Acute Coronary Syndromes in Women: Recent Treatment Trends and Outcomes

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ABSTRACT: In the USA and internationally, women experience far-ranging differences with respect to acute coronary syndrome (ACS) and myocardial infarction (MI). Women suffer from more comorbidities than men, such as smoking, obesity, hypertension, diabetes, and poor mental health. They sometimes exhibit atypical MI presentation symptoms and are overall less likely to present with chest pain. Women are more likely than men to encounter delays between the onset of symptoms and arrival at the hospital or to guideline treatment. The use of various surgical and pharmacological treatments, including revascularization approaches, also differs. Women, on average, have worse outcomes than men following MI, with more complications, higher mortality rates, and poorer recovery. Internationally, outcomes are similar despite various differences in health care and culture in non-US countries. In this review, we detail differences regarding ACS and MI in women, describing their complex correlations and discussing their possible causes. Educational approaches that are tailored to women might help to reduce the incidence of ACS and MI, as well as outcomes following hospitalization. Although outcomes following acute MI have been improving over the years, women may require special consideration in order to see continued improvement.

KEYWORDS: myocardial infarction, acute coronary syndrome, women, comorbidities, disparities, symptoms, diagnosis, treatment, outcomes, international

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Introduction

Despite recent general improvements in health care, significant disparities persist in the cardiovascular care of women even when income, education level, and site of care are taken into consideration.[1] Gender differences are also observed concerning acute coronary syndrome (ACS) and myocardial infarction (MI), spanning categories including risk assessment, disease awareness, comorbidities, presentation, treatment, and outcomes, each of which is detailed in this review.

Some of these differences in ACS/MI may be influenced by the fact that men and women differ in the pathophysiology and mechanisms of heart disease. A significant number of women who angiographically appear to have normal arteries actually show biochemical or imaging evidence of myocardial ischemia. These women may have coronary circulation dysfunction that could lead to vascular constriction and subsequent MI.[2] In addition, women with ACSs are not as likely as men to have significant obstructive coronary artery disease (CAD), but are more likely to have thrombus formation and plaque erosion.[3] Additionally, over one-third of women with MI have plaque rupture and ulceration when examined with intravascular ultrasound, despite having no angiographically demonstrable CAD.[4] Cardiac hemodynamic parameters during MI have also been found to differ by patient gender. One study found that women have increased pulmonary capillary wedge pressure than men during acute ST segment elevation MI (STEMI). This increased left ventricular filling pressure was independent of age, hypertension status, or infarct size, suggesting that it is largely gender dependent.[5] These pathophysiological differences may be associated with differences in ACS/MI symptomology and with options for revascularization.[6,7]

Estimating MI Risk

Addressing cardiovascular disease (CVD) in any population begins with an understanding of risk and risk reduction. Seeking to optimize estimates of CVD risk in women, Cook et al studied a case–cohort sample of 1,722 cases of major CVD (752 MIs, 754 ischemic strokes, and 216 other CVD deaths) and a random subcohort of 1,994 women without prior CVD from the multiethnic Women's Health Initiative Observational Cohort. The researchers estimated CVD risk for these women using three different risk-assessment methods: the Adult Treatment Panel III (ATP-III) score, the Reynolds risk score, and the Framingham CVD model. While comparing actual outcomes with the risk estimates generated by these three models, they found that the ATP-III overestimated the risk for Coronary Heart Disease (CHD) and that the Framingham CVD model overestimated the risk for major CVD. Overall, their results suggest that the Reynolds

risk score is better calibrated to gauge the risk for both black and white women, relative to either of the Framingham-based models.[1]

Another clinical risk score has been developed to predict obstructive CAD, which is defined as ≥50% diameter stenosis in ≥1 epicardial coronary artery.[8] Investigators found that in women with angina pectoris and abnormal stress test findings, independent predictors of CAD included: age ≥55 years, body mass index >30 kg/m^2, smoking, low high-density lipoprotein, a family history of premature CAD, lateral abnormality on stress imaging, and an exercise capacity <5 metabolic equivalents. The risk score they developed based on these seven elements had a negative predictive value of 80%.[8] Besides these predictors, it has also been noted that menopause is an ACS risk factor – one that is interesting because it has no similarly abrupt male equivalent.[9]

