REVIEW ARTICLE

Cardiogenic Shock

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N Engl J Med 2026;394:62-77.
DOI: 10.1056/NEJMra2312086

CME

Cardiogenic shock remains a major unsolved problem despite progress such as implementation of new definitions, staging categories, and detailed phenotyping of this heterogeneous disorder. However, there are few evidence-based strategies to decrease mortality, which remains at 40 to 50% at 30 days after the onset of cardiogenic shock; such strategies currently include revascularization of the culprit lesion in myocardial infarction-related cardiogenic shock and the use of microaxial flow pumps in selected patients with ST-segment elevation myocardial infarction. Here, we summarize recent advances in the management and diagnosis of cardiogenic shock, including staging and therapies, and describe needs that warrant further research.

Definition and Diagnosis

The Shock Academic Research Consortium defined cardiogenic shock as a cardiac disorder that results in both clinical and biochemical evidence of sustained tissue hypoperfusion.[1] Integral elements of this definition are a systolic blood pressure of less than 90 mm Hg for more than 30 minutes or a need for inotropes, vasopressors, or mechanical circulatory support to maintain a blood pressure of 90 mm Hg or higher and evidence of systemic hypoperfusion. There are also subsets of cardiogenic shock, such as normotensive cardiogenic shock, which occurs when the systolic blood pressure is over 90 mm Hg despite evidence of organ hypoperfusion.[1] Although septic shock and hypovolemic shock also manifest with hypotension and end-organ hypoperfusion, mixed shock, defined by cardiogenic shock with at least one additional contributing cause of shock that exists simultaneously, also occurs.[2]

In clinical practice, the diagnosis of cardiogenic shock is based on persistent hypotension without an adequate response to volume replacement and end-organ hypoperfusion, such as cold and poorly perfused extremities, oliguria, or altered mental status. For established cardiogenic shock, an elevated level of arterial lactate is a biochemical marker of inadequate tissue perfusion.[1,3] The diagnosis also requires an echocardiogram that shows cardiac dysfunction. Distinct hemodynamic features measured by right heart catheterization also are used to define cardiogenic shock, such as a low cardiac index (≤2.2 liters per minute per square meter of body-surface area) often combined with a high systemic vascular resistance index (>2200 dynes per centimeter per second).[1,2] These hemodynamic features are also helpful in the differential diagnosis of other types of shock or mixed-shock. Definitions of cardiogenic shock that have been used in major randomized trials of cardiogenic shock often differ from the clinical definition and are shown in Table 1.

The Society for Cardiovascular Angiography and Interventions and the Heart Failure Society of America have also proposed a system for staging cardiogenic shock that is based on the severity of shock.[3] In this system, the five categories of shock are at risk (stage A), preshock or beginning shock (stage B), classic shock (stage C), deteriorating shock (stage D) and extreme shock (stage E) (Fig. 1). The

KEY POINTS

CARDIOGENIC SHOCK

- Cardiogenic shock is associated with early mortality approaching 50%, depending on the underlying cause.
- Immediate revascularization in infarct-related cardiogenic shock reduces mortality.
- In patients with multivessel coronary artery disease, current evidence indicates that only the culprit lesion should be revascularized in the acute setting.
- Mechanical circulatory support decreases mortality in selected patient groups.
- Further research is urgently needed to address the high mortality associated with cardiogenic shock.

stages used in this system are defined by blood pressure, biomarkers (levels of lactate, alanine aminotransferase, and pH), and treatment intensity and are now commonly used in research and clinical practice.[4,9-11] The limitations of this grading system include the need for at least two clinical assessments owing to the dynamic nature of cardiogenic shock. A degree of subjectivity is involved in determining the shock stage, which renders comparisons between studies difficult.[11]

PATHOPHYSIOLOGICAL FACTORS

Cardiogenic shock is characterized by profound decreases in cardiac function and the cardiac index. These changes precipitate a deleterious downward spiral of low blood pressure and coronary ischemia followed by decreased cardiac contractility and further reductions in the cardiac index. There may also be an early period of compensatory systemic vasoconstriction, which may be counteracted in later stages of shock by pathological vasodilation due to inflammatory reactions.[2] The reduction in the cardiac index causes severe tissue hypoxemia that increases levels of arterial lactate. Cardiogenic shock can lead to multiorgan failure, including failure of the heart itself as well as the kidneys, liver, lung, gut, immune system, and coagulation system. Therefore, biomarker levels (in addition to lactate levels) that indicate inflammation and organ dysfunction are also associated with a poor prognosis (Fig. 1).

