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Review

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Disparities in therapies for coronary artery disease with reduced left ventricular ejection fraction

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Abstract

Revascularization through percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is used to manage left ventricular systolic dysfunction (LVSD) due to coronary artery disease (CAD). This review provides an overview of coronary revascularization for CAD with reduced left ventricular ejection fraction (LVEF), focusing on disparities in management. CABG provides more complete revascularization, and lower long-term all-cause mortality and reintervention and MI rates compared to PCI in patients with LVSD and CAD. Consequently, CABG is recommended as the primary revascularization therapy for CAD with reduced LVEF, with PCI being reserved for patients who are high-risk or have unfavorable coronary anatomy. Although LVSD increases revascularization risk, differential outcomes can be attributed to patients' biological, behavioral, and socioeconomic factors as well as health system deficiencies. Women and racially and/or ethnically minoritized patients often present with progressive disease and greater comorbidity, experience delays in diagnosis and treatment, and have higher morbidity and mortality rates post-revascularization. These disparities may be explained by biological differences compounded by social determinants of health. Patients with CAD with LVSD pose unique medical challenges, which may be further complicated by disparities in care. Increased representation of minoritized patients in cardiovascular trials is needed to elucidate these differences and their long-term impact.

Keywords: Coronary artery disease, left ventricular systolic dysfunction, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, disparities

INTRODUCTION

Coronary artery disease (CAD) is the world's leading cause of death due to myocardial infarction, heart failure, and/or sudden death[1,2]. Approximately 125 million people live with CAD worldwide[3]. Risk factors for atherosclerotic CAD notably include smoking, diabetes mellitus, dyslipidemia, hypertension, obesity, and stress[1]. CAD may be asymptomatic or present with minimal symptoms but frequently presents as unstable angina, non-ST-elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI)[1]. CAD may progress to heart failure, usually presenting as shortness of breath, fatigue, and/or fluid overload[4].

Factors generally associated with developing heart failure include older age, male sex, hypertension, diabetes mellitus, CAD, previous myocardial infarction (MI), and valvular heart disease[4]. In adults between the ages of 45 and 95, the lifetime risk of developing heart failure ranges between 20% and 45%. It is estimated that 6.5 million people in the United States are affected by heart failure, with almost 1 million hospitalizations each year[4] and a financial toll of more than 40 billion U.S. dollars[5,6].

Ischemic cardiomyopathy (ICM) refers to systolic left ventricular systolic dysfunction (LVSD) that is primarily due to CAD. Patients with ICM can present with no, minimal, or advanced symptoms of heart failure[3]. ICM accounts for almost half of all heart failure cases[7,8]. It is often due to a mix of irreversible loss of viable myocardium and regions of stunned but viable myocardium[9]. The treatment of ischemic LVSD involves either optimal medical therapy or revascularization in the form of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Treatment decisions are usually based on multiple factors, including but not limited to age, sex, type of disease, and comorbidities. While disparities exist for both CABG and PCI, this review will primarily focus on the growing body of evidence highlighting disparities pertaining to CABG, considering the comparatively smaller body of research on PCI disparities in this specific patient population, who are commonly scheduled for surgical care or conservatively managed with optimal medical therapy.

Burdens particularly affect patients from minoritized and marginalized communities. For example, variations in the prevalence of HF exist, mostly due to differences in sex, race, and/or ethnicity. In White men, this ranges between 30% and 42%, White women 32% and 39%, Black men 20% and 29%, and Black women 24% and 46%[10]. Presentations may also vary, as Black and White men most commonly have heart failure with reduced ejection fraction (HFrEF), while White women more commonly develop heart failure with preserved ejection fraction (HFpEF)[10]. Non-White patients are more likely to suffer from and require hospitalization for heart failure than White patients, yet have lower utilization of ventricular assist devices and heart transplantation, suggesting structural barriers in care[11,12]. Meanwhile, women present with unique forms of heart failure distinct from men, yet clinical trials and guidelines are based on predominantly male patient populations, thereby poorly meeting the needs of diverse populations[13]. In this review article, we present an overview of CAD with reduced left ventricular ejection fraction (LVEF) and tackle the disparities in the management of patients due to differences in race, ethnicity, sex, gender, and other possible factors [Figure 1].

