

Review

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Review

Role of Coronary Revascularization in Patients with Ischemic Heart Disease and Heart Failure with Reduced Ejection Fraction

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Abstract

Heart failure with reduced ejection fraction (HFrEF) is a major contributor to cardiovascular morbidity and mortality, with ischemic heart disease as the leading etiology. Despite advances in optimal medical treatment (OMT), the additional benefit of coronary revascularization in this population remains uncertain. While some studies describe a potential benefit in revascularization - particularly with coronary artery bypass grafting (CABG)- this benefit has not been consistently observed with percutaneous coronary intervention (PCI). Moreover, in this context, the role of myocardial hibernation has been called into question. Additionally, recent advances in the medical management of heart failure complicate the current interpretation of previous studies and underscores the need for new clinical trials.

Keywords: heart failure; ischemic heart disease; reduced ejection fraction; percutaneous coronary intervention; coronary revascularization; coronary artery bypass grafting

1. Introduction

Heart failure (HF) is defined as a clinical syndrome characterized by signs and/or symptoms caused by structural and/or functional cardiac abnormalities, corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. According to left ventricular ejection fraction (LVEF), HF is classified into three categories: HF with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), or preserved ejection fraction (HFpEF), corresponding to LVEF ranges of $\leq 40\%$, 41–49%, and $\geq 50\%$, respectively[1]. The estimated prevalence of HF in adults is 1–2%, increasing progressively with age and exceeding 10% among individuals older than 70 years[2].

Ischemic heart disease is the leading underlying cause of HFrEF, accounting for approximately two thirds of all HF cases [3]. Compared with non-ischemic etiologies, ischemic HF is associated with a higher risk of all-cause mortality, mainly driven by non-sudden cardiac death [4,5]. However, distinguishing ischemic from non-ischemic HFrEF can be challenging, and concomitant coronary artery disease is not infrequently present without being the primary cause of ventricular dysfunction. To standardize definitions, ischemic cardiomyopathy has been proposed as left ventricular dysfunction in the presence of significant coronary artery disease and at least one of the following: prior revascularization or acute myocardial infarction (AMI); $>75\%$ stenosis of the left main coronary artery (LMCA) or left anterior descending artery (LAD); and/or ≥ 2 coronary vessels with $>75\%$ luminal stenosis [6].

Left ventricular dysfunction in ischemic heart disease may result from myocyte loss or prior infarction, with residual scar or fibrosis. Ischemic scar typically follows the distribution of the affected

coronary artery and progresses centrifugally from the endocardium toward the epicardium, becoming transmural in the case of complete infarction [7,8]. In this context, late gadolinium enhancement in cardiac magnetic resonance (LGE-CMR) is highly useful for delineating ischemic scar after infarction and identifying viable myocardium, defined as fibrosis or late enhancement involving <50% of myocardial wall thickness [9].

However, a non-negligible proportion of patients with significant coronary artery disease and HFrEF show no clinical or imaging evidence of prior transmural infarction. In these patients, ventricular dysfunction is thought to be related to dysfunctional or hypocontractile myocardial segments following the distribution of atherosclerotic coronary arteries, but without scar or fibrosis and with preserved, albeit potentially reduced, metabolic activity [10]. This so-called “hibernating” myocardium would remain viable and downregulate contractility to match reduced oxygen supply in response to chronic ischemia [11,12]. Under this premise, subsequent observations suggested that contractile function in these segments might be reversible or improved through coronary revascularization [13].

2. Coronary Revascularization in Ischemic Heart Disease

Two main revascularization strategies are available: coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). Although both approaches increase coronary blood flow and prevent myocardial ischemia, outcomes may differ depending on anatomical complexity and the patient’s clinical context [14].

