Cardiovascular Disease in Women

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Learning Objectives

1. Evaluate the impact of sex on morbidity and mortality from cardiovascular disease (CVD).
2. Evaluate cardiovascular risk factors to determine their relative importance in women versus men.
3. Assess the impact of gender-based biases on CVD morbidity and mortality in women.
4. Distinguish sex-based differences in cardiovascular pathophysiology, presentation, and diagnosis.
5. Formulate an opinion regarding CVD treatment disparities between men and women.
6. Apply knowledge of pharmacokinetic differences between men and women to minimize adverse drug events.
7. Apply current literature regarding treatment effectiveness in women who have coronary artery disease, with special consideration given to aspirin therapy.
8. Detect specific differences in evidence-based treatment guidelines between men and women.
9. Design an optimal pharmaceutical care plan for a woman with CVD.

Introduction

Cardiovascular disease (CVD) annually claims the lives of almost as many women in the United States as the next five leading causes of death combined. For this reason, the disease has emerged as a leading women's health issue. The pathophysiology and morbidity of ischemic heart disease differ significantly between the sexes, and it should not be assumed that all disease outcomes and treatment strategies are equivalent. The innate differences between men and women result in differences in CVD risk, presentation, diagnosis, morbidity, mortality, and treatment. Research has indicated a disparity in diagnosis, use of medical and interventional therapy, and prognosis in women. Compared with men, women are underprevented, underdiagnosed, undertreated, and understudied with respect to ischemic CVD (Box 1-1).

Unfortunately, many areas of CVD remain largely unexamined for sex-based differences, including heart failure, atrial fibrillation, peripheral vascular disease, and cerebrovascular disease. Because of the paucity of sex-specific data on many common CVDs, the chief focus of this chapter is on aspects of ischemic heart disease.

Sex-Related Differences and Gender Bias

An estimated 66,000 more women than men die each year after myocardial infarction (MI) and cardiovascular interventions. Women not only experience higher mortality rates but also poorer outcomes than men. Reasons for the different outcomes are controversial, and the argument centers on the relative contributions of true sex-related differences and gender-related biases.

Baseline Knowledge Resources

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Pilote L, Dasgupta K, Guru V, Humphries KH, McGrath J, Norris C, et al. A comprehensive view of sex-specific issues related to cardiovascular disease. CMAJ 2007;176:S1–S44.
- Huxley VH. Sex and the cardiovascular system: the intriguing tale of how women and men regulate cardiovascular function differently. Adv Physiol Educ 2007;31:17–22.
- Bellasi A, Raggi P, Merz CN, Shaw LJ. New insights into ischemic heart disease in women. Cleve Clin J Med 2007;74:585–94.

Abbreviations in This Chapter

ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
AHA	American Heart Association
BP	Blood pressure
CVD	Cardiovascular disease
ECG	Electrocardiography
FRS	Framingham risk score
GPI	Glycoprotein IIb/IIIa inhibitor
HDL	High-density lipoprotein
hsCRP	High-sensitivity C-reactive protein
LDL	Low-density lipoprotein
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
WHS	Women's Health Study
WISE	Women's Ischemia Syndrome Evaluation

Sex-related effects result from true biologic differences such as structural and functional differences in the coronary systems of men and women. Table 1-1 summarizes the numerous anatomic and physiologic differences between male and female cardiovascular systems. In contrast, gender-related bias stems from psychosocial roles and behaviors imposed by society. For example, bias may manifest as delayed referral for treatment of an acute coronary syndrome (ACS) (referral bias). The impact of these influences, both individually and as a composite, is not fully known. Evidence suggests that both contribute to the increase in morbidity and mortality from CVD in women. Gender bias can be modified through education; however, biologic differences between the sexes will remain.

Sex-Related Risk of CVD

Risk Awareness

Women, more so than men, are likely to underestimate the impact of CVD risk on their health. Surveys indicate that most women drastically underestimate their risk of heart disease. Although 51% of women in a 2004 survey believed breast cancer to be a greater health threat than CVD, only 1 in 30 women die of this cancer, whereas 1 in 3 die of CVD. Data from the Women Veterans Cohort revealed that 42% of women older than 35 were concerned about heart disease, although only 8% to 20% recognized heart disease as the major health threat for women.

Educational initiatives focused on increasing awareness (e.g., Go Red for Women campaign, The Heart Truth) have been somewhat successful in increasing the percentage of women correctly identifying heart disease as the leading cause of death for women. However, minority women and those with no college education underestimated their personal risk of disease in 2005 surveys. Furthermore, a recent American Heart Association (AHA) study found that although women recognized CVD as a leading cause of death, few were able to name the major risk factors associated with the disease.

Risk Factors

Women with both traditional and emerging risk factors should be assessed for initiation of primary prevention strategies including lifestyle interventions, pharmacotherapy, or a combination of the two. Although women share the same overall risk factors for developing CVD as do men (i.e., age, ethnicity, and family history), certain risk factors may exert greater overall risk for women (e.g., diabetes, dyslipidemia, hypertension). In addition, inflammatory markers suggesting risk of disease, such as high-sensitivity C-reactive protein (hsCRP), are higher in women at baseline than in men. The clinical implications of this biomarker with respect to a woman's risk are not fully understood. At this time, risk factor management strategies are virtually identical for the two sexes. Future research may provide more sex-specific prevention strategies.

Diabetes

Women with diabetes are 3–7 times more likely to develop or die of coronary heart disease than women without diabetes. This is much higher than the 2- to 3-fold increased risk experienced by men with diabetes. Women with diabetes have substantially worse short- and long-term prognosis after MI; they experience a higher risk of death, reinfarction, and heart failure than men. Mortality from heart disease in the 1990s declined in women without diabetes by 27%. Paradoxically, it increased in women with diabetes by 23%. Recent data from the National Health and Nutrition Examination Surveys support this earlier finding and suggest that all-cause and CVD mortality has declined in men with diabetes, yet the mortality rates between women with diabetes and women without diabetes have doubled. The reasons for these substantial differences are unknown, and no strategies are available to address this disparity.

Dyslipidemia

Certain lipid components or lipoproteins may pose a greater risk in women than in men and may provide a different target for risk modification. Compared with men, low-density lipoprotein (LDL) cholesterol is lower, on average, and high-density lipoprotein (HDL) cholesterol is higher in premenopausal women. After menopause, LDL cholesterol concentrations rise and HDL cholesterol concentrations decline in women.

An elevated LDL cholesterol and total cholesterol are predictive of coronary risk in men. In contrast, a low HDL cholesterol and higher triglyceride concentration may have greater predictive potential in women than in men.

Box 1-1. Overview of Major Disparities in CVD Between Men and Women

Underprevented
Women are less likely to be identified as high risk
Certain risk factors (e.g., diabetes, hypertension, depression) exert a greater overall risk for women, yet the same prevention strategies are recommended without respect to sex
Women are less likely to enroll in secondary prevention programs such as cardiac rehabilitation because of personal barriers such as lack of time and family obligations
Underdiagnosed
Women are more likely to complain of middle or upper back pain, neck pain, jaw pain, nausea or vomiting, weakness or fatigue, paroxysmal nocturnal dyspnea, shortness of breath, dizziness, and palpitations at acute coronary syndrome presentation
Women are less likely to receive electrocardiography when presenting to the emergency department
Women are referred for cardiovascular diagnostic tests less often
Noninvasive testing has a lower predictive accuracy in women
Women have a higher incidence of silent MI
Undertreated
Women are more likely to attribute their symptoms to noncardiac causes and thus delay seeking medical treatment
Women are less likely to be admitted to telemetry floors
Women are less likely to be treated by a cardiologist for MI during hospital admission
Women receive less evidence-based pharmacotherapy for secondary prevention
Women are less likely to be referred to percutaneous or coronary artery bypass intervention
Women with chest pain are more likely to be found with nonobstructive coronary disease and are considered at lower risk of future cardiovascular events
Understudied
Women remain underrepresented in clinical trials
Women are less likely to be willing participants in clinical research trials
Underappreciated differences
Women underappreciate the impact of CVD on their health
Women are usually older and have more comorbid conditions at the time of presentation
Women are more likely to present with unstable angina than MI, which is more common in men
Women are more likely to have adverse outcomes (e.g., bleeding from invasive procedures)
Women have a different coronary artery pathophysiology than men, which may lead to misdiagnosis or delay in treatment
Short- and long-term mortality rates after MI are greater for women
Social and sociocultural factors may have a greater negative impact on morbidity and mortality in women
Women with heart failure report more symptoms compared with men with heart failure
For primary prevention with aspirin, women derive more protection against stroke and less protection against MI than men

CVD = cardiovascular disease; MI = myocardial infarction.

Information from Mosca L, Banks CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, et al; for the American Heart Association. Evidence-based guidelines for cardiovascular disease prevention in women. Circulation 2007;115:1481–501; and Lansky AJ, Hochman JS, Ward PA, Mintz GS, Fabunmi R, Berger PB, et al. Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association. Circulation 2005;111:940–53.

Table 1-1. Sex-Related Differences in the Cardiovascular System

Parameter	Manifestations
Anatomy	• Dimensions that are smaller in women (adjusted for age and race): left ventricular mass, ventricular wall thickness, left atrial dimension, left ventricular end-diastolic dimension, and vessel size
Hormonal influences	• Estrogen and progesterone are most influential in women; testosterone is predominant in men • Menstruation can affect hematologic and electrocardiographic indices
Cardiovascular function	• Stroke volume in women is 10% less • Pulse rate in women is 3–5 beats/minute faster • Ejection fraction is higher in women
Physiology	• Women have reduced sympathetic and enhanced parasympathetic activity • Women have lower plasma concentrations of norepinephrine
Cardiovascular adaptations	• In response to stress, women experience an increased pulse rate, resulting in increased cardiac output; men increase vascular resistance, resulting in increased blood pressure • Women are more sensitive to altitude or body positioning changes and experience more orthostatic hypotension and syncope
Hematologic indices	• Women have a lower number of circulating red blood cells per unit volume of plasma (resulting in a lower hematocrit) • Because of a lower hemoglobin, women have a lower oxygen-carrying capacity; this is balanced by women having a lower oxygen consumption
Electrocardiographic and electrophysiologic indices	• Women on average have a longer corrected QT interval and a shorter sinus node recovery time • Drug-induced torsades de pointes is more common in women • Sudden cardiac death and atrial fibrillation are less common in women

Information from Huxley VH. Sex and the cardiovascular system: the intriguing tale of how women and men regulate cardiovascular function differently. Adv Physiol Educ 2007;31:17–22.

