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Comprehensive Review

Current Landscape and Future Directions of Coronary Revascularization in Ischemic Systolic Heart Failure: A Review

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ABSTRACT

Ischemic heart disease is the largest cause of death worldwide and the most common cause of heart failure (HF). The incidence and prevalence of HF are increasing owing to an aging population and improvements in the acute cardiac care of previously fatal conditions such as myocardial infarction. Strategies to improve outcomes in patients with ischemic systolic HF are urgently needed. There is systematic underutilization of testing for coronary artery disease in patients with HF, and revascularization is performed in an even smaller minority despite evidence for reduced mortality with coronary artery bypass grafting (CABG) over medical therapy in the Surgical Treatment for Ischemic Heart Failure Extension Study. Percutaneous coronary intervention (PCI) is a less-invasive approach to coronary revascularization; however, the recent Revascularization for Ischemic Ventricular Dysfunction (REVIVED)-British Cardiovascular Intervention Society (BCIS2) trial failed to demonstrate a benefit of PCI compared with that of medical therapy in patients with ischemic systolic HF. The comparative effectiveness of PCI and CABG for patients with ischemic systolic HF remains unknown, particularly in the era of contemporary medical therapy. In this review, we discuss the benefit of CABG in ischemic systolic HF, its underutilization, and the unmet clinical need. We also review the recent REVIVED-BCIS2 trial comparing PCI to medical therapy, as well as upcoming randomized controlled trials of PCI for ischemic systolic HF and persistent evidence gaps that will exist despite anticipated data from ongoing trials. There remains a need for an adequately powered randomized controlled trials to establish the comparative clinical effectiveness of PCI vs CABG in ischemic systolic HF in the era of contemporary revascularization approaches and medical therapy, as well as trials of coronary revascularization in patients with HF with preserved ejection fraction or less severe forms of left ventricular systolic dysfunction.

Ischemic systolic heart failure as a public health concern

Ischemic heart disease (IHD) remains the largest cause of death worldwide (Figure 1),[1] and the leading cause of left ventricular systolic dysfunction (LVSD) and heart failure (HF). The incidence and prevalence continue to increase due to an aging population and improved care of acute myocardial infarction (MI), with more surviving patients with impaired left ventricular function who develop HF.[2] In contemporary randomized controlled trials (RCTs), the etiology of HF was IHD in 60% of patients[3]; in another published report encompassing 43,000 patients across 43 HF trials, IHD was the cause of HF in 65% of patients.[4] This is corroborated by real-world data, with analyses of 156,013 hospitalized patients with HF from 319 US hospitals demonstrating that 59% of patients had coronary artery disease (CAD) as the determined etiology of their HF.[5] Despite optimized medical therapy (MT), mortality from ischemic systolic HF remains high, up to 41% at almost 5 years of follow-up.[6,7]

Low rates of investigation for CAD in HF

The actual contribution of CAD to the incidence of HF may be underestimated as a new diagnosis of HF leads to investigation for CAD in the minority of patients (Table 1). A Cardiovascular Research Network (CVRN)[8] study examined 5878 patients hospitalized with incident HF between 2005 and 2008. From 14 days prior to admission to 6 months after discharge, only 36.9% of patients underwent testing for CAD. A separate study[9] used claims data derived from the Truven Health MarketScan Commercial and Medicare databases for their study of 67,161 hospitalized patients with new-onset HF between 2010 and 2013.

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; HF, heart failure; LMCAD, left main coronary artery disease; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; MT, medical therapy; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

Keywords: heart failure; percutaneous coronary intervention; revascularization.

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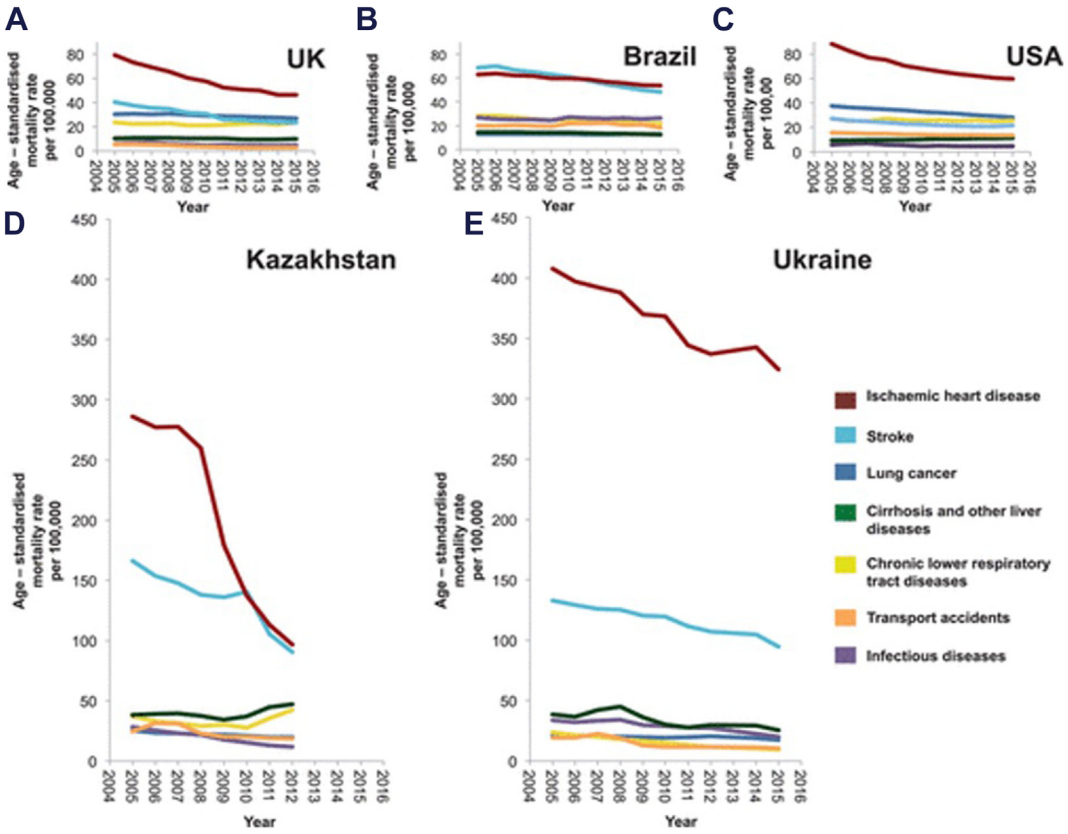


Figure 1.

Mortality trends for major causes of death from 2005 to 2015 in various countries, demonstrating ischemic heart disease as the leading cause of death. Age-standardized mortality rates per 100,000 people from ischemic heart disease (red line), stroke (light blue line), cirrhosis and other liver diseases (green line), chronic lower respiratory tract diseases (yellow line), lung cancer (blue line), transport accidents (orange line), and infectious diseases (purple line). Reproduced with permission from Nowbar et al.[1]

Only 27.4% of patients underwent CAD testing within 90 days after the HF hospitalization. A prospective registry linked to Medicare claims[10] of 17,185 patients with new-onset HF found that 39% of patients underwent testing for CAD within 90 days before or after the index HF hospitalization. Finally, a more contemporary analysis of 558,322 patients with new-onset HF using an administrative claims database of both Medicare and commercial insurance between 2004 and 2019 demonstrated similar results: 34.8% of patients underwent CAD testing and 9.3% underwent revascularization.[11] Importantly, this analysis included both inpatient and outpatient settings and encompassed data reflecting practice patterns after the publication of a large randomized trial,[12] demonstrating mortality reduction with coronary artery bypass grafting (CABG) for patients with ischemic systolic HF. This analysis also demonstrated significant variability in testing patterns across locations and clinicians (Figure 2).

These data are from insured populations in the United States. There are limited data from other countries, but it is likely that rates of investigations for CAD in HF are even lower in less-affluent countries. A recent study of patients presenting to the emergency department with HF in Canada identified 2994 patients classified as having acute ischemic HF based on clinical and biomarker parameters.[13] In this cohort, early angiography was performed in 52.3% of patients and was associated with lower all-cause mortality, although this study is necessarily subject to selection bias.

Table 1. Published studies on testing for coronary artery disease in patients with heart failure and reduced ejection fraction.

Reference, year	Source of included patients	Inclusion criteria	Sample size	Rate of testing for coronary artery disease	Rate of revascularization
Farmer et al,[8] 2014	Patients from 3 participating health plans within the NHLBI-sponsored CVRN heart failure study	Patients hospitalized with incident HF	5878	36.9% of patients (from 14 d before admission to 6 mo after discharge)	Not reported
Doshi et al,[9] 2016	Truven Health MarketScan Commercial and Medicare Supplemental databases	Adult inpatients admitted with a principal diagnosis of HF	67,161	17.5% during the index hospitalization; 27.4% at 90 d	2.1% during the index hospitalization; 4.3% at 90 d
O'Connor et al,[10] 2020	Get With the Guidelines–Heart Failure registry linked to Medicare claims	Patients hospitalized for a new diagnosis of HF	17,185	23% during the index hospitalization; 39% within 90 d	4.7% underwent PCI; CABG rates not reported
Zheng et al,[11] 2022	Optum deidentified Clinformatics DataMart (Optum), a database comprising administrative health claims for members of commercial and Medicare advantage plans across all 50 states	Patients aged 18 years or older with an incident HF diagnosis, including both inpatient and outpatient settings	558,322	34.8% underwent CAD testing during the 90 d before or after their first HF diagnosis	9.3% underwent revascularization (~60% of these were by PCI an 40% by CABG)

CABG, coronary artery bypass grafting; CVRN, Cardiovascular Research Network; HF, heart failure; NHLBI, National Heart, Lung, and Blood Institute; PCI, percutaneous coronary intervention.

