

STATE-OF-THE-ART REVIEW

Revascularization in Ischemic Left Ventricular Dysfunction



A Pathophysiology-Guided, Evidence-Based Approach

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ABSTRACT

Ischemic left ventricular dysfunction (iLVD) is the most prevalent cause of heart failure with reduced ejection fraction and is associated with higher mortality than nonischemic cardiomyopathy. Coronary revascularization was once considered routine for patients with iLVD, yet recent randomized trials have questioned this approach. This state-of-the-art review examines the pathophysiology of iLVD, explores the randomized evidence around coronary revascularization, and outlines which patients with iLVD should still be offered coronary artery bypass grafting or percutaneous coronary intervention (PCI). Finally, a step-by-step guide for planning and performing PCI in this population is provided. Attention is given to shared decision-making, nontechnical factors, and considerations for achieving complete revascularization, with a specific focus on upcoming trials of mechanical circulatory support. (JACC Cardiovasc Interv. 2025;18:2977-2994)

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The development of myocardial dysfunction portends a poor prognosis in patients with ischemic heart disease. Ischemic left ventricular (LV) dysfunction (iLVD) represents a continuum of myocardial consequences of ischemia. Relieving ischemia via coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI) is a theoretically attractive mechanism to interrupt these processes, improve patient

symptoms, and reduce mortality, but randomized trials have yielded conflicting outcomes.

The impact of revascularization on clinical outcomes differs between acute and chronic coronary syndromes (ACS and CCS). Across the spectrum of coronary syndromes, the challenge is to balance the potential benefit against the risk of intervention, requiring treatment tailored to the patient's clinical presentation including symptom burden, potential

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
BCIS = British Cardiovascular Intervention Society
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CV = cardiovascular
GDMT = guideline directed medical therapy
HF = heart failure
IABP = intra-aortic balloon pump
iLVD = ischemic left ventricular dysfunction
LV = left ventricular
LVEF = left ventricular ejection fraction
MCS = mechanical circulatory support
MI = myocardial infarction
PCI = percutaneous coronary intervention
PLVAD = percutaneous left ventricular unloading device
VA-ECMO = veno-arterial extracorporeal membrane oxygenation

for benefit, comorbidities, and anatomical complexity. This risk-benefit balance continues to evolve, with developments in technology, systems of care, and data from randomized trials helping to refine patient selection.

In this state-of-the-art review, we discuss the pathophysiology of iLVD and examine contemporary approaches to the diagnosis of coronary artery disease (CAD) in patients with newly diagnosed LV dysfunction, with emphasis on the role of anatomical and functional imaging modalities. We present an evidence-based framework to identify which patients with iLVD may benefit from CABG and PCI with a focus on recent data, then discuss technical and nontechnical considerations of myocardial revascularization for iLVD, focusing on procedural planning, strategies for high-risk procedures, and postoperative care. Finally, we highlight emerging data and future directions that may further refine the role of PCI in this complex patient population. Although some of this relates to preventing shock and adverse sequelae in high-risk patients who undergo myocardial revascularization, the specific management of established or worsening cardiogenic shock is beyond the scope of this review. We have also not discussed the decision to offer revascularization to patients presenting with ACS, noting that evidence and current guideline recommendations are strongly supportive of a strategy of early revascularization.

ISCHEMIC LV DYSFUNCTION

EPIDEMIOLOGY. CAD is the most common etiology of heart failure (HF) with reduced ejection fraction.¹ In patients with heart failure, an ischemic etiology confers an adverse prognosis over short, medium and long-term follow-up.² The risk of cardiovascular (CV) death is modified by age; in younger individuals the predominant mode of death is CV, whereas non-CV causes predominate in older patients, hence the ability to modify all-cause mortality with CV intervention decreases as patients age. Although contemporary data indicate that CAD is prevalent in 40% to 60% of patients with HF, registries show only 10% to 20% undergo specific investigation including coronary arteriography.^{3,4} The timely and accurate diagnosis of CAD is therefore essential, as it not only refines prognosis but influences management,

HIGHLIGHTS

- Patients undergoing revascularization with left ventricular dysfunction are at high risk of immediate and early adverse events.
- A structured, evidence-based approach to PCI is needed to improve outcomes.
- Upcoming randomized trials of mechanical circulatory support will aid decision-making.

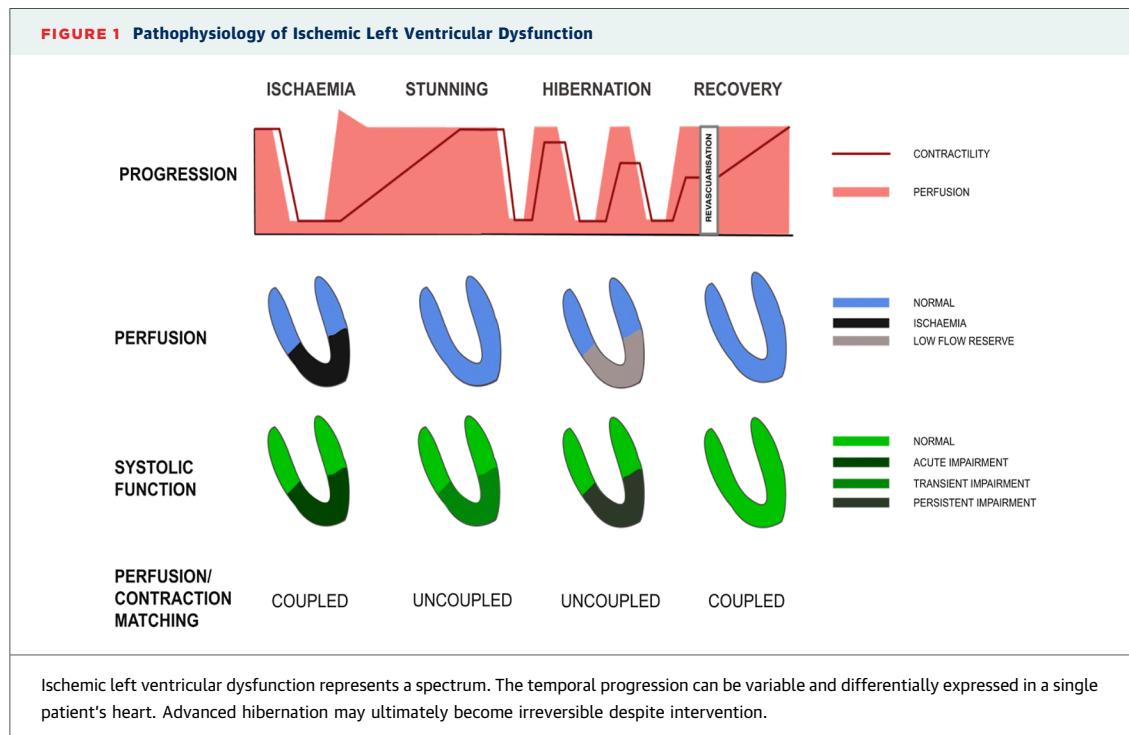
including the consideration of revascularization, device therapy, and intensified guideline-directed medical therapy (GDMT), for example with more aggressive lipid-lowering therapies in addition to HF-oriented GDMT. Conversely, excluding an ischemic cause would make a primary myopathic process more likely, prompting investigation of potential underlying etiologies.

Although LV systolic dysfunction has been identified as a key determinant of outcomes, less than one-half of patients undergoing PCI have a formal assessment of LV function beforehand.^{5,6} Of those who are assessed, 3 in 10 patients undergoing PCI have at least mild LV dysfunction, and 1 in 10 have severely reduced left ventricular ejection fraction (LVEF).^{5,7} Patients with LV dysfunction undergoing PCI tend to be older, require treatment of a greater number of lesions, and are more likely to undergo complex interventions. Single-center studies, registries, and meta-analyses have concluded that the risk of early mortality following PCI is 2 to 5 times higher for patients with severe iLVD.^{5,7}

PATHOPHYSIOLOGY AND ITS CLINICAL RELEVANCE.

