# STATE-OF-THE-ART DIAGNOSTIC TESTING IN WOMEN:

# A RESEARCH UPDATE

Leslee J. Shaw Ph.D, Delia Johnson, PhD, Jennifer H. Mieres MD, Rita Redberg, MD,

Noel Bairey Merz, MD

**Address for Correspondence:** Leslee J. Shaw, PhD, Suite 225, 5665 Peachtree Dunwoody Rd, Atlanta Cardiovascular Research Institute, Atlanta, GA, 30342, Telephone: 678-728-1959, Facsimile: 678-728-1951, E-mail: lshaw@acrionline.org

## Background

For industrialized countries, cardiovascular disease is the leading cause of death for women. Despite advances in the diagnosis and management, nearly 250,000 female lives are claimed each year (www.americanheart.org) with a lifetime risk of cardiovascular disease and its ensuing complications of 25% for a 40-year-old woman (Lloyd-Jones Lancet 1999). The marked reduction in case fatality rate for cardiovascular disease noted for men (35%-50% reduction) have not been realized for women (www.americanheart.org). Research continues to report underrecognition, underdiagnosis, and undertreatment of coronary disease in women causative to higher cardiovascular disease mortality (Shaw Ann Intern Med 1994, Tobin Ann Intern Med 1987, Douglas NEJM 1996, Steingart NEJM 1991, Kilaru JACC 2000, Mark NEJM 1994, Hochleitner J Wom Health Gend Based Med 2000, Wong Circulation 1997, Mosca 1999).

Nonspecific symptoms, such as generalized malaise, fatigure, and dyspnea, in women are imprecise and ineffective discriminators of disease (Bairey Merz JACC 1999). Older age of presentation and delays in atypical symptom recognition contribute to a greater morbidity and mortality for the female patient (Merz Am J Managed Care 2001). Screening of the asymptomatic woman is a topic of much interest due to the fact that the initial presentation of sudden cardiac death occurs more frequently in women as compared with men (63% of women versus 50 % of men).

We believe that a key to affecting significant changes in cardiovascular mortality for women is the appropriate use of a highly accurate diagnostic test that result in early and effective treatment and improved outcome for at-risk women. The current document aims to put forth a synopsis of available evidence on diagnostic testing in women.

## Gender Differences in Noninvasive Diagnostic Testing for CAD

A large body of evidence suggests that there is a diminished diagnostic accuracy for an array of cardiac noninvasive tests for women (Shaw book chapter in Carney, 1998, Mieres JNC 2003 (in press)). Reduced specificity has been noted for exercise electrocardiography and Tl-201 imaging (Hlatky Am J Med 1984, Kwok AJC 1999). A reduced sensitivity has been noted in female populations with single vessel coronary disease who undergo both exercise echocardiography and SPECT imaging. Technical considerations as well as inappropriate patient selection are contributing factors to differences in diagnostic accuracy. However, a major consideration in evaluating diagnostic accuracy is the problem of verification or work-up bias that precludes calculation of "true" sensitivity and specificity (Cecil J Clin Epidemiol 1996). As catheterization is largely performed in patients with provocative ischemia, diagnostic sensitivity will be inflated. Conversely, the calculation of specificity should include clinical follow-up for several years post-test in order to capture the true false negative rate. For this reason, a number of recent reports have examined the prognostic value of noninvasive tests. Although diagnostic accuracy has known limitations in women, recently, a number of reports have noted a gender-neutral enhanced ability to risk stratify patients (Marwick Am J Med 1999, Arruda-Olson JACC 2002, Alexander JACC 1998). As there is a growing body of evidence on the prognostic value of noninvasive testing techniques, this will be the primary focus of this report.

## Assessing Pretest Risk of Coronary Artery Disease in Women

The selection and referral of appropriate at-risk women remains one of the greatest challenges facing clinicians. The ACC/AHA guidelines for exercise testing suggest that symptomatic patients with an intermediate pretest likelihood of coronary disease are candidates for exercise testing (Gibbons Circulation 1997). Additionally, serial testing of patients with established coronary disease with a new onset of stable symptoms is also recommended (O'Rourke JACC 1999). Recent evidence from the WISE study reveals that the most common

symptoms associated with coronary disease are jaw pain, dyspnea, nausea, dizziness, weakness, fatigue, and may be triggers by strong emotions (Johnson et al. JACC). Evidence suggests that these women presenting with atypical symptoms have a lower likelihood of obstructive coronary disease (Douglas, in Braunwald, Diamond & Forrester NEJM 1987). As such, symptoms may be a less than efficient guide to testing. It seems practical that physicians should allow greater latitude in defining symptoms for the female patient and be more inquisitive during the physical examination for changes in perceived well being or a diminished ability to perform routine activities of daily living.

***Evaluation of Asymptomatic Women***

For the asymptomatic women, the current public health challenge is the identification of high-risk subsets that may be at risk for sudden cardiac death or acute myocardial infarction. Due to the greater frequency of presentation without prior symptoms, it may be possible that pre-screening using an array of tests that detect subclinical disease may result in life saving and cost effective care (Goldman JACC 2001). An upcoming Bethesda conference (#34) on the use of atherosclerotic imaging modalities for asymptomatic screening will provide a synopsis of evidence on electron beam tomography, magnetic resonance imaging, carotid intima-media thickness, and brachial reactivity testing, to name a few (Redberg et al. JACC 2003 (in press)).