MI Prevention and Awareness of Risks and Symptoms

As women learn more about CVD and recognize its risk factors, it is hoped that they will take more aggressive actions to help prevent the disease and its negative effect on their health and quality of life. CVD awareness among women has gradually increased over the years – Mosca et al, studying the period from 1997 to 2009, found that awareness that is "CVD is the leading cause of death among women" has been increasing.[10] However, much work remains to be done to convince women to reach out for help: only 53% of those in this study said that they would call 9-1-1, if they thought they had symptoms of a heart attack.[10]

There are racial differences in CVD awareness among women. One study found that black and Hispanic women were less informed about CVD than non-Hispanic white women.[10] A second study reinforced this potential knowledge gap, finding that Hispanic women were less likely than non-Hispanic white women to know that CVD is the leading cause of death among women, or to know the symptoms of a heart attack.[11] The same study noticed that women's perception of their own health status varied by race – Hispanic women were more likely to underestimate their weight.[11] Therefore, women may benefit from communications regarding what constitutes a healthy body with low CVD risk.

Some medications are less likely to be prescribed to women in order to prevent CVD. In a large cohort of patients receiving care for CVD in Veterans Health Administration facilities in 2010 and 2011, women had higher mean low-density lipoprotein cholesterol levels than men, but they were less likely to receive statin treatment according to the recent cholesterol guidelines.[12]

Comorbidities

Women who present with ACS or MI are on average older than male patients and have more comorbidities and lower income.[13,14] However, some comorbidities are more likely in men than in women – older men are more likely to be current smokers,[15] younger men have more obstructive CAD,[15] and in the Horizons Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, men were more likely to have a previous history of MI or revascularization.[13] For women, internationally, comorbidities are similar, despite different cultures and health care systems. Table 1 summarizes comorbidities of acute MI (AMI) in women by age and nation.

Hypertension, smoking, and prior history. Smoking and high blood pressure contribute to the development of CVD, and both are more common in female patients with MI. A 10-year prospective study examined the baseline characteristics of 6,746 STEMI patients undergoing primary percutaneous coronary intervention (PCI; grouped by age: <65 years and ≥65 years). Hypertension was more prevalent in both the age groups of women than in men, and younger women were more likely to be current smokers and to have a family history of CVD than younger men.[15] As one might expect, younger patients are less likely to present with traditional CVD risk factors, regardless of gender, as noted in a study that divided a large cohort of patients with STEMI enrolled in the American Heart Association (AHA)'s GWG-CAD registry into two age categories (≤45 years, >45 years).[16] In an analysis of 3,602 patients in the HORIZONS-AMI trial, women were more likely than men to have hypertension and congestive heart failure.[13] Female patients in the GENdEr and Sex determInantS of cardiovascular disease: From bench to beyond-Premature Acute Coronary SYndrome (GENESIS-PRAXY)[17] cohort of patients with ACS aged 55 years or younger had more hypertension, were more likely to have a family history of CVD, and had more previous CVD events.[14] Results from the Variation In Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO)[18] study showed younger female patients with AMI (aged 18–55 years) had worse CVD-specific health (more angina, stroke, and congestive heart failure) and lower physical function than male patients with AMI in the same age group.[19] In a cohort of younger patients with AMI (≤55 years) from the TRIUMPH study,[20] younger women had more hypertension, lung disease, angina, and lower physical function.[21]

Quality of life. Poor mental health and lower quality of life are also correlated with ACS. In the GENESIS-PRAXY cohort of patients with ACS (18–55 years), women were more likely to report experiencing depression or anxiety before ACS onset.[14] Similarly, in the TRIUMPH study cohort of younger patients with AMI (≤55 years), younger women had more depression and lower quality of life at presentation.[21] Results from the VIRGO study also showed that younger female patients with AMI (aged 18–55 years) had a lower quality of life than male patients with AMI in the same age group.[19]

Diabetes. Diabetes is more prevalent in both younger[14,19,21] and older[15] female patients with MI. Diabetes and its resulting

hyperglycemia may lead to worse MI outcomes: an examination of the association between atherosclerotic risk factors and short-term mortality rates after the first MI found that crude mortality in patients with MI was the highest in those with diabetes.[19] Besides women having a greater incidence of diabetes, they also may not have their diabetes under control – an observational population-based cohort study that included 15,120 women found that in the first year after their diabetes diagnosis, women were less likely than men to be taking cardioprotective medications.[22]