ETIOLOGIC AND EPIDEMIOLOGIC FACTORS AND CARDIOGENIC-SHOCK PHENOTYPES

The causes of cardiogenic shock can be divided into groups on the basis of etiologic factors: acute myocardial infarction; factors not related to myocardial infarction, such as new or acute-on-chronic heart failure; or secondary nonmyocardial causes and postcardiotomy shock (Fig. 2).[1] For decades, ventricular failure after acute myocardial infarction was the most frequent cause of cardiogenic shock, with mechanical complications related to the infarction representing a rarer cause. Because treatment strategies for acute myocardial infarction have advanced with improved prevention and early revascularization, the relative proportion of cardiogenic shock events attributable to myocardial infarction is steadily declining, and non–infarction-related cardiogenic shock now outnumbers infarct-related cardiogenic shock (Fig. 3).[12]

Cardiogenic-shock mortality remains high. An early study of revascularization in patients with infarct-related cardiogenic shock was associated with a mortality of 47%.[5] Today, cardiogenic shock remains the leading cause of death among hospitalized patients with myocardial infarction.[13] Some registries have reported an increase in mortality, which may be explained by an aging population and an increasing prevalence of coexisting conditions and unfavorable risk profiles among patients with cardiogenic shock.[14,15] In addition, 71% of all patients with infarct-related cardiogenic shock have frailty issues.[16]

Among 8974 patients with cardiogenic shock, in-hospital mortality was 48% among patients with mixed-cause cardiogenic shock, 41% among those with infarct-related cardiogenic shock, 31% among those with new heart failure, 31% among those with secondary causes of cardiogenic shock, and 25% among those with acute-on-chronic heart failure–related cardiogenic shock.[12] Causes of death among patients with cardiogenic shock are often difficult to assess because of multiorgan dysfunction or withdrawal of life support.

Table 1. Definitions of Cardiogenic Shock in Major Randomized Trials.*

SHOCK[5]	TRIUMPH[6]	IABP-SHOCK II[7]	CULPRIT-SHOCK[8]	ECLS-SHOCK[4]	DanGer Shock[9]
One of the following: AMI with SBP <90 mm Hg for ≥30 min Support to maintain SBP ≥90 mm Hg Plus both of the following: End-organ hypoperfusion (urine output <30 ml/hr) or cool extremities Heart rate >60 beats/min Hemodynamic criteria†: Cardiac index of ≤2.2 liters/min/m^2 Plus pulmonary capillary wedge pressure ≥15 mm Hg	AMI with patency of infarct-related artery spontaneously or after PCI Refractory cardiogenic shock >1 hr after PCI with SBP <100 mm Hg despite vasopressors (dopamine ≥7 μg/kg/min or norepinephrine or epinephrine ≥0.15 μg/kg/min) End-organ hypoperfusion Clinical or hemodynamic criteria for elevated left ventricular filling pressure LVEF <40%	One of the following: AMI with SBP <90 mm Hg for ≥30 min Catecholamines required to maintain SBP >90 mm Hg Plus clinical pulmonary congestion Plus impaired end-organ perfusion with at least one of the following criteria: Altered mental status Cold, clammy skin and extremities Urine output <30 ml/hr Lactate level >2.0 mmol/liter	AMI with planned early revascularization by PCI Multivessel coronary artery disease defined as >70% stenosis in at least two major vessels (≥2 mm diameter) with identifiable culprit lesion One of the following: SBP <90 mm Hg for >30 min Use of catecholamines required to maintain SBP >90 mm Hg Pulmonary congestion Impaired organ perfusion with at least one of the following criteria: Altered mental status Cold, clammy skin and extremities Urine output <30 ml/hr Lactate level >2.0 mmol/liter	MI with planned early revascularization with PCI or CABG One of the following: SBP <90 mm Hg for >30 min Catecholamine therapy required to maintain SBP >90 mm Hg Impaired organ perfusion with at least one of the following criteria: Altered mental status Cold, clammy skin and extremities Urine output <30 ml/hr Lactate level >3.0 mmol/liter	STEMI <36 hr before randomization Cardiogenic shock with: SBP <100 mm Hg or use of vasopressors to maintain SBP >100 mm Hg Lactate level >2.5 mmol/liter or SVO_2 <55% LVEF <45%

* AMI denotes acute myocardial infarction, CABG coronary-artery bypass grafting, LVEF left ventricular ejection fraction, MI myocardial infarction, PCI percutaneous coronary intervention, SBP systolic blood pressure, STEMI ST-segment elevation myocardial infarction, and SVO_2 mixed venous oxygen saturation.
† Hemodynamic criteria are not required in anterior infarction or if pulmonary congestion is shown on chest radiography.