TREATMENT OF CAD WITH REDUCED LVEF

The Surgical Treatment for Ischemic Heart Failure (STICH, NCT00023595) trial[14] and its extended follow-up study (STICHES)[15] provided the most comprehensive insights into revascularization of CAD with LVSD. Comparing medical therapy plus CABG (n = 610) to medical therapy alone (n = 602), the risk of all-

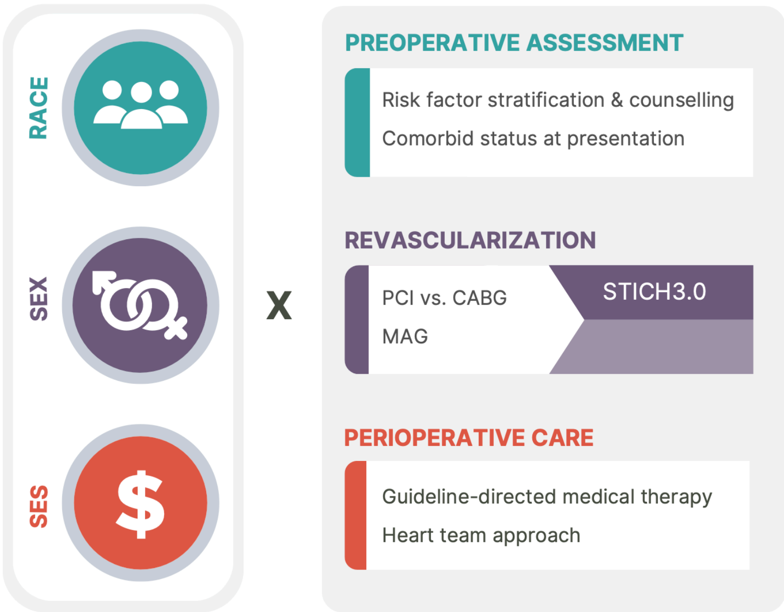

Figure 1. Disparities in CAD with reduced LVEF. CABG: Coronary artery bypass grafting; CAD: coronary arterydisease; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; SES: socioeconomic status.

cause mortality at a median follow-up of 56 months was comparable between groups (HR 0.86 [95%CI: 0.72-1.04])[14]. However, at a median of 9.8 years of follow-up, the addition of CABG was associated with a lower hazard of all-cause mortality (HR 0.84 [0.73-0.97]), suggesting long-term survival benefits for CABG *vs*. medical therapy alone[15]. These late survival benefits were primarily driven by reduced sudden death and fatal pump failure events[16]. It is important to note that optimal medical therapy (OMT) for this subset of patients has had significant changes in the recent past. During the time of the STICH trial, angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose co-transporter-2 inhibitor (SGLT2i) were not yet part of standard OMT[17,18]. Furthermore, the Swedish Coronary Angiography and Angioplasty registry (SCAAR)[19] evaluated long-term outcomes in patients with ischemic heart failure with LVEF < 50% who underwent either PCI or CABG. They also concluded that CABG had a better long-term survival than PCI. Propensity-matched observational evidence from Ontario, Canada, further found increased rates of mortality (HR 1.6 [1.3-1.7]) and major adverse cardiovascular events in patients with severely reduced LVEF who underwent PCI compared to those who underwent CABG at a median follow-up of 5.2 years[20]. The New York State propensity-matched registry study (n = 2,126 matched patients) showed similar mid-term (median follow-up of 2.9 years) survival between second-generation drug-eluting stents and CABG (HR 1.01 [0.81-1.28]), and an increased hazard of MI (HR 2.16 [1.42-3.28]) and repeat revascularization (HR 2.54 [1.88-3.44]), but lower hazard for stroke (HR 0.57 [0.33-0.97]) in the PCI *vs*. CABG group[21]. Lastly, recent meta-analytic findings of comparative studies in patients with CAD and LVEF < 40% (n = 16,191) concluded that revascularization is superior to OMT alone in terms of mortality reduction (CABG: HR 0.66 [0.61-0.72]; PCI: HR 0.73 [0.62-0.85]), consistent with previously discussed studies, and also favored CABG over PCI (HR 0.82 [0.75-0.90])[22].

Less invasive surgical approaches may present further opportunities for patient-centered care by reducing procedural invasiveness. For example, off-pump CABG (OPCAB) may be associated with comparable outcomes and rates of complete revascularization compared to conventional CABG, although evidence in this patient population is limited to smaller studies and mostly single-center experiences with limited follow-up[23]. Simultaneously, improvements in PCI techniques have resulted in improved outcomes over time. The SYNTAX II trial (NCT02015832) compared contemporary *vs*. historical PCI techniques, finding lower composite rates of all-cause mortality, stroke, myocardial infarction, or repeat revascularization at two years of follow-up for modern *vs*. older PCI techniques (13.2% *vs*. 21.9%; $P < 0.001$)[24]. However, this trial did not enroll patients with reduced LVEF, requiring further study in this patient population.

