Predictors of Outcomes in Myocardial Infarction and Cardiogenic Shock

Deepak Acharya, MD, MSPH

Abstract: Myocardial infarction (MI) complicated by cardiogenic shock (MI-CS) is a major cause of cardiovascular morbidity and mortality. Predictors of outcomes in MI-CS include clinical, laboratory, radiologic variables, and management strategies. This article reviews the existing literature on short- and long-term predictors and risk stratification in MI complicated by CS.

Key Words: myocardial infarction, cardiogenic shock

(Myocardial infarction (MI) complicated by cardiogenic shock (MI-CS)) remains a major problem in cardiovascular medicine. Although outcomes have improved over the last 2 decades with early revascularization and modern intensive care, morbidity and mortality remain high.

Many investigators have evaluated predictors of developing cardiogenic shock (CS), as well as mortality after the development of CS, in an attempt to better understand patient populations, to assist in the triage of patients for specific therapies and clinical trials, and to determine prognosis. However, there is wide heterogeneity among these studies, including in the definition of CS, patient populations and risk profiles, the nature of predictors evaluated, therapies available or utilized, and outcome measures. The majority of studies are observational with some selection bias, data quality is sometimes inconsistent, and the results are not generally validated in other populations. Furthermore, not all important variables may have been collected or analyzed, some variables collected may not be routinely available in clinical practice, and many studies were small and had limited power to evaluate multiple predictors. Conversely, the few large randomized studies often had more homogeneous populations and well-defined era-specific management strategies that may not necessarily be applicable to current real-world situations. Therefore, the applicability and accuracy of a particular set of predictors or risk scores to an individual patient in current practice are uncertain. Given the significant heterogeneity in patient populations and management strategies, systematic reviews and meta-analyses have generally not been performed.

This review will summarize current available evidence on the factors that influence or predict outcomes in MI-CS. A wide range of clinical, laboratory, radiologic, and angiographic variables and therapeutic approaches have been evaluated. Predictors from these various domains that have been consistently useful in risk stratification across different patient populations, eras, and management strategies are highlighted. A comprehensive understanding of the most relevant factors may better identify an individual patient trajectory and assist in the development of management strategies, including timing, techniques, and mode of revascularization, the transfer to tertiary centers, the institution of more aggressive mechanical or pharmacological support, appropriate resource utilization, or compassionate palliative care in futile situations. This information may also facilitate discussions of prognosis with family members, provide a framework for risk stratification for future clinical trials, and be valuable for quality assessment and targeted efforts for institutions.

METHODS

Studies were identified through a systematic search of the PubMed database, clinicaltrials.gov, and Cochrane database of Systematic Reviews. No limits were set on language, publication status, and start date. Randomized and nonrandomized studies were included. The literature search was performed until October 31, 2017. Titles and abstracts were screened for potentially relevant articles. All articles that reported on mortality and predictors of outcomes were reviewed. Full-length manuscripts and online appendices of relevant articles were evaluated. Reference lists of primary studies were reviewed for additional references. Studies on CS not exclusively caused by MI were excluded unless there were important findings specific to the MI-CS populations. Predictors reported are those after multivariable analysis unless otherwise noted.

PREDICTORS OF DEVELOPING CS AFTER MI

Multiple clinical criteria have been used to predict the development of CS in patients with MI (Table 1). In the majority of patients, shock develops after admission rather than at presentation. Early reperfusion may prevent the development of CS. Patients at high risk of developing CS may benefit from expedited revascularization, more focused hemodynamic management, intensified monitoring for worsening symptoms and hemodynamic parameters, and early transfer to tertiary care centers with advanced interventional and heart failure facilities.

PREDICTORS OF MORTALITY IN PATIENTS WHO DEVELOP CS

Age

Multiple studies have identified age as an independent predictor of poor outcomes. In a prespecified subgroup analysis of the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial, patients aged 75 years or older did not derive benefit from early revascularization. A detailed analysis of these patients concluded that this finding may have been related to small sample size, the comparator >75-year-old medical therapy group being a lower-risk group with similar survival to patients <75 years, and more unfavorable characteristics including lower left
ventricular ejection fraction (LVEF) and poor intraaortic balloon pump (IABP) response in the elderly revascularization group.21 A subsequent analysis of the SHOCK registry revealed that while older patients have higher risks than younger patients, there is still a significant survival benefit to early revascularization.22 Age >65 years was also an independent predictor of 30-day mortality in the Impella-EUROSHOCK registry of patients with refractory CS receiving the Impella 2.5 device.21 The analyses of patients with MI-CS in the Melbourne Interventional group registry showed that patients 75 years or older had similar 1-year mortality compared to younger patients.23,24 A SHOCK registry analysis found that cardiac power, which incorporates the product of cardiac output and systemic blood pressure, was a significant predictor of 1-year mortality in patients with MI-CS between 1997 and 2006 showing that outcomes had improved over the study duration, and mortality rates became similar (~48%) between those that presented with shock and those that developed shock in the hospital.24,25