In a recent analysis of registry data, persistent cardiogenic shock was the dominant mode of death, followed by arrhythmia, anoxic brain injury, and respiratory failure.[17]

Phenotyping of cardiogenic shock can be performed on the basis of the type of ventricular failure, with the most dominant form being left ventricular failure.[18] However, biventricular failure is also common, and right ventricular involvement was observed in 44% of patients with infarct-related cardiogenic shock and even more common in non–infarction-related cardiogenic shock.[18] Other phenotypes are related to mechanical complications, such as acute ventricular rupture or acute mitral regurgitation in infarct-related cardiogenic shock.[19,20] These phenotypes require specific treatment strategies with respect to fluid management, inotropes and vasopressors, surgery and other interventions, and selection of mechanical circulatory support devices.[21,22]

Another shock phenotype is seen in patients who are resuscitated and comatose after cardiac arrest. These patients may have reduced cardiac function due to cardiac stunning once they have regained spontaneous circulation. Many of these patients have been intubated and sedated, resulting in vasopressor use to counteract the vasodilatory and cardiodepressant effects of these interventions. At the same time, high lactate levels are present owing to long durations of no flow or slow flow; initial lactate levels do not correlate well with the cardiac index in comatose patients after cardiac arrest.[23] In addition, approximately 20 to 30% of patients who are comatose after resuscitation may die from brain injury rather than from circulatory failure.[4,24]

PROGNOSIS ASSESSMENT

There are several clinical factors and biomarkers that have been used to assess prognosis through multiple scoring systems used for patients in the stages of preshock,[25-27] shock,[28,29] and shock with mechanical circulatory support[13] (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In clinical practice, the Society for Cardiovascular Angiography and Interventions shock-stage system should be used (Fig. 1); this system is useful for determining mortality at each stage but is imprecise for individual prognosis.[3]

