Coronary Artery Disease in Women

A 2013 Update

Kavita Sharma*, Martha Gulati*,†

Columbus, OH, USA

ABSTRACT

Coronary artery disease (CAD) is a leading cause of death of women and men worldwide. CAD's impact on women traditionally has been underappreciated due to higher rates at younger ages in men. Microvascular coronary disease disproportionately affects women. Women have unique risk factors for CAD, including those related to pregnancy and autoimmune disease. Trial data indicate that CAD should be managed differently in women. In this review, we will examine risk assessment for CAD in women, CAD's impact on women, as well as CAD's female-specific presentation and management strategies.

For far too long, many believed that coronary artery disease (CAD) was primarily a "man's disease." With increased awareness of the fact that the leading cause of death in women is CAD, this notion is slowly eroding [1]. CAD is a common cause of death or disability in men and women, but CAD manifests differently in women. Furthermore, as women are being increasingly included in CAD trials, management strategies specific to women are emerging [2–6]. In this review, we summarize the current state of knowledge about women and CAD. We will review the impact of CAD on women, risk assessment, unique sex-specific CAD characteristics, and management strategies specific to women in 2013.

PREVALENCE OF CAD IN WOMEN

CAD is the leading cause of death for both men and women in the United States [7]. More women than men die of CAD [7]. More women have died from CAD than of cancer (including breast cancer), chronic lower respiratory disease, Alzheimer disease, and accidents combined [7]. From 1998 to 2008, the rate of death attributable to CAD declined 30.6%, but the rates are increasing in young women (<55 years) [7,8]. CAD mortality is higher in women than in men [7]. Of particular concern is the rise in obese American individuals, with its subsequent impact on diabetes and future development of CAD. The prevalence of obesity is similar in men and women, at 34% of the American population, according to NHANES (National Health and Nutrition Examination Survey) 2007 to 2008 [9]. However, the impact of obesity on the development of CAD appears to be greater in women than in men. Among individuals in the Framingham Heart Study, obesity increased the relative risk of CAD by 64% in women, as opposed to 46% in men [10].

The average age at first myocardial infarction (MI) is 64.5 years for men and 70.3 years for women [7]. The incidence of CAD in women lags behind men by 10 years and by 20 years for more serious clinical events such as MI and sudden death [11]. The consequences of CAD are worse in women than in men. Among individuals with premature MI (under age 50), women experience a 2-fold higher mortality rate after acute MI compared to men [12]. Among older individuals (over the age of 65), women are more likely to die within the first year after MI [7]. In individuals 45 to 64 years of age, women are more likely than men to have heart failure within 5 years of MI [7]. Women have higher rates of angina than do men [7,13]. A female excess of anginal prevalence was demonstrated in a meta-analysis of data from 31 widely varied countries, including non-English speaking countries [13]. The pooled sex ratio of angina prevalence was 1.20 (95% confidence interval: 1.14 to 1.28, $p < 0.0001$) and was true of pre-menopausal and post-menopausal women [13].

The burden of CAD is high among women. However, it appears that the pathophysiology of CAD varies between women and men. On cardiovascular computed tomography, women have been shown to have smaller coronary artery diameters than men do [14]. Women are less likely than men are to have obstructive CAD at the time of coronary angiography [15,16]. Despite the lack of obstructive CAD visualized on cardiac catheterization at the time of acute coronary syndrome (ACS), the prognosis of these women is not benign. Over one-half of symptomatic women without obstructive CAD continue to have signs and symptoms of ischemia and to undergo repeat hospitalization and coronary angiography [17,18].

Recently, disorders of the coronary microvasculature and endothelial dysfunction have been implicated in the occurrence of nonobstructive CAD in women. Han et al. [19] studied men and women with early CAD and found that men have higher degrees of atheroma and epicardial endothelial dysfunction, whereas women have more disease of the microvasculature. Retinal artery narrowing has been shown to be a marker for microvascular disease, and in the ARIC (Atherosclerosis Risk in Communities Study) population, a decrease in retinal artery narrowing assessed on retinal photographs corresponded to an increase in CAD incidence

From the *Department of Medicine (Cardiology), and the †School of Clinical Public Health (Epidemiology), The Ohio State University, Columbus, OH, USA. Correspondence: M. Gulati (martha.gulati@osumc.edu).

GLOBAL HEART

VOL. 8, NO. 2, 2013
ISSN 2211-8160/$36.00.
http://dx.doi.org/10.1016/j.gheart.2013.02.001

in women. This relationship was not seen in men, supporting a more prominent role of microvascular disease in CAD pathophysiology in women as opposed to men [20]. In addition, autopsy data has shown that women have a greater frequency of coronary plaque erosion and distal embolization [21]. In the WISE (Women's Ischemia Syndrome Evaluation) study, approximately one-half of women with chest pain without obstructive CAD had microvascular dysfunction [22]. In a study of post-menopausal women, impairment of flow-mediated dilation of the brachial artery predicted the development of cardiovascular events [23]. Hypertensive post-menopausal women were treated with antihypertensive therapy with both an improvement in flow-mediated vasodilation and an associated improvement in cardiovascular events [24]. Given the occurrence of CAD in women without obstructive CAD, the phrase "female-specific ischemic heart disease" has been recommended when discussing disease of the coronary arteries in women [25].

