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Comprehensive Review

Impact and Implications of Neurocognitive Dysfunction in the Management of Ischemic Heart Failure

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ABSTRACT

Neurocognitive dysfunction is common in heart failure (HF), with 30% to 80% of patients experiencing some degree of deficits in one or more cognitive domains, including memory, attention, learning ability, executive function, and psychomotor speed. Although the mechanism is not fully understood, reduced cardiac output, comorbidities, chronic cerebral hypoperfusion, and cardioembolic brain injury leading to cerebral hypoxia and brain damage seem to trigger the neurocognitive dysfunction in HF. Cognitive impairment is independently associated with worse outcomes including mortality, rehospitalization, and reduced quality of life. Patients with poorer cognitive function are at an increased risk of severe disease as they tend to have greater difficulty complying with treatment requirements. Coronary revascularization in patients with ischemic HF has the potential to improve cardiovascular outcomes but risks worsening neurocognitive dysfunction even further. Revascularization by coronary artery bypass grafting carries inherent risks for delirium, cognitive impairment, neurologic injury, and stroke, which are known to exacerbate the risk of neurocognitive dysfunction. Alternatively, percutaneous coronary intervention, as a less-invasive approach, has the potential to minimize the risk of cognitive impairment but has not yet been evaluated as an alternative to coronary artery bypass grafting in patients with ischemic HF. Therefore, it is paramount to raise awareness of the neurocognitive consequences in ischemic HF and devise strategies for recognition and prevention as an important target of patient management and personalized decision making that contributes to patient outcomes.

Introduction

Heart failure (HF) is associated with a spectrum of cognitive changes, including delirium, mild cognitive impairment (MCI), and dementia. Cognitive impairment adversely affects patients' physical functioning, vitality, quality of life, and ability to comply with treatment requirements or recognize and self-manage disease-worsening symptoms. The American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Clinical Practice Guidelines for the management of HF have provided recommendations for improving physical health,[1,2] but there is limited guidance on neurocognitive management. A recently published ACC Expert Consensus Decision Pathway emphasizes the need for a thorough risk evaluation of patients with heart failure with reduced ejection fraction (HFrEF), together with a subsequent enhancement of guideline-recommended therapies and education to improve patient adherence and clinical outcomes.[3] The document highlights the need for ongoing discussions with patients regarding what they consider unacceptable quality of life as well as their options for palliative care; however,

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICU, intensive care unit; MCI, mild cognitive impairment; PCI, percutaneous coronary intervention; POCD, postoperative cognitive dysfunction.

Keywords: cognitive impairment; coronary artery bypass grafting; coronary revascularization; heart failure; heart failure with reduced ejection fraction; ischemic heart failure; percutaneous coronary intervention; vascular cognitive impairment.

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there is no guidance on the management of cognitive deficit or gold standard tests to assess cognitive function.

In this review, we outline the current evidence and gaps in our understanding of neurocognitive dysfunction in HF and their implications on selection of revascularization strategies in patients with ischemic HFrEF. In addition, disability due to stroke and neurocognitive decline remains the main concern for patients undergoing revascularization. Therefore, it is imperative to increase awareness of neurocognitive status in ischemic HF and formulate strategies for recognition and mitigation as an important target of patient management and patient decision making that contribute to patient outcomes.

Prevalence of neurocognitive dysfunction in HF

In 2 large, pooled cohort analyses comparing patients with HF with HF-free control patients, patients with HF were >60% more likely to have cognitive impairment compared with control patients.[4,5] Data also suggest a greater decline in cognition over time in patients with HF compared with HF-free controls.[5]

Prevalence of cognitive impairment in the HF population varies largely from 30% to 80%.[6,7] This wide range is a result of differences in study design, sample size, inclusion vs exclusion of subjects with delirium/dementia, different patient populations (age and/or severity of HF), inpatient versus outpatient subjects, and differences in cognitive measurements (diagnostic tools and cutoffs). In a pooled analysis including >4000 patients with HF, the prevalence of cognitive impairment in patients with HF was estimated at 43% (95% CI, 30-55).[5] In the HF population, the prevalence of MCI, defined as a transition risk phase between normal aging and dementia involving a single-domain or multiple-domain deficits,[8] was estimated at 32% (95% CI, 22-43).[9] About 1 in 3 people with HF have MCI compared with 1 in 10 people in an age-matched general population without HF.[9]