The SYNTAX study demonstrated that patients with higher anatomical complexity (SYNTAX score ≥ 33) derive greater benefit from surgical revascularization, whereas PCI may be a reasonable alternative in less complex anatomies [15]. Nevertheless, CABG has been associated with a higher risk of atrial fibrillation and stroke [15–20], as well as increased early postoperative complications, including major bleeding, arrhythmias, acute kidney injury, and rehospitalization within the first 30 days [21]. Conversely, PCI is associated with a higher likelihood of repeat revascularization and myocardial infarction during follow-up, particularly in patients with extensive coronary artery disease [17,18,22,23]. Consequently, the choice between strategies should be individualized, taking into account not only coronary anatomy but also the patient’s clinical profile and myocardial viability.

Coronary revascularization has demonstrated benefit in obstructive coronary artery disease for symptom relief and prevention of spontaneous myocardial infarction and other major adverse cardiovascular events (MACE), with some authors suggesting a potential long-term survival benefit [24,25].

According to the classical concept of myocardial hibernation, combining myocardial revascularization with optimal medical therapy (OMT) could improve left ventricular systolic function and prognosis in patients with HFrEF by restoring adequate perfusion to dysfunctional but viable myocardial segments and preventing new ischemic events. However, recent data have generated controversy regarding the routine and early revascularization of patients with HFrEF, the role of PCI versus CABG in complex coronary disease, and the value of ischemia testing in guiding revascularization decisions [14]. Paradoxically, the potential benefit of myocardial revascularization has not been confirmed in studies assessing viability-guided revascularization using LGE-CMR, dobutamine stress echocardiography (DSE), or SPECT, thereby challenging the prognostic role of myocardial hibernation [10].

Importantly, perioperative risk in ICFer patients is substantial due to severe left ventricular dysfunction, anatomical complexity, and reduced coronary flow reserve [11]. Therefore, the benefit of coronary revascularization must be consistently demonstrated and sufficiently large to offset the significant risk of clinical and hemodynamic deterioration associated with revascularization procedures and subsequent recovery.

In recent years, several studies have compared revascularization strategies with each other or with conservative management based on OMT. Among them, the most relevant to date are the STICH

and REVIVED-BCIS2 trials. However, the predominance of observational data and the scarcity of randomized controlled trials have yielded heterogeneous and sometimes contradictory results.

Overall, published evidence is limited, heterogeneous in design, and not always concordant, complicating interpretation and clinical application. Nonetheless, the systematic and detailed analysis of recent evidence presented in this review allows certain conclusions to be drawn regarding the relative efficacy of these therapeutic strategies and their clinical implications.

3. Survival Benefit of Coronary Revascularization in Ischemic HFrEF

The analysis of mortality shows heterogeneous results depending on the strategy compared. The HEART study, which included only 45 revascularized patients (15 treated with PCI and 30 with CABG) compared with 69 patients receiving OMT, concluded that all-cause mortality was similar between groups. However, due to the low number of recruited patients (far below the initially estimated sample size) and the small number of observed events, the results were inconclusive and a potential benefit of revascularization could not be excluded [26].

Indeed, several meta-analyses jointly evaluating both revascularization strategies concluded that revascularization significantly reduces mortality. Nevertheless, based on these studies, it cannot be determined whether the observed benefit is independent of the chosen revascularization strategy (PCI or CABG) [27,28].

PCI had been associated in previous studies and in a recent meta-analysis with a potential reduction in mortality. However, these findings were not confirmed in more recent studies [29]. Among them, the largest randomized clinical trial published in this setting is the REVIVED-BCIS2 trial.

In the randomized REVIVED-BCIS2 trial, PCI (347 patients) was compared with OMT (353 patients) in patients with left ventricular systolic dysfunction (LVEF $\leq 35\%$), extensive coronary artery disease (defined as a British Cardiovascular Intervention Society jeopardy score ≥ 6), and demonstrable myocardial viability in at least four dysfunctional myocardial segments amenable to PCI. After a median follow-up of 41 months (IQR: 28–60), the primary endpoint, a composite of all-cause mortality or hospitalization for any cause, did not differ significantly between groups (HR 0.99 [95% CI 0.78–1.27]), nor did all-cause mortality (HR 0.98 [95% CI 0.75–1.27]) [30].