### Timing of Shock Development

In a Danish study of 444 patients with MI-CS from the thrombolytic era, the majority (59%) had shock within 48 hours of presentation, 11% developed shock on days 3–4, and 30% developed shock after day 4. Late shock was a significant predictor of 30-day mortality compared to early shock (mortality 87% versus 45%). Those with late shock were more likely to be female, a lower proportion received thrombolitics, and a higher proportion had in-hospital reinfarction.26 In the SHOCK registry, the median time from the start of MI symptoms to the onset of shock was 6.2 hours. Among 815 patients, 46.6% had shock within 6 hours, and 74.1% had shock <24 hours. Shock developed later with triple vessel disease compared to single or double vessel disease. Those with late shock had recurrent ischemia and Q waves in two or more leads. In contrast to the Danish study, in a subgroup analysis of the SHOCK registry, the mortality was higher in patients with early versus late shock, but the timing of shock was not an independent predictor of mortality in multivariable analysis.27 A Swiss registry that included 1977 patients with MI-CS between 1997 and 2006 showed that outcomes had improved over the study duration, and mortality rates became similar (~48%) between those that presented with shock and those that developed shock in the hospital. A population-based study from Massachusetts28 of patients admitted between 2001 and 2011 found that the in-hospital mortality of those who had CS before admission increased from 38.9% to 53.6%, whereas mortality decreased for patients who developed CS, either within the first 24 hours of admission or later during hospitalization. Overall in-hospital mortality was 45.7%, 32.8%, and 54.1% for the prehospital, early, or late groups, respectively.28 Aggregate data suggest that although the influence of timing of shock development may differ due to changes in management approaches, most patients develop CS once admitted, therefore, providing an opportunity for early diagnosis and management.

### Duration of Shock

The duration of shock is important because a longer time in shock can lead to systemic inflammatory response failure and multorgan failure, after which time the benefit of revascularization or mechanical support becomes limited. The National Cardiovascular Data Registry (NCDR) Cath-PCI registry recently updated and validated a risk model, in which patients with transient shock had a risk of in-hospital mortality of 15.1%, those with sustained shock or salvage status had a 33.8% risk, and those with sustained shock and salvage, defined as recent cardiopulmonary resuscitation or extracorporeal life support (ECLS), had a 65.9% risk of in-hospital mortality.29 Among patients with shock, earlier revascularization improves outcomes (see Section Timing of PCI).

### Hemodynamic Parameters

A substudy of the SHOCK trial showed that there was a higher rate of improvement of cardiac index and stroke volume index with early revascularization compared to intensive medical management. In multivariable analysis, baseline stroke volume index and follow-up stroke work index and stroke volume index predicted mortality.40 A SHOCK registry analysis found that cardiac power, which incorporates the product of cardiac output and systemic blood pressure, was the most important hemodynamic predictor of mortality.41 An analysis of the Tifarginine Acetate Injection in a Randomized International

### Clinical History and Risk Factors

Prior MI can lead to worse outcomes in those who develop CS, presumably because of a lower reserve to tolerate additional injury.26 Diabetes mellitus (DM) has been identified as an independent risk factor in some studies but not in others.7,10,17,27,28 Anoxic brain injury,29 higher body mass index, cerebrovascular disease, stroke, peripheral vascular disease, history of angina, prior percutaneous coronary intervention (PCI), dialysis, and white race are other risk factors for mortality in individual studies.19,30 Different studies have shown contradictory results regarding a protective effect of either sex on mortality.19,31,32 Cardiac arrest, as expected, is a significant risk factor for mortality.21 However, patients successfully resuscitated from out-of-hospital cardiac arrest and presenting to the hospital in a comatose state or who present with CS to the hospital can still have significant benefit from revascularization.33,34

### TABLE 1. Predictors of Developing Cardiogenic Shock in Patients With Myocardial Infarction

| Authors          | No. of Patients | Predictors of Developing Cardiogenic Shock |
|------------------|-----------------|------------------------------------------|
| Hands et al1     | 845             | Age >65 years, previous MI, LVEF <35%, CK-MB >160 IU/L, DM |
| Mavric et al2    | 291             | Age, previous MI, lactate, urea, cardiothoracic ratio |
| Leor et al3      | 3465            | Age, female gender, history of angina, history of stroke, peripheral vascular disease, peak LDH >4 × normal, hyperglycemia on admission |
| Hasdai et al4    | 1889            | Age, SBP, heart rate, Killip class |
| Hasdai et al5    | 9449            | Age, ST depressions, SBP, angina, enrolling MI, physical exam findings including height, pulse rate, SBP, and rales |
| Conde-Vela et al6| 630             | Female gender, anterior STEMI, proximal culprit lesion, chronic occlusion of other arteries |
| Jeger et al7     | 1977            | Age, ST elevation, HR, lower SBP, lack of lipid lowering drugs, no PCI, IABP |
| Jari et al8      | 1016            | Age >65, SBP <100 mm Hg, anterior wall MI Killip class, NT-proBNP |
| Dziewierz et al9 | 1313            | Age, DM, hypertension, hyperlipidemia, prior heart failure symptoms |
| Bataille et al10 | 2020            | Left main–related MI, creatine clearance <60 mL/min, LAD-related MI, CTO |
| Lin et al11      | 482             | SYNTAX score |

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Study in Unstable MI Patients with Cardiogenic Shock (TRIUMPH) study of 396 patients with refractory CS despite patent artery and 90% IABP use identified baseline SBP to be a powerful predictor of mortality (odds ratio 0.63 for 10 mm Hg increment in SBP). The shock index (SI), defined as HR/SBP, is a simple measure with significant prognostic significance. In an analysis of 644 patients with STEMI, 20% of patients with an SI >0.8 died, whereas 4% of patients with an SI <0.8 died, and the SI was a powerful independent predictor of mortality. Popovic et al evaluated 85 patients with MI-CS and Thrombolysis in Myocardial Infarction (TIMI)-3 flow after revascularization and found that the cardiac power index (defined as stroke work × HR), mean arterial pressure <75 mm Hg at 6 hours, and Simplified Acute Physiology Score (SAPS) II score predicted in-hospital mortality. Patients who continue to have high-risk hemodynamic parameters after revascularization could be considered for mechanical circulatory support.

