Acute Myocardial Infarction in Women

Does a Gender Gap Persist?

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This is to acknowledge that Laura Collins, M.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Collins will not be discussing off-label uses in her presentation.

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Purpose: The purpose of this presentation is to explore whether contemporary studies of acute myocardial infarction in women show a disparity in mortality following AMI (acute myocardial infarction) and define whether there are specific differences in clinical characteristics, comorbidities, pathophysiologic mechanisms, treatment and psychosocial factors that may continue to influence any residual gender gap.

Educational Objectives: At the conclusion of this lecture, the listener will be able to:

1. Identify the different pathophysiologic mechanisms of AMI in young women and understand how they may each affect management.

2. Define how a women's presentation for AMI may differ from that of men with respect to symptomatology, timely presentation and clinical severity.

3. Define potential targets for further decreasing the gender gap for AMI in women.

Introduction:

Over the past two decades, vigorous campaigns to raise women's awareness of their risk of cardiovascular disease ("Go Red for Women" by the American Heart Association and "Heart Truth" (NHLBI)), the greater inclusion of women and minorities in clinical trials (mandated by the NIH and the subsequent greater use of guideline driven therapies for coronary heart disease have likely been responsible for decreasing the cardiovascular mortality in women at a greater rate than that seen in men (fig 1).[1] Despite this marked improvement in cardiovascular mortality for women over the past two decades, cardiovascular disease remains the number one cause of death in women, in the United States and globally. Annually, over 6 million women are affected by coronary heart disease in the U.S. Almost half of these women have a history of myocardial infarction, more than 53,000 will die from an AMI and over 262,000 will be hospitalized for an acute coronary syndrome (AMI and unstable angina).[2] Current data report that 77% of all deaths from coronary heart disease occur out of the hospital or in hospital emergency departments.[3] A recent study found that compared to men, women who had a cardiac arrest in public were *less likely* to be administered bystander CPR (39% vs 45%, p<0.01) and that men had an increased chance of survival compared to women (OR 1.23, (95% CI: 1.12-1.36), p<0.01).[4]

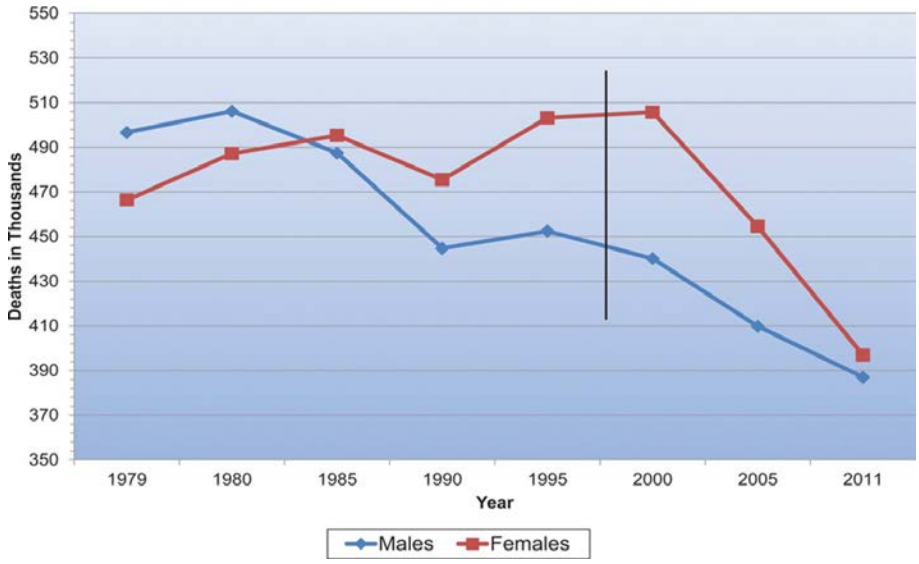

Figure 1. Cardiovascular Mortality Trends in the U.S. for Women and Men 1979-2011 [1]

According to contemporary statistics by the American Heart Association within one year of a first AMI, 23% of women compared to 18% of men will die.[3] This higher mortality for women following AMI continues at 5 and 10 years and is felt to be largely explained (at least in older women) when adjusted for age, risk factors, clinical presentation and treatment.[5] Over two decades ago, it was established that young women (<age 55) have higher adjusted in-hospital mortality (as high as 2-3 fold) and more recent data show a higher rate of readmission (30 days following AMI) compared to young men.[6] Assessment of mortality data following AMI is made difficult by the nonuniformity of the studies in considering age and clinical variables and the methods involved in controlling

for these specifics. Meaningful meta-analyses are difficult to construct due to the heterogeneity of the existing studies. Better understanding of whether sex based differences in plaque morphology and mechanisms of ACS/AMI, awareness of risk, psychosocial and ethnic factors, variable impact of traditional risk factors, risk factors unique to women and underuse of recommended therapies can further explain this gender disparity in young women after AMI.

