REVIEW

Recent development of ischaemic heart disease in sex difference

Wang Shu, Wang Lei, Song Peng

Postgrad Med J 2007;**83**:240–243. doi: 10.1136/pgmj.2006.053140

Despite a dramatic decline in mortality over the past years, coronary heart disease is the leading cause of death and disability in the world. At the same time, with the great improvement of medical science, there is a growing population of postmyocardial infarction, postrevascularisation and heart failure survivors. Furthermore, there are rising rates of cigarette smoking, obesity, hypertension and the metabolic syndrome in the world. All the above contribute to the rising incidence rates of ischaemic heart disease (IHD) among women and men. This review highlights sex-specific issues in IHD presentation, evaluation and outcomes, with several new results published from the Women's Ischemia Syndrome Evaluation study. New evidence on traditional and novel risk markers as well as sex-specific differences in symptoms and diagnostic approaches have also been discussed.

a synopsis of the available evidence on sex-based differences in IHD and outlines important future steps towards enhancing detection aimed at improving outcomes for women.

SEX-SPECIFIC DIFFERENCES IN IHD PREVALENCE AND TRADITIONAL 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), approaching equal prevalence rates for men and women only in their seventh decade of life.⁵ 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 those of 65-year-old women. In a cross-sectional survey of 925 patients (489 men), women with angina were found to be older than men (71 vs 65 years).⁶ The delayed onset of the disease results in a relatively lower likelihood of obstructive CAD for most of the women we evaluate.

There is also substantial sex-related variability in the prevalence and outcome associated with traditional cardiac risk factors. Although overall rates of hypertension and smoking are higher in men, elderly women with hypertension and young female smokers are prominent at-risk subsets.⁷ In a recent study by Frazier *et al*,⁸ hypertension was found to be more prevalent in women than in men with ACS, overall (63% vs 50%) and within every decile of age. In a recent report by Gretchen *et al*,⁹ among women undergoing angiography for suspected ischemia, elevated systolic blood pressure and pulse pressure were found to be potent risk factors in premenopausal women. Premenopausal women with angiographic CAD exhibited a higher systolic blood pressure (147 (35) vs 141 (21) mm Hg) and pulse pressure (66 (27) vs 64 (19) mm Hg) than their postmenopausal counterparts, a difference that became significant after age adjustment ($p = 0.03$ and 0.02 , respectively). Also for women smokers, coronary heart disease mortality risk from cigarettes is equivalent to the risk associated with weighing about 42 kg more than their non-smoking counterparts.¹⁰

Population studies have noted that total cholesterol measurements are higher in men until the fifth decade of life but, over this age, women have

Historically, research on ischaemic heart disease (IHD) has consistently reported that coronary heart disease (CAD) is manifested earlier in the lives of men, so that disproportionately much of the prior research focuses exclusively on men. The more frequent evaluation of men has promoted the perception that IHD is a "man's disease", and the ensuing knowledge gap on the part of physicians and patients alike has created inequities in healthcare access and processes of care that has resulted in suboptimal care for at-risk women.¹ However IHD 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 In America, recent estimates from the Centers for Disease Control (CDC) show that 38% of all deaths in women are related to coronary heart disease compared with 22% resulting from cancer.³ Notably, women with IHD have more adverse outcomes than men.⁴ So, we should be refuting the notion that this is a "man's disease" and suggesting that it might be relabelled a "woman's affliction".

The evaluation of IHD in women presents a unique and sometimes difficult challenge for clinicians, owing to its greater symptom burden, higher rate of functional disability and a lower prevalence of obstructive CAD by coronary angiography in women than in men. Our current understanding and treatment of IHD pathophysiology in women is based on "critical stenosis" diagnostic approaches. The current review provides

See end of article for authors' affiliations

Correspondence to: W Shu, The Laboratory of Cardiovascular Medical Department, The General Hospital of Chinese People of Liberation Army, Fu Xin Road Number 28, Beijing 100853, China; wang-shu2002@163.com