In addition to macrocirculatory hemodynamic disturbances, patients with shock can also have microcirculatory dysfunction. Sublingual perfused capillary density (PCD) predicted a change in the Sequential Organ Failure Assessment (SOFA) score and improvements in PCD with management-predicted better outcomes, and patients with PCD above the median had higher rates of organ recovery. PCD was an independent predictor of 30-day outcome in a multivariable analysis.

Electrocardiographic Predictors

A study of 198 patients from the SHOCK trial with electrocardiograms (ECGs) within 12 hours of onset of shock showed 3 variables to predict 1-year mortality: HR, a prolonged QRS duration in patients in the initial medical stabilization group only, and the sum of ST depressions in patients with inferior MI in the initial medical stabilization group. Early revascularization appeared to eliminate the excess risk associated with these ECG findings. The Manitoba Cardiogenic Shock Registry evaluated 210 patients with MI-CS. The study found that ST elevation >0.5 mm in lead aVR could predict significant left main stenosis (>50%) with sensitivity 59%, positive predictive value 30%, specificity 77%, and negative predictive value 92%.

Echocardiographic and Other Radiologic Predictors

The Multicenter Investigation of Limitation of Infarct Size (MILIS) study, started in 1976, identified LVEF by radionuclide ventriculogram as an independent predictor of mortality in CS. A substudy of the SHOCK trial showed that LVEF <28% and mitral regurgitation (MR) severity (2+ or more) were the only independent echocardiographic predictors of 30-day and 1-year mortality, and there was benefit to early revascularization at all levels of LVEF and MR. In the CREATE trial, LVEF <40% was associated with an odds ratio of 3.78 for 30-day mortality. Another study of 147 patients, patients with no, mild, moderate, and severe MR had 1-year mortality of 8%, 23%, 30%, and 58%, and each grade increase in MR was independently associated with a 71% increase in mortality after accounting for LVEF, multivessel disease, no reflow, age, gender, and prior MI. Right ventricular dysfunction, defined as tricuspid annular plane systolic excursion ≤14 mm, was an independent predictor of long-term survival in patients with STEMI and CS on admission after adjustment for age, admission glucose, and LVEF <40%.

Angiographic Predictors

The importance of collaterals to the infarcted territory was demonstrated by Williams et al, who reported in 1976 that the presence of collateral vessels supplying the infarcted area was associated with a lower incidence of CS and mortality. The culprit artery on angiogram has prognostic implications. Among 1190 patients from the SHOCK registry who had CS from pump failure or mechanical complications, the left anterior descending artery (LAD) was more often the culprit vessel in those with ventricular failure, and circumflex (LCx) was more likely to be involved in patients with mechanical complications. Patients with mechanical complications had worse outcomes. For patients with ventricular failure, angiographic disease severity, culprit lesion location (worse with left main and saphenous graft lesions), and TIMI flow grade were associated with higher in-hospital mortality. Similarly, the SHOCK trial angiographic correlates of 1-year mortality were a higher number of diseased vessels, decreasing initial TIMI flow, and non-right coronary artery (RCA) culprit lesions. A review of 483 patients from the NCDR identified total occlusion of the LAD to be associated with an odds ratio of 2 for in-hospital mortality. A registry study of 1333 patients undergoing PCI for MI-CS found TIMI <3 flow after PCI, 3-vessel disease, and left main disease to be independent predictors of mortality. A series of 25 patients with MI-CS related to left main disease showed 60% in-hospital mortality, with right bundle branch block and low HCO₃⁻ levels as independent mortality predictors. A registry study of 2090 patients with STEMI treated with PCI found that the in-hospital mortality was highly correlated with the infarct-related artery, and left main-, LAD-, LCx- and RCA-related MI-CS were associated with 64.7%, 41.0%, 36.0%, and 30.8% mortality, respectively. In a large NCDR analysis, left main disease and proximal LAD disease were independently associated with mortality. The Society for Cardiovascular Angiography and Interventions (SCAI) Class IV lesions were also associated with higher in-hospital mortality compared to Class I lesions. Other studies have also shown 3-vessel disease to predict 1-year outcomes. In a study of 212 patients with MI-CS who underwent early PCI, there was no difference in 30-day mortality between patients with LAD versus RCA/LCx culprit lesions, suggesting that an early presentation and a successful reperfusion with aggressive PCI and adjunctive therapies may attenuate the historically observed higher mortality with anterior infarctions.

Chronic total occlusion (CTO) in a noninfarct artery indicates a higher total area of jeopardy and fewer potential collateral vessels to the infarct-related artery. The presence of CTO of the noninfarct artery was associated with a hazard ratio of 2.1 for 1-year mortality in 292 patients with MI-CS. Patients with STEMI who develop CS are more likely to have CTOs than those who do not develop CS. Among 141 patients with STEMI and CS on admission, 0% patients with >1 CTO survived, whereas 59.8% of those without CTO were alive at 30 days. In STEMI patients with CS, multivessel disease with and without CTO were predictors of 30-day mortality.