Cognitive functioning is often categorized into domains that broadly include memory, attention, executive functioning, psychomotor speed, language, and visuospatial skills; however, it remains unclear which neuropsychological abilities are the most impacted by HF and what tests have the sensitivity to measure this impact. A pooled meta-analysis including >8000 patients with HF and effect size data for 20 neuropsychological domains reported that patients with HF compared with HF-free controls have the greatest differences in executive functioning, global cognition, complex psychomotor speed, and verbal memory.[10] The highest effect sizes came from Trail-Making Test-Part B, Cambridge Cognitive Examination (CAMCOG), Symbol Digit Modalities Test, and the California Verbal Learning Test. Neuropsychological patterns observed in this study demonstrate diffuse cognitive involvement with higher-level processes being most affected, indicating that completion of everyday tasks may be more effortful for patients with HF.[10]

Prevalence of cognitive impairment appears to be similar in HFrEF and HF with preserved ejection fraction (HFpEF), demonstrating cognitive deficits in the domains of attention/processing speed, language/verbal fluency, and executive functioning[11]; however, in patients with HFrEF, older age (≥63 years) and lower ejection fraction (EF) (<30%) were significantly associated with severity of cognitive decline and worse memory.[12,13] In multivariable analyses, the components of memory most affected by low EF were verbal delayed recall and recognition.[12] When compared with coronary artery disease (CAD) without HF, HFrEF was associated with weaker global cognition and was marginally associated with delayed memory recall.[14] Likewise, other studies found that decrease in cardiac output,[15] longer duration of HF,[16] and higher New York Heart Association class of disease[17] were associated with the severity of the cognitive decline. Whereas the incidence of dementia is relatively low at baseline, affecting approximately 0.8% of patients with HFrEF,[18] the risk increases over time with some MCI progressing to dementia.[19]

Mechanism of neurocognitive dysfunction

The primary pathophysiologic mechanism proposed for cognitive deficits in HF is chronic cerebral hypoperfusion.[20,21] Cerebral blood flow depends on cardiac output, blood pressure and cerebral reactivity. In HF, low cardiac output, low systolic pressure and impaired autoregulatory mechanisms lead to inadequate cerebral perfusion and cerebral hypoxia, causing neuroanatomic and neurophysiological alterations.[22-24] Injury and brain tissue loss have been described in areas involved in cognition such as frontal cortex, hippocampus, insular cortex, and cerebellum.[25-27]

A high burden of cardiovascular risk factors, such as advanced age, hypertension, diabetes, dyslipidemia, peripheral arterial disease, valvular heart disease, obesity, and atrial fibrillation (AF) may also contribute to the progression of cognitive decline in patients with ischemic HF.[20,28-30] The prevalence of stroke is higher than that in the general population, varying between 7% and 10% in both HFrEF and HFpEF.[30] The most frequent cause for cardioembolic stroke in patients with HF is thrombus formation due to left ventricular hypokinesia and/or AF. HF induces a state of hypercoagulability through decreased blood flow velocity, increased thrombocyte aggregation, reduced fibrinolysis, endothelial dysfunction, and sustained inflammatory activation, which increases the risk of developing thromboembolism.[31] Among patients with AF, those with concomitant HFrEF have a 2-fold increase in the incidence of stroke compared with those with AF alone.[32] AF is an independent risk factor associated with a 1.7-fold greater risk of cognitive decline and a 2.3-fold increased risk of dementia.[33] The occurrence of stroke itself seems to be the trigger of rapid cognitive decline, with reports estimating that 10% of patients had dementia before first stroke, 10% developed new dementia soon after first stroke, and more than a third had dementia after recurrent stroke.[34]

Cognitive impairment and depression are common among patients with HF and are frequently linked to poor outcomes.[35] The relationship between HF, cognitive impairment, and depression is complex as cognitive impairment can exacerbate HF, just as HF can worsen cognitive impairment and depression. It is unclear whether cognitive impairment acts as a mediator or a confounder in the HF-depression connection. There is a possibility that HF and depression do not share common neurologic pathways and may manifest distinct cognitive deficits. Present HF guidelines recommend heightened awareness of depression in HF cases, advocating for routine depression screening during hospitalization and follow-up care for patients with HF.[1]

Although the causes of cognitive impairment are multifaceted, it is important to note that medication for HF may increase the risk of cognitive disorders, especially in elderly patients. To assess the potential long-term impacts on cognitive function, more extensive studies are required, particularly concerning β-blockers and the combined angiotensin receptor and neprilysin inhibitor. Such research is crucial due to concerns about potential imbalances in neurotransmitters, amyloid deposition, and the risk of macular degeneration.[36,37]

A cerebral lesion may manifest as ischemic stroke but also may remain clinically undetected as a "silent stroke." The prevalence of silent stroke is 2-fold to 4-fold higher in patients with HF compared with an age-matched population without HF.[38] Silent strokes, however, are not truly silent as they have been linked to deterioration of cognitive function and dementia over time and are more appropriately referred to as "covert."[39,40]