The aggregation and detection of high risk may be accomplished by integrating a number of traditional risk factors, including age, systolic blood pressure, cholesterol, and gender, into an estimated probability of coronary heart disease (**www.nhlbi.nih.gov/guidelines/cholesterol/index.htm**, Greenland Circulation 2000). Currently, the AHA Prevention V conference has re-defined subgroupings of risk using 10-year estimates of cardiac death or nonfatal myocardial infarction from the Framingham study (Greenland Circ 2000). Low risk is defined as an annualized risk of death or infarction <0.6%.

Intermediate and high risk is defined as a risk of death or infarction 0.6%-2.0% and >2.0% per year. From the NIH-NHLBI website, clinicians may download a program for easy calculation of these risk subsets. However, generally speaking, an asymptomatic individual with >1 risk factor is at intermediate risk and, although this remains controversial, may be considered a candidate for screening. Diabetes is now considered a coronary heart disease risk equivalent and is considered high risk due to the lengthy delays in disease diagnosis and the frequency with which macrovascular disease is present.

***Evaluation of Symptomatic Women***

The compilation of risk, including age, traditional cardiac risk factors, and symptoms is aided by the availability of a number of multivariable risk predictions models (Califf JACC 1996). For symptomatic presentation, the secondary prevention Bethesda conference has published a number of gender-based algorithms (Califf). The use of risk prediction models will aid the clinician in defining intermediate as compared with low to high risk patients.

A woman with typical exertional angina has an intermediate-high pretest probability of coronary disease (i.e., probability $\geq$15%). For those with atypical or nonanginal symptoms, concomitant risk factors increase the likelihood of disease. Patients with diabetes are more often asymptomatic due to neuropathy and are at high risk according to the most recent National Cholesterol Education Panel - Adult Treatment Panel III consensus document with an expected annualized risk of cardiac death or MI of 2% (nhlbi website).

Current evidence does not support testing women with a low likelihood of coronary disease (i.e., probability <15%). False positives test results will occur more often when testing low risk patients driving costs of care (Diamond & Forrester NEJM 1987).

***Role of Hormones in Risk Assessment***

The incidence of coronary disease is decidedly diminished in the premenopausal women due to endogenous estrogen. As women enter the perimenopausal state, there is a gradual loss of estrogen; specifically estradiol (E2) produced by the ovaries. By the time a women reaches the age of 55 years, she is considered post-menopausal and her estrogen levels are nearly 1/10 that of her pre-menopausal state. The global risk of cardiovascular disease increases in the post-menopausal state and reaches equivalence to men by the time a woman is in her 7$^{th}$ decade of life (Lerner AHJ 1988).

For the premenopausal woman, endogenous estrogen has a digoxin-like effect that may precipitate ST segment depression, resulting in a false positive test. (Kwok AJC 1999, Morise Am J Med 1993). Physicians testing pre-menopausal women with chest pain or established coronary disease should note the stage of a woman's menstrual cycle. An unfolding body of evidence suggests that stress testing in a women's mid-cycle where estrogen levels are highest may be associated with less inducible ischemia and a lower frequency of chest pain symptoms (Kawano Ann Int Med 2001, Kawano JACC 2001, Schulman JACC 2002). As such, in order to optimize test accuracy, it would be preferable for a premenopausal woman to undergo stress testing in the late stages of the luteal phase (~12 days post-ovulation) or during menses when estradiol levels are lowest. It also seems reasonable for a clinician to query women as to fluctuations that may occur with symptoms that correlate with her menstrual cycle. The documentation of a woman with a history of polycystic ovary syndrome would be of additional importance as they are at increased risk of coronary disease with an increased link to obesity, central obesity, insulin resistance, and diabetes (Lord Hum Fertil (Camb) 2002).

A number of studies have noted that coronary disease may be masked for the women taking hormone replacement therapy due to it's vasodilatory action; resulting in a reduced frequency of chest pain and ischemia as well as improved exercise tolerance (Rosano JACC 2000, Morise Am

J Cardiol 1993, Morise Am J Med 1993, Morise J CV Risk 1997). Due to the adverse risk associated with hormone replacement therapy noted in the HERS and WHI studies, it is likely that fewer women will be presenting for evaluation with concomitant estrogen or combination progestin therapy use (Hulley JAMA 1998, WHI JAMA 2002). However, should they be referred for testing, clinicians should note that the increased risk of major adverse cardiovascular events has been reported for women without and with a prior history of coronary disease. This increased risk is correlated with an increase in HsCRP which has been reported for women taking both estrogen alone and combination estrogen plus progestin therapy (Cushman Circulation 1999). Increasing inflammation is corroborated by the fact that most of the excess risk, as recently reported in the Women's Health Initiative, was in nonfatal MI (Women's Health Initiative Investigators JAMA 2002).

## Asymptomatic Screening

A number of atherosclerotic imaging modalities have been advocated for the evaluation of cardiovascular screening in asymptomatic individuals including ankle brachial index, brachial reactivity, coronary calcium, and carotid intima-media thickness (IMT), to name a few. Although the added value of screening asymptomatics has been inconsistently reported, atherosclerotic imaging modalities, such as coronary calcium, have been shown to provide information independent of traditional risk factors (Mark JACC 2003 (in press), Hecht & Superko JACC 2001). For example, in a recent report in 304 asymptomatic women, percentile coronary calcium scores were not correlated with LDL-cholesterol ($r=0.06$, $p=0.49$).

