AHA Scientific Statement

Acute Myocardial Infarction in Women

A Scientific Statement From the American Heart Association

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Abstract*—**Cardiovascular disease is the leading cause of mortality in American women. Since 1984, the annual cardiovascular disease mortality rate has remained greater for women than men; however, over the last decade, there have been marked reductions in cardiovascular disease mortality in women. The dramatic decline in mortality rates for women is attributed partly to an increase in awareness, a greater focus on women and cardiovascular disease risk, and the increased application of evidence-based treatments for established coronary heart disease. This is the first scientific statement from the American Heart Association on acute myocardial infarction in women. Sex-specific differences exist in the presentation, pathophysiological mechanisms, and outcomes in patients with acute myocardial infarction. This statement provides a comprehensive review of the current evidence of the clinical presentation, pathophysiology, treatment, and outcomes of women with acute myocardial infarction. (Circulation*. 2016;133:00-00. DOI: 10.1161/CIR.0000000000000351.)**

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Cardiovascular disease (CVD) is the leading cause of mortality for women in the United States[1] and globally.[2] Coronary heart disease (CHD) has traditionally been considered a disease of men, but what has been the odyssey for women in the century since its initial description by Herrick in 1912?[3] Despite stunning improvements in cardiovascular mortality for women in the past 2 decades (Figure),[1] CHD remains understudied, underdiagnosed, and undertreated in women. Since 1984, the annual CVD mortality rate has remained greater for women than for men, and the absolute numbers of individuals living with and dying of CVD in the United States are larger for women than for men.[1] Improved survival for women has been attributed equally to improved therapy for established CVD and to primary and secondary preventive interventions. Transformation of the research landscape and the results of landmark randomized, clinical trials have contributed to improved cardiovascular care for women.

Emerging data highlight important sex differences in the pathophysiology, clinical presentation, and clinical outcomes that were spurred by 2 milestone reports from the Institute of Medicine: *Exploring the Biological Contributions to Human Health: Does Sex Matter?*[4] and *Women's Health Research: Progress, Pitfalls, and Promise.*[5] These reports highlight the fact that although major progress has been made in reducing CVD mortality in women, medical research has historically neglected the health needs of

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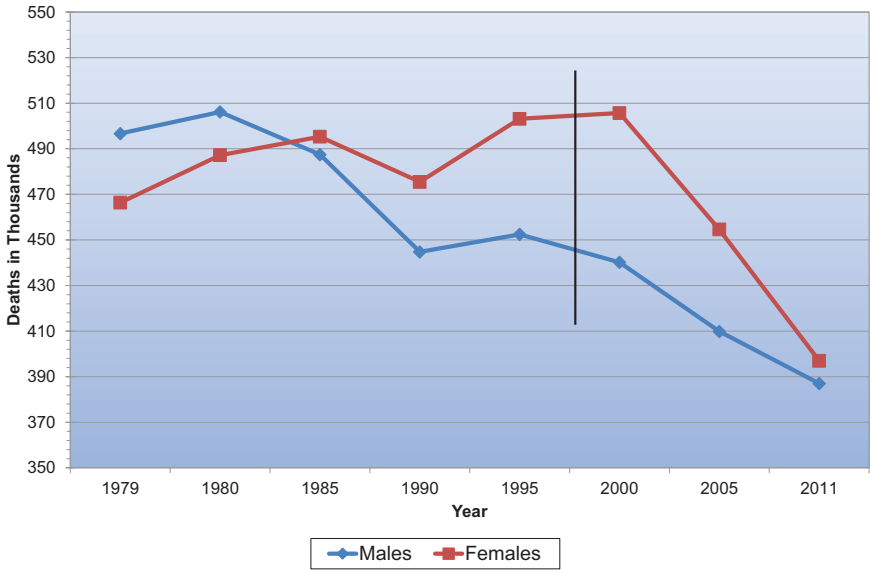

Figure. Cardiovascular disease (CVD) mortality trends for men and women in the United States from 1979 to 2011. CVD excludes congenital cardiovascular defects (*International Classification of Diseases, 10th Revision* codes I00–I99). The overall comparability for CVD between the *International Classification of Diseases, 9th Revision* (1979–1998) and *International Classification of Diseases, 10th Revision* (1999–2011) is 0.9962. No comparability ratios were applied. Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute. Reprinted from Mozaffarian et al.[1] Copyright © 2015 American Heart Association, Inc.

women, apart from reproductive concerns. Women's health involves 2 aspects: sex differences resulting from biological factors and gender differences affected by broader social, environmental, and community factors. Although the emphasis on sex-specific CVD research for the past 2 decades has led to an improved understanding of sex-specific pathophysiology for CHD in women and important insights into an expanded spectrum of coronary atherosclerosis, female research subjects are underrepresented when studies are designed, conducted, and analyzed.

Although obstructive atherosclerotic disease of the epicardial coronary arteries remains the basic cause of acute myocardial infarction (AMI) in both sexes, plaque characteristics differ for women, and recent data have suggested a greater role of microvascular disease in the pathophysiology of coronary events among women.[6] Despite being older and having a greater risk factor burden and a greater symptom burden of angina and consequent morbidity and mortality, women paradoxically have less severe obstructive disease of their epicardial coronary arteries at elective angiography than men.[7] Multiple studies have shown that women with acute coronary syndromes (ACS) are less likely to be treated with guideline-directed medical therapies,[8–10] less likely to undergo cardiac catheterization,[8–11] and less likely to receive timely reperfusion.[9,10,12–16]

Improving CHD morbidity and mortality and closing the knowledge gaps on AMI clinical presentations and treatments for women are public health priorities. This American Heart Association (AHA) scientific statement provides a comprehensive review of the current evidence of the epidemiology, clinical presentation, pathophysiology, treatment, and outcomes of women with AMI. Although sex and gender differences are presented in some sections, the primary intent of this document is to synthesize the current state of the science of AMI in women.

Scope of the Problem

Marked reductions in CVD mortality in women have occurred for the first time this past decade, partly as a result of an increase in awareness, a greater focus on women and their cardiovascular risk, and the application of evidence-based treatments for established CHD. Despite these advancements, CVD remains the leading morbidity and mortality threat affecting millions of American women. Reasons for the increased AMI rates among women are multifactorial and are related to the prevalence of disease and the influence of age, race, and ethnicity.

Prevalence of AMI

CHD afflicts 6.6 million US women annually and remains the leading morbidity and mortality threat in women. Of these, 2.7 million have a history of MI, >53 000 died of an MI, and an estimated 262 000 women were hospitalized for an ACS (AMI and unstable angina).[1] Regardless of age, within a year of a first AMI, more women than men will die (26% of women and 19% of men); within 5 years of a first AMI, more women than men will die (47% of women and 36% of men), have heart failure (HF), or suffer from a stroke.[1] At both 5 and 10 years after AMI, higher unadjusted mortality for women compared with men was explained partially by differences in age, MI risk factors, clinical presentation, and treatment.[17] Studies report a higher prevalence of diabetes mellitus (DM), HF, hypertension, depression, and renal dysfunction in women compared with men. Compared with men, women more commonly present with non–ST-segment–elevation MI (NSTEMI)[18–20] and nonobstructive coronary artery disease (CAD).[18,21,22] Women are also more likely to have unusual pathophysiological mechanisms of CAD such as spontaneous coronary artery dissection (SCAD) or coronary artery spasm (CAS).[23–26] Compared with men, women with ACS and those after coronary revascularization have longer hospitalizations and higher in-hospital mortality, manifest more bleeding complications, and endure

up to 30% more readmissions within 30 days after the index hospitalization.[27–31]

Influence of Age

ACS in young women seems distinctive because premature CHD is relatively rare in this group.[32] Limited existing data on the frequency of AMI among young patients reveal that each year >30 000 women <55 years of age are hospitalized with AMI in the United States.[33] Hospitalizations for AMI increased 2% between 1997 and 2006.[33] From 2001 to 2010, women demonstrated either no change (in women 30–34 and 35–39 years of age) or a slight absolute increase (in women 40–44 and 45–49 years) in hospitalization rates for AMI.[34] Recent data of AMI patients <65 years of age demonstrate a nearly 2-fold higher crude 30-day hospital readmission rate in women compared with men of a similar age, even after adjustment for confounders.[35] Recent data show an unfortunate increase in CHD incidence and deaths among women 45 to 54 years of age.[36] From 2001 to 2011, the annual death rate attributable to CHD declined 39%, and the actual number of deaths declined 25.3%. Among women, death rates fell by 2.6%/y in the 1980s, by 2.4% in the 1990s, and 4.4% from 2000 to 2002; however, when stratified by age, among women 35 to 54 years of age, the average annual rate of death fell by 5.4% and 1.2% and then increased by 1.5%.

The substantial decline in MI event rates or MI deaths in the United States in the past decade is absent in young women. Troubling trends of worse risk factor profiles and higher mortality among younger compared with older women persist, with continuing reports of excess in-hospital, early, and late mortality compared with men.[34,37–44] Consistent evidence suggests an age-sex interaction whereby younger women are at particularly high risk of mortality after AMI even with other prognostic factors taken into account.[37,45,46] The mechanisms, likely multifactorial, contributing to excess risk and inferior health among young women remain unclear.[32,47] Plausible candidates for poor outcomes among young women include unique sex-specific biology and disease manifestations and distinctive gendered (socially constructed with identified roles and expectations) psychosocial stressors that interfere with health behaviors and interact with biology.[47] Many unanswered questions remain about the excess mortality risk in young women with AMI. Publications from the recently completed Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study provide insight into and guidance on sex differences in prognostic factors that affect outcomes in young women with AMI.[48]

Women are often older when they present with their first AMI, at an average age of 71.8 years compared with 65 years for men.[1] The older age of onset of CHD in women compared with men is thought to be due to the protective role of circulating estrogens on the vascular endothelium.[49] This hypothesis is derived largely from the observation that the incidence of AMI rises substantially in postmenopausal women; however, it is difficult to unravel the effect of age from that of menopause. The complex mechanisms by which estrogen influences CHD risk are incompletely understood; however, direct effects of estrogen on the vascular system include increased release of nitric oxide leading to vasodilation,[50,51] regulation of prostaglandin production,[52] and inhibition of smooth muscle proliferation.[53] Population studies have shown that estrogen depletion at menopause increases endothelial dysfunction and lipid deposition in the vasculature, which can precipitate the development of atherosclerosis over time.[54,55] However, despite the cardioprotective effects of endogenous estrogen, studies evaluating exogenous estrogen hormone therapy for the primary prevention of CHD in postmenopausal women have been convincingly negative. The Women's Health Initiative has provided evidence indicating that postmenopausal hormone therapy is not suitable for the prevention of CHD in women who initiate treatment distant from menopause onset,[56] that utility in younger women remains inconclusive, and that more research is needed in this area. Therefore, according to current evidence-based guidelines, postmenopausal hormone therapy is not recommended for the primary or secondary prevention of CVD[57] because hormone therapy does not prevent the progression of established atherosclerosis and precipitates acute CHD events in older women.[56]

