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Standards and Guidelines

SCAI Expert Consensus Statement on Sex-Specific Considerations in Myocardial Revascularization

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Background

Cardiovascular disease (CVD) is the leading cause of death for women world-wide, claiming an estimated 8.5 million lives globally[1,2] and 400,000 in the United States alone on an annual basis.[1-3] Despite significant declines in overall CVD mortality, access and timely delivery of optimal treatment for women lags significantly behind men, resulting in poorer outcomes.[4] Utilization of cardiovascular procedures, such as cardiac catheterization, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), mechanical circulatory support (MCS), and implantable defibrillators, is far lower in women compared with men, independent of disease prevalence or severity.[5,6] Furthermore, women continue to be underrepresented in cardiovascular clinical trials, thereby blunting the chance of understanding sex differences in cardiovascular drug or device outcomes. Accordingly, current society practice guidelines do not address sex-based differences and fail to highlight when insufficient evidence exists regarding cardiovascular outcomes in women. The purpose of this consensus is to summarize the available literature on myocardial revascularization in women and to identify gaps in evidence that can prompt prospective investigation.

Methodology

This statement has been developed according to SCAI Publications Committee policies[7] for writing group composition, disclosure and management of relationships with industry (RWI), internal and external review, and organizational approval. The writing group has been organized to ensure diversity of perspectives and demographics, and appropriate balance of RWI. Relevant author disclosures are included in the Supplementary Material. The work of the writing committee was supported exclusively by SCAI, a nonprofit medical specialty society, without commercial support. Writing group members contributed to this

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effort on a volunteer basis and did not receive payment from SCAI. Literature searches were performed by group members designated to lead each section, and initial section drafts were authored primarily by the section leads in collaboration with other members of the writing group. Recommendations were discussed by the full writing group until a majority of group members agreed on the text and qualifying remarks. All recommendations are supported by a short summary of the evidence or specific rationale. The draft manuscript was peer reviewed in May 2021 and the document was revised to address pertinent comments. The writing group unanimously approved the final version of the document. The SCAI Publications Committee and Executive Committee endorsed the document as official society guidance in December 2021. SCAI statements are primarily intended to help clinicians make decisions about treatment alternatives. Clinicians also must consider the clinical presentation, setting, and preferences of individual patients to make judgements about the optimal approach.

Epidemiology of Ischemic Heart Disease

CVD affects an estimated 422.7 million world-wide and is the cause of death of 17.9 million (47.5% women), with marked regional variation.[2] In the United States, the overall prevalence of CVD is estimated to be 37.4% for men and 35.9% for women ≥20 years of age, and prevalence increases with age in both sexes.[3] Women older than 60 years have a lower prevalence of CAD and myocardial infarction (MI) compared with age-matched men (Supplemental Figure 1); however, in those younger than 60 years men and women have a similar but lower prevalence of approximately 6% for CAD and 2.5% for MI, which likely contributes to the underdiagnosis or delayed diagnosis of CAD in this age group. Women presenting with obstructive CAD are typically older than men, with the most common mechanism of MI caused by atherosclerotic plaque rupture or erosion.[8] While traditional atherosclerotic CVD risk factors, such as diabetes mellitus, hypertension, dyslipidemia, smoking, and obesity, remain important targets for primary and secondary prevention for both women and men, other risk factors, specific to women, may increase risks of CVD. These include preterm delivery,[9] gestational diabetes, breast cancer therapy, autoimmune diseases,[10] hypertensive pregnancy disorders,[11,12] and anxiety and depression.[13,14]

It is increasingly recognized that the etiology of ischemia or MI in women, particularly younger women (<55 years), is more likely to be related to non-obstructive and/or non-atherosclerotic CAD and have been summarized in 2 recent consensus statements.[15,16] MI with non-obstructive coronary arteries (MINOCA) has been reported to be up to 5-fold higher in women compared with men.[17] Underlying causes of MINOCA include non-occlusive plaque rupture/erosion, embolism/thrombosis, vasospasm, coronary microvascular dysfunction (CMD), spontaneous coronary artery dissection (SCAD), and takotsubo cardiomyopathy, and these entities must be suspected when taking care of a woman with an MI[18,19] (Supplemental Table 1 and Supplemental Figure 2).

Gaps in evidence

- True prevalence of obstructive and non-obstructive CAD in women presenting with MI
- Optimal strategies for diagnosing and treating the underlying etiologies in MINOCA
- Mechanisms for decreasing non-traditional risk factors (pregnancy-associated, anxiety/depression) in women that may result in improved outcomes.

Diagnostic Tools to Guide Coronary Revascularization

Non-invasive diagnostic evaluation for myocardial ischemia and viability

Choosing an appropriate diagnostic test for any patient depends on several factors, including test availability, local expertise, patient age, body habitus, ability to exercise, and the pre-test probability of having ischemic heart disease. In women, efforts to limit ionizing radiation should also be considered since the cancer risk is 38% higher in women compared with men for any given radiation exposure.[20] The 2014 American Heart Association (AHA) statement on non-invasive testing in women with suspected ischemic heart disease offers a sex-specific algorithm that incorporates both functional stress and anatomic imaging.[21]

In women, exercise treadmill testing (ETT) has a high negative predictive value but lower diagnostic accuracy compared with imaging stress tests due to a combination of limited maximal exercise ability and hormonally influenced ECG changes, which may result in false positive tests. Stress echocardiography and myocardial perfusion imaging, with either single-photon emission computed tomography (SPECT) or positron emission tomography (PET), offer comparable diagnostic accuracy in both women and men, although the diagnostic accuracy of SPECT may be lower in women due to their smaller heart size[22] and breast attenuation artifacts[23] when compared with PET. To reduce patient radiation exposure with SPECT, consideration should be given to tracer choice and availability (avoidance of thallium and dual-isotope protocols), weight-based dosing, and the use of a stress-only (or stress-first) approach when possible.[24] Stress echocardiography has the advantage over SPECT and PET of not exposing breast tissue to ionizing radiation, but skill in acquiring and interpreting the images varies across institutions. Cardiac magnetic resonance stress imaging (CMR) has superior diagnostic accuracy to SPECT in women and demonstrates equal diagnostic performance in women and men without exposure to ionizing radiation.[22,25] PET and CMR also have the advantage of detecting microvascular ischemia in patients with angina in the absence of obstructive CAD.[26]