More recently, the REVIVED-BCIS2 trial (NCT01920048) compared stable patients with LVEF of 35% or less and no history of hospitalization two years prior to enrollment undergoing PCI (n = 347) *vs*. OMT alone (n = 353)[25]. At a median follow-up of 41 months, the primary composite outcome of all-cause mortality or hospitalization for heart failure was comparable between groups (HR 0.99 [0.78-1.27]). LVEF was similar between the two groups at 6 and 12 months, while quality-of-life scores appeared to initially favor PCI at 6 and 12 months, but there was no significant difference at 24 months. Despite publication before the trial, the most recent 2021 American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines recommendations reflect the findings from the REVIVED-BCIS and STICH(ES) trials [Table 1].

While the role of PCI is not described in detail in the American guidelines, European and Canadian guidelines recommend that PCI may be considered as an alternative revascularization modality in patients with high surgical risk or the presence of one- or two-vessel disease with the potential for complete revascularization[33]. In recent years, advances in PCI, such as later-generation drug-eluting stents, intra-coronary imaging, radial access, physiology-guided PCI, bifurcation techniques, and advances in chronic total occlusion recanalization, have resulted in improved short- and long-term outcomes, and may explain why PCI rates in this patient population have grown over time despite existing trial evidence[34]. These improvements in techniques and outcomes require direct comparison with CABG[33]. Nevertheless, contemporary trials directly comparing PCI and CABG often exclude patients with (very) reduced LVEF, such as in the case of FAME 3 Trial (NCT02100722), where only patients with LVEF > 30% were included[35]. The upcoming STICH3.0 International Consortium (NCT05427370) will provide contemporary insights into the comparative effectiveness of CABG and PCI to manage patients with CAD and LV dysfunction[33,36]. Meanwhile, the Revascularization Choices Among UnderRepresented Groups Evaluation (RECHARGE):Women and RECHARGE:Minorities aim to specifically investigate PCI *vs*. CABG in populations that are underrepresented in existing revascularization trials[37]. Even with increasing research into the nuances of different patient populations, there are limitations to applying trial-derived recommendations to real-world scenarios. Clinical trials abide by strict eligibility criteria that challenge the generalizability of their findings, with half to three-quarters of all real-world patients meeting clinical criteria that would make them ineligible for enrolment in contemporary trials[38,39]. This is one of many benefits of a Heart Team approach, as it interprets multidisciplinary evidence in the context of the patient's unique clinical profile to facilitate shared decision-making and personalized care[40]. However, even with the increasing adoption of Heart Teams, some disparities in clinical outcomes persist.

SURGICAL CONSIDERATIONS IN CAD WITH REDUCED LVEF [Figure 2]

Diagnosis

Initial investigations of reduced LVEF should distinguish isolated ICM from non-ischemic cardiomyopathy. Mixed cardiomyopathy is suspected if the extent of CAD on coronary angiography is disproportionate to the clinical picture or symptom severity. In patients who are minimally symptomatic, inducible ischemia is identified with stress testing. Viability assessment clarifies the benefit of revascularization through late gadolinium enhancement-cardiac magnetic resonance (LGE-CMR) imaging to assess the scar burden and F-18-fluorodeoxy glucose positron emission tomography to rule out systemic inflammatory disease[41].

Table 1. Guidelines for revascularization in reduced left ventricular ejection fraction[26-32]