Myocardial dysfunction in iLVD is typified by ischemic stunning, hibernation, and infarction (Figure 1). The likelihood of each of these processes developing depends on the depth, duration, and frequency of ischemia. This is modified by a range of factors, including presumed genetic susceptibility, which may explain why all patients with severe CAD do not develop LV dysfunction. Stunning, hibernation, and infarction frequently co-exist within the ventricular myocardium of a single patient, which may underlie differential response to revascularization in ACS and CCS.^{8,9}

Myocardial stunning is at one end of the spectrum of dysfunction and is characterized by transient uncoupling of perfusion-contraction matching. After a period of ischemia and reactive hyperemia,



myocardial function is transiently reduced but recovers fully unless another ischemic stimulus occurs.¹⁰ In hibernation, perfusion-contraction matching is persistently uncoupled, and myocardial function is chronically down-regulated in the setting of normal perfusion. Unlike stunned myocardium, hibernating myocardium will remain dysfunctional unless the ischemic substrate is removed. Hibernation is believed to be an adaptive process where myocardial function is sacrificed to promote cell survival, triggered by recurrent nonlethal episodes of ischemia.¹¹ The likelihood of recovery is dependent on the extent of histopathological changes in the myocardium, as well as the duration of hibernation.¹² Most patients with iLVD have imaging evidence of prior myocardial infarction (MI), even where no clinical event has been recognized. Infarction is characterized by ischemia-driven myocyte necrosis, which progresses from the endocardium to epicardium in a wavefront. Infarction is a key driver of arrhythmogenesis and negative remodeling.

CAUSAL VS BYSTANDER CORONARY DISEASE. Despite the high prevalence of iLVD, no international consensus definition or agreed diagnostic criteria exist, which contrasts with other cardiomyopathies

where standardized diagnostic criteria are widely used. Distinguishing iLVD from “bystander” disease is often challenging. As no single test reliably establishes causality, one solution has been to adopt a probabilistic approach, whereby a greater extent and severity of coronary disease is taken to indicate a higher likelihood of an ischemic etiology. For example, a British Cardiovascular Intervention Society (BCIS) myocardial jeopardy score ≥ 6 (indicating at least proximal left anterior descending coronary artery or multivessel disease) has been shown to have high specificity for an ischemic etiology in patients with a LVEF $<35\%$.¹³ Another approach is to assess the extent of MI in relation to segmental dysfunction with noninvasive imaging. However, both these approaches may fail to capture pathophysiological subtleties in a given patient. Where clarity about etiology is likely to impact decision making, multimodal assessment may be required and adjunctive tests for ischemia and/or metabolism may improve confidence in the diagnosis.

Even in cases where the primary etiology is myopathic, the functional and prognostic consequences of superadded ischemia are unclear. It is therefore prudent to consider iLVD as a spectrum from predominantly ischemic to predominantly

myopathic, rather than the traditional binary classification. For patients in the grey zone, a nuanced rather than algorithmic approach may yield the best outcomes, with due consideration given by a multidisciplinary team to the benefits of therapy targeting each of the contributing etiologies.

RANDOMIZED TRIALS OF REVASCULARIZATION IN iLVD

For decades revascularization has been the default strategy in patients with iLVD, largely based on the observation that some patients experienced normalization of LV function. This practice was reinforced by a series of observational studies in which patients receiving revascularization had better outcomes than those who did not. The STICH (Surgical Treatment for Ischemic Heart Failure) and REVIVED-BCIS2 (Revascularization for Ischemic Ventricular Dysfunction) trials were the first completed randomized trials to directly test this assertion in patients with stable CAD and heart failure, focusing on surgical and percutaneous revascularization respectively.

THE STICH TRIAL. The STICH trial was a prospective, international, multicenter, open-label randomized controlled trial designed to determine whether CABG reduced the risk of a primary endpoint of all-cause death in patients with iLVD receiving medical therapy.¹⁴ A total of 1,212 participants were randomized 1:1 to either CABG or medical therapy. Eligibility required CAD amenable to treatment with CABG and LVEF <35%. Key exclusion criteria were limiting angina (Canadian Cardiovascular Society Class 3 or 4), left main disease or a recent MI judged to be an important cause of LV dysfunction. Major secondary endpoints included CV death and the composite of all-cause death and hospitalization for HF.

Participants enrolled in STICH had a median age of 60 years, 40% were diabetic, and 12% were female.¹⁵ There was an early hazard with CABG, with 9% of patients either having died or remaining in hospital 30 days after surgery. At 4.7 years, mortality rates were similar in those assigned to CABG vs medical therapy alone (36% vs. 41%). Given the signal of benefit across several secondary endpoints, an extension study (STICHES [Surgical Treatment for Ischemic Heart Failure Extension Study]) was commissioned, and by 9.8 years, fewer patients in the CABG group had died compared with the medical therapy group (59% vs 66%; $P = 0.02$) (Figure 2A).¹⁶ Over the extended follow-up period, the increase in

life expectancy attributable to CABG was 18 months, with similar reductions noted in death from CV causes and HF hospitalization. These benefits appeared to be restricted to the youngest patients enrolled, with no treatment effect reported between medical therapy and CABG in those older than the median age of 60 at randomization.¹⁷ Of further note, no interaction was observed between the presence of angina or diabetic status and the benefit of CABG.^{18,19} Treatment with CABG was associated with a significant and sustained improvement in quality of life over those treated with medical therapy alone.²⁰

THE REVIVED-BCIS2 TRIAL. The REVIVED-BCIS2 trial was a prospective, multicenter, open-label randomized controlled trial designed to test the hypothesis that PCI reduced the composite primary outcome of all-cause mortality or hospitalization for HF in patients with iLVD receiving medical therapy.²¹ A total of 700 participants were enrolled and randomized on a 1 to 1 basis to either PCI plus medical therapy or medical therapy alone. Eligibility required extensive CAD, LVEF <35%, and evidence of myocardial viability. Follow-up was for a median of 3.4 years.

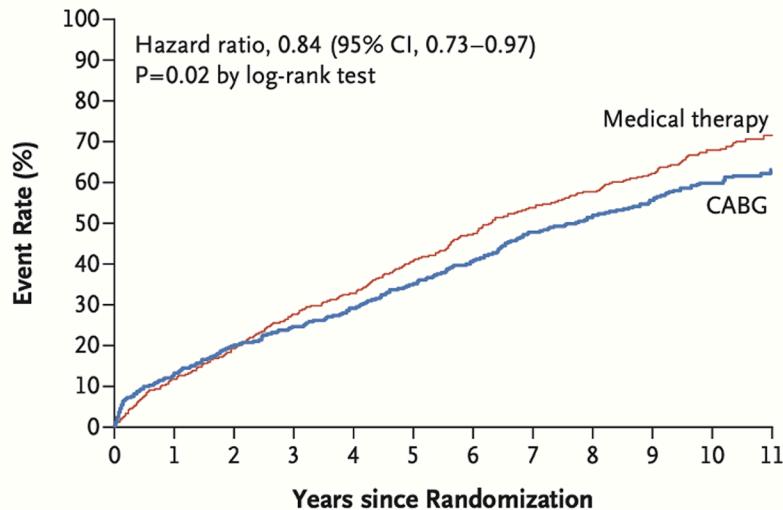
At 3.4 years, the primary outcome occurred equally often in both groups (37% in the PCI group and 38% in the medical therapy group) (Figure 2B). There was also no difference in key secondary endpoints of CV death or LVEF at either 6 or 12 months. Although patients undergoing PCI reported a better quality of life at 6 months, this difference diminished within 2 years of randomization.²²

INDIVIDUAL PATIENT DATA ANALYSIS OF STICH AND REVIVED. REVIVED-BCIS2 and STICH differed in patient characteristics as well as revascularization strategy (summarized in Table 1). To gain further insight, a pooled individual-participant data analysis was recently performed, incorporating multivariable adjustment and propensity matching.²³ The analysis showed significantly lower rates of all-cause mortality and HF hospitalization in patients treated with contemporary medical therapy in REVIVED-BCIS2 than those in STICH, whether assigned to CABG or not.