When comparing cardiac computed tomographic angiography (CCTA) versus functional stress testing, women are less likely to have a positive CCTA (>70% stenosis) than a positive functional stress test result,[27] which may be secondary to higher false positive rates with functional stress testing and/or higher rates of ischemia in the absence of obstructive CAD. That said, a positive CCTA in a woman is more strongly associated with subsequent clinical events than a positive functional stress test result.[27] When adding fractional flow reserve (FFR) to CCTA, women have been found to have less obstructive CAD on invasive coronary angiography, defined as diameter stenosis ≥50%, in the setting of a positive FFR_{CT} and to have a higher FFR_{CT} value for the same degree of stenosis when compared with men.[28] It is possible that these observations may reflect the higher rates of CMD seen in women or the smaller myocardial mass supplied by the culprit lesions. Of note, FFR_{CT} is not universally available, and additional validations are needed (e.g., left ventricular dysfunction) for wider application.

Invasive IVUS and OCT imaging

Women have a smaller heart size and coronary arteries than men. Based on coronary angiography, the average coronary diameter in women is about 0.5 mm smaller (Supplemental Table 2).[29] Intravascular ultrasound (IVUS) measurements of lesion cross-sectional vessel wall, mean vessel area, and mean lumen area are also smaller in women than in men, resulting in comparable plaque burden (plaque area normalized to vessel area) despite lower plaque volume.[30] Despite these anatomical differences, there are no sex-specific recommendations for OCT or IVUS guidance of PCI, although some evidence suggest greater utility of intravascular imaging for women in detecting and managing stent edge dissections, which tend to be more common and complex in women (detected in 30.6% vs. 15.6%, p=0.02 in one series).[31]

Invasive physiology for ischemia testing

Fractional flow reserve (FFR) and non-hyperemic pressure ratios (NHPR), such as iFR and RFR, are commonly used invasive diagnostic tools for the functional assessment of angiographically intermediate

coronary lesions and post-PCI outcomes. While there are currently no data to support sex-specific cut-offs for invasive functional assessments, research has shown that lesions of similar angiographic severity are less likely to be ischemia-producing in women.[32,33] Specifically, in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) substudy, the proportion of functionally significant lesions (FFR $\leq$0.80) was lower in women than in men for lesions with a 50-70% stenosis (21.1% vs. 39.5%, p<0.001) and for lesions with a 70%-90% stenosis (71.9% vs. 82.0%, p=0.019). Possible mechanisms for these findings include higher rates of CMD seen in women, smaller areas of compromised myocardial territory, and less accurate stenosis severity estimation in women due to smaller vessels.[34] It is also possible that higher resting coronary blood flow seen in women could affect any index that is dependent on resting flow or a net change in flow.[35] Such a hypothesis is supported by the finding that an FFR-guided strategy based on the clinically validated threshold ($\leq$0.80) is associated with a higher rate of revascularization than an iFR-guided strategy ($\leq$0.89) in men but not in women.[36] That said, current data have shown that the clinical outcomes of an FFR- versus iFR-guided strategy are similar in both women and men, implying that both FFR and iFR can be effectively used to guide revascularization, regardless of sex[38] (Supplemental Table 2). However, emerging studies on the diastolic pressure ratio during the diastolic wave-free period (dPR_{WFP}) have shown significant discordance between and even within the sexes when compared with FFR, so it is certainly possible that optimal thresholds for some physiologic indices may need to be sex-based.[37]

Gaps in evidence

- Intravascular imaging versus angiography guidance for PCI optimization in women and men
- Sex-based validation of the non-hyperemic pressure ratios (RFR, dPR, DPR, DFR)
- Clinical validation of thresholds of physiologic indices based on sex

Revascularization for Chronic Coronary Syndromes

Revascularization versus optimal medical therapy in chronic coronary syndromes

The goal of revascularization in chronic coronary syndromes (CCS) is angina relief rather than improvement in mortality. Therefore, when considering medical or PCI treatment options, consideration should be given to women's higher burden and frequency of angina (Table 1). The Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation (COURAGE) trial showed that PCI was more likely to result in lower rates of hospitalization for heart failure and repeat revascularization in women compared with men, despite no significant sex-specific difference in all-cause death and non-fatal MI.[38] Recent meta-analyses of randomized trials evaluating routine revascularization with medical therapy compared with medical therapy alone in CCS have demonstrated that randomization to elective revascularization led to reduced cardiac mortality compared with medical therapy alone and a lower rate of spontaneous MI.[39] Whereas all-cause mortality was not reduced by revascularization, another meta-analysis was consistent in showing a reduction in spontaneous MI and greater freedom from angina.[40] Whether sex-specific treatment differences will emerge from the recent ISCHEMIA trial is unknown, but results may provide needed insight into the interplay between sex, angina, atherosclerosis, and options for treatment and diagnosis.[41]

Revascularization with PCI versus CABG in stable chronic multivessel CAD and left main disease

CABG is the guideline-recommended standard of care for patients with multivessel disease (MVD) $\pm$ left main disease (LMD) and high anatomic complexity (i.e., SYNTAX score >33),[42-44] and women with MVD or LMD may benefit more from CABG than PCI compared with men (Table 1). Despite a lower anatomic burden of MVD, women in the SYNTAX trial had higher mortality rates with PCI compared with CABG at 5 years,[45] and similar trends were seen in women with LMD in the Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial.[46] These results are aligned with a recently published meta-analysis of 1,909 women from 6 randomized trials, demonstrating that women with MVD and/or LMD had a 30% reduction in the composite of death, MI, or stroke 1-5 years after treatment with CABG compared with PCI.[47] This difference in outcomes for women is reflected in the SYNTAX II score, which adjusts female sex by a factor of 1.6 for PCI such that for any given set of criteria the SYNTAX II score will predict a higher 4-year mortality in women for PCI compared with CABG[48]; however, due to the limitations of the original SYNTAX trial (specifically that <12% of patients were women and that first-generation drug-eluting stents were used), contemporary studies are needed to evaluate the effects of sex on outcomes after CABG versus PCI for MVD or LMD and to determine whether sex-specific thresholds for judging anatomic complexity are needed.