Guidelines	Setting	Recommendation for CABG *vs.* PCI in CAD with LVSD	COR	LOE
AHA/ACC/ACCP/ASPC/NLA/PCNA - chronic CAD, 2023[26]	PCI *vs.* CABG in chronic CAD	In patients with chronic coronary disease (CCD) who have significant left main disease or multivessel disease with severe LVSD (LVEF ≤ 35%), CABG, in addition to GDMT, is recommended over medical therapy alone to improve survival	1	B-R
		In patients with CCD and multivessel disease with severe LVSD, CABG added to GDMT is of intermediate economic value compared with medical therapy alone	Cost value statement: intermediate value	B-NR
AHA/ACC/HFSA - heart failure, 2022[27]	Revascularization for CAD in HF	In selected patients with HF with reduced EF (EF ≤ 35%), and suitable coronary anatomy, surgical revascularization plus GDMT is beneficial in improving symptoms, cardiovascular hospitalizations, and long-term all-cause mortality	1	B-R
ACC/AHA/S CAI - revascularization, 2021[28]	Revascularization to improve survival in symptomatic ischemic heart disease (SIHD) compared with medical therapy	In patients with SIHD and multivessel CAD appropriate for CABG with severe LVSD (LVEF < 35%), CABG is recommended to improve survival	1	B-R
		In selected patients with SIHD and multivessel CAD appropriate for CABG and mild-to-moderate LVSD (LVEF 35%-50%), CABG (to include a left internal mammary artery graft to the LAD) is reasonable to improve survival	2a	B-NR
ESC - heart failure, 2021[29]	Myocardial revascularization in patients with heart failure with reduced ejection fraction	CABG should be considered as the first-choice revascularization strategy in patients suitable for surgery, especially if they have diabetes and for those with multivessel disease	2a	B
		PCI may be considered as an alternative to CABG based on Heart Team evaluation considering coronary anatomy, comorbidities, and surgical risk	2a	C
CCS/CHF - Heart Failure, 2021[30]	New pharmacologic standard of care for heart failure with reduced ejection fraction	No recommendations on PCI *vs.* CABG	N/A	N/A
ESC/EACTS- revascularization, 2018[31]	Revascularizations in patients with chronic heart failure and systolic left ventricular dysfunction (ejection fraction < 35%)	In patients with severe LVSD and coronary artery disease suitable for intervention, myocardial revascularization is recommended	1	B
		CABG is recommended as the first revascularization strategy choice for patients with multivessel disease and acceptable surgical risk	1	B
		In patients with one- or two-vessel disease, PCI should be considered an alternative to CABG when complete revascularization can be achieved	2a	C
		In patients with three-vessel disease, PCI should be considered based on the evaluation by the Heart Team of the patient's coronary anatomy, the expected completeness of revascularization, diabetes status, and comorbidities		
CCS - Heart Failure, 2017[32]	Heart failure - revascularization and CAD	We recommend consideration of coronary artery bypass surgery for patients with chronic ICM, LVEF < 35%, graftable coronary arteries, and who are otherwise suitable candidates for surgery, irrespective of the presence of angina and HF symptoms, to improve mortality, repeat hospitalization, and	Strong	Moderate

	quality of life		
	We suggest consideration of PCI for patients with HF and limiting symptoms of cardiac ischemia, and for whom coronary artery bypass grafting (CABG) is not considered appropriate	Weak	Low

ACC: American College of Cardiology; ACCP: American College of Clinical Pharmacy; AHA: American Heart Association; ASPC: American Society for Preventive Cardiology; CCD: chronic coronary disease; CCS: Canadian Cardiovascular Society; COR: class of recommendation; EACTS: European Association for Cardio-Thoracic Surgery; ESC: European Society of Cardiology; HFSA: Heart Failure Society of America; LOE: level of evidence; LVSD: left ventricular systolic dysfunction; NLA: National Lipid Association; PCNA: Preventive Cardiovascular Nurses Association; SCAI: Society for Cardiovascular Angiography and Interventions; SIHD: stable ischemic heart disease.

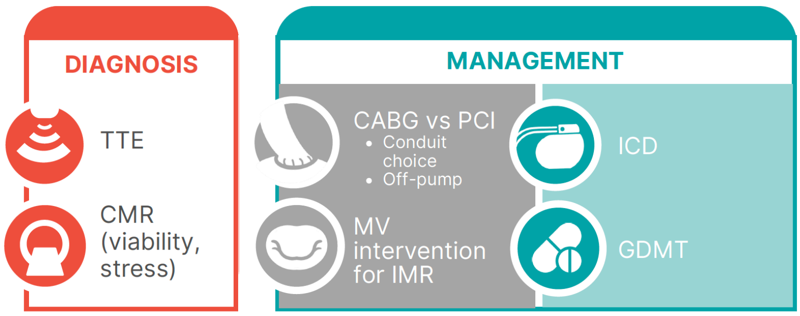

Figure 2. Considerations for the Management of CAD with reduced LVEF. CABG: Coronary artery bypass grafting; CMR: cardiac magneticresonance; GDMT: guideline-directed medical therapy; ICD: implantable cardioverter-defibrillator; IMR: ischemic mitral regurgitation; MV: mitral valve; TTE: transthoracic echocardiography.

Greater than 50% transmural scar involvement on LGE-CMR predicts poor regional recovery after revascularization[42]; however, this understanding has been challenged in other studies[43], with the STICH trial not demonstrating the ability of viability testing to predict survival benefit from CABG[44]. The presence of dense scar formation often cinches the decision against operative revascularization in patients who are already high-risk.

In the clinical setting, CMR has greater utility in women for quantification of ventricular size and function since transthoracic echo image quality can be compromised by breast tissue attenuation. As outlined by the AHA 2014 consensus statement on the role of non-invasive testing in women, stress CMR is a reasonable index diagnostic test in symptomatic women with intermediate-high risk of CAD and resting ST-segment abnormalities or exercise intolerance[45,46]. In pre-menopausal women with functional disability, stress CMR may also be appropriate for the identification of obstructive CAD and prognostication[45].