STEMI Versus Non-STEMI

Cardiogenic shock occurs in a smaller proportion of patients with non-STEMI (NSTEMI) compared to those with STEMI, but mortality is high in either condition once shock develops. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) IIb trial which enrolled patients between 1994 and 1995, those with NSTEMI who developed CS were older, had a higher prevalence of diabetes and 3-vessel coronary artery disease, and less TIMI 0 flow on angiography than STEMI patients who developed shock. Shock developed at a median of 76.2 hours in the NSTEMI group compared with 9.6 hours in the STEMI group. The 30-day mortality was 10% higher in the NSTEMI shock group, and NSTEMI was an independent predictor of mortality in multivariable analysis. A report from the SHOCK trial registry revealed similar differences in baseline characteristics and also found that NSTEMI patients were less likely to undergo angiography. The rates of revascularization and in-hospital mortality were similar in the 2 groups in the SHOCK registry. A more contemporary analysis from the NCDR showed that NSTEMI shock patients were older, more likely to be female, have DM, a history of MI, revascularization, and congestive heart failure compared
with STEMI shock patients. The NSTEMI group was more likely to develop shock after hospitalization, whereas the STEMI group was more likely to present with shock. The NSTEMI group also had more 3-vessel disease and lower LVEF. The rates of revascularization were significantly lower in the NSTEMI than in the STEMI group (56.5% versus 95.8%), and the NSTEMI patients who were revascularized had significantly longer times to PCI or coronary artery bypass grafting (CABG) compared to STEMI patients. Mortality risk was higher in NSTEMI versus STEMI (40.8 versus 33.1%).

Patient characteristics and comorbidities may influence management approaches in NSTEMI shock. However, for those who are candidates for aggressive management and reperfusion, approaching the situation with the same urgency as STEMI shock may provide an opportunity to improve outcomes.

**Metabolic and Laboratory Derangements**

Hyperlactatemia can reflect impaired tissue perfusion, intracellular metabolic derangements, and hepatic dysfunction. In one study, lactate > 6.5 mmol/L was a powerful independent predictor of 30-day mortality. In another study, each mmol increase in lactate was associated with an odds ratio of 1.14 for mortality, and fewer than 30% of patients with peak lactate >10 μmol/L survived to discharge. Lactate clearance <10% can also predict intensive care unit and 90-day mortality. Impaired lactate clearance may reflect ongoing hypoperfusion and poor oxygen delivery or impaired clearance because of renal or liver dysfunction. In the Impella-EUROSHOCK registry, lactate >3.8 mmol/L on admission was a strong predictor of 30-day mortality, and lactate levels decreased with Impella support. In the CREATE trial of 518 Chinese patients, admission glucose levels >7.8 mmol/L and sodium <130 mmol/L were among independent predictors of 30-day mortality. Based on the available evidence, hyperlactatemia or impaired clearance with standard therapies are easily available measures that could be utilized as triage variables for more aggressive measures.

**Renal Failure**

Acute renal failure is an important predictor of mortality, both as a marker of the severity of shock, and also as a direct mediator of poor outcomes. Patients with MI-CS who are older, have lower LVEF, or require mechanical ventilation are more likely to develop acute kidney injury. The development of acute renal failure within 24 hours of onset of shock was associated with an 87% mortality in one series. In another, an increment of 10mL/min in creatinine clearance was associated with an odds ratio of 0.77 for mortality. Baseline renal insufficiency was associated with an odds ratio of 3.45 in 210 patients with CS. Several other studies have shown impaired renal function to predict mortality. A IABP-SHOCK II substudy evaluated novel renal function biomarkers, including neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, and cystatin C, and several equations to calculate renal function. Serum creatinine had a better individual predictive value than any of these biomarkers, and the biomarkers did not provide incremental prognostic information in multivariable analysis after accounting for creatinine.

**Inflammatory Response**

There is increasing recognition that CS is not simply a low perfusion state. Particularly with severe or late-stage shock, there is systemic inflammation associated with a low systemic vascular resistance and vasopressor resistance. Mediators of these pathways are not well understood.

In a study of 87 patients, those with CS (mostly from MI) had higher interleukin(IL)-6 levels than noncritically ill patients but lower IL-6 levels than patients with septic shock. However, once CS patients developed multiorgan failure, IL-6 levels were similar to those found in septic shock. Furthermore, elevated IL-6 levels in CS patients who were not in multorgan failure at the time of sampling predicted progression to multiorgan failure. In an analysis of 38 patients with MI-CS, higher IL-6 concentrations were associated with a higher vasopressor requirement and independently associated with higher 30-day mortality. In another study, the IL-6 level was the strongest early independent predictor of 30-day mortality. In addition to IL-6, elevations in IL-8 and IL-10 and lower IL-7 levels were associated with higher mortality in the IABP-SHOCK trial.

In 52 patients with acute coronary syndrome, C-reactive protein (CRP) levels were significantly higher in CS patients compared to those with unstable angina or NSTEMI. CRP levels were not statistically higher in CS versus STEMI without CS. Procalcitonin levels were highest in the CS group, followed by STEMI, then unstable angina/NSTEMI. The authors conclude that CRP better reflects myocardial ischemia and related inflammatory responses, and procalcitonin reflects a higher degree of inflammatory activation seen in shock. In another study, admission levels of CRP and plasminogen activator inhibitor-1 were independent predictors of in-hospital and 1-year mortality.