Gaps in evidence

- Randomized evaluation of CABG versus PCI in women with MVD
- Randomized evaluation of CABG versus PCI in women with LMD
- Optimal revascularization strategy and guidance in women with CCS

Revascularization for Non–ST-Elevation Myocardial Infarction

An early invasive approach in patients with non–ST-elevation myocardial infarction (NSTEMI) has been associated with improved outcomes and decreased mortality, particularly in high-risk patients.[49-52] Nevertheless, PCI is performed less often in younger (<55 years) women compared with men, which may partially explain the up to 50% higher risk of in-hospital and long-term mortality in women after a NSTEMI.[53-55] In a recent patient-level meta-analysis, the benefits of an early invasive strategy were limited to patients with a Global Registry of Acute Events (GRACE) risk score >140 (relative risk [RR] for death 0.7, 95% confidence interval [CI] 0.52-0.95) and biomarker-positive patients (RR for death 0.76, 95% CI 0.58-1.00)[50] independent of patient sex. Accordingly, the introduction of high-sensitivity troponin assays with sex-specific thresholds has improved the diagnosis of NSTEMI (increase in acute MI detection by 11.5% in women and 9.8% in men compared with standard troponin assays) and the identification of high-risk patients in both sexes[56] and may serve to decrease the sex disparities in NSTEMI outcomes.

Gaps in evidence

- Impact of high-sensitivity cardiac troponin assays on time-to-treatment intervals
- Optimal tools for reliable diagnosis, risk stratification, and treatment of young women with NSTEMI
- Impact of CABG versus PCI on long-term outcomes in women presenting with NSTEMI
- Identifying tools to improve shorter symptom onset to presentation time in women

Revascularization for ST-Elevation MI

Sex-specific disparities in treatment for STEMI

Approximately 23-40% of patients presenting with ST-elevation myocardial infarction (STEMI) are women.[57-64] Female sex has been associated with delays in symptom onset to hospital presentation[57-60] and delays to intervention for STEMI,[58,59,61,62] which have been attributed, in part, to atypical symptoms in women.[65] Furthermore, women are

Table 1
Sex-Based Substudies of Randomized Clinical Trials in Chronic Coronary Syndromes

Trial	Follow-up	Population	Study intervention	Main study findings	Summary
FAME[32]	2-year	744 men and 261 women with multivessel CAD	Intervention: FFR-guided PCI (384 vs. 125) Comparator: Angiography-guided PCI (360 vs. 136)	The proportion of functionally significant lesions (FFR ≤0.80) was lower in women than in men for lesions with 50% to 70% stenosis (21.1% vs. 39.5%, p<0.001) and for lesions with 70% to 90% stenosis (71.9% vs. 82.0%, p=0.019). Although women were older and had significantly higher rates of hypertension than men, there were no differences in the rates of MACE (20.3% vs. 20.2%, p=0.923) or the individual components of MACE at 2 years, irrespective of treatment strategy.	In women, angiographic lesions of similar severity were less likely to be ischemia producing than in men. FFR-guided PCI is equally beneficial in women and men
COURAGE[38]	Median 4.6-years	1949 men and 338 women with single, double, or triple vessel, stable CAD	Intervention: PCI and OMT (979 vs. 169) Comparator: OMT (968 vs. 169)	There was no difference in treatment effect by sex for the primary endpoint (death or myocardial infarction; HR 0.89, 95% CI 0.77-1.03 for women and HR 1.02, 95% CI 0.96-1.10 for men; $p_{interaction}$= 0.07). Compared with men, women assigned to PCI had fewer hospitalizations for heart failure compared with OMT alone (HR 0.59; 95% CI 0.40-0.84, p<0.001 for women and HR 0.86, 95% CI 0.74-1.01, p=0.47 for men, $p_{interaction}$= 0.02). There was a sex-based differential treatment effect for randomization to PCI despite both sexes experiencing significantly reduced need for subsequent revascularization (HR 0.72; 95% CI 0.62-0.83, p<0.001 for women; HR 0.84; 95% CI 0.79-0.89, p<0.001 for men; $p_{interaction}$=0.02).	There were no significant differences in treatment effect on major outcomes between men and women. Women assigned to PCI demonstrated a greater benefit compared with men, with a reduction in heart failure hospitalization and need for future revascularization.
ISCHEMIA[41]	Enrollment data of participants	6256 men and 2262 women with CAD and moderate or severe ischemia	Intervention: Revascularization Comparator: OMT Analysis of combined treatment groups	Women were more likely to have no obstructive CAD (<50% stenosis in all vessels on CCTA); 353 of 1022 [34.4%] vs. 378 of 3353 [11.3%]). Women had more angina at baseline than men (median [interquartile range] Seattle Angina Questionnaire Angina Frequency score: 80 [70-100] vs. 90 [70-100]). Women had less severe ischemia on stress imaging (383 of 919 [41.7%] vs. 1361 of 2972 [45.9%] with severe ischemia; 386 of 919 [42.0%] vs. 1215 of 2972 [40.9%] with moderate ischemia; and 150 of 919 [16.4%] vs. 394 of 2972 [13.3%] with mild or no ischemia). Female sex was independently associated with greater angina frequency (OR 1.41, 95% CI 1.13-1.76)	Women in the ISCHEMIA trial had more frequent angina, independent of having less extensive CAD, and less severe ischemia than men.
EXCEL[46]	3-year	1464 men and 441 women with unprotected left main disease	Intervention: PCI (722 vs. 226) Comparator: CABG (742 vs. 215)	In multivariable analysis, sex was not independently associated with either the primary endpoint (HR 1.10; 95% CI 0.82-1.48, p=0.53) or all-cause death (HR 1.39, 95% CI 0.92-2.10, p=0.12) at 3 years. Women had a lower SYNTAX score at baseline vs. men. (mean SYNTAX score 24.2 vs. 27.2, p<0.001). The 3-year rate of the composite primary endpoint in women was 19.7% with PCI vs. 14.6% with CABG, and in men 13.8% with PCI vs. 14.7% with CABG ($p_{interaction}$=0.06).	In patients with unprotected left main disease in the EXCEL trial, sex was not an independent predictor of adverse outcome after revascularization. Women undergoing PCI had a trend for worse outcomes, related to associated comorbidities and increased periprocedural complications.
SYNTAX, PRECOMBAT, and BEST patient-level analysis[45]	Median 1806 days	2486 men and 794 women with MVD and unprotected LMD	Intervention: PCI (1222 vs. 419) Comparator: CABG (1264 vs. 375)	In SYNTAX, female sex favored CABG compared with PCI (HR for PCI: 2.213; 95% CI 1.242–3.943, p=0.007). In trials performed in Asia (PRECOMBAT and BEST), the treatment effect was neutral between both strategies. Sex interaction with treatment strategy was evident in the SYNTAX (western) trial ($p_{interaction}$=0.019) but not in the Asian trials (PRECOMBAT, $p_{interaction}$=0.469; BEST, $p_{interaction}$=0.472; I^2=58%).	This meta-analysis suggests presence of heterogeneous sex–treatment interaction across Asian and Western trials.
CARDia[176]	1-year	378 men and 132 women with diabetes and MVD or complex single-vessel disease	Intervention: CABG (197M vs. 57F) Comparator: PCI (181M vs. 75F)	There was no interaction between sex and combined outcome of death, MI, or stroke at 1 year (HR 2.13, 95% CI 0.68-6.68 for women; HR 1.07, 95% CI 0.59-1.93 for men, $p_{interaction}$=0.289). There was no interaction between sex and combined outcome of death, MI, stroke, or repeat revascularization (HR 2.4, 95% CI 0.87-6.61 for women; HR 1.62, 95% CI 0.95-2.74 for men, $p_{interaction}$=0.489).	There was no sex-based benefit for PCI or CABG on 1-year outcomes studied.