Epidemiologic data suggest that increased HDL cholesterol concentrations in women confer greater protection from CVD than for men.

Recent research in raising HDL cholesterol by means of the cholesterol ester transfer protein inhibitor showed initial promise; however, a significant increased risk of cardiovascular events and death in patients receiving torcetrapib halted further drug development. Still, genetic studies have shown an association between the cholesterol ester transfer protein and future risk of MI, supporting continued investigation in this area.

Two other products, dalcetrapib and anacetrapib, are presumed to have safer adverse effect profiles and are in phase II and phase III studies. Whether the effect of an intervention to raise HDL cholesterol on cardiovascular events will differ in men and women is unknown at this time.

Elevated triglycerides are a risk factor for CVD in men and perhaps even more so in women. Meta-analysis of 17 prospective population-based studies revealed a 37% increased risk of CVD events in women with higher concentrations of triglycerides compared with a 14% increased risk in men. Randomized clinical trials have not shown a consistent reduction in mortality by lowering triglycerides in men and women, yet subgroup analyses of a prospective study using fenofibrate suggest that triglyceride lowering in this manner decreases total cardiovascular events in women but not men. Outcomes data are not robust enough at this time to warrant sex-specific treatment recommendations for hypertriglyceridemia.

Hypertension

Hypertension is a common modifiable risk factor for both CVD and cerebrovascular disease, to which women are particularly susceptible. The prevalence of hypertension in women exceeds that in men by the sixth decade of life. The disease is more prevalent and severe in women of African American descent than any other ethnic group.

Prehypertension, defined as a blood pressure (BP) of 130–139/84–89 mm Hg, is associated with a 2.5 higher risk of cardiovascular death, MI, stroke, and heart failure in women, whereas it confers only a 1.6 greater risk in men. These findings underscore the importance of recognizing and treating hypertension in women, especially because lower rates of BP control are achieved in women than in men. Postmenopausal, elderly, and Mexican American women have the lowest rates of BP control. Although an individual's sex has an important influence on hypertension, the effectiveness of antihypertensive therapies does not differ between men and women despite the increased risk found in women.

Sex-specific factors influencing hypertension in women include their shorter stature and arterial tree, which result

in faster pulse rates and lower diastolic BP. Women with hypertension are at a greater risk of developing left ventricular hypertrophy and symptomatic heart failure with preserved ejection fraction than are men. After menopause, women experience a steep age-related stiffening of the arterial wall. Estrogen's influence on the vasculature includes maintaining endothelial function through nitric oxide production and reduction in sympathetic nervous system activity. Estrogen also reduces plasma renin and angiotensin-converting enzyme (ACE) activity. Furthermore, salt sensitivity increases after the loss of estrogen through menopause or ovariectomy. Dietary factors therefore become a more important influence over BP control after menopause and may explain some of the differences in BP control rates between the sexes.

White-Coat Hypertension

White-coat hypertension is defined as a BP greater than 140/90 mm Hg in the clinic but less than 135/85 mm Hg by ambulatory BP monitoring. White-coat hypertension is present in around 20% of all patients with untreated hypertension and is more common in women than in men. This sex-related difference may be attributable to the faster resting pulse rates in women. Anxiety-induced tachycardia may increase systolic BP in the brachial arteries while maintaining normal carotid and aortic pressures in women. An area for future research is whether ambulatory BP measurements are of benefit in the diagnosis and treatment outcomes for women with hypertension.

Depression

In addition to traditional cardiovascular risk factors, psychosocial risks may contribute significantly to the pathogenesis of CVD in both men and women. Depression, the most common psychological disorder, is twice as common in women as in men. Depression is associated with as much as a 70% increased risk of CVD, making it a major risk factor for women. Furthermore, patients who have coronary heart disease coupled with depression may have a worse prognosis than those without depression.

Depression may increase a woman's risk of CVD by elevating atherosclerotic and inflammatory biomarkers, reducing pulse rate variability, impairing the hypothalamic-pituitary-adrenal axis and vascular function, and enhancing platelet activation. Depression increases the risk of drug nonadherence and contributes to behavioral risk factors associated with CVD, such as smoking, poor diet, and physical inactivity, with physical inactivity more common in women. Because depression contributes to the overall risk of CVD in women, a recommendation for primary prevention in women includes screening for depression. Women were uniquely identified over men as candidates for depression screening as a primary prevention strategy until the 2008 publication of the AHA Depression and Coronary Heart Disease Advisory. Currently, both men and women with heart disease are recommended to receive screening, referral, and treatment for depression. Studies are needed to address whether antidepressant therapy can offset some of the increased mortality in women with depressive symptoms.

Obesity, Physical Inactivity, and Metabolic Syndrome

Obesity, physical inactivity, and metabolic syndrome are important risks contributing to cardiovascular morbidity and mortality. In the United States, the prevalence of obesity and metabolic syndrome is similar between men (33.3% and 34.4%, respectively) and women (35.3% and 34.5%, respectively); however, meta-analyses of prospective studies have concluded that metabolic syndrome confers a greater overall cardiovascular risk in women, who have a 30% higher relative risk than men. The risk associated with physical inactivity is comparable with that observed for hypertension, dyslipidemia, or cigarette smoking. Yet physical inactivity is reportedly higher in women (12%) than in men (8.4%), and women are less likely than men to engage in vigorous exercise (33.3% vs. 44%).

Lifestyle factors contribute significantly to the overall risk of developing coronary events in both sexes, yet women have been observed in epidemiologic studies to be more sensitive to favorable changes in diet, exercise, and alcohol. Future research should focus on lifestyle interventions and their impact on mortality as related to sex.

Surgical and Pregnancy-Induced Risks

An emerging risk factor for CVD of unique significance to women is a history of pregnancy-related problems. The presence of hypertension and diabetes in pregnancy may indicate a higher risk of CVD as women age. Women with preeclampsia/eclampsia during pregnancy are significantly more likely to develop hypertension and cerebrovascular disease later in life. In addition, women who experience abruption and infarction of the placenta, poor fetal growth, or intrauterine fetal death have a subsequently higher risk of CVD events.

These pregnancy-related problems are attributable to many factors, yet they seem to share endothelial dysfunction, perhaps indicating premature vascular disease in the woman. Although not included in any CVD risk-scoring systems, these pregnancy-related risks may be an important consideration in assessing a woman's risk of developing CVD. Finally, women who undergo surgical menopause (hysterectomy with simultaneous bilateral oophorectomy) before natural menopause have been reported to be at higher risk of a future cardiovascular event, presumably because of premature loss of estrogen's protective effects.

Cardiovascular Risk Equations for Women

Framingham Risk Assessment

Because men and women differ in their risk of CVD, researchers have sought risk equations suitable to predict the risk of CVD in women. The historical standard, originally formulated in 1976, is the Framingham risk score

(FRS), which estimates the patient's probability of experiencing a coronary artery disease event during a 10-year period. Although an FRS greater than 20% can accurately identify a woman at high risk, a lower score has the potential to underestimate a woman's true risk of a CVD event.

According to the Framingham cohort and offspring data, 98% of asymptomatic women younger than 59, and 92% of those age 60–69, would be classified as low risk. A woman younger than 70 would be unlikely to score high enough to qualify for targeted pharmacotherapy for cardiac risk reduction. This age-related bias of the FRS precludes women with subclinical CVD from receiving earlier, more beneficial, intensive preventive therapy. Other limitations of the FRS specific to women's risk include no consideration of family history, ethnicity, presence of the metabolic syndrome or its components, CRP concentrations, and hysterectomy status.

The FRS, originally designed to predict only CVD events, may inaccurately predict the risk of CVD in women affected earlier in life by stroke, angina, and heart failure instead of coronary events (e.g., sudden cardiovascular death, MI). Data from the Framingham study demonstrated that the first manifestation of CVD is MI in 51% of men and only 44% of women. In the Women's Health Study (WHS), women experienced strokes as first events more commonly than coronary events, underscoring the variation between men and women. When using the FRS to evaluate cardiovascular risk in women, the practitioner must be aware of its limitations.

Primary Prevention Risk Stratification

It is essential to evaluate younger women accurately for their broad spectrum of disease risk. Although CVD is responsible for the deaths of more women older than 65 than men of a similar age, the risk of disease is not limited to older women. Cardiovascular disease is the third leading cause of death in women between age 25 and 45. Estimating lifetime risk may be more important in younger women than in older individuals: the presence of one risk factor at age 50 years is associated with an increased lifetime risk and shorter duration of survival from CVD.

Data from the Framingham Heart Study indicate that the lifetime risk of CVD for healthy women is about 32% at age 40 and about 39% at age 50. This latter percentage exceeds the lifetime risk of breast, lung, and colorectal cancers combined. Furthermore, although more men than women experience sudden cardiac death, two-thirds of women who die suddenly have had no previous symptoms of coronary disease, compared with about 50% of men. These facts underscore the importance of recognizing primary prevention strategies early in a woman's life and assessing a woman's risk beyond a 10-year period.

The AHA's Primary Prevention of CVD in Women Guideline provides a risk assessment alternative to the FRS. The guideline may overcome some of the limitations of the FRS such as addressing a woman's lifetime risk, including a broader assessment of risk factors, and advocating for an earlier and more aggressive approach to lifestyle modification. For example, smoking is the only lifestyle factor included in the FRS. A middle-aged woman with unhealthy lifestyle habits alone would therefore have a low predicted 10-year risk, according to the FRS, and might not receive adequate education on future cardiovascular health and risk modification. Recognizing the limitations of the FRS among women with unhealthy lifestyle habits is important for aggressive risk reduction.

