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Comprehensive Review

Mechanical Circulatory Support Devices in Acute Myocardial Infarction-Cardiogenic Shock: Current Studies and Future Directions

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ABSTRACT

Cardiogenic shock (CS) caused by acute myocardial infarction (AMI) accounts for most deaths in the population with AMI and continues to be associated with high short-term mortality. Several temporary mechanical circulatory support (MCS) devices have been developed to treat CS and studied in randomized controlled trials (RCTs) of patients with AMI-CS. Unfortunately, none of these RCTs has demonstrated an improvement in survival with temporary MCS in AMI-CS. Potential reasons for these negative results in RCTs are numerous and reflect the challenges of enrolling critically ill patients with CS. Researchers have used observational study designs to provide insights about outcomes associated with the use of temporary MCS in AMI-CS. These observational studies have yielded conflicting results, in some cases contrary to the results of RCTs. Several limitations pertinent to both RCTs and observational analyses, mostly relating to selection bias and failure to consider unmeasured confounding variables and population heterogeneity, preclude drawing strong inferences regarding the effects of temporary MCS on survival in populations with AMI-CS. Understanding these limitations is essential to correctly interpreting the literature regarding temporary MCS to treat AMI-CS and is necessary to inform the design of future studies that will potentially provide stronger evidence. Optimally matching temporary MCS devices to the needs of individual patients with AMI-CS will presumably be more successful than indiscriminate application in unselected patients. In this review, we discuss the existing literature on temporary MCS to treat AMI-CS and describe the specific challenges that must be overcome to develop an improved evidence base for guiding clinical practice.

Introduction

Cardiogenic shock (CS) affects 5%-10% of patients with acute myocardial infarction (AMI), accounting for most in-hospital deaths in this population.[1-3] Despite advances in percutaneous coronary intervention (PCI) and systems of care in AMI, the prevalence of CS caused by AMI (AMI-CS) has not declined and may in fact be rising.[4-6] The short-term mortality in patients with AMI-CS remains high (approximately 30%-50% at 30 days) despite early coronary artery reperfusion and use of increasingly sophisticated temporary mechanical circulatory support (MCS) devices.[5,6] Few randomized controlled trials (RCTs) have adequately tested interventions in AMI-CS, and most have shown negative results.[7,8] Even the groundbreaking SHOCK trial failed to show a difference in the primary outcome of 30-day survival, although survival at 6 months improved with early revascularization.[9] Nonetheless, mortality remains high even after successful reperfusion therapy, so enhanced therapies and treatment strategies are urgently needed to improve the dismal outcomes for patients with AMI-CS.

During the past decade, there has been expanding utilization of MCS in AMI-CS.[10-12] However, although MCS devices can improve forward cardiac output and coronary perfusion and reduce pulmonary congestion, these beneficial effects may be offset by bleeding and vascular complications.[11] Unfortunately, developing high-quality evidence to support the safety and efficacy of temporary MCS devices in AMI-CS has been challenging. This report aimed to summarize the results from previous studies (observational and randomized) examining the utility of MCS in AMI-CS, describe the limitations of these studies, and review the ongoing trials with the greatest potential to provide class I evidence to inform future clinical decision making in this high-risk population.

Abbreviations: AMI, acute myocardial infarction; CA, cardiac arrest; CS, cardiogenic shock; IABP, intra-aortic balloon pump; LV, left ventricular; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; pVAD, percutaneous ventricular assist device; RV, right ventricular; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

Keywords: acute myocardial infarction; cardiogenic shock; extracorporeal membrane oxygenator; intra-aortic balloon pump; mechanical circulatory support; ventricular assist device.

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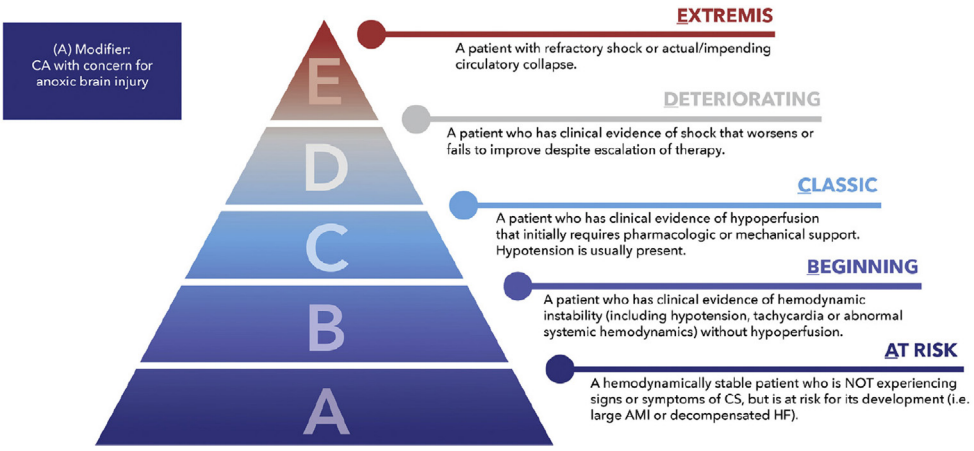


Figure 1.
Updated SCAI SHOCK classification schema. Reproduced with permission from Naidu et al.[14] AMI, acute myocardial infarction; CS, cardiogenic shock; HF, heart failure; SCAI, Society for Cardiovascular Angiography & Interventions.