Racial/Ethnic Disparities

Racially and ethnically diverse women with AMI have distinct experiences in terms of presentation, risk factor burden, evidence-based care, and long-term outcomes. Ethnically diverse women present with their incident MI at a younger age than white women.[58,59] The prevalence of MI is higher in black women than in all other racial and ethnic groups of women.[1,58,60–62] Black women also have a higher incidence of sudden cardiac death (SCD) as the first manifestation of CHD than white women,[62–64] and their survival rate after out-of-hospital arrest is about one third that of whites.[65] Asian Indian women have greater proportionate mortality burden from CHD compared with non-Hispanic white women (proportional mortality ratio, 1.12 versus 0.92).[66–69] In stark contrast to other racial and ethnic groups, CHD mortality rates in Asian Indians were higher in 2010 than in 2003.[66] Data from the INTERHEART registry suggest that Asian Indians have a greater burden of cardiovascular risk factors, particularly at a younger age.[69]

Compared with non-Hispanic white women, black and Hispanic women have more comorbidities (eg, DM, hypertension, HF, and obesity) at the time of presentation with AMI.[59,62,70,71] At the time of presentation, 60% of older black women and 54% of younger black women have a clustering of ≥3 risk factors.[72] The high prevalence of comorbidities is the hypothesized driver of higher rates of MI and a significant contributor to poorer long-term outcomes in black women.[60,62,70] In the Corpus Christi Heart Project, rates of hospitalization for AMI were higher in Mexican American women than in non-Hispanic white women.[73] Even with their adverse cardiovascular risk profiles, Hispanics appear to have less SCD than non-Hispanics.[71] Although not applicable to all Hispanic subgroups, the prevailing Hispanic paradox of relatively low cardiac mortality despite poor risk factor profiles is thought to be partially explained by greater social support, optimism, and strong family ties among Hispanics.[71] More than one third of American Indian women have ≥3 cardiac risk factors.[74] A staggering 78% of cardiovascular events in American Indian women occurred in diabetics.[75] At a time when other groups are experiencing a decline, the rate of coronary events in American Indian women is increasing to levels that are almost 2-fold higher than in the US population.[75–77]

AMI prevalence by race and ethnicity interacts with age. In women <55 years of age with AMI, black women have higher mortality rates than white women even after adjustment for chronic renal failure, time to presentation, insurance, and treatment in the first 24 hours.[78] Young black women have higher hospitalization rates for AMI than young white women, and they have more comorbidities, including hypertension, DM, chronic kidney disease, and HF, than white women.[34,72,79] At the time of presentation with AMI, older black and Hispanic women have a significantly higher prevalence of DM, hypertension, physical inactivity, and abdominal obesity with less well-controlled blood pressure and lipid levels than non-Hispanic white women.[70,72,80] Across all age groups, annual rates of hospitalization for AMI have decreased less rapidly for black women than for white women.[81,82]

Blacks, Hispanics, and American Indians as a whole present later to the hospital after AMI symptoms.[83] The American College of Cardiology–National Cardiovascular Data Registry shows that women from all ethnic backgrounds were less likely to undergo percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG) than their male counterparts.[58] Multiple studies have documented disparities in rates of referral of black women to coronary angiography and reperfusion compared with white women and black men.[59,79,84] Even after baseline differences were controlled for, black women are least likely to be referred for reperfusion therapy and coronary angiography.[79,83,85] The difference in rates of use of these interventions across ethnically diverse women has decreased over time.[34,79,86]

Despite more cardiac risk factors, secondary prevention efforts are less commonly used for black and Hispanic women. Rates of lipid-lowering medication use and counseling for smoking cessation are lower among nonwhite women.[87] Disparities are even more pronounced for younger black women compared with young white women.[72] Even in institutions participating in quality initiatives that demonstrate narrowing of racial gaps in the use of preventive medications after MI at 30 days, notable differences remain by 12 months, with black and Hispanic women having the lowest risk-adjusted adherence to angiotensin-converting enzyme (ACE) inhibitors and β-blockers.[88] Data suggest that increased adherence to guidelines may reduce these disparities for black and Hispanic women.[79,89,90]

Pathophysiology of AMI

The scientific evidence supports pathophysiological differences between women and men with AMI. Underlying causes are multifactorial and are related to the pathophysiological sex differences in CHD. Coronary pathology interacts with the biological sex characteristics of women to produce differences in plaque characteristics (rupture versus erosion) and prevalence of CAS and SCAD.

Plaque Rupture and Erosion

Autopsy studies from past decades have established that there are predominantly 3 major vascular events underlying thrombotic coronary occlusions responsible for AMI: plaque rupture, plaque erosion, and calcific nodule. Plaque rupture is by far the most common cause, responsible for 76% of men and 55% of women with fatal MI.[91] Originally described 3 decades ago, ruptured plaques are associated with positive remodeling and characterized by a large necrotic core and a thin fibrous cap that is disrupted and infiltrated by foamy macrophages, T cells, and matrix metalloproteinases.[92] As a consequence, tissue factor at the core is exposed to flowing blood, leading to activation of the coagulation cascade, and is ultimately responsible for formation of occlusive atherothrombus. Plaque erosion is another mechanism for coronary thrombosis without plaque rupture.[93,94] Erosions are distinguished by an absent or denuded endothelium overlying a plaque that is characterized by abundant proteoglycans and greater proliferation of smooth muscle than inflammatory cells. Coronary obstruction is precipitated largely by the thrombi that develop on the dysfunctional intima of plaque erosions. Downstream microembolization is more commonly associated with plaque erosion than with plaque rupture, resulting in focal myocardial necrosis.[95,96] Finally, ≈2% to 7% of coronary thrombosis in STEMI might originate from calcific nodules, seen more frequently in the right coronary artery.[94]

Although plaque rupture was responsible for 76% of fatal AMI events among men in a worldwide survey, only 55% of these events in women were found to be due to plaque rupture.[91] Autopsy studies have shown an increased prevalence of plaque erosion in women compared with men, particularly in younger women.[97] This is of significant interest given that MI without obstructive CAD is more common at younger ages and among women.[98,99] With the advent of optical coherence tomography (OCT), plaque erosion has been characterized in living patients with STEMI[100,101] and NSTEMI[102] after thrombus aspiration. Plaque erosion accounted for 27% of patients with STEMI and 31% of NSTEMI in these studies.[101,102] Female sex and premenopausal status are the only 2 risk factors that have been shown to predict type of thrombotic coronary lesion in autopsy studies. Although in vivo assessment with OCT shows that ACS patients with erosions are younger, have less severe obstructive stenosis, and less often present with STEMI than those with plaque rupture, there are no sex-related differences in prevalence of erosions.[102] This can be explained partly by differences in the respective cohorts of SCD versus ACS patients. In a recent small study of 140 patients, plaque rupture was the most frequent cause of coronary thrombus; however, there were no sex differences in culprit plaque morphology or factors associated with coronary thrombosis between age-matched men and women presenting with STEMI undergoing primary PCI. An important limitation of the study is that the age-matching algorithm may have inherently lessened sex differences in baseline clinical characteristics, including reduced enrollment of younger women who are known to have a higher prevalence of plaque erosion.[104] Plaque rupture is especially rare in premenopausal women, perhaps suggesting a protective effect of estrogen.[105] Contrasting results have been reported for the relationship of hypercholesterolemia, DM, and smoking with type of coronary thrombotic occlusion.[106–109] Hypertension does not favor any particular type of thrombosis.[106] Some circulating biomarkers, including myeloperoxidase, have been found to be at higher levels in patients with OCT-defined plaque erosions compared with rupture.[105] Additionally, between 7% and 32% of women with MI have no angiographically demonstrable

obstructive CAD (>50% stenosis).[18,98,99,110] Their MI may be due to plaque rupture and ulceration, plaque erosion, vasospasm, and embolism.[97,111]

Characterization of the plaque pathology is not routinely performed because of limited availability of advanced imaging techniques, including OCT, that allow the discrimination of intact fibrous cap from ruptured fibrous cap with a much higher resolution compared with intravascular ultrasound.[112] Although stenting is known to significantly improve outcomes with plaque rupture, it has been argued that reliable characterization of plaque morphology might justify alternative approaches, including aspiration thrombectomy and catheter-directed lytic therapy without stent implantation, as the initial strategy for treatment in patients with plaque erosions. In a recent study, 31 patients presenting with STEMI who underwent thrombectomy and were found to have plaque erosions by OCT were randomized to dual antiplatelet therapy without PCI and standard angioplasty and stenting.[100] After a median follow-up of 2 years, there was no difference in need for revascularization in the 2 groups. However, randomized, controlled trials are needed to evaluate long-term outcomes of these alternative management strategies in patients with plaque erosions before they are incorporated into clinical practice.

A caveat to these studies is the relative absence of evidence on the reliability of differentiating plaque rupture from erosion, including at autopsy and with OCT. Methods that can be trusted to accurately differentiate these underlying causes and to create a taxonomy that might ultimately have utility for prevention and treatment are needed. In young women, there is great heterogeneity in the pathophysiology of AMI. Approximately 1 of 8 young women with AMI in the VIRGO study did not fit in the current classification schemes for AMI, and as a result, the authors have proposed a new, more inclusive taxonomy that may provide a framework for improved understanding and investigation into risk factors, treatment strategies, and outcomes in young women.[113] For now, it is intriguing that the underlying mechanism of AMI varies by sex, with implications for treatment, yet more scientific investigation is needed in the realm.