A second improvement with the Primary Prevention Risk Assessment is the assessment of lifetime risk compared

Table 1-2. Lifetime Risk Stratification for the Primary Prevention of CVD in Women

Optimal Risk	At Risk	High Risk
• 10-year Framingham global risk score < 10% AND • Healthy lifestyle AND • No risk factors	1 or more of the following: • Smoking • Poor diet • Inactivity • Obesity • Family history of early CVD • Hypertension • Hyperlipidemia • Subclinical vascular disease (i.e., abnormal coronary artery calcium scores and/or carotid intima-media thickness, and high ankle-brachial index) • Poor exercise capacity on a treadmill test • Abnormal pulse rate recovery after exercise	Any one of the following: • Established coronary heart disease • Cerebrovascular disease • Peripheral artery disease • Abdominal aortic aneurysm • Hemodialysis or peritoneal dialysis • Chronic kidney disease • Diabetes • 10-year Framingham global risk score > 20%

CVD = cardiovascular disease.

Adapted from Mosca L, Banks CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, et al; for the American Heart Association. Evidence-based guidelines for cardiovascular disease prevention in women. Circulation 2007;115:1481–501.

Table 1-3. Comparison of Current Assessments for Estimating a Woman's Risk of CVD

	Framingham Risk Score	Primary Prevention Risk Assessment	Reynolds Risk Score	Recalibrated Framingham Risk Assessment
Risk prediction	10 year	Lifetime	10 year	10 year
Events predicted	MI, cardiovascular death	Any cardiovascular event	Global CVD events including MI, stroke, cardiovascular death, and cardiovascular revascularization	Global CVD events and/or individual specific events including coronary heart disease, stroke, peripheral artery disease, or heart failure
Parameter assessment	Age, smoking status, sex, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension (FRS criteria)	Any known risk assessed by FRS criteria or other major risk factor for CVD not included in FRS (obesity, metabolic syndrome) or any evidence of subclinical disease (i.e., coronary calcification); see Table 1-3	FRS criteria, family history of CVD, hsCRP, and A1C (in women with diabetes)	FRS criteria and diabetes status
Applicable population	Men and women > 20 years	Women > 20 years	White women > 45 years	Men and women aged 30–74 years
Research population	Framingham population: 2489 men and 2856 women, African Americans and whites in the United States with 12 years' follow-up	Not derived from a single study population	Women's Health Study; 24,558 women (95% white) age 45 and older; median follow-up = 10.2 years	8491 Framingham study participants (4522 women); African Americans and whites in the United States; more than 12 years' follow-up

CVD = cardiovascular disease; FRS = Framingham risk score; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; MI = myocardial infarction.

with the shorter 10-year risk offered by the FRS. Table 1-2 outlines the lifetime risk stratification endorsed by the AHA Primary Prevention Guideline for women. This risk assessment tool places women into one of three categories: high risk, at risk, or optimal lifetime risk. This framework considers factors in the FRS and additional information necessary to predict more accurately the risk of lifetime cardiovascular events.

The AHA guideline may better estimate a woman's risk of cardiovascular events because of the inclusion of lifestyle factors, family history, premature CVD, and subclinical evidence of vascular disease. Cardiovascular performance measured by exercise capacity and pulse rate recovery during stress testing is also a component of the Primary Prevention Risk Assessment. The presence of one of the above-mentioned risks would indicate the woman is at risk of a CVD event at some point in her life. This at-risk indication, as suggested by the Primary Prevention Guideline, would provide the clinician more flexibility to aggressively treat a woman with multiple marginal cardiometabolic risk factors, which become important over a lifetime even though the shorter-term 10-year risk may not be increased. In contrast, practitioners using the Third Adult Treatment Panel may defer pharmacotherapy for hyperlipidemia until a high-risk FRS status is achieved.

Other Risk Assessments

Other risk assessment scoring evaluations specific to women are undergoing exploration and validation (Table 1-3). The Reynolds risk score was developed from the WHS, which observed almost 25,000 women age 40 and older for 10.2 years for incident stroke and coronary heart disease events, plus other outcomes including revascularization. After 35 risk factors were carefully examined, two particular risk factors beyond those included in the FRS were found to add greater predictability for CVD events. When hsCRP and family history were added to the risk algorithm, 30% of women without diabetes and 45% more women with diabetes were classified as higher or lower risk with improved accuracy. Similar to the FRS, the Reynolds model predicts only 10-year risk. Other limitations of this risk assessment tool include the narrow population studied

(95% white). Therefore, this tool's usefulness cannot be extrapolated to women from different ethnic groups.

In addition, a recalibrated FRS has been suggested to predict 10-year risk of cerebrovascular events, peripheral artery disease, and heart failure, as well as coronary events such as sudden cardiac death and MI. Whether routinely incorporating these additional risk equations into decision-making will result in a reduction of a woman's morbidity and mortality is unknown. These newer risk assessments remain to be validated in diverse groups of patients as well as compared directly with other tools to determine the most accurate mechanism for assessing a woman's risk. Based on the health threat of CVD in women, using a lifetime risk assessment appears most appropriate.

CVD Among Women

Disease Presentation

Compared with men, women usually present with CVD at an older age and with more comorbid conditions. The complex and multifactorial presentations have led to diagnostic confusion and misdiagnosis, which may explain the poorer outcomes in women. Men present more often with ST-segment elevation MI (STEMI), whereas women more commonly present with non–ST-segment elevation ACS without elevation of troponin concentrations. As a group, women have a higher incidence of unrecognized or silent MI than men.

Evidence suggests that a difference in pain perception exists between the sexes, which might explain some of the variability in presenting symptoms. Commonly, both men and women with ACS present with chest pain; however, women are more likely than men to present with so-called atypical symptoms (e.g., dyspnea, shortness of breath, indigestion, middle or upper back pain, paroxysmal nocturnal dyspnea, indigestion, nausea and vomiting, unexplained weakness and fatigue, a sense of doom). Retrospective data have documented prodromal symptoms in women including unusual fatigue, anxiety, or sleep disturbances reported hours to days before the development of ACS symptoms.

Failure to recognize the presenting symptoms of CVD by both the patient and the physician may contribute to referral bias, a delay in aggressive medical treatment in women. Because women are more likely to attribute their symptoms to noncardiac causes further complicates timely treatment. In most studies of ACS, women have delayed seeking help for their acute symptoms longer than men. In one large cohort, a delay of more than 4 hours from the onset of ACS symptoms to hospital arrival occurred in 34% of women and only 27% of men. After hospital arrival, men were treated an average of 7 minutes earlier than women.

Other disparities at ACS presentation are evident. For women, these include a lower likelihood of hospitalization compared with men (2 times less likely if older than 55 and 7 times less likely if younger than 55), less likely to have electrocardiography (ECG), and less likely to have care by a cardiologist (53% vs. 63%) during hospitalization for ACS.

Because treatment delays can increase mortality, educating women at risk of disease is essential. Time delays and presenting circumstances make the diagnosis of CVD in women more challenging than in men. The clinician must weigh the likelihood of CVD based on vague symptoms and the unique risks of the woman. The effect of these disparities on women's outcomes after ACS is unknown.

Disease Findings

Anatomic and physiologic differences between the sexes contribute to the idea that heart disease is different in women and men. The degree of sex-related disparities associated with coronary artery disease has only recently been characterized and has yet to be addressed in a significant manner that affects outcomes. The findings of the National Institutes of Health (NIH)-sponsored Women's Ischemia Syndrome Evaluation (WISE) study group have contributed to the understanding of some of these differences.

Ischemic heart disease in women is characterized by structural and functional differences in the coronary vasculature compared with men. Women present with more diffuse coronary disease and have fewer obstructive lesions. Data from WISE indicated that almost half of all women presenting with anginal pain had nonobstructive or almost normal-looking arteries at the time of angiography.

Despite a lack of flow-limiting disease in the epicardial coronary arteries, women with persistent chest pain fared worse than women without continued pain. A significantly higher combined end point of death, MI, stroke, and heart failure occurred in women with persistent angina (14.4% vs. 8.5%) at 4 years. Traditionally, in the absence of obstructive disease, these women would be considered at low risk; thus, they might not receive aggressive therapies for primary prevention or even stable angina. Yet in WISE, a 9.4% absolute risk of MI or death was apparent in women with minimal or no obstructive disease on undergoing angiography at the 4-year follow-up. An important clinical point from WISE is that regardless of near-normal coronary angiographic findings, women with angina should be considered at risk.

Other differences include the finding that younger women are more prone to plaque erosion (nonruptured erosions of plaque that contribute to thrombus formation), whereas older women and men are more likely to present with plaque rupture. A subset of women in the WISE study underwent intravascular ultrasonography, which demonstrated intramural atherosclerosis in women rather than the traditional protrusion of plaque into the coronary lumen. Magnetic resonance imaging has further documented subendocardial myocardial ischemia in women. Endothelial dysfunction, underlying microvascular disease, and inflammation-mediated atherosclerosis may be a cause of angina-like chest pain in women without angiographic evidence of obstructive artery disease.

Based on these findings, a heightened awareness of the differing disease pathology is necessary if all women at risk are to be identified and treated. Future research must focus on the differences between men and women in pathophysiology of coronary artery disease, with emphasis on vascular and endothelial dysfunction. Given that sex-specific strategies to reduce mortality are unavailable, research in this area is of utmost importance.

Diagnostic Testing Challenges

Noninvasive exercise testing is an inexpensive tool that is helpful in the diagnosis and evaluation of coronary disease. However, traditional tests used to identify evidence of obstructive coronary disease (e.g., the exercise tolerance test) are less sensitive and specific in women. Although the false-negative rate is comparable with that in men, higher false-positive rates make the test less accurate for women.

The proposed theories for the sex-related difference in accuracy include less obstructive disease, lower pulse rate responses to exercise, and the effect of estrogen on the ST segment in women. Regardless of the accuracy rates, exercise testing is commonly undertaken in women, and the pretest probability of disease should be considered if this strategy is used. For women with a low probability of disease, higher false positives from exercise testing might increase recommendations for unnecessary invasive workups, although several studies have suggested that women with positive stress tests are examined less aggressively than their male counterparts.

The addition of scores obtained from noninvasive coronary artery calcium screening improves the predictability of disease events over traditional risk factors alone in both women and men, yet some evidence suggests that women have a greater risk of events than do men at each level of calcification. Even though coronary artery calcium scoring may be an additional tool to quantify subclinical atherosclerosis, there is controversy about how to use the information in treatment decisions, especially whether patients with high calcium scores but no other symptoms would benefit from invasive strategies.