Rationale and pitfalls of temporary MCS in AMI-CS

CS is defined by end-organ hypoperfusion resulting from ineffective cardiac output, typically with associated systemic arterial hypotension.[13,14] Treatment strategies for CS emphasize hemodynamic stabilization to restore systemic perfusion.[2,3,13] Vasopressors and inotropes can be used for this purpose but, often, provide inadequate support and can produce cardiac and noncardiac toxicity and complications.[13] An expanding array of temporary MCS devices has been developed with the goal of supporting the circulation and improving perfusion in patients with CS while minimizing the need for inotropes or vasopressors to foster myocardial recovery.[11,12] The intra-aortic balloon pump (IABP) was first introduced more than 50 years ago and remains the most commonly used temporary MCS device in the United States in the contemporary era despite a decrease in its use over time.[4,6,10,15-18] Multiple percutaneous ventricular assist devices (pVADs) have been introduced, the most widely used being the Impella family of devices (Abiomed), with the TandemHeart family of devices (LivaNova) used less frequently.[12] Venoarterial extracorporeal membrane oxygenation (VA-ECMO) support has also been available for many years, with recently increasing use for treatment of CS because of acute and chronic cardiac disease.[6,10,15,18,19]

Temporary MCS devices can increase cardiac output and arterial pressure to restore tissue perfusion, facilitate vasopressor and inotrope weaning, and unload the left ventricle.[11] It is logical that these favorable hemodynamic effects would translate directly into improved patient outcomes for patients with AMI-CS, presuming that they are not outweighed by device-related complications. Short-term mortality has been the focus of most RCTs for determining the efficacy of temporary MCS devices in AMI-CS, whereas long-term survival has been examined less frequently in this context.[20] Other relevant nonfatal patient-centered end points such as heart, kidney and other organ failure, vascular complications, stroke, and bleeding may be assessed. However, clinical improvements with MCS devices have not been demonstrated in any published RCT to date, with possible explanations ranging from trial design issues (small sample size or enrollment of patients not likely to benefit) to true lack of efficacy or even harm.[7,8,20-22] As reviewed further, neither have the results of observational studies been conclusive.

Substantial heterogeneity exists within the population with AMI-CS, the presence of which in previous studies may have contributed to the failure to demonstrate treatment efficacy of temporary MCS devices. The hemodynamic patterns, shock severity, presence of established organ failure, and complicating factors can differ markedly among patients with AMI-CS due to left ventricular (LV) failure.[23] CS is characterized by a downward spiral starting with initial LV dysfunction leading to systemic hypoperfusion and end-organ ischemia.[13] This can culminate in the development of a "hemometabolic" shock phenotype that may not respond to hemodynamic support alone, resulting in a dissociation between the acute hemodynamic efficacy of temporary MCS and its ability to improve outcomes.[24] The term hemometabolic shock, also called cardiometabolic shock, has been used to describe an end stage of CS where accumulated metabolic abnormalities (eg, lactic acidosis) from multiorgan failure create a self-perpetuating shock state.[24,25] Although there is no universal definition of hemometabolic shock, one proposed definition involves the combination of Society for Cardiovascular Angiography & Interventions (SCAI) SHOCK stage D/E CS with severe metabolic (lactic) acidosis and multiorgan failure.[25] Using machine learning clustering based on laboratory variables, a hemometabolic shock phenotype was identified within the population with CS that demonstrated severe shock, right-sided congestion, marked lactic acidosis, transaminitis, and acute kidney injury.[26,27] Thus, delayed deployment of temporary MCS after established end-organ failure (ie, hemometabolic shock) may fail to improve survival despite successful hemodynamic stabilization.

Temporary MCS devices are likely to exhibit different risk-benefit profiles across hemodynamic phenotypes and shock severity, and it

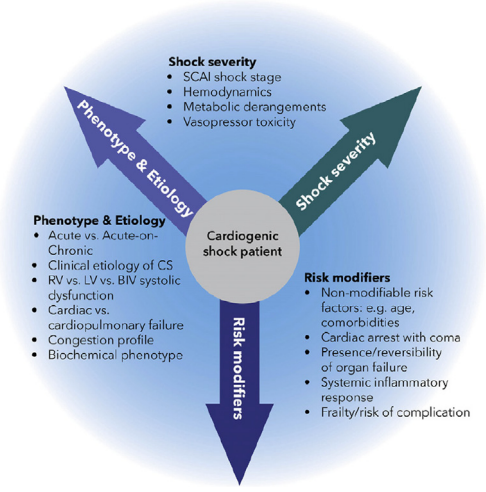


Figure 2.
SCAI SHOCK Classification 3-axis model for conceptualization of patients with CS. Reproduced with permission from Naidu et al.[14] CS, cardiogenic shock; LV, left ventricle; RV, right ventricle; SCAI, Society for Cardiovascular Angiography & Interventions.

Table 1. Published randomized trials of temporary MCS in AMI-CS.