Obesity. Obesity and other metabolic problems are also correlated with an increased risk of MI. Younger female patients with AMI in the VIRGO study (aged 18–55 years) had worse preevent health than men, including dyslipidemia and obesity, regardless of CAD history.[19] In the HORIZONS-AMI trial, women were also more likely than men to have hyperlipidemia.[13] Obesity disproportionately affects black women, who on average have a higher body mass index, fat mass, and fat-free mass than white women.[23] Researchers suspect that this might be due to black women's lower resting metabolic rates when expressed relative to body weight, with lower cardiorespiratory fitness levels explaining 25% of this difference in metabolism.[23] Interventions aimed at reducing rates of obesity and dyslipidemia in the black community may lead to lower MI risk and better post-MI outcomes within this racial group.

Presentation

When women arrive at the hospital with an MI, their typical presentation differs from that of men in many ways. Women are less likely to present with chest pain and may instead show atypical symptoms. Their cardiac parameters and biomarker levels differ from those of men. Women also receive different final diagnoses – GENESIS-PRAXY female study subjects were less likely than men to have received a diagnosis of STEMI and were more likely to have received a diagnosis of non-ST segment elevation MI (NSTEMI) or unstable angina.[14] We need to fully understand these gender-based differences in presentation to ensure that they do not worsen women's medical outcomes.

When a patient presents with chest pain, this symptom is likely to initiate diagnostic testing for ACS. However, a substantial fraction of patients with AMI do not report having chest pain (up to 35%), which increases the chance of delayed or mistaken diagnosis and could worsen outcomes. Female patients with ACS, comprising 30% of the GENESIS-PRAXY[17] study population (aged ≤55 years) were more likely than men to present without chest pain. This was not associated with markers of severity of coronary disease, including ACS type, troponin level, or coronary stenosis.[24] Overall, women monitored by the National Registry of Myocardial Infarction (NRMI) were also more likely than men to present without chest pain (12-year cohort, 1,143,513 patients, and 481,581 women).[25] Specifically, younger women (aged <45 years) were 30% more likely than younger men to present without chest pain.[25] However, this was not the case for women of advanced age – women in both the age groups of 65–74 years and 75+ years were actually more likely to present with chest pain than similarly aged men.[25]

Women's CVD symptoms may also be related to their race and ethnicity. An analysis of a Women's Ischemia Syndrome Evaluation study cohort found that black women undergoing coronary angiography for suspected ischemia reported fewer chest-related, and more stomach-related, symptoms than white women.[26] This finding suggests that, in some cases, an atypical presentation of MI in black women could contribute to delayed diagnosis and treatment.

High-sensitivity troponin assays improve the diagnosis of MI in both men and women compared with older, less-sensitive assays. One study sought to optimize how these improved assays can facilitate MI diagnosis in women.[27] Investigators combined a high-sensitivity troponin assay with sex-specific diagnostic thresholds, comparing this setup against a standard, single-threshold contemporary assay in a cohort of 1,126 patients with MI (46% women). They found that using sex-dependent criteria along with the high-sensitivity assay doubled the diagnosis of MI in women, without affecting the diagnosis rates in men. Women with MI identified by this high-sensitivity assay procedure additionally were at a higher risk for death or recurrent MI within 12 months.[27] These results suggest that using contemporary assays with a single threshold disproportionately underdiagnoses MI in women and may contribute to sex-based disparities in treatments and outcomes.

Hospitalization, Diagnosis, and Treatment

Women with AMI are more likely than men to encounter delays between the onset of symptoms and arrival at the hospital or to guideline treatment. They are less likely to be hospitalized and ultimately receive different surgical and pharmacological treatments. Understanding these variances, their causes, and their consequences fully will be critical for improving women's post-MI outcomes.