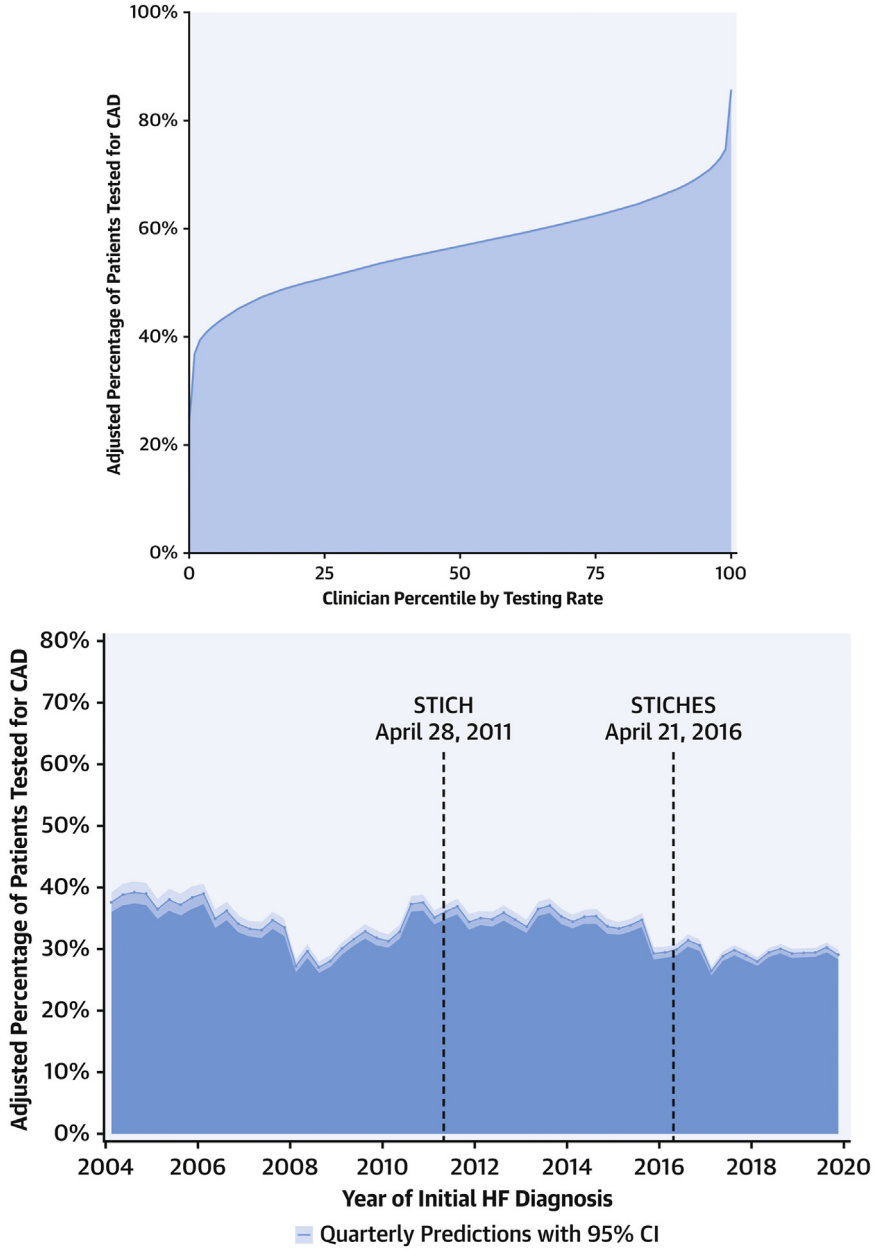


Figure 2.
(**Top panel**) Significant variability demonstrated in cumulative distribution curves of cardiologists ordering CAD testing. (**Bottom panel**) CAD testing rates shown with the publication dates of the STICH and STICHES publications denoted, with no significant increase in rates of CAD testing after these publications. Reproduced with permission from Zheng et al.[11]
CAD, coronary artery disease.

One caveat to the low rates of investigation for CAD is that a certain proportion of patients may not undergo testing due to their own unwillingness or due to prior knowledge of the coronary anatomy. Such factors are difficult to discern from the large-scale studies of administrative databases that have been performed; nevertheless, this is unlikely to represent a large proportion of the patients included in these studies.

Low rates of CAD testing for patients with new-onset HF is in the context of class IIa European and American guideline recommendations (albeit with level of evidence C).[14,15] When CAD is tested for and found, it confers an adverse prognosis in patients with HF. Ischemic etiology of HF has been shown to be an independent predictor of mortality, as does the extent of CAD.[16]

Appropriate testing for CAD has potential downstream benefits beyond determining the etiology of a patient's HF. Patients can be appropriately triaged to a different treatment pathway that involves guideline-directed medical therapy for both CAD and LVSD and evaluation for candidacy of revascularization.

The relative merits of different modalities of CAD testing are unclear, and low rates of CAD testing in HF may reflect uncertainty regarding their value for improving outcomes. There is currently no RCT evidence for improved outcomes with any imaging modality in patients with HF. Future trials will need to examine the use of various testing strategies for CAD in order to establish whether outcomes can be improved by systematic assessment for CAD in patients with HF. Future areas of study could also focus on CAD testing in various HF populations: specifically, hospitalized and nonhospitalized patients and those with reduced or preserved ejection fraction (EF).

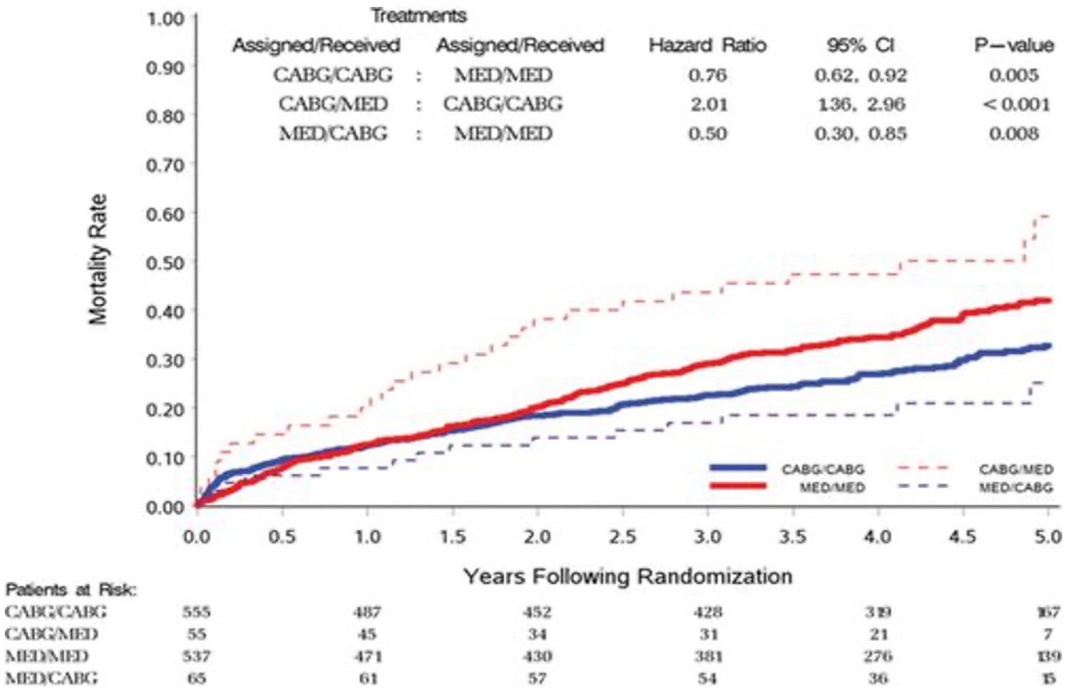


Figure 3.
Kaplan-Meier analysis of patients assigned to coronary artery bypass graft (CABG; blue lines) or medical therapy alone (MED; red lines) either adhering (per-protocol) or not adhering (crossover) to their randomly assigned treatment. This analysis demonstrated that CABG reduced mortality in the intention-to-treat, per-protocol, and crossover populations. Reproduced with permission from Doenst et al.[17]

The benefit of CABG in ischemic systolic HF

The effect of CABG on mortality in patients with CAD and LVSD was evaluated in the Surgical Treatment for Ischemic Heart Failure (STICH) trial.[7] In this trial, patients with CAD amenable to CABG and EF ≤35% were randomly assigned to CABG plus MT vs MT alone, with a primary end point of all-cause mortality. Patients with significant left main coronary artery disease (LMCAD), severe angina, or recent acute MI were excluded. A total of 1212 patients were enrolled, with 602 patients randomized to MT and 610 patients randomized to CABG plus MT. In the initial report of the trial, at a median length of follow-up of 4.7 years, 244 patients in the MT arm had died compared with 218 patients in the CABG arm (hazard ratio [HR], 0.86; 95% CI, 0.72-1.04; $P = .12$). Although the primary outcome of all-cause mortality did not demonstrate a significant benefit with CABG, the effect on cardiovascular death (HR, 0.81; 95% CI, 0.66-1.00; $P = .05$) and the composite of all-cause mortality or hospitalization for cardiovascular causes (HR, 0.74; 95% CI, 0.64-0.85; $P < .001$) were both significantly reduced with CABG. In extended follow-up at a median follow-up duration of 9.8 years (STICH Extension Study [STICHES]), the benefit of CABG over MT on all-cause mortality was now statistically significant (HR, 0.84; 95% CI, 0.73-0.97; $P = .02$).[12] The number needed to treat to prevent 1 death was 14 patients (95% CI, 8-55 patients). Per-protocol and as-treated analyses, which accounted for crossovers within 1 year, suggested a greater benefit than that seen in the primary intention-to-treat analysis (Figure 3).[7,17] It should be acknowledged that because the primary end point for STICH was neutral, subsequent analyses should strictly speaking be considered hypothesis-generating.