Due to differences in the onset of disease, artery size, as well as the prevalence of traditional risk parameters, a number of reports have identified gender differences in the extent and prognostic value of atherosclerotic measurements. The results of brachial reactivity testing also require gender adjustment as women have a greater vasodilator response than men (Redberg et

al. JACC 2003, in press). (**Rita, this has to be premenopausal women? Or no?**) In general, the overall prevalence of imaging abnormalities is lower and lags approximately 10 years in female populations when compared with men (Newman Circulation 2001, Hoff Am J Cardiol 2001, Raggi et al. (submitted), Wong Am Heart J 1994). Despite this, recent evidence from the Atherosclerosis Risk in Communities Study reported that carotid IMT was a stronger predictor of outcome in women as compared with their male counterparts (Chambless Am J Epidemiol 2000). Similarly, due to small artery size, a given extent of coronary calcification was associated with a worsening survival when compared to a given calcium score (Raggi et al. JACC (submitted)) Thus, a given amount of coronary calcification represents a greater burden of atherosclerosis (Redberg JACC 2003, in press).

Inflammatory markers have been implicated in worsening prognosis (Ridker *Circulation* 1998, Ridker *Circulation* 1998, Ridker *N Engl J Med* 2000). High sensitivity C-reactive protein is an acute phase reactant and has been reported to correlate with one's risk of myocardial infarction and stroke. There is a directly proportional relationship between HsCRP and cholesterol levels. With regards to atherosclerotic imaging, however, there is a reported lack of association between HsCRP and coronary calcium in post-menopausal women (Redberg JACC 2000). Although there appears to be a lack of consensus in the published literature, it is likely that coronary calcium is not a good predictor of acute ischemic events due to the fact that calcification does not correlate with functional coronary stenosis, flow limiting disease, or to plaque vulnerability (Falk & Fuster, in Hurst's The Heart, Ch. 35, 2001, O'Rourke Circulation 2000, Newman Circulation 2001, Shemesh, Am J Cardiol 1988) but rather may provide a measure of the global burden of atherosclerosis (Raggi et al. Radiology 2003, in press).

Despite the differing reports on prognosis, controversy remains as to the specifics of patient management strategies for screening. One of the challenges with screening, for example with

coronary calcium, is that calcification increases with age. Coronary calcium is present in approximately ½ of elderly women (Newnam Circulation 2001) and has been shown to be less predictive of cardiac death or nonfatal myocardial infarction in older populations (Detrano Circulation 1999). The predictive value of coronary calcium has been controversial and limited by numerous methodologic limitations (O'Rourke JACC 2001). Recent data suggest that the optimal value of calcium screening may be individuals in age ranges of ~50<70 years.

There are clearly still challenges in risk thresholds where published reports have noted anything from detectable calcium to calcium scores greater than 680 (O'Rourke et al., JACC 2001). Despite this, it is clear that 5-year survival exceed 99% in women and men with a low risk calcium score <10 (Callister Radiology 2003 (in press)). Survival decrementally worsens for women with increasingly higher calcium scores (**Figure x**). Due to small artery size, any given amount of calcium is associated with worsening survival in women as compared with men; as such lower thresholds of risk may be required for women.

**Recommendations For Cardiovascular Risk Screening In Women**

Based upon existing evidence, we have formulated a preliminary management strategy for the evaluation of at-risk women (**Figure x**). This includes screening intermediate risk post-menopausal women or premenopausal women with diabetes. Arguments may also be put forth that women with metabolic syndrome or polycystic ovary syndromes should have a multifactorial risk assessments performed (at a minimum) and considered as candidates for screening. Despite the lower prevalence of disease in younger women, the European Society of Cardiology is soon to recommend predicting risk at age 60 years for a given risk assessment. That is, for 40-year-old women with multiple risk factors, her estimation of risk should be calculated at age 60 years of age (**www.escardio.org/**).

A woman's whose calcium score exceed 400 has an annualized risk of death of 2% and should be considered at high risk. A follow-up ischemia test should be considered (He et al. Circulation 2001). Re-testing may be considered for women with a score ranging from 100 to <400 where rates of progression >15% are associated with an increased risk of nonfatal myocardial infarction (Raggi et al. Achenbach Circ 2002). Aggressive risk factor management should be undertaken in women with evidence of atherosclerosis. In two prior reports, the use of statin therapy has been associated with a reduction in the calcium volume score (Achenbach Circulation 2002, Callister NEJM 1998).

## Diagnostic Testing for the Evaluation of Symptomatic Women

### Exercise Electrocardiography

The exercise electrocardiogram has been reported to have a lower diagnostic accuracy in women (Hlatky Am J Med 1984, Heller book chapter). Several reviews on the diagnostic sensitivity and specificity have revealed lower accuracy of ≥1 mm of ST segment depression for women compared to men with an average sensitivity and specificity for the exercise ECG in women is 61% and 69% respectively (Heller book chapter). The lower diagnostic accuracy of exercise ECG may in part be due the fact that women are older and have higher rates of functional impairment leading to a diminished exercise capacity, an inability to attain maximal stress, and provoke ischemia. Additional critical factors that have been reported to affect test accuracy in women include resting ST-T wave changes in hypertensive women, lower ECG voltage, and hormonal factors (endogenous estrogen in premenopausal women and the use of hormone replacement therapy).

A major key to enhanced accuracy of exercise ECG is to include other factors than ST segment depression when interpreting the test. The integration of parameters such as the simple

Δ ST/heart rate index and the Duke treadmill score dramatically improve the diagnostic and prognostic accuracy of testing in women (Okin Circ 1995, Alexander JACC 1998).

Thus, the accuracy of the exercise ECG test in women, is highly variable and influenced by multiple factors including, exercise capacity, and hormonal status. Despite this, the current ACC/AHA guidelines for exercise testing recommend this test as a first line test for those with a normal resting 12-lead ECG and for those capable of performing maximal stress. For those patients with resting ST-T wave abnormalities that preclude interpretation of changes at peak exercise, a cardiac imaging modality is recommended.