(*continued on next page*)

Table 1 (*continued*)

Trial	Follow-up	Population	Study intervention	Main study findings	Summary
BARI-2D[177]	5-year	759 men and 318 women with type 2 diabetes mellitus and stable coronary artery disease	PCI and CABG stratum with each stratum randomized to revascularization vs. medical therapy, and then insulin provision vs. insulin sensitization	Women were more likely than men to have angina (67% vs. 58%, p<0.01) despite less disease on angiography (Myocardial Jeopardy Index 41±24 vs. 46±24, p<0.01; number of significant lesions 2.3±1.7 vs. 2.8±1.8, p<0.01). Over 5 years, no sex differences were observed in death/myocardial infarction/cerebrovascular accident: HR 1.11, 99% CI 0.85-1.44) after adjustment for baseline variables. Women reported more angina than men (adjusted OR 1.51, 99% CI 1.21-1.89, p<0.0001) and had lower scores for the Duke Activity Status Index (adjusted beta coefficient: -1.58, 99% CI: -2.84 to -0.32, p<0.01).	There were no sex differences in outcomes in the BARI-2D trial. After 5 years of medical therapy with or without prompt revascularization, women had persistently higher angina rates and lower Duke Activity Status Index scores despite less anatomic disease at baseline.
FREEDOM[178]	5-year	1356 men and 544 women with diabetes and multivessel CAD	Intervention: PCI (698 vs. 255) Comparator: CABG (658 vs. 289)	There was no interaction between sex and 5-year composite event rates for death, myocardial infarction, or stroke (PCI vs. CABG, 27% vs. 18% for men and 26% vs. 21% for women, $p_{interaction}$=0.46).	There was no sex-based benefit for PCI or CABG on 5-year outcomes studied.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCTA = coronary computed tomographic angiography; CI = confidence interval; FFR = fractional flow reserve; HR = hazard ratio; LMD = left main disease; MACE = major adverse cardiac events; MVD = multivessel disease; OMT = optimal medical therapy; OR = odds ratio; PCI = percutaneous coronary intervention.

less likely to receive invasive therapies in STEMI, possibly due to more comorbidities and frailty on admission and less obstructive CAD on angiography.[66,67] Together, these delays and disparities in care have contributed to worse in-hospital mortality in women presenting with STEMI, particularly in younger women although the gap in risk-adjusted mortality rates have narrowed over time with the transition from thrombolytic therapy to primary angioplasty.[58,60,61,63,68-78] Once treatment has been initiated, rates of procedural success, postprocedural epicardial flow, myocardial perfusion, and ST-segment resolution are similar in both sexes after primary PCI.[62,79]

Reperfusion considerations for women presenting with STEMI

While primary PCI remains the standard of care for all STEMI patients, thrombolytic therapy is utilized when primary PCI is not available. Women with STEMI are less likely to receive pharmacologic reperfusion therapy compared with men,[61,63,80-82] predominantly due to delayed hospital presentation and older age.[81] Despite there being no difference in the treatment effect between women and men treated with thrombolysis, women with STEMI have a worse mortality and morbidity after thrombolytic therapy, due in part to advanced age and higher risk comorbidities at the time of presentation as well as to an increased risk for intracranial bleeding.[58,60,62,79,83-92]

Data from the Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial support complete revascularization and treatment of the non-culprit lesions at the time of primary PCI for STEMI or as a staged procedure[93]; however, subgroup analyses demonstrated a trend toward effect modification by sex (p interaction = 0.08), with women showing no cardiac mortality benefit with complete revascularization. Furthermore, sex-specific data are lacking regarding the differential effects of FFR guidance in non-culprit lesions in the setting of STEMI from the DANish Study of Optimal Acute Treatment of Patients With ST-Elevation Myocardial Infarction-3 (DANAMI-3) and COMPARE-ACUTE trials.[94,95]

Revascularization in the setting of STEMI and cardiogenic shock

Cardiogenic shock, heart failure, and right ventricular infarction occur more frequently in women with STEMI than in men. Women also have lower blood pressures and lower cardiac outputs[96,97] compared with men in the setting of cardiogenic shock, although no clear sex-specific pattern in change in LV dysfunction has been identified.[88,90,98] Dedicated analyses of several trials, including the (Should we emergently revascularize Occluded Coronaries for Cardiogenic shock) (SHOCK) trial and the CULPRIT-SHOCK trials, have failed to show a sex-specific benefit for intra-aortic balloon pump use or early multivessel revascularization in this setting.[96,99,100] Although randomized data on the use of MCS are lacking, one registry (N=180) reported that women with cardiogenic shock (n=49) had similar improvement in hemodynamics and derived greater clinical benefit than men with early initiation of the Impella MCS device.[101] Nevertheless, several studies have suggested that women presenting with acute MI and shock were less likely to receive MCS devices.[102-106]

Supplemental Table 3 summarizes the RCTs and observational studies describing the prevalence, management, and outcomes of women compared with men with cardiogenic shock complicating acute MI.