Activated protein C is involved in inflammatory and coagulation pathways, and low levels were associated with higher mortality in septic patients. Recombinant activated protein C (APC) was developed, approved, and marketed for severe sepsis, but later withdrawn from the market due to lack of efficacy and complications. A report of 43 patients with MI-CS showed lower APC levels in CS patients compared to MI patients who did not have CS. Nonsurvivors had lower levels of APC at day 2, and APC levels were inversely correlated with IL-6.

Catalytic iron is involved in free radical generation. In an IABP-SHOCK II substudy, higher catalytic iron levels were associated with higher mortality, and the authors advocate further studies to evaluate the therapeutic role of chelation therapy in this situation. Despite individual studies illustrating inflammatory derangements, there is significant physiologic complexity and pathway redundancy, which presents challenges in identifying and developing therapeutic targets. As an example, preclinical studies demonstrated that inflammation can lead to induced nitric oxide synthase (NOS), resulting in excess inhaled nitric oxide production and systemic vasodilation. Small clinical studies suggested a benefit of NOS inhibitors in MI-CS. However, in the larger TRIUMPH trial, NOS inhibition with targinine did not influence 30-day mortality in patients with MI and refractory CS despite patent infarct-related artery. Further investigation into the biochemical and molecular mechanisms of shock is necessary before targeted drugs can be developed.

**Integrated Multisystem Scores**

Further supporting the influence of the systemic inflammatory response in outcomes, several investigators have found that risk scores initially created for sepsis or medical intensive care unit patients have prognostic value in MI-CS patients. Kellner et al evaluated 41 patients with MI-CS and found that the mean admission Acute Physiology and Chronic Health Evaluation (APACHE II), APACHE III, SAPS II, and SOFA scores were higher in nonsurvivors versus survivors. Maximum scores of APACHE II, APACHE III, and SAPS II also had prognostic significance.

**Other Biomarkers**

The use of novel biomarkers for risk stratification in MI-CS is at a relatively early stage compared to other conditions such as sepsis. Table 2 summarizes novel biomarkers that have been evaluated in MI-CS. Studies of multiscale approaches to identify a wide range of molecular biomarkers, gene expressions, and pathophysiology cascades in an effort to better understand the pathophysiology of CS and identify therapeutic strategies are underway.
Biomarker studies have the potential to greatly improve our understanding of molecular and pathophysiological alterations in MI-CS, and the relative ease of biomarker studies makes them attractive targets of investigation. However, important recognized limitations of biomarker studies include study quality heterogeneity, inadequate methodology, and publication and interpretation biases. These limitations and the distinction between association and causation may limit the clinical utility of some biomarker studies.

### Integrated Risk Scores

Several groups have developed risk scores that integrate different clinical parameters in an attempt to predict outcomes. The relevant factors vary, but age, success of revascularization, and measures of end-organ perfusion are consistently in risk scores across multiple studies (Table 3). In addition to these studies, the CardShock study derived a risk score from a population of CS patients with and without acute coronary syndromes and validated it in the IABP-SHOCK II population. Independent in-hospital mortality predictors were acute coronary syndrome etiology, prior CABG, confusion, previous MI, blood lactate, LVEF, age, and SBP. Estimated glomerular filtration rate was added to these variables to create a CARDSHOCK score.

### MANAGEMENT STRATEGIES

**Reperfusion**

The ability to successfully restore perfusion in the infarct-related artery has been consistently shown to be a crucial determinant of in-hospital, 30-day, and long-term survival. In the SHOCK trial, 30-day survival was 65% with successful PCI and 20% with unsuccessful PCI. TIMI score ≤ 2 post-PCI had an odds ratio of 19.5 for 30-day mortality in a study of 45 patients with STEMI and CS.

**Timing of PCI**

The timing of reperfusion is also important. A longer time from randomization to PCI was associated with higher mortality in the SHOCK trial. Early revascularization not only influenced early mortality but was associated with a 67% relative improvement in 6-year survival in SHOCK. In a German registry of 1333 patients with MI-CS, a longer time interval between symptom onset and admission was associated with higher mortality, and each hour delay between symptom onset and PCI was an independent predictor of in-hospital mortality (odds ratio 1.04).

In the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction trial (CAPTIM), among patients randomized within 2 hours of symptom onset, those receiving thrombolytics had a lower incidence of CS development and mortality than those receiving PCI, who on average got revascularized 1 hour later than thrombolytic administration. Very early reperfusion may decrease the incidence of CS and mortality.

### Culprit Vessel Versus Multivessel PCI

In several studies, including the SHOCK, NCNR registry analysis, and Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK)-PCI registry, and the CULPRIT-SHOCK study, multivessel as compared to single vessel PCI was associated with a higher mortality. In the IABP-SHOCK II trial and several other studies, mortality was similar with multivessel or single-vessel PCI. In contrast, several studies have shown that the ability to achieve complete revascularization in those with multivessel disease and CS is associated with higher in-hospital survival. A meta-analysis of 10 observational studies showed that multivessel PCI was associated with increased risk of short-term mortality compared to culprit vessel-only PCI (relative risk (RR) 1.26, P = 0.001). Long-term mortality was not different between the groups.