Regarding CABG, one of the most important studies to date was the STICH trial and its extension, STICHES.

The STICH trial was a multicenter randomized clinical trial comparing CABG (610 patients) with OMT (602 patients) in patients with coronary artery disease (of whom $<3\%$ had left main disease and 60% had three-vessel disease, defined as $\geq 50\%$ stenosis) and left ventricular dysfunction (median LVEF 28% [IQR: 21–34] in the OMT group and 27% [IQR: 22–33] in the CABG group). After a median follow-up of 56 months (IQR: 48–68), CABG did not show a significant benefit in all-cause mortality (HR 0.86 [95% CI 0.72–1.04]) but did demonstrate a significant reduction in cardiovascular mortality (HR 0.81 [95% CI 0.66–1.00]) and in the composite of all-cause mortality or cardiovascular hospitalization (HR 0.74 [95% CI 0.64–0.85]). In subgroup analyses, patients with LVEF $\leq 27\%$ showed significantly lower all-cause mortality in the CABG group (HR 0.77 [95% CI 0.60–0.98]), as did patients with three-vessel disease (HR 0.79 [95% CI 0.62–0.99]) [31].

Subsequently, Bonow et al. performed a subanalysis of this trial to assess whether the identification of myocardial viability by imaging influenced survival and response to CABG in patients with reduced LVEF and coronary artery disease. With a median follow-up of 5.1 years, the presence of prespecified viable myocardium was not associated with lower mortality after adjustment for baseline prognostic variables (HR 0.64 [95% CI 0.48–0.86]; $P=0.003$ before adjustment; $P=0.21$ after adjustment) [32].

The STICHES study extended the follow-up of STICH to a median of 9.8 years (maximum 13.4 years) and concluded that, in contrast to the initial study, CABG significantly reduced all-cause mortality (HR 0.84 [95% CI 0.73–0.97]), cardiovascular mortality (HR 0.79 [95% CI 0.66–0.93]), and the composite of mortality or cardiovascular hospitalization (HR 0.72 [95% CI 0.64–0.82]) in patients with

ischemic cardiomyopathy and severe ventricular dysfunction. This difference remained significant for other outcomes, including hospitalization for any cause, hospitalization for HF, repeat revascularization, non-fatal myocardial infarction, or non-fatal stroke[33].

In conclusion, the initial analysis of the STICH trial did not show significant differences in the primary endpoint between study groups (CABG vs. OMT) [31]. However, after nearly 10 years of follow-up, this difference became significant in favor of CABG [33]. This finding supports the hypothesis that the mortality benefit of revascularization may be delayed and requires prolonged follow-up to be detected. These results may suggest that the survival benefit observed in previously mentioned meta-analyses evaluating revascularization as a whole may be largely driven by studies in which patients were treated with CABG.

Consistent with the findings of the STICH and REVIVED-BCIS2 trials, several meta-analyses and registries comparing both revascularization strategies have reported a mortality reduction associated with CABG compared with PCI, as well as reductions in other events such as myocardial infarction or repeat revascularization. However, the results of these meta-analyses are largely influenced by the STICH/STICHES trials, given the limited number of randomized clinical trials in this setting [17,18,22,29,34].

Among the most recent registries, the study published by Bloom et al. deserves mention, as it represents one of the largest worldwide and highlights the long-term benefits associated with CABG in patients with ischemic HFrEF, albeit with an increased risk of periprocedural stroke and longer hospital stay [16].

The FAME 3 trial is one of the few randomized clinical trials comparing both revascularization strategies. Published in 2022, it was a non-inferiority randomized trial comparing FFR-guided PCI (757 patients) with CABG (743 patients) in patients with three-vessel disease, of whom 17.8% had LVEF \leq 50% (18.2% in the PCI group and 17.6% in the CABG group) [21].