Received 4 September 2006
Accepted 16 October 2006

Abbreviations: CAD, coronary heart disease; CDC, Centers for Disease Control; hsCRP, high-sensitivity C reactive protein; IHD, ischaemic heart disease; MDCT, multi-detector row computed tomography; SPECT, single-photon emission computed tomography; WISE, Women's Ischemia Syndrome Evaluation

greater values.⁷ Furthermore, sex differences in high-density lipoprotein values diminish with advancing age. Women typically experience a relatively mild decline in high-density lipoprotein cholesterol at the time of menopause.^{3, 4} Difference in plasma levels of high-density lipoprotein cholesterol may cause men to be more prone than women to develop lipid-loaded, unstable coronary atherosclerotic plaques, which could explain the increased risk of coronary death and myocardial infarction in men.¹¹ Hypertriglyceridaemia is also a more potent independent risk factor for IHD in women compared with men. In a recent report by Acarturk *et al*,¹² of the total 608 patients who had CAD, hypertriglyceridaemia was an independent risk factor for CAD only in women ($p < 0.05$). There was also a positive correlation between triglyceride concentrations and the number of diseased vessels only in women ($p = 0.001$, $r = 0.2$).

Although younger-aged women with diabetes (ie, < 45 years) have an equally low prevalence of atherosclerosis,¹³ several studies have reported a significantly higher cardiovascular mortality for women with diabetes compared with men with diabetes.¹⁴ Notably, the age-adjusted prevalence of cardiovascular disease is nearly twofold higher in women with diabetes than in those without diabetes.⁷ In a recent report by Juutilainen *et al*,¹⁵ diabetes without any prior evidence of CHD (myocardial infarction or angina pectoris or ischemic ECG changes) indicates a higher risk for death from CHD than diabetes without prior evidence of CHD in women without diabetes (hazard ratio (HR) 3.5, 95% confidence interval (CI) 1.8 to 6.8). Thus, it appears that diabetes eliminates the “female advantage” of a predominantly lower CAD prevalence and outcome risk of women.

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 directly associated with obstructive CAD or adverse cardiovascular events after adjusting for other risk factors ($p = 0.05$ – 0.88).¹⁶ Hence, the obesity itself is not an independent predictor of disease, but the metabolic syndrome is a link between obesity and cardiovascular disease. Women with the metabolic syndrome have an increased prevalence of subclinical disease, and they are at an intermediate cardiovascular disease mortality risk when compared with those with normal glucose levels or frank diabetes.¹⁷ In a recent report by Marroquin *et al*,¹⁷ the 4-year RR of cardiac events was increased approximately twofold for women with the metabolic syndrome compared with those with a normal metabolic status.

THE ROLE OF SEX HORMONES IN THE PROCESS OF IHD

In premenopausal women, endogenous sex hormones including oestrogen are hypothesised as the primary reason for their low incidence of IHD compared with age-matched men. During menopause, a woman’s oestrogen levels are approximately one-tenth of those during her premenopausal years. Basic science work shows that oestrogen protects blood vessels through such channels: enhances vessel wall elasticity, antioxidative and anti-inflammatory properties and so on.¹⁸ Oestradiol is the predominant source of oestrogen in the premenopausal years, whereas oestrone is the main source during a woman’s postmenopausal years. It is reasonable, therefore, to hypothesise that the endogenous oestrogen type might provide relative protection from IHD premenopausally.¹⁸

The WISE study results suggest that endogenous oestrogen deficiency in young women may be a potent risk factor for IHD.¹⁹ The authors observed in premenopausal women that a stress-induced central disruption in ovulatory cycling with resulting hypoestrogenaemia was associated with a 7.4-fold

increased risk of obstructive CAD (measured at coronary angiography) in women with suspected ischemia.¹⁹ Premenopausal oestrogen deficiency could explain the more adverse prognosis experienced by younger women’s postmyocardial infarction when compared with age-matched men. Finally, although this discussion has focused on oestrogen, androgens have been shown to express atherosclerotic-related genes in men but not in women, perhaps contributing to the sex-related differences in CAD prevalence.²⁰