Apart from hard clinical end points such as mortality, health-related quality of life (QoL) remains an important outcome among patients. A prespecified secondary end point analysis of STICH[18] evaluated self-reported angina-related and HF-related QoL using the Seattle Angina Questionnaire and the Kansas City Cardiomyopathy Questionnaire (KCCQ), respectively. Compared with baseline, there were significant improvements in QoL by 4 months in both arms that were sustained at 36 months of follow-up. Importantly, patients assigned to CABG plus MT had significantly greater improvements in QoL compared with patients assigned to MT throughout the follow-up period, with a needed to treat of 9 to 14 for clinically meaningful improvements in HF-specific QoL.

The mortality benefit of CABG emerging over MT at longer-term follow-up, rather than at 5 years, has several plausible explanations. Most obviously, extended follow-up allowed for accrual of more events, meaning there was enhanced precision around the point estimate and narrowing of the CI. Additionally, time-varying analyses demonstrate an early mortality hazard with CABG: at 30 days, CABG was associated with a 3-fold increase in mortality compared with MT, and the overall number of deaths was higher with CABG than MT for 2 years before the benefit of CABG emerged.

An unmet clinical need

Despite this RCT evidence of the benefit of CABG, it is not widely applied to this patient population. Observational studies suggest only 4.3% of patients hospitalized for HF underwent revascularization within 90 days of the index hospitalization, and only 1.3% are revascularized with CABG.[9] Patients presenting with HF are also among the least likely to be offered revascularization[19,20] and represent an important unmet clinical need.[21] Potentially increasing the number of patients deemed appropriate candidates for revascularization could improve clinical outcomes in HF and broadly improve public health.[22]

Why is CABG underutilized for ischemic HF?

RCTs are necessarily conducted within the confines of their inclusion and exclusion criteria, and depending on how narrow the criteria may be, applicability of their findings to routine clinical practice could be limited. In STICH, patients were deemed suitable for surgical revascularization by the treating clinical and research teams. In real-world practice, it may be

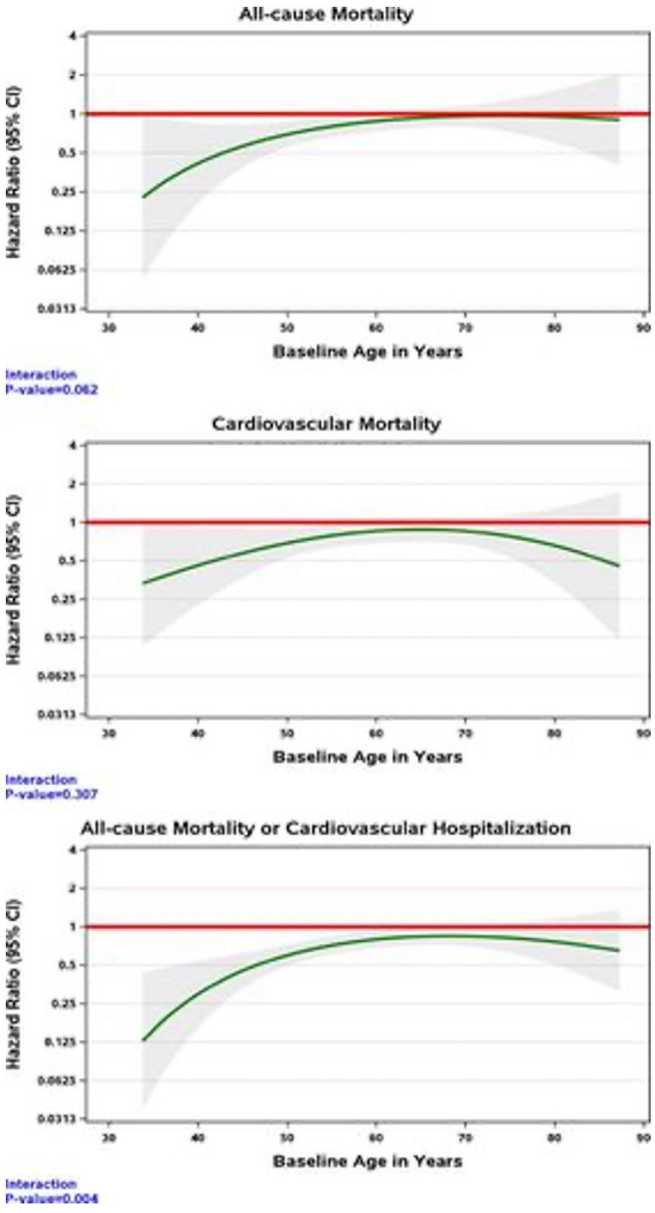


Figure 4.
Hazard ratio (solid line) and 95% CI (gray area) for the effect of coronary artery bypass grafting vs medical therapy across the range of ages. The effect of CABG on reducing clinical events was greater in the younger (<54 years) compared with older patients (>67 years). Reproduced with permission from Petrie et al.[25]

that physicians do not feel their patients are acceptable candidates for surgery. This issue, common to all RCTs, might be magnified for the population studied in STICH where severe LVSD marks patients at elevated risk. In the Outcomes of Percutaneous Revascularization for Management of Surgically INeligible Patients with Multivessel or Left Main Coronary Artery Disease (OPTIMUM) registry, which evaluated patients with multivessel or LMCAD deemed ineligible for CABG, severe cardiomyopathy was the primary and secondary reason for surgical turndown in 14.6% and 22.3% of patients, respectively.[23] The included patients had a high burden of comorbidities, with a predicted perioperative mortality rate by the evaluating cardiac surgeon of 10.4% ± 12.3%. Moreover, observational data have demonstrated that patients undergoing treatment for CAD are more likely to develop multiple comorbidities as they age, which may render them less optimal candidates for CABG.[19,24] Most patients with HF are elderly, and the benefit of CABG in STICH diminished with increasing patient age (Figure 4).[25]

Furthermore, STICH demonstrated an early hazard with CABG: 25% of patients developed serious complications within 30 days.[26] These severe complications were associated with subsequent mortality and can help to explain why early mortality was higher with CABG than with MT in STICH. Many physicians and patients may not feel comfortable assuming this upfront risk, even with demonstrated long-term benefits. Analyses from STICH also demonstrate that this risk varies markedly across patients and can be moderately predicted from the Society of Thoracic Surgeons and European System for Cardiac Operative Risk Evaluation-2 risk scores.[27] Using these risk scores to predict risk can help in potentially avoiding performing surgery on patients at higher risk of having poor outcomes.

Another factor that may negatively influence utilization of CABG in this scenario is the risk of stroke. In STICH, 11 patients in the CABG arm experienced a stroke within 30 days after randomization (1.8%), compared with 1 patient in the MT arm (0.2%), and large observational studies have also demonstrated increased risk of stroke with CABG compared with percutaneous coronary intervention (PCI) in patients with HF and multivessel CAD.[28] Mechanistic explanations for increased stroke risk with CABG include embolic risks associated with cardiopulmonary bypass and crossclamping of the aorta, as well as risks of cerebral hypoperfusion related to intraoperative hypotension and general anesthesia. An individual patient-level pooled analysis of 11 RCTs[29] comparing CABG and PCI in people without HF demonstrated significantly lower stroke rates after PCI at 30 days. This is particularly pertinent as cardiac patients consider stroke a worse outcome than death,[30,31] and therefore, avoidance of neurologic complications and disability is likely to influence patient preference when being assessed for revascularization.

The rationale for using PCI as a method of revascularization in patients with HF

Despite the results of the STICH trial, few patients undergo CABG for ischemic systolic HF. On the other hand, patients considered high or prohibitive surgical risk are increasingly being referred for high-risk PCI. Compared with CABG, PCI is a less-invasive revascularization modality that may offer an avenue for increased adoption of revascularization in this setting if trial evidence were available demonstrating clinical benefit.

The prospective multicenter OPTIMUM registry described the characteristics, clinical management, and outcomes of patients with complex multivessel or LMCAD declined for CABG who were managed with PCI plus MT. Baseline synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score was 32.4 ± 12.2, with 45.3% of patients having highly complex CAD (SYNTAX ≥ 33). Among the 726 patients, 51% had chronic HF, over half of which had some degree of systolic HF (46.4% systolic HF, 15.9% combined systolic and diastolic HF). Almost half of the patients had New York Heart Association class III to IV symptoms, and almost one-fourth of patients with LVSD had severely reduced EF of ≤30%. The most common indications for PCI included symptom relief (39.8%), acute coronary syndrome ([ACS] 27.1%), treatment of cardiomyopathy (24.1%), and ischemia reduction (13.6%). All-cause mortality was 5.6% at 30 days and 12.3% at 6 months; early mortality was predominantly due to cardiac death. Interestingly, all-cause mortality rates after PCI were similar to the predicted surgical risk as estimated by the Society of Thoracic Surgeons and European System for Cardiac Operative Risk Evaluation -2 scores, lower than surgeons' estimates (observed-to-expected ratio, 0.59; 95% CI, 0.42-0.76) and significantly higher than the National Cardiovascular Data Registry CathPCI risk model (observed-to-expected ratio, 4.46; 95% CI, 2.35-7.99), which reflects the higher risk nature despite a less-invasive revascularization approach in this patient cohort with extensive comorbidities and complex coronary anatomy.