Prognosis and Treatment Outcomes

Cardiovascular death rates have decreased 35% to 50% during the past 20 years because of advances in the diagnosis and treatment of heart disease, yet the reductions obtained in women do not match those in men. Accumulated data show that in the setting of obstructive coronary disease, women have an overall worse prognosis than men. Short- and long-term mortality rates from MI are greater for women than for men regardless of age or comorbidity. The risk of subsequent MI, heart failure, and death is substantially higher in women.

Based on 2009 AHA statistics, 23% of women 40 and older will die within 1 year of MI compared with 18% of men. Within 5 years of MI, 43% of women older than 40 will die compared with only 33% of men. Registry data indicate women younger than 75 contribute significantly to the sex-related disparity in mortality after an MI, whereas a woman older than 75 who experiences an MI has the same risk of death as a man. In terms of morbidity, the sex-related disparity is still evident; significantly more women will have a stroke or develop heart failure than men after an MI. The heart failure experienced after an MI is more often debilitating for women despite preserved ejection fraction. The many sex-specific differences in heart failure are outlined in Table 1-4.

Several factors may contribute to the prognostic difference between the sexes after ACS. As previously discussed, women are generally older and present with more comorbid conditions such as diabetes and hypertension. Women have an increased risk of complications (e.g., reinfarction, death, heart failure, stroke, need for transfusion) during hospitalization for ACS than their male counterparts. Furthermore, outcomes between the sexes may be influenced by referral

Table 1-4. Sex-Specific Heart Failure Findings

Comorbidities and Disease Findings	Laboratory Findings	Medication Concerns
Women with heart failure are more likely to have hypertension	B-type natriuretic peptide values > 500 pg/mL have been observed to be stronger predictors of mortality in women than in men	Most trials for heart failure caused by systolic dysfunction have not evaluated treatments in a sex-specific fashion
Women with heart failure are more likely to have preserved left ventricular function		
Women with decompensated heart failure are more commonly found with thyroid disease		Meta-analyses suggest mortality reductions in women treated with ACE inhibitors and β-blockers for systolic dysfunction
Women with heart failure have a lower quality of life than men with heart failure		
Retrospective data from SOLVD suggest women are at increased risk of thromboembolic events associated with heart failure		

ACE = angiotensin-converting enzyme; SOLVD = Studies of Left Ventricular Dysfunction (trial).

bias. Finally, the sex-based differences in the pathophysiology of the disease also contribute to the prognostic differences between men and women. Efforts should focus on reducing the variability in the application of life-saving ACS treatments while research explores targeted therapeutic strategies based on sex.

Treatment Disparity Among Men and Women

Interventional Therapies

Percutaneous Coronary Intervention

One common finding worldwide is the underuse of proven interventional and medical therapy for CVD in women. In the United States, only one-third of the 1.6 million percutaneous coronary intervention (PCI) surgical procedures performed each year are in women. Despite the lower use of PCI in women, risk-adjusted analyses of short- and long-term outcomes indicate high-risk women derive benefits similar to men from this procedure. This finding from a highly effective and widely used intervention is encouraging. Nonetheless, women have a higher incidence of bleeding and vascular complications; therefore, a careful assessment of the risk-to-benefit ratio of an invasive strategy must be undertaken when PCI is considered.

According to one meta-analysis of 12 PCI trials, vascular complications such as bleeding occurred 1.5–4 times more often in women than in men. Because of the higher risk of morbidity from vascular complications, the benefit from PCI in women with ACS may be limited to only the highest-risk women (e.g., women with elevated troponin concentrations). The 2007 Unstable Angina/Non–ST-segment Myocardial Infarction (UA/NSTEMI) guideline supports a conservative strategy in women with low-risk features and an earlier invasive strategy for women with higher risk (i.e., positive biomarkers).

Coronary Artery Bypass Graft

Women account for about one-third of patients undergoing coronary artery bypass graft surgery in the United States. Unfortunately, they derive less symptom relief and have lower functional gains after surgery than men. Women undergoing coronary artery bypass graft differ from men in baseline comorbid conditions, referral patterns, procedural characteristics, and postoperative care; women have historically been reported to have higher risks from surgery than men. Recent data have suggested certain procedural factors to benefit survival and long-term graft patency, especially in women. These include the use of internal thoracic artery graft and off-pump procedures.

After coronary artery bypass graft, women have significantly lower referral and attendance rates for cardiac rehabilitation and have been reported to have higher readmission rates than men. The influence of sex on contemporary outcomes after coronary artery bypass graft should be explored through further research.

Pharmacotherapy

Use of Evidence-Based Pharmacotherapy

Similar to the underuse of interventional procedures and surgery, women with ACS have received less evidence-based drug therapy than their male counterparts. Before primary PCI was available for acute MI, studies showed that women were less likely to undergo fibrinolysis but that, when they did, they experienced a larger number of adverse events from the therapy.

Unfortunately, despite great advancements in the field, treatment still differs between women and men. Recent data from ACS registries within the United States show that at time of admission, women are less likely to receive heparin, an ACE inhibitor, or glycoprotein IIb/IIIa inhibitor (GPI), even when elevated troponin values are documented. Furthermore, at time of discharge, women are less likely to be prescribed aspirin (87.5% vs. 90.4% in men) and statin therapy (55.9% vs. 63.4% in men). This is despite current guidelines indicating that women derive the same benefit as men from aspirin, clopidogrel, anticoagulants, β-blockers, ACE inhibitors, and statins.

Pharmacotherapy for chronic stable angina is also underprescribed in women, even though women are at a higher risk of 1-year cardiac events compared with their male counterparts. Data from the Euro Heart Survey of Stable Angina documented a statistically significant lower use of statins in women (45% vs. 51% in men). Use of aspirin was also lower in women (73% vs. 81% in men). These findings were apparent both initially and at 1 year after diagnosis of angina, with women receiving significantly less pharmacotherapy.

Alarmingly, even after adjustments for age, heart failure, diabetes, disease severity, and pharmacotherapy differences, women in this survey had double the rate of nonfatal MI and death compared with their male counterparts at 1-year follow-up. Increased awareness and lack of bias may improve adherence to guideline-based management for women. Whether application of guideline-based therapies to women results in improvement in clinical outcomes of coronary heart disease is an area for future research.

Medication-Related Adverse Events

Women experience more drug-related adverse events than men. The U.S. Food and Drug Administration, through its Adverse Event Reporting System, has noted that 53% of reported events from 1969 to 2002 concerned female patients, whereas only 35% were reported in male patients (12% did not report sex). Differences in body mass, volume of distribution, liver metabolism, and kidney function may account for differences in adverse effects from cardiovascular medications in women (Table 1-5).

Genomic research has shown a sex-based influence on gene expression that can contribute to both disease and drug response differences among men and women. The clinical importance of these differences should be the focus of future study.

Table 1-5. Sex-Based Differences in the Pharmacokinetic Response of Cardiovascular Drugs

Drug Absorption	Drug Distribution	Drug Metabolism	Drug Elimination
Differences include: • A 25% increased absorption of verapamil in women • A 40% increased absorption of aspirin in women	General differences include: • A larger percentage of body fat is found in women (resulting in lower serum concentrations of lipophilic medications) • Women have a smaller body water compartment, intravascular volume, and muscle mass (resulting in higher serum concentrations of hydrophilic medications)	Sex-specific CYP alterations include: • Drugs processed by CYP3A4 (e.g., amiodarone, amlodipine, atorvastatin, simvastatin, gemfibrozil, verapamil) are metabolized 20% to 40% faster in women than in men • The CP450 1A2 enzyme is more active in men than in women, affecting drugs such as clopidogrel and propranolol • Sex-specific data are limited with respect to metabolism of drugs by CYP2D6 and CYP2C9 (e.g., carvedilol, metoprolol, losartan, irbesartan, warfarin, rosuvastatin) Glucuronidation of drugs during phase 2 metabolism occurs more rapidly in men, speeding inactivation of epinephrine, norepinephrine, and dopamine	Age-adjusted glomerular filtration is about 20% lower in women

CYP = cytochrome P450.
Information from Spencer AP, Wingate S. Cardiovascular drug therapy in women. J Cardiovasc Nurs 2005;20:410–9.

Finally, when evaluating the risk of adverse effects between men and women, the prevalence of the use of specific drugs in women versus men should be carefully considered. Men are more likely to develop diuretic-induced gout, whereas women are more likely to develop diuretic-induced hyponatremia and hypokalemia. In clinical trials, amlodipine caused more peripheral edema in women (14.6% vs. 5.6% in men). Women are twice as likely to develop ACE inhibitor–induced angioedema compared with their male counterparts, and they have a 3-fold higher risk of an ACE inhibitor–related cough.

QT Prolongation

The incidence of life-threatening torsades de pointes triggered by drugs that alter cardiac repolarization occurs about twice as often in women as in men. There is a greater prevalence of drug-induced torsades de pointes in women with antiarrhythmics such as quinidine, disopyramide, ibutilide, and sotalol, as well as non-antiarrhythmic drugs such as haloperidol, erythromycin, thioridazine, and clarithromycin. Women have about 12% to 18% lower clearance rates of dofetilide than do men, even after correction for weight and creatinine clearance. Because of the higher risk of torsades de pointes when antiarrhythmic agents are prescribed to women, ensuring that serum potassium and magnesium concentrations are within normal limits and that the dosage has been appropriately adjusted for renally cleared agents such as dofetilide and sotalol are important clinical considerations.

The mechanisms responsible for the sex-related difference in risk of proarrhythmia may be related to the sex hormone influence on the cardiac myocyte. After puberty, the corrected QT interval shortens in men and, comparatively, a slower cardiac repolarization and a longer corrected QT interval are noted in women. Although not consistent in all research, women have demonstrated a greater QT prolongation during the first half of the menstrual cycle, when estrogen concentrations rise and peak just before ovulation. Ibutilide causes a heightened prolongation of the QT interval during the first half of the menstrual cycle. Furthermore, drug-induced QT prolongation can be potentiated by estradiol. In animal studies, sex hormone alteration of the rapidly activating delayed rectifier potassium current, the transient outward potassium current, and the L-type calcium current has been noted. The influence of progesterone and/or estradiol on these ion currents in humans is yet another area for further research.

