Treatment of Coronary Artery Disease in Women

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ABSTRACT: Despite advances in the diagnosis and treatment of coronary artery disease (CAD), gender-related disparities continue to exist, and ischemic heart disease mortality in women remains higher than in men. This review will highlight gender-specific differences in the treatment of CAD that may impact outcomes for women. Further studies are needed to clarify the unique pathophysiology of CAD in women and, in turn, create more specific guidelines for its diagnosis, management, and treatment in this patient population.

INTRODUCTION

Cardiovascular disease is the leading cause of death for women in the United States and globally.[1] Although cardiovascular mortality in women has seen a significant reduction due to increased awareness, a greater focus on women's cardiovascular risk, and the application of evidence-based treatments for CAD,[2] women continue to have poorer cardiovascular outcomes than men. This can be attributed to a multitude of factors, including underuse of evidence-based medical therapies, delays in presentation, diagnosis, and treatment, and lack of gender-specific data regarding the appropriate treatment of CAD in women.[3] The goal of this paper is to review the current literature regarding gender-specific treatment of CAD across the spectrum of presentations, from acute coronary syndromes to nonobstructive coronary artery disease.

ACUTE CORONARY SYNDROMES

Multiple studies have examined the differences in presentation of acute coronary syndromes (ACS) in men versus women. While most patients with ACS present with typical symptoms such as central chest pain or pressure, women are more likely to experience anginal equivalents such as fatigue, dyspnea, indigestion, or jaw pain.[4,5] Differences in presentation may explain some of the gender disparities in ACS outcomes, since a number of studies have shown that women tend to present later in the course of acute myocardial infarction (AMI) and have longer ischemic times than men.[6,7] In the Variation In Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) trial, young women with AMI who were eligible for and received reperfusion therapy were more likely to present with atypical chest pain or no symptoms, to present greater than 6 hours after symptom onset, and to be untreated compared with young men. Women also were more likely to exceed in-hospital and transfer-time guidelines for percutaneous coronary intervention than men and more likely to exceed door-to-needle times.[6] Multiple studies have shown that women with ACS are less likely to be treated with evidence-based medical therapy, cardiac catheterization, and timely reperfusion.[7,8]

Spontaneous coronary artery dissection (SCAD) is an important and often under-recognized cause of ACS in women. In women under 60 years of age, SCAD can account for 20% to 35% of ACS presentations.[9] The ideal management strategy for SCAD has yet to be determined as there have been no randomized trials to guide therapy. A recent study, which prospectively followed 327 SCAD patients, showed that a conservative treatment strategy was associated with low rates of adverse events and beta-blocker therapy was associated with a reduced risk of recurrent SCAD. Almost 63% of these patients had evidence of extracoronary fibromuscular dysplasia. Importantly, recurrent MI due to recurrent SCAD was not uncommon in long-term follow-up, with a recurrent MI event rate of almost 17%.[9]

REPERFUSION STRATEGIES

NSTEMI

Management strategies for ACS appear to have different efficacy in women than in men. Much of the initial data seemed to indicate that an early invasive strategy was less beneficial in women versus men with regard to outcomes such as death or recurrent non-ST-elevation myocardial infarction (NSTEMI, or MI) and, in fact, that there was a trend toward increased harm in women. Many investigators have attributed at least some of the gender-associated excess risk to greater age at presentation, greater presence of comorbid conditions, and smaller body size.[10,11]

The FRISC II trial (The Fragmin and fast Revascularization during InStability in Coronary artery disease) compared the effectiveness of an early invasive versus noninvasive strategy for preventing death and MI in patients with unstable CAD. In a subgroup analysis of women enrolled in the study, there were no differences in MI or death at 12 months among women in

the invasive and noninvasive groups; however, there was a favorable effect in the men who received invasive treatment. In fact, women who were treated with invasive therapies had significantly worse outcomes compared to those treated with a conservative strategy.[12] The RITA 3 trial (Randomized Intervention Trial of unstable Angina), which randomized patients with NSTEMI to strategies of early intervention or conservative care, showed a beneficial effect in men who received an early interventional strategy that was not seen in women.[13] There were, however, several limitations to these studies that may have accounted for the trend toward increased harm in women. The FRISC II trial showed a much lower prevalence of CAD in women at angiography compared with other studies, and a markedly higher event rate was observed in women compared with men in the invasive group that required CABG.[12] Additionally, patients in the RITA trial were a lower risk cohort overall, with lower rates of death and MI at 1 year in women in both the invasive and conservative groups than those in the FRISC II and TACTICS-TIMI 18 trials**.** In the TACTICS-TIMI 18 trial, there was a 28% odds reduction in the primary end point of death, MI, or rehospitalization for ACS at 6 months in women randomized to an early invasive strategy.[14] Of note, the invasive strategy was performed earlier than in FRISC II, with patients undergoing angiography within the first 48 hours as opposed to approximately the fifth day.