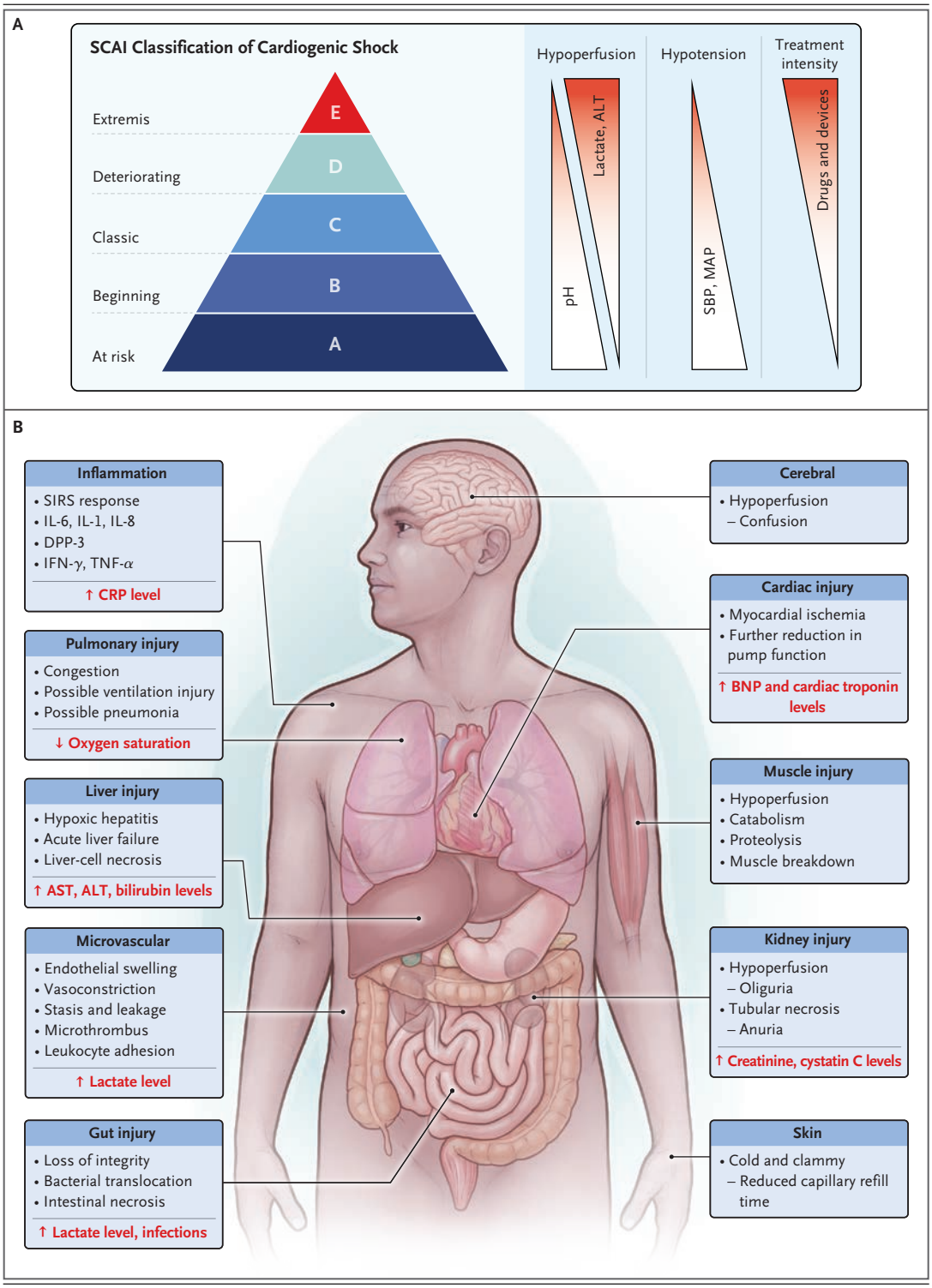
TREATMENT

SYSTEMS OF CARE

Patients with cardiogenic shock should be treated at specialized tertiary-care centers that have the ability to start and escalate mechanical circulatory support and provide cardiac interventions and that have cardiac intensive care units and cardiac surgery facilities on site.[22,30] Observational studies have shown that mortality is lower in centers with the highest quartile of mean annual cardiogenic shock case volume (≥107 cases per year).[31,32] In addition, the collaboration of expert multidisciplinary shock teams — usually consisting of intensivists, interventionalists, perfusionists, and cardiothoracic surgeons — and regionalized shock-care systems may be an independent factor in improving outcomes.[33,34]

GENERAL INTENSIVE CARE UNIT TREATMENT

Treatment in the intensive care unit should follow guideline-recommended supportive approaches, including blood glucose level control; lactate measurements, performed at a high frequency (every hour) until stabilization; adequate oxygen delivery; thromboprophylaxis; stress-ulcer prophylaxis; and early enteral feeding after initial stabilization.[35] All vasoactive medication must be given intravenously. If mechanical ventilation is used, lung-protective strategies (tidal volume of 6 to 8 ml per kilogram of predicted body weight) should be implemented if feasible.[36] Noninvasive ventilation with continuous positive airway pressure may be an option to prevent intubation in borderline situations, although care must be taken when right heart failure dominates. Measurements of urinary volume and serial assessments of creatinine levels should be obtained, and renal replacement therapy should be initiated in patients who have acute renal failure with clinical signs of uremia, otherwise-untreatable volume overload, metabolic acidosis, or refractory hyperkalemia. Earlier initiation of renal replacement therapy in the absence of these conventional emergent indications has been shown to have no effect on outcome.[37] In major trials of cardiogenic shock, renal replacement therapy was initiated for 18% of patients in the IABP-SHOCK II (Intraaortic Balloon Pump in Cardiogenic Shock II) trial,[7] 14% in the CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock) trial,[8] and 11% in the



ECLS-SHOCK (Extracorporeal Life Support in Cardiogenic Shock) trial.[4] In an analysis from the DanGer Shock (Danish–German Cardiogenic Shock) trial, renal replacement appears to have been initiated sooner than in other cardiogenic shock trials.[4,7,8,38] However, the appropriate time at which to start renal replacement therapy still remains unclear.

Figure 1 (facing page). Organ Involvement and Staging of Cardiogenic Shock.

