability in the

onset, relative risk, and the synergy of traditional and novel risk factors creates a tremendous challenge to busy clinicians possibly resulting in suboptimal management and inequities in access for women in today's healthcare environment. Emerging data suggest a unique risk profile in women including hypoestrogenemia coupled with the adverse effects of a protracted dysmetabolic state on promoting an inflammatory milieu and/or vascular or metabolic alterations that may provoke both symptoms and ischemia in the setting of non-obstructive CAD.

Additionally, for the growing proportion of women without obstructive CAD, chest pain symptoms and functional limitations may be more related to metabolic alterations resulting in shifting energy substrates toward myocardial and peripheral glucose (anaerobic) metabolism. Thus, traditional stress testing that is based on demand ischemia often performs poorly to detect obstructive CAD in cohorts of women without a significant coronary stenosis. The poor performance of cardiac imaging tests, such as stress echocardiography and SPECT imaging, for the diagnosis of obstructive CAD has been circumvented by the application of these techniques for risk assessment purposes. There is now substantial evidence in large female cohorts that both stress echocardiography and SPECT imaging techniques have a high degree of accuracy for the estimation of near-term prognosis (i.e., two- to five-year event-free survival) in women with chest pain symptoms. Furthermore, these data illustrate that there is an apparent disconnect between obstructive disease burden and the overall ensuing risk of provocative ischemia in women. This



paradigm of risk assessment as a guide for test decision making may provide the key to identifying at-risk women. We need to devise paradigms for testing in women that include the assessment of asymptomatic and symptomatic women (Fig. 6). In part II, we will further examine gender differences in the extent and severity of CAD and its resultant impact on major adverse cardiac events.

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