A 2008 meta-analysis comparing outcomes of early invasive versus conservative strategies in NSTEMI showed a comparable benefit from an invasive strategy in unstable angina (UA) and NSTEMI for reducing the odds of death, MI, or rehospitalization in both men and high-risk women, defined as those presenting with elevated biomarkers. An invasive strategy did not appear to substantially benefit women without biomarker elevation, and it could potentially increase the risk of death or MI (Table 1).[15] The meta-analysis also showed a significant 33% reduction in death, MI, or rehospitalization for ACS in women treated invasively. As such, the recent ACC/AHA NSTEMI guidelines recommend an early invasive strategy as a Class I, Level of Evidence A recommendation in women with high-risk features.[16]

STEMI

Women tend to have more complications than men with regard to ST-elevation MI (STEMI), such as shock, heart failure, reinfarction, recurrent ischemia, bleeding, and stroke. Although the prognosis has significantly improved in women treated with primary percutaneous coronary intervention (PCI), a meta-analysis of observational studies that included 18,555 women reported that women have a higher risk of in-hospital mortality, even after adjustment for baseline differences, although there is no gender difference in 1-year mortality.[17]

Outcomes in women are more favorable when treated with PCI as opposed to thrombolytic therapy in the setting of STEMI. Women treated with thrombolytics have higher morbidity and mortality than men, which is partially explained by less favorable baseline characteristics including age and rates of diabetes, hypertension, and heart failure.[18,19] Use of primary angioplasty virtually eliminates the risk of intracranial bleeding and was an independent predictor of survival in women.[20] The favorable mortality benefit of primary PCI in women 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.[21]

Stent Selection

While the safety and efficacy of drug-eluting stents (DES) for treating CAD has been extensively assessed in many randomized controlled trials, none of these trials were powered to assess safety and efficacy in women since there were far fewer female study participants. However, a large pooled analysis showed that the use of DES in women is more effective and safe than bare metal stents during long-term follow-up. Women treated with DES had significantly lower rates of death or MI as well as a better safety profile, with less stent thrombosis and lower rates of target lesion revascularization.[22]

BIOMARKER STATUS	INVASIVE STRATEGY	CONSERVATIVE STRATEGY	ODDS RATIO (95% CI)
Biomarker-positive women	118	156	0.67 (0.50-0.88)
Biomarker-negative women	152	163	0.94 (0.61-1.44)
Biomarker-positive men	260	382	0.56 (0.46-0.67)
Biomarker-negative men	229	300	0.72 (0.51-1.01)

Table 1.
Death, myocardial infarction, or rehospitalization with acute coronary syndrome based on biomarker status in trials of invasive versus conservative treatment for non–ST-segment elevation acute coronary syndromes.[15]

Periprocedural Complications

Studies continue to show that women have increased periprocedural bleeding and vascular complications. In a large quality-controlled multicenter registry of contemporary PCIs, women had three times as many vascular complications, nearly twice as much contrast-induced nephropathy, and more than twice as many transfusions as men. In addition, gastrointestinal bleeding, infection, and stroke/transient ischemic attack were more often found in women, and death occurred more frequently in women as well. After further adjustment for chronic kidney disease and low body surface area, however, the odds ratios of major adverse cardiac events (MACE) and death for women were no longer statistically significant (Table 2).[10] This suggests that small body size and renal dysfunction are the primary contributors to adverse outcomes in women.[10]

Use of radial access has been shown to decrease the risk of bleeding and vascular access complications, but many trials comparing radial to femoral access have underrepresented women. The SAFE-PCI for Women trial, a randomized trial designed to compare radial to femoral access in women, did not show a statistically significant reduction in bleeding or vascular complications in women undergoing PCI, although there was a trend toward benefit. Access site crossover occurred more often in women assigned to radial access.[23] A subgroup analysis from the RIVAL trial did show a significant reduction in major vascular complications with radial access when compared to femoral access but again demonstrated higher crossover rates to femoral access.[24] The higher crossover rate may be due to the fact that women have smaller radial arteries that could make them more prone to spasm, a major cause of radial procedure failure.