Coronary Artery Spasm

CAS is a well-known phenomenon for recurrent chest pain episodes at rest with associated transient ST-segment elevation,[114] but it is also a rare mechanism for AMI.[115,116] The pathogenesis of CAS is multifactorial and includes vagal withdrawal, vascular smooth muscle hyperactivity, endothelial dysfunction, and an imbalance of the autonomic nervous system.[117,118] Cigarette smoking is a major risk factor for CAS,[119] and possible triggers include variation in autonomic activity,[120] cocaine use,[121] ephedrine alkaloids,[122] and other drugs.[123,124] Provocative testing with ergonovine, acetylcholine, or hyperventilation during coronary angiography can be helpful in diagnosing CAS.[125–127]

Data on sex differences associated with CAS are limited. One study demonstrated that women with CAS were typically older, had a lower incidence of smoking, and had less significant obstructive CHD compared with men with CAS. Five-year major adverse cardiovascular event (MACE) rates were similar in both sexes, but further analysis revealed that younger women with CAS had a significantly lower survival rate than older women, perhaps because of higher tobacco use in the younger cohort.[128]

In a small study of patients with vasospastic angina who underwent repeated coronary angiography, persistent vasospasm was associated with progressive atherosclerosis, whereas reduced vasospastic activity was associated with atherosclerosis regression.[129] CAS plays a significant role in the development of an AMI via thrombin generation resulting in thrombus formation[130] and impaired fibrinolytic activity resulting in thrombus preservation.[131] In patients with ACS from the Coronary Artery Spasm in Patients With Acute Coronary Syndrome (CASPAR) study, ≈25% had no obstructive culprit lesion on coronary angiography. CAS was present in almost 50% of the patients who underwent acetylcholine provocative testing.[116] Provoked CAS is an independent predictor of major adverse cardiac events.[132] The incidence of recurrent or persistent angina is high in the long term follow-up of patients with CAS; however, rates of AMI and cardiac mortality are low.[133,134]

Spontaneous Coronary Artery Dissection

SCAD is a very rare cause of AMI that occurs more frequently in women and should be suspected in any young woman who presents with an ACS without typical atherosclerotic risk factors.[135] The true prevalence of SCAD is unknown, but available data suggest a prevalence of 0.2% to 4%[136–138] of patients undergoing cardiac catheterization, and it is reported to occur in 10.8% of women <50 years of age who present with an ACS or AMI.[136] SCAD is associated with peripartum and postpartum status, oral contraceptive use, exercise, connective tissue disorders, and vasculitides (including fibromuscular dysplasia). In some cases, there are no identifiable coexisting conditions.[139–141]

The clinical presentation of SCAD can vary among unstable angina, MI, ventricular arrhythmias, and SCD. Single-vessel SCAD most frequently involves the left anterior descending artery; however, multivessel involvement has also been reported.[139] There are no definitive guidelines on the optimal treatment strategy for patients with SCAD. Treatment of SCAD has varied among conservative management, thrombolytic therapy (in the pre-PCI era), PCI, and CABG[139,142,143]; however, it has been proposed that patients with ongoing ischemia should be revascularized either percutaneously or surgically.[135] Regardless of therapeutic choice, the overall early mortality rate is low but complication rates are high in the PCI-treated patients because of propagation of the dissection flap with instrumentation of the vessel or failure to cross into the distal true lumen.[139] Some dissections resolve without any coronary intervention.[144,145]

The Mayo Clinic has the largest series of SCAD patients and has reported a high recurrence rate of 17% (occurring solely in women), a 10-year mortality rate of 7.7%, and a high MACE (death, recurrent SCAD, MI, and HF) rate of 47.4%.[139] These rates are higher than in previously reported registries, perhaps as a result of referral-related differences in patient populations.[136,146] In a recent analysis of 189 patients who presented with a first SCAD episode, the rates of procedural complications and PCI failure requiring emergency CABG were high, even in those who presented with vessel patency.

Those treated with conservative measures predominantly had favorable early outcomes, aside from a minority with SCAD progression within 7 days of presentation. Importantly, revascularization did not preclude the development of recurrent SCAD or late target vessel revascularization, so these patients need close follow-up over the long term.[147] The management of SCAD is controversial. Conservative measures for the most part have favorable outcomes, and revascularization is not without risk and perhaps should be performed in extreme circumstances such as ischemia caused by total vessel occlusion. There is a paucity of clinical data on the true prevalence and optimal management strategy of SCAD; much of what is currently known is based on angiographic and autopsy case reports/series.

Cardiovascular Risk Factors

Evolving sex-specific research has demonstrated that although men and women share similar risk factors for CHD, certain risk factors are more potent in women. These include tobacco abuse, type 2 DM, depression, and other psychosocial risk factors. The INTERHEART study data identified 9 potentially modifiable risk factors (smoking, hypertension, DM, waist-to-hip ratio, dietary patterns, physical activity, alcohol consumption, plasma apolipoproteins, and psychosocial factors) that account for 96% of the population-attributable risk of MI in women.[148] For young women with favorable levels of all 5 major traditional risk factors (smoking, hypertension, DM, serum cholesterol, and body mass index), CHD is a rare event, but unfortunately, only ≈20% of US women <40 years of age meet these low-risk criteria.[149] Almost 50% of women have a clustering of ≥3 metabolic risk factors for ischemic heart disease.[150] Data from the VIRGO study demonstrate that the prehealth status (physical and mental function, quality of life) of young women with AMI is poor compared with men.[151] A recent study of young women with AMI reported that women fail to accurately assess their personal risk of heart disease despite having a family history of CVD; women also reported limited access to preventive cardiac care before the AMI.[152] These studies reinforce the need for improved cardiovascular knowledge among women, including an emphasis on access to medical care for preventive measures.

Cigarette Smoking

Smoking is the single most important preventable cause of MI in women and a leading cause of MI in women <55 years of age, increasing their risk 7-fold.[153] In the INTERHEART study, a history of smoking had a stronger association with MI in men compared with women; however, current smoking history did not have significant variation by sex.[148] The triad of tobacco abuse, dyslipidemia, and familial CHD is common in young patients with AMI.[154,155] Among patients with AMI, women <55 years of age have a higher prevalence of tobacco abuse and obesity compared with older women.[72] The risk of AMI in women is substantially reduced within 1 or 2 years of smoking cessation and falls to the level of the risk of nonsmokers within 10 to 15 years.[1,156,157] Despite a general decline in tobacco use in the US population, this decline in recent decades has been less pronounced in women than in men.[158]

Hypertension

Hypertension is a major risk factor for MI in women, with a population-attributable risk of 36%, indicating that the risk of MI could be reduced by 36% if hypertension is eliminated as a risk factor. Hypertension is more strongly associated with MI in women compared with men.[148] In older women, isolated systolic hypertension is the most common form of hypertension. Women with a systolic blood pressure >185 mm Hg have a 3-fold increase in cardiac death compared with women with a level of ≤135 mm Hg.[159] Unfortunately, national surveys continue to show low rates of hypertension awareness, treatment, and control among women, although these rates have increased over time.[160,161]

Dyslipidemia

Elevated levels of total cholesterol and low-density lipoprotein cholesterol predict cardiac death in both middle-aged (<65 years) and older (≥65 years) women, but the strength and consistency of these relationships in older women are diminished.[162] Reduced high-density lipoprotein cholesterol and high triglyceride levels are powerful risk factors for CHD in women. Among 32 826 postmenopausal women from the Nurses' Health Study, high-density lipoprotein cholesterol was the lipid parameter that best discriminated risk of CHD.[163] Lipoproteins levels are associated with long-term cardiovascular risk; however, in the AMI setting, there is a lipid paradox: Patients with significantly lower triglycerides and low-density lipoprotein cholesterol levels have higher in-hospital[164] and 30-day mortality rates.[165] This seeming paradox may be due to competing risks of collider (index event) bias resulting from the selection of a diseased population[166] such as older age and higher rates of DM in those with lower lipoprotein levels in the acute setting. Sex specific data examining lipids at admission and AMI outcomes are lacking.

Obesity and Type 2 DM

One third of US women are obese and 7% are extremely obese, defined as a body mass index ≥40 kg/m^2.[1] Obesity is especially prevalent among black women: 54% are obese and 15% extremely obese.[167] Among women ≥60 years of age, the prevalence of obesity increased 6.6% between 2003 to 2004 and 2011 to 2012.[168] Increasing body weight is associated with increasing coronary risk, and women in the heaviest category show a 4-fold higher risk for cardiovascular events compared with lean women.[169] Obesity is a major risk factor for AMI in women and increases their risk almost 3-fold.[170] The risk of AMI associated with the metabolic syndrome is higher in younger women than any of the other groups, increasing their odds of AMI almost 5-fold.[171] DM, related to obesity and the metabolic syndrome, is associated with a higher relative risk of coronary events in women compared with men, in part as a result of a higher rate of coexisting risk factors in women with DM[170] and better survival (relative to men) of women without DM.[172] DM is an especially powerful risk factor in young women, increasing their risk of CHD, including ACS, by 4- to 5-fold.[173] For both men and women with DM, mortality after STEMI or UA/NSTEMI is significantly increased compared with their nondiabetic counterparts at 30 days and 1 year.[174]

Depression and Other Psychosocial Risk Factors

There is growing evidence that psychological factors and emotional stress can influence the onset and clinical course of ischemic heart disease, especially in women. In the INTERHEART study, an aggregate exposure to psychosocial risk factors, including depression, perceived home/work stress, low locus of control, and major life events, was significantly associated with AMI in women, with an adjusted odds ratio of 3.5.[148] Young women compared with young men presenting with AMI in the VIRGO study had significantly higher perceived stress scores.[175] These women had significantly higher rates of DM, depression, and previous PCI compared with men. They were also more likely to report stressful life events in the past year, including intrafamily conflict, major personal injury or illness, and death of a close family member. Compared with men, women also had worse physical and mental health. High stress at baseline was associated with worse recovery in multiple health outcomes 1 month after AMI.

Depression is ≈2-fold more prevalent in women than in men in the general population[176] and is an important risk factor for incident MI or cardiac death, increasing a woman's risk by at least 50%.[177,178] Recent evidence suggests that depression in women is a powerful predictor of early-onset MI, showing a more robust association with MI and cardiac death in young and middle-aged women than in men of similar ages.[179] Compared with young men, young women with AMI in the VIRGO trial were more likely to have a history of depression. Even after adjustment for socioeconomic, clinical, and disease severity characteristics, young women with AMI had 60% greater odds of having significant depressive symptoms than young men.[180] Severe childhood adversities such as physical and sexual abuse are emerging independent risk factors for the incidence of ischemic heart disease among women.[181,182] A recent meta-analysis showed that anxiety is a moderate but independent risk factor for incident ischemic heart disease and cardiac death in both men and women, although individual study results are heterogeneous.[183]

Clinical Presentation

Sex differences in clinical presentation among patients with ACS are increasingly evident.[184–186] Although most patients with AMI present with typical chest pain or chest discomfort, women often present with atypical chest pain and angina-equivalent symptoms such as dyspnea, weakness, fatigue, and indigestion, as illustrated in Table 1.[187] Sex differences in clinical presentation have consequences for timely identification of ischemic symptoms, appropriate triage, and judicious diagnostic testing and management. The detrimental consequences for women are misdiagnosis, delayed revascularization, and higher AMI mortality rates.