Clinical Presentation of Acute Myocardial Infarction

Women compared to men present with their first MI at an older age (72 years old in women vs 65.6 years old in men),[4] have more atypical symptoms, comorbid conditions and are more ill (higher Killip class). Historically, women have had longer delays in the time to presentation after the onset of AMI symptoms and this has been attributed to more atypical symptoms (thus delayed recognition by the patient) and psychosocial factors (competing responsibilities of families, spouses, job and embarrassment or fear of bothering others).[7]

In 2010 the CRUSADE and NCDR-GWTW Registries (n=125,161, 40% women) reported that despite the educational/awareness campaigns of the AHA and NHLBI that there had been no improvement in presentation times for AMI (NSTEMIs) in women from 2002-2007 and the median time of presentation from onset of symptoms was significantly longer in women compared to men (3.0 hours vs 2.8 hours, 95% CI 1.0-5.92, p<0.001) even after adjustment for clinical variables.[8] Longer time to presentation for women STEMI patients also persists.[9] Diagnosis of the acute event may be even further delayed upon presentation to the hospital due to failure of the health care team to promptly recognize the AMI presentation in women due to more atypical presentations in women or provider bias. While some studies[9,10] have reported longer door to balloon time in women compare to men, others have shown that these delays are no longer present after controlling for age, comorbidities and clinical variables.[11,12]

VIRGO Study:

Recently, the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients; n=2985, 67% women; recruitment 2008-2012) Study reported that women (age < 55) and men presenting with an AMI report complaints of chest pain (described as pain, pressure, tightness, discomfort) with the same frequency (~ 90% of the time; 87% of women, 89.5% of men), however it was more common for women to present with a constellation of associated symptoms (e.g. epigastric symptoms, shortness of breath and pain in the upper back, jaw, neck or arms 61.9% women vs 54.8% of men, p<0.001).[13] Most of these young patients in VIRGO had one or more traditional coronary artery disease risk factor, similar to other studies, women were more likely to present with NSTEMI (non-ST elevation MI) and men were more likely to present with a STEMI. Women presenting with a STEMI (ST elevation myocardial infarction) were more likely to present *without* chest pain (OR 1.51, 95% CI (1.03-2.22) compared to men.[13] Those women in VIRGO without chest pain at presentation were more likely to have diabetes mellitus, prior stroke, transient ischemic attack, chronic kidney disease or chronic lung disease than women presenting with chest pain. Women were also almost twice as likely than men to attribute their symptoms to anxiety (20.9% vs 11.8%, p<0.001) and presented to the hospital later for their symptoms (3.2 vs 2.4 hours; p<0.004).[13] At least 30% of the women in VIRGO sought care for various prodromal symptoms in the weeks leading to their event and were more likely than men (53% vs 37%,

p<0.001) to have their symptoms attributed to a non-cardiac etiology by their providers.[13] These findings demonstrate that the diagnosis of coronary artery disease is more complex, particularly in young women, and underscores the importance of providers having a heightened sense of awareness for underlying CAD in young women with risk factors and/or other comorbid conditions even if their presenting symptoms are more atypical.

Awareness of Risk

Although there has been an increase in women's awareness that cardiovascular disease is the leading cause of death among women over the last two decades (30% in 1997 vs 56% in 2012) this has not been equivalent across minority ethnic groups and lower socioeconomic groups (figure 2), which are the highest risk populations.[14] Although minority women have a higher prevalence of MI and worse mortality than non-Hispanic white women, their level of awareness that they will die from cardiovascular disease is almost two-fold lower than non-Hispanic white women. In general, levels of awareness that cardiovascular disease is the number one killer of women have plateaued over the past decade, suggesting that current educational paradigms are not reaching the highest risk populations. More innovative ways of reaching these populations (social media, at places of worship or community centers) must be evaluated to narrow this gap in awareness among racial/ethnic groups.

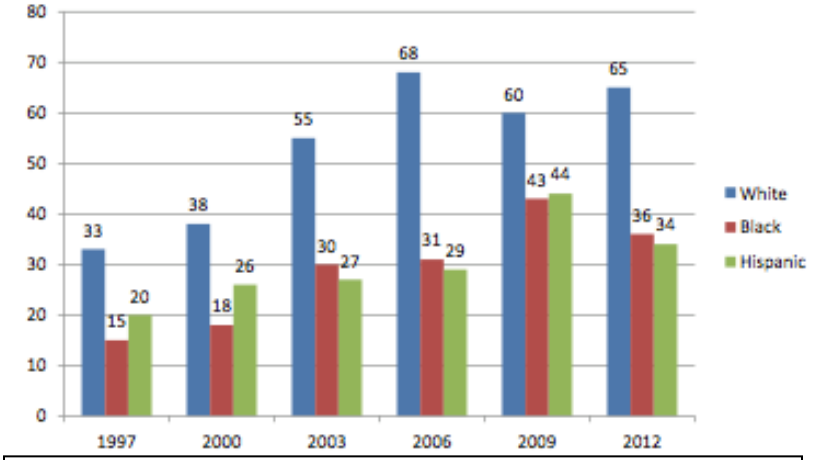

Figure 2. Trends in Awareness that Heart Disease is leading Cause of death for Women[14]