RISK ASSESSMENT IN WOMEN

There are multiple ways to assess an asymptomatic woman's risk. The "2010 American College of Cardiology/American Heart Association Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults" recommends obtaining a Framingham-like (global) risk score that incorporates multiple traditional cardiovascular risk factors for all asymptomatic adults without a history of CAD as a class I indication [26].

The "Effectiveness-Based Guidelines for the Prevention of Coronary Artery Disease in Women—2011 Update" recommends risk-stratifying women based on their risk scores into 3 categories: 1) high risk; 2) at risk; and 3) optimal risk [27]. High-risk individuals include all women with known CAD, peripheral arterial disease, symptomatic carotid artery disease, abdominal aortic aneurysm, end-stage or chronic kidney disease, or who have a 10-year predicted CAD risk $\geq$10%. At-risk status is defined as having 1 or more of the following risk factors: cigarette smoking; systolic blood pressure $\geq$120 mm Hg, diastolic blood pressure $\geq$80 mm Hg, or treated hypertension; total cholesterol >200 mg/dl, high-density lipoprotein cholesterol <50, or treated dyslipidemia; obesity (particularly central adiposity); poor diet; physical inactivity; family history of premature CAD occurring in first-degree relatives in men <55 years of age or in women <65 years of age; metabolic syndrome; evidence of advanced subclinical atherosclerosis (e.g., coronary calcification, carotid plaque, or thickened intima-media thickness); poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise; systemic autoimmune collagen-vascular disease (e.g., lupus or rheumatoid arthritis); or history of pre-eclampsia, gestational diabetes, or pregnancy-induced hypertension. Optimal risk is defined as having all of the following factors: total cholesterol <200 mg/dl (untreated); blood pressure <120/<80 mm Hg (untreated); fasting blood glucose <100 mg/dl (untreated); body mass index <25 kg/m^2; abstinence from smoking and a healthy (DASH [Dietary Approaches to Stop Hypertension]-like) diet (Table 1) [27].

Traditional risk factors such as age, family history of CAD, hypertension, diabetes, dyslipidemia, smoking, and physical inactivity are important predictors of risk in women. In contrast to the linear increase in CAD in men as they age, there is a more exponential increase in CAD in women after the age of 60 [28]. The NCEP ATP III (National Cholesterol Education Panel Adult Treatment Panel III) considers the age of 55 years or above to be a risk factor for women, compared with 45 years for men. Irrespective of this, there is higher mortality among younger women, as opposed to men, with acute MI [12]. Premature CAD in a first-degree female relative is a relatively more potent risk factor than is premature CAD in male relatives [29]. Hypertension is more prevalent in women, particularly older women [30]. Women with hypertension have a higher risk of developing congestive heart failure than men do [31]. The presence of diabetes is a relatively greater risk factor for CAD in women versus men, increasing a woman's risk of CAD by 3- to 7-fold, with only a 2- to 3-fold increase in diabetic men [32]. Furthermore, women with diabetes have a greater than 3-fold increase in CAD risk than nondiabetic women do [32]. After the fifth decade of life, women have higher cholesterol levels than men do [33]. Elevated triglycerides have been shown to be of greater risk to women than to men [34—36]. Lack of physical fitness is a predictor of mortality. In the St. James Women Take Heart Project, asymptomatic women who were unable to achieve 5 metabolic equivalents (MET) on a Bruce protocol have a 3-fold increased risk of death compared with women who achieved >8 MET, even after controlling for traditional risk factors [37]. Focus on risk factors is important in the prevention of CAD in women, just as it is in men. When women with 2 or more risk factors were compared to women with no risk factors, those without risk factors had a substantially lower lifetime risk of CAD (8.2% vs. 50.2%) [38].

Addressing those risk factors that are unique to women is also important. Though it is unclear if high-sensitivity C-reactive protein (hsCRP) is an independent risk factor for CAD, it may improve risk detection in women [39—41]. HsCRP may add prognostic information in women with metabolic syndrome. In 1 study [42] of apparently healthy women, those women with the metabolic syndrome and a baseline hsCRP >3.0 mg/l had almost twice the risk of future cardiovascular events than did those with metabolic syndrome and a hsCRP <3.0 mg/l. The Reynolds risk score, a risk assessment tool, incorporates hsCRP and has been shown to improve risk prediction in women [43].