NOVEL RISK FACTORS FOR IHD

High-sensitivity C reactive protein

A review of evidence shows that the compilation of traditional risk factors underestimates risk in women.^{21, 22} This pattern of under-recognition in women has prompted additional research to assess the value of novel risk markers that may provide improved accuracy for the detection of CAD in women.^{21, 22} Recently, a novel risk marker, high-sensitivity C reactive protein (hsCRP), has suggested an improved predictive accuracy above and beyond traditional risk factors in estimating cardiovascular disease risk in women.²³ 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 epidemiological cohorts of women.²² For example, in the Women’s Health study, a prospective cohort of approximately 30 000 middle-aged, predominantly postmenopausal apparently healthy women, the RR of future vascular events increased as the level of hsCRP went from low–normal to high–normal.²⁴

hsCRP also acts synergistically with other risk factors in estimating prognosis. Notably, hsCRP has also been related to other markers of cardiovascular risk including the metabolic syndrome, type 2 diabetes and congestive heart failure.²⁵ The risk of cardiovascular events for women with the metabolic syndrome and high levels of hsCRP was similar to that of women with diabetes.¹⁷ This illustrates that the combination of risk markers approach may improve risk assessment for female cohorts.

Anaemia

Anaemia has also recently been considered to be a maker of worsening outcomes in women. The WISE study group recently reported on the prognostic significance of hemoglobin values in women with suspected ischemia. In this report, anaemic 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-anaemic women. Additionally, in a risk-adjusted study, decreasing hemoglobin values were associated with a higher risk of adverse outcomes (HR 1.20, $p = 0.002$). 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.²⁶

SEX-SPECIFIC DIFFERENCES IN THE ASSESSMENT OF SYMPTOMS AND DIAGNOSTIC APPROACHES

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 when they occur. For women, prodromal symptoms are often unusual, including fatigue, sleep disturbance and shortness of breath. In some reports, women present less often than men with exertional chest pain that may be defined as “typical” angina.

There appears to be an interaction effect of symptom presentation with age, in that older women often present similarly as men. However, women <65 years are also 50% more likely than younger men to be discharged with a diagnosis of unstable angina. When evaluated for symptoms suggestive of myocardial ischemia, women have been found to have lower rates of obstructive CAD at angiography.²² In the WISE study, women with typical or atypical chest pain symptoms have calculated obstructive CAD probabilities substantially less than that of men. 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.²⁷ Do symptom differences suggest a sex-specific pathophysiology? How should we use the symptoms for assessment of IHD in women?

Exercise ECG evaluation

The exercise ECG is the most frequently performed diagnostic test. However, the exercise ECG has a lower diagnostic accuracy (sensitivity and specificity for significant coronary artery obstruction 60–70%) in women compared with men (with diagnostic sensitivity and specificity measures of 80%).²⁸ This diminished accuracy in women is related to their lower CAD prevalence, functional impairment, a lower QRS voltage and hormonal factors. These reasons may suggest that exercise ECG alone for IHD detection may be imprecise and more precarious in women than in men.

However, Rautaharju *et al*²⁹ found that the relative risk of mortality for ECG abnormalities is the same in women as in men. Also exercise stress test risk scores (eg, Duke treadmill score) have been shown to improve prognostication in women. Women who achieve <5 metabolic equivalents are at an increased risk of cardiac events.³⁰ Recently, the 12-item Duke Activity Status Index questionnaire has been shown to risk stratify women. In the WISE study, women with evidence of lower Duke Activity Status Index scores were also found to be significantly more likely to have risk factors and obstructive CAD (44% vs 26%; $p < 0.001$).¹⁶

Peak and recovery heart rate measures also improve risk assessment and diagnostic accuracy for IHD in women. Recent reports emphasise the importance of tracking heart rate responses in the recovery phase of exercise. By subtracting 2-min recovery from the peak heart rate value, a decrease of <44 beats is found to be inversely related to all-cause mortality in women.³¹

Stress-induced left ventricular wall motion abnormality assessment

Left ventricular wall motion abnormality has been an evaluation associated with a higher diagnostic specificity of IHD disease,²⁸ and stress ECG is the most commonly applied test for wall motion assessment. However, it is limited to obesity or lung disease limiting acoustic windows and reducing exercise tolerance. Despite these limitations, based on several decades of experience, exercise ECG is considered highly accurate in detecting CAD in women. Additionally, more recent evidence also supports the use of stress ECG techniques for the estimation of prognosis in women. In a recent report on 4234 women, the extent of ischemic wall motion abnormalities was found to be highly predictive of cardiac death.³² Significantly higher cardiac death rates were noted for those women undergoing dobutamine stress ECG with annualised death rates ranging from 1% to 3% ($p < 0.001$) for zero-vessel to three-vessel ischemia.³²