In these studies, the strategy of multivessel PCI versus culprit lesion-only PCI was at the discretion of the operator and not randomized. The 2013 American College of Cardiology/American Heart Association STEMI guidelines do not provide a specific recommendation for culprit vessel versus multivessel PCI in AMI-CS.

The 2012 ESC STEMI guidelines recommend multivessel PCI “in the presence of multiple, truly critical (≥90% diameter) stenoses or highly unstable lesions (angiographic signs of possible thrombus or lesion disruption) and if there is persistent ischemia after PCI of the supposed culprit lesion.” The clinical uncertainty in management of these patients was partly reflected in a Cath-PCI registry analysis of 56,497 patients with AMI-CS, which revealed that rates of multivessel PCI actually decreased from 31.5% to 25.7% between 2005 and 2013.

CULPRIT-SHOCK is a recently published randomized trial designed to provide a more definitive answer to this question. Investigators randomly assigned 706 patients with MI-CS from STEMI or NSTEMI to immediate multivessel PCI or culprit lesion-only PCI with the option of staged PCI of nonculprit vessels. At 30 days, those with culprit vessel-only PCI had lower mortality (RR 0.84, 95% confidence interval 0.72–0.98, P = 0.03) and lower composite primary endpoints of death and renal replacement therapy (RR 0.83, 95% confidence interval 0.71–0.96, P = 0.01). Future guideline recommendations will likely benefit from this study.

### TABLE 2. Selected Biomarkers With Prognostic Value in MI-CS

| Authors          | No of Patients | Outcome(s)          | Predictive Biomarker | Comments                                                                 |
|------------------|----------------|---------------------|----------------------|---------------------------------------------------------------------------|
| Katayama et al   | 42             | 1-year mortality    | Adrenomedullin       | Adrenomedullin had predictive value in patients who underwent successful revascularization. Patients with NT-proBNP >12,782 pg/mL had 90% mortality despite successful revascularization. NT-proBNP provided additional prognostic value when combined with interleukin-6. Osteoprotegerin predictor in univariate but not multivariate analysis. Negative prognostic association of elevated FGF-23 only significant in patients with serum creatinine above median (117 umol/L). FGF-23 improved ROC curves in combination with lactate. Predictive value of increased angiopoietin levels increase over time. |
| Jarai et al      | 58             | 30-day mortality    | NT-proBNP            |                                                                           |
| Fuernau et al    | 190            | 30-day mortality    | Growth differentiation factor 15 |                                                                           |
| Fuernau et al    | 182            | 30-day mortality    | Fibroblast growth factor 23 (FGF-23) |                                                                           |
| Poss et al       | 189            | 30-day mortality    | Angiopoietin         |                                                                           |

MI-CS indicates myocardial infarction complicated by cardiogenic shock; NT-proBNP, N-terminal pro B-type natriuretic peptide; ROC, receiver operating characteristic.
recommendations are likely to change in favor of culprit vessel–only PCI in light of the CULPRIT-SHOCK findings.  

Catheterization Approach

A meta-analysis of 8 observational studies with 8131 patients undergoing angiography or intervention in the setting of CS revealed that when compared with the transfemoral access, the transradial access was associated with a lower risk of mortality (unadjusted risk ratio 0.6) and fewer major adverse cardiac and cerebral events (unadjusted risk ratio 0.68). The benefit of the transradial approach over the transfemoral approach for PCI was observed even in patients who had femoral IABP in place. Another prospective study of 101 patients with MI-CS in a radial first center showed that transradial access was feasible in 73% of patients, that patients undergoing transfemoral PCI were sicker, and that transradial PCI was associated with lower mortality rates and fewer bleeding events. These were all observational studies with potential selection bias, and no randomized trials specifically evaluating access site and outcomes in MI-CS are currently available.

Coronary Artery Bypass Grafting

In the SHOCK trial, patients undergoing CABG had similar outcomes to those receiving PCI despite having more coronary artery disease and a higher incidence of DM. With contemporary
management, in-hospital mortality with isolated CABG in MI-CS is 18%, with higher mortality in those that require mechanical circulatory support.1,12 A recent report of 506 patients with MI-CS undergoing isolated CABG identified serum lactate >4 as the strongest predictor (odds ratio 4.78) of in-hospital mortality. Other predictors were age >75 years, LVEF <30%, and STEMI.13 No randomized study has compared multivessel PCI to CABG in patients with multivessel coronary artery disease and MI-CS.

**Inotropic and Vasopressor Agents**

Dobutamine is the preferred inotropic agent, and norepinephrine is the recommended vasopressor agent in most clinical guidelines.106,114 A Cochrane database systematic review evaluating trials of inotropic and vasodilator agents until 2013 concluded that there was no convincing evidence to support any particular agent over others to improve survival.115 Scarce data exist regarding the optimal vasopressor agent. A subgroup analysis of a randomized study comparing norepinephrine versus dopamine demonstrated that in CS, which in the majority of patients was caused by MI, norepinephrine was associated with a lower 28-day mortality than dopamine.116

**Mechanical Circulatory Support**

While inotropic and vasopressor agents may improve cardiac output and blood pressure, they also increase myocardial work and oxygen demands and, in the setting of CS and MI, have the potential to exacerbate injury. When there is severe shock from large amounts of myocardial necrosis, vasoactive agents simply may not be adequate to maintain cardiac output and end-organ perfusion.