After one year of follow-up, the primary endpoint (a composite of all-cause mortality, myocardial infarction, stroke, or repeat revascularization) was significantly higher in the FFR-guided PCI group (HR 1.5 [95% CI 1.1–2.2]), failing to meet the non-inferiority margin ($P=0.35$ for non-inferiority), regardless of LVEF [21]. This study is relevant because it incorporated routine use of FFR to guide PCI and employed contemporary drug-eluting stents, representing recommended revascularization practices associated with improved short- and long-term outcomes compared with angiography-guided PCI or OMT alone [35,36]. Among its limitations, the reported follow-up was limited to one year, whereas the potential long-term benefit of CABG has been demonstrated in studies such as STICHES (33). In addition, FAME 3 excluded patients with severe left ventricular dysfunction (LVEF $<30\%$) [21].

The survival benefit associated with CABG is thought to be partly related to a “collateralization effect,” whereby bypass grafts provide protection against future myocardial injury beyond diseased epicardial territories in the event of plaque rupture or vessel occlusion, events that more commonly occur in proximal and mid segments of epicardial vessels [37,38]. Furthermore, grafts—particularly arterial grafts—may remain patent for longer periods compared with PCI-treated coronary lesions [39].

In contrast, PCI treats only the focal atherosclerotic area where the stent is implanted, limiting its preventive effect or even creating a substrate for future events. Indeed, even if the treated segment remains permanently patent, myocardial ischemia may still occur in other segments of the same coronary artery [40].

When drawing conclusions regarding the optimal management of patients with ischemic cardiomyopathy and HFrEF, an important question is whether the main studies discussed are truly comparable. The two most relevant trials, REVIVED-BCIS2 and STICH, differ in several key aspects (Table 1). In REVIVED-BCIS2, patients were on average 10 years older than those in STICH, had a higher prevalence of chronic kidney disease (16% vs. 8%), and had experienced fewer prior myocardial infarctions (50% vs. 78%). In addition, fewer patients had three-vessel disease (38% vs. 60%), and a higher proportion were asymptomatic for angina at baseline (66% vs. 36%)[41].

Under these premises, the lesser benefit of PCI may be explained by a lower amount of myocardium at risk, reduced functional reserve, and higher all-cause mortality driven by key predictors such as age and chronic kidney disease [41].

Two further key differences between both trials should be highlighted. First, patients in REVIVED-BCIS2 were followed for a shorter period than those in STICH, potentially missing a late survival benefit of PCI similar to that observed with extended follow-up in STICHES (41). Moreover, given the lower extent of coronary artery disease, it cannot be excluded that some REVIVED-BCIS2 patients had left ventricular dysfunction not clearly attributable to ischemic etiology, which may also have influenced the lower observed efficacy of revascularization.

Second, patients in REVIVED-BCIS2 received more contemporary HF medical therapy (90% received renin-angiotensin-aldosterone system inhibitors, 90% beta-blockers, and 48% mineralocorticoid receptor antagonists). Agents such as ARNIs or SGLT2 inhibitors were not available during STICHES or the early phase of REVIVED-BCIS2. In addition, patients in REVIVED-BCIS2 were more frequently treated with ICD/CRT (21%/53% vs. 2%/19%). This is a key consideration when interpreting the results of both studies, as mortality and HF hospitalization rates were significantly lower in patients treated with OMT alone in REVIVED-BCIS2 compared with any of the STICHES groups [41].

Table 1. Main differences between REVIVED-BCIS and STICH trials.

	REVIVED-BCIS	STICH/STICHES
Mean age	70 years	60 years
Chronic kidney disease	16%	8%
Prior myocardial infarction	50%	78%
Three-vessel disease	38%	60%
Angina-free at baseline	66%	36%
Follow-up (median)	41 months	56 months (STICH) 9.8 years (STICHES)
HF medical therapy	90% ACEi/ARB/ARNI 90% beta-blockers 48% MRA	90% ACEi/ARB 88% beta-blockers 46% MRA ARNI/SGLT2i not available
ICD / CRT use	21% / 53%	2% / 19%

Based on the above, although the most relevant studies to date have not demonstrated that PCI improves survival, comparisons between revascularization strategies (PCI vs. CABG) should be interpreted with caution. Prognostic differences in background medical therapy may influence outcomes; therefore, comparisons across studies remain speculative and should primarily be considered hypothesis-generating [41,42].