Maximal oxygen consumption may be predicted using the Duke Activity Status Index (DASI) (von Dras Soc Sci Med 1997). Women incapable of performing a minimum of 5 METs of exercise should be considered candidates for pharmacologic stress testing. Five METs of exercise is consistent with a submaximal level of exercise (Brown Circulation 1999). Although maximal stress may be defined by achieving ≥85% of predicted maximal heart rate, care should be taken when interpreting a women's heart rate response. For deconditioned patients, an exaggerated response to physical work may result in marked increases in heart rate. Thus, the test should be continued until maximal symptom-limited exercise capacity. As stated previously, candidates for pharmacologic stress testing may include those who prematurely fatigue.

**Gated Myocardial Perfusion SPECT**

Gated myocardial perfusion SPECT is a nuclear-based technique that provides a combination of risk parameters that aid in the detection of disease and risk in women including perfusion deficits, global and regional ventricular function, and left ventricular volumes (Berman in Hurst's The Heart). Of the imaging modalities, SPECT imaging is the most commonly performed stress test in the US, being performed in approximately 7 million patients every year. Nuclear imaging has been reported to have technical limitations in women (Mieres JNC (in

press)). The limitations to testing in women include the false positive results due to breast attenuation, small left ventricular chamber size, and a higher prevalence of single vessel disease. (Mieres JNC (in press)).

Factors associated with suboptimal accuracy have been related to several factors such as small heart size, soft tissue attenuation, and the prevalence of single vessel coronary artery disease. For example, the accuracy of thallium-201 SPECT imaging was reduced in patients with small hearts, more commonly seen in women than men. (Hansen JACC 1996). When using Tl-201 as the radioisotope in women, false positive test results may be the result of soft-tissue (breast) attenuation in the anterior and antero-lateral segments [Mieres JNC (in press), Goodgold Radiol 1987]

Despite these limitations, significant improvements in stress myocardial perfusion imaging have resulted in substantial improvements in the accuracy of testing (Taillefer JACC 1997). The lower energy isotope thallium-201 is less accurate in women when compared to men (Kwok AJC 1999). The use of technetium-based imaging agents improves accuracy, particularly using gated SPECT imaging (Mieres JNC (in press)). In a small-randomized trial comparing the diagnostic accuracy of Tl-201 as compared with gated Tc-99m sestamibi SPECT, test specificity was 67% versus 92%, respectively [Taillefer JACC 1997]. The higher count profile that is exhibited with Tc-99m sestamibi results in an enhanced image quality and improved accuracy and in women [Mieres JNC (in press)]. Amanullah and colleagues reported on 130 women undergoing adenosine Tc-99m sestamibi SPECT revealing that a moderately to severely abnormal perfusion scan (i.e., summed stress score >8) was associated with a sensitivity and specificity of 91% and 70% for the detection of multivessel coronary disease [Amanullah AJC 1997].

Reports from several large female samples have reported that for both Tc-99m sestamibi (rest and exercise) and for dual isotope myocardial perfusion SPECT, there is an added incremental

prognostic value of myocardial perfusion data as compared to clinical and exercise variables in women [Travin AHJ 1997, Hachamovitch JACC 1996]. From a recent multicenter registry of 3,402 women with stable chest pain symptoms, risk stratification was similar by gender (84% underwent Tc-99m sestamibi, **Figure x – we will have to get permission to use this slide and that of the Arruda-Olson paper. Maybe you can get Roberta to check with the journals on how to do this.**) [Marwick Am J Med 1999]. By the number of vascular territories with ischemia, 3-year survival ranged from 98.5% to 85% for none to 3-vascular territories [Marwick Am J Med 1999].

**Pharmacologic SPECT Myocardial Perfusion Imaging in Women:**

Approximately 30-40% of patients who are referred for myocardial perfusion studies for the evaluation of known or suspected coronary artery disease are candidates for pharmacologic stress imaging. Since, women are generally older when they present with coronary artery disease and have a higher incidence of decreased exercise capacity, many with known or suspected coronary artery disease are not able to complete a symptom - limited exercise protocol and are therefore candidates for pharmacologic stress testing. Many more women may be candidates for pharmacologic stress testing if more strict guidelines were established for those incapable of maximal exercise.

**Exercise Echocardiography**

Stress echocardiography is another commonplace noninvasive test. A number of reports have examined both the diagnostic and prognostic accuracy of stress echocardiography in women (Williams Am J Cardiol. 1994, Marwick J Am Coll Cardiol 1995, Kwok AJC 1999). Overall advantages to the use of exercise echocardiography are the lack of ionizing radiation, the portability and cost of the equipment allows for greater use and affordability in the outpatient setting, and an increased ability to image cardiac structures and function. The evaluation of valve

disease is particularly helpful for women with chest pain whose differential diagnosis includes mitral valve prolapse. **Table x** reports data from a meta-analysis comparing the diagnostic accuracy of stress electrocardiography, echocardiography, and Tl-201 imaging (Kwok AJC 1999). Given the fact that inducible wall motion abnormalities appear later on in the ischemic cascade, there is greater test specificity when compared to intermediate stenosis that may cause flow limitations and perfusion deficits with perfusion-based techniques. As a result, however, there is a lower accuracy for detection of 50-70% lesions and those with single vessel coronary disease (Williams Am J Cardiol. 1994).

Although there is a long-standing tradition in calculating diagnostic accuracy (i.e., sensitivity and specificity), these values are confounded by verification bias, as previously noted. Most physicians want to be assured that a negative test is associated with a low risk of events and, in the case of positive study, who should be sent to catheterization? In the case of stress echocardiography, a recent report from the Mayo Clinic in 2,476 women revealed that event-free survival was 97% for women with no inducible wall motion abnormalities as compared with 88% for those with a wall motion score index $\geq$1.25 (defined as the sum of segmental scores / number of segments visualized with new or worsening abnormalities) (**Figure x,** Arruda-Olson JACC 2002).