Revascularization considerations for non-atherosclerotic causes of ST-elevation myocardial infarction

Spontaneous coronary artery dissection (SCAD)

SCAD is a non-atherosclerotic, non-traumatic etiology of MI due to coronary obstruction by luminal compression caused by either a dissection flap or by propagation of an intramural hematoma.[108] Although accounting for less than 1% of all acute MIs, approximately 90% of patients with SCAD are women presenting between 47 and 53 years of age.[107]

Furthermore, SCAD accounts for 25-33% of MIs in women younger than 50 years and is the most common cause of pregnancy-associated MI (43%).[107] Fibromuscular dysplasia is commonly associated with SCAD, suggesting some aspect of vascular pathology or dysfunction in the etiology of SCAD. Additionally, 15% of SCAD cases are pregnancyrelated, typically occurring in the postpartum period, thereby implicating hormonal shifts as another possible etiological mechanism. In addition, triggers such as emotional and physical stress may also play a role.[108]

Revascularization in the setting of SCAD is associated with increased complications,[102] including a higher risk of iatrogenic dissection, abrupt vessel closure, and hematoma propagation. As a result, it is reasonable to defer revascularization in patients with preserved coronary flow, minimal ischemia, and distal coronary involvement,[108] particularly since spontaneous healing of the vessel has been shown to occur in 95% of patients after 30 days.[109] In the absence of high-risk clinical features (e.g. left main and/or proximal LAD involvement, progression to occlusion after initial conservative therapy, unstable cardiac rhythm and/or hemodynamics), most patients can be managed with conservative therapy. While LV systolic dysfunction with SCAD should be treated with guideline-based heart failure medications, including beta-blockers, angiotensin receptor/neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA), and sodium-glucose co-transporter 2 (SGLT2) inhibitors,[110,111] the benefit of these agents in the setting of preserved LV function remains unclear, with the exception of beta-blockers, which may reduce recurrence of SCAD.[112] Scarce data exist regarding the benefit (or harm) of anticoagulants, antiplatelets, and statins in the setting of SCAD. Expert consensus recommends limiting anticoagulation to only those undergoing PCI.[110] While the use of dual antiplatelet therapy (DAPT) is recommended during the acute phase of SCAD, optimal duration of DAPT and aspirin monotherapy remain unclear.[110] Due to a 5-10% incidence of in-hospital recurrent MI or unplanned revascularization (often due to propagation of the dissection), it is the current consensus that patients with SCAD remain in hospital for 3-5 days.[107]

Takotsubo cardiomyopathy

Takotsubo cardiomyopathy, also known as stress cardiomyopathy, occurs when a stressful emotional or physical event results in dilation of the left ventricle, often with associated ST-segment elevation on electrocardiogram. While over 90% of patients with takotsubo cardiomyopathy are postmenopausal women,[113] the pathophysiology of the disorder remains unknown. Proposed mechanisms include release of catecholamines, decrease in circulating estrogen levels, or vascular dysfunction.[113] Due to the similarities in emergency presentation between patients with takotsubo cardiomyopathy and atherosclerotic plaque rupture, coronary angiography should be performed to confirm the diagnosis as well as cardiac MRI to assess myocardial global and regional function, inflammation, necrosis and perfusion and to rule out coronary embolization as an underlying cause. Treatment is supportive and includes management of acute heart failure with hemodynamic support as needed. Patients presenting with takotsubo cardiomyopathy generally have a good prognosis with recovery of LV function in 95% of patients within several weeks.[114]

Gaps in evidence

- Management and timing of non-culprit lesions in women with STEMI and multivessel disease
- Sex-specific algorithms for management of cardiogenic shock in women
- Sex-specific pathogenesis and risk factors associated with recurrence for SCAD and takotsubo cardiomyopathy

Revascularization Considerations for Specific Patient Populations

Revascularization in the setting of ischemic cardiomyopathy

Coronary bypass grafting (CABG) improved survival in ischemic cardiomyopathy patients with LV dysfunction in trials conducted predominantly in men (>80%).[140-143] With advanced age and comorbidities, women undergoing cardiac surgery have a higher long-term mortality compared with men,[115] and the risk-benefit ratio of CABG is not well defined for women with ischemic cardiomyopathy. Less invasive revascularization strategies in this patient population have not been evaluated but may offer an advantage for women.

Revascularization in the setting of diabetes

Diabetes is more prevalent and a stronger risk factor for CAD in women than in men and is associated with worse outcomes after revascularization.[116] Randomized trials have demonstrated a benefit of CABG over PCI in diabetic patients with obstructive CAD and MVD.[117-119] While subgroup analyses have shown no treatment interaction by sex, women (25%) are under-represented in these studies.

Revascularization in the setting of chronic kidney disease

Chronic kidney disease (CKD) has also been shown to be more common in women than in men.[120] Among patients with CCS, moderate-to-severe ischemia, and advanced CKD, an initial invasive strategy was not associated with a reduction in death or nonfatal MI compared with an initial conservative approach in the ISCHEMIA-CKD trial; however, there was no subgroup analysis reported based on sex.[121] Further studies are needed to identify the optimal revascularization strategy in women with CKD.