Cognitive impairment correlates with worse acute and long-term outcomes

A large body of evidence supports the association of cognitive impairment with poorer clinical outcomes in patients with HF. In patients hospitalized with HF, delirium was identified as an independent

predictor of increased in-hospital mortality. In a propensity score–matched analysis of 153,023 patients with HF from the Nationwide Inpatient Sample database, patients hospitalized for HF with concomitant diagnosis of delirium had a 64% increased risk of in-hospital mortality, 47% longer stay, and 44% excess hospital cost.[41] Potential mechanisms by which delirium can increase mortality include prolonged hospital and intensive care unit (ICU) stay, infections, and medications used to treat delirium. Among ICU patients requiring mechanical ventilation, delirium was identified as an independent predictor of long-term cognitive impairment.[42]

In a study including 1113 patients (aged ~78 years) hospitalized for HF, in-hospital mortality occurred in 18% of subjects with cognitive impairment and 3% of subjects with normal cognition ($P < .0001$), whereas 1-year mortality was 27% in the cognitive impairment group and 15% in the normal cognition group ($P < .0001$).[43] In multivariable regression models, cognitive deficits were associated with a 5-fold increase in-hospital mortality (risk ratio, 4.9; 95% CI, 2.9-8.3) after adjusting for several potential confounders.[43] Similar results were observed in another study including 166 stable outpatients (aged ~65.6 years) with left ventricular ejection fraction (LVEF) < 40%, where 1-year mortality was 13%, and in logistic regression analysis, poorer global cognitive score as determined by the Mini-Mental State Examination, working memory, memory, psychomotor speed, and executive function were significant predictors of mortality.[44] In addition, patients with HF who experienced severe dependence for basic activities of daily living were 42% more likely to die at 12 months (hazard ratio [HR], 1.42; $P = .002$).[45] At 3-year follow-up, the risk of death increased by 82% in patients with MCI (HR, 1.82; $P = .038$) and by 2.7-fold in patients with severe cognitive impairment (HR, 2.71; $P = .011$).[46]

Patients with HF and cognitive impairment are also at a higher risk of 30-day rehospitalization (pooled risk ratio, 1.63; 95% CI, 1.19-2.24), and the risk remains high after excluding patients with HF and dementia.[47]

The link between neurocognitive dysfunction and poor outcomes is, however, multifactorial and may account for advanced HF disease, greater comorbidities, and limited ability of these patients to adhere to treatment plans, including compliance with dietary and fluid restrictions and pharmacologic management. Therefore, defining cognitive health is especially important for patients with HF, who often need additional care and whose treatment compliance is essential for their survival.[48]

Effect of ischemic HF treatment selection on neurocognition

Revascularization by coronary artery bypass grafting

Revascularization in ischemic HFrEF can improve left ventricular function and clinical outcomes. The only contemporary randomized trial that provided evidence for the management of patients with severe left ventricular dysfunction (LVEF ≤ 35%) and CAD amenable to revascularization was the STICH (Surgical Treatment for Ischemic Heart Failure) trial, comparing revascularization by coronary artery bypass grafting (CABG) with medical therapy. At a median extended follow-up of 9.8 years achieved in 1187 patients, CABG in addition to guideline-directed medical therapy showed a long-term mortality benefit compared with medical therapy alone. Patients who underwent CABG had significantly fewer all-cause deaths (HR, 0.84; 95% CI, 0.73-0.97; $P = .02$) and cardiovascular-related deaths (HR, 0.79; 95% CI, 0.66-0.93; $P = .006$) than those in the medical therapy alone group[49]; however, the risk of death within 30 days postrandomization was 3-fold higher in the CABG group than that in the medical therapy alone group (HR, 3.12; 95% CI, 1.33-7.31; $P = .006$), and a significant mortality benefit favoring CABG did not begin to accrue until after 2 years following surgery.[50] Left ventricular size, renal dysfunction, advanced age, and AF/atrial flutter were significant preoperative predictors of mortality within 30 days.[51] Unfortunately, the STICH trial did not report the impact of CABG on cognitive function.

CABG and neurologic procedural complications

Beyond potential short-term mortality risk, CABG carries inherent risks for procedural complications known to contribute to further deterioration of neurocognitive status, including delirium, cognitive impairment, neurologic injury, and stroke. In the absence of specific data in patients with HF undergoing CABG, existing data on neurologic complications post-CABG in the general population are presented below.