Operative management

Beyond the revascularization strategy, there are several operative considerations for patients with LVSD. Multiple arterial grafting (MAG) may offer superior conduit patency with the surgeons' expertise and preference determining the choice of an on-pump or off-pump strategy[3]; however, routine use of MAG is cautioned in ICM for a few reasons. Firstly, perioperative administration of high-dose vasopressors predisposes arterial grafts to spasm[47]. Secondly, the initial flow of arterial grafts is less than that of vein grafts due to smaller luminal diameter, thus posing the risk of early coronary hypoperfusion[48]. Further, arterial grafts may be of insufficient length for direct aortocoronary bypass in dilated hearts, and can only be used in composite or sequential grafting, techniques that are often deferred to dedicated coronary surgeons. Lastly, the complexity and additional operative time of performing MAG may be poorly tolerated in severe LVSD. There is also the argument that patients with very low LVEF do not receive the long-term benefit of

MAG and should be spared from its associated risks[49,50]. Evidence also suggests that epicardial lead placement is beneficial and should be considered in patients undergoing concomitant surgery with QRS ≥ 120 ms and LBBB, or patients requiring chronic ventricular pacing[3].

Despite its potential benefits, MAG remains underutilized among women. In the Society of Thoracic Surgeon (STS) database from 2011-2019, women were significantly less likely to receive left internal thoracic artery, bilateral internal thoracic artery (BITA), or radial grafts[51]. Rate of increasing BITA use is higher in men, and although propensity score matching removed significant differences in BITA and radial artery graft use between men and women, there was still greater use of ≥ three artery MAG in men than women (10.5% *vs*. 7.3%; $P = 0.048$)[52]. Hesitancy towards performing MAG in women can be a result of small target vessel and arterial conduit size, risk of sternal dehiscence with BITA, and higher preoperative risk profile[53]. Women are known to have worse early[54] and late mortality, and greater risk of postoperative major adverse cardiac and cerebrovascular events post-CABG than men[55]. In a New York State registry study, MAG is associated with improved survival and a lower rate of major adverse cardiac events among low-risk patients regardless of sex. This was not seen among high-risk patients, with different risk thresholds between sexes when the benefit of MAG is lost[56]. In addition, a propensity-matched analysis between MAG *vs*. single arterial grafting revealed lower seven-year mortality in men who received MAG (HR 0.80 [0.73-0.87]), but not for women (HR 0.99 [0.84-1.15])[56]. The upcoming ROMA:Women trial (NCT03217006) will explore the role of MAG in women; however, the joint impact of sex and LVSD remains to be established as patients with LVEF ≤ 35% will be excluded[57].

Within surgical revascularization, women appear to derive disproportionately greater benefit from off-pump CABG (OPCAB) than men for rates of postoperative death, stroke, and major cardiac events[58]. Adding the additional context of LVSD, OPCAB in the modern era has been associated with comparable, if not better, early survival than on-pump CABG[59], with potentially higher five-year mortality, potentially due to suboptimal longitudinal management rather than surgical strategy[60]. The merit of OPCAB in women with reduced LVEF remains to be explored.

Other operative considerations include addressing moderate-severe ischemic mitral regurgitation at the time of CABG through mitral repair or replacement[61,62], concomitant tricuspid valve repair for moderate-severe tricuspid regurgitation[63], and arrhythmia surgery for atrial fibrillation (AF) for restoration of atrial kick to complement CABG in LVEF recovery[64]. Women have worse age-standardized mortality after combined CABG/mitral valve surgery compared to men[65].

A 90-day waiting period post-revascularization is recommended before proceeding with primary prevention implantable cardioverter-defibrillator (ICD) implantation in patients who have LVEF ≤ 35% despite guideline-directed medical therapy (GDMT)[66]. In a multinational European registry study on primary prevention ICD, fewer women than men undergo ICD implantation; however, women also have lower mortality and receive fewer appropriate ICD shocks after multivariate adjustment[67]. In a race-based subanalysis of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT, NCT00000609) on primary prevention ICD for LVEF ≤ 35% in ICM and non-ischemic cardiomyopathy, survival benefits conferred by ICD was independent of race[68]. Furthermore, the incidence of ICD refusal and medication non-compliance were comparable between Black and Caucasian patients[68], suggesting that the lower rates of specialist consultation and ICD implantation in eligible patients who do not identify as White may be attributed to biases in health care delivery[69].