Symptoms of AMI

Compared with men, women are more likely to have high-risk presentations and less likely to manifest central chest pain.[41,185,188] Pain in the upper back, arm, neck, and jaw, as well as unusual fatigue, dyspnea, indigestion, nausea/vomiting, palpitations, weakness, and a sense of dread, occur more frequently in women compared with men.[189–193] Ischemic symptoms in young black women include unusual fatigue, shortness of breath, chest discomfort, or frequent indigestion, with older white women displaying fewer symptoms.[188,194] Shoulder pain and arm pain are twice as predictive of an ACS diagnosis in women compared with men.[195]

Table 1. Typical Versus Atypical Symptoms in Women Presenting With AMI

Typical Symptoms	Atypical Symptoms
Chest pain/discomfort (pressure, tightness, squeezing)	Chest pain: sharp, pleuritic, burning, aching, soreness, reproducible
Additional symptoms with chest pain Radiation of pain to jaw, neck, shoulders, arm, back, epigastrium Associated symptoms: dyspnea, nausea, vomiting, lightheadedness, diaphoresis	Other symptoms excluding chest pain Unusual fatigue Unusual shortness of breath Upper back/chest pain Neck, jaw, arm, shoulder, back, epigastric pain Flu-like symptoms Dizziness Generalized scared/anxiety feeling Generalized weakness Indigestion Palpitations

AMI indicates acute myocardial infarction.

Among young patients in the Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome (GENESIS PRAXY) study, chest pain was the most prevalent symptom in both sexes, regardless of the type of ACS. However, women were more likely to present with more symptoms but less chest pain compared with men.[185] Similarly, compared with men, women ≤45 years of age with AMI are significantly more likely to present without chest pain and to have higher in-hospital mortality.[41] A qualitative study of women 30 to 55 years of age with AMI found that although they reported a diverse range of symptoms from discomfort or pain (eg, chest, neck and jaw) to more general symptoms (eg, sweating, anxiety, fatigue, and dizziness), the majority reported chest pain.[152] Other women reported more nuanced symptoms that would pass, recur, or build over days, weeks, and months before the AMI. These young women failed to consider CHD as the potential underlying cause of their symptoms, and fear of being perceived as hypochondriacal if they were not in fact having an AMI was a predominant theme.[152] Women not only have unique symptoms but also have less obstructive CHD along the spectrum of ACS.[99] Ischemic symptoms independently predict subsequent ACS in women despite normal coronary arteries, and plaque disruption is evident in almost 40% of women with ACS and nonobstructive CHD.[111,196]

Variance in clinical presentation may explain some of the sex disparities in mortality. Women have longer presentation and treatment times, which may contribute to their worse in-hospital mortality.[197] Coronary angiography is used less often in women, largely because their risk is underestimated, yet women have significantly higher mortality rates than men regardless

of age.[30] What accounts for this excess risk is unclear, but the absence of chest pain may be more predictive of mortality in younger women with MI than in other similar age groups.[41]

Sudden Cardiac Death

The incidence of SCD in the United States has been estimated to be 200 000 to 400 000 per year.[198] Few studies have addressed sex differences in rates, causes, or presentation to the emergency room. Analyses of SCD by sex have been largely limited by small sample sizes.

Association With AMI

SCD is relatively common in the era of modern coronary interventions, yet even with guideline-based therapies, SCD after MI accounts for 50% of overall mortality.[199] The rates of survival from SCD remain an abysmally low 5%.[200] The prevalence of SCD is increasing in the United States, with women now making up 40% of all cases.[201] The frequency of SCD among MI survivors was lower among 1004 patients in Germany and Finland who receive optimized medical therapy compared with those who did not (1.2% versus 3.6%; $P<0.01$).[202] Pathogenesis of SCD was examined in an analysis of 105 autopsy records from patients enrolled in the Valsartan in Acute Myocardial Infarction Trial (VALIANT).[199] Nearly 50% of cases were attributed to recurrent MI (26.6%), cardiac rupture (12.4%), or pump failure (3.8%) within 1 month of the index MI. In contrast, after 3 months, SCD was attributed predominantly to arrhythmia. Data from this study were not disaggregated by sex. History of atrial fibrillation (AF) has also been associated with a higher incidence of ventricular fibrillation after MI. Among 500 consecutive patients, ventricular fibrillation was higher in patients presenting with AF compared with those without AF. This study found a circadian variation in only men, with time of occurrence of SCD more likely during the hours of 4 and 8 am (13.1%) and 8 pm and midnight (19.8%; $P<.05$).[203]

Predictors of SCD

Severe left ventricular dysfunction has been associated with an increased risk of SCD and remains the major indication for implantation of implantable cardioverter-defibrillators (ICDs).[204] However, in a community-wide study of 714 patients, a higher proportion of women had normal left ventricular ejection fraction.[204] Characteristics associated with normal left ventricular function and SCD included younger age, female sex, seizure disorder, specific medications, and a lower likelihood of recognized CAD.[204] In a small Chinese study, T-wave alternans predicted SCD in post-MI patients; however, women were underrepresented in this study. Subanalysis by sex was not possible because only 10 deaths occurred.[205] A retrospective study of 2665 cases of SCD in Greece showed a circadian rhythm of SCD, with the peak incidence during 8 pm to midnight and a low incidence during the hours of 4 to 8 am. This pattern was seen in both men and women but was not significant in women.[206]

Delay in Presentation

Time to Presentation

Prehospital median delay times in seeking treatment for symptoms of AMI have ranged from 1.4 to 53.7 hours.[207,208] However, the majority of studies suggest the median delay ranges from 2 to 5 hours,[209] exceeding AHA recommendations by hours, not minutes. One study showed that women tend to call 9-1-1 more often than men when experiencing an AMI; however, rates for both sexes are not optimal and suggest the need for educational initiatives to increase awareness of when to call 9-1-1.[210] Compared with young men with AMI in the VIRGO trial, young women who were eligible for and received reperfusion therapy were more likely to present with atypical chest pain or no symptoms (16% versus 10%; $P=0.008$) and more likely to present >6 hours after symptom onset (35% versus 23%; $P=0.002$).[16]

Factors Associated With Delay

A number of studies have shown that women present later to treatment for AMI than men.[209,211,212] In 1 study, the median delay time was 53.7 hours for women and 15.6 hours for men.[213] Delays in seeking medical care for symptoms plausibly contribute to poorer outcomes for women.[214] Delay in seeking treatment for AMI is often due to lack of awareness of risk, passivity, inaccurate symptom attribution, and barriers to self-care.[152,215] Additional factors associated with increased delay in seeking treatment for AMI include older age, female sex, Black or Hispanic race, and lower education and socioeconomic levels.[209] Having a history of angina, DM, hypertension, HF, or dyslipidemia is also associated with longer treatment-seeking delays. Living alone, interpreting symptoms as nonurgent and temporary, consulting with a physician or family member, fear, and embarrassment also lead to treatment-seeking delays.[209]

Treatment of AMI

Women are less frequently referred for appropriate treatment during an AMI compared with men despite proven mortality benefits of therapy. Regardless of treatment strategy with thrombolytic therapy or PCI, women manifest worse outcomes than men, but this is often due to other confounding risk factors. Women have a more favorable outcome with PCI compared with thrombolytic therapy in the setting of STEMI and benefit from an early invasive strategy in the setting of a NSTEMI.[216,217] Table 2 summarizes the key findings for the reperfusion strategies and pharmacotherapy in the treatment of AMI in women. All recommendations in the table were derived from previously published American College of Cardiology (ACC)/AHA guidelines.[57,216,217]

STEMI Revascularization

Thrombolytic Therapy

Thrombolytic therapy, especially when administered early, reduces mortality regardless of sex and age.[218] In the recent ACC/AHA STEMI guidelines, thrombolytic therapy is recommended in patients without contraindications who present to a non–PCI-capable hospital and there is an anticipated delay to performing PCI within 120 minutes of first medical contact (Class I, Level of Evidence A)[216]; however, there are no sex-specific recommendations. Women treated with thrombolytics have higher morbidity and mortality rates than men, explained partly by worse baseline clinical profiles (including age and rates of DM, hypertension, and HF).[18,37,219,220] In addition to increased mortality, the Global Utilization of

Table 2. Treatment of AMI in Women: Outcomes and Guideline-Based Recommendations

STEMI reperfusion strategies	
Thrombolytics	Higher risk of mortality and bleeding complications compared with PCI
	Use at non–PCI-capable hospitals when a significant delay to performing primary PCI within 120 min of first medical contact is anticipated[216]
	No sex-specific recommendations for utility of agents
PCI	Primary PCI has a lower 30-d mortality compared with thrombolytics
	Reduced risk of intracranial bleeding compared with thrombolytics but still high risk of vascular complications
	Decreased MACEs and target vessel revascularization with stenting compared with angioplasty
	PCI is preferred reperfusion strategy compared with thrombolytics,[216] but there are no sex-specific recommendations
CABG	Women have increased risk of in-hospital mortality compared with men
	No sex-specific data or recommendations on utility
NSTEMI revascularization strategies	
PCI	Reduced mortality and recurrent MI with early invasive strategy in high-risk women Women with high-risk features should undergo an early invasive strategy[217]
Medical management	Reduced risk of recurrent ischemic events with aspirin
	Reduced risk of thrombotic complications with antithrombotic agents
	Increased bleeding risks in women with antiplatelet and antithrombotic agents; careful attention should be given to weight and renal calculation of doses when indicated[217]
	Women with NSTEMI should be managed with the same pharmacological therapy (aspirin, $P2Y_{12}$ receptor inhibitors, anticoagulants, statins, β-blockers and ACE inhibitors) as men in the acute setting and for secondary prevention[217]
	No sex-specific recommendations for STEMI patients
Aggressive behavioral interventions	Smoking cessation[57,216,217]
	Referral to a comprehensive CR program that includes education on lifestyle and stress management, appropriate weight maintenance, dietary changes, and physical activity[57,216]

This table summarizes findings from the literature review of AMI in women (see text). It is not the intent of the writing group to formulate specific treatment recommendations; this table provides a synopsis of the available data. All recommendations are cited from previously published American College of Cardiology/American Heart Association guidelines.[57,216,217] ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; CR, cardiovascular rehabilitation; MACE, major adverse cardiovascular event; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial showed that women have more nonfatal complications such as shock, HF, reinfarction, recurrent ischemia, bleeding, and stroke compared with men.[15] The increased risk of reinfarction in women was confirmed in the Assessment of the Safety of a New Thrombolytic (ASSENT-2) trial and was associated with less aggressive management and higher mortality compared with men.[221] The use of enoxaparin as an adjunct to thrombolytic therapy reduced the 30-day rate of death and reinfarction in women but increased the risk of bleeding.[222] Despite these clinical outcome differences, thrombolytic success as judged by 90-minute patency rates and global ejection fraction (immediate and at day 7) was similar between women and men in the GUSTO trial.[220] Conversely, there was greater hyperkinesis of the noninfarct zone and a trend for higher reocclusion (8.7% versus 5.1%; P=0.14) in women after thrombolytic therapy.