Bleeding Complications

Bleeding risk is higher in women who receive fibrinolytic therapy or anticoagulants in the setting of PCI. When PCI is planned, special safety considerations should be given to anticoagulant dosing in women, particularly with renally cleared agents such as GPIs and low-molecular-weight

heparins. Data from the CRUSADE registry demonstrate that excessive dosing of GPIs was almost 3 times more common in women (46.4% vs. 17.2% in men). In general, women tend to be older, have a lower body weight, and have more comorbid conditions influencing kidney function. Without the proper assessment of kidney function by an estimation of creatinine clearance, excessive dosing is more likely to occur. Women had higher rates of major bleeding if treated with GPIs (15.8% vs. 7.3% in men) and even if a GPI was not given (8.5% vs. 5.4% in men). This indicates that some but not all of the excess bleeding risk in women was attributable to drug administration. Bleeding was significantly lower for both women and men who received proper dosage adjustment.

Data suggest similar results with fibrinolytics and enoxaparin, with independently higher risks of bleeding complications and potential death when these agents are used in women. The key to closing this sex-based gap is better characterization of the disparity and outcomes data regarding alternative management strategies in women. Enrolling a sufficient number of women in clinical trials powered to detect sex-based differences for this highly significant adverse effect is of utmost importance.

The model for obtaining sex-based dosing recommendations is available; the alternative dosing strategy for the elderly contained in the enoxaparin-prescribing information for STEMI is an example researchers should embrace for other populations at high risk of bleeding with anticoagulant therapies. Future research based on sex-specific and estimated creatinine clearance–based dosing may lead to an improved dosing strategy for enoxaparin and other antithrombotic agents in women.

Evidence-Based Treatment Guidelines

Enrolling a larger number of women in clinical trials has permitted the development of evidence-based guidelines specific to women. Three sets of guidelines have been devoted solely to the care of women and include an evidence-based guideline for CVD prevention, a scientific statement for PCI and adjunctive pharmacotherapy, and a scientific statement outlining the role of noninvasive testing in the clinical assessment of women with suspected coronary artery disease.

In addition, sex-specific subsections are included in the 2007 UA/NSTEMI guideline from the AHA and the American College of Cardiology. Furthermore, the eighth edition of the American College of Chest Physicians Evidence-Based Clinical Practice Guideline on antithrombotic therapy and the U.S. Preventive Services Task Force Guideline have sex-specific discussions with respect to aspirin therapy (Table 1-6). With few exceptions, the recommendations to prevent and treat CVD in women do not

Table 1-6. Evidence-Based Guidelines Specific for Women

Guidelines	General Recommendations
Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update	Provides a risk stratification system specific for women
	Recommends against using drug classes (e.g., those that block the renin-angiotensin-aldosterone system) in pregnancy or in women who plan to become pregnant
	Recommends against the use of hormone therapy for primary and secondary prevention of CVD in women
	Recommends the use of aspirin for primary prevention as an age- and sex-based approach[a]
2008 CHEST Guidelines	Recommends the use of aspirin for primary prevention as an age- and sex-based approach[a]
2009 U.S. Preventive Services Task Force	Recommends the use of aspirin for primary prevention as an age- and sex-based approach[a]
Percutaneous Coronary Intervention and Adjunctive Pharmacotherapy in Women (2005)	Medication recommendations do not differ by sex; however, unique risks of PCI in women are highlighted
Role of Noninvasive Testing in the Clinical Evaluation of Women with Suspected Coronary Artery Disease (2005)	Notes no major differences between the recommendations for diagnostic testing between the sexes
ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non–ST-Elevation Myocardial Infarction	Recommends a noninvasive, conservative strategy for women who present with low-risk features
	Notes that GPIs may lack efficacy in women without elevated troponin concentrations

[a]For a detailed comparison of evidence-based guidelines on the use of aspirin for the primary prevention of disease in women, see Table 1-7.
ACC = American College of Cardiology; AHA = American Heart Association; CVD = cardiovascular disease; GPI = glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction.

Table 1-7. Sex-Based Comparison of Recommendations for Aspirin Use in the Primary Prevention of CVD

Guideline	Men	Women
2007 Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women	N/A	High-risk women: 75–325 mg of aspirin daily unless contraindicated At-risk or healthy women ≥ 65: aspirin 81 mg daily or 100 mg every other day if blood pressure is controlled and benefit for ischemic stroke and MI prevention likely outweighs risk of GI bleeding or hemorrhagic stroke At-risk or healthy women ≤ 65: aspirin 81 mg daily or 100 mg every other day when benefit for ischemic stroke prevention is likely to outweigh adverse events
2008 CHEST Guidelines	Men at moderate risk of a coronary event (based on age and cardiac risk factor profile with a 10-year risk of a cardiac event > 10%): aspirin 75–100 mg daily is recommended	Women > 65 at risk of ischemic stroke or MI: aspirin 75–100 mg daily Women < 65 at risk of ischemic stroke; aspirin 75–100 mg daily
2009 U.S. Preventive Services Task Force Recommendation[a]	Men aged 45–79 in whom the potential MI benefit outweighs the potential harm caused by an increase in GI hemorrhage: aspirin 75 mg daily (as effective as higher doses) is recommended Men aged > 80[a]: no recommendation	Women aged < 54: aspirin is not recommended because of small benefits from reducing ischemic stroke and moderate evidence for harm Women aged 55–79: aspirin 75 mg daily (as effective as higher dosages) is recommended when the potential benefit from reduction in ischemic stroke outweighs the potential harm from GI hemorrhage Women > 80[a]: no recommendation

[a]Data for aspirin use in men and women older than 80 are lacking. The USPSTF guideline states that the net benefit of aspirin in individuals older than 80 is probably best in those without risk factors for GI bleeding and in those who could tolerate a GI bleeding episode.
CVD = cardiovascular disease; GI = gastrointestinal; MI = myocardial infarction; N/A = not applicable.

differ greatly from those in men. However, in each of these guidelines, proper attention is paid to women's increased risk of morbidity and mortality from CVD and whether disparities exist with respect to its treatment.

Sex-Specific Drug Therapy

The NIH Revitalization Act of 1993 promoted the inclusion of more women in clinical trial research. Large studies of women have only now been completed, and the results have been applied to practice. In addition, contemporary studies report outcomes stratified by sex, and post hoc analyses of older data stratified by sex have emerged (Table 1-8). However, although it will soon be two decades since the NIH Act, many of the treatments for heart disease (e.g., after an MI) are still based on studies consisting primarily of middle-aged men. Other therapies (e.g., aspirin for primary prevention of heart disease) have been updated because of the emergence of sex-specific data.

Aspirin

Before the WHS, most data on the use of aspirin for primary prevention were derived from five large trials that enrolled mostly men. The data uniformly supported the efficacy of aspirin in preventing MI while observing no significant effect on stroke prevention. In 2005, the WHS found the inverse of the Physician's Health Study; in women, aspirin therapy demonstrated no effect on MI, yet the incidence of stroke was decreased. In a subgroup analysis of women older than 65, older women experienced a decreased risk of MI, similar to the benefits experienced by men. Because of these data, sex-specific recommendations for aspirin have been updated in three sets of evidence-based guidelines. Table 1-7 summarizes these recommendations.

A limitation of the sex-specific aspirin recommendation is that no single trial offers direct comparisons between male and female participants in significant numbers. Patient risk may have influenced aspirin's protective benefit according to age because younger women experience fewer MIs compared with men of the same age. Furthermore, the dosing used in the WHS (100 mg every other day) was different from that shown to reduce cardiovascular events in men. Aspirin resistance has been reported to be 2–4 times higher in women, and a limitation of the WHS was that an effective dosage of aspirin might not have been used. Further studies are required to provide evidence that aspirin at equivalent dosages is therapeutically equivalent in both sexes, as well

Table 1-8. Sex-Specific Outcomes from Major Cardiovascular Trials

Study	Study Drugs	n (% Women)	End Points and Sex-Specific Findings	Findings Similar Between Sexes
Acute Coronary Syndrome				
ISIS-1	Atenolol vs. placebo	16,027 (23)	↓ Mortality	Y
ISIS-2	ASA vs. placebo; streptokinase vs. placebo; ASA + streptokinase vs. placebo	17,187 (23)	↓ Mortality	Y
GUSTO V	Retaplase vs. abciximab + half-dose retaplase	16,588 (25)	↑ Mortality (nonsignificant in overall population)	Y
GUSTO V substudy (Impact of Female Sex on Death and Bleeding)	Retaplase vs. abciximab + half-dose retaplase	16,588 (25)	Significant ↑ mortality in women; ↑ moderate and severe bleeding in women	
ExTRACT-TIMI 25	Planned fibrinolytic therapy with enoxaparin vs. UFH	20,479 (23)	↓ Death or nonfatal MI at 30 days	Y
ExTRACT-TIMI 25 substudy (Outcomes in Women with STEMI)	Planned fibrinolytic therapy with enoxaparin vs. UFH	20,479 (23)	Similar bleeding among men and women receiving enoxaparin but in women receiving enoxaparin compared with UFH Greater absolute risk reduction of enoxaparin on death, nonfatal MI, or nonfatal major bleeding in women	
OASIS-6	Fondaparinux vs. UFH	12,092 (28)	↓ Composite of death or reinfarction at 30 days	Y
COMMIT	75 mg of clopidogrel + 162 mg of ASA	45,852 (28)	↓ Composite of death, reinfarction, or stroke; ↓ death from any cause	Y
COMMIT/CCS-2	Early metoprolol vs. placebo	45,852 (28)	No benefit from early intravenous metoprolol therapy with composite of death, reinfarction, or cardiac arrest	Y
CLARITY-TIMI 28	Fibrinolytic + clopidogrel (300-mg load + 75 mg daily) vs. placebo	3491 (20)	↑ Patency rate of the infarct-related artery; ↓ ischemic complications with clopidogrel	Y
ACUITY	Heparin + GPI, bivalirudin + GPI, or bivalirudin alone	13,819 (30)	Bivalirudin alone was noninferior to heparin + GPI in the primary composite ischemia end point with significantly ↓ bleeding Bivalirudin + GPI was noninferior to heparin + GPI in rates of composite ischemia or bleeding	Not reported
ACUITY substudy (Impact of Gender on Antithrombin Strategy)	Heparin + GPI, bivalirudin + GPI, or bivalirudin alone	13,819 (30)	Similar ↓ 30-day mortality and composite ischemia end point but ↑ bleeding in women vs. men	
PROVE IT-TIMI 22	Atorvastatin 80 mg vs. pravastatin 40 mg	4162 (22)	↓ Death, MI, unstable angina, revascularization, and stroke	Y
Dyslipidemia				
4S	Simvastatin	4444 (29)	↓ Mortality	Y