Delays. A meta-analysis of the literature from 1960 to 2008 found that women consistently encounter longer prehospital delays than men (starting from the onset of symptoms).[28] Across numerous publications, median prehospital delays were found to range from 1.8 to 7.2 hours for women versus 1.4 to 3.5 hours for men.[28] Factors associated with delay in women included advanced age, a marital status of single, having a previous history of MI, being alone during symptom onset, and the patient not wanting to bother anyone.[28] As one might expect, the delay between symptom onset and treatment is also longer in women – in the HORIZONS-AMI trial, symptom-onset-to-balloon time was longer, driven largely by late arrival at the hospital.[13] Another study found that after arrival at the hospital, female patients with STEMI had delays in both door-to-code and

Table 1. Prevalence of comorbidities in patients with MI (or ACS).

	YOUNGER PATIENTS	OLDER PATIENTS	ALL AGES
More prevalent in women	*U.S.; <65 years*		*U.S.*
	Current smoker[15]	*U.S.; >55 years*	Hypertension[13,15]
	Family history of cvd[14,15]	Diabetes[15,19]	Advanced age[13]
	U.S.; <55 Years		Hyperlipidemia[13]
	Lower income[14]		Congestive heart failure[13]
	Diabetes[14,21]		*Germany*[50]
	Hypertension[14,21]		Advanced age
	Lung disease[21]		Diabetes
	Previous cvd events[14]		Hypertension
	Depression[14,21]		Renal insufficiency
	Anxiety[14]		*China*[52]
	Dyslipidemia and obesity[19]		Advanced age
	Angina[19,21]		*Vietnam*[53]
	Stroke[19]		Advanced age
	Congestive heart failure[19]		Hyperlipidemia
	Lower physical function[19,21]		Hypertension
	Lower quality of life[19,21]		Diabetes
	China; <60 years[52]		
	Hypertension, diabetes		
	Canada; <55 years[48]		
	Diabetes, heart failure, renal failure, Malignancies		
More prevalent in men	*U.S.; <65 years*	*U.S.; ≥65 Years*	*U.S.*
	Obstructive cad[15]	Current smoker[15]	Previous mi[13]
	China; <60 years	*China; >60 Years*	Previous
	Current smoker[52]	Prior AMI[52]	Revascularization[13]
			Vietnam
			Current smoker[53]

code-to-balloon times.[29] Delays were longer with advanced age and more comorbidities.[29] Independent determinants of delay in door-to-balloon times included female sex, hypertension, maximum ST elevation, office hours, and triage category.[29] The investigators concluded that women experienced delays in both STEMI diagnosis and receiving PCI.[29] Another study shows the same effect for younger women – in an analysis of the AHA's Get with the Guidelines (GWG)-CAD registry, younger female patients with STEMI (aged ≤45 years) had a longer delay in door-to-thrombolytic time than younger male patients.[16]

Hospitalization rates. Women are less likely to be hospitalized for MI than men. Medicare Part A data on >four million hospital admissions for AMI between 1992 and 2010 indicate that the rates of hospitalization for AMI were lower in both black and white women compared with men, which is a difference that persisted as overall hospitalization rates for AMI declined during the study period.[30] Interestingly, although women are less likely to be hospitalized for MI, in the US patients from 2001 to 2010 (aged 30–54 years), women had longer hospital stays than men.[31]

Diagnostic testing. When physicians put forth different options and recommendations for diagnostic testing to patients with ACS, patients need to make choices. Some previous studies have suggested that the lower cardiac catheterization rates seen in women with ACS are partially due to women's own preferences, and therefore Golden et al examined patient preferences for cardiovascular testing after the evaluation of chest pain to determine how doctor–patient discussions influence these preferences. They found gender-based differences in physicians' CAD-related patient counseling and subsequent recommendations for testing. Physicians were less likely to tell women that their symptoms could result from heart disease or to recommend cardiovascular testing or cardiac catheterization. No patients in this study refused their doctors' recommendations,[32] implying that differences in

catheterization rates may be driven largely by physicians and not by the decisions of female patients.