Study	Year of publication	N	Mortality[a] with intervention, %	Mortality[a] with comparator, %	RR (95% CI)[b]	Additional findings
IABP vs medical therapy						
Arias et al[36]	2005	40	32.3	55.6	0.58 (0.27-1.26)	–
TACTICS[37]	2005	57	30.0	33.3	0.90 (0.42-1.93)	No difference in complications. Terminated early owing to slow enrollment (planned n = 538)
IABP-SHOCK[38]	2010	40	36.8	28.6	1.28 (0.45-3.72)	No improvement in organ failure or hemodynamics with IABP
IABP-SHOCK-II[21]	2012	598	39.7	41.3	0.96 (0.79-1.17)	No difference in complications
Pooled	–	735	38.2	40.3	0.95 (0.79-1.13)	–
TandemHeart vs IABP						
Thiele et al[39]	2005	41	42.9	45.0	0.95 (0.48-1.90)	Better hemodynamics and more complications with pVAD
Burkhoff et al[40]	2006	33	47.4	35.7	1.33 (0.57-3.10)	Better hemodynamics with pVAD. Terminated early owing to slow enrollment (planned n = 90)
Pooled	–	74	45.0	41.2	1.09 (0.64-1.85)	–
Impella vs IABP						
ISAR-SHOCK[41]	2008	26	46.2	46.2	1.00 (0.44-2.29)	Better hemodynamics with pVAD
IMPRESS[42]	2017	48	45.8	50.0	0.92 (0.51-1.66)	More bleeding with pVAD
IMPELLA-STIC[43]	2020	12	33.3	0.0	5.00 (0.29-84.44)	More bleeding with pVAD. Terminated early owing to slow enrollment (planned n = 60)
Pooled	–	86	44.2	41.9	1.06 (0.65-1.72)	–
VA-ECMO vs no MCS ± rescue ECMO						
ECLS-Shock[44]	2019	42	19	33	0.57 (0.19-1.66)	No difference in major complications
ECMO-CS[45]	2022	117	50.0	47.5	1.11 (0.66-1.87)	Similar risk of serious complications
Pooled	–	159	45.6	48.8	0.93 (0.67-1.30)	–

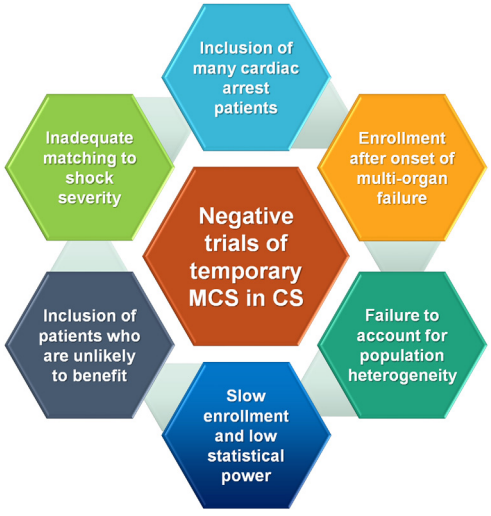
CS, cardiogenic shock; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LV, left ventricular; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; pVAD, percutaneous ventricular assist device; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

[a] Either in-hospital or 30-day mortality. [b] Relative risk (RR) and 95% CIs are those reported in each study; if the RR was not reported, it was calculated using available data. Crude pooled RR values were calculated based on the total number of events in each group.[7,8,18,20]

would be ideal to match the severity of CS to the type and magnitude of support. In some patients, right ventricular (RV) failure is the predominant cause of AMI-CS and determinant of its prognosis.[28,29] Isolated LV temporary MCS in a patient with biventricular or RV-predominant CS may provide inadequate hemodynamic support.[23,30] The SCAI SHOCK classification (Figure 1) offers a standardized approach to define shock severity that has proven to be clinically relevant and facile.[14,23,31] Patients with CS will show several clinical or demographic variables that will influence their response to treatment, likelihood for recovery, and survival.[23] The prognostic factors that influence decision making can be conceptualized using a 3-axis model of CS (Figure 2), as proposed by the SCAI SHOCK classification working group.[14,32] For example, cardiac arrest (CA) occurs in approximately half of patients with AMI-CS and is consistently associated with greater shock severity, advanced organ failure, and worse outcomes often driven by the presence of anoxic brain injury, which may not be modifiable even if temporary MCS provides myocardial recovery.[7,32-35] Hence, there is no reason to expect that universal application of a single type of temporary MCS device across a heterogeneous population with AMI-CS would improve outcomes, even if temporary MCS may be beneficial in certain subgroups.

Randomized trials of temporary MCS in CS

The few RCTs that have been performed examining the use of temporary MCS in AMI-CS (Table 1) have failed to demonstrate improvement in outcomes owing to several potential reasons (Central Illustration).[7,20-22,36-46] The IABP-SHOCK trial in 40 patients with AMI-CS observed minimal improvement in hemodynamic end points, organ dysfunction, or severity of illness with IABP compared with that with vasopressors and inotropes alone.[38,47] The largest and highest-quality RCT of temporary MCS in AMI-CS published to date is the IABP-SHOCK-II trial, in which 600 patients with AMI-CS who underwent early revascularization were randomly assigned to routine IABP use and medical therapy alone.[21] Mortality at 30 days was similar with IABP and control therapy (relative risk [RR], 0.96; 95% CI, 0.79-1.17), although complications did not differ between the groups; however,



Central Illustration.

Potential reasons why published RCTs of temporary MCS in AMI-CS have not demonstrated significant differences in mortality. AMI-CS, acute myocardial infarction related cardiogenic shock; MCS, mechanical circulatory support; RCT, randomized controlled trial.

Table 2. Ongoing randomized trials of temporary MCS in AMI-CS.