Collectively, these findings suggest that the dramatic evolution in medical and device therapy might have contributed to the discrepant results between STICH and REVIVED-BCIS2. Additional factors not systematically captured in either trial include evolution of care pathways and geographic variation in

FIGURE 2 Event-Free Survival in the STICH and REVIVED-BCIS2 Randomized Trials

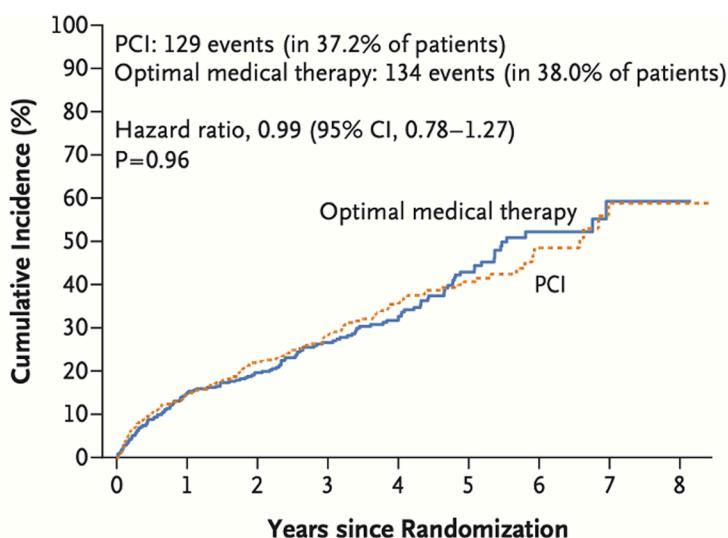
A Death from Any Cause (Primary Outcome)



No. at Risk

	Medical therapy	602	532	487	435	404	357	315	274	248	164	82	37
	CABG	610	532	487	460	432	392	356	312	286	205	103	42

B



No. at Risk

	PCI	347	295	262	179	130	80	32	14	3
	Optimal medical therapy	353	299	276	191	142	82	33	10	1

Kaplan-Meier survival curves from the STICHES (Surgical Treatment for Ischemic Heart Failure Extension Study) (A) and REVIVED-BCIS2 (Revascularization for Ischemic Ventricular Dysfunction) (B) randomized controlled trials. In STICH, the initial hazard of coronary artery bypass graft surgery (CABG) was offset by 2 years, though a statistically significant difference in all-cause death was only apparent after extended follow up. In REVIVED-BCIS2, no between-group difference in outcomes was observed at any time point. PCI = percutaneous coronary intervention.

TABLE 1 STICH and REVIVED-BCIS2

	STICH (N = 1,212)	REVIVED-BCIS2 (N = 700)
Inclusion criteria	LVEF ≤35% Coronary disease suitable for CABG	LVEF ≤35% Extensive coronary disease (BCIS-JS ≥6) Viability in ≥4 myocardial segments treatable with PCI
Exclusion criteria	Recent MI as a cause of LVSD Cardiogenic shock More than 1 prior CABG Aortic valve disease needing intervention	MI within 4 wk Acute decompensated heart failure Sustained ventricular arrhythmia Valve disease needing imminent intervention
Recruitment	2002 to 2007 99 centers in 22 countries	2013 to 2020 40 centers in the UK
Patient characteristics		
Age, y	60 ± 9	70 ± 9
Sex, male	88%	88%
LVEF, %	27 ± 6	27 ± 7
NYHA functional class 3/4	37%	25%
At randomization		
RAAS inhibitor	92%	90%
Beta-blocker	85%	91%
MRA	46%	50%
ICD	2%	21%
Primary outcome	All-cause death At 5 y, HR: 0.86 (95% CI: 0.72-1.04) At 9.8 y, HR: 0.84 (95% CI: 0.73-0.97)	Composite: all-cause death or hospitalization for heart failure At 3.4 y, HR: 0.99 (95% CI: 0.78-1.27) Extended follow-up awaited
Quality of life (KCCQ-OSS)		
Baseline	62 (44-77)	62 (41-81)
MT at 36 mo	80 (60-92)	76 (53-90)
CABG/PCI at 36 mo	83 (65-93)	80 (53-95)
Subgroups	Neither ischemia nor viability were associated with treatment effect. Greatest benefit in younger patients with more extensive disease and more severe LVSD	Neither ischemia nor viability were associated with treatment effect.

BCIS-JS = British Cardiovascular Intervention Society jeopardy score; CABG = coronary artery bypass graft surgery; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; LVEF = left ventricular ejection fraction; LVSD = ischemic left ventricular systolic dysfunction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; MT = Medical Therapy; PCI = percutaneous coronary intervention; RAAS = renin-angiotensin-aldosterone system; REVIVED-BCIS2 = Revascularization for Ischemic Ventricular Dysfunction trial; STICH = Surgical Treatment for Ischemic Heart Failure trial.

health care resources. Several important questions remain unanswered or are raised by the analysis itself: would STICH show a similar prognostic benefit of CABG if patients were treated with contemporary medical therapy? Could a benefit of PCI emerge with longer-term follow-up, especially in younger patients? And how would PCI compare with CABG in patients with similar baseline risk treated with similar medical and device therapy?

THE ROLE OF FUNCTIONAL TESTING

Ischemia and viability tests are often used to select patients with CCS and HF for revascularization. However, emerging data have prompted a reappraisal of this practice. In the PARR-2 (PET and Recovery Following Revascularization-2) trial, 430 patients with iLVD being considered for revascularization were randomly assigned to a viability-guided management (using positron emission tomography) vs standard care. No difference was observed in the

primary outcome of cardiac death, MI, or subsequent CV hospitalization at 1 year.²⁴ The STICH viability study included 601 patients who underwent viability testing. Stress echocardiography or single-photon emission tomography were used with modality-specific definitions of the presence or absence of viability. No interaction was observed between viability and the risk of death.²⁵ After adjustment for baseline covariates, binary viability status failed to predict the likelihood of all-cause mortality, in patients treated with or without CABG.²⁶ The REVIVED-BCIS2 viability study included 610 participants in whom viability was assessed using CV magnetic resonance imaging or stress echocardiography. No interaction was observed between the extent of viability, treatment with PCI, and the risk of experiencing a primary outcome event.²⁷ The risk of adverse events was associated with the extent of irreversibly damaged myocardium (scar) rather than the extent of dysfunctional, but potentially recoverable (viable), myocardium.

Although the landmark trials that targeted patients with demonstrable ischemia (such as ISCHEMIA [International Study of Comparative Health Effectiveness With Medical and Invasive Approaches] and COURAGE [Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation]) failed to show a benefit of revascularization over medical therapy alone in reducing all-cause mortality, they excluded patients with severe impairment of LV function. Ischemia testing was not mandated in either the STICH or REVIVED-BCIS2 trials, but discretionary testing was performed in a large proportion of cases.^{28,29} There was no association between the extent of ischemia and the likelihood of survival or the efficacy of revascularization in either trial. Consequently, contemporary evidence does not support using viability or ischemia tests to decide whether a patient with iLVD and stable CAD should undergo revascularization to improve prognosis.

Advanced imaging might play a role in planning revascularization in those who have a robust indication, such as limiting angina. Although the risks of CABG are primarily determined by patient factors and the impact of a sternotomy and bypass, the risk of a PCI procedure is highly dependent on the complexity and number of target lesions. In PCI, ischemia and viability imaging can permit a more selective approach, targeting those lesions with the largest extent of viability and ischemia and deferring those in which the myocardium is either non-ischemic or extensively infarcted. The efficacy and safety of such approaches have not yet been tested in randomized trials.

SHARED DECISION-MAKING AND THE ROLE OF THE HEART TEAM

Shared decision-making is central to management of patients with iLVD being considered for revascularization. Patients should be supported and allowed time and resources needed to make the right decision for them, remembering that some patients place greater importance on maintaining quality of life than living longer or the risk of reintervention, particularly those who are older or frail.³⁰ In those being considered for high-risk PCI, discussion will often extend beyond procedural risks and benefits to wider aspects of care. Information on procedural complications should be tailored to the individual, acknowledging the inherent uncertainty and balanced against anticipated health benefits.^{31,32} A patient's right to decline recommended treatment must be respected and documented, and the same diligence maintained with patients and their

relatives who decline or are turned down for high-risk interventions. Medical therapy should be meticulously optimized, preferably under the care of HF teams, and the involvement of palliative care specialists considered where the options for disease-modifying therapy are limited, prognosis is short, or symptoms are not controlled.