**Cardiovascular Magnetic Resonance Imaging**

Perhaps no other imaging modality is undergoing such rapid development as that of cardiovascular magnetic resonance imaging (CMR). CMR has many features that make it suitable for evaluating patients with a wide range of cardiovascular disease including; fast examination times, excellent tissue characterization (high soft-tissue contrast), three-dimensional volumetric acquisition/display, and the ability to quantify blood flow. Furthermore, CMR is attractive due to the fact that is does not require the use of ionizing radiation nor are contrast

agents nephrotoxic. CMR is capable of yielding superior temporal and spatial resolution and may image the great vessels, congenital abnormalities, valvular heart disease, pericardial disease, as well as left ventricular mass and function, perfusion, wall thickness, and myocardial perfusion and blood flow (including contrast enhanced differentiation of subendocardial and epicardial flow).

MR perfusion for the diagnosis has not been extensively studied in women but the overall sensitivity and specificity values are in the 70% to 80% range (Panting NEJM 2002, Keijer J Magn Reson Imaging 2000). Interestingly, CMR is capable of separating subendocardial from epicardial perfusion deficits (Panting NEJM 2002). A recent report from the Royal Brompton Hospital in London reveals that women with syndrome x (chest pain, evidence of provocative ischemia, and nonobstructive coronary disease) have subendocardial ischemia noted with MR perfusion imaging (Panting NEJM 2002). Additionally, with the 3-dimensionality of CMR, wall motion abnormalities may be superior to other modalities and detect coronary disease in 74% patients with less extensive (i.e., 1 vessel) disease in 74% of cases (Nagel Circulation 1999).

One of the benefits of MR perfusion estimates is that absolute reductions in perfusion may be determined. This is compared to the fact that SPECT determines regional deficits in perfusion by normalizing the myocardium, as such, nuclear imaging assesses relative perfusion. Recently, data from the WISE study has assessed the importance of coronary flow reserve in diagnosing perfusion deficits (Doyle J Mag Reson Imaging (in press)). Their results indicate that the interpretation of perfusion abnormalities is reliant upon an adequate hyperemic response to stress. It is likely that impaired flow reserve detected by CMR is precipitating regional deficits in perfusion; in the absence of a flow-limiting stenosis. As a consequence, CMR is capable of detecting deficits in perfusion in the subendocardium that may provide a better estimator of

provocative ischemia; even in women with nonobstructive coronary disease (Panting NEJM 2002).

MR angiography (MRA) has been shown in preliminary reports to have a similar diagnostic accuracy when compared to invasive cardiac catheterization (Kim NEJM 2001). Imaging is currently most reliable for proximal stenosis (in particular, left anterior descending) and, as such, this modality still requires substantial validation. Despite this, women may benefit from initial screening with MRA. Approximately half of women undergoing diagnostic coronary angiography and due to its invasive nature carries a slight but notable risk of complications (Shaw ACC 2002a, Bairey Merz JACC 1999).

In women with normal coronaries, recent evidence has identified with MR a unique imaging method using P31 MR spectroscopy to identify high-energy phosphates (Buchtal S et al., NEJM 2000). A reduction in phosphocreatine / adenosine triphosphate (PCr/ATP) provides a measure of metabolic dysfunction representing myocardial ischemia. **Figure x** reveals that a reduced PCr/ATP ratio $\geq$20% is noted in 1/3 of women with normal coronaries (Buchtal NEJM – going to need permission for this). A recent update from this investigative group reveals that women with P31 are at increased risk of major adverse cardiac events; in particular a substantially higher rate of acute coronary syndromes (at 2 years of follow-up) (Buchtal ACC 2002 abstract). It appears that although survival may be excellent in women with nonobstructive coronary disease that a subset of patients may have microvascular disease precipitating metabolic dysfunction and leading to continuing symptoms and unstable angina. However, in this small group of women, a reduced PCr/ATP ratio does not appear to be a marker for downstream obstructive disease. Longer-term follow-up and validation of these results is required to clearly establish the relationship between major adverse cardiac events and P31 spectroscopic results.

**New Horizons for Cardiovascular Imaging for Women**

Although we have discussed a number of imaging modalities that are under development, it is noteworthy to identify a few additional techniques that may provide a potential value in the assessment of at-risk women. Computed tomographic methods assessing angiographic (CTA) extent and severity of disease is currently undergoing rapid development and testing. It appears that CTA may also provide the promise in a noninvasive assessment of coronary disease in women; similar to MRA.

Historic assessments of prognosis with cardiac imaging modalities have been limited to the estimation of ischemic events including cardiac death or nonfatal myocardial infarction. Increasing evidence, in particular with CT and MR methods, visualize the importance of aortic, carotid, and peripheral atherosclerosis. In the future, we will see more reports on the detection of coronary and non-coronary atherosclerosis and its association of global cardiovascular disease burden.

Increasing evidence suggests that risk of cardiovascular disease is multifactorial with new standards of assessment including integrated risk factor scoring (nih webstie). Historically, imaging markers have not been well integrated into laboratory and other historical parameters. Given the increased complexity in the diagnosis and assessment of risk in women, new research must aim at integrating historical, hormonal, traditional and emerging risk factors along with cardiovascular imaging data in the assessment of major adverse cardiac outcomes in sufficiently large female samples. It is likely that algorithms for at-risk women will be more complex than their male counterparts due to the differences in symptom presentation, comorbidity, frequency of microvascular disease, functional impairment, and hormonal imbalances that influence cardiovascular risk factors and outcome. **Figure x** provides a detail of our current understanding of the complexity for assessing atherosclerotic imaging modalities in women. In this proposed model, the loss of estrogen (e.g., post-menopause) has been shown to result in decreased

coronary flow reserve and reduced myocardial perfusion. The combination of estrogen loss with the effects of traditional factors results in microvascular disease that, in the setting of stress, may produce metabolic dysfunction. Concurrent functional limitations, as a result of comorbidity, may limit the provocation of ischemia due to impaired physical work capacity. It is likely that vasodilator stress agents (e.g., IV Adenosine) may be most effective due to the induction of coronary steal away from areas of impaired flow.