Women are at particular higher risk of bleeding complications, and in the GUSTO-1 trial, the risk of moderate or severe bleeding was increased 1.43-fold in women.[15] Female sex is an independent predictor of intracranial bleeding with thrombolytic therapy.[223] Moreover, women often have multiple relative contraindications (advanced age, hypertension, and small body size) that make physicians reluctant to use thrombolytic therapy in female patients. There was no significant increase in severe bleeding in menstruating women compared with nonmenstruating women.[224] There was, however, a significant increase in moderate bleeding that was offset by the benefits of fibrinolytic therapy.

Overall, thrombolytics are beneficial and have been shown to significantly reduce mortality and morbidity within 12 hours of symptom onset. Fibrinolytics have an important role in the treatment of STEMI patients without contraindications to thrombolytics who have an anticipated delay of >120 minutes to a PCI-capable facility.[216]

Primary PCI

Complications of thrombolytic therapy and its perceived lack of eligibility have limited its use in most developed countries. Because women have the most complications from thrombolytic therapy, it would stand to reason that they benefit the most from primary PCI. A pooled analysis of 22 trials[225] that randomized 6763 STEMI patients to primary PCI versus thrombolytics found that women had lower 30-day mortality with primary PCI, regardless of whether they presented within the first 2 hours of symptom onset (7.7% versus 9.6%) or after >2-hour delay (8.5% versus 14.4%). Of note was the extremely high mortality in women with delay in presentation treated with thrombolytic therapy.

Use of primary angioplasty virtually eliminates the risk of intracranial bleeding and was an independent predictor of survival in women.[226] The greater mortality benefit of primary PCI compared with thrombolytic therapy was confirmed in the GUSTO II-B angioplasty substudy, with primary PCI preventing 56 deaths in women compared with 42 deaths in men per 1000 treated.[227] Despite the improved prognosis in women treated with primary PCI, a recent meta-analysis of observational studies reported that even after adjustment for baseline differences, women have a higher risk of in-hospital mortality (relative risk, 1.48; 95% confidence interval, 1.07–2.05).[228]

Although primary PCI has a reduced risk of intracranial bleeding compared with thrombolytic therapy, women remain at higher risk of non–central nervous system bleeding events. Vascular complications and the need for blood transfusions occur more frequently in women, even when weight-adjusted antithrombin agents are used,[229,230] and female sex remains an independent predictor of bleeding.[231]

Although early-generation stenting was associated with higher mortality in women,[232] later studies found that bare metal stenting during primary PCI compared with angioplasty in women reduced MACE rates and target vessel revascularization, without influencing death or reinfarction rates.[229] A patient-level pooled analysis comparing stent choice in women found that newer-generation drug eluting stents (DES) were associated with reduced death or MI and reduced target vessel revascularization compared with both early-generation DES and bare metal stents; however, these data were not exclusively from STEMI patients.[233]

CABG Surgery

Although multivessel disease is observed in 50% of STEMI patients who undergo urgent catheterization, use of emergency CABG during AMI is extremely rare. Typically, the culprit vessel is treated with primary PCI if the culprit vessel is occluded. Once patency is restored, the patient may be reassessed for CABG at a later time. No sex-specific studies were found addressing STEMI patients undergoing CABG; therefore, studies of all-comers were reviewed. Both a systematic review of 23 published CABG studies that reported data stratified by sex[234] and a mandatory registry of 40 000 patients undergoing CABG in California[235] showed that women are older and sicker at the time of CABG. Adjusting for baseline differences reduced, but did not eliminate, an increased risk of in-hospital mortality in women. Moreover, women were less likely to receive an internal mammary graft[235] and had more postoperative complications such as renal failure neurological complications, and postoperative MI.[236]

NSTEMI Revascularization

Women with NSTEMI have more complications than men, including bleeding, HF, shock, renal failure, reinfarction, stroke, and readmission. Numerous studies have found that women benefit from invasive management of NSTEMI,[237–239] and in the recent ACC/AHA NSTEMI guidelines, an early invasive strategy is a Class I, Level of Evidence A recommendation in women with high-risk features.[217] This recommendation is based on several studies using post hoc sex analyses[239–241] and a meta-analysis[238] that demonstrated a significant reduction in death and MI at 1 year with an early invasive strategy in women with high-risk features. The meta-analysis also showed a significant 33% reduction in death, MI, or rehospitalization for ACS (odds ratio, 0.67; 95% confidence interval, 0.50–0.88) in women treated invasively. Evidence-based guidelines recommend that myocardial revascularization is reasonable in pregnant women with NSTEMI if medical therapy was ineffective for the management of life-threatening complications (Class IIa, Level of Evidence C).[217]

Studies investigating the use of DES found no sex differences in short- and long-term outcomes, including cardiac death, AMI, MACEs, or target vessel revascularization.[242–244] Recent pooled data show that newer-generation DES have a better safety and efficacy profile compared with older-generation DES and bare metal stents.[233] However, these data on DES are not specific to AMI patients.

Women with NSTEMI who undergo CABG have more postoperative complications such as need for vasopressors, intra-aortic balloon pump, ventilator support, dialysis, and transfusions,[27,234,235,242–244] but the long-term risk of death, MI, or stroke is similar between women and men.[245] Although some of the early randomized, clinical trials found that a higher event rate in the invasive arm was due to complications from CABG in women,[240] more recent studies suggest a more favorable prognosis in women who require CABG.[246]

Medical Therapies

The goals of pharmacotherapy are to reduce morbidity and mortality, to prevent complications, and to improve quality of life. The core post-MI medications are antiplatelet agents, β-blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), and statins.[216,217] The efficacy and safety of these medications have been established through rigorous randomized, clinical trials that have included both men and women. Firm data on sex differences in treatment efficacy and safety are somewhat limited because many post-MI intervention trials enrolled few women. However, similar benefits have been observed regardless of sex. The 2014 ACC/AHA NSTEMI guidelines recommend that women with NSTEMI be treated with the same pharmacological agents as those used in men for both acute care and secondary prevention of MI.[217] This is a Class I, Level of Evidence B recommendation that also recommends consideration of weight and renal dosing of antiplatelet and anticoagulant agents because of the higher bleeding risks in women.[8,247–249] Despite this evidence for efficacy, observational studies show consistent underuse of these guideline-recommended therapies among women compared with men with AMI.[8,30,250] Women with nonobstructive CAD and MI are less likely to be prescribed medications for secondary prevention of MI (including antiplatelet agents and statins),[251] and these women have increased rates of readmission, reinfarction, and death in the first year after MI.[252–254]

Equally important for women after AMI is the discontinuation of harmful drugs or drugs that are of no benefit. Hormone therapy with estrogen plus progestin or estrogen alone should not be given de novo to postmenopausal women after AMI for secondary prevention of coronary events. Furthermore, postmenopausal women who are already taking estrogen plus progestin or estrogen alone at the time of their MI, in general, should discontinue taking these agents.[216,217] If women wish to continue hormone therapy for another compelling indication, they should weigh the risks and benefits, recognizing the greater risk of cardiovascular events. Antioxidant vitamin supplements (eg, vitamins E and C and beta-carotene) and folic acid, with or without B_6 and B_{12}, should not be used for secondary prevention after MI because there is no evidence of benefit.[57,216,217]

Antiplatelet Agents and Anticoagulant Therapy

In secondary prevention trials, the benefit of aspirin in preventing recurrent ischemic events was similar in men and women.

The Second International Study of Infarct Survival (ISIS-2) trial found that the reduction in vascular mortality with aspirin versus placebo therapy after AMI was 22% for men and slightly lower at 16% for women.[255] In a 2009 meta-analysis, placebo-controlled secondary prevention trials that compared antiplatelet therapy (primarily aspirin) with placebo were analyzed in men and women.[256] Antiplatelet agents were found to reduce the overall risk of any serious vascular event by 19% and to reduce the risk of ischemic stroke by 22%. A meta-analysis of randomized, clinical trials of aspirin documented that among both men and women with prior vascular disease, aspirin treatment reduced the risk of subsequent cardiovascular events by ≈25%.[257] Studies have compared the efficacy of aspirin and other antiplatelet agents in men versus women. In an analysis evaluating 11 265 patients with a history of MI and 6765 patients with a history of cerebrovascular disease (transient ischemic attack or stroke), aspirin reduced the risk of a major coronary event—nonfatal MI or coronary death—to a similar degree in men and women (19% reduction in men and 25% reduction in women) and reduced the risk of stroke (17% reduction in men and 22% reduction in women) to a similar degree.[258] The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial showed no significant difference in the composite risk of cardiovascular death, MI, and stroke between higher- (300–325 mg daily) and lower- (75–100 mg daily) maintenance-dose aspirin among ACS patients; consistent treatment effects were seen among men and women in prespecified subgroup analyses (interaction P=0.59).[259]

In a meta-analysis of 5 large randomized, clinical trials, clopidogrel treatment was associated with a significant overall cardiovascular risk reduction compared with placebo in both men and women. Women made up 20% to 39% of the total population in these studies. However, the reduction in risk among women was significant only for MI, not for stroke or all-cause mortality, whereas significant reductions in all 3 end points were seen for men. There was no statistically significant heterogeneity when the effect of clopidogrel was compared between the sexes, suggesting that this observation could be the result of chance alone.[260] For higher-potency $P2Y_{12}$ receptor inhibitors such as prasugrel and ticagrelor, no significant interaction with sex was observed in studies of the effect of each drug on MACEs.[261–263]

A significant interaction between treatment and sex has been observed in trials of glycoprotein IIb/IIIa inhibitors with respect to cardiovascular events. Although glycoprotein IIb/IIIa inhibitor use was associated with a significantly lower incidence of death or MI at 30 days compared with placebo among men with ACS, women had worse outcomes with glycoprotein IIb/IIIa inhibitor treatment.[264,265] When risk was further stratified by troponin level, no sex differences were seen. More recent studies in the setting of concurrent clopidogrel use have not shown sex-related differences in outcomes associated with glycoprotein IIb/IIIa inhibitor use.[265] Among STEMI patients, early glycoprotein IIb/IIIa inhibitor use was associated with enhanced patency of the infarct-related artery before primary PCI and improved epicardial flow and reduced mortality after primary PCI in women.[266]