Impact of Traditional Cardiac Risk factors on Risk of Mortality in Acute MI:

Overall, the traditional risk factors for coronary heart disease are the same for women and men, some risk factors have been identified as being more detrimental in women (type II diabetes mellitus, tobacco, depression and other psychosocial risk factors).[1] Risk factors act synergistically to increase one's cardiovascular risk. Most women presenting with an AMI have two or more risk factors. The INTERHEART Study identified nine modifiable risk factors (fig, 3) for both men and women (smoking, diabetes, hypertension, abdominal obesity (waist:hip ratio),

dietary patterns (consumption of fruits and vegetables), alcohol consumption, plasma apolipoproteins, physical activity and other psychosocial factors) which account for 94% of population attributable risk of acute myocardial infarction in women and 90% in men at all ages and in all regions (fig. 3) This study found an increased risk in women compared to men associated with diabetes and hypertension and a greater protective effect of alcohol and exercise for women.[15]

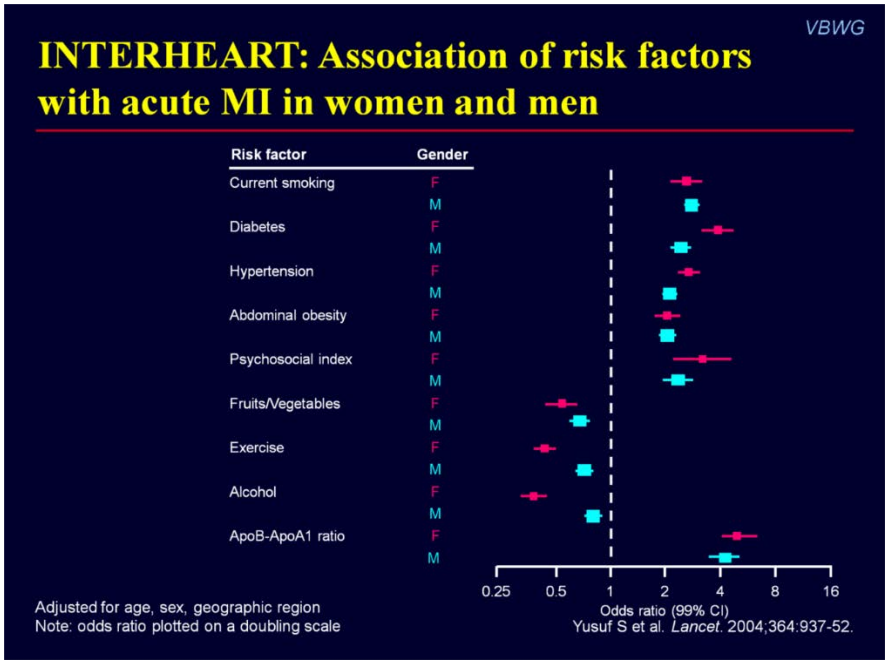

Figure 3. Association of Risk Factors with Acute MI in Women[15]

Depression/Psychosocial Risk Factors

Depression is twice as likely to affect women than men.[1] Young women vs young men presenting with AMI in the VIRGO Study had higher perceived stress scores with higher rates of DM, depression (2-fold increase) and prior PCI.[16] The strong association of depression and AMI in young women, persists even after adjustment for socioeconomic, clinical characteristics and disease severity.[1] Recent research has identified childhood physical and sexual abuse as probable risk factors for coronary heart disease in women.[1]

Risk Factors Unique to Women:

Autoimmune Diseases

The 2011 AHA's Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women identified systemic autoimmune collagen vascular disease (e.g. systemic lupus erythematosus and rheumatoid arthritis) as a risk factor for CAD in women.[17] It is currently recommended that women with these disorders, without clinically evident coronary artery disease undergo screening for other cardiovascular risk factors.

Hormonal Considerations

On average, women present ten years later than men with coronary heart disease. This is likely due to benefits conferred by endogenous estrogen on the vascular endothelium and lipids to the pre-menopausal women.[18] Interestingly, the WHI (Women's Health Initiative (a primary prevention randomized clinical trial) and HERS (Heart and Estrogen/progestin Replacement Study (a secondary prevention randomized clinic trial) concluded that estrogen/progestin does not protect against coronary heart disease events in post-menopausal women. [19,20] In the WHI, there was an increase in strokes and coronary heart disease events in women on estrogen/progestin. Criticism of both trials was that women were enrolled too long after becoming menopausal and thus it is unclear whether a reduction of coronary vascular disease events may have been realized in a younger population of menopausal women treated with combined hormonal therapy. Currently, there is no role for hormonal replacement therapy in the prevention of coronary heart disease and if a woman presents with an acute coronary syndrome or stroke on hormonal therapy, it should be discontinued.