After revascularization, routine statin and anti-platelet therapies prevent cardiovascular disease progression[70]. Further anticoagulation may be desired for LV thrombus, AF, and after surgical ventricular restoration[3]. HFrEF is managed with foundational quadruple medical therapy of angiotensin-converting enzyme inhibitor, angiotensin type II receptor blocker, or preferentially angiotensin receptor neprilysin inhibitor; beta-blocker; mineralocorticoid receptor antagonist; and sodium-glucose co-transporter 2 inhibitor[71]. Despite a similar predominance of White men in the enrollment of landmark heart failure trials, equivalent GDMT efficacy in women and men has been shown through meta-analysis[72]. Underprescription of GDMT remains an issue, but there may be no significant racial disparity in prescription patterns; in fact, Black patients are more likely to achieve the target dose due to baseline hypertension[73,74]. Patients with poor LVEF recovery are followed closely for chronic issues of cardiorenal syndrome, congestive hepatopathy, pulmonary hypertension, and evaluation of candidacy for advanced heart failure therapies.

DISPARITIES IN MANAGEMENT AND OUTCOMES OF CAD WITH REDUCED LVEF

There is growing evidence pointing to various psychosocioeconomic disparities that impact the prevalence, prognosis, access to care, and outcomes of patients with ICM. Social factors that have been associated with differential prevalence of CAD and resulting outcomes include sex, gender, race, ethnicity, socioeconomic status, social isolation, and stressful lifestyles[75-78].

Women with CAD commonly present with atypical symptoms, such as abdominal discomfort and heartburn, nausea or vomiting, and fatigue or dizziness, while women with acute coronary syndrome (ACS) tend to present at an older age with more comorbidities, including obesity, smoking, depression, hypertension, diabetes, and chronic kidney disease, compared to men[79-87]. At hospital presentation, they experience delays in diagnostic testing (duration to ECG: 7.5 min *vs*. 5.7 min in men)[88], and are less likely to receive evidence-based treatment, including dual antiplatelet therapy (89% *vs*. 93.5%; $P < 0.001$), heparin (66.7% *vs*. 71.2%; $P < 0.001$), or reperfusion therapy with fibrinolysis and/or PCI (50.2% *vs*. 59.5%; $P < 0.001$). Women also experience higher in-hospitality mortality rates than men, even after adjusting for age and clinical variables (adjusted OR 1.20 [1.01-1.43])[89]. According to the Framingham Heart Study, despite women being associated with fewer diagnoses of obstructive CAD (≥ 50% stenosis), women with obstructive CAD are at higher risk for 30-day (RR 1.75 [1.48-2.07]) mortality compared to men[90]. They are also at a greater risk of developing symptomatic heart failure without an antecedent MI (RR 11.4% [9.6%-13.2%]) for men and 15.4% [13.5%-17.3%] for women)[87,90]. The incidence of CAD rises in menopausal/post-menopausal compared to pre-menopausal women (age 45-54 years: OR 2.5; $P < 0.01$)[91].

The incidence of CAD per 1,000-person years is impacted by patients' race, gender, and comorbidities: Black women 5.1% [4.2-6.2], Black men 10.6% [8.9-12.7], White women 4.0% [3.5-4.6], and White men 12.5% [11.5-13.7][92]. Hypertension is significantly associated with CAD in Black women (HR 4.8 [2.5-9.0]), while diabetes mellitus is predictive among White women (HR 3.3 [2.4-4.6])[92]. Further, racial and/or ethnic minority patients present with ACS at a younger age (66 years *vs*. 73 years old; $P < 0.001$) with multiple comorbidities including hypertension (66% *vs*. 54%; $P < 0.001$), hypercholesterolemia (49% *vs*. 34%; $P < 0.001$), and diabetes (48% *vs*. 24%; $P < 0.001$) compared to White patients[93,94]. White patients with ICM are more likely to get admitted for invasive diagnostic testing compared to Black, Asian, and Indigenous patients in the United States ($P < 0.01$)[95]. Once diagnosed with ICM, the use of implantable cardioverter-defibrillator among women (3.5% *vs*. 10.2%; $P < 0.001$) and Black patients (5.4% *vs*. 8.1%; $P < 0.001$) is significantly lower compared to men and White patients, respectively[96,97]. In addition, while GDMT for heart failure is underprescribed for all racial and ethnic groups, Black patients with hFrEF are more likely to get discharged with optimal GDMT[98], particularly β-blockers (OR 1.45, 95%CI: 1.10-1.90; $P = 0.008$) and angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker (OR 1.57, 95%CI: 1.13-2.18; P = 0.008), compared to White patients due to higher rates of hypertension among Black patients[98,99]. Further, compared to White patients, Black patients with heart failure have a higher hospitalization rate (percentage relative to White patients: 229% for men and 240% for women)[100]. While mortality rates in ICM declined in the past few decades, Black women aged 35-54 years experienced the least improvement in mortality rates (1.5%) compared to women of other race/ethnicity groups (3.5% in Asian women, 3.2% in White women, and 2.3% in Hispanic women)[101].