Calcium scoring has been shown to improve risk prediction in women. In MESA (Multi-Ethnic Study of Atherosclerosis), 3,601 women were studied, and 90% were classified as low risk. Prevalence of any coronary calcium was associated with a 6-fold increased risk of CAD, adjusted for age, ethnicity, body mass index, low-density lipoprotein,

TABLE 1. Classification of CAD risk in women

Risk Status	Criteria
High risk (≥1 high-risk state)	• Clinically manifest CHD • Clinically manifest cerebrovascular disease • Clinically manifest peripheral arterial disease • Abdominal aortic aneurysm • End-stage or chronic kidney disease • Diabetes mellitus • 10-year predicted CAD risk >10%
At risk (>1 risk factor)	• Cigarette smoking • SBP >120 mm Hg, DBP >80 mm Hg, or treated hypertension • Total cholesterol >200 mg/dl, HDL-C <50 mg/dl, or treated for dyslipidemia • Obesity, particularly central adiposity • Poor diet • Physical inactivity • Family history of premature CAD occurring in first-degree relatives in men <55 years of age or in women <65 years of age • Metabolic syndrome • Evidence of advanced subclinical atherosclerosis (e.g., coronary calcification, carotid plaque, or thickened IMT) • Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise • Systemic autoimmune collagen-vascular disease (e.g., lupus or rheumatoid arthritis) • History of pre-eclampsia, gestational diabetes, or pregnancy-induced hypertension
Ideal coronary artery health (all of these)	• Total cholesterol <200 mg/dl (untreated) • BP <120/<80 mm Hg (untreated) • Fasting blood glucose <100 mg/dl (untreated) • Body mass index <25 kg/m^2 • Abstinence from smoking • Healthy (DASH-like) diet

CAD, coronary artery disease; CHD, coronary heart disease; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; SBP, systolic blood pressure.
Adapted, with permission, from Mosca et al. [27].

high blood pressure, smoking, estrogen, and statin therapy. A calcium score of ≥300 was associated with an 8.6% absolute risk of CAD. The presence of coronary calcium therefore redefined a group of women improperly labeled as low risk by Framingham criteria [44].

Autoimmune diseases are more prevalent in women and have been implicated in higher CAD risk. Rheumatoid arthritis and systemic lupus erythematosus (SLE) have been associated with a significantly increased relative risk for CAD [45]. Women in the Framingham Offspring Study ages 34 to 44 years with SLE were 50× more likely to have an acute MI than were women of the same age without SLE [46]. This increased CAD burden in women with SLE has been demonstrated in other studies, including 1 study of women with SLE who underwent single-photon emission computed tomography (SPECT), and the presence of myocardial perfusion defects was independently associated with an increased risk of CAD, beyond the Framingham risk score alone [47]. In a longitudinal study of patients with lupus, serial carotid ultrasounds demonstrated that 28% had progressive atherosclerosis over a 34-month follow-up period, averaging approximately a 10% progression per year [48].

Unique to women are the hormonal changes that occur over their lifetimes and ultimately affect CAD risk. Dysfunction in ovulation has been associated with increased CAD risk. A meta-analysis found that women with polycystic ovarian syndrome have an increased prevalence of impaired glucose tolerance, metabolic syndrome, and diabetes when compared with women without polycystic ovarian syndrome [49]. Functional hypothalamic amenorrhea, a cause of ovarian dysfunction, has been shown to be associated with premature coronary atherosclerosis [50]. Early age at menarche (<12 years) is also associated with increased risk of CAD events, CAD mortality, and overall mortality in women, and the association appeared to be only partly mediated by increased adiposity [51].

Women with a history of pre-eclampsia have double the risk of subsequent ischemic heart disease, stroke, and venous thromboembolic events over the 5 to 10 years following the pregnancy [52]. Gestational diabetes increases the risk for future diabetes [53], thereby increasing the risk for future CAD. Accordingly, a history of pre-eclampsia or gestational diabetes categorizes a woman as "at risk" for CAD, based on the 2011 "Effectiveness-Based Guidelines for Prevention of CAD in Women" [27]. Another risk factor to consider in women is the effect of breast cancer therapy on future CAD risk. As was recently reported, although advances in breast cancer therapies are improving survival in early breast cancer, the gains are being attenuated by increasing CAD risk [54]. Whether the increased CAD risk is due to the breast cancer therapies or to the disease itself (which is associated with some of the same risk factors for CAD) remains unknown.

DIAGNOSIS OF MYOCARDIAL ISCHEMIA IN WOMEN

An exercise stress test is used commonly in the evaluation of suspected CAD. In women, ST-segment depression noted on exercise stress testing is felt to be less accurate than it is in men; in women, the sensitivity and specificity of ST-segment depression is lower than in men [55]. The negative predictive value is high in both men and women, however [56]. A negative exercise stress test, therefore, can effectively rule out the diagnosis of CAD in women. The Duke treadmill score, which incorporates exercise time, ST-segment deviation, and an anginal score, is particularly useful in women and performs better in women than in men for predicting significant CAD [57]. Exercise is a powerful predictor of CAD. Importantly, a nomogram has been established defining age-predicted exercise capacity in women (Fig. 1) [58]. As mentioned earlier, women who are unable to reach 5 METs or perform <85% of age-predicted fitness level on an exercise stress test have a higher risk of MI and all-cause mortality [37,58].