Pregnancy Induced Vascular Complications:

In 2011, the AHA Update on cardiovascular risk factors in women identified pregnancy induced complications (including gestational hypertension, pre-eclampsia, gestational diabetes, spontaneous preterm delivery and having a small for gestational age baby) as risk factors for future cardiovascular disease. [17] It is estimated that 10% of pregnancies, globally are affected by these complications and these women have a 1.5-3-fold increased risk of cardiovascular disease even after adjusting for age, hypertension and diabetes.[17,21] Whether these conditions may simply be associated with pre-pregnancy risks and serve as a marker for future disease is unclear. Additional research is warranted to determine the presence of the conditions themselves serve to further mediate cardiovascular risk through hypothesized effects on endothelial dysfunction, vascular stiffness, and/or inflammation.[21]

Pathophysiology of Acute Myocardial Infarction in Women

The differential diagnosis of acute coronary syndrome/AMI in young women is broader and more diverse than other populations. The potential etiology for the event is often not fully defined until after angiography. Usually, the event is a result of plaque disruption (typically plaque rupture or erosion as discussed below), however there are a minority of patients (more women than men) who will present with alternative etiologies for their cardiovascular event. These other mechanisms include myocardial infarctions occurring without plaque mediated disruption in the setting of obstructive CAD (traditionally termed type II myocardial infarctions), MINOCA (Myocardial infarction in the setting of Non-Obstructive CAD) and then non-atherosclerotic mechanisms (including but not limited to coronary artery vasospasm, spontaneous coronary artery dissection (SCAD), embolism, microvascular dysfunction (Syndrome X) and Takotsubo Cardiomyopathy). It is interesting to note that Takotsubo Cardiomyopathy Syndrome is more common in women (at least 80% of cases) and at least one study suggests microvascular dysfunction as the pathogenic mechanism.[22] It is important to remain vigilant and define these alternative mechanisms (more common in women) in the cardiac catheterization lab, as there are significant implications for management and prognosis.

Spatz et al. developed a novel taxonomy for young (≤ age 55) adults with acute myocardial infarction to attempt to better define the variable phenotypes present in young women (fig. 4**).** In their population only 82.5% of young women fit into a Class I myocardial infarction compare to 94.9% of young men. They propose their taxonomy as a frame work that can be altered as future research defines new phenotypes and redefines existing ones. This classification which can be used clinically and for research purposes will start to define optimal treatments, prognosis and outcomes for acute coronary syndromes, particularly in young women.[23] I suspect that we will discover significant overlap within each class, particularly with respect to microvascular dysfunction and the underlying presence of coronary artery disease.

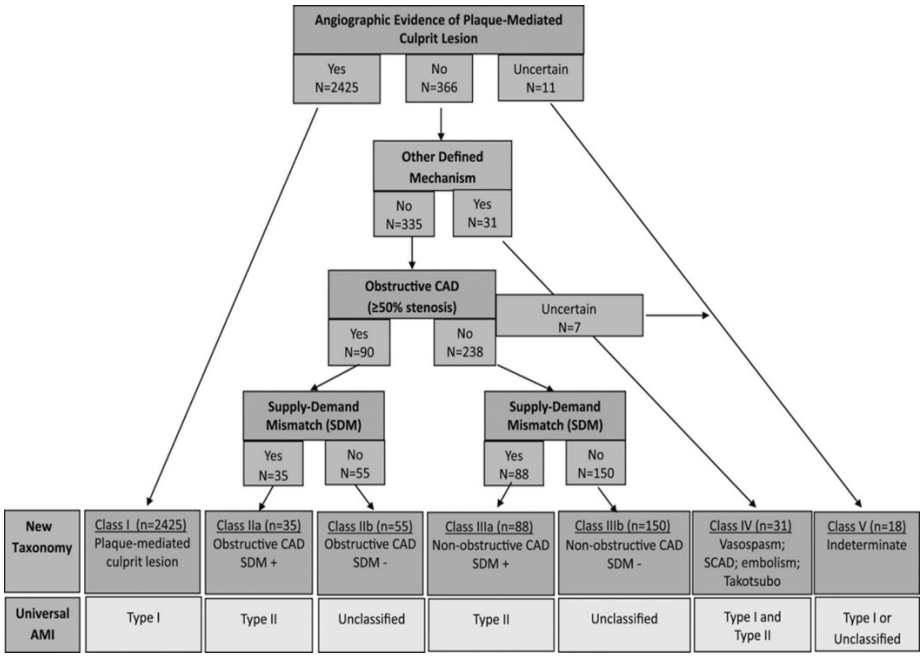

Figure 4. Novel Taxonomy for Acute MI in Young Adults[23]