Gaps in evidence

- Best revascularization strategy (CABG versus PCI) for women with ischemic cardiomyopathy
- Best revascularization strategy (CABG versus PCI) for women with diabetes and/or CKD

Device Considerations During Percutaneous Revascularization

Drug-eluting stents (DES)

DES are one of the few device classes that has been well studied in women with generally similar outcomes between women and men. A patient-level pooled analysis of 26 randomized DES trials that included 43,904 patients and 11,557 women (26.3%) clearly demonstrated that DES, both first and newer generation, are associated with approximately 60% lower rates of target lesion revascularization compared with BMS in women and that the outcomes of death, MI, and stent thrombosis in women have improved with newer generation DES.[122] Angiographic studies of DES assessing late lumen loss have demonstrated similar degrees of neointimal hyperplasia in women and men, suggesting that drug elution profiles are effective in both sexes.[123]

Atherectomy devices

There are 3 FDA-approved atherectomy devices: orbital atherectomy (OA), rotational atherectomy (RA), and laser atherectomy. Retrospective analyses of trial data evaluating RA have demonstrated that women are at increased risk of procedural complications and major adverse cardiac events (MACE) compared with men.[124] In a recent propensity matched series of 765 consecutive patients (37% women) undergoing RA followed for a median of 4.7 years, the primary endpoint of net adverse cardiac events (net adverse clinical events: all-cause death, myocardial infarction, stroke, and target vessel revascularization plus any procedural complication) occurred more often in women (15.1 vs. 9.0%; adjusted OR 1.81, 95% CI 1.04-3.13, p=0.037). This was driven by an increased risk of procedural complications rather than procedural MACE. Specifically, women were more likely to experience coronary dissection (4.6 vs. 1.3%; p=0.008), cardiac tamponade (2.1 vs. 0.4%; p=0.046), and

significant bleeding (BARC ≥2: 5.3 vs. 2.3%; p=0.028). Procedural complications during RA were associated with almost double the incidence of MACE at long-term follow-up (HR 1.92; 95% CI 1.34-2.77, p<0.001). When RA was compared with modified balloon angioplasty for the treatment of severely calcified lesions, there was a significant interaction by sex, suggesting that RA may be beneficial in men but not women, although it is important to note that only 23 women were included in this study.[125] While there are insufficient data available to conclusively determine the safety of atherectomy devices in women, including no studies on laser atherectomy, current evidence suggests that caution is needed when using RA in women.

Intravascular lithotripsy

Intravascular lithotripsy (IVL) emits sonic pressure waves from an angioplasty balloon to fracture circumferential coronary calcium. The safety and effectiveness of IVL was evaluated in 3 single-arm studies, DISRUPT CAD I, II, and III, which enrolled a total of 631 patients.[126-128] In a patient-level pooled analysis of 628 patients (22.9% women), women had similar extent and severity of calcium compared with men. Despite women having more comorbidities and smaller vessel size (2.7±0.4 mm vs. 3.0±0.5 mm, p<0.001), there were no differences in the primary safety endpoint of 30-day MACE (8.3% vs. 7.1%, p=0.61) or the primary effectiveness endpoint defined as stent delivery with a residual in-stent stenosis ≤30% without in-hospital MACE (91.7% vs. 92.6%, p=0.72) between women and men. Importantly, IVL related serious angiographic complications (flow-limiting dissection, perforation, abrupt closure, slow flow, no-reflow) were uncommon and similar for women and men (1.6% vs. 2.3%, p=0.75). While additional evidence is needed, these results taken in the context of outcomes with atherectomy devices suggest that IVL may emerge as a first-line therapy for plaque modification of calcified lesions in women specifically.[129]

Gaps in evidence

- Sex differences in the efficacy and safety of various device-based strategies for calcified plaque modification

Lesion Considerations During Percutaneous Revascularization

Chronic total occlusions

Percutaneous revascularization of chronic total occlusions (CTO) carries high procedural complexity. Although women comprise less than 20% of trial participants, complications after CTO intervention, including coronary perforation, bleeding, and contrast-induced nephropathy are observed more commonly in women.[130] Nevertheless, a registry of 2002 patients (17% women) suggested that CTO procedural success and mortality reduction is similar in women and men.[131] Furthermore, a meta-analysis of 9 studies including 30,830 CTO patients treated with PCI found that female sex was not an independent risk factor for MACE or PCI success rate.[132] Overall, these non-randomized studies suggest that female sex should not be a factor in withholding CTO PCI.

Gaps in evidence

- Randomized evidence of medical therapy versus revascularization for CTO in women

Vascular Access in Women

With respect to femoral catheterization, vascular complication rates with vascular closure devices (VCDs) in women are inconsistent across studies.[133,134] The Instrumental Sealing of Arterial Puncture Site – CLOSURE Device versus Manual Compression (ISAR-CLOSURE) trial reported similar rates of vascular access-site complications in women receiving a VCD compared with those receiving manual compression (8.6% vs. 9.8%; p=0.451),[133] whereas other studies have reported reduced or even higher vascular complications with VCD in women.[135-137] As such, the optimal manner of achieving hemostasis at the access site in women undergoing transfemoral cardiac catheterization is not defined.

Radial access is recommended in women to reduce bleeding and vascular complications including retroperitoneal hemorrhage (Supplemental Table 4).[138-142] The MATRIX Access trial randomized 8404 patients (26.6% women) to femoral versus radial access for PCI.[141] While women were noted to have a higher bleeding risk compared with men in this trial, the benefit of radial access was relatively greater in women for the primary endpoint of MACCE (composite of death, MI, or stroke; RR 0.73; p=0.019) and net adverse events (composite of MACCE or major bleeding; RR 0.73, p=0.012).[141] In contrast, the Safety and Efficacy of Femoral Access vs Radial Access in ST-Segment Elevation Myocardial Infarction (SAFARI) trial (N=2292), which evaluated radial versus femoral access in the setting of STEMI, did not demonstrate a significant difference in the primary endpoint of all-cause mortality in either women or men.[143] Nevertheless, a meta-analysis of RCTs including the STEMI-RADIAL trial demonstrated that a radial approach was associated with decreased non-CABG related bleeding (odds ratio [OR] 0.56, 95% CI 0.44-0.72), vascular complications (OR 0.49, 95% CI 0.32-0.75), and MACCE (OR 0.73, 95% CI 0.58-0.93) in women,[140,144] suggesting that the radial artery should be the preferred access site for women to reduce procedural-related complications. Since women may be more prone to radial artery tortuosity or spasm (which could lead to unsuccessful radial access), administration of vasodilators and anxiolytics as well as procedural techniques to navigate the forearm vascular anatomy should be employed liberally.