Over the past few decades, there have been persistent, albeit declining, disparities in the utilization of revascularization among women and racial and/or ethnic minority patients. This applies to both patients with and without reduced LVEF[93,102,103]. Women present for revascularization at an older age with higher comorbidity profiles[52]. Women also experience delays in revascularization from symptom onset compared to men (14.4 h *vs*. 7.2 h)[88]. Following CABG, women have higher major adverse cardiac and cerebrovascular events, with a higher incidence of MI and repeat revascularization compared to men[104]. These differences persist despite off-pump surgery and MAG[104]. Overall, women have higher mortality following CABG compared to men even after risk adjustment (65% and 31% at 10 and 20 years, respectively, *vs*. 74% and 41%; $P \leq 0.0001$)[105]. With regards to PCI, women have higher major adverse cardiac events (OR 1.17 [1.01-1.36]) and myocardial infarction (OR 1.42 [1.07-1.87]) rates compared to men but similar all-cause mortality, cardiac mortality, and target lesion revascularization[106]. Recognizing that the majority of the sex-based analyses for revascularization outcomes are derived from patients with preserved LV function, the impact of revascularization strategy on women with reduced LVEF remains to be investigated.

Additionally, non-White patients requiring revascularization are likely to present with higher comorbidity burden (hypertension: 69.8% *vs*. 64.0% and CHF: 25.6% *vs*. 18.2%) and greater acuity requiring emergency admissions (30.1% *vs*. 24.6% in White patients), which are associated with higher mortality[107,108]. When they undergo CABG, non-White patients have a 33% higher risk-adjusted mortality rate (4.8% in non-White *vs*. 3.8% in White patients) compared to White patients (OR, 1.33 [1.23-1.45]) that were only partially explained by socioeconomic status or hospital quality (adjusted OR 1.16 [1.05-1.27])[75,107,109]. Assessing the intersection of racial and sex-based disparities, Black women experience the highest in-hospital mortality, followed by Asian women, White women, Black men, and Hispanic women compared to White men using logistic regression after controlling for covariates ($P < 0.001$)[110]. Black patients also experience longer hospital stays and higher rates of surgical site infections, sepsis, stroke, and pneumonia following CABG[108]. Following PCI, Black patients have a higher risk of readmission, with 90 days of discharge (adjusted OR 1.62 [1.32-2.00]) and cumulative mortality compared to White patients (adjusted HR 1.45 [1.30-1.61])[111]. Indigenous patients in the United States experience greater in-hospital and long-term mortality rates following CABG compared to White (OR 3.8 [1.5-9.8]), African American (OR 3.4 [1.1-9.9]), Hispanic (OR 7.1 [2.5-20.3]), and Asian (OR 2.8 [1.1-7.0]) patients[112,113]. Cardiac rehabilitation referral is associated with a 40% lower 3-year all-cause mortality, yet women are 12% less likely to receive a referral than men at time of discharge, and Black, Hispanic, and Asian patients are 20, 36, and 50% less likely to receive referrals than White patients[114]. Compared to men, women are also less likely to receive physical activity recommendations (OR 0.91 [0.86-0.96]) after admission for CAD or peripheral vascular disease.

Causes of disparities in CAD with reduced LVEF

The etiology of these disparities, whether genetic in origin (i.e., "nature") or attributable to non-physiological factors such as culture, lifestyle, and environment (i.e., "nurture"), has led to great debate and remains to be clarified[115]. Studies suggest multiple interrelated causes.

In terms of biological predisposition, particularly at an older age, there is evidence that women lose the cardioprotective benefits of estrogen following menopause[116]. Additionally, early menopause, pregnancy-associated conditions, such as gestational hypertension, gestational diabetes, preeclampsia and eclampsia, and maternal autoimmune disease, all increase the risk of premature CAD in women[117,118]. In addition, studies suggest differential pathophysiology of CAD in White *vs*. Black patients[78]. CAD in Black patients may be manifested by small-vessel disease resulting in chronically increased oxygen demand, while it is related to greater epicardial vessel atherosclerosis and acutely decreased oxygen supply in White patients[78]. With regards to revascularization, Asian patients may have coronary arteries that are smaller in diameter than those in White patients, leading to more challenging CABG procedures[119]. Moreover, Asian individuals have a unique antiplatelet feature, also known as the "East Asian paradox", with patients suffering from higher bleeding rates and lower ischemic events after undergoing PCI[120]. However, further research is needed to elucidate whether these physiological differences are predominantly mediated by environmental, social, or genetic factors.