Name	NCT No.	Started recruiting	Projected N	Intervention
Populations with AMI-CS				
ECLS-SHOCK	NCT03637205	Yes	420	VA-ECMO
EUROSHOCK[a]	NCT03813134	Yes	428	VA-ECMO
ANCHOR	NCT04184635	Yes	400	VA-ECMO
DanGer Shock	NCT01633502	Yes	360	Impella CP
ULYSS	NCT05366452	No	204	Impella CP
RECOVER-IV	NCT05506449	No	560	Impella CP
Patients with CS receiving ECMO				
REVERSE	NCT03431467	Yes	96	Impella CP
UNLOAD ECMO	NCT05577195	No	198	Impella CP
ECMOsorb	NCT05027529	Yes	54	Cytosorb
AMI + preshock				
SCAI-B	NCT04989777	No	512	IABP

AMI-CS, acute myocardial infarction-cardiogenic shock; CS, cardiogenic shock; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; VA-ECMO, venoarterial extracorporeal membrane oxygenation.
From clinicaltrials.gov search on October 31, 2022.
[a] This study was terminated early owing to slow recruitment and other factors.

survival between the groups remained similar during a long-term follow-up (Figure 3).[21,48,49] Of note, the IABP was placed after revascularization in 86.6% of patients, although mortality was independent of the timing of IABP insertion. A Cochrane meta-analysis of all RCTs did not demonstrate a decrease in mortality with IABP in AMI-CS.[22] The lack of efficacy and potential for an increased risk of stroke with routine IABP use in AMI-CS led to a class III recommendation in recent guidelines.[3]

Early RCTs showed greater hemodynamic improvements with pVAD compared with IABP in AMI-CS.[20,39-41,43] Unfortunately, an adequately powered RCT of pVAD and IABP (or medical therapy only) comparison to assess clinical outcomes has not been completed. A meta-analysis including 148 patients from 4 RCTs did not find a difference in survival between pVAD and IABP groups (pooled RR, 1.01; 95% CI, 0.70-1.44), and complications increased with pVAD use.[20,42] Unfortunately, most of these trials were stopped prematurely because of slow enrollment. In addition to being underpowered, these studies were limited by patient selection criteria.[33] For example, the largest RCT to date (IMPRESS, n = 48) enrolled patietns with high-risk AMI-CS requiring mechanical ventilation, nearly all of whom had experienced CA; in-hospital and 6-month mortality were similar with IABP and pVAD treatments, and the cause of death was anoxic brain injury in approximately half of the patients who died.[42]

The ECLS-Shock pilot study compared 30-day and 1-year mortality in 42 patients with AMI-CS who were randomly assigned to VA-ECMO vs no MCS, finding no differences in mortality at either time point, major complications, or neurologic outcomes between the groups.[44,46] The recently-published multicenter ECMO-CS trial is the largest reported RCT of advanced MCS devices in CS, comparing a strategy of early VA-ECMO vs rescue VA-ECMO in 122 patients with CS of SCAI SHOCK stages D or E of various etiologies (two-thirds due to AMI); patients who were comatose after CA were excluded.[45] Delayed (rescue) VA-ECMO was used in 39% of the rescue control group. Unfortunately, the ECMO-CS trial did not demonstrate a significant difference between the groups in the 30-day primary end point of death, resuscitated CA, or escalation of MCS (63.8% vs 71.2% respectively; hazard ratio, 0.72; 95% CI, 0.46-1.12),[45] nor did the 30-day mortality differ (50.0% vs 47.5% respectively). Serious adverse events were frequent in both groups (60.3% vs 61.0%).[45] Ongoing RCTs examining temporary MCS use in AMI-CS are summarized in Table 2, several of which are adequately powered for mortality assessment.[50,51]

Observational studies of temporary MCS devices in CS

The association between IABP use and outcomes in patients with AMI-CS has been examined in numerous studies, culminating in several meta-analyses with conflicting results.[52] Some, but not all, recent observational analyses using propensity adjustment methods have shown a potential association between IABP use and lower mortality in various CS cohorts.[4,53-56] One study using inverse probability of treatment weighting suggested a benefit of IABP in a mixed CS cohort, particularly in the lower SCAI SHOCK stages.[53] However, other recent studies have failed to demonstrate an improvement in outcomes and

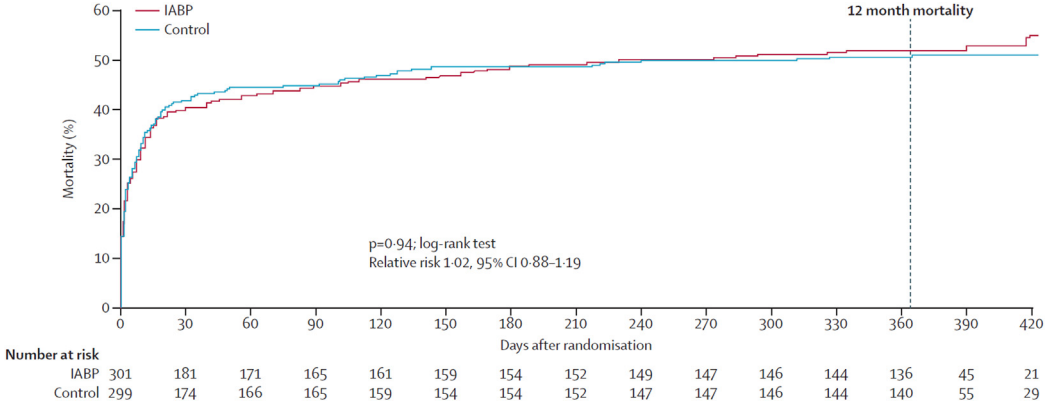


Figure 3.
Kaplan-Meier curves demonstrating long-term mortality in patients with AMI-CS who were randomized to IABP vs medical therapy in the IABP-SHOCK-II trial. Reproduced with permission from Thiele et al.[48] AMI, acute myocardial infarction; CS, cardiogenic shock; IABP, intra-aortic balloon pump.