Although the benefits of heart teams are well documented, it should also be acknowledged that an adversarial dynamic can sometimes emerge, fueled by differing perceptions of risk and weighting of short- and long-term outcomes. Shared decision-making is particularly challenging in complex cases, compounded by guideline discordance and noncardiac comorbidities. Bridging these gaps requires effective communication, navigating cognitive biases, acknowledging concerns, and actively building mutual trust with the interests of the patient maintained as the primary focus.³³

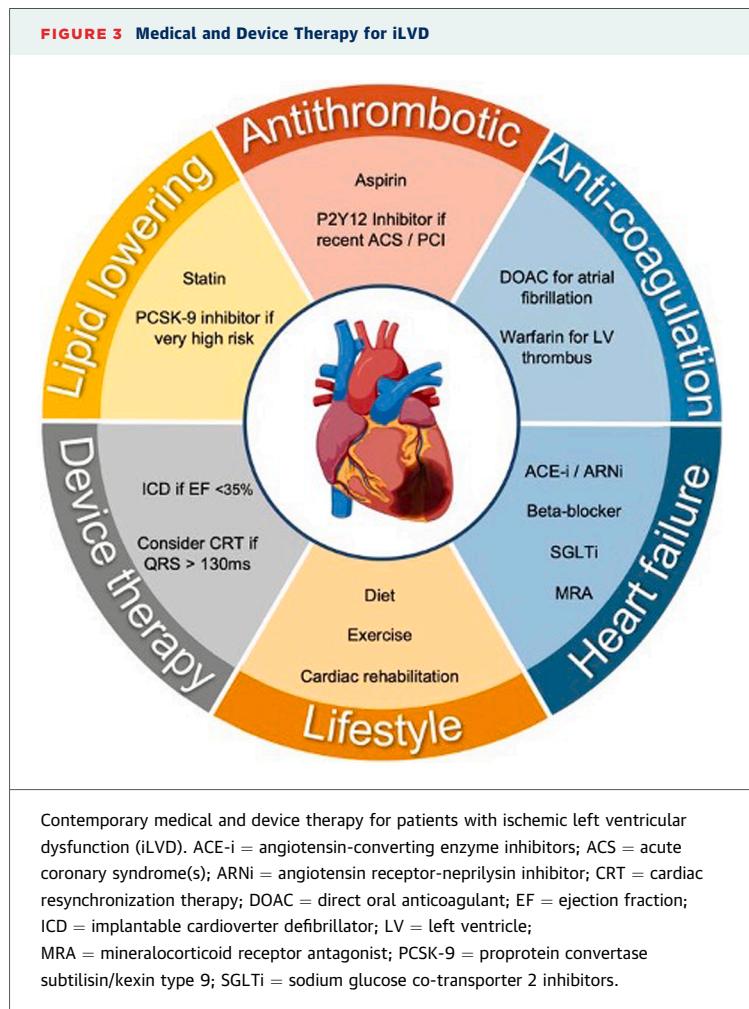
MEDICAL AND DEVICE THERAPY FOR iLVD

PHARMACOTHERAPY. Regardless of decisions on revascularization, guideline-directed medical and device therapy for heart failure (GDMT) is the cornerstone of managing iLVD (Figure 3). A recent meta-analysis estimated that compared with placebo, treatment with the “4 pillars” of GDMT (renin-angiotensin-aldosterone system inhibitors with angiotensin neprilysin inhibitors preferred, betablocker, mineralocorticoid receptor antagonist, and sodium glucose co-transporter 2 inhibitor) was associated an estimated gain in life expectancy of 8 years at age 50 and 5 years at age 70 years.³⁴ GDMT should be provided in combination with regular physical activity or supervised cardiac rehabilitation, dietary interventions, and screening for depression.

Despite limited evidence to guide the use of statins in patients with iLVD (who do not have standard CAD recommendations for primary or secondary prevention) contemporary guidelines for the management of chronic coronary syndromes recommend lipid-lowering therapy for all patients with CAD regardless of LVEF.³⁵⁻⁴⁰ Similarly, the evidence base for aspirin prescription in ILVD patients who have not undergone revascularization is weak, with some concerns that aspirin may reduce the effectiveness of angiotensin-converting enzyme inhibitors via prostaglandin inhibition.

CARDIAC IMPLANTABLE ELECTRONIC DEVICE THERAPY FOR iLVD. Reduction in ischemia and potential improvements in LV function by coronary revascularization have historically been assumed to

FIGURE 3 Medical and Device Therapy for iLVD



reduce the risk of sudden cardiac death, which in turn has led to the potential underutilization of implantable cardioverter-defibrillators in patients pending coronary revascularization. In the REVIVED-BCIS2 arrhythmia analysis, the rate of all-cause death or aborted sudden death was high (40%) and not affected by PCI compared with medical therapy alone.⁴¹ A likely explanation is that scar plays a greater role than ischemia in the genesis of ventricular arrhythmia in patients with severe iLVD.^{29,42} Cardiac resynchronization therapy remains recommended for patients with LV systolic dysfunction and a prolonged QRS duration, regardless of the etiology of HF. The evidence to date does not support deferral of cardiac implantable electronic device implantation in stable iLVD patients who are due to undergo revascularization.

**WHEN SURGICAL REVASCULARIZATION MIGHT BE
CONSIDERED INSTEAD OF PCI.** International guide-
lines provide strong recommendations for surgical

revascularization in iLVD, largely based on the historical STICH trial (**Table 2**). Both European and American revascularization and heart failure guidelines make Class I, Level of Evidence: B recommendations for CABG in patients with iLVD defined as an ejection fraction <35%, multivessel disease, and acceptable surgical risk.^{38,40,43}

There have been no randomized head-to-head comparisons of CABG and PCI for patients with severe iLVD. In a study using in-silico modelling to overcome selection bias, there was a signal that patients undergoing PCI have worse outcomes than those who have CABG, but given that most PCI is undertaken after Heart Team discussions where the patient is felt unsuitable for CABG, it is possible that modelling may not have accounted for all aspects of baseline risk.⁴⁴

Assessment of surgical risk is facilitated by validated risk scores, although they usually underestimate mortality in people with iLVD.⁴⁵ Although the STS and EuroSCORE II scores accurately predicted short-term mortality in STICH,⁴⁶ in general, calibration is suboptimal in patients where the estimated risk of in-hospital mortality is >5%.

Coexistent severe valve disease has also been traditionally considered an indication for CABG in patients who need revascularization. Surgery receives a strong recommendation in patients with severe primary mitral regurgitation and symptoms of heart failure. For severe ischemic secondary mitral regurgitation in patients undergoing CABG, surgery is recommended in symptomatic low-risk patients. These guidelines are based on a substudy of the STICH trial that showed an association between concomitant mitral valve repair at the time of surgery and reduced mortality at 5 years.⁴⁷ Guidance for PCI in patients undergoing transcatheter edge-to-edge repair with concomitant CAD is less well-defined; these recommendations may be revised with the increasing evidence for these procedures in those with HFrEF.

PLANNING AND PERFORMING PCI IN iLVD. Reduced LVEF is the strongest independent predictor of adverse outcomes during and immediately following PCI,^{5,6} underscoring the importance of assessing LV function in all cases. Preprocedure planning enhances procedural efficiency, allows risks to be identified and mitigated, and provides an opportunity for operators, the wider catheter lab team, and patients and their relatives to appropriately prepare.