Stress echocardiography has similar high levels of sensitivity and specificity in women and men [59,60]. Its lack of radiation is particularly attractive in younger women. Myocardial perfusion imaging using SPECT has been well studied in women. The incorporation of technetium-99 sestamibi radiotracer and the use of gating technology have improved the sensitivity and specificity of SPECT imaging in women to nearly 90% (Table 2) [61–78]. SPECT stress imaging effectively risk-stratifies women [79–81]. In women with a normal myocardial perfusion study using SPECT imaging, the annual CAD death rate is very low (0.6%/year), in contrast to a much higher event rate (5%/year) in those with abnormal myocardial perfusion [81].

There is increasing interest in the use of stress cardiac magnetic resonance (CMR) imaging in the assessment of women. A recent study of predominantly female patients with chest pain and nonobstructive CAD who underwent adenosine CMR found that subendocardial ischemia was frequently present when compared with images of control

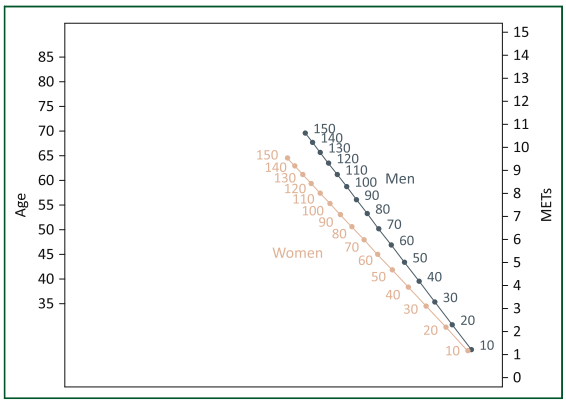

FIGURE 1. Nomogram to calculate percent of predicted exercise capacity for age for men and women. Constructing a line from the patient's achieved metabolic equivalents (METs) in an exercise stress test and age will intersect with the patient's percentage of predicted exercise capacity for age, based on sex. Established using the following regression lines based on age and sex: Men: Predicted METs = 14.7 − (0.11 × age); Women: Predicted METs = 14.7 − (0.13 × age). Adapted, with permission, from Gulati et al. [58].

subjects [82]. In women with ACS and normal coronary arteries who underwent CMR, abnormalities on late gadolinium enhancement consistent with ischemia were frequently noted [83]. In a small substudy from the WISE cohort, women with nonobstructive CAD with an abnormal stress-induced CMR had an increase in adverse cardiovascular events [84]. CMR and its applications to women and CAD are only beginning to be explored; much remains to be learned about CMR's prognostic implications.

MANAGEMENT OF OBSTRUCTIVE CAD IN WOMEN

Why is mortality due to ACS higher in women than in men [7]? Trials and registry studies suggest women with ACS are treated less aggressively than men are. In the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) initiative [85], women were less likely to receive heparin and glycoprotein (GP) IIb/IIIa inhibitors and less likely to undergo cardiac catheterization and revascularization than men were. Women with ACS have also been shown to be less likely to receive early aspirin, beta-blockers, reperfusion, and timely reperfusion [86].

Strategies for ACS may have different efficacy in women than in men. A meta-analysis of randomized controlled trials of ACS showed that an invasive strategy was more beneficial in women with positive biomarkers in contrast to women with negative biomarkers; such a difference was not seen in men [2]. After percutaneous coronary intervention, women have been shown to have a higher mortality in ST-segment elevation and non–ST-segment elevation MI [87].

TABLE 2. Diagnostic value of various stress testing modalities in women

Stress Testing Modality	Sensitivity, %	Specificity, %	Negative Predictive Value	Positive Predictive Value
Exercise ECG [63–68]	31–71	66–78	78	47
Exercise echocardiography [68–70]	80–88	79–86	98	74
Exercise SPECT [71–74]	78–88	64–91	99	87
Pharmacological echocardiography [75–77]	76–90	85–94	68	94
Pharmacological SPECT [61,62,78]	80–91	65–86	90	68

ECG, electrocardiogram; SPECT, single-photon emission computed tomography.
Adapted, with permission, from Kohli and Gulati [60].

Furthermore, in ACS patients, women without raised biomarkers did not benefit from GP IIb/IIIa inhibitors, unlike men; when women had raised biomarkers, they did receive a risk reduction with GP IIb/IIIa inhibitors [3]. Women were found in 1 trial [88] to experience higher rates of bleeding with percutaneous intervention; however, this has been shown to be largely attributable to body size and renal function.

Several recent trials have specifically examined drug-eluting stent placement in men and women and, overall, have found similar outcomes after stent placement [89,90]. Among patients undergoing coronary artery bypass grafting (CABG), however, female sex is an independent risk factor for morbidity and mortality. Women have a higher risk of morbidity and mortality and they experience less relief from angina than do men after CABG, despite comprising less than 30% of the CABG population [4,5]. Interestingly, this sex discrepancy appears to be reduced when an off-pump CABG is performed [91].