SURGICAL TREATMENT

Treatment for multivessel or complex CAD usually defaults to coronary artery bypass grafting (CABG) regardless of sex. Postoperative morbidity and mortality following CABG seems to be higher for women than for men. A longitudinal study from the Cleveland Clinic between 1972 and 2011 examined 57,943 patients who underwent CABG, 19% of whom were women. Overall, women had lower survival than men after CABG, even after risk adjustment.[25] A retrospective review of 15,440 patients in Midwestern hospitals between 1999 and 2000 compared outcomes in women versus men undergoing CABG. Women at the time of CABG were older, had a higher rate of diabetes and valvular disease, and were more likely to present in shock. The operative mortality was significantly higher for women than men. Even after adjustment for all comorbidities, female gender remained an independent predictor of increased mortality.[26]

There have been many randomized controlled trials and observational studies examining outcomes for CABG versus PCI in an effort to determine which procedure is preferable for whom, but few studies have examined relative differences between men and women.[25] Data from New York State clinical registries for PCI and CABG demonstrate consistently higher adverse outcome rates in women for both procedures.[27]

The gender gap for CABG-related morbidity and mortality does appear to be closing. A retrospective analysis from the Nationwide Inpatient Sample database included all patients undergoing CABG from 2003 to 2012, 623,423 of whom were women. Again, female gender remained an independent predictor of mortality after multivariate adjustment across all age groups. However, in-hospital mortality has decreased at a faster rate in women than in men.[28] A review of 42,477 primary CABG cases from the Society of Thoracic Surgeons National Cardiac Database demonstrated that use of the off-pump CABG technique seemed to reduce gender disparity in clinical outcomes, with similar risks for death, MI, and prolonged ventilation and hospital stay between men and women.[29]

PHARMACOLOGIC THERAPY

Women are underrepresented in many pharmacotherapy trials.[30] Despite this, available data seems to show essentially equivalent benefit in both sexes for most guideline-based medications, with a few exceptions.

Unlike for men, aspirin has not been proven to reduce the risk of MI in women when used for primary prevention.[31,32] Its efficacy in secondary prevention may also be reduced when compared to men. The International Study of Infarct Survival-2 (ISIS-2) trial showed that aspirin reduced vascular mortality after acute MI by 22% in men but only 16% in women.[33] The thienopyridines, specifically clopidogrel, prasugrel, and ticagrelor, have all demonstrated a significant benefit in both men and women.[34,35] Prasugrel, however, is contraindicated due to an increased risk of bleeding in patients with body weight < 60 kg, which may be relevant when choosing an antiplatelet agent for a frail, older woman.

The effects of statins on cardiovascular risk reduction have been well defined in men; however, women have typically been underrepresented in randomized controlled trials evaluating statins for secondary prevention. An analysis from the PROVE IT-TIMI 22 trial comparing the benefits of intensive lipid-lowering therapy (atorvastatin 80 mg daily) or standard lipid therapy (pravastatin 40 mg daily) in women and men hospitalized for ACS showed that women had dramatic and significant reductions in clinical events with intensive therapy.[36] A large sex-based meta-analysis of statin therapy for secondary prevention

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OUTCOME	OR	95% CI	P VALUE	OR	95% CI	P VALUE	OR	95% CI	P VALUE
Any CABG	0.83	0.63-1.10	.19	0.76	0.56-1.02	.07	0.74	0.53-1.03	.07
Emergency CABG	0.90	0.58-1.41	.65	0.84	0.53-1.34	.46	0.78	0.47-1.30	.34
Vascular complication	3.02	2.44-3.75	< .0001	3.00	2.38-3.77	< .0001	2.82	2.19-3.63	< .0001
Contrast-induced nephropathy*	1.76	1.47-2.09	< .0001	1.52	1.27-1.83	< .0001	1.76	1.44-2.15	< .0001
Nephropathy requiring dialysis	1.40	0.75-2.63	.29	1.45	0.70-2.98	.31	2.09	0.95-4.57	.07
Postprocedure transfusion	2.31	2.03-2.64	< .0001	2.12	1.84-2.44	< .0001	2.04	1.75-2.37	< .0001
Gastrointestinal bleeding	1.63	1.25-2.14	.0004	1.50	1.13-1.99	.0004	1.56	1.14-2.13	.005
Infection and/or sepsis	1.66	1.36-2.03	< .0001	1.54	1.25-1.89	< .0001	1.48	1.17-1.86	.001
Repeated revascularization†	1.13	0.81-1.59	.47	1.18	0.83-1.68	.36	1.08	0.73-1.60	.70
Stroke or TIA	1.89	1.21-2.96	.005	2.28	1.42-3.66	.0006	2.16	1.27-3.67	.005
Postprocedure MI	0.98	0.79-1.23	.89	0.93	0.73-1.18	.53	0.86	0.66-1.12	.25
Death	1.52	1.16-2.01	.003	1.25	0.93-1.68	.14	1.25	0.90-1.74	.20
MACE‡‡	1.12	0.98-1.29	.11	1.05	0.91-1.22	.50	0.97	0.82-1.14	.70

OR: odds ratio; CI: confidence interval; P: probability; BSA: body surface area; CrCl: creatinine clearance; CABG: coronary artery bypass graft; TIA: transient ischemic attack; MI: myocardial infarction; MACE: major adverse cardiac events

*Defined as peak minus baseline creatinine ≥ 0.5 mg/dL; patients with a history of renal failure on dialysis are excluded.