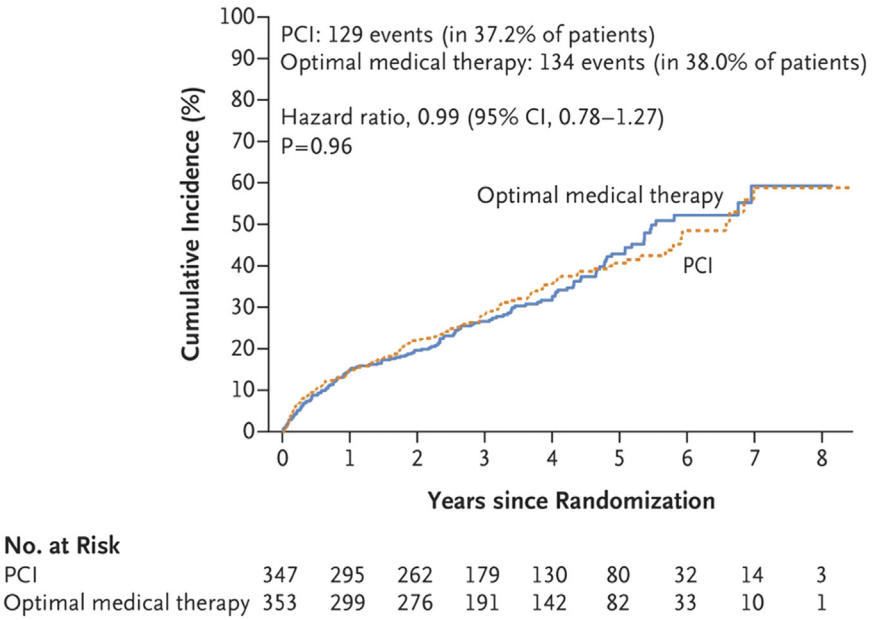


Figure 5.
Kaplan-Meier estimates of the cumulative incidence of all-cause mortality or hospitalization for heart failure in the REVIVED-BCIS2 trial. Reproduced with permission from Perera et al.[6]

Another recent single-arm observational study of selected patients with ischemic cardiomyopathy undergoing high-risk PCI with hemodynamic support with an Impella device suggested potential improvements in ejection fraction at 90 days.[32] There is also evidence from trials in patients without HF that PCI is not associated with the same early procedural risk hazards as CABG.[33–36] It is not known if this would apply to patients with HF as there are no randomized comparisons of PCI vs CABG in this patient population at this time.

Clinical outcomes after randomization to PCI or medical therapy in ischemic systolic HF: the REVIVED-BCIS2 trial

The first randomized evaluation of PCI vs MT for patients with ischemic systolic HF[37] has recently been published.[6] Inclusion criteria for the 700-patient open-label, UK-based trial were EF $\leq$ 35%, extensive CAD, and demonstrable myocardial viability. Extensive CAD was defined as coronary anatomy with a British Cardiovascular Intervention Society (BCIS) jeopardy score $\geq$6, which could include significant left main, proximal left anterior descending, or at least proximal 2-vessel CAD. This was therefore the first RCT to allow randomization of patients with left main disease to medical therapy. The primary outcome was a composite of all-cause mortality or hospitalization due to HF. Patients were randomized to PCI (n = 347) or MT (n = 353). At baseline, 14% of patients presented with LMCAD, and the mean BCIS jeopardy score was 10. After a median follow-up of 3.4 years, there was no significant difference in the primary outcome between the 2 groups: HR, 0.99; 95% CI, 0.78-1.27; P = .96 (Figure 5). The mortality rate in both groups was high despite more contemporary MT (31.7% in the PCI group and 32.6% in the MT group; HR, 0.98; 95% CI, 0.75-1.27). Results were similar when stratified according to the degree of LVSD (EF $\geq$ 29% and $<$ 29%). Unlike STICH, there was no increased upfront procedure-related mortality with PCI, but this did not translate into longer-term overall reductions in death. There was a reduction in spontaneous MI with PCI, with no overall significant difference in MI due to the occurrence of periprocedural MI in 37.8% of PCI patients. Unplanned revascularization occurred in 10.5% of the MT arm compared with 2.9% of the PCI arm (HR, 0.27; 95% CI, 0.13-0.53). Finally, PCI was associated with improved QoL as assessed by the KCCQ and EuroQol (EQ-5D-5L) at 6 and 12 months, but this difference was attenuated by the 24-month time point (which may be reflective of the increased revascularization crossovers seen in the MT arm over time).

The results of the Revascularization for Ischemic Ventricular Dysfunction (REVIVED)-BCIS2 trial inform clinical practice by demonstrating that mortality or hospitalization for HF were not improved with PCI compared with MT for selected patients with EF $<$ 35%, extensive CAD and viable myocardium. The results are not applicable to patients with angina or those presenting with ACS as patients with ACS were excluded and most patients had either no angina or minimal angina when enrolled. In addition, the question regarding the utility of myocardial viability evaluation prior to revascularization in ischemic systolic HF is again raised because viability was mandated but this did not translate into a mortality reduction with PCI compared with that with MT; this is broadly consistent with prior data from STICH.[38] The trial was also potentially underpowered with regards to all-cause mortality, and there were 37 fewer primary-outcome events than were estimated in the power calculation for the trial to have 85% power for the primary outcome. Finally, there was no invasive physiology assessment mandated, and severity of CAD was determined purely by angiographic assessment. There have been questions raised with regards to whether the BCIS jeopardy score of 6 was sufficiently "extensive" CAD for patients determined to have an ischemic cardiomyopathy. Future data regarding the angiographic severity of the CAD will be welcomed, as will reports of longer-term follow-up when available.

It is also important to underline that the findings of the REVIVED-BCIS2 trial do not inform any comparisons between PCI and CABG for the treatment of ischemic systolic HF. First, indirect comparisons of therapeutic modalities assessed in different trials are necessarily subject to bias and inherently speculative by nature. Second, the comparator group of MT differed markedly between the REVIVED-BCIS2 and STICH trials, with increased use of contemporary prognostic therapies such as angiotensin receptor-neprilysin inhibition (ARNI) in REVIVED-BCIS2, and the increased use of implantable cardioverter-defibrillator therapy (54% in REVIVED-BCIS2 vs 18.6% in STICH). Most importantly, patients randomized in REVIVED-BCIS2 were those deemed not suitable for CABG. A true assessment of the comparative effectiveness of CABG and PCI in patients with HF can only be obtained by an appropriately

Table 2. Ongoing randomized controlled trials examining the role of percutaneous coronary intervention in patients with ischemic systolic heart failure.

Trial	ClinicalTrials.gov registration	Study population		Treatment groups		Planned sample size	Primary outcome	Planned follow-up duration	Anticipated completion date
		Inclusion criteria	Key exclusion criteria	Experimental arm	Control arm				
PROTECT IV	NCT04763200	Patients with a chronic coronary syndrome or NSTEMI with LVEF ≤ 40% or STEMI ≥ 24 h and <30 d after symptom onset with LVEF ≤ 30%, planned for complex PCI after heart team discussion	STEMI ≤ 24 h from the onset of ischemic symptoms, mechanical complications of STEMI, cardiogenic shock, CPR related to current admission unless extubated >24 h with full neurologic recovery, contraindication, or inability to Impella placement in both the left and right common femoral arteries	Impella-supported PCI	Standard-of-care PCI with or without IABP	1252	Composite of all-cause death, stroke, MI, or hospitalization for cardiovascular causes	All patients will undergo follow-up for 3 y after randomization. The primary end point will be assessed after the last randomized patient reaches 1 y follow-up	Recruitment expected to complete in 2024 with reporting in 2026
CHIP-BCIS3	NCT05003817	Patients with extensive coronary disease and LVEF ≤ 35% scheduled to undergo complex PCI	Cardiogenic shock or acute STEMI at presentation, contraindication to pLVAD	PCI with LV unloading; pLVAD inserted at the start of procedure	PCI without pLVAD. Alternative mechanical circulatory support devices such as IABP or ECMO will only be permitted in case of complications	250	Composite hierarchical outcome such as death, stroke, spontaneous MI, cardiovascular hospitalization, or periprocedural MI analyzed using a win ratio method	Minimum 12 mo of follow-up (up to 4 y)	Recruitment has recently begun; expected to complete in 2025 with reporting in 2026

CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; pLVAD, percutaneous left ventricular assist device; STEMI, ST-segment elevation myocardial infarction.

powered randomized comparison of the 2 therapies in a cohort of patients deemed potentially suitable for both therapies.

The comparative effectiveness of PCI vs CABG

There is no RCT comparing PCI and CABG in patients with ischemic systolic HF; moreover, low EF was an exclusion criterion in RCTs comparing PCI and CABG for other indications. In the absence of randomized comparisons, we can draw on 2 sources of data to inform evaluations of the 2 modalities for this indication: observational data comparing PCI and CABG in patients with ischemic systolic HF and RCT data comparing PCI and CABG in patients with normal EF.

Observational data comparing PCI and CABG in ischemic systolic HF

Observational data in this domain are conflicting; observational data are also subject to residual confounding and a poor substitute for RCTs. A 2016 observational study[28] compared outcomes of 2126 propensity-matched patients selected from the New York state registries with multivessel disease and EF ≤ 35% who underwent PCI with drug-eluting stents (DES) or CABG. This study demonstrated similar survival with the 2 therapies at a median follow-up of 2.9 years (HR, 1.01; 95% CI, 0.81-1.28; $P = .91$). PCI was associated with increased risk of MI and repeat revascularization but reduced risk of stroke.

A retrospective cohort study from Ontario included 2397 propensity-matched pairs of patients with EF ≤ 35% undergoing CABG or PCI. At a median follow-up of 5.2 years, the risk of all-cause mortality was greater with PCI than CABG (HR, 1.6; 95% CI, 1.3-1.7). Except for stroke, all secondary end points also favored CABG. This benefit for CABG persisted in all tested subgroups and across all sensitivity analyses. A more recent observational study from Sweden also demonstrated improved long-term survival with CABG compared with that with PCI for patients with reduced EF and multivessel CAD.[39] Nevertheless, these studies are susceptible to bias in the form of unmeasured confounders and, importantly, indication bias: it cannot be assumed that included patients were considered eligible for both strategies, and it may be that PCI was performed in patients deemed too high risk for CABG in accordance with guideline recommendations such as seen with the patients in the OPTIMUM registry.