The initial step in planning PCI is selecting target lesions. In iLVD, this involves reviewing the coronary anatomy alongside myocardial imaging with

TABLE 2 Randomized Trials of Mechanical Circulatory Support in High-Risk PCI

Trial	Recruitment Period	Inclusion Criteria	Study Groups	Primary Outcome	Result
BCIS-1	2005-2009	LVEF ≤30% BCIS-JS ≥8	N =301 Randomized 1:1 elective IABP vs no planned IABP	Composite of in-hospital MAE capped at 28 d (death, MI, stroke/TIA, repeat revascularization)	No difference in MAE (15.2% vs 16.0%; OR: 0.94; P = 0.85)
PROTECT II	2007-2010	LVEF ≤35% with unprotected left main or LVEF ≤30% with last patent vessel/ 3-vessel disease	N = 452 (of planned 600) Randomized 1:1 elective Impella 2.5 vs elective IABP	30-day composite MAE (death, stroke/TIA, MI, repeat revascularization, cardiac/vascular surgery, AKI, CPR/arrhythmia, aortic valve damage, severe hypotension, angiographic failure)	No difference in MAE (30.1 vs 40.1%; RR: 0.88%; P = 0.28)
CHIP-BCIS3	2021-2024	LVEF ≤35%, (or ≤45% if severe MR) BCIS-JS ≥8 Planned complex PCI ^a	N = 300 Randomized 1:1 elective LV unloading with pLVAD vs no planned MCS	Hierarchical composite: death, stroke, spontaneous MI, CV hospitalization, periprocedural MI (win ratio) at ≥12 mo	Expected 2026
PROTECT IV	2021-2025	LVEF <40% if CCS/NSTEMI, (≤30% if convalescent STEMI) Planned complex PCI ^b	N = 1,252 Randomized 1:1 Impella (2.5 or CP) vs SOC (± elective IABP)	Composite of all-cause death, stroke, MI, unplanned revascularization, durable LVAD implantation or heart transplantation or CV hospitalization at ≥12 mo	Expected 2027

^aUnprotected left main stem coronary artery (LMS) in the presence of 1) occluded right coronary artery (RCA) or 2) left dominant circulation or 3) disease involving the entire bifurcation (medina 1,1,1 or 0,1,1) OR intended advanced calcium modification in 1) multiple vessels, 2) LMS, 3) final patent conduit, 4) where the syntax score ≥32 OR target vessel is a chronic total occlusion (CTO) with planned retrograde approach. ^bThree-vessel disease with planned PCI of ≥2 vessels or planned PCI of 2 separate complex lesions (long ≥28-mm lesion, severe angiographic calcification, LMS disease not involving bifurcation, non-left main bifurcation, CTO, giant thrombus, saphenous vein graft OR LMS disease with planned treatment of LMS and at-least 2 daughter vessels OR LMS equivalent disease (medina 0,1,1) OR final patent conduit.

AKI = acute kidney injury; CCS = chronic coronary syndrome(s); CPR = cardiopulmonary resuscitation; CV = cardiovascular; IABP = intra-aortic balloon pump; LV = left ventricular; LVAD = left ventricular assist device; MAE = major adverse event(s); MR = mitral regurgitation; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SOC = standard of care; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; other abbreviations as in Table 1.

estimation of the relative risk and benefit of treating each stenosis. Simple lesions subtending fully viable and ischemic myocardium represent the optimum target, whereas complex lesions subtending regions with minimal viability or ischemia are less attractive. After considering the relative merit of treating each lesion, both the minimum and ideally achievable completeness of myocardial revascularization should be determined, as well as whether this is best achieved in single or staged procedures.

Intraprocedural ischemia may result in immediate complications. Ischemic stunning will worsen cardiac performance, potentially triggering periprocedural collapse, whereas the longer-term impact of myocardial necrosis, increasing scar burden and worsening ventricular function could offset any potential benefits of revascularization. Consequently, PCI procedures in iLVD require distinct strategies to those than might be used in patients with preserved LV function (**Central Illustration**). Determinants of hemodynamic compromise include the likely extent, duration, and depth of ischemia and stunning, caused both in an attritional manner or abruptly should an acute vessel closure occur. The need to avoid side branch occlusion may affect bifurcation strategies, whereas a need to reduce the duration of

ischemia may affect the calcium modification techniques employed.

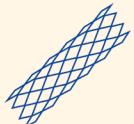
Clinical factors increasing the likelihood of compromise include decompensated heart failure with pulmonary or systemic congestion, reduced cardiac output, hypotension, pulmonary hypertension, recent MI or critical care admission, or a prior failed attempt at PCI due to hemodynamic instability or pulmonary edema (**Figure 4**). The presence of right ventricular dysfunction and significant valve disease are important predictors of procedural instability.

Given that the coronary disease causing iLVD tends to be both complex and extensive, PCI best-practice principles particularly apply to this subset. Intracoronary imaging is worth special mention as its use improves short- and long-term outcomes, particularly in complex lesion subsets, and now receives a Class I recommendation for specific conditions in both American and European guidelines.^{37,48,49} However, the pursuit of lesion-level quality metrics such as the minimum stent area should be balanced against real-time hemodynamic status on a case-by-case basis.

NONTECHNICAL FACTORS INFORMING PCI SUCCESS IN iLVD

High-risk interventions require specialized

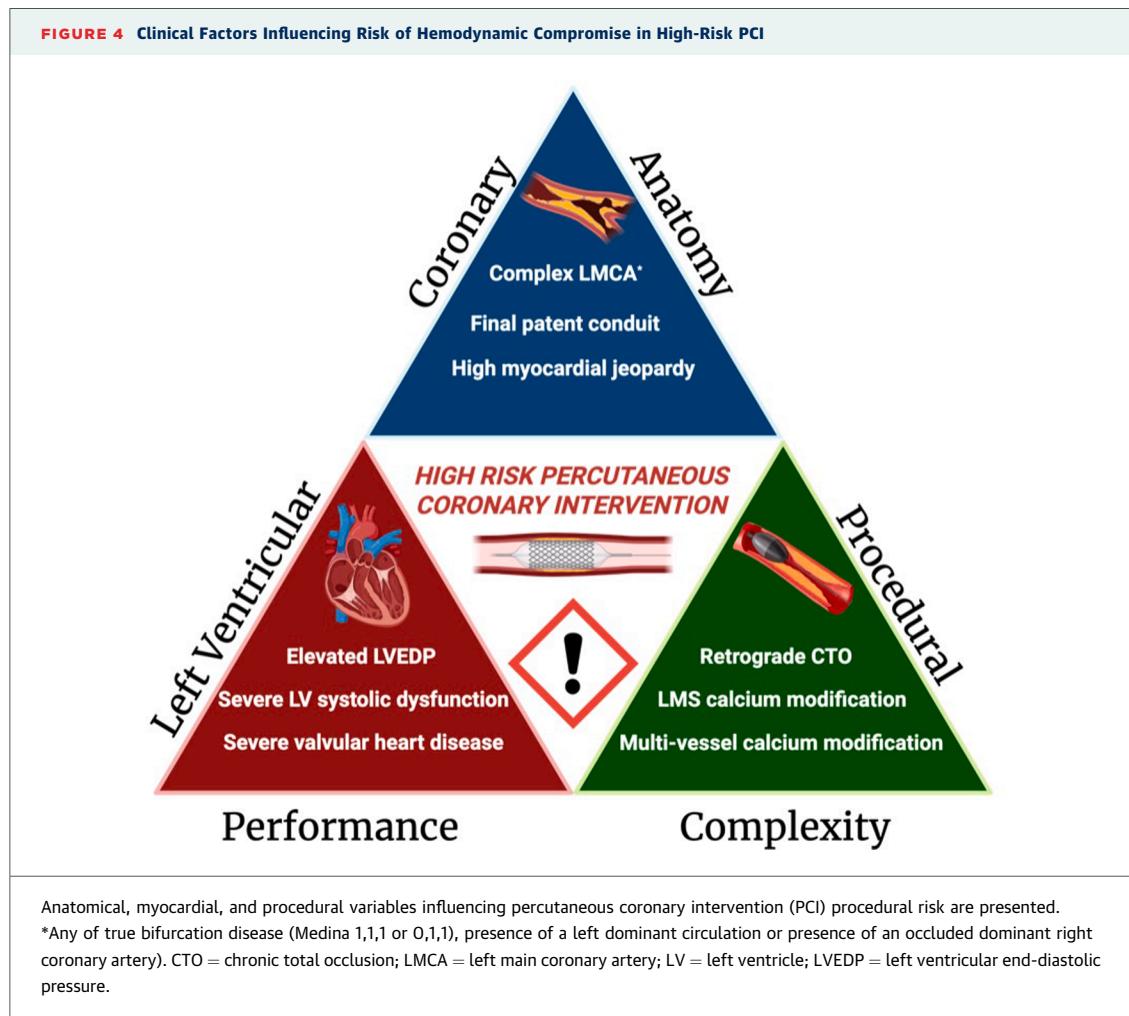
CENTRAL ILLUSTRATION State-of-the-Art Revascularization in Ischemic Left Ventricular Dysfunction
Foundations of Revascularization for Patients With Ischemic Left Ventricular Dysfunction