Delirium. The incidence of delirium after CABG varies widely from 3% to >50%, perhaps reflecting differences in patient characteristics, definitions, and methods of observation.[52,53] Compared with orthopedic, abdominal, and head and neck surgery types, the delirium rate after CABG is nearly 2 times higher.[54] The presence of delirium doubles hospital length of stay, increases ICU time, and predicts worse mortality.[53,55] In older patients, delirium was associated with subsequent cognitive dysfunction and dementia.[56,57] In a study including 114 patients (aged ≥70 years) who underwent cardiac surgery, 30 (26.4%) developed dementia during the 5-year follow-up; 87% of those who later developed dementia had postoperative delirium.[56]

Postoperative cognitive dysfunction. Postoperative cognitive dysfunction (POCD) incidence at 1 to 3 months after cardiac surgery varies from approximately 10% to 16% (for a drop of 2 reliable change index units) to approximately 40% (estimate for a 1 SD drop in test scores).[52] Most studies show POCD rates decrease over time from 3 months to 1 year after surgery. In an early study of 261 patients undergoing CABG, 53% of patients experienced a significant cognitive decline (≥1 SD decline in neurocognitive scores) at discharge. When followed longitudinally, 36%, 24%, and 42% of these patients had a significant cognitive decline at 6 weeks, 6 months, and 5 years, respectively.[58] A subsequent systematic review including 3373 patients determined that after CABG, 34.0% of patients had early POCD and 27.6% of patients had late cognitive dysfunction.[59] The magnitude of the neurocognitive changes after CABG, however, remains controversial due to inconsistencies in definitions.[60] Long-term cognitive decline after CABG was less frequently investigated, with a few reports suggesting that some patients remain cognitively stable in the first year following CABG while others face a rapid decline in cognition beyond 6 months postsurgery.[61,62] Importantly, there has been no prospective, long-term, randomized study applying standardized cognitive measurement tools in patients with HF undergoing revascularization.

The key risk factors for delirium and cognitive decline following CABG were reported in a large, pooled meta-analysis including >60,000 patients in the general population.[62] The risk factors for delirium included preoperative cognitive impairment, depression, stroke history, higher European System for Cardiac Operative Risk Evaluation (EuroSCORE), increased intubation time, postoperative presence of arrhythmia, and longer ICU stay. The risk factors for acute cognitive decline included preoperative depression, older age, increased intubation time, postoperative presence of delirium, and longer ICU stay. The presence of preoperative depression was a common risk factor for both delirium and cognitive decline; it at least doubled the risk of post-CABG delirium in hospital and cognitive decline acutely and up to 6 months following surgery.[62] In patients analyzed in the Neuropsychiatric Outcomes After Heart Surgery study, the presence of depression at baseline increased the risk of cognitive decline at 1 month by 41.7% compared with a 13.1% risk in the absence of depression.[63] When adjusted for age, sex, education, and/or cognitive performance, results showed an even greater discrepancy,

Table 1. Periprocedural mechanisms accountable for stroke and neurocognitive deficits associated with CABG vs PCI.

Mechanism	CABG	PCI
Proembolic		
Manipulation of the aorta	Cannulation/crossclamping of the aorta leads to endovascular injury and can dislodge atherosclerotic plaque. Techniques avoiding aortic manipulation are associated with less stroke.[68,69]	Endovascular approach avoids need to manipulate aorta
New-onset atrial fibrillation	Common after CABG and can increase the risk of stroke	Not associated with PCI
Anticoagulation reversal	Protamine, commonly used in CABG, has not been associated with increased stroke in patients undergoing carotid endarterectomy, although use of tranexamic acid was shown to be associated with seizure risk after CABG[70,71]	Not needed for PCI. Common use of DAPT following the procedure is likely protective[72]
Hypoperfusion		
Intraoperative cerebral hypoperfusion	Cerebral hypoperfusion is possible, especially in patients with poor cerebral blood flow autoregulation ability[73,74]	Not associated with PCI
Inflammation		
Neuroinflammation after procedure	The postsurgical inflammatory response, exacerbated by contact with inorganic materials during CPB and prolonged anesthesia, can disrupt the blood-brain barrier[75,76]	Typically requires only conscious sedation

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

with subjects depressed at the time of surgery having more than 6 times increase in the odds of cognitive decline relative to euthymic patients.

Stroke. In >150,000 CABG procedures performed in the Unites States in 2018, periprocedural stroke was reported in 1.3% of procedures.[64] This rate was higher in combined procedures, with additional aortic valve repairs, mitral valve repairs, and mitral valve replacements performed in combination with CABG raising these rates to 2.3%, 2.2%, and 3.4%, respectively.[64,65] Using optimized criteria for poststroke cognitive impairment, a study showed that in a cohort of patients who survived stroke, 80% of them experienced MCI and 20% had dementia at 6-month follow-up.[66] The elderly are at a higher risk of experiencing perioperative neurocognitive deficits and stroke following CABG.[67]