Treatments. The rates at which different treatments are administered to address MI vary by gender. Women diagnosed with MI are less likely to be referred to a cardiologist, or to undergo coronary angiography or PCI.[27] In Medicare Part A data between 1992 and 2010, the rates of PCI within 30 days of AMI were persistently lower for both black and white women.[30] In the GENESIS-PRAXY cohort of patients with ACS (18–55 years), female patients with STEMI were less likely to have reperfusion therapy than males, and females with NSTEMI were less likely to have PCI, although the proportions of male and female patients with NSTEMI who had cardiac catheterization were similar.[14] Determinants of reduced access to care included anxiety, more risk factors, and lack of chest pain at presentation.[14] In a study of 91,088 AMI hospitalizations for STEMI and NSTEMI, women were older than men for both diagnoses and were less likely to be treated with PCI or coronary artery bypass grafting (CABG) for either diagnosis.[33] Women may also receive treatments after a delay – in the GENESIS-PRAXY study, they were less likely to receive an electrocardiography or fibrinolytic therapy within established time benchmarks but did not differ from men in timely PCI.[14]

Many MIs occur in patients who are already hospitalized for other reasons. Out of 62,021 STEMI procedures across 303 hospitals from 2008 to 2011, 3,068 procedures were performed on patients hospitalized for non-ACS indications.[34] Members of this group, who experienced STEMI as inpatients, were more likely to be older and female and less likely to undergo cardiac catheterization or PCI. These patients had >threefold greater in-hospital mortality rates.[34]

Discharge medications. Following MI, women are more, and less, likely to be prescribed certain medications than men. Women were also found to be more often treated with medication management alone in the HORIZONS-AMI trial.[13] The trial also found that women were more likely to receive warfarin and diuretics on discharge, whereas men more often received β-blockers and statins.[13] A second study also found that women diagnosed with MI are less likely to be prescribed statin treatment on discharge.[27] In Medicare patients admitted for AMI, researchers examined whether racial/ethnic or gender differences in usage of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins have persisted since inception of the Medicare Part D prescription drug benefit. No racial/ethnic difference was found in the usage of these drugs at 30 days post discharge, but women were less likely than men to be using angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β-blockers than men. Regardless of the medications a patient is prescribed, patient adherence to them is key to minimizing readmission or other adverse outcomes. At 12 months post MI, black and Hispanic women were the least likely group to be medication adherent, followed by white, Asian, and other women, and by black and Hispanic men.[35]

Outcomes

The incidence of death from CVD has been declining over the decades – age-adjusted CVD mortality rates in the USA from 1980 to 2002 have declined by 52% among men and 49% among women.[36] Despite this good news, most studies on outcomes following MI have found that women have higher mortality rates than men. Women also are disproportionately affected by other negative outcomes, ranging from major bleeding to reinfarction. Internationally, outcomes are similar despite various differences in health care and culture in these non-US countries. Table 2 summarizes the incidence of MI outcomes by gender, age, and nation.

In-hospital mortality. Women have higher in-hospital mortality rates than men following MI.[30] NRMI data (126,173 STEMI and 235,257 NSTEMI patients) revealed that in-hospital mortality rates were higher in women than in men for both STEMI and NSTEMI, with this difference being more pronounced for patients with STEMI.[37] Age was a factor – younger women experienced larger gender-based mortality differences than older women (STEMI and NSTEMI).[37] Another analysis using NRMI data (12-year cohort, 1,143,513 patients, and 481,581 women) also found greater in-hospital mortality rates for women.[25] In the analysis of the AHA's GWG-CAD registry, younger patients with STEMI (aged ≤45 years), as one might expect, had lower in-hospital mortality rates than older patients (aged >45 years), but younger women had poorer quality of care and still had higher in-hospital mortality rates than younger men.[16] In the US patients aged 30–54 years from 2001 to 2010, women had more in-hospital mortality rates than men.[31] Over the same timeframe, some improvement was noted, as in-hospital mortality rates declined for women but not for men.[31] In a study of 91,088 AMI hospitalizations for STEMI and NSTEMI, female patients with STEMI aged <79 years, and patients with NSTEMI aged <69 years, had higher in-hospital mortality rates than similarly aged men.[33]

Short- and long-term mortality. Besides in-hospital mortality, women also have a higher chance of post-MI death at time points spanning as many as 10 years in the future. Short-term mortality rates (ie, 30 days) were found to be higher in women than men using adjusted analyses based on Medicare Part A data during the period 1992–2010.[30] In the study on cardiac hemodynamics, women with STEMI also had a higher 30-day mortality rate than men.[5] Medium-term mortality (ie, one year) appears to be more complex – in patients undergoing primary PCI (grouped by age: <65 years, and ≥65 years), younger women had a higher risk of mortality at 30 days and at one year than younger men, whereas older women had an increased risk of mortality only at 30 days, but not at one year, compared with older men.[15] An analysis of

Table 2. Incidence of outcomes in patients with MI.