Many nonrandomized and some randomized studies in the thrombolytic era have shown a survival benefit of IABP in MI-CS.117-121 In the PCI era, several meta-analyses and the IABP-SHOCK I and IABP-SHOCK II randomized trials did not show a mortality benefit of IABP as the primary hemodynamic support device for all patients.120-122 Therefore, IABP recommendations have been downgraded in the American College of Cardiology/American Heart Association and European Society of Cardiology STEMI guidelines.106,107

In the majority of the aforementioned clinical trials, the timing of IABP insertion was left to the discretion of the operator, and in the IABP Shock II trial, under 15% had IABP before revascularization.123 More recently, however, animal studies have demonstrated better outcomes with unloading before reperfusion, and there has been renewed interest in the ideal timing of IABP insertion.124 In one study, postponing the insertion of IABP after PCI was a strong independent predictor (odds ratio 5.2) of in-hospital mortality.125 A study of 218 patients with STEMI-CS showed that IABP before PCI was associated with a longer door-to-balloon time but improved myocardial perfusion as assessed with myocardial blush grade and resolution of ECG ST elevation. Independent risk factors for 12-month mortality were door-to-balloon time, IABP support after PCI, and acute kidney injury. The actual survival did not differ between the IABP before PCI and IABP after PCI groups.126 Another study of 102 patients with MI-CS found age, resuscitation before PCI, IABP after PCI, acute renal failure, and vasopressor use to be independent predictors of in-hospital mortality.127 Another single-center study showed that age <60 years and IABP alone, as opposed to IABP in combination with inotropic support, were independent predictors of survival. Although this could indicate that deleterious effects of inotropes play a role in poor outcomes, treatment assignment was not randomized, so patients in the combination group may represent a sicker cohort.128 In another cohort of 508 patients undergoing CABG for MI-CS, IABP before CABG was associated with a 14% lower in-hospital mortality than IABP after CABG.129 Not all studies, however, have found that earlier IABP improves outcomes.130,131

Other percutaneous mechanical support devices, such as Impella and Tandemheart, are increasingly being utilized for hemodynamic support. Many observational studies have suggested benefit, sometimes dramatic, but randomized trials have not shown survival advantage over IABP, in part because they have been small studies and may have been underpowered to demonstrate survival benefit.132-134 Significant hemodynamic improvement is seen with percutaneous mechanical circulatory support.135 The USpella registry showed that the use of Impella 2.5 was associated with improved survival and more complete revascularization compared to insertion of Impella 2.5 after PCI.136 A more recent analysis from the catheter-based Ventricular Assist Device registry showed similar findings with early utilization of Impella Cardiac Power (CP) or 2.5 devices before PCI and before high-dose inotropic support. Multivariate predictors of survival were early implantation of mechanical circulatory support before PCI and the use of mechanical circulatory support before requiring inotropes and vasopressors.137 The IMPRESS-SHOCK trial of 48 patients with late severe MI-CS (>90% with cardiac arrest, 100% ventilated) randomized to IABP versus Impella CP did not show a survival benefit to Impella over IABP. However, the primary cause of death was neurologic, highlighting the fact that hemodynamic support late in the course of shock has limited benefit. There was a trend towards lower mortality if IABP/Impella was initiated prior to PCI (25% versus 53%, P = 0.16).138

Extracorporeal membrane oxygenation (ECMO) is another widely used modality in the management of profound CS, and multiple investigators have reported on its utility in MI-CS (Table 4).139-144 In one study of patients with profound CS, ECMO-assisted PCI was associated with better survival, and ECMO support resulted in odds ratio of 0.22 for 30-day mortality in multivariable analysis.145 Another single-center study of 98 patients with MI with refractory CS or cardiac arrest showed 67% in-hospital mortality with ECLS. No patients were bridged to transplant or were reported to have durable left ventricular assist device (LVAD) because of local regulations, donor availability, and other logistical considerations. Predictors of mortality were unsuccessful reperfusion, asystole or pulseless electrical activity before ECLS introduction, and ECLS-related complications.146 A single center study of 77 patients with MI-CS requiring ECMO identified preimplantation lactate, creatinine, and cardiopulmonary resuscitation as independent predictors of 30-day mortality. Of 77 patients, 40 died on ECMO, 19 were weaned, of whom 15 survived to 30 days. Of 18 patients who failed the ECMO weaning trial, 13 underwent LVAD placement and 5 were transplanted. All 5 transplants and 10 of the 13 (77%) LVAD patients were alive at 30 days, highlighting the utility of ECMO as a valuable bridging strategy for more durable support.147 An innovative study evaluated outcomes of 119 patients weaned off ECMO. Seventy-seven of these patients had been initially cannulated for CS for a variety of indications, including MI. In-hospital mortality was 26%. Independent predictors of in-hospital mortality were mean arterial pressure, daily urine output on the second day after ECMO removal, and SOFA score on the day of ECMO removal. Patients with a SOFA score ≤13 had 13.2% mortality compared to 67.9% mortality in those with SOFA scores >14. Those with acute kidney injury in the 48 hours post ECMO removal had mortality of 45.1% versus 6.5% in those who did not have kidney injury.148 These high-risk patients may be considered for reinitiation of mechanical support or durable support if otherwise suitable.