A recent meta-analysis of 18 studies and 11,686 patients[40] suggested similar 30-day mortality between the 2 therapies (HR, 1.18; 95% CI, 0.89-1.56; $P = .25$) but lower long-term (follow-up ≥ 12 months) mortality after CABG than that after PCI in patients with severely reduced EF (HR, 0.70; 95% CI, 0.43-0.85; $P < .01$). CABG was associated with an increased risk of stroke within 30 days (HR, 2.88; 95% CI, 1.07-7.77; $P = .04$) but not beyond 12 months (HR, 1.18; 95% CI, 0.74-1.87; $P = .49$). It should be acknowledged that only 2 of the included studies were RCTs, and these contributed only 139 patients; therefore, this analysis is susceptible to the inherent limitations of observational data when assessing competing therapies.

Observational data comparing PCI and CABG in acute HF

There are limited data comparing outcomes with CABG and PCI for patients with acute HF. A prospective cohort study in Korea[41] evaluated short-term and long-term outcomes in 717 patients admitted with acute HF who underwent revascularization during the index hospitalization with either PCI (n = 590) or CABG (n = 127). Compared with patients who underwent PCI, those who underwent CABG were younger, had lower EF, and were more likely to have diabetes and complex CAD. Patients who received PCI were more likely to present with concomitant ACS/MI.

Table 3. Guideline recommendations for treatment and assessment of coronary artery disease in patients with reduced ejection fraction.

Guideline	Year	Recommendations
ESC guidelines for the diagnosis and treatment of acute and chronic heart failure[15]	2021	• Invasive coronary angiography is recommended in patients with angina despite pharmacologic therapy or symptomatic ventricular arrhythmias (class I, level B) • Invasive coronary angiography may be considered in patients with an intermediate to high pretest probability of CAD and the presence of ischemia in noninvasive stress test (class IIb, level B) • CTCA should be considered in patients with a low to intermediate pretest probability of CAD or those with equivocal noninvasive stress tests to rule out coronary artery stenosis (class IIa, level C) • Noninvasive stress imaging (CMR, stress echocardiography, SPECT, and PET) may be considered for the assessment of myocardial ischemia and viability (class IIb, level B) • 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 IIa, level B) • Coronary revascularization should be considered to relieve persistent symptoms of angina in patients with coronary anatomy suitable for revascularization, despite OMT including antianginal drugs (class IIa, level C) • Coronary revascularization may be considered to improve outcomes after careful evaluation of the individual risk to benefit ratio, including coronary anatomy (class IIb, level C) • PCI may be considered as an alternative to CABG, based on heart team evaluation, considering coronary anatomy, comorbidities, and surgical risk (class IIb, level C)
ACCF/AHA guideline for the management of heart failure[14]	2013	• Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with de novo HF, who have known CAD and no angina, unless the patient is not eligible for revascularization of any kind (class IIa, level C) • When ischemia may be contributing to HF, coronary arteriography is reasonable for patients eligible for revascularization (class IIa, level C) • Coronary artery revascularization through CABG or percutaneous intervention is indicated for patients on GDMT with angina and suitable coronary anatomy, especially for a left main stenosis (>50%) or left main equivalent disease (class I, level C) • CABG to improve survival is reasonable in patients with mild to moderate LV systolic dysfunction (EF = 35%-50%) and significant (≥70% diameter stenosis) multivessel CAD or proximal left anterior descending coronary artery stenosis when viable myocardium is present in the region of intended revascularization (class IIa, level B) • CABG may be considered with the intent of improving survival in patients with ischemic heart disease with severe LV systolic dysfunction (EF < 35%) and operable coronary anatomy whether or not viable myocardium is present (class IIb, level B)
Appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease[58]	2017	• CABG recommended for patients with EF 35%-50% (class IIa, level B) • CABG recommended for patients with EF < 35% without significant left main CAD (class IIb, level B) • Insufficient data to make recommendation for PCI

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; CTCA, computed tomography coronary angiography; EF, ejection fraction; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; LV, left ventricular; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

At a median follow-up of 4 years, propensity-matched analysis of 95 patient pairs suggested lower all-cause mortality with CABG (HR, 0.57; 95% CI, 0.34-0.96; $P = .033$), with a trend toward decreased cardiovascular and HF rehospitalization. Complete revascularization was achieved in 72.4% of patients who underwent CABG compared with 43.5% of patients who underwent PCI. This study illustrates the issues of confounding by indication in observational datasets comparing CABG and PCI, whereby the 2 groups had significant baseline imbalances and further residual confounding that cannot be accounted for by propensity matching; it is likely that many of the patients treated with PCI may not have been candidates for CABG. RCT data in the domain of acute HF are therefore needed.

RCTs comparing PCI and CABG in patients without ischemic systolic HF

There have been many randomized comparisons of PCI vs CABG in a range of clinical settings. A meta-analysis of 5 RCTs comparing PCI with DES and CABG for the treatment of LMCAD, including 4612 randomized patients with a weighted mean follow-up of over 5.5 years, demonstrated equivalent long-term mortality between the 2 therapies (relative risk, 1.03; 95% CI, 0.81-1.32; $P = .78$).[42] Furthermore, 2 trials[43,44] have now reported 10-year mortality after randomization to PCI or CABG, with no difference in outcomes.[45] An individual patient-level meta-analysis of 4 RCTs and 4394 patients with LMCAD treated with PCI or CABG also demonstrated no significant difference in the 5-year rates of all-cause mortality (HR, 1.10; 95% CI, 0.91-1.32; $P = .33$).[46] In Bayesian analyses, there was an 85.7% probability that death at 5 years was less with CABG than that with PCI, but this difference was likely <1% (or a difference of <0.2% per year).

The fractional flow reserve (FFR) vs Angiography for Multivessel Evaluation (FAME) 3 trial randomized patients with 3-vessel CAD to either FFR-guided PCI with second-generation DES or CABG.[47] Patients with significant LMCAD, LVEF < 30%, recent ST-segment elevation myocardial infarction (STEMI), and cardiogenic shock were excluded. Around 18% of patients had LVSD and 22% had at least 1 chronic total occlusion (CTO); the mean SYNTAX score was 26 (18% with SYNTAX score > 32). At 1 year, patients who underwent CABG had lower rates of major adverse cardiac and cerebrovascular events (MACCE) vs those who received FFR-guided PCI (6.9% vs 10.6% [HR for PCI, 1.5; 95% CI, 1.1-2.2; $P = .35$ for noninferiority]). The results remained consistent regardless of baseline LV function (LVEF > 50% vs 30%-50%). Of note, intravascular imaging was used in only 12% of PCI cases; 3-year follow-up data have been published recently.[48] At 3 years, there was no significant difference in the primary end point between the 2 groups (12.0% vs 9.2%; HR, 1.3; 95% CI, 0.98-1.83; $P = .07$). The rates of all-cause mortality were essentially identical (4.1% vs 3.9%; HR, 1.0; 95% CI, 0.6-1.7; $P = .88$). Patients with more severe, extensive CAD (as defined by a functional SYNTAX score > 22) had better outcomes with CABG, whereas those with lower function SYNTAX scores had equivalent outcomes with PCI and CABG.

In contrast to the data for LMCAD, the overall RCT evidence for the treatment of multivessel disease favors CABG over PCI for survival, particularly in patients with diabetes.[49] Older data from the balloon angioplasty and bare-metal stent era suggested no difference in long-term mortality between PCI and CABG other than in patients with diabetes.[50] Subgroup analyses looking at both normal vs reduced LV function and HF vs no HF at presentation suggested consistent treatment effects (P for interaction nonsignificant for both comparisons).

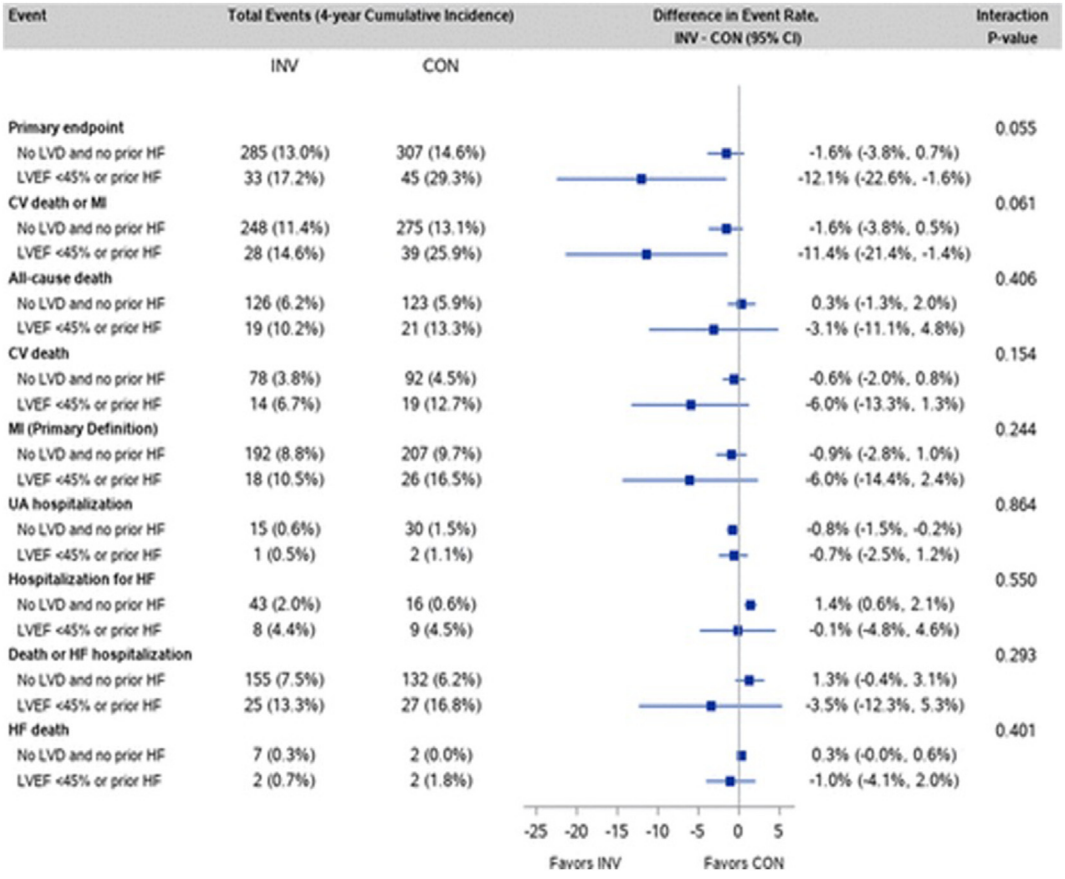


Figure 6.