Anticoagulant therapy prevents thrombus formation at the site of arterial injury and reduces thrombotic complications during PCI and is, according to the ACC/AHA guidelines, a Class I recommendation for STEMI[216] and NSTEMI[217] patients, regardless of the revascularization strategy. Early studies conducted primarily in the era before the routine use of early invasive strategies and dual antiplatelet therapy showed a reduction in cardiovascular events with the addition of unfractionated heparin to aspirin therapy.[267] Low-molecular-weight heparins were found to have similar efficacy among patients with NSTEMI ACS and those with STEMI treated with fibrinolysis compared with unfractionated heparin.[268–270] The direct thrombin inhibitor bivalirudin was also found to be noninferior to either unfractionated or low-molecular-weight heparin in combination with glycoprotein IIb/IIIa inhibitors among NSTEMI ACS patients and reduced cardiovascular death among STEMI patients. Bivalirudin is not considered a preferred agent over the combination of unfractionated heparin and glycoprotein IIb/IIIa inhibitors in the NSTEMI and STEMI guidelines, with the exception of patients undergoing PCI who are at a high risk of bleeding. In those patients, it is reasonable to use bivalirudin monotherapy in preference to these agents.[216,217,271,272] Patients treated with fondaparinux, a selective factor Xa inhibitor, had ischemic outcomes similar to those treated with enoxaparin or unfractionated heparin.[273,274] Sex differences in the effectiveness of these anticoagulants have not been well described. In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, no differences were observed in the 1-year composite ischemia or mortality end point in women who received bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitor.[248] Prespecified subgroup analyses for fondaparinux also showed no significant differences in efficacy between men and women.[273]

Antiplatelet therapy is of proven benefit in the treatment of women after MI. Antiplatelet therapy has also been shown to be safe; however, women have significantly higher rates of bleeding after MI than men.[216] The 2013 ACC/AHA STEMI guidelines state that female sex is a risk factor for bleeding complications after STEMI, but there are no sex-specific recommendations for indications for the use of antiplatelet or anticoagulant therapies.[216] The recent 2014 ACC/AHA NSTEMI-ACS guidelines recommend that women receive pharmacotherapy similar to that given to men in the acute setting of an NSTEMI and for secondary prevention; however, to reduce bleeding risk in women, careful attention to weight and renal function when dosing antiplatelet and anticoagulant agents is warranted (Class I, Level of Evidence B).[217] Clinicians should also be cognizant that in premenopausal women who are still menstruating, antiplatelet therapy may significantly increase menstrual bleeding.[217]

β-Blockers

β-Blocker therapy after MI has been associated with improved outcomes.[275] Treatment with a β-blocker decreases the incidence of ventricular arrhythmias, recurrent ischemia, reinfarction, infarct size, and mortality. Treatment with β-blockers is associated with a 21% reduction in mortality, a 30% reduction in sudden death, and a 25% lower reinfarction rate,[276,277] with reportedly similar benefits in women and men in some

studies.[278] Despite this evidence of benefit, β-blockers, like other cardiovascular therapies, are often underused in women.[8] Nonselective β-blockers should be avoided in patients whose AMI is due to coronary arterial vasospasm because these medications can exacerbate vasospasm, which is probably explained by the blockade of vasodilator coronary β_2 receptors, resulting in unopposed vasoconstrictor α-adrenergic receptors.[118]

ACE Inhibitors/ARBs

Use of ACE inhibitors has been shown in numerous randomized, clinical trials to improve survival and to attenuate left ventricular dilatation after MI.[279–282] ARBs have been shown to be as effective as ACE inhibitors and are considered an alternative treatment option.[283] Women are underrepresented in trials examining ACE inhibitors and ARBs in post-MI care, and no sex-specific trials have been found. A meta-analysis of ACE inhibitor studies demonstrated a favorable trend toward improved survival (13.14% versus 20.1%) and in the combined end point of mortality and hospitalization (20.2% versus 29.5%) in women treated with ACE inhibitors compared with those not on the drug.[284] Another meta-analysis showed that both women and men with symptomatic HF benefit from ACE inhibitors. However, in asymptomatic HF patients, a significant mortality benefit was not seen in women but was seen in men.[285]

ACE inhibitors taken during pregnancy have been reported to cause congenital malformations, stillbirths, and neonatal deaths and thus are contraindicated. The number of drug-related adverse events has been considerably lower with ARBs than ACE inhibitors,[286] but the risks of hyperkalemia,[287] renal dysfunction,[288] and teratogenicity[289] are equivalent between ARBs and ACE inhibitors. ACE inhibitors and ARBs are pregnancy category C (animal studies have shown an adverse effect on the fetus) for the first trimester of pregnancy and are labeled pregnancy category D (human fetal risk has been shown) during the second and third trimesters.

Statins

Statin therapy is another mainstay of post-MI pharmacotherapy. The Scandinavian Simvastatin Survival Study (4S) trial, a secondary prevention study of 4444 patients who had angina or prior MI and elevated cholesterol, showed a relative risk of cardiac death of 0.70 in subjects randomized to receive statin.[290] In a subgroup analysis of 420 women in the treatment group, the relative risk of CHD mortality was 0.86 (95% confidence interval, 0.42–1.74) compared with 407 women on placebo. Another large statin trial, the Cholesterol and Recurrent Events (CARE) study, evaluated 4159 subjects with prior MI but only modestly elevated cholesterol levels and found that after 5 years of treatment with a statin, both men and women had fewer cardiovascular events.[291] In a substudy of 576 women in the CARE trial, within 6 to 12 months after therapy began, women randomized to a statin had a 43% lower risk in death resulting from CHD and a 57% reduction in recurrent MI. A secondary prevention trial, the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, analyzed a subgroup of 1516 women and found that women experienced a benefit from lipid-lowering therapy with a statin similar to that seen in men.[292] In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, which included 21.9% women, intensive therapy in women was associated with a significant 25% relative reduction in the primary composite end point in women compared with a 14% reduction in men. There were no sex-related differences with respect to safety.[293]

These studies demonstrate a beneficial role of statin therapy in patients at risk for CHD, regardless of sex. A meta-analysis found that statin therapy was an effective secondary prevention intervention in both men and women but that there was no benefit on stroke or all-cause mortality among women.[294] A recent study evaluating the impact of sex on lipid lowering, cardiovascular events, and adverse events in 6 large, randomized, clinical trials found that changes in lipids were similar in men and women.[295] In women but not men, low-density lipoprotein cholesterol was a significant predictor of stroke. Discontinuation rates resulting from adverse events were higher in women in most of the trials reviewed. It is important to note that all statins are pregnancy category X, meaning studies in animals or humans have demonstrated fetal abnormalities, so they must not be used during pregnancy.

Nonpharmacological Treatment

Cardiac Rehabilitation Referral and Participation

Cardiac rehabilitation (CR) is an essential component of comprehensive care after AMI, is internationally endorsed,[296–300] is integrated in effectiveness-based guidelines for women,[57] and reveals incontrovertible morbidity and mortality benefits.[301–304] CR after AMI is a Class I recommendation in evidence-based guidelines.[57,216,217,305,306] Although referral to CR is designated as a performance measure of healthcare quality after AMI,[307,308] CR has failed to reach >80% of eligible women in the last 3 decades.[57,296,299,300,307,309] Women particularly absent from CR include the uninsured, unmarried, socioeconomically disadvantaged, smokers, depressed, obese, sedentary, elderly, and nonwhite and those with less education, less social support, and competing family obligations.[310–317] Depressive symptoms are linked to suboptimal CR attendance, and depressed women have a 2-fold increased risk of noncompletion.[318–320] Evidence suggests that CR exercise training improves depression in women.[320,321]

The prevailing paradigm of CR is based largely on research conducted in men.[303] Therefore, interventions for increasing CR referral, enrollment, and adherence of women are scarce, although tailored approaches increase the likelihood of success.[322,323] Even with a CR referral, women participate in CR and complete it less frequently than men. Patient-oriented, medical, and healthcare system factors variably account for poor CR attendance among eligible women.[300,315,324–326] A primary predictor of dismal attendance is lack of physician endorsement of CR.[324,327]

Novel strategies for secondary prevention for women, an underserved segment of CR populations, are warranted, given their adverse psychosocial profiles and poor completion rates.

One recent randomized, controlled trial examined the effects of a motivationally enhanced CR designed exclusively for women with CHD compared with traditional CR on physiological and psychosocial outcomes.[328] Women completing the tailored intervention had significantly improved quality of life and depressive symptoms that were sustained at 6 months compared with those completing traditional CR.[320,329] The tailored intervention also improved 4 dimensions of health: vitality, social functioning, general health, and mental health.[330] Compared with traditional CR, the tailored intervention resulted in significantly greater attendance and higher completion rates.

Home-based CR models may be an effective and realistic alternative or supplement for women with significant barriers to attending structured outpatient programs. Novel healthcare models using mobile phones, the Internet, and other communication technologies to deliver CR services to patients in their homes are being investigated.[331–333]

Sexual Counseling

Sexual dysfunction among women after an AMI has received less attention compared with counseling for men,[334] and few AMI patients receive adequate information about sexual health and sexual activity.[335–337] In the VIRGO study, only 12% of young women reported discussing sexual activity with a physician in the month after AMI.[338] Those who did were commonly given restrictions on sexual activity not supported by evidence-based guidelines. Guidelines for the safe return to sexual activity are available to assist healthcare professionals to provide individualized and culturally sensitive sexual counseling.[339,340] Women recovering from an AMI require information specific to their concerns, which might include vaginal dryness, decreased libido, orgasmic problems, or adverse drug effects. Psychological factors, including fear, anxiety, and depression, can negatively influence the resumption of sexual activity of women and their partners after an AMI. Sexual counseling with cognitive behavioral techniques should begin with a face-to-face discussion with both the patient and partner to ensure that sexual problems are addressed and that both receive the same counseling information and benefit from the education and support of the healthcare team.[336] Discussions can be supplemented with pamphlets and other resources provided for review in the outpatient setting. CR is an ideal setting in which to discuss sexual activity within the context of exercise recommendations.

Complications After AMI

Complication rates after MI are higher in women than in men despite similar success rates with treatment. Women with AMI are more likely to suffer from bleeding complications, which are often secondary to pharmacological therapies or invasive procedures. Mechanical complications and HF are more likely to develop in women, whereas ventricular arrhythmias occur at similar rates in both sexes after an AMI. Aside from traditional prognostic risk factors, psychosocial risk factors have now also been implicated in the development of adverse outcomes in post-MI women.

Bleeding Complications

Antithrombotic and antiplatelet agents are central to the treatment of AMI in women, but they also pose risks of bleeding. Data from 24 045 patients of the Global Registry of Acute Coronary Events (GRACE) trial indicated that women versus men had a 43% increased risk of bleeding during hospitalization[341]; the risk appears to be even higher in the setting of STEMI (odds ratio, 1.71). Women undergoing PCI also showed a significantly higher incidence of in-hospital major bleeding, including access-related complications, compared with men.[249] This increased bleeding risk appears to be related at least in part to inappropriate dosing of antithrombotic therapies.[342] In these analyses, women had a higher risk for bleeding with antithrombotic therapy independently of age, weight, baseline blood pressure, renal function, baseline hematocrit, and other potential confounders. Most bleeding is procedure related and is associated with high morbidity and mortality.[343–345] Vascular access site bleeding is the most common type of bleeding after STEMI, and trials have identified female sex as one of the risk factors for femoral access site bleeding.[346] Other factors associated with access site bleeding are larger sheath size, postprocedural heparin use, higher activated clotting times, and late postprocedural sheath removal.