Gender Differences in Plaque Morphology

Autopsy studies have defined three major vascular events (plaque rupture, plaque erosion and calcific nodule) which lead to thrombotic coronary occlusions (see fig 5). Plaque rupture is the most common accounting for 76% of fatal myocardial infarctions in men and 55% in women.[1] Plaque rupture typically occurs in an atherosclerotic lesion with a necrotic lipid core and thin fibrous cap which becomes fractured leading to infiltration of foamy macrophages, other inflammatory cells and matrix metalloproteinases with subsequent activation of the coagulation cascade and thrombotic occlusion. Plaque erosion occurs when the endothelium overlying a plaque becomes denuded, exposing proteoglycans and smooth muscle cells (rather than inflammatory cells) and thrombus formation/occlusion occurs on the intimal surface and there is more association with distal microembolization. There is an increased prevalence of plaque erosion in women, particularly younger pre-menopausal women who smoke and those with a clinical history of pre-eclampsia.[24,25] It has been postulated that endothelial dysfunction and inflammation likely play a role in the pathology of pre-eclampsia and mediate the development of premature cardiovascular disease, characterized by plaque erosion.[25] It is now possible to

identify plaque morphology with OCT (optical coherence tomography is a catheter-based invasive imaging system, using light rather than ultrasound), This technology more commonly identified plaque erosion in the young patient, but unlike autopsy studies,[24] OCT did not find any specific sex related differences in the prevalence of plaque erosions.[1] The least common cause (seen in 2-7%) of acute thrombotic occlusion in STEMI may originate from calcific nodules which erupt through a plaque and are more common in the right coronary artery and the elderly

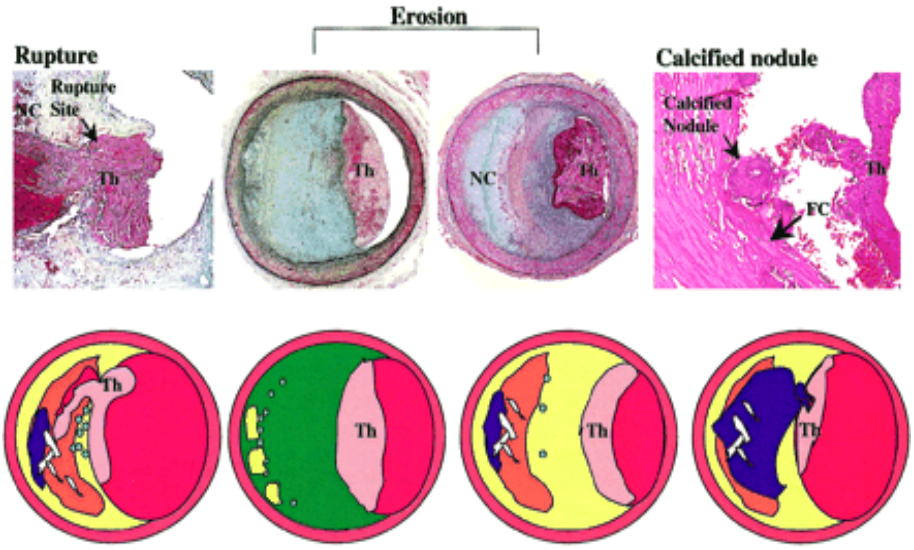

Figure 5: Major Vascular Events Leading to Thrombotic Occlusion of a Coronary[24]

It is uncertain whether characterization of plaque morphology during an ACS would have implications for treatment (i.e. aspiration of thrombus or intracoronary lytic therapy without stent implantation in the setting of plaque erosion and non-obstructive CAD).

Diagnosis and Management of Acute Myocardial Infarction

Diagnosis: Biomarkers

Concentrations of cardiac troponin (cTn) are lower in women than men (~50% lower at 99th percentile) which may be due to a lower left ventricular mass.[26] A fourth-generation assay for cardiac TnT (troponin T) is used at CUH/Zale and a hs-cardiac TnT assay has been in place at PMH for about 3 months. The lower limit of detection of the cardiac TnT assay is 0.01 ng/ml which is at the 99th percentile cut point for men, thus it would not be possible to have a lower cut point for women, despite their lower troponin levels using this assay. Serial measurements are performed over time to increase sensitivity. Parkland is the only UTSW facility offering a hs-cTnT assay and its interpretation does not utilize gender specific cut points. This assay focuses on very low initial values of cTn (ng/L range) and then assesses the dynamic change over very short follow up periods (1-3 hours), thus the 99th percentile value is irrelevant and there is no need for sex-based cut points.[27] It is unlikely, for the above reasons that either the fourth-generation troponin assay or the current algorithm being utilized at Parkland for hs-cardiac troponin T assay are underdiagnosing ACS in women.