Patient-specific risk factors for perioperative stroke include age, hypertension, hyperlipidemia, diabetes mellitus, smoking, heart failure, renal disease, AF, and previous stroke or transient ischemic attack.[65] Perioperative mechanisms accountable for stroke and neurocognitive deficits associated with CABG include proembolic aortic manipulation, postoperative AF, and intraoperative hypoperfusion (Table 1).[68-76] Reduction of aortic manipulation by avoiding aorta cannulation with no or partial aortic clamping in off-pump CABG procedures did not show a significant difference in stroke rates compared with traditional on-pump CABG with aortic cross-clamping; however, complete elimination of all manipulation with aortic "no-touch" or anaortic off-pump CABG technique reduced postoperative stroke by 78% compared with traditional on-pump CABG and by 52% compared with off-pump CABG.[68] Intraoperative cerebral hypoperfusion and a postprocedural low cardiac output may also contribute to the total cognitive insult associated with CABG. Perioperative complications such as neurovascular damage and neuroinflammation are associated with POCD and dementia after CABG.[77]

Although a diverse array of mechanical circulatory support devices is readily accessible, it is important to acknowledge the significant comorbidities that can accompany their use, making prudent device selection crucial for achieving favorable outcomes. Despite these challenges, it is undeniable that mechanical circulatory support has led to substantial improvements in the outcomes of patients with the highest risk profiles undergoing coronary revascularization.[78] Nonetheless, employing these devices could introduce an additional risk of stroke or potentially reduce cerebral perfusion that ultimately affects cognitive function.

Revascularization by percutaneous coronary intervention

Revascularization by percutaneous coronary intervention (PCI) is a less-invasive approach that has demonstrated equivalence to CABG in a range of clinical scenarios[79] and has also demonstrated lower rates of periprocedural complications (including stroke) in non-HF populations.[80,81] PCI is not an established revascularization approach in the HF population according to current guidelines. Expanding revascularization access for patients with HF with underlying CAD to PCI may improve outcomes and reduce procedural complications. In addition, revascularization by PCI reduces the risk of perioperative mechanisms accountable for stroke and neurocognitive deficits associated with CABG (Table 1); however, challenges exist because CABG has the advantage of overcoming chronic occlusions, especially in multivessel disease, and requires fewer repeated revascularizations, which can pose a burden due to recurrent hospitalization and periprocedural risk.[82] Patients with ischemic HFrEF already exhibit an increased risk profile for perioperative events, and an early recognition of the risks would be beneficial for short-term and long-term outcomes. There are no randomized controlled trials to inform optimal revascularization strategy (PCI vs CABG) in patients with ischemic HFrEF.

In a non-HF population, compelling evidence of significantly lower risk of periprocedural strokes with PCI than that with CABG is provided by a patient-data pooled analysis including 11,518 patients with multivessel and left main CAD from 11 randomized trials.[83] At 30 days, the rates of stroke were 0.4% after PCI and 1.1% after CABG (HR, 0.33; $P < .001$) (absolute incremental risk of ~0.7% with CABG). At 5-year follow-up, stroke remained significantly lower after PCI (2.6% vs 3.2%; HR, 0.77; $P = .027$). Of note, patients who experienced a stroke within 30 days of the procedure had significantly higher 5-year mortality vs those without a stroke after both PCI (45.7% vs 11.1%; $P < .001$) and CABG (41.5% vs 8.9%; $P < .001$).[83] The stroke rates at 5 years were comparable between patients on single or dual antiplatelet therapy independent of revascularization strategy. Moreover, the initial short-term benefit of PCI vs CABG on the composite of all-cause mortality or stroke was lost at 5-year follow-up in patients with diabetes or with high SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) scores.[83]

In the ischemic HFrEF population, limited data are available from real-world registries and propensity score–matched analyses comparing PCI with CABG (Table 2).[82,84-93] Among 11 studies, 6 showed similar stroke rates in both groups, 2 reported numerically lower stroke rates with PCI, and 3 studies provided strong evidence of lower risk of stroke with PCI in comparison with CABG. Significantly lower rates of stroke after PCI than with CABG at 30 days were reported in 2 propensity score–matched analyses (0.1% vs 1.8%; HR, 0.05; $P = .004$; 0.7% vs 1.3%; HR, 0.5; $P = .02$)[84,91] and a multicenter retrospective analysis (0.3% vs 3.6%; $P < .001$)[89] (Table 2). At long-term follow-up, significantly lower stroke rates with PCI were reported in 2 propensity score–matched analyses (Table 2).[84,91] In one analysis, at a median of

Table 2. Stroke rate in PCI vs CABG in patients with HFrEF and coronary artery disease.