(continued on the following page)

Table 1-8. Sex-Specific Outcomes from Major Cardiovascular Trials *(continued)*

Study	Study Drugs	n (% Women)	End Points and Sex-Specific Findings	Findings Similar Between Sexes
HPS	Simvastatin 40 vs. placebo	20,536 (25)	↓ Stroke, MI, revascularization	Y
JUPITER	Rosuvastatin 20 mg vs. placebo	17,802 (38.2)	↓ MI, stroke, unstable angina, CV death, revascularization, and hospitalization	Y
FIELD	Fenofibrate vs. placebo	14,247 (37)	No ↓ in primary outcome of coronary events; ↓ in total cardiovascular events because of fewer nonfatal MIs and revascularizations; in subgroup analysis, women benefited from fenofibrate more than men	Y
ILLUMINATE	Torcetrapib + atorvastatin vs. atorvastatin	15,067 (22)	↑ Death, nonfatal MI, stroke, unstable angina, hospitalization	Not reported
High-Risk CAD				
HOPE	Ramipril vs. placebo	9297 (27)	↓ Composite MI, stroke, CV death	Y
HOPE substudy in women	Ramipril vs. placebo	2480 (100)	↓ Composite MI, stroke, CV death	Y
ONTARGET	Ramipril vs. telmisartan vs. ramipril + telmisartan	25,620 (27)	Telmisartan and ramipril were equal in ↓ death, MI, stroke, and hospitalization from heart failure; combination therapy had ↑ ADEs without benefit	Y
Hypertension				
ALLHAT	Chlorthalidone vs. amlodipine vs. lisinopril vs. doxazosin-based therapy	42,418 (47)	↓ Combined CVD events	Y
ASCOT-BPLA	Amlodipine (± perindopril) vs. atenolol (± thiazide)	19,257 (23)	Amlodipine-based regimen nonsignificantly lowered nonfatal MI and CHD events; men and women favored amlodipine arm	Y
ACCOMPLISH	Benazepril + amlodipine vs. benazepril vs. HCTZ	11,506 (40)	Benazepril-amlodipine ↓ CV events superior to benazepril-HCTZ	Y
Atrial Fibrillation				
Re-LY	Dabigatran or adjusted-dose warfarin	18,113 (36)	Dabigatran 110 mg was similar to warfarin in ↓ stroke and systemic embolism; dabigatran 150 mg ↓ stroke and embolism but was similar in major bleeding	Y
ATHENA	Dronedarone 400 mg twice daily vs. placebo	4628 (46.9)	Dronedarone ↓ hospitalizations caused by CV events and death	Y

ACCOMPLISH = Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension; ACUITY = Acute Catheterization and Urgent Intervention Triage strategY; ADEs = adverse drug events; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASA = acetylsalicylic acid (aspirin); ASCOT-BPLA = Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm; ATHENA = A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter; CCS-2 = Second Chinese Cardiac Study; CHD = coronary heart disease; CLARITY-TIMI = Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction; COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction Trial; CV = cardiovascular; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes (study); 4S = Scandinavian Simvastatin Survival Study; ExTRACT = Enoxaparin and Thrombolysis Reperfusion for ACute myocardial infarction Treatment; GPI = glycoprotein IIb/IIIa inhibitor; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; HCTZ = hydrochlorothiazide; HOPE = Heart Outcomes Prevention Evaluation (study); HPS = Heart Protection Study; ICH = intracranial hemorrhage; ILLUMINATE = Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (trial); ISIS = International Study of Infarct Survival; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MI = myocardial infarction; OASIS = Organization for the Assessment of Strategies for Ischemic Syndromes (trial); ONTARGET = ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; OR = odds ratio; PROVE IT-TIMI = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (analysis); Re-LY = Randomized Evaluation of Long Term Anticoagulant Therapy; UFH = unfractionated heparin.

as the sex-based dosages required to elicit optimal effects in men and women.

The bleeding risk should be considered when assessing a woman's potential benefit from aspirin therapy. In the WHS cohort older than 65 years, the number needed to treat was 47, and the number needed to harm was 128. This is a generally favorable risk-to-benefit ratio. In women aged 55–64, the number needed to treat was 2001, and the number needed to harm was 196. When considering the limited benefit in women younger than 65, the bleeding risk from aspirin therapy is unacceptably high to be routinely recommended. Aspirin therapy must be individualized and based on the relative benefits and risks of the specific patient.

Current secondary prevention guidelines state that women derive the same benefit from aspirin as men, although much of this evidence comes from older secondary prevention trials that did not explore the risk/benefit of aspirin therapy in a sex-specific fashion. Few women were enrolled in these trials, but subgroup analyses pointed to similar benefits derived between the sexes. Despite the specific recommendations for aspirin use as the primary prevention of CVD in women, the use of aspirin as secondary prevention of CVD is recommended without respect to sex or age at this time.

Other Drugs in Women

Although the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure does not suggest a sex-based approach to hypertension, the presence of certain conditions in women may influence the selection of antihypertensive therapy. For example, certain antihypertensive agents can cause developmental abnormalities and fetal demise (e.g., ACE inhibitors, angiotensin receptor blockers, renin inhibitors) and are inappropriate for use in pregnancy and lactation. Thiazide diuretics may be of particular benefit in women at risk of osteoporosis because they reduce renal calcium excretion, and retrospective studies have shown as much as a 30% reduction in hip fracture with their use.

Finally, numerous clinical trials have established the cardiovascular risk associated with estrogen therapy. Although these data are not new, research focused on the timing of hormone therapy has suggested potential benefit from estrogen when given closer to the time menopause begins. Future research will determine whether our understanding of estrogen therapy will come full circle again. The AHA and other professional organizations designate hormone therapy for the primary or secondary prevention of heart disease in the woman with a class III or harmful recommendation.

Role of the Pharmacist

While we await further research on how sex may influence the potential prevention and treatment of CVD, increased awareness on the part of women and health professionals may improve the delivery of care to women. An important role of the pharmacist is education of adult female patients that includes a focused discussion on the risks of CVD. There is a great need for active participation from women in reducing their risk factors for CVD.

Pharmacists in all practice settings can become involved in public awareness campaigns. In addition, the pharmacist can help women know their goal BP, lipid concentrations, and A1C values and can educate them about the warning signs of ACS so that treatment is not delayed. The pharmacist should make a concerted effort to counsel women from underserved communities because these women have the least awareness of CVD.

Community-based research is required to address some of the remaining questions surrounding sex-based differences in CVD. Pharmacists can be involved in research interventions that determine the most effective approach to educating women about signs and symptoms of cardiovascular events, as well as strategies to avoid delay in seeking treatment. Research is needed to determine how best to promote adherence to lifestyle interventions to prevent coronary disease. Unique risk factors for disease in women can be identified and addressed in all practice areas. Studies are required to confirm the effectiveness of pharmacist intervention on women at risk of CVD.

Willingness to participate in clinical trials has been examined in randomized prospective fashion, demonstrating that women are less likely to participate because of a lower trust of researchers and a greater perceived risk from research participation. Pharmacists who conduct clinical trials should use awareness of these sex-based differences in perceived risks and benefits to improve the participation of women. In addition, recruitment efforts should focus on the inclusion of older women and women from diverse ethnic groups in ongoing research.

In the clinical setting, pharmacists should ensure proper dosage adjustment to reduce the risk of bleeding and other adverse events from antithrombotic agents used in ACS. Pharmacists can promote the use of primary and secondary prevention guidelines to improve drug use and improve adherence to interventions known to effectively reduce the risk of CVD. Aggressive methods to prevent and treat CVD continue to be underused in women; potential exists for pharmacists to collaborate in improving the application of evidence-based therapy in appropriate women at risk of CVD. Precise application of evidence-based therapy has the potential to improve the outcomes for women with CVD.

Conclusion

Cardiovascular disease remains the leading cause of mortality in women; it is responsible for almost as many deaths in the United States as the next five leading causes of death combined. Emerging data suggest that both bias and true physiologic differences play key roles in the sex-related differences in CVD.

Continued education of both patients and health care providers is important in increasing awareness about CVD. As the awareness of true disparities and sex-related differences increases, the care of women is likely to improve. Greater recruitment and enrollment of women in clinical trials is essential to providing sex-specific results. Sex-related considerations in administering drugs may maximize the benefits and reduce the risks of adverse events from aspirin, GPIs, and other agents in women. A better understanding of sex- and gender-based differences in CVD may help tailor prevention or treatment strategies more effectively to improve the care of women.

Annotated Bibliography

1. Mosca L, Banks CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. Circulation 2007;115:1481–501.

   This update to the 2004 publication focuses on the primary prevention of CVD in women. It reflects current literature specific to women, as well as a comprehensive review of primary prevention strategies known to be effective in both sexes. With few exceptions, recommendations to prevent CVD in women do not differ from those in men. The sex-specific role of aspirin in the primary prevention of CVD and cerebrovascular disease is reviewed, as are recommendations for avoiding certain drugs in pregnancy. The guideline acknowledges that almost all women are at risk of CVD, and this risk is likely to be underestimated. Risk stratification was updated to include three categories and to reflect lifetime risk, providing more information than assessing risk only by the FRS. The limitations of the FRS in women are also reviewed. This guideline is limited, not only because many prevention strategies have not been studied extensively in women, but also because it is not comprehensive in this respect.

2. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case control study. Lancet 2004;364:937–52.