4. Effect of Revascularization on Ventricular Function: Myocardial Hibernation and Viability Assessment

One of the potential benefits of revascularization, in relation to the myocardial hibernation hypothesis, would be improvement in ventricular function.

In a prespecified secondary analysis of the REVIVED-BCIS2 trial (including 87% of patients from the original trial), the investigators sought to determine whether a significant correlation existed between the extent of viable myocardium, assessed by LGE-CMR or dobutamine stress echocardiography. The median increase in LVEF was 4.7% (IQR: -2.2% to 12.5%) at 6 months; however, this improvement was not determined by the extent of viable myocardium and did not differ significantly between the PCI group and the group receiving OMT alone [43].

Accordingly, the results of this study did not support the use of myocardial viability assessment to guide revascularization in patients with HFrEF and called into question the traditional concept of myocardial hibernation, in which improvement of viable myocardium would be expected after

revascularization [43]. The authors suggested that current viability imaging techniques may not specifically detect myocardial hibernation or that the hibernation paradigm itself may require revision, as although ischemia may trigger the hibernation process, revascularization alone may not be sufficient to effectively reverse it [44,45].

Nevertheless, this secondary analysis of REVIVED-BCIS2 did show that a greater extent of non-viable myocardium was associated with lower event-free survival, driven by a higher incidence of fatal ventricular arrhythmias, suggesting that myocardial viability assessment may still be useful for risk stratification [43].

Conversely, in the PARR-2 trial, viability-guided revascularization using FDG-PET in patients with severe left ventricular dysfunction and suspected coronary artery disease did not demonstrate a benefit compared with standard management. A reduction in cardiovascular events at 1 and 5 years was observed only in a subanalysis of centers with greater imaging expertise and in patients who closely adhered to management recommendations [46,47]. For this reason, the authors suggested that PET-based viability assessment might be useful when these conditions are likely to be met [47].

A recent publication suggests that the extent of viable myocardium, with or without contractile dysfunction, may help identify patients who derive greater benefit from revascularization. However, the authors advocate for a broader concept of viability assessment, emphasizing multidisciplinary management and optimization of OMT, for which robust evidence exists [48].

In this context, the use of myocardial viability testing in patients with ischemic left ventricular dysfunction remains controversial, as randomized clinical trials have not demonstrated clear benefits of viability-guided revascularization, highlighting current limitations in appropriate patient selection.

5. Effect of Revascularization on Other Clinical Outcomes

Symptomatic Improvement

Another rationale for considering revascularization in patients with HFrEF is symptomatic improvement and, consequently, enhanced quality of life, either through improved ventricular function or reduced ischemia during daily activities. This benefit was demonstrated in earlier trials such as COURAGE and ISCHEMIA; however, these studies systematically excluded patients with HFrEF (mean LVEF 61% and 60%, respectively) [49,50].

In the REVIVED-BCIS2 trial, a significant improvement in quality of life was observed at 6 months, but this benefit was no longer present after 24 months of follow-up. A key limitation of the study was that 66% of patients were angina-free and 77% were in NYHA class I or II prior to revascularization [30].

Therefore, these results cannot be extrapolated to patients whose angina significantly impairs quality of life or to those presenting with acute coronary syndromes. PCI should not be recommended solely to achieve short-term symptomatic improvement, as although a significant benefit was observed during the first six months after revascularization, this effect was not sustained at 1 and 2 years of follow-up. A possible explanation for the loss of long-term benefit is that PCI initially improves ischemia and its clinical manifestations, leading to a subjective perception of improved well-being. Over time, however, progression of atherosclerotic disease—either in the treated vessel or in remote territories—may attenuate this initial benefit, resulting in convergence of health status with patients treated with OMT alone [30,51].