Study	Procedures performed	Follow-up	Arm	Stroke rate, %	PCI vs CABG	
					HR (95% CI)	*P*
Bangalore et al[84] (propensity score–matched analysis: New York State registries)	January 2008-December 2011	30 d	CABG	1.8	0.05 (0.01-0.39)	.004
			PCI	0.1		
		2.9 y (median)	CABG	5.9	0.57 (0.33-0.97)	.04
			PCI	3.9		
Bianco et al[85] (propensity score–matched analysis: University of Pittsburgh Medical Center registry)	2011-2018	30 d	CABG	2.5	—	.63
			PCI	3.1		
Marui et al[86] (CREDO-Kyoto PCI/CABG Registry Cohort-2)	January 2005-December 2007	5.12 y (median)	CABG	8.0	0.93 (0.30-2.85)	.89
			PCI	8.0		
Thuijs et al[87] (EXCEL trial, HFrEF subgroup analysis)	September 2010- March 2014	30 d	CABG	0.0	—	—
			PCI	0.0		
		3 y	CABG	4.2	0.75 (0.13-4.49)	.74
			PCI	5.5		
Hawranek et al[88] (pooled analysis: COMMIT-HF and ICSD registries)	NR	In-hospital	CABG	0.8	—	.72
			PCI	0.4		
		30 d	CABG	1.1	—	.42
			PCI	0.4		
		1 y	CABG	2.3	—	.97
			PCI	2.5		
Iribarne et al[89] (multicenter retrospective analysis: NNEDCSG)	2004-2014	30 d	CABG	3.6	—	<.001
			PCI	0.3		
Kang et al[90] (patient-level meta-analysis; pooled data: IRIS-MAIN, IRIS-DES, and Asan Multivessel registries)	NR	5 y	CABG	4.1	1.52 (0.73-3.125)	.26
			PCI	6.4		
Buszman et al[82] (REHEAT prospective trial)	January 2002-December 2003	30 d	CABG	1.8	—	.9
			PCI	0.0		
		30 d-1 y	CABG	1.9	—	.9
			PCI	0.0		
Sun et al[91] (propensity score–matched cohorts: CorHealth Ontario registry)	October 2008-December 2016	30 d	CABG	1.3	0.5 (0.3-0.9)	.02
			PCI	0.7		
		5.2 y (median)	CABG	6.1	0.7 (0.5-0.9)	.006
			PCI	4.0		
Toda et al[92] (observational single-center study)	October 1992-September 1997	30 d	CABG	4.0	—	.999
			PCI	4.0		
Yang et al[93] (retrospective, single-center, propensity score–matched population)	January 2003-December 2010	2.67 y (median)	CABG	5.0	0.94(0.22-4.04)	.934
			PCI	5.0		

CABG, coronary artery bypass grafting; COMMIT-HF, COnteMporary Modalities in Treatment of Heart Failure; EXCEL, Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; ICSD, Institutional Cardiac Surgery Database; IRIS-DES, Interventional Research Incorporation Society-drug-eluting stents; IRISMAIN, Interventional Research Incorporation Society-Left MAIN Revascularization; NNECDSG, The Northern New England Cardiovascular Disease Study Group; NR, not reported; PCI, percutaneous coronary intervention; REHEAT, Revascularization in Ischemic Heart Failure Trial.