Table 3. Observational comparative studies comparing short-term mortality in patients with AMI-CS treated with advanced temporary MCS devices published in the past 5 years.

Study	Year	Design	N	Mortality with MCS, %	Mortality with comparator, %	OR (95% CI)[a]	Complications
pVAD vs IABP							
Schrage et al[61]	2019	Retrospective, propensity adjusted	230	45.2	46.1	0.97 (0.57-1.62)	More complications with pVAD
Helgestad et al[18]	2020	Retrospective, propensity adjusted	80	40.0	77.5	0.19 (0.07-0.52)	No difference in complications
Dhruva et al[62]	2020	Retrospective, propensity adjusted	3360	45.0	34.1	1.58 (1.38-1.82)	More complications with pVAD
Vallabhajosyula et al[63]	2020	Retrospective, propensity adjusted	2838	28.4	26.7	1.09 (0.92-1.28)	More complications with pVAD
Desai et al[64]	2021	Retrospective, propensity adjusted	886	40.5	36.8	1.17 (0.89-1.54)	More complications with pVAD
Jin et al[65]	2022	Retrospective, propensity adjusted	10,230	49.6	29.0	1.72 (1.25-2.38)	More complications with pVAD
Miller et al[66]	2022	Retrospective, propensity adjusted	1634	36.2	25.8	1.63 (1.32-2.02)	More complications with pVAD
ECMO vs pVAD							
Garan et al[67]	2019	Prospective	51	45.0	45.2	0.99 (0.32-3.08)	No difference in complications
Schiller et al[68]	2019	Retrospective	94	34.7	37.5	0.89 (0.38-2.06)	Complications not reported
Karami et al[69]	2020	Retrospective	128	52.7	49.0	1.22 (0.57-2.56)	More complications with ECMO
Karatolios et al[70]	2021	Retrospective, propensity adjusted	183	61.4	49.4	1.63 (0.88-3.03)	More complications with ECMO

AMI-CS, acute myocardial infarction-cardiogenic shock; CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; pVAD, percutaneous ventricular assist device.

[a] Odds ratio (OR) and 95% CI values are those reported in each study; if the OR was not reported, it was calculated using available data. Single-arm studies such as the NCSI[71] and PROTECT-III[72] are not included in this table.

have reported a greater risk of complications with IABP use in AMI-CS, consistent with the results of most meta-analyses.[4,55-57] The observed association between IABP use and outcomes in AMI-CS may vary based on the use of PCI vs thrombolytic therapy and perhaps the timing of IABP use in relation to PCI (pre-PCI preferred in most studies).[56,58-60] Overall, these conflicting observational studies do not provide strong support for the routine use of IABP in AMI-CS.

More controversial is the interpretation of observational trials of pVAD use in AMI-CS. Recent retrospective and prospective comparative observational studies of pVAD and VA-ECMO use in AMI-CS are summarized in Table 3.[61-72] Retrospective observational studies examining outcomes with Impella vs IABP in AMI-CS from administrative or insurance claim databases have often used propensity matching to try to adjust for differences in baseline covariates between the groups. One cohort analysis matched patients who received an Impella in a registry to patients from the IABP-SHOCK-II study, finding no benefit and a greater risk of complications with Impella.[61] Other propensity-adjusted studies have demonstrated worse outcomes with Impella in comparison with IABP, including higher mortality and more complications.[62-65,73] Recent observational studies examining the use of VA-ECMO in AMI-CS have shown similar survival rates during short-term and long-term follow-ups when compared with patients receiving Impella, and the largest study showed more complications with VA-ECMO after propensity adjustment.[67-70] Several studies have focused on the question of whether using an IABP or Impella to unload the LV during VA-ECMO support is beneficial, with most studies suggesting better survival when either device is used for this purpose despite a higher risk of vascular complications and bleeding.[71,74-77]

By comparison, the prospective National Cardiogenic Shock Initiative (NCSI) protocol incorporating early Impella placement before PCI in AMI-CS showed improved outcomes compared with historical controls, and a meta-analysis of observational studies suggested that Impella placement before PCI may be beneficial in AMI-CS.[72,78-80] The single-arm NCSI results suggest that a structured protocol for AMI-CS care incorporating up-front Impella placement and other best practices may be associated with improved survival and that bleeding and vascular complications may be reduced with meticulous attention to large-bore vascular access and closure.[72,79] The implementation of a shock team can streamline the utilization of temporary MCS to provide individualized care with the potential to improve outcomes in patients with CS.[81,82] In the Critical Care Cardiology Trials Network (CCCTN) registry (Figure 4), centers with an institutional shock team used less temporary MCS overall but were more likely to use advanced MCS; patients with CS at centers with a shock team showed lower mortality, suggesting that judicious use of temporary MCS might be beneficial.[81]

Collectively, these conflicting retrospective observational studies have not provided compelling evidence that routine use of advanced temporary MCS devices improves clinical outcomes in unselected patients with AMI-CS, and the relative risks for serious complications are uncertain. As discussed further, these studies seem to be affected by confounding by indication because sicker patients receive escalating therapies (ie, pVAD or ECMO), and traditional adjustment models are incapable of fully measuring and adjusting for this source of bias.