Gaps in evidence

- Optimal method of arterial hemostasis in women undergoing transfemoral cardiac catheterization
- Comparative outcomes based on sex of vascular closure devices

Considerations Regarding Adjunctive Antithrombotic and Antiplatelet Pharmacology

Antithrombotic agents for the treatment of acute coronary syndromes

Antithrombotic therapy is the cornerstone of treatment in patients undergoing coronary revascularization, and studies have suggested that women are undertreated with guideline-recommended therapies.[145,146] Although sex-specific differences in the pharmacokinetic (PK) profiles of antithrombotic drugs may cause variability in pharmacodynamic (PD) responses between women and men and may have a role in modulating bleeding risk, RCTs evaluating antithrombotic medications indicate that both women and men have similar therapeutic benefits.[147-149]

Antiplatelet agents for the treatment of acute and chronic coronary syndromes

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) is the standard of care for preventing thrombotic events after PCI (Supplemental Table 5). Increased platelet reactivity has been shown among women receiving aspirin, although these PD differences have not resulted in significant heterogeneity in aspirin efficacy between the sexes.[147-149] Although reduction in ischemic events has been shown to be greater in men with all oral P2Y12 inhibitors, most studies have shown no significant interactions between specific P2Y12 inhibitor treatment and sex,[150] and sex has not been shown to be an independent predictor of bleeding complications with use of specific agents.[151]

The minimum required duration of use for an oral P2Y12 receptor inhibitor varies according to the clinical setting (Figure 1).[145]

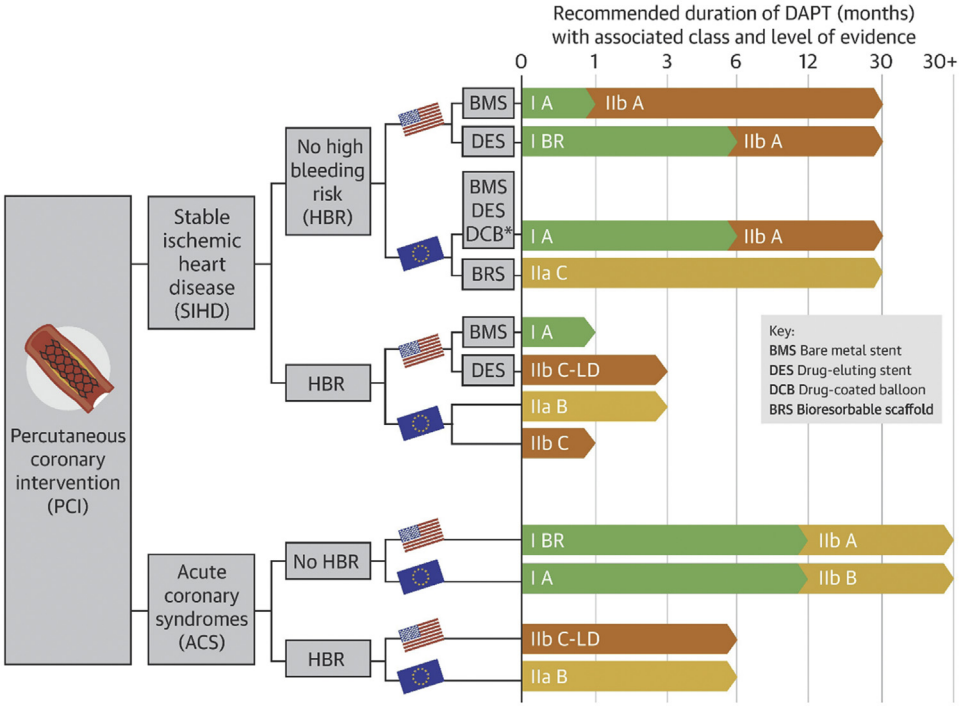

Figure 1. Recommended Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention. *While not marketed in the United States, DCBs are available for clinical use in Canada, with 1-3 months of DAPT recommended. *DAPT = dual antiplatelet therapy; LD, limited data. Reprinted from Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA versus ESC guidelines on dual antiplatelet therapy: JACC guideline comparison. J Am Coll Cardiol. 2018;72(23 Pt A):2915-2931, with permission from Elsevier.*

Prolongation of DAPT beyond this time frame reduces ischemic events and increases bleeding and hence this strategy is reserved for patients who remain at increased risk for ischemic recurrences but who are at low risk for bleeding.[145,152] Although randomized controlled trials have shown similar efficacy and safety outcomes between the sexes, results of real-world registries have consistently shown increased bleeding among women with all P2Y12 inhibitors.[153,154] Increased bleeding in women compared with men may be attributed to factors modulating the PK effects of a drug such as a smaller volume of distribution, a lower glomerular filtration rate (by 10-25%), and differential activity of hepatic enzymes (Supplemental Figure 3).[147-149] Several strategies may reduce bleeding complications, including shortening DAPT duration, discontinuation of aspirin therapy and maintaining P2Y12 inhibitor monotherapy after a brief period of DAPT, and de-escalation of P2Y12 inhibiting therapy (i.e., from prasugrel or ticagrelor to clopidogrel).[145,155-157] Discontinuation of aspirin therapy after the peri-PCI period (e.g., time of discharge up to 1 week) has also emerged as a strategy to reduce the risk of bleeding among patients with atrial fibrillation requiring oral anticoagulation undergoing PCI.[158] Sex-based analyses of ongoing studies adopting such bleeding reduction strategies will provide important insights toward optimizing the choice and duration of antiplatelet therapy in women.