   The INTERHEART study was an international case-control study of risk factors for MI that included 15,152 cases and 14,820 controls. The study objective was to determine the relationship of certain known risk factors (i.e., smoking, hypertension, and diabetes) with emerging risk factors (i.e, waist/hip ratio, dietary patterns, physical activity, alcohol consumption, blood apolipoproteins, and psychosocial factors) in the development of an MI. Participants were observed for 4 years. Worldwide, the nine risk factors studied accounted for 90% of the risk of a first MI in both sexes at all ages. The odds ratios for the association of acute MI with elevated lipid concentrations and abdominal obesity were similar for men and women, but sex-specific risk factors were also observed. Population-attributable risks from psychosocial factors were higher in women than men (45.2% vs. 28.8%), and the increased risk of MI associated with hypertension and diabetes was greater in women than in men. Women seemed to benefit more than men from the protective effects of exercise and alcohol. Limitations of these data include the observational design and lack of randomization. These findings should be hypothesis generating for future research on lifestyle modification (diet, exercise, and alcohol) and its influence on sex-specific mortality reduction.

3. Samad A, Wang TY, Frazier CG, Shah SH, Dolor RJ, Newby LK. Closing the gap: treating hypertension in women. Cardiol Rev 2008;16:305–13.

   This review focuses on sex-specific factors that contribute to hypertension in women. Women, despite clear evidence of benefit from BP lowering, have among the worst rates of BP control. Compared with men, women have different risks associated with hypertension (e.g., greater incidence of left ventricular hypertrophy, heart failure with preserved ejection fraction, arterial stiffness associated with age). Sex-specific hemodynamic characteristics seen in women are reviewed. Estrogen's role over BP regulation, including the renin-angiotensin-aldosterone system, is summarized. Data outlining risk factors specific to women for the development of hypertension are explored, including hormone therapy, oral contraceptive use, alcohol, and other nutritional factors. This review closes by summarizing the available evidence of drug therapy by class, noting where adverse effects are more likely to occur in women. Clinicians treating patients with hypertension will find this review useful with respect to sex-specific influences on this disease.

4. Lichtman JH, Bigger JT, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lesperance F, et al. Depression and coronary heart disease. Recommendations for screening, referral, and treatment. A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research. Circulation 2008;118:1768–75.

   Until the 2008 AHA Science Advisory incorporated evidence from more than 60 prospective studies, the only mention of screening and referral for depression with coronary heart disease as a sex-specific recommendation for women was in the Cardiovascular Disease Prevention in Women guideline in 2004. The mechanisms by which depression contributes to coronary heart disease are discussed, including reduced pulse rate variability, hypothalamic-pituitary-adrenal axis abnormalities, enhanced platelet activation, and vascular dysfunction. The need to screen everyone with coronary heart disease for depression is emphasized in this guideline. Patient questionnaires are provided to identify patients with depression and assist in finding and treating those with the greatest need for supportive treatment. Although data suggest depression affects women more than men, this guideline is limited because it does not review depression or the need to treat depression in a sex-specific fashion. The guideline recommends citalopram and sertraline as safe agents for patients with CVD.

5. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women. The Reynolds risk score. JAMA 2007;297:611–9.

   The Reynolds risk score is an important contribution to the primary prevention literature and provides a framework for evaluating emerging risk factors for CVD in women. Limitations to the six parameters used by the FRS prompted researchers to identify additional risk factors. Using data from 24,558 initially healthy women (95% white) age 45 and older enrolled in the WHS, researchers developed a risk algorithm considering 35 variables (and possible interactions between them) for predicting cardiovascular events including MI, ischemic stroke, coronary revascularization, and cardiovascular death. A random selection of 16,400 women (prediction cohort) was used to derive the new risk model, and the remaining one-third (n=8158, validation cohort) was used to validate the model by comparing 10-year predicted and actual rates of events over a median follow-up of 10.2 years. Two models, a best-fit comprehensive algorithm and a simplified version, were derived that more accurately predicted actual event rates than the FRS model. By including family history and hsCRP, the simplified version of the Reynolds risk score reclassified about 50% of women at intermediate risk (according to the FRS) into higher or lower risk categories. The Reynolds risk score performed as well as the FRS in women whom the FRS classified in the lowest and highest risk categories. A major limitation of the Reynolds risk score model is that it cannot be extrapolated to men or nonwhite women. Research is under way to determine the validity of this risk tool in these other populations.

6. Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ, et al. Symptom presentation of women with acute coronary syndromes. Myth vs reality. Arch Intern Med 2007;167:2405–13.

   Published literature lacks standardized reporting of presenting symptoms in ACS. This systematic review examined sex-related differences in the presentation of ACS with the goal of determining whether sex-related differences in presentation are significant enough to warrant separate public health awareness messages for women and men. Sixty-nine studies, including cohorts and registries, single-center reports, and personal interviews from 35 years of research, were reviewed. Women were more likely to present with unstable angina than MI, which was more common in men. Chest pain was the most common presentation for both men and women, yet in more than 25% of smaller reports and in 33% of large cohort studies, patients presented without chest pain. Women with ACS are more likely than men to complain of middle or upper back pain, neck pain, jaw pain, nausea or vomiting, weakness or fatigue, paroxysmal nocturnal dyspnea, shortness of breath, dizziness, and palpitations. Women with chest pain are more likely to have nonobstructive coronary disease.

   The authors summarize the importance of accurate symptom recognition to improve treatment in women. Limitations to this type of review include an examination of studies that based the definition of ACS on chest pain or discomfort, thereby excluding those with ACS in the absence of chest pain. In addition, advanced age rather than sex may have contributed to the difference in presentation. Interviews are included, which can introduce recall bias because they are retrospective. Further research, including a standardized data collection for sex-related presentation symptoms in ACS adjusted for age, is required. On the basis of their findings, the authors indicate that the public health message on ACS should remain unaltered for women and men at this time.

7. Daly C, Clemens F, Lopez Sendon JL, Tavazzi L, Boersma E, Danchin N, et al; on behalf of the Euro Heart Survey Investigators. Gender differences in the management and clinical outcomes of stable angina. Circulation 2006;113:490–8.

   This multinational evaluation of sex-based management of chronic stable angina is important because it documents a significant lower use rate of diagnostic procedures and other treatments in women with angina. The study included 2197 men and 1582 women with a new diagnosis of angina with 1-year follow-up. Women with angina received less exercise testing (48% vs. 73% in men) and less coronary angiography (31% vs. 49% in men). Women were offered coronary revascularization less often (13% vs. 29% in men) and were treated less often with statin and aspirin therapy. The 12-month follow-up documented a 2-fold higher risk of nonfatal MI and death in women, even after adjustment for comorbid conditions. Among patients with confirmed artery disease by angiography, women were more likely to have angina at follow-up (57% vs. 47% in men) and were less likely to receive optimal secondary prevention therapy. Statin therapy was prescribed in 76% of women with documented disease compared with 81% of men (p=0.05). Secondary prevention therapies with antiplatelet and lipid-lowering drugs were given less often to women (71% vs. 79% in men, p=0.02). Female sex was independently associated with increased risk of MI and death in individuals with confirmed coronary disease, even after adjustment for age, revascularization, use of secondary prevention drugs, and other variables. One limitation of this study is that it is based in European cardiology practices; as such, it may not be representative of other populations.

8. Challenging existing paradigms in ischemic heart disease: the NHLBI-sponsored women's ischemia syndrome evaluation (WISE). J Am Coll Cardiol 2006;47(suppl S):1S–71S.

   Intended to provide an overview of new information on ischemic heart disease in women, this supplement includes many contributions from the WISE study in the pathophysiology, diagnosis, and outcomes of women. The design of WISE was a prospective cohort, recruited by experts in ischemic heart disease at four centers. Key objectives of WISE were determining the most accurate ways of diagnosing suspected ischemic heart disease in women, including the assessment of myocardial ischemia in the absence of obstructive coronary disease, as well as advancing hypotheses relative to the pathophysiology of CVD in women. A 1-year pilot study of 256 women was conducted, focused on diagnosis and pathophysiology. A 3-year study of 680 additional women followed, assessing adverse events and

the relationship to diagnostic test findings in all 936 participants. This supplement contains only a few of the most pertinent substudies and viewpoints the WISE study group has contributed. Opinions on clinical evaluation and prognosis of women with nonobstructive coronary disease are provided with the intent of improving the understanding of the underlying disease process and innovative management approaches. Clinicians not familiar with sex-related differences in CVD will find this supplement valuable because of the expert reviews and editorials in addition to pertinent study findings.

9. Lansky AJ, Hochman JS, Ward PA, Mintz GS, Fabunmi R, Berger PB, et al. Percutaneous coronary intervention and adjunctive pharmacotherapy in women. A statement for healthcare professionals from the American Heart Association. Circulation 2005;111:940–53.

   This scientific statement from the AHA reviews the current knowledge and understanding of PCI in women; this was one of the first guidelines to address sex-specific issues in interventional cardiac care. The guideline evaluates the available safety and efficacy data of interventional therapies in women and offers a thorough review of adjunctive pharmacotherapy in women based on clinical trial data. Women have a 1.5–4 times increased risk of vascular complications after PCI than men and have lower rates of successful outcomes from invasive procedures. This statement is limited because no data are available to offer sex-specific treatment recommendations for women undergoing PCI.

10. Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, et al. 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.

    The CRUSADE registry, consisting of 35,875 patients, 41% of whom were women, can be useful for determining gender biases and sex-specific data in the contemporary treatment of ACS. At the time of this review, women were less likely to have ECG performed within 10 minutes of presentation to the hospital (25.2% vs. 29.3% in men). In addition, women were less likely to receive care from a cardiologist during hospitalization (53.4% vs. 63.4% in men). Women were less likely to receive heparin (adjusted odds ratio [OR] = 0.91; 95% confidence interval [CI], 0.87–0.95), GPIs (adjusted OR = 0.86; 95% CI, 0.81–0.92), or an ACE inhibitor (adjusted OR = 0.93; 95% CI, 0.88–0.98). At discharge, women were significantly less likely to receive aspirin (adjusted OR = 0.91; 95% CI, 0.85–0.98), ACE inhibitors (adjusted OR = 0.93; 95% CI, 0.88–0.98), or statins (adjusted OR = 0.92; 95% CI, 0.88–0.98), but they were just as likely as men to receive β-blockers and clopidogrel. Women experienced a 15% to 20% excess of hospital complications, which may be related to a higher incidence of comorbidities, because after adjustment for baseline characteristics, the only statistically significant difference between the sexes was the requirement for transfusion. This article demonstrates the value of registry data in determining potential gender biases and sex-specific observations.