The potential role each of these interactive forces plays on clinical outcome is also summarized in this figure. The smaller size of coronary arteries contributes to a greater atherosclerotic burden in the setting of a given amount of coronary calcium. As such, women with risk factors and coronary calcium are at increased risk of clinical outcomes that include all types of cardiovascular mortality and other forms of vascular diseases and their sequelae. Additionally, even in the setting of nonobstructive coronary disease, women with evidence of provocative ischemia (most likely subendocardial) are potentially at increased risk for major adverse cardiac events that include unstable angina, myocardial infarction, and sudden cardiac death. Repetitive bouts of ischemia, left untreated, and recurrent myocardial infarction leading to left ventricular dysfunction would predispose a women to heart failure and cardiac death.

**Recommendations For Diagnostic Testing In Women**

For the symptomatic women, clinicians should carefully consider two critical factors when deciding upon test choice: functional capacity and hormonal factors. Testing should optimize the lowest estrogen level so that provocative ischemia may be elicited. Additionally, women who are incapable of exercising to 5 metabolic equivalents (METs) should be considered candidates for pharmacologic stress testing. Use of the Duke Activitiy Status Index, that estimates functional capacity in maximal oxygen consumption (divide by 3.5 to calculate METs) can be applied in the pre-testing setting to provide insight into activities of daily living (von Dass Soc Sci Med

1997). As such, use of a coronary vasodilator that creates coronary steal may prove to be the test of choice for most women. This being said, functional capacity remains one of our greatest prognosticators. As such, exercise testing or the use of predicted exercise capacity questionnaires should be employed to acquire some measure of physical work capacity.

Routine cardiac imaging, commonly using stress echocardiography and SPECT, should include measures of left ventricular function and extent and severity of provocative ischemia. For echocardiography, the extent and severity of inducible wall motion abnormalities is determined from changes at exercise from resting images. For SPECT, the extent and severity of regional perfusion deficits is usually calculated using a 17- or 20-segment myocardial model. The intensity of post-test management is then graded to increasing risk. Those at highest risk should be considered candidates for coronary angiography. Intermediate stress test results should prompt both risk factor modification and anti-ischemic therapy for the control of symptoms. Additionally, repeat testing on medications may allow the clinician to measure the effectiveness of therapy. Low risk patients require no additional follow-up testing (unless clinical status worsens) with management including treating risk factors to current goals as well as control of symptoms. However, care should be taken in evaluating a lack of provocative ischemia, in particular for women with submaximal levels of exercise. It is also likely that for women with nonobstructive coronary disease that subendocardial ischemia during exercise may not elicit ST segment changes or wall motion abnormalities but may only be detected by CMR.

## Conclusions

Our current paradigm of diagnostic testing requires substantial variation when applied to the female patient. We have yet to fully appreciate the multifactorial role of reproductive hormones on the vascular system. The interaction of small artery size with the effects of traditional risk factors (e.g., hypercholesterolemia) on artery responsiveness leads to microvascular disease in a

sizeable proportion of women. Primary phase reactant inflammation and atherosclerosis may ensue. Thus, even in the absence of obstructive coronary disease, the risk in the post-menopausal women with risk factors may be underappreciated. However, current guidelines recommend asymptomatic screening in the intermediate likelihood women (based upon the NCEP risk calculation). The post-test management of women following asymptomatic screening has yet to be fully elucidated. But, ischemia testing can be attempted in patients with high risk screening results.

For women whose symptomatology is more nonspecific, there may be much more of a "blurring" between the classification of symptomatic and asymptomatic status. This may be particularly true for the women with functional impairment. Extreme care should be employed in the selection of stress testing and in interpretation of test results for the work-up of symptomatic women. Consideration of hormonal status and functional impairment are critical factors to minimizing both false negative and positive test results. The intensity of post-test management should be directly proportional to the extent and severity of inducible ischemia and consideration of left ventricular function.

An abundance of evidence suggests that women are less often counseled for risk factor control, less often receive effective medical and surgical therapies, and evidence of ischemia is more often left untreated (Shaw Ann Intern Med 1994, Tobin Ann Intern Med 1987, Douglas NEJM 1996, Steingart NEJM 1991, Kilaru JACC 2000, Mark NEJM 1994, Hochleitner J Wom Health Gend Based Med 2000, Wong Circulation 1997, Mosca 1999). Certainly, the complexity of management that is required for the female patient has yet to be fully assimilated into clinical guidelines and into every day clinical practice. However, the lack of mortality reduction that has been noted for women in the US belies consideration of a few critical factors. Traditional risk factors should be treated to goal. Post-menopausal women should undergo an NCEP risk

calculation and consideration of screening. Ischemia, even in the setting of nonobstructive coronary disease, requires risk-reducing therapy. This being said, our understanding of both risk assessment and therapeutic intervention for women is an understudied area. We require substantially more evidence in order to provide higher quality data to support clinical decision making for at-risk women.