Case Selection	Decision	PCI Planning	Procedure	Future
Recent ACS Limiting angina  Revascularization	 or   Prioritize patient factors and choices	 Define minimum acceptable and ideal completeness of revascularization  Consider myocardial viability when setting goals  Detailed team brief	 Hemodynamic monitoring with early response  MCS decisions informed by evidence base  Human factors	Upcoming data: STICH-3 to inform decisions on PCI or CABG CHIP-BCIS3 and PROTECT-IV to inform decisions on elective MCS
Stable No symptoms  Conservative management	 Prioritize patient factors and choices	 Detailed team brief	 Human factors	Future focus: Consensus criteria for diagnosis Influence of a mixed ischemic/non-ischemic etiology Postprocedural ischemic burden

Shared Decision-Making, Heart Team, GDMT

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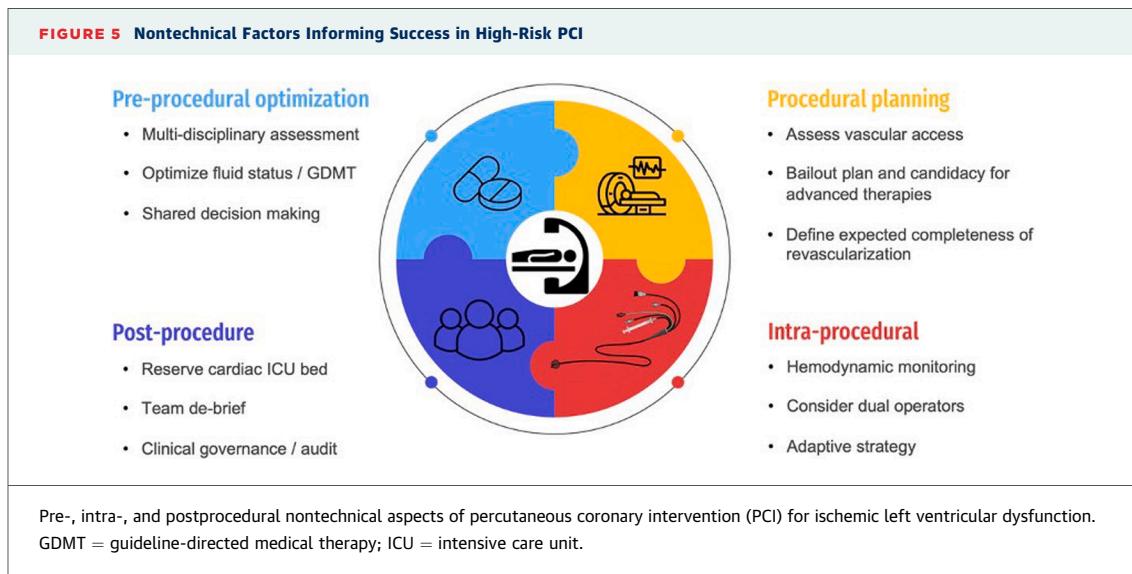
Shared decision-making, heart team involvement, and optimized medical and device therapy remain the foundations of care for patients with ischemic left ventricular dysfunction. The pathway to success in revascularization can be broken down into case selection, the decision to revascularize, and then planning and performing with success in mind. Case selection should be informed by the evidence base: patients who are stable without symptoms should be managed conservatively, whereas patients with recent acute coronary syndrome or limiting angina should be considered for revascularization. The choice of percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery should be informed by patient factors and choices, rather than institutional preference. Once a decision to perform PCI is made, effective preparation involves defining clear goals, both as minimum acceptable and ideal target, developing a plan for PCI bearing in mind the myocardial substrate and completing a detailed team brief. When performing the procedure, close attention should be given to hemodynamic monitoring with early response, and decisions on mechanical circulatory support should be informed by the evidence base. Human factors are critical to success in performing these procedures. There are exciting data coming via CHIP-BCIS3 (Controlled Trial of High-risk Coronary Intervention With Percutaneous Left Ventricular Unloading), PROTECT IV (Impella®-Supported PCI in High-Risk Patients With Complex Coronary Artery Disease and Reduced Left Ventricular Function), and the international STICH3 consortium (STICH-3.0 International Trial Consortium). GDMT = guideline-directed medical therapy; MCS = mechanical circulatory support.



decision-making, equipment, and technical expertise best achieved by operators with experience in performing these procedures (Figure 5).⁵⁰ Multiple observational analyses demonstrate that rates of short- and long-term procedural morbidity and mortality relate to operator and institution volumes of complex high-risk PCI.^{51–53} Much of the hospital-level variation in in-hospital mortality relates to strategies to avoid as well as manage procedural complications, including cardiac arrest or cardiogenic shock in the cardiac catheterization laboratory.^{54,55} The apparent paradox, that patients at highest risk of complications also tend to be those that stand to derive the greatest benefit from PCI, underscores the importance of making a complete assessment of the relative risk or benefit of a procedure, rather than the level of comfort or skill of an individual operator.

Cardiac catheterization laboratory teams engaged in high-risk PCI should possess experience with

hemodynamic assessment and optimization, mechanical circulatory support, as well as prevention, recognition, and management of complications. Pre-procedural considerations for higher-risk procedures include anesthesia evaluation, placement of defibrillator pads, insertion of central venous access (for immediate vasopressor delivery), blood bank notification, preparation of equipment for mechanical circulatory support, and reservation of a post-procedure cardiac intensive care unit bed. Immediate preprocedure review of detailed patient and procedure specific vulnerabilities, anticipated hazards and challenges, technical strategies, key equipment, complication management, team member roles and responsibilities, and emergency response protocols, should occur before the start of every procedure. Although data are mixed regarding the benefits of multiple vs single operators, several advantages to this “pilot and copilot” strategy include collaborative performance of tasks, with mitigation of mental and



physical fatigue, and attention deficit to procedural hazards that may precipitate CV collapse.⁵⁶

Whenever possible, medical optimization should precede high-risk complex PCI to both reduce procedural risk and need for mechanical circulatory support (MCS).⁵⁰ Vascular access should be assessed and delineation of candidacy for rescue veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and follow-on heart replacement therapies should also be established. At a systems level, ongoing mental and physical task training and rehearsal, including simulation training, may foster an optimal mix of procedural efficiency, safety, and quality. Immediate postprocedure ad hoc after-action reviews and formal morbidity and mortality meetings should reinforce best practices, identify gaps in optimal care delivery, and establish priorities for improvement.^{57,58}

RIGHT HEART CATHETERIZATION. Right heart catheterization provides real time and in-depth information about cardiac performance, for which systemic hemodynamic measures are poor surrogates.⁵⁹ The cardiac index and LV filling pressures are particularly useful in understanding ventricular reserve and the potential for hemodynamic instability, as well as informing the use of mechanical circulatory support. Measures of right heart function and pulmonary vascular resistance may also provide a more complete understanding of procedural risk. During PCI, continuous right heart monitoring (most readily pulmonary artery diastolic pressure but with emerging options for continuous measurement of cardiac index) can provide early warning of

hemodynamic deterioration. In cases where mechanical support devices are used, hemodynamic parameters may also provide a framework to guide weaning of support. Further data are needed to evaluate the impact of right heart catheterization, including larger-scale prospective studies.