11. Bugiardini R, Bairey-Merz CN. Angina with "normal" coronary arteries. A changing philosophy. JAMA 2005;293:477–84.

    This thorough clinical review presents the evidence for a poorer prognosis in women with chest pain despite normal or nonobstructive coronary disease. The authors searched MEDLINE and the Cochrane Database of Systematic Reviews from the inception of the database to 2004; they also provide evidence from cohort, registry, and trial data. The authors include therapeutic strategies studied in patients exhibiting chest pain without obstructive coronary findings, although no randomized trial data are available to compare these therapies with cardiovascular event reduction in patients with "normal" coronary arteries. Data on the analgesic effect of imipramine are reviewed, as well as the efficacy from calcium channel blockade, β-blockade, blockade of the renin-angiotensin-aldosterone system, and statin therapy. This review provides the clinician with the viewpoint that nonobstructive coronary disease, found more often in women, is not benign.

12. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, et al. ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2007;50:e1–157.

    Section 6 of this updated guideline adds to the evidence-based recommendations for the care of special populations with UA/NSTEMI. Four class I recommendations are made specifically for women; these include the same drug therapy as men for both hospitalization and secondary prevention, with special attention to weight-based antiplatelet and anticoagulant dosages and adjustments for kidney dysfunction. The guideline reviews the presentation of ACS and risk data between men and women, including the pathophysiology of nonobstructive coronary artery disease. Disparities in drug treatment are discussed, whereby women receive aspirin and other antithrombotic agents less often than men. This guideline states that women derive the same benefit as men from aspirin, clopidogrel, anticoagulants, β-blockers, ACE inhibitors, and statins, but evidence is provided that GPIs lack efficacy in women without elevated troponin concentrations. Differences in invasive versus conservative strategies in women presenting with UA/NSTEMI are outlined with respect to high- or low-risk features, with a conservative strategy recommended in women at low risk of an event. All pharmacists caring for women with ACS should be familiar with section 6 of these guidelines.

13. O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, 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.

This meta-analysis involving 3075 women and 7075 men from eight randomized trials demonstrated that an early invasive strategy reduced the composite cardiovascular end point of death, MI, or recurrent ACS in men more than in women (27% vs. 19%). Men who presented with elevated cardiac biomarkers had the greatest benefit from an invasive strategy, with a significant 44% lower odds ratio of death, MI, or rehospitalization. When women presenting with positive biomarkers at baseline were compared with women lacking this finding, an invasive strategy reduced the risk of the event by 33% versus 6% (p=0.08), establishing that women at high risk may benefit from invasive strategies to the same extent as men. In contrast, women who experienced unstable angina without cardiac biomarker elevation had a nonsignificant 35% increased risk of MI or death after an early invasive procedure. A criticism of these findings is that a greater percentage of preexisting comorbid conditions in women could have influenced complications after the procedure. The findings of no significant benefit and potential for harm from angiography in women with low-risk features are consistent with the recommendation from the American College of Cardiology/AHA 2007 UA/NSTEMI guideline for a biomarker-specific treatment approach in women.

14. Alexander KP, Chen AY, Newby LK, Schwartz JB, Redberg RF, Hochman JS, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from 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.

    Using retrospective data from the CRUSADE registry database of 32,601 patients with non–ST-segment elevation ACS, this study explored the relationship between sex, GPI use, dosage, and bleeding. Excessive dosing of GPI was almost 3 times more common in women (46.4% vs. 17.2% in men), potentially because of incorrect assessment of a woman's creatinine clearance. Excessive dosing was associated with increased risk of bleeding in both sexes (OR women = 1.72; 95% CI, 1.30–2.28 vs. OR men = 1.27; 95% CI, 0.97–1.66), although women had higher rates of bleeding (15.7% vs. 7.3% in men, p<0.0001). The bleeding risk attributable to excessive dosages was much higher in women (25% vs. 4.4% in men) because of their greater exposure (46.4% excess dosages in women vs. 17.2% excess dosages in men, p<0.0001). Women experienced more bleeding even without treatment with a GPI (8.5% vs. 5.4% in men, p<0.0001). Bleeding was significantly lower for both women and men who received proper dosage adjustments, indicating that correct dosing with these agents adjusted for kidney function can reduce some but not all of the higher risk of bleeding events in women. The authors speculated that one-fourth of the difference in bleeding risk with GPI between women and men would be avoidable with appropriate dosing. These data, although derived retrospectively, represent an important observation of increased bleeding risk in women. Proper adjustment of GPI dosages in women will likely improve the care of women with non–ST-segment elevation ACS.

15. Mega JL, Morrow DA, Ostor E, Dorobantu M, Qin J, Antman EM, et al. Outcomes and optimal antithrombotic therapy in women undergoing fibrinolysis for ST-elevation myocardial infarction. Circulation 2007;115:2822–8.

    This substudy from the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction, Study 25 (ExTRACT-TIMI 25) trial, demonstrating the superiority of enoxaparin over unfractionated heparin as an adjunct to fibrinolysis for STEMI, reported data from more than 4000 women. Women were older, had more comorbid conditions, and had a 25% greater adjusted risk of mortality than did men. Enoxaparin reduced the composite risk of recurrent MI and death significantly at 30 days over unfractionated heparin in both men and women. The risks of major, minor, and combined major and minor bleeding were all significantly increased in women assigned to the enoxaparin treatment group. No bolus was administered to patients older than 75, and the dosage of enoxaparin was reduced by 25% because most older patients had diminished kidney function. There was no dosage adjustment for female sex, although the average creatinine clearance was lower in women than in men. A criticism of this trial was that enoxaparin was administered until hospital discharge (median, 7 days), whereas unfractionated heparin was administered for only 48 hours. Although the duration of therapy for enoxaparin could have contributed to the increased bleeding versus unfractionated heparin, ExTRACT should serve as a model for future research directed at the careful dosing of antithrombotic regimens in women, especially those with decreased kidney function.

16. Reynolds HR, Farkouh ME, Lincoff AM, Hsu A, Swahn E, Sadowski ZP, et al. Impact of female sex on death and bleeding after fibrinolytic treatment of myocardial infarction in GUSTO V. Arch Intern Med 2007;167:2054–60.

    The Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) V trial investigators set out to determine whether female sex was an independent risk factor for death and/or bleeding in STEMI. The initial randomized study enrolled 16,588 patients presenting with STEMI to receive either reteplase (two 10-unit boluses, 30 minutes apart) or a combination of abciximab (standard dose of a 0.25-mg/kg bolus and a 0.125-mcg/kg/minute infusion for 12 hours) and a half-dose of reteplase (two 5-unit boluses, 30 minutes apart) intravenously. All patients received heparin; patients for whom immediate PCI was planned were excluded. The primary end point was all-cause mortality 30 days after randomization. After adjusting for comorbidities, female sex was independently associated with death (9.8% vs. 4.4% at 30 days; OR = 2.00; 95% CI, 1.59–2.53) and bleeding (6.5% vs. 2.5%; OR = 1.31; 95% CI, 1.18–1.45) at 30 days, independent of body weight and heparin dose. A higher risk of death between 30 days and 1 year was noted in women (3.8% vs. 2.5% in men, p<0.01). Stroke rates were higher in women, and women were more likely to have an intracranial hemorrhage (1.2% vs. 0.4% in men, p<0.01) regardless of treatment assignment. Women were more likely than men to have complications from MI such as reinfarction, heart failure, and atrial fibrillation. Underuse of aspirin and β-blockers at discharge was noted

in the women of this study. This study is a subgroup analysis of the initial GUSTO V trial, which was not initially designed to determine sex-related differences in presentation, management, or outcome.

17. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293–304.

    This large, randomized, placebo-controlled study is important because it is the first primary prevention study of aspirin conducted solely in women. Randomized trials have previously shown cardiovascular benefit for men with aspirin use, with little protection from ischemic stroke. Although data have been extrapolated for the primary prevention of CVD in both sexes, few women were included in most of these studies. The authors of the WHS randomly assigned 39,876 healthy women age 45 and older to receive aspirin 100 mg every other day or placebo and observed them for 10 years to determine the risk reduction of first cardiovascular events (i.e., nonfatal MI, nonfatal stroke, or death from cardiovascular cause). Overall, a 17% reduction in stroke risk (p=0.04), a 24% reduction in ischemic stroke risk (p=0.009), and a nonsignificant increase in hemorrhagic stroke were found in the aspirin group. Fatal stroke rates were not different between placebo and treatment groups; however, the aspirin group had a 19% decreased risk of nonfatal stroke (p=0.02). No benefit from aspirin was seen in MI or death from cardiovascular causes, except in the subgroup of women older than 65. This age-based difference serves as the basis for both the 2007 Primary Prevention of Cardiovascular Disease in Women and the 2008 CHEST Guideline recommendation regarding aspirin use in women. These two guidelines endorse an age-based approach, even though there were considerable criticisms of the WHS. The aspirin dosage used (100 mg every other day) has not been shown to prevent cardiovascular events, and women tend to experience stroke earlier in life than MI, so the dosing and risk-based end points chosen in this study are limitations.

18. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force Recommendation Statement. U.S. Preventive Services Task Force. Ann Intern Med 2009;150:396–404.

    This update from the 2002 U.S. Preventive Services Task Force focuses on the benefits and harms of aspirin for the primary prevention of CVD. The task force recommendations are made according to age and sex. Clinicians whose practices focus on risk factor modification and the primary prevention of CVD will find this document helpful because it provides detailed tables, calculating the estimated benefit from aspirin on prevented stroke and MI based on the FRS, age, and sex. In addition, estimated harms from aspirin therapy are calculated on the basis of sex and age. One limitation of this guideline is that estimated benefits from aspirin rely partly on the FRS. Because the FRS was used to determine the risk level at which the benefit from aspirin exceeds harm, patients with an underestimated FRS may not be perceived to benefit from aspirin therapy.