Stress-induced perfusion abnormality assessment

In the procedure of the ischemic cascade, reductions in myocardial perfusion occur earlier than either ECG or ventricular wall motion abnormalities, and may provide a more precise measure for estimating IHD risk. Although many other techniques can be applied, myocardial perfusion single-photon

emission computed tomography (SPECT) is most commonly used for the evaluation of women presenting with chest pain symptoms. However, the accuracy of SPECT techniques is diminished in women with a limited exercise capacity,³³ although the diagnostic specificity can be influenced by breast tissue compared with men. Furthermore, 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. For this reason, the higher energy Tc-99m radioisotopes are preferred in women, as they can reduce soft tissue attenuation artefacts.³³

A large observational series has noted such technology to have similar abilities to risk stratify women and men with chest pain symptoms.³⁴ When 3402 women with stable chest pain symptoms from a multicentre registry were stratified by the number of vascular territories with ischemia, 3-year survival was found to be similar and to range from 98.5% to 85% for 0 to 3 coronary artery territories. On a summary meta-analysis, the RR of cardiac death or non-fatal myocardial infarction with a high-risk perfusion scan was found elevated ninefold (95% CI 6.9 to 11.7) and to be similar to recent prognostic evidence with stress ECG.³⁴

Cardiovascular magnetic resonance assessment

Cardiovascular MRI may also provide unique clinical utility for the evaluation of subendocardial ischemia. There are specific advantages in using such technology, including excellent soft tissue characterisation and contrast, three-dimensionality, an absolute quantitation of blood flow, and overall superior temporal and spatial resolution to image vascular and myocardial abnormalities. Although not in common practice, magnetic resonance techniques have been applied for the evaluation of suspected myocardial ischemia in female patients with chest pain symptoms. Magnetic resonance could also delineate subendocardial perfusion from epicardial perfusion and may provide corollary evidence as to the aetiology of chest pain symptoms in women, particularly in the absence of obstructive CAD. There may be a close relationship between subendocardial ischemia and chest pain in women with angina but without obstructive CAD.

Additionally, ³¹P magnetic resonance spectroscopy identifies changes in high-energy phosphates, providing a direct assessment of metabolic myocardial ischemia. The WISE study report noted worsening event-free survival (predominantly chest pain hospitalisations) for those women with a reduced phosphocreatine/adenosine triphosphate ratio $\leq 20\%$ and non-obstructive coronary arteries. Thus, this evidence suggests that chest pain in the setting of non-obstructive CAD, a prevalent condition, may be less benign than previously considered.

Multi-detector row computed tomographic assessment

Over the last few years, multidetector row computed tomographic (MDCT) cardiac imaging has continued to rapidly develop and evolve from the experimental research setting to become a useful clinical tool. The increasing availability of MDCT presents today's clinicians with an additional non-invasive diagnostic cardiac imaging method, in particular for the coronary arteries. Kuettner *et al*³⁵ detected 936 coronary vessel segments of 72 patients and found that 16-slice MDCT showed a specificity of 98% compared with the invasive coronary angiography.

With the advent and increasing clinical use of 16-detector row machines, and now with the imminent clinical emergence of 64-channel machines, the improvements in spatial and temporal resolution and sophisticated ECG gating are allowing motion-free, fast, accurate, detailed, contrast-enhanced cardiac

imaging that begins to approach the accuracy of traditional invasive diagnostic techniques. It is hoped that non-invasive coronary angiography with multi-detector row computed tomography will be powerful enough to act as a filter for suspected female patients with CAD with chest pain symptoms, who have a lower prevalence of obstructive CAD by coronary angiography compared with men.