MCS FOR ELECTIVE HIGH-RISK PCI. Several MCS strategies are available, which are summarized in the following text, followed by a discussion of the factors influencing device selection and the timing of implantation.

INTRA-AORTIC BALLOON PUMP. The intra-aortic balloon pump (IABP) has the lowest access profile, provides effective augmentation of coronary blood flow, but has negligible effects on cardiac output.⁶⁰ In the BCIS-1 (Balloon pump-assisted Coronary Intervention), 301 patients with LVEF ≤30% undergoing PCI with extensive CAD were randomized 1:1 to either elective IABP insertion or no planned MCS; elective IABP use failed to reduce major adverse CV outcomes.⁶¹ One in 8 patients in the no planned support group required bailout IABP insertion due to persistent hypotension. Long-term follow-up demonstrated significantly lower 5-year all-cause mortality in patients randomized to IABP. As this was neither prespecified nor powered, and lacks a clear mechanistic explanation, the results are merely hypothesis generating.⁶² Consequently, the IABP should be primarily deployed as a bailout device to relieve ischemia, for example, reduced flow due to coronary dissection, as opposed to scenarios where more robust support is required to maintain systemic hemodynamics.

TABLE 3 Current Guidelines for Revascularization in iLVD With Chronic Coronary Syndromes

Guideline	Chronic Coronary Syndromes ESC/EACTS 2024 ³⁷	Chronic Coronary Disease AHA/ACC/ ACCP/ASPC/NLA/PCNA 2023 ³⁸	Heart Failure ESC 2021 ³⁹	Heart Failure AHA/ACC/HFSA 2022 ⁴⁰
Indication	In CCS patients with persistent angina or anginal equivalent, despite guideline-directed medical treatment, myocardial revascularization of functionally significant obstructive CAD is recommended to improve symptoms (Class I, LoE A).	In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms (Class I, LoE A).	Coronary revascularization may be considered to improve outcomes in patients with HFrEF, CCS, and coronary anatomy suitable for revascularization, after careful evaluation of the individual risk to benefit ratio, including coronary anatomy (ie, proximal stenosis >90% of large vessels, stenosis of left main or proximal LAD), comorbidities, life expectancy, and patient's perspectives (Class 2b, LoE C).	In patients with HF and CAD who are candidates for coronary revascularization, noninvasive stress imaging (stress echocardiography, SPECT, CMR, or PET) may be considered for detection of myocardial ischemia to help guide coronary revascularization (Class 2b, LoE B).
Modality	CABG: In surgically eligible CCS patients with multivessel CAD and LVEF ≤35%, myocardial revascularization with CABG is recommended over medical therapy alone to improve long-term survival (Class 1, LoE B). PCI: In selected CCS patients with functionally significant multivessel disease and LVEF ≤35% who are at high surgical risk or not operable, PCI may be considered as an alternative to CABG (Class 2b, LoE B).	CABG: In patients with CCD who have significant left main disease or multivessel disease with severe LV dysfunction (LVEF ≤35%), CABG in addition to medical therapy is recommended over medical therapy alone to improve survival (Class I, LoE B). PCI: In patients with CCD who are appropriate for revascularization but poor candidates for surgery, it is reasonable to choose PCI over CABG to improve symptoms and reduce MACE (Class 2a, LoE B).	CABG: 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 (Class 2a, LoE B). PCI: PCI may be considered as an alternative to CABG, based on heart team evaluation, considering coronary anatomy, comorbidities, and surgical risk (Class 2b, LoE C).	CABG: In selected patients with HF, reduced EF (EF ≤35%), and suitable coronary anatomy, surgical revascularization plus GDMT is beneficial to improve symptoms, cardiovascular hospitalizations, and long-term all-cause mortality (Class 1, LoE B). PCI: No specific recommendation made.

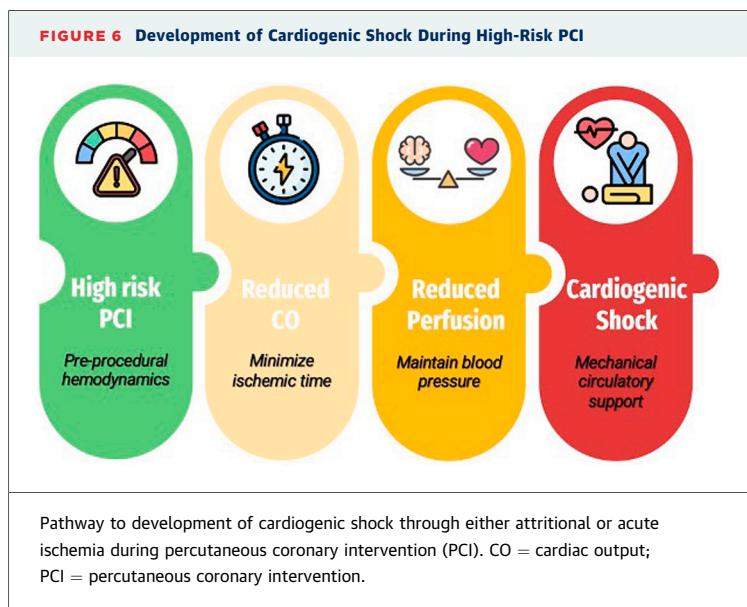
ACC = American College of Cardiology; ACCP = American College of Clinical Pharmacy; AHA = American Heart Association; ASPC = American Society for Preventive Cardiology; CAD = coronary artery disease; CCD = chronic coronary disease; CCS = chronic coronary syndrome(s); CMR = cardiovascular magnetic resonance imaging; EACTS = European Association for Cardio-Thoracic Surgery; EF = ejection fraction; ESC = European Society of Cardiology; GDMT = guideline directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; LAD = left anterior descending coronary artery; LoE = level of evidence; MACE = major adverse cardiovascular event(s); NLA = National Lipid Association; PCNA = Preventive Cardiovascular Nurses Association; PET = positron emission tomography; SPECT = single-photon emission tomography; other abbreviations as in Tables 1 and 2.

PERCUTANEOUS LV ASSIST DEVICES. Compared to the IABP, percutaneous left ventricular assist devices (pLVAD) such as the Impella CP (Abiomed) have uncertain effects on coronary perfusion yet provide substantially greater augmentation of cardiac output.^{63,64} Current technology requires large-bore arterial access (up to 15.5 F), which can lead to vascular injury, limb ischemia, and bleeding, although lower-bore devices are in development, and their evaluation is anticipated.⁶⁵

The PROTECT II trial (Protect II, A Prospective, Multicenter Randomized Controlled Trial) randomized participants to either elective Impella 2.5 or IABP-supported PCI. The trial was stopped early due to perceived futility. In the 452 patients who were randomized, no between-group difference was observed in the primary outcome of a composite of major adverse CV events (ranging from death to repeat revascularization (including planned procedures and angiographic failure of PCI at 30 days).⁶⁶ In a secondary analysis, a statistically significant difference in 90-day outcomes was observed in favor of the Impella 2.5, though this was largely driven by higher rates of repeat revascularization, cardiopulmonary

resuscitation, and hypotension requiring treatment, whereas there was an absolute increase in the risk of death of 2.6% in the participants randomized to Impella 2.5.⁶⁶

Two relevant prospective randomized clinical trials have recently completed recruitment (CHIP-BCIS3 [Controlled Trial of High-risk Coronary Intervention With Percutaneous Left Ventricular Unloading] NCT05003817; and PROTECT IV [Impella®-Supported PCI in High-Risk Patients With Complex Coronary Artery Disease and Reduced Left Ventricular Function] NCT04763200). Although addressing the same hypothesis, there are important differences in the design and delivery of these trials (Table 3). CHIP-BCIS3 randomized 300 participants at 21 centers in the United Kingdom who were scheduled to undergo complex PCI with both high myocardial jeopardy and iLVD to elective pLVAD implantation or no elective MCS.⁶⁷ Complexity is defined as PCI to the left mainstem, multivessel calcium modification, or treatment of a chronic total occlusion with retrograde access, with additional enrichment criteria. The hierarchical primary outcome consisting of death, stroke, spontaneous MI, CV hospitalization,



periprocedural myocardial injury will be analyzed using the win ratio method after a minimum 12-month follow-up.