MANAGEMENT OF NONOBSTRUCTIVE CORONARY DISEASE IN WOMEN

Among women with symptoms of myocardial ischemia who have been demonstrated to have angiographically nonobstructive CAD, the prognosis was initially felt to be benign [92,93]. However, more recent data have shown that the prognosis is not benign and the risk of cardiovascular events is higher than it is for asymptomatic women [18,94]. Patients with unstable angina and no critical coronary obstruction still had a 2% risk of death and MI at 30 days after MI [95]. Among women with persistent chest pain but no obstructive CAD at cardiac catheterization for suspected ACS, cardiovascular outcomes were worse in those with continued chest pain [17]. Symptomatic women in the WISE study with nonobstructive CAD (lesions 1% to 49%) had a CAD event rate of 16% versus only 7.9% in women with no CAD and only 2.4% in asymptomatic age- and race-matched control subjects [94].

The focus of treatment of nonobstructive CAD has been on symptom improvement or vascular function response. Statins and angiotensin-converting enzyme inhibitors have been shown to improve endothelial function and symptoms [96–99]. Statins have been demonstrated to improve microcirculation [100]. Chest pain syndromes have been effectively treated with beta-blockers [101]. Imipramine has been shown to improve symptoms in women with chest pain and nonobstructive CAD, possibly related to a visceral analgesic effect [102]. L-arginine has been shown to improve endothelial function and symptoms in patients with nonobstructive CAD [103], although concerns about its safety have arisen [104]. The effects of ranolazine are promising. A recent pilot study demonstrated that women with angina, myocardial ischemia, and no obstructive CAD had an improvement in angina with ranolazine [6]. Randomized control data on women with chest pain and nonobstructive CAD are currently lacking; further research in this area is needed.

THE UNDERTREATMENT OF CAD IN WOMEN

Awareness of the tremendous effect CAD has on women is slowly increasing. In 1997, only 30% of American women surveyed were aware that the leading cause of death in women is CAD; this increased to 54% in 2009 [1]. In a survey performed in 2004, fewer than 1 in 5 physicians recognized that more women than men die each year from CAD [105]. Unfortunately, women are less likely to receive preventive recommendations, such as lipid-lowering therapy, aspirin, and lifestyle advice, than are similarly scoring Framingham-risk men [105,106]. Hypertensive women are less likely to have their blood pressure at goal [107]. Women are less likely to be treated to reach goal for low-density lipoprotein cholesterol [108]. Female diabetics, the group at highest risk for CAD, have the greatest sex disparity in achieving low-density lipoprotein cholesterol targets [109]. Cardiac rehabilitation after MI is underused, particularly in women, as demonstrated in numerous national studies [110–113]. Women are 55% less likely to participate in cardiac rehabilitation than men are [110].

SUMMARY

Women are affected by CAD in large numbers and to a large degree. CAD is the leading cause of mortality in women. The manifestation of CAD has unique characteristics in women. Increasing data demonstrate that some treatment strategies have sex-specific effectiveness. Further research regarding the pathophysiology of CAD in women, diagnosis, and

treatment strategies specific to women is required. CAD is not a "man's only" disease, and we eagerly await future studies that examine its unique presence in women.