CONCLUSIONS

In this review, we have synthesised a large body of evidence on sex-related differences in cardiovascular epidemiology about disease prevalence, variability in the RR, the synergy of traditional and novel risk factors, and associated clinical outcomes for women. Emerging data suggest a unique risk profile in women, including hypoestrogenaemia coupled with the adverse effects of a protracted dysmetabolic state on promoting an inflammatory milieu and/or metabolic changes 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 changes. In the WISE study database, nearly 60% of women undergoing invasive evaluation for investigation of chest pain do not have any flow-limiting coronary stenoses at angiography. However, there is now substantial evidence in large female cohorts that cardiac imaging tests such as stress ECG and SPECT imaging techniques have a high degree of accuracy for the estimation of near-term prognosis (ie, 2- to 5-year event-free survival) in women with chest pain symptoms. In a recent report by Shaw *et al.*,³⁶ the prognostic value of either stress echocardiography or SPECT reveals that a high-risk scan is associated with a 10-fold increased risk of cardiac death or myocardial infarction. Hence, these cardiac imaging tests could be applied for prognosis assessment purposes. This change has also allowed us to introduce new modalities to assess female risk. Therefore, a shift in reliance on prognostic risk versus diagnostic obstructive lesion detection may be particularly helpful in women, especially in minimising the role of disease-based terminology. It could also be a guide for test decision making, which could be useful in identifying at-risk women.

ACKNOWLEDGEMENTS

We thank our advisor Professor Yang Ting Shu, all the research fellows of the WISE study for giving us new and in-depth views of the problem, *BMJ* for their permission to use some of their results.

Authors' affiliations

Wang Shu, Wang Lei, Song Peng, Chinese Medical Association, Beijing, China

Competing interests: None declared.