	YOUNGER PATIENTS	OLDER PATIENTS	ALL AGES
More common in women	*U.S.; <55 years*	*U.S.; 60–69 Years*	*U.S.*
	In-hospital mortality[16,31]	In-hospital mortality[37]	In-hospital major bleeding[13]
	U.S.; <60 Years	In-hospital mortality (NSTEMI)[33]	In-hospital major bleeding (PCI)[42]
	In-hospital mortality[37]	*U.S.; 60–80 Years*	30-Day major bleeding[13]
	In-hospital mortality	In-hospital mortality (STEMI)[33]	3-Year major bleeding[13]
	(STEMI & NSTEMI)[33]	*Canada; 55–74 years*[48]	In-hospital mortality[13,25]
	U.S.; <65 Years	30-Day mortality	In-hospital mortality (STEMI)[37]
	1-Year mortality[15]		In-hospital mortality (PCI)[42]
	Canada; <55 years[48]		30-Day mortality[5,13,15,30]
	30-Day mortality		1-Year mortality[38]
			3-Year mortality[13]
			5-Year mortality[39]
			10-Year mortality[39]
			In-hospital re-infarction[13]
			In-hospital re-infarction (PCI)[42]
			30-Day re-infarction[13]
			30-Day re-infarction (STEMI)[5]
			3-Year re-infarction[13]
			1-Year acs rehospitalization[44]
			1-Year ami rehospitalization[38]
			30-Day rehospitalization[43]
			In-hospital, 30-day, or 3-year tvr for ischemia[13]
			In-hospital, 30-day, or 3-year stroke[13]
			Higher stress during recovery[46]
			1-Month angina[46]
			1-Month lower quality of life[46,47]
			1-Month worse mental health[46]
			6-Month, 12-month lower hrql[47]
			Spain[49]
			6-Month rehospitalization
			6-Month lower hrql scores
			Germany[50]
			In-hospital major bleeding
			In-hospital mortality
			1-Year mortality
			China[52]
			In-hospital mortality
			Vietnam[53]
			Heart failure
			In-hospital mortality
More common in men		*U.S. ≥70 years*	*U.S.*
		In-hospital mortality (NSTEMI)[33,37]	30-month mortality (PCI)[42]
		U.S. ≥80 years	
		In-hospital mortality (STEMI)[33]	
		Canada; ≥75 years[48]	
		30-day mortality	

Medicare beneficiaries between 1999 and 2010 also indicated that women had a greater risk of one-year mortality post AMI than men.[38] When it comes to long-term survival (ie, >one year), a systematic review of AMI mortality from 1966 to 2012 found that most studies report higher unadjusted mortality rates in women at both five- and 10-years post MI.[39] These gender-based differences in long-term mortality were largely explained by age, comorbidities, and treatments used.[39] Another study agrees, finding that sex is not a significant mortality predictor when adjusting for age, suggesting that unfavorable prognosis and risk post MI is predominantly driven by age-related factors.[40]

Contrary to these post-MI mortality trends, among older patients, women appear to fare better than men. Among patients with NSTEMI aged ≥70 years, in-hospital mortality rate differences between men and women were reversed, with women exhibiting better in-hospital survival than men of the same age.[37] In the study of 91,088 AMI hospitalizations for STEMI and NSTEMI, female patients with both STEMI aged 80–89 years and NSTEMI aged ≥70 years had lower in-hospital mortality rate than similarly aged men with the same type of MI.[33]

Mortality and race. Mortality rates among women differ by their race and ethnicity, although these racial differences have narrowed between 1992 and 2010, according to adjusted analyses based on Medicare Part A data.[30] The Women's Ischemia Syndrome Evaluation study found that black women undergoing coronary angiography for suspected ischemia also had greater all-cause and cardiovascular mortality than white women.[26] Interestingly, in a study of the gender gap in CHD mortality rates among 39,614 subjects across 542,605 person-years of follow-up, white male patients (aged 45 years) had a sixfold increased risk of death compared with white women, whereas black males had only a twofold increased risk of fatal CHD when compared with black women.[41] By 95 years of age, men and women were at equal risk for CHD mortality in both blacks and whites. Adjusting for CHD risk factors did not explain this racial disparity in male–female CHD mortality.[41]