Reperfusion Strategies:

In the thrombolytic era, less women than men received reperfusion due to concern by physicians for relative contraindications (smaller body size, more hypertension and fear of bleeding complications). Although more complications were seen in women, most studies showed similar mortality between the genders once outcomes were adjusted for clinical characteristics and comorbidities. Once primary percutaneous coronary intervention (PCI) became available for reperfusion of AMI and was routinely utilized in women, complication and mortality rates declined even further and continued to remain gender neutral if revascularization was utilized. Women with AMI continue to be referred less often than men for angiography, percutaneous revascularization and CABG even after adjusting for comorbidities and degree of CAD.[28] Women are also often less willing to accept percutaneous or surgical revascularization over medical therapy, despite medical advice.[29]

ST Elevation Myocardial Infarction:

The current ACC/AHA STEMI guidelines recommend thrombolytic therapy for patients presenting within 12 hours of symptoms of a STEMI (to a non-PCI center) if there will be longer than a 120 minutes delay of PCI (assuming transfer to a PCI center).[30] No sex specific recommendations are provided by the guidelines as to whether there is a preferable lytic agent to use. GUSTO II-B showed that primary PCI prevented more deaths compared to thrombolytic therapy for STEMI in women (56 deaths per 1,000 treated) vs men (42 deaths per 1,000 treated). [31] In the primary PCI era, a notable decrease of intracranial hemorrhage in women has been noted, but women are still at increased risk for vascular complications and other bleeding. Outcomes in women further improved with the use of stenting over angioplasty and newer generation drug eluting stents in women have reduced death and MI even further (not exclusively from STEMI patients).[1]

NSTEMI Revascularization

Numerous studies have shown that women benefit from invasive management of NSTEMI.[1,32] A meta-analysis and TACTICs-TIMI 18 suggest that this benefit is limited to those women with positive biomarkers.[32,33] The current ACC/AHA NSTEMI guidelines recommend an *early* invasive strategy in women with high risk-features.[34] There are no sex specific differences in the recommended pharmacologic therapy during the acute or management of a NSTEMI (aside from dosing of antiplatelet agents/anticoagulants based on body weight and renal function) or for secondary prevention (see section on adjunctive medical therapy

CABG:

Due to the natural history of coronary artery disease in women, they are typically referred for CABG at an older age with more comorbidities and suffer higher in hospital mortality and complications. A recent report from the Nationwide Inpatient Sample Database (n>2 million patients, 27% women) shows a higher adjusted inpatient mortality for women (OR 1.4, 95% CI 1.36-1.4, p<0.01) after CABG and a higher adjusted rate of stroke, respiratory failure, cardiogenic shock and wound infection.[35] Surprisingly, women had a lower risk of bleeding than men. They reported a faster rate of decline in the in-hospital mortality rate for

women (RR -29.1%, p trend of 0.002 vs RR -25.7%, p trend <0.0001) after CABG compared to men from 2003 to 2012.[35] This same report also reported a significant increase in the use of IMA (internal mammary artery) grafts over this time span, but they have not yet reported on long-term mortality. A prior analysis of 10 randomized trials have found that the long-term follow-up after CABG looks gender neutral with similar risk of death, MI or stroke in men and women .[36]

Complications of Acute Myocardial Infarction

Bleeding Complications:

Bleeding complication rates after AMI due to invasive procedures, thrombolytic therapy and antiplatelet/anticoagulant therapy are more common in women than men.[1] Predictors of bleeding after thrombolytic therapy include female sex, low body weight and older age. Even in the PCI era, the bleeding risk is two-fold higher in women. A matched cohort (n=6702) of men and women who underwent PCI (while enrolled in 7 randomized clinical trials) found that only access site bleeding occurred more in women than in men and was independently associated with ~ 2-fold increase in one-year mortality. [37] Access site bleeding can be reduced in women with the use of avoidance strategies including radial approach, closure devices and use of bivalirudin.[1] Recent data from the MATRIX investigators support transradial over transfemoral access regardless of ACS type due to significant reduction in NACE (Net Adverse Clinical Events, which includes bleeding risk). They noted a higher crossover rate in women, likely due to vasospasm and smaller artery size, but did not find an increase in procedural or fluoroscopic time for the transradial approach. [38]

Cardiogenic Shock and Heart Failure:

Cardiogenic shock complicates 4-9% of STEMI and 1.5-2.5% of NSTEMI.[39] Women have a higher incidence of cardiogenic shock and heart failure, despite less CAD burden and infarct size. Early revascularization is indicated for AMI complicated by cardiogenic shock or heart failure. Left ventricular support (e.g. IABP (intra-aortic balloon pump, Impella) is recommended in those patients who fail to respond to pharmacotherapy or revascularization. Women should receive guideline indicated agents for CHF at presentation and upon discharge (ACEi or ARB are recommended within 24 hours of presentation of AMI with heart failure, anterior wall MI or LVEF $\leq$ 40%, β-blockers and addition of an aldosterone antagonist after target doses of β-blockers and ACEi/ARB are reached; in the absence of contraindications).[1] Contemporary studies show no gender differences in adjusted mortality after PCI for AMI in the setting of cardiogenic shock. [39] Recent data from the National Readmissions Database found that women (even after adjustment for several clinical variables and complications) compared to men, are at a higher rate of 30-day readmissions after AMI complicated by cardiogenic shock.[40] It is not surprising that in their cohort, less women underwent revascularization and left ventricular support during their index hospitalization,[40] stressing the importance of adherence to guideline recommendations.