PROTECT IV is an international multicenter trial that has randomized 1,252 participants undergoing complex PCI with an iLVD to receive either elective Impella CP implantation or control (either no support or elective IABP implantation, at operator discretion).⁶⁸ Complexity is defined by the need for multivessel PCI in patients with 3-vessel disease, left main bifurcation disease or equivalent, intervention on a last remaining vessel, or the need to treat more than 2 complex lesions defined by length, calcification, chronic occlusion, thrombus, or location within a vein graft. The study has a composite primary endpoint (all-cause death, stroke, durable LVAD implantation, or heart transplantation, MI, or CV hospitalization up to 3 years) analyzed on a time-to-first event basis 1 year after the final participant is recruited. Both trials are expected to report in 2026 or 2027; cumulatively, the 2 trials should provide evidence to rationalize the role of elective pLVAD during PCI in patients with iLVD.

VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION. VA-ECMO has the highest incidence of vascular and bleeding complications. Although providing substantial blood flow and oxygenation, the retrograde infusion of pressurized blood into the arterial system increases afterload on a vulnerable left ventricle, leading to pulmonary oedema, stasis of blood, and potential thrombus formation.⁶⁹ Although case series have described

elective use of VA-ECMO for high-risk PCI it is best reserved for bailout scenarios such as the development of profound cardiogenic shock or cardiac arrest.

MCS STRATEGY AND TIMING OF IMPLANTATION

MCS-supported PCI has been associated with more complete revascularization and increased use of adjunctive calcium modification during the index procedure. Whether this reflects greater opportunity due to hemodynamic stability or operators feeling obliged and/or enabled to maximize revascularization once MCS is deployed remains unclear. Equally, whether more complete revascularization in a single procedure benefits patients or exposes them to greater procedural risk compared with a staged approach is unknown. The flexibility to stage revascularization is an advantage of PCI over CABG, allowing for symptomatic reassessment between procedures. CHIP-BCIS3 and PROTECT IV may permit exploration of how randomized MCS use influences staging decisions and whether a single-stage MCS-supported strategy or a stepwise unsupported strategy is superior in terms of patient outcome, health status, and fiscal cost.

Upfront use of MCS has 2 key goals; to protect the left ventricle from ischemic stunning from attritional ischemia or an abrupt insult such as acute vessel closure and to maintain systemic hemodynamics and end-organ perfusion (Figure 6). Alternatively, MCS may be reserved for “bailout” or rescue situations where support aims to ameliorate ischemia and restore systemic perfusion from a decompensated state. Observational data consistently show a higher mortality in patients receiving bailout MCS compared with those receiving elective MCS; however, these data are heavily confounded by the deployment of MCS after hemodynamic deterioration has already occurred;⁷⁰ the available evidence does not indicate whether bailout MCS use improves outcomes compared with not using any bailout MCS devices (even when the patient becomes unstable). Whether it is intended to use MCS upfront or there is a possibility of needing bailout MCS, preprocedural imaging of the aortic and iliofemoral vasculature should be carried out to allow an assessment of vascular risk and plan for safe access, including involvement of cardiologists with peripheral vascular skillsets, vascular surgeons, or interventional radiologists as needed.

Until prospectively derived selection criteria emerge, it is reasonable to base the decision to use elective MCS on the extent of myocardium at risk,

expected ischemic time during the procedure, and hemodynamic reserve, countered by the risk of bleeding and vascular injury.

GAPS IN THE EVIDENCE AND ONGOING CONTROVERSY

The lack of consensus criteria for the diagnosis of iLVD remains a barrier to progress. Likewise, whether the efficacy of revascularization on symptoms or prognosis is influenced by a mixed ischemic/non-ischemic etiology, and whether “bystander” coronary disease truly can influence disease trajectory and symptoms are prime areas for further research.

As evidenced by the divergent recommendations of the American and European bodies, integrating the results of STICH and REVIVED-BCIS2 into clinical practice guidelines and appropriate use criteria remains controversial (**Table 3**). Specific challenges are how to address the nuance in the benefits of CABG in STICH and whether REVIVED-BCIS2 alone provides sufficient evidence to provide a Class 3 recommendation for PCI in stable patients. Though single positive trials have previously supported guideline recommendations with Level of Evidence A, sole neutral or negative trials do less often result in major change.

Although this paper has focused on iLVD, heart failure with preserved ejection fraction (HFpEF) is a rapidly growing problem. Around one-half of patients with HFpEF have significant CAD, yet there is no randomized evidence on the safety or efficacy of revascularization in these patients, and little observational data to even understand the impact of HFpEF on short- and long-term outcomes of patients undergoing revascularization for other indications. These questions are starting to be addressed, including in the forthcoming REPRIEVED Trial (REvascularization for heart failure with PReserved Ejection Fraction and Ischemia: EValuation of Efficacy and mechanistic Description; [NCT012843546](#)), in which patients with HFpEF and CAD will be randomized to either PCI or a placebo procedure, with quality of life as the primary endpoint.

Current randomized evidence has not demonstrated that routine percutaneous revascularization in patients with iLVD confers prognostic benefit above optimal medical therapy alone in the absence of a recent MI. Two further trials of PCI in iLVD are in recruitment in South Korea. The RESTORE-PCI trial (Revascularization Versus Medical Treatment in Patients With Ischemic Left Ventricular Dysfunction;

[NCT05828719](#)) aims to randomize 900 patients with ischemic LV systolic dysfunction, to medical therapy and PCI with mandatory intracoronary imaging and physiology testing against medical therapy alone. The primary outcome will be major adverse CV events at 2 years from enrolment of the final patient. The smaller IMPROVE-ICMP trial (Restoration of Myocardial Function by PeRcutaneous cOronary interVEntion in Patients With Ischemic CardioMyoPathy; [NCT06930092](#)) aims to include 158 patients with iLVD who will be randomized to PCI vs conservative management, with a primary outcome of difference in LVEF on CV magnetic resonance imaging at 6 months. At the time of writing, these results are anticipated in approximately 5 years.

The benefits of CABG above contemporary medical and device therapy (and the applicability of the STICHES trial results) remain unclear. This hypothesis is currently being tested in MASS-4 (HF) (Evaluation of a randomized comparison between patients with coronary artery disease associated with ischemic cardiomyopathy submitted to medical or surgical treatment), a single-center trial being conducted in São Paulo, Brazil, which will randomize 600 patients with LV dysfunction, CAD, and ischemia to either conservative management or CABG.

Furthermore, although viability or ischemia testing has not proved useful thus far in selecting specific patients for prognostic revascularization, it remains the case that LV function is observed (in nonrandomized series) to improve in some patients with iLVD. Prospectively identifying phenotype (and possibly genotype) stratified treatments that lead to improvements in randomized controlled trials remains the undiscovered holy grail.

There is a clear indication for revascularization in iLVD patients presenting with acute MI or limiting angina despite optimized medical therapy. Whether PCI or CABG are preferred will be addressed in STICH3 (STICH-3.0 International Trial Consortium; [NCT05761067](#)), an international consortium of 9 randomized trials addressing the hypothesis that CABG is superior to PCI in patients with iLVD and an indication for revascularization. The individual trials have composite primary endpoints but with an aggregate sample size in excess of 2,500 subjects, the overall study will have adequate power to detect a difference in all-cause mortality in the long term. Results are expected to be available after 2030, as the trial designs all incorporate a minimum follow-up of 2 years.

There are limited data on the change in ischemic burden following revascularization, particularly with reference to the volume of viable myocardium. It is unclear whether the lack of benefit in iLVD trials is because of a failure of the functional effectiveness of revascularization in removing the ischemic substrate over and above medical therapy. Future studies focusing on postprocedural change in ischemic burden are essential to clarify the true physiological impact of both PCI and CABG in this population.

Finally, CHIP-BCIS3 and PROTECT IV will provide crucial data to inform decisions on mechanical circulatory support with pLVAD; there is exciting potential for combined and secondary analyses that may help to identify subpopulations who derive

particular benefit and provide tools to support decision-making.

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