In studies of fibrinolytic therapy for AMI, women have significantly more bleeding than men. Female sex, even after adjustment for the presence of other factors, is a potent predictor of bleeding, especially intracranial hemorrhage.[319,347] In multivariate analyses, the 3 most powerful independent predictors of hemorrhage are older age, lower body weight, and female sex.

Lifelong antiplatelet therapy is recommended for women after MI. Several antiplatelet therapies have specific dosing instructions by age, weight, and renal function of the patient.[348] For women, careful monitoring of antithrombotic therapy has been shown to decrease bleeding.[349,350] The effectiveness of various bleeding avoidance strategies (vascular closure devices, bivalirudin, radial access, and combined approach) was studied in a large cohort of >500 000 from the CathPCI registry. Investigators found that the use of any bleeding avoidance strategy differed slightly between women and men (75.4% versus 75.7%; P=0.01) and that women had significantly higher rates of bleeding than men when bleeding avoidance strategies were not used (12.5% versus 6.2%; P<0.01).[351] The Study of Access Site for Enhancement of PCI for Women (SAFE-PCI) was the first randomized trial of specific PCI access strategies that was exclusive to women only. The trial demonstrated reductions in bleeding or vascular complications with the radial access approach in women undergoing elective or urgent cardiac catheterization. Fewer than 7% of patients were converted from radial to femoral approach as a result of arterial spasm. In a subgroup analysis of women undergoing PCI, radial access showed a trend toward benefit but did not significantly reduce bleeding or vascular complications. A major limitation of this study is the early termination of enrollment because of lower-than-expected bleeding or vascular complication rates; as a result, the PCI cohort sample size was much smaller than expected.[352]

Women continue to have almost twice the rate of bleeding after PCI as men.[249,353] It is prudent to pay careful attention

to body weight, renal function, and dosing guidelines in women.[349,350] It is also important to continue evaluating for effective strategies to limit post-PCI bleeding in women.

Cardiogenic Shock

Cardiogenic shock (CS) associated with AMI is most often due to pump failure in the setting of extensive anterior AMI.[354,355] Other causes of CS include mechanical complications of AMI and right ventricular infarct.[357] CS usually occurs within 24 hours of presentation and carries a mortality rate of 48% to 70%.[354,356–358] Early revascularization has been shown to reduce mortality from AMI-associated CS and may account for the recent reduction in in-hospital mortality attributed to CS.[357–362]

Women are at increased risk of developing CS in the setting of AMI despite presenting with less extensive CAD and smaller infarct size.[15,354,363,364] Patient factors that may contribute to the increased prevalence of CS in women with MI include older age, higher rates of DM and hypertension, and higher incidence of underlying HF.[9,247,365–369] Given the significant mortality benefit of early revascularization in the setting of AMI-associated CS, early revascularization (PCI or CABG) is recommended for all patients without contraindication who develop CS as a result of pump failure after AMI.[359,362,370] The use of an intra-aortic balloon pump is reasonable for hemodynamic support for women with CS that does not quickly stabilize with pharmacological therapy. Those patients with refractory shock may be considered candidates for circulatory support with alternative left ventricular assist devices.[357,360]

Heart Failure

Women are more likely to develop symptoms of HF in the setting of AMI.[15,247,371] Several studies have identified that women have a higher Killip class at presentation for AMI.[9,363,372] This may be related to higher rates of underlying hypertension, DM, and HF or may be due to longer delay in presentation to the hospital.[12,14,15,247,365–369] Given the significant mortality benefit of early revascularization for patients with ACS, women with AMI-associated HF should undergo early angiography with subsequent risk stratification and revascularization when appropriate.[216,217,354] Medical stabilization with diuretics, vasodilators, inotropes, and percutaneous mechanical support should be provided when clinically indicated.[216,217,357,360]

Even after adjustment for age, comorbidities, and disease severity, several studies have identified that women with AMI are less likely to receive appropriate medications on presentation or at hospital discharge, including ACE inhibitors, β-blockers, and statins.[8–10] In the absence of contraindications, STEMI patients with anterior location, HF, or reduced left ventricular ejection fraction of <40% should receive an ACE inhibitor or ARB within 24 hours of presentation.[216,217] After stabilization of HF, women with AMI-associated HF should receive a β-blocker.[216,217] If women with AMI-associated HF are receiving therapeutic doses of an ACE inhibitor and β-blocker and have a left ventricular ejection fraction ≤40%, they should be prescribed an aldosterone antagonist in the absence of contraindications.[216,217]

Mechanical Complications

Mechanical complications account for 12% of cases of AMI-associated CS.[354] Mechanical complications after AMI are associated with high mortality rates and usually require urgent surgical intervention.[354,373–375] Women are at a higher risk of developing mechanical complications after MI, but sex-specific data on treatment are sparse.

Women are at increased risk of developing acute severe mitral regurgitation after AMI.[373] Acute severe mitral regurgitation represents 7% of all cases of AMI-associated CS and can be related to papillary muscle rupture or post-AMI left ventricular remodeling with displacement of the papillary muscles and tethering of the mitral valve leaflets.[354,373,376,377] Acute severe mitral regurgitation often occurs within 24 hours of presentation, results in rapid hemodynamic deterioration, and carries a mortality rate of 55%.[354,373,378] Emergent surgery should be pursued for suitable surgical candidates with papillary muscle rupture.[373] Medical therapies and intra-aortic balloon pump or other mechanical support devices are indicated for stabilization while the patient awaits surgery.[216] Mitral valve replacement is usually necessary owing to the presence of friable tissues.[373] Ischemic mitral regurgitation often can be treated with early revascularization and medical therapy, although mitral valve repair or replacement may be necessary.[216]

Women, older patients, and nonsmokers are at increased risk of ventricular septal rupture after AMI.[375,379] Ventricular septal rupture complicates <1% of all AMIs but accounts for 4% of AMI-associated shock.[354,379,380] It usually occurs within 24 hours of presentation, often in patients with no history of MI.[375,379] Without surgical intervention, the mortality rate is 94% to 100%.[375,379,381] With surgical repair, 30-day mortality improves to 45% to 80%.[375,379,381] Because of the significant mortality benefit of surgical repair of AMI-associated ventricular septal rupture, urgent surgery is indicated.[216]

Left ventricular free wall rupture and tamponade are more common in women after AMI.[382–384] Older age, anterior AMI, and delayed thrombolysis are additional risk factors.[374,382,383,385] Primary PCI is protective against free wall rupture, likely because of the reduction in hemorrhagic transformation of the infarcted myocardium.[384] Although the incidence of free wall rupture is low, complicating <1% of AMI and representing 1.4% of AMI-associated CS, it carries a 55% to 60% mortality rate and is the second most common cause of death after left ventricular pump failure following AMI.[354,374,382–384] Most cases of free wall rupture occur within 1 week of AMI.[384] Free wall rupture often presents dramatically, with abrupt development of electromechanical dissociation and asystole, sometimes immediately preceded by recurrent chest pain and ST-segment elevation on ECG.[384,386] In a small, prospective study of subacute ruptures, approximately one third of ruptures did not have signs of tamponade initially when the rupture site was sealed; this is an important cohort of patients to identify early for successful treatment of a potential lethal complication of AMI.[387] Although there is some evidence that women may be less likely to survive cardiac rupture than men, immediate surgery is indicated for all women with free wall rupture.[374,384]

Arrhythmias

Women and men appear to be at similar risk for the development of ventricular arrhythmias after AMI.[388] Ventricular arrhythmias occur in 6% to 10% of patients with AMI.[388,389] Both early (<2 days) and late (>2 days) ventricular arrhythmias are associated with increased mortality, with late arrhythmias carrying a worse prognosis.[388,389] Peri-infarction β-blockers have been associated with reduced incidence of ventricular arrhythmias.[390] In the absence of contraindication, women with AMI should be started on β-blocker therapy within 24 hours of presentation.[217] Women with sustained ventricular arrhythmias occurring >48 hours after AMI, in the absence of other reversible causes, should have an ICD placed before hospital discharge for secondary prevention of SCD.[391–394] Women with reduced ejection fraction after AMI should be reassessed for ICD candidacy for primary prevention of SCD ≥40 days after discharge.[394–396] Currently, there are no sex-specific guidelines with respect to ICD use; however, women are less likely to receive an ICD for primary or secondary prevention of SCD compared with men.[397] Substudies of large, randomized trials have shown lower appropriate ICD shock rates in women compared with men; however, there are variable results in terms of ICD mortality benefit, perhaps a result of the low number of women in these post hoc substudies.[398,399] Two meta-analyses have shown contradictory results for all-cause mortality benefit in women with ICDs.[400,401] Additionally, women have a better prognosis after cardiac resynchronization therapy compared with men.[402] Women were underrepresented in these ICD trials, once again highlighting the need for increased enrollment of women in clinical trials or sex-specific trials.