Association between randomized treatment and outcomes for patients with and without heart failure (HF) or left ventricular dysfunction (LVD) at baseline. A total of 398 patients had a history of HF or LVD (214 in the invasive arm and 184 in the conservative arm). Outcomes in the invasive arm seem to be better in patients with HF or LVD, particularly for the primary end point and for the end point of cardiovascular death or myocardial infarction. Reproduced with permission from Lopes et al.[59]

Observational data comparing PCI and CABG in patients without ischemic systolic HF

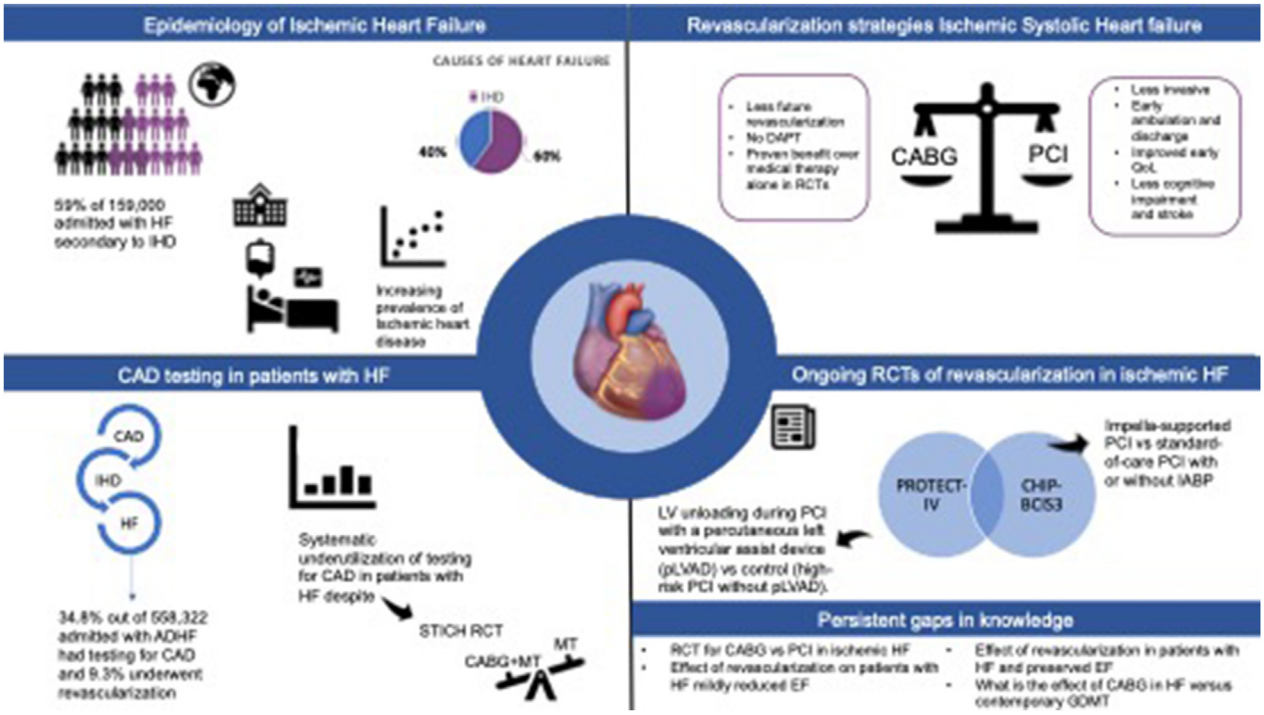
After the landmark SYNTAX trial,[43] the SYNTAX II study[51] evaluated outcomes of contemporary PCI in patients with 3-vessel CAD who had clinical equipoise for either PCI or CABG based on the SYNTAX II score. Outcomes were also compared with historical PCI or CABG controls from the original SYNTAX I trial. Contemporary PCI included the use of second-generation DES, coronary physiology to guide revascularization, intravascular imaging to optimize stent deployment, advanced techniques in bifurcation PCI utilized in accordance with the European Bifurcation Club consensus, and dedicated expert CTO operators using contemporary CTO PCI techniques with the goal of complete revascularization. Patients with significant left main disease and acute MI were excluded. At 5 years, SYNTAX II patients demonstrated significantly lower rates of MACCE compared with SYNTAX I PCI controls (21.5% vs 36.4%; HR, 0.54; 95% CI, 0.41-0.71; $P < .001$), including lower rates of all-cause mortality, cardiac death, MI, repeat revascularization, and stent thrombosis. There were also no significant differences in MACCE rates between the SYNTAX II and SYNTAX I CABG control patients (21.5% vs 24.6%; HR, 0.87; 95% CI, 0.64-1.17; $P = .35$). These data are nonrandomized, and in particular, comparisons with the historical SYNTAX I cohorts should be considered hypothesis-generating only. The mean LVEF was ~58%, so it is also unknown if these results would apply to patients with advanced ventricular dysfunction. These results do, however, support the use of contemporary techniques to optimize PCI outcomes, and future randomized comparisons of PCI and CABG should consider a similar approach to PCI.

In summary, the collective RCT data demonstrate that CABG has a mortality benefit over PCI in patients with multivessel disease and diabetes but no apparent difference is seen in patients with multivessel disease without diabetes or in patients with LMCAD, both with and without diabetes. Observational data suggest that contemporary "state-of-the-art" PCI could potentially afford similar benefits in patients with multivessel disease. However, these results have limited applicability to patients with HF. Combining these findings with inconclusive observational data in HF patients calls for a pressing need for a definitive randomized comparison of PCI and CABG for patients with ischemic systolic HF.

Potential advantages and disadvantages of PCI and CABG in HF

There may be theoretical benefits to a less-invasive therapy. Stroke rates are lower with PCI than those with CABG in RCTs in non-HF populations[29] and in large observational data sets of patients with ischemic systolic HF and multivessel disease.[28] Patients with HF commonly have concomitant cognitive problems[52] and cardiovascular risk factors and may, therefore, be more susceptible to the potentially deleterious neurologic effects of cardiac surgery and cardiopulmonary bypass.[53]

In addition, earlier ambulation and hospital discharge with the less-invasive therapy may translate into improvements in QoL. In previous RCTs comparing PCI and CABG for patients with LMCAD, there was greater early QoL benefit with PCI that attenuated over time.[54]



Central Illustration.

IHD is the most common cause of HF, with rising prevalence worldwide. Coronary evaluation in HF remains widely underutilized, and revascularization remains low despite demonstrated mortality benefit of CABG. While each strategy offers unique advantages, there are currently no direct comparisons on clinical effectiveness between percutaneous versus surgical revascularization. Despite ongoing trials on percutaneous revascularization in ischemic systolic HF, persistent evidence gaps exist. CABG, coronary artery bypass grafting; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; HF, heart failure; IHD, ischemic heart disease; QoL, quality of life; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

Similarly, the OPTIMUM registry demonstrated significantly improved health status after complex PCI among patients who remained alive at follow-up. Significant improvements in angina-related and HF-related QoL were demonstrated at 6 months compared with those at baseline, with 58% of patients having clinically meaningful improvements in angina-related QoL (Seattle Angina Questionnaire summary score $\geq$ 5 points) and 62% having clinically meaningful improvements in HF-related QoL (KCCQ $\geq$ 7.5 points). Compared with patients in the STICH trial, patients in the OPTIMUM registry had poorer self-reported baseline health status (mean KCCQ 55.8 vs 60.3-61.3) but were able to achieve similar levels of HF-specific health status. These benefits were observed regardless of the completeness of revascularization (34.3% of patients achieved a residual SYNTAX score of $\leq$8).

One of the main theoretical advantages of CABG over PCI is the greater likelihood of achieving complete revascularization (CR). This has been proposed as one of the primary mechanisms by which CABG offers benefit over PCI in patients with complex multivessel CAD.[55] Data from RCTs of PCI vs CABG for multivessel or LMCAD in patients without ischemic systolic HF showed that long-term mortality was greater among patients who received PCI with incomplete revascularization vs those who underwent PCI with CR or underwent CABG.[56,57] The 10-year analyses from the SYNTAX study suggest that if CR is achieved with PCI, then survival is comparable with that of CABG.[57] This was true regardless of the presence of diabetes, multivessel CAD, and anatomical complexity (SYNTAX score).

The potential advantages of PCI should be weighed against an increased risk of repeat revascularization procedures in patients undergoing PCI compared with those of CABG. Patients with severe HF are often older and may have calcific CAD, which can lead to increases in both procedural complexity and risk, which are magnified in patients with LVSD. They may also have difficulty tolerating dual antiplatelet therapy due to their elevated bleeding risks. Any reductions in post-operative complications and lengthy recovery with CABG would need to be weighed against potential procedural complications with PCI, and issues of bleeding, graft and stent failure and other complications can only be evaluated in randomized comparisons.

Ongoing trials of revascularization in ischemic systolic HF

New randomized data examining the role of PCI in ischemic systolic HF is being generated (Table 2). Impella-Supported PCI in High-Risk Patients with Complex Coronary Artery Disease and Reduced Left Ventricular Function (PROTECT IV [NCT04763200]) will recruit 1252 high-risk patients with complex CAD and reduced LV function undergoing PCI with a goal of CR. Patients will be randomized to Impella-supported PCI or standard-of-care PCI with or without intra-aortic balloon pump. The primary outcome is the composite of all-cause death, stroke, MI, or hospitalization for cardiovascular causes at the 3-year follow-up. This is not purely a trial of HF patients as eligible patients will have chronic CAD or non-STEMI with EF $\leq$ 40% or STEMI for $\geq$24 hours and <30 days after symptom onset with EF $\leq$ 30%.