Strengths and limitations of observational studies and randomized trials

The well-known limitations of both RCTs and observational studies are magnified in AMI-CS (Table 4). Only RCTs can establish a causal relationship between a therapy and benefit or harm. However, RCTs on AMI-CS typically have enrolled highly selected patients and have been performed at experienced tertiary-care referral centers with high resource availability and substantial local expertise, representing a best-case scenario for complex device usage. It has been estimated that only one-third of patients with CS in contemporary practice would have qualified for entry into major RCTs, and substantial differences between trial-eligible and trial-ineligible patients have been observed suggesting that RCT results may not generalize to the broader population with AMI-CS represented in observational studies.[83] Indeed, patients with AMI-CS enrolled in RCTs generally differ from those in registries, with a lower overall risk profile and more aggressive care.[84] Moreover, observational studies experience a selection bias in the choice of device for individual patients, and the composition of the AMI-CS population in a given study can strongly affect the findings.[33,83,84] Prospective single-arm studies, including the NCSI and PROTECT-III studies, can provide important information about the outcomes observed using temporary MCS devices in experienced hands and selected patients, but the lack of a control group is a substantial limitation.[72,79,80,85]

Confounding and suboptimal data quality of observational studies in AMI-CS

Confounding by indication is highly problematic in observational analyses of AMI-CS treatments, and patients who receive temporary MCS typically dramatically differ from patients who are not chosen to

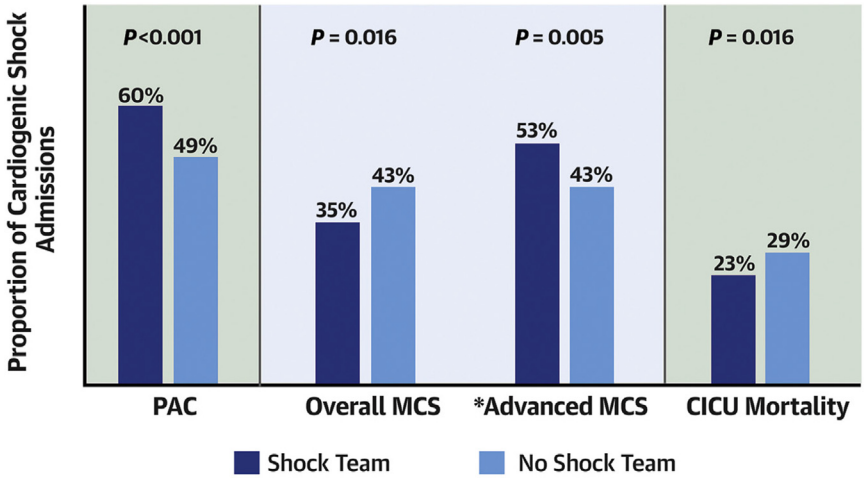


Figure 4.
Utilization of temporary MCS and mortality for patients with CS in centers participating in the Critical Care Cardiology Trails Network (CCCTN) based on the presence of an institutional shock team. *Advanced MCS includes percutaneous LVADs and ECMO. Reproduced with permission from Papolos et al.[81] CICU, critical intensive care unit; CS, cardiogenic shock; MCS, mechanical circulatory support; PAC, pulmonary artery catheter.

receive this therapy. It is challenging to identify the reasons that one MCS device was chosen rather than another in studies from administrative databases, with the use of advanced MCS devices typically reflecting the need for more potent support in sicker patients with a greater hemodynamic compromise. Multivariable analysis and propensity methods are thus frequently used to adjust for measured differences in patient characteristics that drive treatment decisions but have limitations.[86] Examples have been published in which propensity-adjusted observational analyses of noncritical cardiovascular interventions replicated the findings of RCTs; however, the feasibility and reliability of determining propensity in the setting of critical illness may differ from the outpatient setting.[87,88] Traditional patient-level clinical factors such as sex and comorbidities that are used to estimate the propensity for elective or nonurgent cardiovascular treatments are not the crucial prognostic variables that drive decision making in AMI-CS treatment.[87,88] As emphasized by the SCAI SHOCK classification 3-axis model, the salient variables for decision making regarding temporary MCS use in AMI-CS treatment encompass measures of shock severity, clinical or hemodynamic phenotype, and nonmodifiable risk modifiers such as anoxic brain injury from CA that cannot often be gleaned from observational data sets.[12,14,23] Numerous important risk factors for mortality in patients with CS cannot be reliably identified or quantified from administrative databases, including success of revascularization, SCAI SHOCK stage, ventricular function, hemodynamics, clinical phenotype, vasopressor requirements, circumstances of CA, magnitude of lactic acidosis, degree of end-organ failure, baseline functional status, frailty, code status, and goals of care.[14,23,25-29,32,35] Therefore, even well-conducted propensity-adjusted observational studies drawn from administrative databases generally offer a low level of evidence because they cannot incorporate the most crucial variables and should be considered at best hypothesis generating.[73]

Most importantly, even the most sophisticated statistical adjustments cannot account for unmeasured confounders in observational studies. Anticipated prognosis, resuscitation status, goals of care, and patient preferences also influence these decisions yet are not captured in administrative or claims databases. Escalation from one temporary MCS device to another can be challenging to categorize in observational analyses; such patients are a particularly high-risk group that should be recognized as failure of the original device rather than ascribed to the "higher-level" device, a common error.[19,29,67] A related challenge relates to the availability and quality of relevant data, particularly from administrative data based on billing/claims for which the inaccuracy of discharge diagnoses may influence the findings.[89] This highlights the importance of using a standardized shock severity assessment such as the SCAI SHOCK classification, but such categorization is not typically captured in administrative databases, which can likewise not reliably differentiate the hemodynamic phenotypes of AMI-CS or quantify the severity of complications such as organ failure.[14] Prospective observational studies with dedicated case report forms collecting the essential variables (such as NCSI and PROTECT-III[72,79,80,85]) can overcome some but not all these limitations. Therefore, propensity-adjusted analyses are not a valid surrogate for RCTs on AMI-CS.