REFERENCES

1. Mosca L, Mochari-Greenberger H, Dolor RJ, Newby LK, Robb KJ. Twelve-year follow-up of American women's awareness of cardiovascular disease risk and barriers to heart health. Circ Cardiovasc Qual Outcomes 2010;3:120–7.
2. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs. conservative treatment strategies in women and men with unstable angina and non—ST-segment elevation myocardial infarction: a meta-analysis. JAMA 2008;300:71–80.
3. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 2002;359:189–98.
4. Abramov D, Tamariz MG, Sever JY, et al. The influence of gender on the outcome of coronary artery bypass surgery. Ann Thorac Surg 2000;70:800–5. discussion 806.
5. Edwards FH, Carey JS, Grover FL, Bero JW, Hartz RS. Impact of gender on coronary bypass operative mortality. Ann Thorac Surg 1998;66:125–31.
6. Mehta PK, Goykhman P, Thomson LE, et al. Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. J Am Coll Cardiol Img 2011;4:514–22.
7. Roger VL, Go AS, Lloyd-Jones DM, et al, for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 2012;125:e2–220.
8. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. J Am Coll Cardiol 2007;50:2128–32.
9. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among U.S. adults, 1999—2008. JAMA 2010;303:235–41.
10. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med 2002;162:1867–72.
11. Thom TJ, Kannel WB, Silbershatz H, D'Agostino RB Sr. Cardiovascular diseases in the United States and prevention approaches. In: Fuster V, Alexander RW, O'Rourke RA, Roberts R, Spencer BK III, Weller JJ, eds. Hurst's the Heart. 10 edition. New York, NY: McGraw-Hill; 2001. 3–18.
12. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med 1999;341:217–25.
13. Hemingway H, Lanfenberg C, Damant J, Frost C, Pyörälä K, Barrett-Conor E. Prevalence of angina in women versus men: a systematic review and meta-analysis of international variations across 31 countries. Circulation 2008;117:1526–36.
14. Dickerson JA, Nagaraja HN, Raman SV. Gender-related differences in coronary artery dimensions: a volumetric analysis. Clin Cardiol 2010;33:E44–9.
15. Sharaf BL, Pepine CJ, Kerensky RA, et al, for the WISE Study Group. Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation [WISE] Study Angiographic Core Laboratory). Am J Cardiol 2001;87:937–41, A3.
16. Kennedy JW, Kilip T, Fisher LD, Alderman EL, Gillespie MJ, Mock MB. The clinical spectrum of coronary artery disease and its surgical and medical management, 1974—1979. The Coronary Artery Surgery study. Circulation 1982;66:III16–23.
17. Johnson BD, Shaw LJ, Pepine CJ, et al. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI—sponsored Women's Ischaemia Syndrome Evaluation (WISE) study. Eur Heart J 2006;27:1408–15.
18. Shaw LJ, Merz CN, Pepine CJ, et al, for the WISE Investigators. The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health—National Heart, Lung, and Blood Institute—sponsored Women's Ischemia Syndrome Evaluation. Circulation 2006;114:894–904.
19. Han SH, Bae JH, Holmes DR Jr, et al. Sex differences in atheroma burden and endothelial function in patients with early coronary atherosclerosis. Eur Heart J 2008;29:1359–69.
20. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. JAMA 2002;287:1153–9.
21. Burke AP, Farb A, Malcolm GT, Liang Y, Smialek J, Virmani R. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation 1998;97:2110–6.
22. Reis SE, Holubkov R, Conrad Smith AJ, et al, for the WISE Investigators. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. Am Heart J 2001;141:735–41.
23. Rossi R, Nuzzo A, Origliani G, Modena MG. Prognostic role of flow-mediated dilation and cardiac risk factors in post-menopausal women. J Am Coll Cardiol 2008;51:997–1002.
24. Modena MG, Bonetti L, Coppi F, Bursi F, Rossi R. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. J Am Coll Cardiol 2002;40:505–10.
25. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. J Am Coll Cardiol 2009;54:1561–75.
26. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010;56:e50–103.
27. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. Circulation 2011;123:1243–62.
28. Wenger NK, Speroff L, Packard B. Cardiovascular health and disease in women. N Engl J Med 1993;329:247–56.
29. Scheuner MT, Setodji CM, Pankow JS, Blumenthal RS, Keeler E. Relation of familial patterns of coronary heart disease, stroke, and diabetes to subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis. Genet Med 2008;10:879–87.
30. Centers for Disease Control and Prevention. Health, United States, 2009: With Special Feature on Medical Technology [pdf]. 2010. Available from: http://www.cdc.gov/nchs/data/hus/hus11.pdf. Accessed April 12, 2013.
31. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557–62.
32. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73–8.
33. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003;289:76–9.
34. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986;111:383–90.
35. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3:213–9.
36. Reuterwall C, Hallqvist J, Ahlbom A, et al, for the SHEEP Study Group. Higher relative, but lower absolute risks of myocardial infarction in women than in men: analysis of some major risk factors in the SHEEP study. J Intern Med 1999;246:161–74.
37. Gulati M, Pandey DK, Amsdorf MF, et al. Exercise capacity and the risk of death in women: the St. James Women Take Heart Project. Circulation 2003;108:1554–9.
38. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113:791–8.

39. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. Ann Intern Med 2006;145:21–9.

40. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836–43.

41. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. 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.

42. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. Circulation 2003;107:391–7.

43. Wenger NK. The Reynolds Risk Score: improved accuracy for cardiovascular risk prediction in women? Nat Clin Pract Cardiovasc Med 2007;4:366–7.

44. Lakoski SG, Greenland P, Wong ND, et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med 2007;167:2437–42.

45. Salmon JE, Roman MJ. Subclinical atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus. Am J Med 2008; 121(Suppl 1):S3–8.

46. Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol 1997;145:408–15.

47. Nikpour M, Gladman DD, Ibañez D, Bruce IN, Burns RJ, Urowitz MB. Myocardial perfusion imaging in assessing risk of coronary events in patients with systemic lupus erythematosus. J Rheumatol 2009;36: 288–94.

48. Roman MJ, Crow MK, Lockshin MD, et al. Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2007;56:3412–9.

49. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2010;16:347–63.

50. Bairey Merz CN, Johnson BD, Sharaf BL, et al, for the WISE Study Group. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. J Am Coll Cardiol 2003;41:413–9.

51. Lakshman R, Forouhi NG, Sharp SJ, et al. Early age at menarche associated with cardiovascular disease and mortality. J Clin Endocrinol Metab 2009;94:4953–60.

52. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007;335:974.

53. Ratner RE. Prevention of type 2 diabetes in women with previous gestational diabetes. Diabetes Care 2007;30(Suppl 2):S242–5.

54. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol 2007;50:1435–41.

55. Hemingway H, McCallum A, Shipley M, Manderbacka K, Martikainen P, Keskimäki I. Incidence and prognostic implications of stable angina pectoris among women and men. JAMA 2006;295: 1404–11.

56. Barolsky SM, Gilbert CA, Faruqui A, Nutter DO, Schlant RC. Differences in electrocardiographic response to exercise of women and men: a non-Bayesian factor. Circulation 1979;60:1021–7.

57. Alexander KP, Shaw LJ, Shaw LK, Delong ER, Mark DB, Peterson ED. Value of exercise treadmill testing in women. J Am Coll Cardiol 1998;32:1657–64.