Complications and rehospitalization. Women have more both in-hospital complications and readmissions following PCI than men. An analysis of data from the National Cardiovascular Data Registry (NCDR) Vatherization Percutaneous Coronary Intervention (CathPCI) Registry (2004–2008) found that women had more in-hospital complications, including mortality, MI, bleeding, and vascular complications.[42] In a study of post-PCI outcomes in the short-term (ie, 30 days), data from 36,060 PCI patients were used to develop models predicting rehospitalization. Significant pre-PCI predictors of readmission within 30 days included age, female sex, use of Medicare or state insurance, congestive heart failure, and chronic kidney disease.[43] Post-PCI predictors included lack of a β-blocker prescription at discharge, post-PCI vascular complications, and extended length of stay.[43] In the medium term (ie, 30 months post PCI), gender differences appear to attenuate. In the NCDR CathPCI Registry (2004–2008) study, women had a slightly lower adjusted risk for death at 30 months post PCI, and there were also no sex-related differences in adjusted rates of MI, bleeding, or revascularization.[42] Males and females benefited similarly from the use of drug-eluting stents.[42]

Another possible outcome following MI is rehospitalization for ACS. In the 1999–2010 analysis of Medicare beneficiaries, women had a greater risk of one-year rehospitalization for AMI than men.[38] Based on a cohort of patients with AMI enrolled in the Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health (TRIUMPH) study, the most significant predictors of rehospitalization for ACS within one year were CABG prior to hospitalization for the AMI, female gender, and in-hospital PCI, but not type of stent.[44] In the same study, the strongest predictors of subsequent revascularization were multi-vessel disease and in-hospital PCI with a bare metal stent.[44] In another analysis of the TRIUMPH study, younger women (aged <55 years) had a higher crude one-year rehospitalization rate.[21] It has also been noted that thyroid dysfunction is associated with worse outcomes and higher risk of reinfarction in patients with ACS and MI.[45]

Cardiovascular events. Other cardiovascular events following MI are also of particular concern for women. Compared with men, women in the HORIZONS-AMI study had higher levels of major adverse cardiovascular events defined as follows: death, major bleeding, reinfarction, target vessel revascularization for ischemia, or stroke either in-hospital, at 30 days, or at three years.[13] In the study on cardiac hemodynamics, women with STEMI were found to have a higher 30-day reinfarction rate than men.[5]

Recovery. Worse post-AMI recovery experienced by women might be explained in part by a lower quality of life and higher levels of perceived stress. In one study of young and middle-aged patients, women had higher baseline stress, mostly explained by their comorbidities, the state of their physical and mental health, intra-family conflicts, caregiving demands, and financial hardship.[46] This higher stress was associated with worse female recovery at one month post AMI, specifically measured by angina, overall quality of life, and mental health.[46] A study to distinguish the effects of societal gender roles versus biological sex on health-related quality of life (HRQL) after ACS used data from 1,213 patients aged 18–55 years who were enrolled in the GENESIS-PRAXY study. At the baseline and at one, six, and 12 months, women had lower HRQL scores than men, and the differences were clinically significant. Social support and social–gender-related variables (eg, housework responsibility) were predictors of physical limitation, angina frequency, and disease perception, but biological gender alone predicted only one of these outcomes – physical limitation.[47]

MI in Women Internationally

Beyond the USA, women in other countries also demonstrate differences from men regarding MI. This similarity in the

experience of women – despite living in countries with vastly different political, cultural, and health system contexts – highlights the importance of viewing MI risk assessment and treatment through a gender-specific lens to effect meaningful improvements in outcomes.