Mechanical Complications After Myocardial Infarction:

Mechanical complications after AMI account for approximately 12% cases of all cardiogenic shock complicating AMI. All mechanical complications (including acute severe mitral regurgitation,

ventricular septal rupture and free wall rupture with tamponade) have been reported to occur more frequently in women.[1] These complications have a high morbidity and mortality and require prompt recognition and surgical intervention.

Arrhythmias:

Ventricular arrhythmias occur equally among men and women after AMI. Ventricular arrhythmias occurring 48 hours after an AMI require an ICD for secondary prevention. Following an AMI, new onset atrial fibrillation is more common in women and older patients and is typically associated with HF, CS, stroke, and increased 90-day mortality. Thromboembolic protection with anticoagulation in this setting will be challenging due to the concomitant need for antiplatelet agents. Finally, women are at more risk for the development of high degree AV block in the setting of an AMI.[1]

Post AMI Care

Adjunctive Medical Therapy:

Standard medical therapy for secondary prevention (for either STEMI or NSTEMI) include the use of DAPT (dual antiplatelet therapy with ASA and a thienopyridine), statin, beta-blocker and ACE (angiotensin converting enzyme) inhibitors/ARBs (angiotensin receptor blockers) if the LVEF is <40%.[34] It is important to remember that women with non-obstructive CAD should treated with the same guideline-based therapies as women with AMI and obstructive CAD. This former group of women has been traditionally undertreated and suspect to morbidity and mortality due to this oversight. Despite recommendations from the guidelines for NSTEMI and the recent Scientific Statement for Acute Myocardial Infarction in Women, several studies report underuse of evidence based therapies in in women compared to men even after extensive adjustment of many clinical factors and age.[1]

Cardiac Rehabilitation:

Although cardiac rehabilitation following AMI has a class I indication and has been shown to improve quality of life and depressive symptoms, most women qualifying for cardiac rehabilitation do not attend. Women with depression have a two-fold greater rate of not completing the program compared to women without depression. Traditional cardiac rehabilitation programs are not reaching women who have psychosocial issues, smokers, obese and sedentary individuals. After six months of completion, cardiac rehabilitation programs tailored for women show improved quality of life and less depressive symptoms over traditional programs. Alternative cardiac rehabilitation programs using mobile phone apps and/or other forms of social media are being advocated to reach more women.[1]

Psychosocial Factors after AMI:

More than 40% of young women who present with AMI meet criteria for major depression following an AMI and this is associated with a 3-fold increase in the risk of death.[1] Explanations

are likely multifactorial (and may include, but are not limited to poor medication and appointment compliance, poor attendance at cardiac rehabilitation, poor awareness of recurrent ischemic symptoms, suicide and ongoing ischemia.

Contemporary Mortality Data: Do we still have a gender gap?

Over the past twenty years it has become apparent that sex related early mortality differences following AMI are more confined to the younger population (<60 years of age).[41] This section will primarily address this younger group of AMI patients vs older cohorts of women and try to establish whether a gender gap persists in these young patients with regards to outcomes.

In-Hospital Mortality:

Nationwide Inpatient Sample: Using the Nationwide Inpatient Sample n=230,684), Gupta et al. found that in young patients (30-54 years old, from 2000-2010) that AMI hospitalization rates for young people have not declined for either gender.[42] The actual prevalence of comorbidities at presentation were higher among women and increased for both sexes throughout the study period. Women were found to have high length of hospital stays and higher in hospital mortality than men across all age groups. In-hospital mortality over the study period was found to significantly decline for women (from 3.3% to 2.3%, p for trend <0.0001), but not for men (from 2% to 1.8%m p=0.6). Another analysis using the Nationwide Inpatient Sample (n=194,071, 2009-2010) by Rodriguez et al. found that compared to young (>65 years of age) white men, all groups of young women (black, followed by Hispanic and then white) were less likely to undergo invasive procedures (angiography, PCI or CABG). After adjustment for comorbidities, young Hispanic women were found to have a higher in-hospital mortality after AMI (OR 1.5, 95% CI 1.2-1.9) compared to younger white men. Both black and white women were more likely to have higher in hospital mortality compared to white men, but the finding was not statistically significant.[43]

National Registry of Myocardial Infarction (NRMI): Vaccarino et al. found that between 1994-2006 that young women (<age 55 years of age) had the greatest mortality reduction (52.9%) compared to young men (<age 55 years of age) who had the lowest mortality reduction (33.3%). The absolute decrease in mortality was almost 3-fold larger for young women (2.7% vs 0.9%). The excess mortality in young women fell from an OR of 1.93 (95% CI 1.67-2.24) in 1994-1995 to 1.32 (95% CI 1.07-1.67) compared to young men.[41] In contrast to other studie,[44,45] they concluded that changes in comorbidities and clinical severity features at admission was responsible for 93% of the improved mortality trends. Although young women still had higher in-hospital mortality at study end (2.4% vs 1.8%) the authors concluded that these findings indicate that the gender gap is narrowing after AMI for younger women.