**References**

***Background – Epidemiology of Cardiovascular Disease in Women***


1. American Heart Association; Heart and Stroke facts: 2002 statistical supplement, Dallas, 2002, American Heart Association.
2. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. Lancet 1999;353:89-92.
3. www.americanheart.org/
4. Shaw, LJ Miller DD, et al. Gender Differences in the Noninvasive Evaluation and Management of Patients with Suspected Coronary Artery Disease. Ann Int Med 1994; 120: 559-556.
5. Tobin JN, Wassertheil-Smoller S, Wexler JP, et al: Sex bias in considering coronary bypass surgery. Ann Int Med 1987; 107:19-25.
6. Douglas PS, Ginsburg GS: The evaluation of chest pain in women. N Eng J Med 1996;334:1311-1315.
7. Steingart RM, Packer M, Hamm P, et al: Sex differences in the management of coronary artery disease. Survival and Ventricular Enlargement Investigators. N Eng J Med 1991;325:226-230.
8. Kilaru PK, Kelly RF, Calvin JE, Parillo JE: Utilization of Coronary angiography and revascularization after acute myocardial infarction in men and women risk stratified by the American College of Cardiology/ American Heart association guidelines. J Am Coll Cardiol 2000;35:974-979.
9. Mark DB, Shaw LK, Delong ER et al: Absence of sex bias in the referral of patients for cardiac catheterization. N Eng J Med 1994;330:1101-1106.

10. Hochleitner M: Coronary heart disease: Sexual bias in referral for coronary angiogram. How does it work in a state- run health system ? J Wom Health Gend Based Med 2000;9:29-34.
11. Wong CC, Froelicher ES, Bacchetti P et al : Influence of gender on cardiovascular mortality in acute myocardial infarction patients with high indication for coronary angiography. Circulation 1997;96:II-51-57.
12. Mosca L., Circulation 1999
13. Merz NB, Johnson BD, Kelsey PSF, Reis SE, Lewis JF, Reichek N, Rogers WJ, Pepine CF, Shaw LJ. Diagnostic, prognostic, and cost assessment of coronary artery disease in women. Am J Managed Care 2001;7(10):959-965.
14. Merz CN, Kelsey SF, Pepine CJ, Reichek N, Reis SE, Rogers WJ, Sharaf BL, Sopko G. The Women's ischemia syndrome evaluation (WISE) study: protocol design, methodology and feasibility report. JACC 1999;33:1453-1461.

***Gender Differences in Noninvasive Diagnostic Testing for CAD***

15. Shaw LJ, Peterson ED, Johnson LL. Non-invasive stress testing, in Coronary Artery Disease in Women: What all physicians need to know, edited by P Charney, American College of Physician's Women's Health Series, Philadelphia, 1999:327-350.
16. Mieres JH, Shaw LJ, Hendel RC, Miller DD, Bonow R, Berman DS, Heller GV. American Society of Nuclear Cardiology: task force on women and coronary artery disease. J Nucl Cardiol (in press).
17. Hlatky MA, Pryor DB, Harrel FE Jr, et al: Factors affecting sensitivity and specificity of exercise electrocardiography: Multivariable analysis. Am J Med 1984; 77:64-71
18. Kwok YS, Kim C, Grady D et al: meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999;83:660-666.

19. Taillefer R, DePuey EG, Udelson JE, Beller GA, Latour Y, Reeves F; Comparative Diagnostic Accuracy of Tl-201 and Tc-99m Sestamibi SPECT Imaging (Perfusion and ECG Gated SPECT) in Detecting Coronary Artery Disease in Women. J Am Coll Cardiol 1997,29:69-77.
20. Cecil MP, Kosinski AS, Jones MT, Taylor A, Alazraki NP, Pettigrew RI, Weintraub WS. The importance of work-up (verification) bias correction in assessing the accuracy of SPECT thallium-201 testing for the diagnosis of coronary artery disease. J Clin Epidemiol 1996;49(7):735-742.
21. Marwick T, Shaw L, Lauer M, Kesler K, Hachamovitch R, Heller G, et al. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. Am J Med 1999;106:172-178.
22. Arruda-Olson JACC 2002;39:625.
23. Alexander KP, Shaw LJ, Delong ER, et al: Value of exercise treadmill testing in women. J Am Coll Cardiol 1998; 32: 1657-1664.

***Assessing Pretest Risk of Coronary Artery Disease in Women***

24. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, et al. ACC/AHA guidelines for exercise testing: Executive Summary. Circulation 1997;96:345-354.
25. O'Rourke JACC 2000
26. Johnson BD. Et al. JACC
27. Douglas, in Braunwald,
28. Diamond & Forrester NEJM 1987
29. Goldman JACC 2001

***Evaluation of Asymptomatic Women***

30. Redberg et al. JACC 2003 (in press)

31. **www.nhlbi.nih.gov/guidelines/cholesterol/index.htm**

32. Greenland P, Abrams J, Aurigemma GP, et al. Prevention Conference V: Beyond secondary prevention: Identifying the high-risk patient for primary prevention: Noninvasive tests of atherosclerotic burden. Circulation 2000;101:E12-E15.

***Evaluation of Symptomatic Women***

33. Califf JACC 1996

***Role of Hormones in Risk Assessment***

34. Lerner AHJ 1988

35. Morise AP, Dalal JN, Duval RD: value of a simple measure of estrogen status for improving the diagnosis of coronary artery disease in women. Am J Med 1993;94:491-496.

36. Kawano H, Motoyama T, Ohgushi K et al: Menstrual Cyclic Variation of Myocardial Ishemia in Premenopausla Women with Variant Angina. Ann Int Med 2001;135:977-981.