†Repeated revascularization in the same site

‡‡Any CABG, stroke or TIA, MI, death, or repeated PCI (same site)

Table 2.
Parsimonious fully adjusted models for 13 outcomes estimating the odds ratio for female versus male risk. Reprinted with permission from Elsevier.[10]

further confirmed that statins reduce the risk of recurrent cardiovascular events and cardiovascular mortality in women.[37] The use of statins in primary prevention for women has been more controversial since primary prevention trials have been underpowered with respect to female enrollment. A large meta-analysis of 22 statin therapy trials with > 174,000 participants (27% women) demonstrated that statin therapy has similar effectiveness for preventing both primary and secondary major CVD events and CVD-related mortality in women and men.[38]

Sex differences can also play a role when determining anticoagulation strategy during PCI, as women experience more bleeding in the course of routine care for ACS. A significant interaction between treatment and sex has been observed in trials of glycoprotein IIb/IIIa inhibitors (GPI) with respect to cardiovascular events, with a treatment benefit seen in men but not in women. A meta-analysis by Boersma et al. found that once patients were stratified according to troponin concentration, there was no evidence of a sex difference in treatment response, and a risk reduction was seen in men and women with raised troponin concentrations.[39] Women are significantly more likely to receive excess doses of GPI despite obvious differences in body size, age, and comorbidities, all of which contribute significantly to the excess bleeding risk that can be seen in women using GPI.[40]

NONOBSTRUCTIVE CORONARY ARTERY DISEASE

Presentation and Outcomes

Women are less likely to have flow-limiting obstructive CAD compared to men who present with similar ischemic symptoms. Half of all women with chest pain who undergo coronary angiography do not have CAD compared with 17% of men.[41] Emerging data shows that this subset of patients with stable angina and normal coronary arteries or nonobstructive CAD has elevated risks of MACE and all-cause mortality compared to a reference population without ischemic heart disease.[42] Data from the Women's Ischemia Syndrome Evaluation (WISE) study demonstrated that women who were diagnosed with nonobstructive CAD after undergoing angiography to evaluate symptoms of ischemic heart disease had a 2.5% yearly risk of MACE during 5-year follow-up, which was 3 times higher than the case-matched asymptomatic reference cohort.[43] Given their impaired prognosis, additional testing should be considered to attempt to identify processes, such as endothelial and/or microvascular dysfunction, that may influence treatment and long-term outcomes.[42]

Treatment

Microvascular angina, also known as cardiac syndrome X, is characterized by anginal chest pain, at least one cardiovascular risk factor, an abnormal stress test, and normal coronary arteries on angiography. Treatment typically is aimed at relieving symptoms and improving vascular function.[44] Many studies that evaluate the efficacy of various treatment strategies are limited by small sample sizes. At present, treatment strategies including exercise, beta-blockers, ACEs, ranolazine, and statins have all shown some benefit in this population, with improvements in angina symptoms, quality of life, and exercise tolerance.[44,45] An alternative treatment approach for patients with recurrent chest pain, normal coronary arteries, and coronary endothelial dysfunction is the long-term oral administration of L-arginine. Lerman and colleagues found that patients receiving L-arginine showed significant improvements in coronary blood flow response to acetylcholine and significant improvements in angina symptom scores compared to patients receiving placebo.[46] Further studies are needed to determine whether specific therapies are associated with improved symptoms and improved long-term outcomes such as survival.

KEY POINTS

- Women continue to have poorer cardiovascular outcomes than men due to a multitude of factors, including underuse of evidence-based medical therapies, delays in presentation, diagnosis, and treatment, and lack of gender-specific data regarding the appropriate treatment of coronary artery disease in women.
- Women presenting with NSTEMI and high-risk features including elevated biomarkers benefit from an early invasive strategy, whereas low-risk, biomarker-negative women do not substantially benefit and may have an increased risk of harm.
- Women tend to have more complications related to acute myocardial infarction such as shock, heart failure, recurrent ischemia, bleeding, and stroke compared to men, and they fair better with PCI as opposed to lytic therapy.
- Further studies are needed to clarify the unique pathophysiology of CAD in women, with the goal of creating more specific guidelines for treatment and improving outcomes in women.

CONCLUSIONS

This article highlights aspects of coronary artery disease that are specific to women across the spectrum of presentations—from acute coronary syndromes to nonobstructive CAD. Despite advances in the diagnosis and treatment of CAD, gender-related disparities continue to exist, and ischemic heart disease mortality in women remains substantial. Further studies are needed to clarify the unique pathophysiology of CAD in women,

with the goal of creating more specific guidelines for diagnosis, management, and treatment of CAD in women and ultimately improving outcomes.

Conflict of Interest Disclosure:
The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

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