From a "nurture" perspective, many social factors may compound to impact patients' access to care and outcomes. Health literacy, particularly as it pertains to cardiovascular disease, tends to be lower among women, lower socioeconomic, and racial and/or ethnic minority patients[121,122]. The prolonged ischemic duration among women with ACS has been historically associated with decreased symptom recognition by patients and providers[121,123]. From the care delivery perspective, young women with CAD are less likely to be asked about their cardiovascular risk factors[124] or receive counseling on risk modification[125]. Additionally, patients from racially and/or ethnically minoritized groups may experience systemic racism that predisposes them to worse outcomes. Following an acute myocardial infarction, Black patients experience greater case fatality rates than White patients living in low- and medium-income areas, suggesting compiling social factors that underlie social disparities in outcomes[126]. Despite having a greater comorbidity burden, racially and/or ethnically minoritized groups are more likely to have lower socioeconomic means, leading them to present to low-volume and/or low-quality facilities in the United States[77,107,108,112]. Racial and/or ethnic disparities in revascularization may be explained by racial segregation, referral patterns, and geographic proximity to cardiac centers[107,127]. Therefore, multilevel systemic interventions targeting healthcare providers and vulnerable communities are needed to promote health literacy, identify high-risk patients, and provide them with comprehensive cardiovascular care.

KNOWLEDGE GAPS AND WAYS FORWARD

Despite the poorer outcomes observed among women and racialized and/or minoritized patients, they have been historically underrepresented in cardiovascular trials, further exacerbating the gaps in care[128,129]. This may be the result of mistrust in healthcare, historical discrimination, insufficient diversity of research leadership, and related social factors such as socioeconomic status, geographical location, education, and health literacy[107,128,130]. Promoting diverse representation in clinical trial leadership and trial participants is the first step in identifying and addressing gaps in cardiovascular care delivery. There is a need to address the barriers and causes of underrepresentation and variable enrollment of different populations in cardiovascular trials[129]. Moreover, further investigation is warranted to determine to what extent the observed differences in outcomes are the result of genetic factors, risk factors, sociodemographic factors, and systemic factors. For instance, the regionality of atherosclerosis may differ across different ethnicities, which can contribute to observed differences in outcomes[130]. Lastly, intersectionality in disease burdens[126], access to care, and outcomes after care must be recognized to reflect patients' unique intersecting identities, whereas differential patient preferences and needs must be respected. In response, the National Institute of Health Revitalization Act of 1993 established "policy and guidelines for the inclusion of women and minorities as subjects in clinical research", with its 2017 update adding the requirement for Phase III clinical trials to submit results of sex/gender, race, and/or ethnicity analysis to Clinicaltrials.gov[131]. To optimize treatment for our diverse patient populations, further research, increased inclusion, improved patient engagement, and more honest reflection are necessary.

Furthermore, patients' broader social determinants of health must be properly recognized to ensure adherence to OMT, long-term follow-up, and lifestyle changes, each of which has been negatively associated with low socioeconomic status, low health literacy, and other determinants after both PCI and CABG[132,133]. In addition, biases in care must be evaluated and addressed, as women and patients of low socioeconomic status observe lower rates of multiple arterial grafting[132-134]. Unconscious bias training may reduce differential practices between patient populations that are not fully guided by clinical indications[135]. Simultaneously, engaging patients and communities through community-based participatory research and patient-centered outcomes can strengthen the physician-patient relationship, highlight gaps in care that may be bridged, and promote shared decision-making[136,137]. These efforts should be rooted in the context and culture of the local community as patient preferences and community values may vary considerably by country and population.

CONCLUSION

CAD with LVSD poses unique challenges. Current guidelines are based on limited randomized and observational evidence for LVSD, requiring direct trial evidence comparing CABG and PCI in patients with LVSD. Ongoing trials, such as the STICH3C trial (NCT05427370) and the broader STICH3.0 International Consortium, will shed further light on the management of this complex patient population. In addition, further work is needed to elucidate and address disparities in access to and outcomes after coronary revascularization, which will require the engagement of multidisciplinary Heart Teams, primary care physicians, researchers, and patients.

DECLARATIONS

Authors' contributions

Writing the manuscript; performed the literature search and review; made substantial contributions to the conception, design, and edition of the manuscript: Ghunaim AH, Vervoott D, Elfaki LA, Deng MX, Marquis-Gravel G, Fremes SE

Prepared the figures and tables: Ghunaim AH, Vervoott D, Elfaki LA, Deng MX

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All authors declared that there are no conflicts of interest.

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