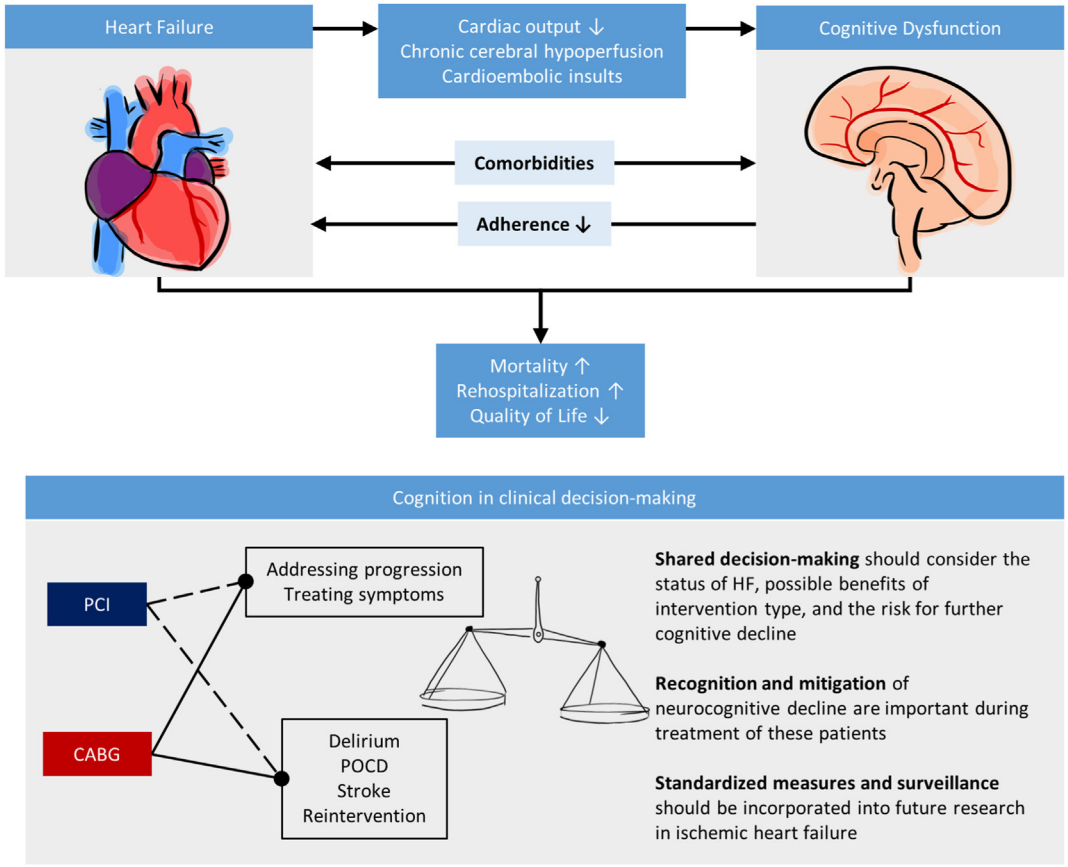
2.9 years postprocedure, PCI was associated with a lower risk of stroke compared with CABG (3.9% vs 5.9%; HR, 0.57; $P = .04$), a similar risk of death (25.2% vs 21.0%; HR, 1.01; $P = .91$), a higher risk of myocardial infarction (11.3% vs 5.6%; HR, 2.16; $P = .0003$), and a higher risk of repeat revascularization (22.3% vs 11.5%; HR, 2.54; $P < .0001$).[84] It is worth mentioning that the ongoing PROTECT IV (Impella-Supported PCI in High-Risk Patients With Complex Coronary Artery Disease and Reduced Left Ventricular Function) trial aims to compare Impella-assisted complete revascularization with PCI to complete revascularization with PCI without any planned hemodynamic support in HFrEF patients for the primary composite end points of all-cause death, stroke, myocardial infarction, or hospitalization for cardiovascular causes.[94] The PROTECT IV trial is anticipated to provide high-quality evidence to guide management and improve clinical outcomes in ischemic HFrEF with complex CAD. Nevertheless, a potential risk of stroke or silent brain infarct may exist due to the iatrogenic cerebral embolization caused by the Impella device crossing the aortic valve.

PCI is a lesser-invasive revascularization strategy compared with CABG and is expected to have a reduced impact on cognitive function; however, little is known about the impact of PCI on neurocognitive outcomes. In a substudy of the Stent or Surgery trial for multivessel disease in non-HF population, evaluation of cognitive function at 6 and 12 months after the procedure failed to demonstrate a significant difference in neuropsychological outcomes in patients randomized to PCI vs CABG.[95] Nonetheless, testing at 6 months postprocedure does not rule out the possibility of early neurocognitive deficit. In a meta-analysis assessing the prevalence of new postoperative silent brain lesions on diffusion-weighted magnetic resonance imaging, the mean number of lesions per patients was numerically higher following CABG compared with that after PCI (2.11 ± 0.25 vs 1.88 ± 1.02). The pooled postoperative rates of covert brain lesions were 0.25 (95% CI, 0.15-0.35) after CABG and 0.14 (95% CI, 0.10-0.19) after PCI.[96] The occurrence, number, location, and the size of silent brain lesions are likely to be important factors in determining the patient risk of future neurologic complications.

Why are revascularization decisions in ischemic HF important?

Revascularization represents a major opportunity to improve outcomes in patients with ischemic HFrEF. CABG is currently recommended as the first revascularization strategy of choice, largely owing to its proven long-term mortality benefit; however, many patients with HF are deemed high risk, and only a minority are ever referred to revascularization.[49] Having additional revascularization options for these patients is critical.

Revascularization is underutilized as a therapy for ischemic heart failure as almost three-quarters of patients with new-onset HF do not receive any ischemic CAD testing within 90 days of index admission.[97,98] In a large claims data set, among 67,161 patients identified with new-onset HF, fewer than a third (27%) underwent testing for CAD, and <5% actually underwent revascularization.[97] Several factors may



Central Illustration.
Neurocognitive dysfunction and the management of ischemic heart failure. CABG, coronary artery bypass grafting; HF, heart failure; PCI, percutaneous coronary intervention; POCD, postoperative cognitive dysfunction.

account for the underutilization of revascularization for ischemic HF. First, while European myocardial revascularization guidelines recommended CABG as a first-line strategy for ischemic HF and LVEF of ≤35% since 2019,[99] US guidelines introduced this recommendation in 2022.[100] Second, despite the long-term mortality benefit demonstrated at 10 years, the inherent procedural risks associated with CABG continue to limit the use of surgical revascularization.