58. Gulati M, Black HR, Shaw LJ, et al. The prognostic value of a nomogram for exercise capacity in women. N Engl J Med 2005; 353:468–75.

59. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999;83:660–6.

60. Kohli P, Gulati M. Exercise stress testing in women: going back to the basics. Circulation 2010;122:2570–80.

61. 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.

62. Amanullah AM, Kiat H, Friedman JD, Berman DS. Adenosine technetium-99m sestamibi myocardial perfusion SPECT in women: diagnostic efficacy in detection of coronary artery disease. J Am Coll Cardiol 1996;27:803–9.

63. Ellestad MH, Wan MK. Predictive implications of stress testing: follow-up of 2,700 subjects after maximum treadmill stress testing. Circulation 1975;51:363–9.

64. Linhart JW, Laws JG, Satinsky JD. Maximum treadmill exercise electrocardiography in female patients. Circulation 1974;50:1173–8.

65. Hlatky MA, Pryor DB, Harrell FE Jr, Califf RM, Mark DB, Rosati RA. Factors affecting sensitivity and specificity of exercise electrocardiography: multivariable analysis. Am J Med 1984;77:64–71.

66. Sketch MH, Mohiuddin SM, Lynch JD, Zencka AE, Runco V. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. Am J Cardiol 1975;36: 169–73.

67. Weiner DA, Ryan TJ, McCabe CH, et al. Exercise stress testing: correlations among history of angina, ST-segment response and prevalence of coronary-artery disease in the Coronary Artery Surgery Study (CASS). N Engl J Med 1979;301:230–5.

68. Sanfilippo AJ, Abdollah H, Knott TC, Link C, Hopman W. Stress echocardiography in the evaluation of women presenting with chest pain syndrome: a randomized, prospective comparison with electrocardiographic stress testing. Can J Cardiol 2005;21:405–12.

69. Marwick TH, Anderson T, Williams MJ, et al. Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women. J Am Coll Cardiol 1995;26: 335–41.

70. Williams MJ, Marwick TH, O'Gorman D, Foale RA. Comparison of exercise echocardiography with an exercise score to diagnose coronary artery disease in women. Am J Cardiol 1994;74:435–8.

71. Hung J, Chaitman BR, Lam J, et al. Noninvasive diagnostic test choices for the evaluation of coronary artery disease in women: a multivariate comparison of cardiac fluoroscopy, exercise electrocardiography and exercise thallium myocardial perfusion scintigraphy. J Am Coll Cardiol 1984;4:8–16.

72. Mieres JH, Makaryus AN, Cacciabaudo JM, et al. Value of electrocardiographically gated single-photon emission computed tomographic myocardial perfusion scintigraphy in a cohort of symptomatic postmenopausal women. Am J Cardiol 2007;99: 1096–9.

73. Santana-Boado C, Candell-Riera J, Castell-Conesa J, et al. Diagnostic accuracy of technetium-99m-MIBI myocardial SPECT in women and men. J Nucl Med 1998;39:751–5.

74. Bokhari S, Shahzad A, Bergmann SR. Superiority of exercise myocardial perfusion imaging compared with the exercise ECG in the diagnosis of coronary artery disease. Coron Artery Dis 2008;19: 399–404.

75. Elhendy A, Geleijnse ML, van Domburg, et al. Gender differences in the accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery disease. Am J Cardiol 1997;80:1414–8.

76. Geleijnse ML, Krenning BJ, Soliman OI, Nemes A, Galema TW, ten Cate FJ. Dobutamine stress echocardiography for the detection of coronary artery disease in women. Am J Cardiol 2007;99:714–7.

77. Dionisopoulos PN, Collins JD, Smart SC, Knickelbine TA, Sagar KB. The value of dobutamine stress echocardiography for the detection of coronary artery disease in women. J Am Soc Echocardiogr 1997; 10:811–7.

78. Kim C, Kwok YS, Heagerty P, Redberg R. Pharmacologic stress testing for coronary disease diagnosis: a meta-analysis. Am Heart J 2001; 142:934–44.

79. Mieres JH, Shaw LJ, Arai A, et al. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery

disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Circulation 2005;111: 682–96.

80. Marwick TH, Shaw LJ, Lauer MS, et al, for the END Study Group. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. Am J Med 1999;106: 172–8.

81. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol 2004;11:171–85.

82. Panting JR, Gatehouse PD, Yang GZ, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. N Engl J Med 2002;346:1948–53.

83. Reynolds HR, Srichai MB, Igbal SN, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. Circulation 2011;124:1414–25.

84. Johnson BD, Shaw LJ, Buchthal SD, et al. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health—National Heart, Lung, and Blood Institute—Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004;109:2993–9.

85. Blomkalns AL, Chen AY, Hochman JS, et al, for the CRUSADE Investigators. Gender disparities in the diagnosis and treatment of non—ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. J Am Coll Cardiol 2005;45:832–7.

86. Jneid H, Fonarow GC, Cannon CP, et al, for the Get With the Guidelines Steering Committee and Investigators. Sex differences in medical care and early death after acute myocardial infarction. Circulation 2008;118:2803–10.