Logistic challenges of randomized trials in AMI-CS

Randomized trials offer substantial benefits compared with observational data, most importantly balancing the rates of unmeasured confounders between the study groups. However, conducting RCTs in patients with AMI-CS introduces numerous hurdles that must be overcome, such as the ability to rapidly obtain informed consent from critically ill patients (including those who may be unresponsive) or from their legal representatives (who may be distraught or not physically present). In addition, many physicians have an implicit bias in believing that MCS devices are either mandatory for patient survival or, conversely, are harmful without proven evidence of benefit. Because they perceive lack of equipoise, both these physician groups have declined participation in previous AMI-CS RCTs. Hence, published AMI-CS RCTs have been limited by small sample sizes leading to inconclusive evidence from underpowered analyses, with most being terminated before their planned recruitment was achieved.

Even completed adequately powered RCTs may not be large enough to evaluate important subgroups, and negative findings from a large subgroup may mask a positive treatment effect in other patients. For example, in the SHOCK trial (in which the primary end point of 30-day mortality was not reduced by early revascularization), only one-quarter of patients (n = 73) were randomly assigned within 6 hours of symptom onset.[9] This subgroup showed a significant reduction in 30-day mortality, whereas no difference in survival was seen in those patients randomized beyond 6 hours; this plausible interaction would ideally be examined in larger RCTs but has not been.[9] Whether there is an important interaction between the time from symptom onset to AMI-CS and the use of MCS is unknown, but equally critical to establish. In a second example, nearly half of the patients in the IABP-SHOCK-II

Table 4. Comparative strengths and weaknesses of observational studies and randomized trials in AMI-CS.

Randomized controlled trials	Observational analyses
Strengths	
• Able to prove causality	• Effectiveness under real-world conditions
• Randomization ensures that unmeasured confounding variables are balanced	• Enhanced external generalizability owing to representative population sample
• Isolates treatment effect under ideal circumstances	• Nationally representative cohorts may be queried
• Stringent diagnostic criteria ensure a homogenous population	• Enrolls a broader population such as underrepresented groups
• Ideally includes patients most likely to benefit	• Lower cost
• Detailed case report form prospectively collects all baseline features and outcomes	• Large sample size improves statistical power, especially for subgroup analyses
• Stratified randomization can further balance groups on important covariates	• Can explore low frequency safety outcomes
• Low loss to follow-up with end point adjudication ensures accurate outcomes	
• Can provide insights into pathophysiology, utility of biomarkers, imaging, etc	
• Detailed assessment of the severity of shock and organ failure is possible	
• Temporary relationships between variables and outcomes can be ascertained	
Weaknesses	
• Only a few patients in contemporary practice may be trial-eligible	• Unmeasured confounding variables may mediate observed effects
• Enrolled patients may not be representative of the general disease population	• Confounding by indication often occurs, with substantial differences between groups based on treatments received
• Highly selected population with strict inclusion/exclusion criteria	• Typically includes a mix of patients who may and may not benefit
• Many eligible patients cannot be enrolled leading to limited sample size, especially for subgroups	• Can only demonstrate associations
• Slow enrollment may bias results due to changes in care over time and uncertainty about clinical equipoise	• May not differentiate cause vs consequence due to uncertainties about timing
• Data not recorded on case report form may not be available in retrospect	• Poor granularity of data, especially retrospective administrative or claims databases
• Enrollment occurs at tertiary-care centers with experience and established treatment protocols which may reduce external generalizability	• Differences in care practices between centers may affect outcomes
• Risk of selection bias	• Risk of selection bias
• High cost	• Limited information regarding disease severity and indications for device use
• Randomization may not ensure balance in measured and unmeasured covariates when sample size is small	• Limited mechanistic insights available
	• Differential loss to follow-up and inconsistent end point definitions can bias results
	• Variable/changing diagnostic criteria results in a mix of disease states in cohort
	• Changes in care during study period can affect results
	• Data not recorded in the health record cannot be obtained

trial experienced CA; there is no sound reason to expect that an IABP would ameliorate death from anoxic brain injury.[21] Conversely, to date, most RCTs in AMI-CS have included predominantly patients with SCAI SHOCK stage C and D, which leaves uncertainties about interventions in patients with greater or lesser shock severity.[7] Despite these challenges, RCTs are considered the highest level of evidence and the gold standard for determining safety and efficacy. Observational analyses, which are often drawn from much larger datasets, may provide important complementary exploratory evidence about low frequency adverse events and usage patterns of drugs and interventions in real-world practice.

Where does this leave the practicing physician?