Similarly, the HEART study failed to demonstrate a significant improvement in quality of life in revascularized patients compared with those treated with OMT alone. However, most enrolled patients had minimal symptoms or had modified their lifestyle to avoid symptom onset, making it more difficult to detect improvements during follow-up [26].

Heart Failure Hospitalizations and Other Major Adverse Cardiovascular Events

Overall, studies including PCI as a treatment strategy did not demonstrate significant differences compared with conservative management with OMT [27,28,30,52]. In contrast, when CABG was the selected revascularization strategy, as in the STICH trial and its extension STICHES, a reduction in cardiovascular hospitalizations—particularly for heart failure—was observed. This benefit emerged early and increased over time during the 10-year follow-up [31,33,53].

6. Current Recommendations and Future Perspectives

Current European Society of Cardiology (ESC) guidelines highlight the complexity of revascularization decisions in patients with chronic coronary syndrome and HFrEF, recommending individualized evaluation by a multidisciplinary Heart Team. Based on available evidence, CABG is more strongly recommended to improve long-term prognosis in patients with multivessel disease who are suitable surgical candidates (Class I-C), whereas PCI may be considered in patients at high surgical risk or deemed inoperable (Class IIb-B). Additionally, coronary revascularization is recommended for symptom relief in patients with persistent angina or angina equivalents despite OMT (Class I-A) [42].

Despite the available evidence, uncertainty remains regarding the incremental benefit of coronary revascularization over OMT alone in patients with HFrEF, even in the context of recent advances in medical therapy and PCI techniques.

Ongoing randomized multicenter trials with adequate statistical power, such as STICH3-BCIS4 (NCT05427370) and STICH-SWEDEHEART (NCT05329285), which directly compare PCI and CABG in patients with multivessel disease and HFrEF, are expected to clarify optimal revascularization strategies in clinical practice [54,55].

7. Conclusions

Myocardial revascularization with CABG has demonstrated greater effectiveness than conservative management with OMT in reducing long-term mortality and hospitalizations in patients with ischemic cardiomyopathy and HFrEF, particularly in those with multivessel disease. PCI, although associated with transient symptomatic improvement and quality-of-life benefits, has not shown consistent advantages in terms of mortality reduction, sustained improvement in LVEF, or reduction of major adverse cardiovascular events compared with OMT. The choice between CABG and PCI should be individualized, considering coronary anatomy, clinical profile, and comorbidities, within a multidisciplinary team approach.

The role of myocardial viability testing to guide revascularization in patients with HFrEF remains controversial, as it has not reliably predicted functional recovery or prognostic improvement, thereby challenging the traditional paradigm of myocardial hibernation.

Conflicts of Interest: Declare conflicts of interest or state “The authors declare no conflicts of interest.”.

Abbreviations

The following abbreviations are used in this manuscript:

ACEi	Angiotensin-Converting Enzyme Inhibitor
AMI	Acute Myocardial Infarction
ARB	Angiotensin II Receptor Blocker
ARNI	Angiotensin Receptor–Neprilysin Inhibitor
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CMR	Cardiac Magnetic Resonance
CRT	Cardiac Resynchronization Therapy
DSE	Dobutamine Stress Echocardiography
ESC	European Society of Cardiology
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography

FFR	Fractional Flow Reserve
HF	Heart Failure
HFmrEF	Heart Failure with Mildly Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
ICD	Implantable Cardioverter-Defibrillator
IQR	Interquartile Range
LAD	Left Anterior Descending (coronary artery)
LGE-CMR	Late Gadolinium Enhancement Cardiac Magnetic Resonance
LMCA	Left Main Coronary Artery
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Events
MRA	Mineralocorticoid Receptor Antagonist
NYHA	New York Heart Association
OMT	Optimal Medical Therapy
PCI	Percutaneous Coronary Intervention
SGLT2i	Sodium–Glucose Cotransporter 2 Inhibitor
SPECT	Single Photon Emission Computed Tomography

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