87. Lansky AJ. Outcomes of percutaneous and surgical revascularization in women. Prog Cardiovasc Dis 2004;46:305–19.

88. Alexander KP, Chen AY, Newby LK, et al, for the CRUSADE Investigators. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) initiative. Circulation 2006;114:1380–7.

89. Solinas E, Nikolsky E, Lansky AJ, et al. Gender-specific outcomes after sirolimus-eluting stent implantation. J Am Coll Cardiol 2007; 50:2111–6.

90. Lansky AJ, Costa RA, Mooney M, et al, for the TAXUS-IV Investigators. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. J Am Coll Cardiol 2005;45: 1180–5.

91. Puskas JD, Edwards FH, Pappas PA, et al. Off-pump techniques benefit men and women and narrow the disparity in mortality after coronary bypass grafting. Ann Thorac Surg 2007;84:1447–54, discussion 1454—6.

92. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. J Am Coll Cardiol 1986;7:479–83.

93. Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. J Am Coll Cardiol 1995;25:807–14.

94. Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St. James Women Take Heart Project. Arch Intern Med 2009;169:843–50.

95. Diver DJ, Bier JD, Ferreira PE, et al. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-IIIA Trial). Am J Cardiol 1994;74:531–7.

96. Pizzi C, Manfrini O, Fontana F, Bugiardini R. Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase in cardiac Syndrome X: role of superoxide dismutase activity. Circulation 2004;109:53–8.

97. Danaoğlu Z, Kültürsay H, Kayikçioğlu M, Can L, Payzin S. Effect of statin therapy added to ACE-inhibitors on blood pressure control and endothelial functions in normolipidemic hypertensive patients. Anadolu Kardiyol Derg 2003;3:331–7.

98. Kayikçioğlu M, Payzin S, Yavuzgil O, Kultursay H, Can LH, Soydan I. Benefits of statin treatment in cardiac syndrome-X1. Eur Heart J 2003;24:1999–2005.

99. Chen JW, Hsu NW, Wu TC, Lin SJ, Chang MS. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. Am J Cardiol 2002;90:974–82.

100. Manfrini O, Pizzi C, Morgagni G, Fontana F, Bugiardini R. Effect of pravastatin on myocardial perfusion after percutaneous transluminal coronary angioplasty. Am J Cardiol 2004;93:1391–3, A6.

101. Lanza GA, Colonna G, Pasceri V, Maseri A. Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X. Am J Cardiol 1999;84:854–6. A8.

102. Cannon RO 3rd, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. N Engl J Med 1994;330:1411–7.

103. Lerman A, Burnett JC Jr, Higano ST, McKinley LJ, Holmes DR Jr. Long-term L-arginine supplementation improves small-vessel coronary endothelial function in humans. Circulation 1998;97:2123–8.

104. Dzavík V, Cotter G, Reynolds HR, et al, for the SHOCK-2 Investigators. Effect of nitric oxide synthase inhibition on haemodynamics and outcome of patients with persistent cardiogenic shock complicating acute myocardial infarction: a phase II dose-ranging study. Eur Heart J 2007;28:1109–16.

105. Mosca L, Linfante AH, Benjamin EJ, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. Circulation 2005;111:499–510.

106. Abuful A, Gidron Y, Henkin Y. Physicians' attitudes toward preventive therapy for coronary artery disease: is there a gender bias? Clin Cardiol 2005;28:389–93.

107. Chou AF, Scholle SH, Weisman CS, Bierman AS, Correa-de-Araujo R, Mosca L. Gender disparities in the quality of cardiovascular disease care in private managed care plans. Womens Health Issues 2007;17: 120–30.

108. Gu Q, Burt VL, Paulose-Ram R, Dillon CF. Gender differences in hypertension treatment, drug utilization patterns, and blood pressure control among U.S. adults with hypertension: data from the National Health and Nutrition Examination Survey 1999—2004. Am J Hypertens 2008;21:789–98.

109. Bird CE, Fremont AM, Bierman AS, et al. Does quality of care for cardiovascular disease and diabetes differ by gender for enrollees in managed care plans? Womens Health Issues 2007;17:131–8.

110. Witt BJ, Jacobsen SJ, Weston SA, et al. Cardiac rehabilitation after myocardial infarction in the community. J Am Coll Cardiol 2004;44: 988–96.

111. Suaya JA, Shepard DS, Normand SL, Ades PA, Prottas J, Statson WB. Use of cardiac rehabilitation by Medicare beneficiaries after myocardial infarction or coronary bypass surgery. Circulation 2007; 116:1653–62.

112. Evenson KR, Rosamond WD, Luepker RV. Predictors of outpatient cardiac rehabilitation utilization: the Minnesota Heart Surgery Registry. J Cardiopulm Rehabil 1998;18:192–8.

113. Thomas RJ, Miller NH, Lamendola C, et al. National Survey on Gender Differences in Cardiac Rehabilitation Programs. Patient characteristics and enrollment patterns. J Cardiopulm Rehabil 1996; 16:402–12.