In a Canadian study, the assessment of AMI hospitalizations (aged ≥20 years) found that women had more comorbidities than men and that this gender-based difference was more pronounced between younger patients, narrowing as age increases. Younger women were more likely to have diabetes, heart failure, renal failure, and malignancies than similarly aged men. Age-standardized AMI hospitalization rates declined similarly for men and women. However, women in the age group of ≤55 years experienced an increase in AMI hospitalization rates, which did not occur in men in this age group. The 30-day mortality rate declined for both sexes over the 10 years of the study, but women in the age group of 20–55 years had 45% higher odds of 30-day mortality than men of the same age, and this persisted over the course of the study. Only in the oldest group (≥75 years) women had marginally better mortality rates than men.[48]

A small follow-up study of 175 patients with AMI in Spain looked at sex differences in HRQL at three and six months post the event. Men in this study were more likely to have had revascularization at the time of the AMI, but women were more likely to have had revascularization later. Women also had higher six-month rehospitalization rates and lower six-month HRQL scores than men.[49]

German female patients with STEMI admitted for primary PCI were older than men and, at presentation, had higher incidence of diabetes, hypertension, and renal insufficiency. The women encountered longer prehospital and in-hospital delays. PCI was performed with equal frequency in male and female patients, but women were less likely to receive glycoprotein IIb/IIIa blockers or drug-eluting stents. At discharge, women were less likely to be prescribed β-blockers or lipid-lowering drugs. Women had more in-hospital bleeding complications, and unadjusted in-hospital mortality rate was higher in women than in men. This mortality difference persisted through one year.[50]

A study of patients with STEMI and NSTEMI in Italy found that women and patients with less education were less likely to be treated with either primary PCI or CABG. Despite that, no differences were found in either in-hospital or one-year mortality rates.[51]

In a study set in China, data from a nationally representative sample of 11,986 patients with STEMI from 2001, 2006, and 2011 showed that women diagnosed with STEMI were on average older than men. Women aged <60 years were more likely to have hypertension and diabetes than men and were less likely to smoke. Women aged >60 years were less likely to have had a prior AMI. These differences were attenuated in older age groups. Clinical presentation also differed by gender. Younger women had worse renal function and higher LDL cholesterol levels than male peers at presentation. Women <60 years were more likely to have had symptoms for >24 hours before hospital admission and women ≥60 years were less likely to have experienced chest pain than men. Younger women had higher systolic blood pressure, higher heart rates, and fewer cardiac arrests at presentation than either men of the same age or older women. Younger women were less likely than similarly aged men to receive clopidogrel or statin therapy, and women aged 60–69 years were less likely to receive aspirin, clopidogrel, or β-blockers within 24 hours of hospitalization, or statins during hospitalization. Women aged <80 years, especially those <60 years, were less likely to receive any reperfusion, including primary PCI within 24 hours than men of the same age. All women were less likely to have cardiac catheterization, and those who were 60–79 years old were less likely than their male peers to undergo PCI or revascularization. Overall in-hospital mortality rate was nearly twice as high for women, and this difference remained significant even after adjusting for patient characteristics, hospital characteristics, and year of study. A greater chance of mortality with increasing age also persisted after adjusting for a wide range of confounders.[52]

Female patients hospitalized with their first AMI in Hanoi, Vietnam, were older than men: more likely to delay seeking medical treatment, less likely to have smoked, and more likely to have diagnosed hyperlipidemia, hypertension, and diabetes. Medical management was similar for males and females, but women were less likely to have undergone cardiac catheterization or PCI during the first 24 hours. Women were also more likely to develop heart failure and had higher in-hospital mortality rates than men.[53]

Conclusion

Although outcomes following AMI have been improving over the years, women may require special consideration in order to continue the improvement of outcomes in the future. Because women differ in MI presentation symptoms and physiology, avenues for both diagnosing and treating MI must be developed in a gender-dependent fashion. Women may also require a different post-hospitalization approach, as they report having lower HRQL and higher stress, which may impair recovery. Of course, prevention of CVD in women would be ideal, and this will require focused effort because comorbidities are more common in women and they are less informed on MI symptoms, are reluctant to call for help, and overestimate their own "good" health status. When surveying international studies of AMI, just as in the USA, women exhibit more comorbidities than men and appear to encounter other MI trends similar to those experienced by women in the USA.

Author Contributions

Conceived the concepts: GG. Analyzed the data: GG. Wrote the first draft of the manuscript: GG. Developed the structure and arguments for the paper: GG. Made critical

revisions: GG. The author reviewed and approved of the final manuscript.

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