The Controlled trial of High-risk coronary Intervention with Percutaneous left ventricular unloading (CHIP-BCIS3 [NCT05003817]), which has just started enrolling, will include 250 participants in the United Kingdom with EF $\leq$ 35% and extensive CAD planned to undergo complex PCI. Patients will be randomized to either LV unloading during PCI with a percutaneous left ventricular assist device or control (high-risk PCI without percutaneous left ventricular assist device). The choice of the device will be at the discretion of the operator.

The persistent evidence gaps and a roadmap for the generation of clinical evidence

Even allowing for the results that will be generated from trials currently recruiting, there remains a need for a randomized comparison of PCI vs CABG for patients with ischemic systolic HF. The 2017 Appropriate Use Criteria for Coronary Revascularization[58] recommends CABG for patients with LVSD (class IIa for patients with EF 35%-50% and class IIb for patients with EF < 35%) and states there are insufficient data to make recommendations for PCI. The 2021 European Society of Cardiology guidelines[15] for HF also provide a IIa recommendation (level of evidence B) for CABG; PCI is given a IIb recommendation as an alternative to CABG, but the level of evidence supporting this recommendation is C. Current guideline recommendations for the assessment and treatment of CAD in patients with HF are summarized in Table 3.

Recalling the factors that define the unmet clinical need of extending revascularization for ischemic systolic HF emphasizes the urgency with which further RCT data are needed: ischemic systolic HF is prevalent, lethal, and costly; revascularization with CABG reduces mortality but is performed in only a small fraction of patients.

Beyond this, there is currently no RCT evidence for revascularization in any form for patients with less severe forms of LVSD or with preserved EF. In a recent substudy of the ISCHEMIA trial,[59] patients with a history of HF and EF < 45% (but ≥35%) were observed to have clinical benefit of invasive compared with conservative management (Figure 6). This substudy included only 398 participants, and the benefit observed was for an initial invasive strategy rather than for revascularization per se. Future clinical trials should focus on the effect of revascularization (both CABG and PCI) in patients with preserved EF and milder forms of reduced EF. Furthermore, trials could focus separately on ambulatory patients with chronic HF and patients hospitalized with acute HF.

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial substudy also raises the issue of imaging studies for patients with CAD and HF because in the STICH trial, the presence of ischemia on imaging did not identify patients with worse prognosis or those who derived greater benefit from CABG.[60] In STICH, there was also no interaction between the presence of viability and the beneficial effect of CABG,[38] although viability testing was not performed at random and was according to the discretion of the recruiting team. Viability was classified as present or absent in a binary fashion and single-photon emission computed tomography and dobutamine echocardiography were utilized. Future trials are needed, focused on other imaging modalities such as magnetic resonance imaging or positron emission tomography. In REVIVED-BCIS2, demonstrable myocardial viability was an inclusion criterion for the trial; however, there was no benefit to revascularization with PCI over medical therapy. There are other potential benefits to the use of advanced imaging modalities such as magnetic resonance imaging, which can also be helpful to exclude infiltrative diseases such as amyloidosis; the benefits of revascularization in such patients is unclear, and patients may be candidates for targeted therapy.

Conclusions

Ischemic systolic HF is an urgent public health issue, with rising prevalence, incidence, and health care costs, and remains the leading cause of death (Central Illustration). These high mortality rates have endured despite advances in medical therapy and implantable cardioverter-defibrillator therapy, which was confirmed in the recent REVIVED-BCIS2 trial. Rates of testing for CAD are alarmingly low in patients with HF, and revascularization is performed in only a minority of patients despite reduction in mortality with CABG as demonstrated in STICHES. PCI has not been shown to improve clinical outcomes compared with medical therapy in stable outpatients with EF < 35%, extensive CAD, and viable myocardium in the BCIS-REVIVED 2 trial, although there was no evidence of increased harm. However, PCI continues to be performed particularly in surgically turndown patients at highest risk of adverse outcomes. There remains no randomized comparison of PCI and CABG in these patients, and there is an urgent need for an adequately powered RCT to establish the comparative clinical effectiveness of PCI and CABG in our sickest patients with ischemic systolic HF in the era of contemporary MT.

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Editor in Chief Alexandra J. Lansky had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Guest Editor Philippe Généreux.

Declaration of competing interest

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Ethics statement and patient consent

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References

1. Nowbar AN, Gitto M, Howard JP, Francis DP, Al-Lamee R. Mortality from ischemic heart disease. *Circ Cardiovasc Qual Outcomes*. 2019;12(6):e005375. https://doi.org/10.1161/CIRCOUTCOMES.118.005375
2. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol*. 2014;171(3):368–376. https://doi.org/10.1016/j.ijcard.2013.12.028
3. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993–1004. https://doi.org/10.1056/NEJMoa1409077
4. Gheorghiade M, Sopko G, De Luca L, et al. Navigating the crossroads of coronary artery disease and heart failure. *Circulation*. 2006;114(11):1202–1213. https://doi.org/10.1161/CIRCULATIONAHA.106.623199
5. Shore S, Grau-Sepulveda MV, Bhatt DL, et al. Characteristics, treatments, and outcomes of hospitalized heart failure patients stratified by etiologies of cardiomyopathy. *J Am Coll Cardiol HF*. 2015;3(11):906–916. https://doi.org/10.1016/j.jchf.2015.06.012
6. Perera D, Clayton T, O'Kane PD, et al. Percutaneous revascularization for ischemic left ventricular dysfunction. *N Engl J Med*. 2022;387(15):1351–1360. https://doi.org/10.1056/NEJMoa2206606
7. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med*. 2011;364(17):1607–1616. https://doi.org/10.1056/NEJMoa1100356
8. Farmer SA, Lenzo J, Magid DJ, et al. Hospital-level variation in use of cardiovascular testing for adults with incident heart failure: findings from the cardiovascular research network heart failure study. *J Am Coll Cardiol Img*. 2014;7(7):690–700. https://doi.org/10.1016/j.jcmg.2014.02.008
9. Doshi D, Ben-Yehuda O, Bonafede M, et al. Underutilization of coronary artery disease testing among patients hospitalized with new-onset heart failure. *J Am Coll Cardiol*. 2016;68(5):450–458. https://doi.org/10.1016/j.jacc.2016.05.060
10. O'Connor KD, Brophy T, Fonarow GC, et al. Testing for coronary artery disease in older patients with new-onset heart failure: findings from get with the guidelines-heart failure. *Circ Heart Fail*. 2020;13(4):e006963. https://doi.org/10.1161/CIRCHEARTFAILURE.120.006963
11. Zheng J, Heidenreich PA, Kohsaka S, Fearon WF, Sandhu AT. Variability in coronary artery disease testing for patients with new-onset heart failure. *J Am Coll Cardiol*. 2022;79(9):849–860. https://doi.org/10.1016/j.jacc.2021.11.061

12. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med*. 2016;374(16):1511–1520. https://doi.org/10.1056/NEJMoa1602001
13. Kosyakovsky LB, Austin PC, Ross HJ, et al. Early invasive coronary angiography and acute ischaemic heart failure outcomes. *Eur Heart J*. 2021;42(36):3756–3766. https://doi.org/10.1093/eurheartj/ehab423
14. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147–239. https://doi.org/10.1016/j.jacc.2013.05.019
15. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726. https://doi.org/10.1093/eurheartj/ehab368
16. Bart BA, Shaw LK, McCants CB, et al. Clinical determinants of mortality in patients with angiographically diagnosed ischemic or nonischemic cardiomyopathy. *J Am Coll Cardiol*. 1997;30(4):1002–1008. https://doi.org/10.1016/S0735-1097(97)00235-0
17. Doenst T, Cleland JGF, Rouleau JL, et al. Influence of crossover on mortality in a randomized study of revascularization in patients with systolic heart failure and coronary artery disease. *Circ Heart Fail*. 2013;6(3):443–450. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000130
18. Mark DB, Knight JD, Velazquez EJ, et al. Quality-of-life outcomes with coronary artery bypass graft surgery in ischemic left ventricular dysfunction: a randomized trial. *Ann Intern Med*. 2014;161(6):392–399. https://doi.org/10.7326/M13-1380
19. Bortnick AE, Epps KC, Selzer F, et al. Five-year follow-up of patients treated for coronary artery disease in the face of an increasing burden of co-morbidity and disease complexity (from the NHLBI Dynamic Registry). *Am J Cardiol*. 2014;113(4):573–579. https://doi.org/10.1016/j.amjcard.2013.10.039
20. Pandey A, McGuire DK, de Lemos JA, et al. Revascularization trends in patients with diabetes mellitus and multivessel coronary artery disease presenting with non-ST elevation myocardial infarction: insights from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry-Get with the Guidelines (NCDR ACTION Registry-GWTG). *Circ Cardiovasc Qual Outcomes*. 2016;9(3):197–205. https://doi.org/10.1161/CIRCOUTCOMES.115.002084
21. Ahmad Y, Lansky AJ, Velazquez EJ. Current landscape and future directions of coronary revascularization in patients with heart failure. *JAMA Cardiol*. 2022;7(6):577–578. https://doi.org/10.1001/jamacardio.2022.0659
22. Flaherty JD, Rossi JS, Fonarow GC, et al. Influence of coronary angiography on the utilization of therapies in patients with acute heart failure syndromes: findings from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2009;157(6):1018–1025. https://doi.org/10.1016/j.ahj.2009.03.011
23. Salisbury AC, Grantham JA, Brown WM, et al. Outcomes of medical therapy plus PCI for multivessel or left main CAD ineligible for surgery. *J Am Coll Cardiol Intv*. 2023;16(3):261–273. https://doi.org/10.1016/j.jcin.2023.01.003
24. Venkitachalam L, Kip KE, Selzer F, et al. Twenty-year evolution of percutaneous coronary intervention and its impact on clinical outcomes: a report from the National Heart, Lung, and Blood Institute–sponsored, multicenter 1985–1986 PTCA and 1997–2006 dynamic registries. *Circ Cardiovasc Interv*. 2009;2(1):6–13. https://doi.org/10.1161/CIRCINTERVENTIONS.108.825323
25. Petrie MC, Jhund PS, She L, et al. Ten-year outcomes after coronary artery bypass grafting according to age in patients with heart failure and left ventricular systolic dysfunction: an analysis of the extended follow-up of the STICH Trial (Surgical Treatment for Ischemic Heart Failure). *Circulation*. 2016;134(18):1314–1324. https://doi.org/10.1161/CIRCULATIONAHA.116.024800
26. Wrobel K, Stevens SR, Jones RH, et al. Influence of baseline characteristics, operative conduct, and postoperative course on 30-day outcomes of coronary artery bypass grafting among patients with left ventricular dysfunction: results from the Surgical Treatment for Ischemic Heart Failure (STICH) trial. *Circulation*. 2015;132(8):720–730. https://doi.org/10.1161/CIRCULATIONAHA.114.014932
27. Bouabdallaoui N, Stevens SR, Doenst T, et al. Society of Thoracic Surgeons Risk Score and EuroSCORE-2 appropriately assess 30-day postoperative mortality in the STICH trial and a contemporary cohort of patients with left ventricular dysfunction undergoing surgical revascularization. *Circ Heart Fail*. 2018;11(11):e005531. https://doi.org/10.1161/CIRCHEARTFAILURE.118.005531
28. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Hannan EL. Revascularization in patients with multivessel coronary artery disease and severe left ventricular systolic dysfunction: everolimus-eluting stents versus coronary artery bypass graft surgery. *Circulation*. 2016;133(22):2132–2140. https://doi.org/10.1161/CIRCULATIONAHA.115.021168
29. Head SJ, Milojevic M, Daemen J, et al. Stroke rates following surgical versus percutaneous coronary revascularization. *J Am Coll Cardiol*. 2018;72(4):386–398. https://doi.org/10.1016/j.jacc.2018.04.071
30. Ahmad Y, Nijjer S, Cook CM, et al. A new method of applying randomised control study data to the individual patient: a novel quantitative patient-centred approach to interpreting composite end points. *Int J Cardiol*. 2015;195:216–224. https://doi.org/10.1016/j.ijcard.2015.05.109
31. Stolker JM, Spertus JA, Cohen DJ, et al. Rethinking composite end points in clinical trials: insights from patients and trialists. *Circulation*. 2014;130(15):1254–1261. https://doi.org/10.1161/CIRCULATIONAHA.113.006588
32. Wollmuth J, Patel MP, Dahle T, et al. Ejection fraction improvement following contemporary high-risk percutaneous coronary intervention: RESTORE EF study results. *J Soc Cardiovasc Angiogr Interv*. 2022;1(5), 100350. https://doi.org/10.1016/j.jscai.2022.100350
33. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med*. 2016;375(23):2223–2235. https://doi.org/10.1056/NEJMoa1610227
34. Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med*. 1996;335(4):217–225. https://doi.org/10.1056/NEJM199607253350401
35. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367(25):2375–2384. https://doi.org/10.1056/NEJMoa1211585
36. Mäkikallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet*. 2016;388(10061):2743–2752. https://doi.org/10.1016/S0140-6736(16)32052-9
37. Perera D, Clayton T, Petrie MC, et al. Percutaneous revascularization for ischemic ventricular dysfunction: rationale and design of the REVIVED-BCIS2 trial: percutaneous coronary intervention for ischemic cardiomyopathy. *J Am Coll Cardiol HF*. 2018;6(6):517–526. https://doi.org/10.1016/j.jchf.2018.01.024
38. Panza JA, Ellis AM, Al-Khalidi HR, et al. Myocardial viability and long-term outcomes in ischemic cardiomyopathy. *N Engl J Med*. 2019;381(8):739–748. https://doi.org/10.1056/NEJMoa1807365
39. Völz S, Redfors B, Angerås O, et al. Long-term mortality in patients with ischaemic heart failure revascularized with coronary artery bypass grafting or percutaneous coronary intervention: insights from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Eur Heart J*. 2021;42(27):2657–2664. https://doi.org/10.1093/eurheartj/ehab273
40. Pei J, Wang X, Xing Z, Zheng K, Hu X. Short-term and long-term outcomes of revascularization interventions for patients with severely reduced left ventricular ejection fraction: a meta-analysis. *ESC Heart Failure*. 2021;8(1):634–643. https://doi.org/10.1002/ehf2.13141
41. Lee SE, Lee HY, Cho HJ, et al. Coronary artery bypass graft versus percutaneous coronary intervention in acute heart failure. *Heart*. 2020;106(1):50–57. https://doi.org/10.1136/heartjnl-2018-313242
42. Ahmad Y, Howard JP, Arnold AD, et al. Mortality after drug-eluting stents vs. coronary artery bypass grafting for left main coronary artery disease: a meta-analysis of randomized controlled trials. *Eur Heart J*. 2020;41(34):3228–3235. https://doi.org/10.1093/eurheartj/ehaa135
43. Thuijs DJFM, Kappetein AP, Serruys PW, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet*. 2019;394(10206):1325–1334. https://doi.org/10.1016/S0140-6736(19)31997-X
44. Park DW, Ahn JM, Park H, et al. Ten-year outcomes after drug-eluting stents versus coronary artery bypass grafting for left main coronary disease: extended follow-up of the PRECOMBAT trial. *Circulation*. 2020;141(18):1437–1446. https://doi.org/10.1161/CIRCULATIONAHA.120.046039
45. Ahmad Y, Howard JP, Arnold AD, et al. Drug-eluting stents versus bypass surgery for left main disease: an updated meta-analysis of randomized controlled trials with long-term follow-up. *Am J Cardiol*. 2020;132:168–172. https://doi.org/10.1016/j.amjcard.2020.06.059
46. Sabatine MS, Bergmark BA, Murphy SA, et al. Percutaneous coronary intervention with drug-eluting stents versus coronary artery bypass grafting in left main coronary artery disease: an individual patient data meta-analysis. *Lancet*. 2021;398(10318):2247–2257. https://doi.org/10.1016/S0140-6736(21)02334-5
47. Fearon WF, Zimmermann FM, De Bruyne B, et al. Fractional flow reserve-guided PCI as compared with coronary bypass surgery. *N Engl J Med*. 2022;386(2):128–137. https://doi.org/10.1056/NEJMoa2112299
48. Zimmermann FM, Ding VY, Pijls NHJ, et al. Fractional flow reserve–guided PCI or coronary bypass surgery for 3-vessel coronary artery disease: 3-year follow-up of the FAME 3 trial. *Circulation*. 2023;148(12):950–958. https://doi.org/10.1161/CIRCULATIONAHA.123.065770
49. Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet*. 2018;391(10124):939–948. https://doi.org/10.1016/S0140-6736(18)30423-9
50. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet*. 2009;373(9670):1190–1197. https://doi.org/10.1016/S0140-6736(09)60552-3
51. Banning AP, Serruys P, De Maria GL, et al. Five-year outcomes after state-of-the-art percutaneous coronary revascularization in patients with de novo three-vessel disease: final results of the SYNTAX II study. *Eur Heart J*. 2021;7:ehab703. https://doi.org/10.1093/eurheartj/ehab703
52. Cannon JA, Moffitt P, Perez-Moreno AC, et al. Cognitive impairment and heart failure: systematic review and meta-analysis. *J Card Fail*. 2017;23(6):464–475. https://doi.org/10.1016/j.cardfail.2017.04.007
53. Selnes OA, Gottesman RF, Grega MA, Baumgartner WA, Zeger SL, McKhann GM. Cognitive and neurologic outcomes after coronary-artery bypass surgery. *N Engl J Med*. 2012;366(3):250–257. https://doi.org/10.1056/NEJMra1100109

54. Baron SJ, Chinnakondepalli K, Magnuson EA, et al. Quality-of-life after everolimus-eluting stents or bypass surgery for left-main disease: results from the EXCEL trial. *J Am Coll Cardiol*. 2017;70(25):3113–3122. https://doi.org/10.1016/j.jacc.2017.10.036
55. Ahmad Y, Petrie MC, Jolicoeur EM, et al. PCI in patients with heart failure: current evidence, impact of complete revascularization, and contemporary techniques to improve outcomes. *J Soc Cardiovasc Angiogr Interv*. 2022;1(2), 100020. https://doi.org/10.1016/j.jscai.2022.100020
56. Ahn JM, Park DW, Lee CW, et al. Comparison of stenting versus bypass surgery according to the completeness of revascularization in severe coronary artery disease: patient-level pooled analysis of the SYNTAX, PRECOMBAT, and BEST trials. *J Am Coll Cardiol Intv*. 2017;10(14):1415–1424. https://doi.org/10.1016/j.jcin.2017.04.037
57. Takahashi K, Serruys PW, Gao C, et al. Ten-year all-cause death according to completeness of revascularization in patients with three-vessel disease or left main coronary artery disease: insights from the SYNTAX extended survival study. *Circulation*. 2021;144(2):96–109. https://doi.org/10.1161/CIRCULATIONAHA.120.046289
58. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;69(17):2212–2241. https://doi.org/10.1016/j.jacc.2017.02.001
59. Lopes RD, Alexander KP, Stevens SR, et al. Initial invasive versus conservative management of stable ischemic heart disease in patients with a history of heart failure or left ventricular dysfunction: insights from the ISCHEMIA trial. *Circulation*. 2020;142(18):1725–1735. https://doi.org/10.1161/CIRCULATIONAHA.120.050304
60. Panza JA, Holly TA, Asch FM, et al. Inducible myocardial ischemia and outcomes in patients with coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol*. 2013;61(18):1860–1870. https://doi.org/10.1016/j.jacc.2013.02.014