Gaps in evidence

- Sex-specific differences in the optimal choice and duration of antiplatelet therapy in women at high-bleeding risk

Health Status Outcomes in Women After Revascularization

Multiple studies have found sex differences in health-related quality of life (HRQoL) in patients diagnosed with CAD with women reporting poorer HRQoL compared with men.[159-164] While it has been hypothesized that this discrepancy is due to higher rates of comorbidities in women at the time of CAD presentation, several studies have demonstrated that HRQoL differences between women and men persist after controlling for age and other cardiac-related risk factors.[159,160] Indeed, multivariable regression analyses of data from the recent ISCHEMIA trial demonstrated that female sex was independently associated with more frequent anginal symptoms at baseline despite less extensive ischemia and CAD on non-invasive testing, thereby suggesting that there are other factors at play.[41] Higher rates of poor social support and depression have been identified as other contributing etiologies for worse clinical outcomes[165,166] and worse HRQoL[160,167] in women.

Few studies have specifically evaluated sex differences in HRQoL after revascularization for CAD. An analysis of 16,517 ACS patients (22.9% women) who were treated with PCI demonstrated that female sex was independently associated with significantly poorer mobility, more issues with personal care, and greater symptoms of anxiety and depression at 30 days, despite no sex difference in rates of bleeding, stroke, or MACE.[168] Similarly, a single center study of 1072 patients (27.5% women) who underwent CABG demonstrated that women reported experiencing only about 50% of the physical functional improvement at 6 months compared with men.[169] These findings have been shown to be consistent in the younger population as well. An analysis of the Variation In Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study, which included 3,501 patients (67% women age 18 to 55 years of whom ~75% received revascularization), also found more physical limitations and greater angina out to 1 year in women compared with men presenting with ACS.[170]

While women do experience improvement after PCI for both ACS and stable CAD, their HRQoL remains poorer when compared with men, both in the short term as well as out to 1 year.[170,171] These findings suggest that there are additional etiologies (such as abnormal coronary flow reserve[35]) for anginal symptoms beyond that which can be treated by PCI. While compliance with optimal medical therapy and regular participation in cardiac rehabilitation programs may be able to improve residual angina, studies have shown that depression, pain, caregiving demands, and poorer socioeconomic status all impact the ability of patients to engage in recommended medical care.[172-175] The development

DIAGNOSTIC GAPS

Epidemiology of Ischemic Heart Disease

- True prevalence of obstructive and non-obstructive CAD in women presenting with MI
- Optimal strategies for diagnosing and treating the underlying etiologies in MINOCA
- Mechanisms for decreasing non-traditional risk factors (pregnancy associated, anxiety/depression) in women that may result in improved outcomes.

Diagnostic Tools to Guide Coronary Revascularization

- Intravascular imaging versus angiography guidance for PCI optimization in women and men
- Sex-based validation of the non-hyperemic pressure ratios (RFR, dPR, DPR, DFR)
- Clinical validation of thresholds of physiologic indices based on sex

OUTCOME GAPS

Revascularization for Chronic Coronary Syndromes

- Randomized evaluation of CABG versus PCI in women with MVD
- Randomized evaluation of CABG versus PCI in women with LMD
- Optimal revascularization strategy and guidance in women with CCS

Revascularization for Non–ST-Elevation Myocardial Infarction

- Impact of high-sensitivity cardiac troponin assays on time-to-treatment intervals
- Optimal tools for reliable diagnosis, risk stratification, and treatment of young women with NSTEMI
- Impact of CABG versus PCI on long-term outcomes in women presenting with NSTEMI
- Identifying tools to improve shorter symptom onset to presentation time in women

Revascularization for ST-Elevation MI

- Management and timing of non-culprit lesions in women with STEMI and multivessel disease
- Sex-specific algorithms for management of cardiogenic shock in women
- Sex-specific pathogenesis and risk factors associated with recurrence for SCAD and takotsubo cardiomyopathy

Revascularization Considerations for Specific Patient Populations

- Best revascularization strategy (CABG versus PCI) for women with ischemic cardiomyopathy
- Best revascularization strategy (CABG versus PCI) for women with diabetes and/or CKD

Health Status Outcomes in Women After Revascularization

- Utility of targeted programs to identify and address limitations for women at risk for poor HRQoL with CAD after revascularization

PROCEDURAL GAPS

Device Considerations During Percutaneous Revascularization

- Sex differences in the efficacy and safety of various device-based strategies for calcified plaque modification

Lesion Considerations During Percutaneous Revascularization

- Randomized evidence of medical therapy versus revascularization for CTO in women

Vascular Access in Women

- Optimal method of arterial hemostasis in women undergoing transfemoral cardiac catheterization
- Comparative outcomes based on sex of vascular closure devices

Considerations Regarding Adjunctive Antithrombotic and Antiplatelet Pharmacology

- Sex-specific differences in the optimal choice and duration of antiplatelet therapy in women at high-bleeding risk

Central Illustration. Gaps in Evidence for Myocardial Revascularization in Women. CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCS = chronic coronary syndromes; CKD = chronic kidney disease; CTO = chronic total occlusion; HRQoL = health-related quality of life; LMD = left main disease; MI = myocardial infarction; MINOCA = myocardial infarction with non-obstructive coronary arteries; MVD = multivessel disease; NSTEMI = non -ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; SCAD = spontaneous coronary artery dissection; STEMI = ST-elevation myocardial infarction.

of targeted programs to address limitations affecting female participation in cardiac rehab and medical follow-up as well as early identification of women with poorer HRQoL at baseline may be useful to improve the health status of women with CAD after revascularization.

Gaps in evidence

- Utility of targeted programs to identify and address limitations for women at risk for poor HRQoL with CAD after revascularization

Conclusions

This consensus provides a summary of available literature on myocardial revascularization in women in relevant disease states and identifies important gaps in evidence (Central Illustration). In many clinical scenarios, the level of evidence supporting clinical decisions in women is poor due to insufficient data, however clinicians can use the observations highlighted in this document to guide practice. Until further investigation in women is performed, interventional cardiologists should continue to apply relevant randomized trial evidence to inform clinical judgment and best practices in women undergoing PCI.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at https://doi.org/10.1016/j.jscai.2021.100016.

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