REFERENCE

- O'Meara JG, Kardis SL, Armon JJ, *et al.* Ethnic and sex differences in the prevalence, treatment, and control of dyslipidemia among hypertensive adults in the GENOA study. *Arch Intern Med* 2004;**164**:1313–18.
- Bell DM, Nappi J. Myocardial infarction in women: a critical appraisal of gender differences in outcomes. *Pharmacotherapy* 2000;**20**:1034–44.
- Make Every Mother and Child Count. Available at www.cdc.gov/od/spotlight/nwhw/whlth05.htm (accessed 23 Nov 2005).
- American Heart Association. Heart disease and stroke statistics: 2004 update. <http://americanheart.org/downloadable/heart/107296976694> OHSSStats2004Update.pdf (accessed 15 Jan, 2004).
- Strangl V, Baumann G, Strangl K. Coronary atherogenic risk factors in women. *Eur Heart J* 2002;**23**:1738–52.
- Crilly MA, Bundred PE. Gender inequalities in the management of angina pectoris: cross-sectional survey in primary care. *Scott Med J* 2005;**50**:154–8.
- Centers for Disease Control and Prevention. www.cdc.gov/nccddp/burdenbook2004/index.htm (Accessed 30 Dec 2005).
- Frazier CG, Shah SH, Armstrong PW, *et al.* Prevalence and management of hypertension in acute coronary syndrome patients varies by sex: observations from the Sibrafin versus aspirin to Yield Maximum Protection from ischemic Heart events postacute coronary syndromes (SYMPHONY) randomised clinical trials. *Am Heart J* 2005;**150**:1260–7.
- Gretchen L, Gierach MPH, Johnson BD, *et al.* Hypertension, menopause, and coronary artery disease risk in the women's ischemia syndrome evaluation (WISE) study. *J Am Coll Cardiol* 2006;**47**(Suppl 1):S50–8.
- Populations Collaboration. Smoking, body weight, and CHD mortality in diverse populations. *Prev Med* 2004;**38**:834–40.
- Bonaa KH. An alternative hypothesis explaining the gender differences in risk of coronary heart disease. *Tidsskr Nor Lægeforen*, 200210, **122**:1783–7.
- Acarturk E, Cayli M, Akpinar O, *et al.* Relation between age and gender differences in plasma triglyceride concentrations and coronary artery disease in Southern Turkey. *Clin Chim Acta* 2004;**339**:123–8.
- Hoff JA, Quinn L, Sevrakov A, *et al.* The prevalence of coronary artery calcium among diabetic individuals without known coronary artery disease. *J Am Coll Cardiol* 2003;**41**:1008–12.
- Raggi P, Shaw LJ, Berman DS, *et al.* Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol* 2004;**43**:1663–9.
- Juutilainen A, Lehto S, Ronnema T, *et al.* Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. *Diabetes Care* 2005;**28**:2901–7.
- Wessel TR, Arant CB, Olson MB, *et al.* Relationship of physical fitness vs body mass index with coronary artery disease and cardiovascular events in women. *JAMA* 2004;**292**:1179–87.
- Marroquin OC, Kip KE, Kelley D, *et al.* The metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from WISE. *Circulation* 2004;**109**:714–21.
- Kaplan JR, Manuck SB, Anthony MS, *et al.* Premenopausal social status and hormone exposure predict postmenopausal atherosclerosis in female monkeys. *Obstet Gynecol* 2002;**99**:381–8.
- Bairey Merz CN, Johnson BD, Sharaf BL, *et al.* Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. *J Am Coll Cardiol* 2003;**41**:13–19.
- Ng MK, Quinn CM, McCrohan JA, *et al.* Androgens up-regulate atherosclerosis-related genes in macrophages from males but not females: molecular insights into gender differences in atherosclerosis. *J Am Coll Cardiol* 2003;**42**:1306–13.
- Chambless LE, Heiss G, Shahar E, *et al.* Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities study. *Am J Epidemiol* 2004;**160**:259–69.
- Shaw LJ, Lewis JF, Hlatky MA, *et al.* Women's Ischemic Syndrome Evaluation: current status and future research directions, report of the National Heart Lung Blood Institute (NHLBI) workshop, section 5: gender-related risk factors for ischemic heart disease, October 2–4, 2002. *Circulation* 2004;**109**:56e–8e.
- Raggi P, Shaw LJ, Berman DS, *et al.* Gender-based differences in the prognostic value of coronary calcium. *J Women Health* 2004;**13**:273–88.
- Ridker PM, Rifai N, Rose L, *et al.* Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;**347**:1557–65.
- Tracy RP. Inflammation in cardiovascular disease: cart, horse or both—revisited. *Arterioscler Thromb Vasc Biol* 2002;**22**:1514–15.
- Arant CB, Wessel TR, Olson MB, *et al.* National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation study. Hemoglobin level is an independent predictor for adverse cardiovascular outcomes in women undergoing evaluation for chest pain: results from the National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation study. *J Am Coll Cardiol* 2004;**43**:2009–14.
- Johnson BD, Kelsey SF, Bairey Merz CN. Clinical risk assessment in women: chest discomfort. Report from the WISE study. In: Shaw LJ, Redberg RF, eds. *Coronary disease in women: evidence-based diagnosis and treatment*. Totowa, NJ: Humana Press, 2003:129–42.
- AHRQ. *Diagnosis and treatment of coronary heart disease in women: systematic reviews of evidence on selected topics*. Summary, evidence report/technology assessment: Number 81, AHRQ Publication No.03-E036. Rockville, MD: Agency for Healthcare Research and Quality, 2003. <http://www.ahrq.gov/clinic/epsums/chdwtosum.htm> (Accessed 23 Nov 2005).
- Rautaharju PM, Ge S, Nelson JC, *et al.* Comparison of mortality risk for electrocardiographic abnormalities in men and women with and without coronary heart disease (from the Cardiovascular Health Study). *Am J Cardiol* 2006;**97**:309–15.
- Gulati M, Pandey DK, Arnsdorf MF, *et al.* Exercise capacity and the risk of death in women. *Circulation* 2003;**108**:1554–9.
- Shetler K, Marcus R, Froelicher VF, *et al.* Heart rate recovery: validation and methodologic issues. *J Am Coll Cardiol* 2001;**38**:1980–7.
- Shaw LJ, Vasey C, Sawada S, *et al.* Impact of gender on risk stratification by exercise and dobutamine stress echocardiography: long-term mortality in 4,234 women and 6,898 men. *Eur Heart J* 2005;**26**:447–56.
- Mieres JH, Shaw LJ, Hendel RC, *et al.* American Society of Nuclear Cardiology: task force on women and coronary artery disease. *J Nucl Cardiol* 2003;**10**:95–101.
- Shaw LJ, Iskandrian AE. Prognostic value of stress gated SPECT in patients with known or suspected coronary artery disease. *J Nucl Cardiol* 2004;**11**:171–85.
- Kuettner A, Beck T, Drosch T, *et al.* Diagnostic accuracy of noninvasive coronary imaging using 16-detector slice spiral computed tomography with 188 ms temporal resolution. *J Am Coll Cardiol* 2005;**45**:123–7.
- Shaw LJ, Vasey C, Sawada S, *et al.* Impact of gender on risk stratification by exercise and dobutamine stress echocardiography: long-term mortality in 4,234 women and 6,898 men. *Eur Heart J* 2005;**26**:447–56.