37. Kawano JACC 2001;37:735

38. Schulman JACC 2002;39:238

39. Lord J, Wilkin T. Polycystic ovary syndrome and fat distribution: the central issue? Hum Fertil (Camb) 2002;5:67-71.

40. Rosano JACC 2000;36:2154,

41. Morise Am J Cardiol 1993;72:1197,

42. Morise J Noninv Cardiol 1997;1:27,

43. Morise J CV Risk 1997;3:507

44. Hulley JAMA 1998

45. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA 2002;288:321-333.

***Asymptomatic Screening***

46. Cushman Circulation 1999;100:717-722.

47. Mark et al. JACC 2003 (in press)

48. Hecht & Superko JACC 2001;37:1506

49. Redberg JACC (in press)

50. Newman Circulation 2001;104:2679

51. Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol 2001;87:1335-9.

52. Raggi et al. (submitted)

53. Wong ND, Kouwabunpat D, Vo AN et al. Coronary calcium and atherosclerosis by ultrafast computed tomography in asymptomatic men and women: relation to age and risk factors. Am Heart J 1994;127:422-30.).

54. Chambless Am J Epidemiol 2000;151:478-487.

55. Ridker PM et al. *Circulation* 1998;98:731-733.

56. Ridker PM et al. *Circulation* 1998;97:2007-2011.

57. Ridker PM et al. *N Engl J Med* 2000;342:836-843.

58. Redberg JACC 2000;36:39

59. Falk & Fuster, in Hurst's The Heart, Ch. 35, 2001

60. O'Rourke Circulation 2000;102(1):126-140

61. Shemesh, Am J Cardiol 1988;81:271

62. Raggi et al. Radiology 2003, in press

63. Detrano Circulation 1999

64. Callister et al. Radiology 2003 (in press)

65. www.escardio.org/-use **the guidelines section**

66. He et al. Circulation 2001

67. Achenbach S, Ropers D, Pohle K, Leber A, Thilo C, Knez A, Menendez T, Maeffert R, Kuses M, Regenfus M, Bickel A, Haberl R, Steinbeck G, Moshage W, Daniel WG. Influence of lipid-lowering therapy on the progression of coronary artery calcification: A prospective evaluation. Circulation 2002;106:1077-1082.

68. Callister et al., NEJM 1998

***Exercise Electrocardiography***

69. Heller GV, Fossati AT. Chapter 18: Detection of coronary artery disease in women. in Nuclear Cardiology: State of the Art and Future Directions. (2nd Edition), eds. Zaret B, Beller G. Mosby,

70. Okin PM, Kligfield PM: Gender-specific criteria and performance of the exercise electrocardiogram. Circulation 1995;92:1209-1216

71. von Dras DD, Siegler IC, Williams RB, Clapp-Channing N, Haney TL, Mark DB. Surrogate assessment of coronary artery disease patients' functional capacity. Soc Sci Med 1997;44:1491-1502.

72. Brown K, et al. Circulation 1999-my cv

***Gated Myocardial Perfusion SPECT***

73. Hansen CL, Crabbe D, Rubin S: Lower diagnostic accuracy of thallium-201 SPECT myocardial perfusion imaging in women : an effect of smaller chamber. J Am Coll Cardiol

74. Goodgold HM, et al: Improved Interpretation of exercise Tl-201 myocardial perfusion scintigraphy in women: characterization of breast attenuation artifacts. Radiology 1987;165:361-366.

75. Amanullah A, Berman D, Erel J, Kiat H, Merz C, Cohen I, et al. Incremental diagnostic value of adenosine myocardial perfusion single-photon emission computed tomography in women with suspected coronary artery disease. Am J Cardiol 1998;82:725-730.

76. Amanullah AM, Berman DS, Hachamovitch R, Kiat H, Kang X and Friedman JD. Identification of Severe or Extensive Coronary artery Disease in Women by Adenosine Technetium- 99m Seatamibi SPECT. Am J Cardiol 1997;80:132-137.

77. Travin MI, Katz MS, Moulton AW et al: Accuracy of dipyridamole SPECT imaging in identifying individual coronary stenosis and mutlivessel disease in women versus men. J Nuc Cardiol 2000;7:213-220.

78. Travin M, Duca M, Kline G, Herman S, Demus D, Heller G. Relation of gender to physician use of test results and prognostic value of technetium 99m myocardial single-photon emission computed tomography scintigraphy. Am Heart J 1997;134:78-82.

79. Hachamovitch R, Berman D, Kiat H, Merz C, Cohen I, al e. Effective risk stratification using exercise myocardial perfusion single-photon emission computed tomography SPECT in women: gender-related differences in prognostic nuclear testing. J Am Coll Cardiol 1996;28:24-44.

***Exercise Echocardiography***

80. Williams MJ, et al. Am J Cardiol. 1994;74:435

81. Marwick T, et al. J Am Coll Cardiol. 1995;26:335

***Cardiovascular Magnetic Resonance Imaging***

82. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, Pennell DJ. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. NEJM 2002;346:1948-1953.

83. Keijer JT, van Rossum AC, van Eenige MJ, Bax JJ, Visser FC, Teule JJ, Visser CA. Magnetic resonance imaging of regional perfusion in patients with single-vessel coronary artery disease. J Magn Reson Imaging 2000;11(6):607-615.).
84. Nagel Circulation 1999;99:763-770.
85. Doyle J Mag Reson Imaging (in press)
86. Kim WY, Danias PG, Stuber M, Flamm SD, Plein S, Nagel E, Langerak SE, Weber OM, Pedersen EM, Schmidt M, Botnar RM, Manning WJ. Coronary magnetic resonance angiography for the detection of coronary stenoses. NEJM 2001;345:863-869.
87. Shaw ACC 2002-my cv
88. Buchtal NEJM