Get with the Guidelines-CAD Database (GWTG): Jneid et al**.** found that in a very large cohort of patients with AMI (n=78, 254, ~40% women, but mean age (67.8 for men & 72.6 for women; data not separately analyzed in the young)) that gender differences (after multivariable adjustment) for in-hospital mortality were not present in the overall cohort, however women STEMI patients were found to have higher in-hospital mortality rates (10.2% vs 5.5%, p<0.0001; adjusted OR 1.12, 95% CI 1.02-1.23). The higher in hospital morality rate was attributed to less use of evidence

based treatments, including less early use of aspirin and/or β-blockers, less timely reperfusion, less invasive angiography and revascularization following AMI. [44]

(AMIS Plus, Swiss Registry): Radovanovic et al**.** found that over a 20-year period (1997-2016) for both genders showed a decline for in hospital mortality after AMI, however the magnitude of the effect was greater for women after both STEMI and NSTEMI than men. This improved reduction in mortality was even more pronounced in women under the age of 60, but not in men of the same age.[45] Again, this study also shows the gender gap to be narrowing for younger women with AMI. The authors attributed the observed mortality improvements to the increase use of reperfusion therapy in women.

Mental Stress Induced Myocardial Ischemia in Young Women & Microvascular Dysfunction

A recent study has found that young women (compared to young men) within 8 months following an AMI have a 2-fold increase risk of mental stress induced myocardial ischemia (MSIMI, as measured by peripheral arterial tonometry and reactive hyperemia) and a similar increase in conventional stress induced ischemia (degree of ischemia on myocardial perfusion imaging) for young women (despite less severe CAD burden). The authors concluded that this ongoing ischemia with both mental stress and conventional stress in young women with less severe CAD (compared to young men) after MI implicates microvascular dysfunction and stress induced peripheral vasoconstriction in the etiology of the ischemia noted post MI. Importantly, they also felt that these findings could not be accounted for by psychosocial and clinical risk factors.[46] These findings may help to better understand the mechanisms of the increases mortality after AMI in young patients and optimize management strategies.

Late Mortality:

SWEDEHEART Registry: In this large registry(n=180,000), Alabas et al. found that women compared to men with AMI had no difference in all-cause mortality at 1 and 5 years after AMI, but women did have excess mortality compared to men even after adjustment for age, year of hospitalization and comorbidities at 1 and 5 years. Once adjusting for the use of evidence-based treatments, these differences either markedly diminished or disappeared. Excess mortality in women with STEMI was significantly higher in women compared to men even after adjustment for treatments.[47] The authors concluded that adherence to guideline driven therapies was crucial in preventing premature cardiovascular death in women.

ISAR-RISK and ART Studies: In this cohort (n=802) of AMI survivors in England and Germany, matched cohort for sex, age, left ventricular ejection fraction, cardiovascular risk factors and revascularization strategy, women had an increased mortality (HR 1.61, p=0.045)) compared to men in the first year following MI, however there was no significant difference at 65 years of follow up. These findings suggest gender differences in the pathophysiology of CAD, possible gender differences in response to therapies and negative psychosocial responses in the first year after AMI in women.[47]

Conclusions:

In conclusion, over the past two decades there has been vast improvements in management of acute myocardial infarction in women with a more rapid decline in the mortality rate for women. Despite these improvements, young women with AMI continue to have a higher in-hospital mortality rate which may be explained by later and more atypical presentations, being told more often by their medical provider that their symptoms are not cardiac related, decreased level of awareness, worse risk factor profiles and more adverse psychosocial situations. Women in general continue to undergo less diagnostic and interventional invasive procedures and receive less guideline proven therapies after AMI. These disparities are more pronounced for women of minority ethnic/racial groups who have the lowest awareness that they are at risk. Women compared to men undergoing CABG are at increased risk for adjusted in-hospital mortality, but long-term outcomes after CABG appear gender neutral. Future efforts to close the gender gap and further improve care to women with AMI should focus on: 1) Better understanding of the pathophysiology of AMI/ACS and the identification of unique phenotypes at the time of presentation, 2) Characterization of gender differences in plaque morphology, 3) Understanding how the cardiometabolic complications of pregnancy lead to increased cardiovascular risk, 4) Development of innovative educational programs aimed to raise awareness of cardiovascular risk in women at the highest risk, 5) Reduction of the modifiable cardiovascular risk factors, 6) Better management of depression and adverse psychosocial factors which predispose women to an increased cardiovascular risk and worse outcomes after an AMI, 7) Better adherence to current gender-neutral guideline recommended therapies for AMI management in women, 8) Development of tailored and personalized cardiac rehabilitation programs that will engage more women and 9) Increasing the enrollment of women in randomized clinical trials.

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