New-onset AF occurs in 6% to 9% of patients with AMI and is associated with HF, CS, stroke, and increased 90-day mortality.[380,403] Women and older patients are at increased risk of developing AF in the setting of AMI.[403] Stroke prevention in this setting can be challenging, given the requirements for dual antiplatelet therapy after stent placement. Anticoagulation on hospital discharge in patients with AMI-associated AF has been shown to reduce the incidence of stroke and mortality.[403] For suitable candidates with AMI-associated AF and risk factors for stroke, anticoagulation should be considered on hospital discharge with an understanding that fatal and nonfatal bleeding risks will be high.[404]

Overall, 7% of patients hospitalized with AMI develop significant bradyarrhythmias.[380,405] Women are at increased risk for developing high-degree atrioventricular block in the setting of AMI.[405] Atrioventricular block complicates 12% to 13% of patients presenting with an inferior MI and is associated with increased 30-day, 6-month, and 1-year mortality.[405–407] Bradyarrhythmias associated with inferior AMI are usually self-limited, but temporary pacing should be used for symptomatic bradycardia refractory to medical management.[216,408] When high-degree atrioventricular block is associated with anterior AMI, the prognosis is significantly worse, likely reflecting greater extent of infarct.[405] In this setting, prophylactic temporary pacemaker placement is recommended.[216] Permanent pacemaker implantation is indicated only for persistent high-degree atrioventricular block.[409]

Prognostic Factors for Adverse Outcomes After AMI

Markers of Disease Severity

Little is known about prognostic factors for adverse outcomes after MI specific for women. A number of risk prediction models that incorporate routinely measured medical history factors and clinical severity indicators such as the GRACE[410] and TIMI[411] scores are commonly used in patients with ACS. However, they were developed in patient populations that were at least two thirds male; their performance in women is not well established. In a study of patients presenting to the emergency department with chest pain, the TIMI risk score performed well in both men and women for the prediction of death or MI at 30 days.[412] In another recent study, prognostic indicators such as left ventricular ejection fraction and ECG parameters (heart rate, heart rate variability, non–sinus rhythm, and QRS width) predicted 5-year mortality in both women and men, but there were some differences in magnitude of effects between women and men. For example, the absence of sinus rhythm was associated with a hazard ratio of 7.6 in women and 3.2 in men.[413]

Presentation Characteristics

Women with MI who present without chest pain[41] and with a STEMI[43] have a higher risk of hospital death in all age groups. The absence of chest pain appears to be a stronger marker of mortality risk among women than men, especially among young women.[41] Compared with NSTEMI, STEMI is also a more robust short-term prognostic indicator in women than in men, with higher mortality rates in the initial 24 hours of hospitalization.[10,99] DM is another powerful prognostic factor after MI among women, approximately doubling their risk of long-term mortality; again, this effect is larger in women than in men.[414,415]

Age

Although age is a potent prognostic indicator after MI in all patients, the relationship between age and mortality after MI is less pronounced in women than in men. The reason is that young women, that is, those who experience early-onset MI (before ≈60 years of age), have a higher short-term mortality than men in the same age group; this difference declines with age.[9,37,416] This disparity is also seen after hospital discharge up to 2 years[39] but is less evident in the long-term after ≥5 years.[17]

Traditional Coronary Risk Factors

Women hospitalized with an AMI have a high prevalence of cardiovascular risk factors, including hypertension, hypercholesterolemia, current smoking, DM, and obesity, which are established prognostic indicators. Black women have especially high risks. Among 2369 AMI patients from 19 centers, 72% of patients had ≥2 risk factors and 40% had ≥3; black women had the largest risk factor burden of any subgroup, with 60% of older black women and 54% of younger black women having ≥3 risk factors.[72] Despite their elevated risk factor profile, black women and black men were less likely than their white counterparts to receive secondary prevention

efforts such as smoking cessation counseling and antihypertensive and lipid-lowering medications.

Psychosocial Risk Factors

Women with MI, especially young women with early-onset MI, have a disproportional burden of psychosocial risk factors, even though indicators of AMI severity are similar or more favorable in women compared with men of similar age or older women.[417,418] Emerging evidence links psychosocial factors to adverse outcomes in patients with ischemic heart disease, especially depression, which is now a recognized prognostic factor after ACS.[419] The prevalence of depression is ≈20% in post-MI patients, several times higher than in the general population, and is about twice as high in women with MI as in men with MI.[419] Depression is especially common in young female MI patients (<60 years old).[417,418,420] Fifty percent of post-MI women ≤50 years of age and >40% of post-MI women between 50 and 60 years of age meet the diagnostic criteria for major depression.[418] Among women with MI or other forms of ischemic heart disease, depression is associated with an ≈3-fold increased risk for death or subsequent cardiac events independently of severity of depression.[421–423] In addition to having high levels of depression, women with premature MI are often from minority groups and have high rates of poverty and trauma exposure during childhood, especially sexual abuse.[418]

Marital stress is an understudied but potentially important risk factor for recurrent events in post-MI women. A series of studies of Scandinavian women with ACS have demonstrated robust associations of marital stress with subsequent cardiac events[424] and with progression of CAD measured with quantitative coronary angiography.[425] Conversely, social support appears to be an important mitigating factor in post-MI recovery among women; those with higher social support experience better mental functioning, better quality of life, and fewer depressive symptoms at 12 months.[426]

Young women in the VIRGO trial reported poorer physical and mental health functioning, more symptoms of angina, and poorer quality of life over a 12-month period after AMI compared with men of a similar age.[427] The future challenge is to determine what interventions would mitigate deterioration in perceived health status among young women in the year after AMI.

Consistent with an important prognostic role of psychosocial stress in women with AMI, myocardial ischemia caused by emotional stress, induced experimentally through a standardized mental stress test, is common in women with ischemic heart disease, especially young women after MI. Studies of patients with stable CHD have reported higher rates of mental stress–induced ischemia, assessed by echocardiography, in women than men.[428] Such differences are even more pronounced among young post-MI patients. Women up to 50 years of age who have survived an MI in the past 6 months show twice the rate of mental stress–induced ischemia, measured with myocardial perfusion imaging, compared with age-matched men, a difference that is not observed among older patients.[418] Mental stress–induced ischemia is associated with a 2-fold increased risk of mortality or recurrent events in patients with ischemic heart disease.[429] Thus, it could be an important, albeit unrecognized, prognostic indicator in women with MI. Because mental stress ischemia induced in the laboratory correlates with ischemia in daily life,[430] it could also be a more frequent trigger of AMI in young women than in other groups. Recent evidence also links depression to mental stress–induced ischemia,[431,432] providing a new explanatory pathway for the worse prognosis of MI patients with depression, many of whom are women, compared with those without depression.

Table 3. Gaps in Knowledge of AMI in Women

What is driving the mortality disadvantage among young women compared with young men with ACS?
What are the unique pathophysiological atherosclerotic manifestations among women with MI?
What are effective interventions for decreasing treatment delays (time to presentation, time to diagnosis, time to treatment) for ethnically diverse women with AMI?
What are the causal mechanisms for mechanical complications among women after MI, and what effective strategies will reduce these complications?
What are the mechanisms by which psychosocial factors influence the development of and recovery from MI?
What are the most effective interventions and strategies for improving cardiovascular health behaviors among women across the life span and across racial and ethnic groups?
What is the relative influence of biological, pathophysiological, and psychosocial risk factors on CHD development and progression among women?
What are the most effective interventions for decreasing the ethnic and racial disparities in the diagnosis and treatment of women with AMI?
What are the modifiable factors contributing to sex disparities in applying evidence-based guidelines in the prevention and treatment of women with CVD?

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; CHD, coronary heart disease; CVD, cardiovascular disease; and MI, myocardial infarction.

Future Directions: Closing the Gap in Sex Disparities

Despite their substantial burden of CVD, women have been underrepresented in clinical trials of CVD, generally making up only ≈20% of enrolled patients, even though women represent 40% to 50% of participants in longitudinal studies and registries. Even when women were included in clinical trials, data often were not disaggregated by sex, limiting the evidence-based information available to healthcare providers and patients.[433] The first step to personalized medicine is attention to sex-specific characteristics, and attention to sex disparities likely will improve the awareness, prevention, recognition, treatment, and outcomes of CHD in women. It is recognized that the safety and efficacy of cardiovascular drugs and devices may vary by sex. Although the new US Food and Drug Administration mandate has a legislative requirement for sex-specific data in drug studies, it only recommends, but does not mandate, sex-specific data in device studies. Women constituted only about one third of participants in the 78 clinical trials of cardiovascular devices from 2002 to 2007, and the proportion of women has not increased over time. More policy solutions should be developed for an increase in the

Table 4. Priorities to Improve Outcomes in Women With AMI

Increase awareness of women, healthcare providers, the public, and policymakers of MI risk and sex-specific symptoms and clinical presentation
Examine genetic-environment interactions in the prediction of early-onset CHD in women
Evaluate the mechanisms by which psychosocial risk factors (eg, depression, perceived stress, marital conflict, anxiety, poor social support) influence CVD development and progression
Improve methods to diagnose and treat CAS, SCAD, and microvascular CAD in women
Offer sexual counseling to all women and their partners before hospital discharge after ACS
Increase pharmacological treatment rates for secondary prevention, with particular emphasis on adherence to guidelines, by both the clinician and the patient
Implement effective psychological treatments to reduce barriers and to improve adherence to guideline-based recommendation and to improve quality of life
Develop and evaluate novel, adaptive, tailored secondary prevention strategies for women after AMI as an alternative to center-based CR programs using mobile technology, peer support, health coaches, community health workers, and telehealth
Develop and test effective primary and secondary prevention behavioral interventions that are culturally appropriate for women across the life span and in a variety of clinical and community settings
Develop strategies to increase the inclusion of women of all ages in cardiovascular clinical research (raise mandatory inclusion rates, require sex-stratified data reporting)

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CAS, coronary artery spasm; CHD, coronary heart disease; CR, cardiac rehabilitation; CVD, cardiovascular disease; MI, myocardial infarction; and SCAD, spontaneous coronary artery dissection.

percentage of women in all cardiovascular trials, which are not sex specific, to improve outcomes.

Closing the research gap requires sex-specific examination of coronary pathophysiology; optimal diagnostic strategies; effective lifestyle, pharmacological, and invasive interventions; and exploration of subpopulations of women socially disadvantaged because of race, ethnicity, income level, or educational attainment. Table 3 reviews current gaps in knowledge concerning AMI in women. Adverse outcomes likely reflect both bias and biology, defining the need for sex-specific basic and clinical research. Exclusion of elderly patients from clinical trials doubly disadvantages women whose coronary events occur predominantly at an older age.

Women's heart health is not solely a medical issue but also involves economic, legal and regulatory, psychosocial, ethical, faith-based, cultural, environmental, community, health systems, and political and public policy issues locally and globally.[3] Table 4 is a summary of the priorities to improve outcomes in women with AMI. Therefore, women's cardiovascular health research should involve not only basic and multidisciplinary clinical research scientists but also healthcare providers, women and their families, governmental officials and agencies, and members of Congress.

Conclusions

CVD is an equal-opportunity killer, and since 1984 the mortality burden has been higher in women than men, but a significant decline has occurred since 2000. This dramatic decline may be the result of the application of evidence-based therapies and education to improve the public and medical communities' awareness of heart disease in women. This is encouraging, but there remains an excess in mortality in women that is multifactorial. This document reviews the different factors plausibly responsible in the setting of an AMI. Sex differences occur in the pathophysiology and clinical presentation of MI and affect treatment delays. Recommended perfusion therapies for AMI in women are similar to those in men, yet bleeding risks and other complications remain greater in women. Women are undertreated with guideline-based recommendations, leading to worse outcomes and increased rates of readmission, reinfarction, and deaths in the first year after MI. CR is underused and underprescribed for women, but novel approaches to increase participation by women are promising. To further compound undertreatment, women's adherence to these evidence-based recommendations is suboptimal. There is a need for continued public health messages and interventions to target racial and ethnic minority women, given the burden of risk factors and continued disparity in outcomes. Multidisciplinary research teams are urged to examine innovative secondary prevention models of care that are age appropriate, culturally sensitive, and personalized to women's psychosocial and physiological characteristics.

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*Modest.

†Significant.

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