The conflicting findings between studies regarding potential benefits and harms of temporary MCS in AMI-CS and the lack of adequately powered RCTs have left providers with uncertainty regarding whether and in whom to use these devices. In addition, the high cost of some temporary MCS devices raises important issues regarding cost-effectiveness.[64] Moreover, not all operators are facile at large bore femoral or alternative vascular access and closure (as is necessary for pVADs and VA-ECMO), resulting in hesitancy by some physicians to use these devices without irrefutable evidence of their benefit. Differences in baseline care (such as the success of revascularization) and variable timing of device implantation add additional layers of complexity.[58-60] Local standards of care and treatment protocols may vary with provider experience (volume-outcome relationships), availability of cardiac intensivists, and presence of shock teams (including the distinction between hubs and spoke centers).[80,81] Not surprisingly, there is marked variability in temporary MCS device utilization for CS across centers (Figure 5) and between countries, an undesirable situation that can only be rectified by a new generation of high-quality evidence resulting in strong uniform guideline recommendations.[10,15-17]

Suggestions for future research

Large-scale multi-national RCTs with adequate statistical power and appropriate enrollment of a population that not only mirrors the typical AMI-CS population encountered in clinical practice but excludes patients not likely to benefit are essential to establish standards of care.[50,51] Such studies may be sponsored by the investigators (often with governmental funding support) or industries. Emergency exception from informed consent has been successfully used to enroll critically ill patients in the setting of CA is being used to facilitate enrollment in future AMI-CS trials.[90,91] Pragmatic RCTs embedded into usual clinical practice could evaluate different strategies that are within current standards of care, either comparing different temporary MCS devices or care protocols incorporating these devices. Trial efficiency can be improved with factorial designs testing multiple interventions in combination or using an adaptive design.[92,93] Finally, cluster randomization at the hospital level may obviate the need for individual patient informed consent but is less robust than multicenter individual patient RCTs owing to potential bias resulting from differences in patient profiles, operator skill and systems of care. Observational studies continue to have value in AMI-CS outcomes research. However, we must move away from retrospective analyses of administrative databases to prospective enrollment of patients in registries using dedicated case report forms that collect reasons for MCS device usage, shock stage and other critical prognostic factors, and adjudicate outcomes. Identifying which patients are likely to benefit, experience a neutral effect, or can be harmed by temporary MCS device usage is essential to optimize outcomes in this extremely high-risk patient cohort.

Conclusions

The great variability in studies published to date regarding the safety and efficacy of temporary MCS devices in AMI-CS poses a challenge for operators and health care systems to select the appropriate patients in whom these devices should be used. Implementation of a multidisciplinary shock team can facilitate matching the right device to the right patient at the right time, and emerging observational data suggests that this process of care is associated with survival.[81] Quality improvement protocols should enable institutions to assess their own temporary MCS practices to learn from their successes and failures,

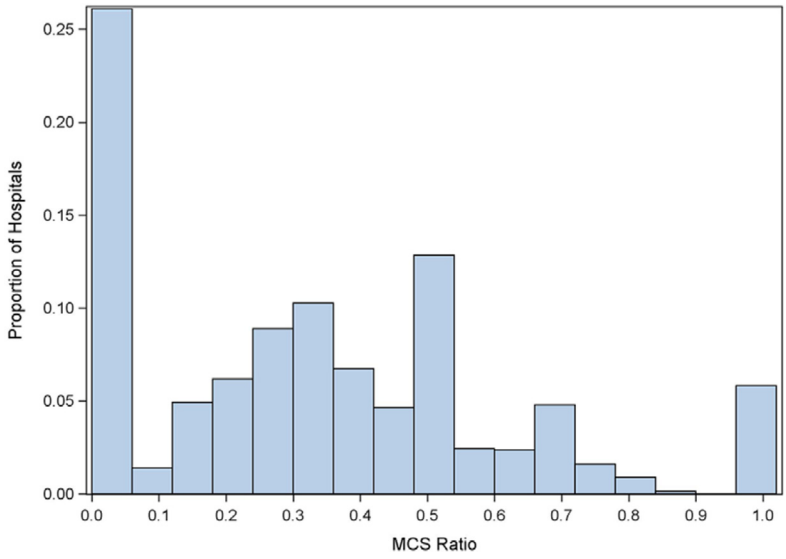


Figure 5.
Variability in the use of temporary MCS devices for AMI-CS in the United States Nationwide Inpatient Sample in 2014. MCS ratio denotes proportion of AMI-CS hospitalizations using temporary MCS. Reproduced with permission from Strom et al.[16] AMI, acute myocardial infarction; CS, cardiogenic shock; MCS, mechanical circulatory support.

applying rigorous methodology that can allow these findings to translate to the research arena. As with all technology, it is likely that selective rather than indiscriminate use of temporary MCS devices will optimize outcomes and cost-effectiveness. Although developing the next generation of temporary MCS devices that provide even more potent hemodynamic support with a lower rate of complications will be helpful, learning how best to apply these devices in the right situations (ie, survivable patients) is even more essential. Moving the field forward will require a deeper understanding of the core pathophysiologic mechanisms that drive heterogeneity and outcomes in AMI-CS. The strengths and limitations of existing and ongoing observational studies and RCTs need to be appreciated to properly interpret the present evidence base. Most importantly, acknowledging the lack of high-quality evidence regarding MCS device use in AMI-CS and the marked variability between centers in the adoption of these devices is the definition of equipoise and should compel widespread and enthusiastic investigator participation into ongoing and future RCTs to generate the highest level of evidence as soon as possible.

Declaration of competing interest

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This was a review article and therefore no patient contact or patient-level data was involved. The authors adhered to relevant ethical guidelines.

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