Given that the prevalence of CAD among patients with HF is 65%, current guidelines recommend noninvasive imaging to detect myocardial ischemia in patients presenting with new-onset HF and coronary angiography in patients with HF eligible for revascularization.[1] Despite guidelines, CAD testing is underutilized. Fewer than 1 in 10 patients (7.9%) with new-onset HF received noninvasive ischemic testing (defined as exercise or pharmacologic testing with or without an imaging modality such as myocardial perfusion imaging or echocardiography) during index hospitalization and only 14.6% of patients receive testing at 90 days after the index admission.[97] By contrast, patients with baseline CAD were more likely to undergo an invasive CAD assessment (defined as coronary angiography) than those without baseline CAD during the index hospitalization (9.7% without CAD vs 12.3% with known CAD; $P < .001$) and within 90 days (15.4% without CAD vs 17.5% with known CAD; $P < .001$).[97] In multivariable analyses, smoking and HFrEF were associated with greater odds of invasive ischemic CAD testing. In addition, data from the Get With The Guidelines—Heart Failure registry showed that testing for CAD among older (aged ≥65 years) patients hospitalized for new-onset HF occurred in 39% of patients, and half of them had HFrEF (LVEF ≤ 40%).[98]

Given that CAD is the most common cause of HF, expanding revascularization access for patients with ischemic HF is warranted. PCI is a less-invasive approach than surgical CABG and has the potential to reduce the risk of procedural complications and improve clinical outcomes. The European guidelines recommend revascularization by PCI in HFrEF (EF ≤ 35%) after careful evaluation of comorbidities and coronary anatomy, in the presence of viable myocardium, and when expected completeness of revascularization can be achieved[99]; however, robust evidence of the clinical benefits of PCI in ischemic HFrEF is lacking. The REVIVED-BCIS2 (Revascularisation for Ischemic Ventricular Dysfunction) trial, which compared PCI with medical therapy in CABG-ineligible patients with ischemic HFrEF failed to demonstrate a benefit of PCI in a selected population.[101]

In addition, a less-invasive revascularization strategy has the potential to reduce perioperative complications associated with neurologic deficits and mitigate the cognitive impairment common in the HF population; however, whether PCI reduces neurologic events in ischemic HFrEF compared with CABG has not yet been investigated in a randomized trial. Long-term disability due to stroke and neurocognitive decline remains the main concern of patients undergoing invasive cardiac procedures.[102] In 1 large-scale survey, >80% of respondents stated that disability from stroke was their main concern of invasive cardiac procedures, and they would sacrifice longevity for improved quality of life. These considerations may contribute to patients' preference for a less-invasive revascularization strategy.[18]

Finally, it is important to emphasize the assessment and management of neurocognitive dysfunction in patients with HF as a pivotal aspect for enhancing treatment adherence, overall quality of life, and outcomes. This includes the implementation of routine cognitive screening both before and after interventions, facilitating referrals for comprehensive neuropsychological evaluations and incorporating

cognitive rehabilitation programs as essential strategies.[40,103] In addition, there is a growing recognition of the significance of preoperative cognitive training, or prehabilitation, in optimizing surgical outcomes, particularly in cardiac surgery. Recent studies indicate a potential reduction in postoperative delirium incidence among elderly surgical patients through this approach.[104] Furthermore, promising results have been observed with cognitive-behavioral therapy for addressing anxiety and depression, suggesting its potential to complement rehabilitation programs and foster self-care practices.[105,106] Several therapeutic avenues for HF, including both pharmacological and non-pharmacological/behavioral strategies aimed at enhancing cognitive function, require thorough evaluation. Personalized approaches, tailored to each patient's specific needs and circumstances, are essential for optimizing results in managing neurocognitive dysfunction in HF.

Conclusion

Recognition and mitigation of neurocognitive decline in patients with ischemic HFrEF is often overlooked, but this is a high priority to this patient population (Central Illustration). Invasive revascularization strategies carry the risk of worsening cognitive function in a population already predisposed to neurocognitive deficits. Disabilities due to stroke and neurocognitive deficits remain the main concern of these patients, who would prefer to sacrifice longevity for a less-invasive approach and better quality of life. Therefore, devising strategies for recognition and mitigation of neurocognitive decline as an important target of patient management and personalized decision making may contribute to improved outcome in the HF population. Agreement on standardized measures and broader surveillance of neurocognitive status are of great importance moving forward and should be incorporated in the design of future studies.

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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 interests

Yousif Ahmad is a consultant for Shockwave Medical and Cardiovascular Systems Inc and is on the Medical Advisory Board for Boston Scientific. Other authors reported no financial interests.

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Ethics statement and patient consent

This work adhered to relevant ethical guidelines.

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