For those patients who have persistent shock despite inotropes or short-term devices, or those who stabilize with temporary mechanical circulatory support but cannot be weaned off, surgical LVAD may offer an effective long-term management strategy.149 An overall strategy of aggressive management with early revascularization and tailored hemodynamic support with all available devices, including IABP, ECMO, LVAD, and subsequent transplantation is associated with better outcomes compared to more conservative approaches.150
TABLE 4. Extracorporeal Life Support in MI-CS

| Authors          | No. of Patients | CPR Before ECMO (%) | Mortality Predictors of Mortality |
|------------------|-----------------|---------------------|-----------------------------------|
| Chung et al138   | 20              | 14 (70)             | 50% (discharge)                   |
| Kim et al139     | 27              | 21 (77.8)           | 37% (30 days)                     |
| Tang et al140    | 21              | 10 (48)             | 24% (30 days)                     |
| Park et al141    | 96              | 61 (63.5)           | 53.1% (in-hospital)               |
| Lee et al142     | 51              | N/A                 | 39% (30 days)                     |
| Muller et al143  | 138             | 79 (57)             | 52.8% (ICU mortality)             |
| Chung et al144   | 65              | N/A                 | 43% (30 days)                     |

BMI indicates body mass index; BUN, blood urea nitrogen; CPR, cardiopulmonary resuscitation; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MI-CS, myocardial infarction complicated by cardiogenic shock.

**Hypothermia**

Given the proven benefit of therapeutic hypothermia post cardiac arrest, there has been interest in its role in MI-CS without cardiac arrest, but the data are limited. The 40-patient randomized SHOCK-COOL trial of mild therapeutic hypothermia in MI-CS patients without standard indications for hypothermia failed to show any survival benefit of therapeutic hypothermia at 30 days.151

**Ivabradine**

A small but randomized study evaluated HR lowering with ivabradine in 58 patients with MI-CS. In-hospital mortality was 6.75% in the ivabradine group and 14.3% in the control group (P = NS).152 This was a relatively low-risk cohort as evidenced by the mortality rates, but poses interesting questions regarding ideal HR and myocardial demand.

**SYSTEMS OF CARE**

Given the complexity of decision-making, the lack of an evidence base for standardized society guidelines, and multiple management approaches in MI-CS, there exists the possibility for significant heterogeneity in patient management and delays in care. Therefore, in-hospital multidisciplinary shock teams, protocol-driven management, care bundles, shock centers, and regional systems of care with clear predefined algorithms and channels of communication have been proposed as strategies to improve outcomes associated with hypothermia.153 The few small studies that have evaluated these strategies have included acute MI and nonacute MI patients and have demonstrated that shock teams can decrease time to intervention and may improve mortality.154-156 Also, the interhospital transport of CS patients with mobile CS or ECMO teams is feasible.157,158 A recent pilot study also demonstrated that in MI-CS patients, a protocol-driven collaborative management approach among several hospitals that included early identification, relatively liberal mechanical circulatory support (Impella) implant criteria, unloading before reperfusion, hemodynamic monitoring, and escalation based on hemodynamics was associated with 76% survival to discharge.159 The absolute magnitude of benefit of these interventions is not known given the absence of a “standard” management/control group, but the results are encouraging, and larger validation studies are underway.

**POST-HOSPITALIZATION AND LONG-TERM OUTCOMES**

In the GUSTO 1 trial, 30-day survivors of MI-CS had an annual mortality of 2%-4% during years 2-11, no different from patients who had acute MI without shock. Predictors of higher long-term mortality in 30-day survivors were older age, male gender, DM, higher Killip class, hypertension, previous MI, current smoking, anterior infarct, previous cardiovascular disease, prior CABG, and higher HR.160 This excellent long-term survival in GUSTO 1 preceded the routine utilization of modern heart failure therapies. The “calm after the storm” was also seen in the SHOCK trial, where 62% of those in the early revascularization arm who survived hospitalization were alive 6 years later. Predictors of higher long-term mortality were similar to those observed for 30-day mortality and included older age, shock on admission, creatinine ≥1.9 mg/dL, history of hypertension, and noninferior wall location. LVEF was also predictive of mortality, but hemodynamic variables such as cardiac power index and cardiac index that predicted 30-day mortality did not predict long-term mortality.161 In older Medicare patients who have MI-CS and survive to discharge, the risk of death was higher than in nonshock patients for the first 60 days, but comparable to nonshock patients after 60 days. Over 30 independent predictors of 1-year survival were noted, including age, LVEF, and peak creatinine level.162

**CONCLUSIONS**

Several findings are consistently observed across many studies. Revascularization has benefit at all risk levels. Hemodynamic parameters and measures of end-organ perfusion, including lactate and creatinine, are important predictors of outcomes. Mechanical circulatory support has a role in improving outcomes, but defining appropriate population and best mode of support has been difficult. Earlier MCS appears to be beneficial, but when is too early and when is too late has not been conclusively determined and needs further study. Emerging concepts of “door-to-unloading” time and well-defined bundles of management approaches await large multicenter clinical trials. Despite high clinical acuity at presentation, many MI-CS patients can have excellent long-term outcomes with some recovery of contractile function and physiologic accommodation. Therefore, a focus on improvement in early mortality via the thorough understanding of the inflammatory response and prevention or early reversal of end-organ dysfunction may provide these critically ill patients with improved quality and longer duration of life.

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