Panel A shows the cardiogenic shock staging system recommended by the Society for Cardiovascular Angiography and Interventions (SCAI) and the associated degree of hypoperfusion and hypotension and degree of treatment intensity. Stage A denotes risk for cardiogenic shock development but no current presence of signs or symptoms of shock and a lactate level of up to 2 mmol per liter. Stage B denotes beginning cardiogenic shock with clinical evidence of relative hypotension or tachycardia without hypoperfusion and a lactate level of up to 2 mmol per liter. Stage C denotes classic cardiogenic shock with a lactate level greater than 2 mmol per liter, cardiac index of less than 2.2 liters per minute per square meter of body-surface area and pulmonary capillary wedge pressure over 15 mm Hg. Stage D denotes deteriorating cardiogenic shock with a rising lactate level or a lactate level that is consistently higher than 2 mmol per liter and hemodynamic signs that lead to escalating doses of vasopressors or the addition of mechanical circulatory support. Stage E denotes extreme cardiogenic shock with a lactate level greater than 8 mmol per liter and hemodynamically profound hypotension despite maximal hemodynamic support. (Panel A is adapted from the SCAI SHOCK Classification pyramid.[3]) Panel B shows multisystem organ involvement in cardiogenic shock with associated clinical signs and laboratory markers. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, BNP brain natriuretic peptide, CRP C-reactive protein, DPP-3 dipeptidyl peptidase 3, IFN-γ interferon-γ, IL interleukin, MAP mean arterial blood pressure, SBP systolic blood pressure, SIRS systemic inflammatory response syndrome, and TNF-α tumor necrosis factor α.

HEMODYNAMIC MONITORING

In general, echocardiography — or at least a point-of-care ultrasound — is the first method to be used to delineate the cause of cardiogenic shock and for further phenotyping.[30,39,40] Currently, there is no consensus on the appropriate method of invasive hemodynamic monitoring to assess and guide treatment of cardiogenic shock. Guidelines and scientific statements suggest using pulmonary artery catheters early in the treatment course for selected patients who do not have a response to initial therapy or in cases of diagnostic or therapeutic uncertainty, such as in mixed shock.[2,30,39,40] The understanding of the etiologic factors in cardiogenic shock has changed in the past decade, and several hemodynamic profiles have been defined in which the prognosis is affected by right ventricular or biventricular failure.[18] However, data are not yet available from randomized trials exploring a benefit of pulmonary artery catheters (see Table 2 for a description of an ongoing trial) or other hemodynamic monitoring on outcomes.

PHARMACOLOGIC MANAGEMENT OF CARDIOGENIC SHOCK

FLUID MANAGEMENT

In patients who have central hypovolemia without congestion and in whom hemodynamics improve after a leg-raise test, administration of crystalloid solutions may improve hemodynamics.[41] Intravenous loop diuretics may reduce fluid retention and pulmonary edema in cases of volume overload. Avoiding hypovolemia is crucial, and fluid management should be based on pathophysiological considerations and may differ on the basis of right ventricular–dominant or left ventricular–dominant failure.[42]

INOTROPES AND INODILATORS

Contractility can be enhanced by inotrope therapy, although the effect of these agents on outcomes is not well established. The first-line choice of an inotrope lacks a clear consensus[30,39,40] and the selection of inotropes for treating patients in cardiogenic shock varies widely.[43] Although dobutamine is commonly used as the primary inotrope agent in patients with left ventricular failure, levosimendan and phosphodiesterase 3 inhibitors such as milrinone might serve as an alternative or additional option when dobutamine proves ineffective. A Cochrane analysis found insufficient evidence to establish the superiority of any particular inotrope in terms of mortality.[44] In a randomized trial, no differences in outcomes were observed between milrinone and dobutamine.[10] Levosimendan, a calcium-sensitizer, increases cardiac inotropy and reduces afterload.[30] In a recent randomized trial, levosimendan did not facilitate weaning from veno-arterial extracorporeal membrane oxygenation (ECMO).[45] Results from other randomized trials in cardiogenic shock are lacking, although there are ongoing relevant clinical trials (Table 2).

VASOPRESSORS

In a randomized comparison of 1679 patients with diverse causes of shock, treatment with dopamine was associated with substantially more arrhythmic events than treatment with norepinephrine but with no difference in mortality.[46] Epinephrine and norepinephrine had similar

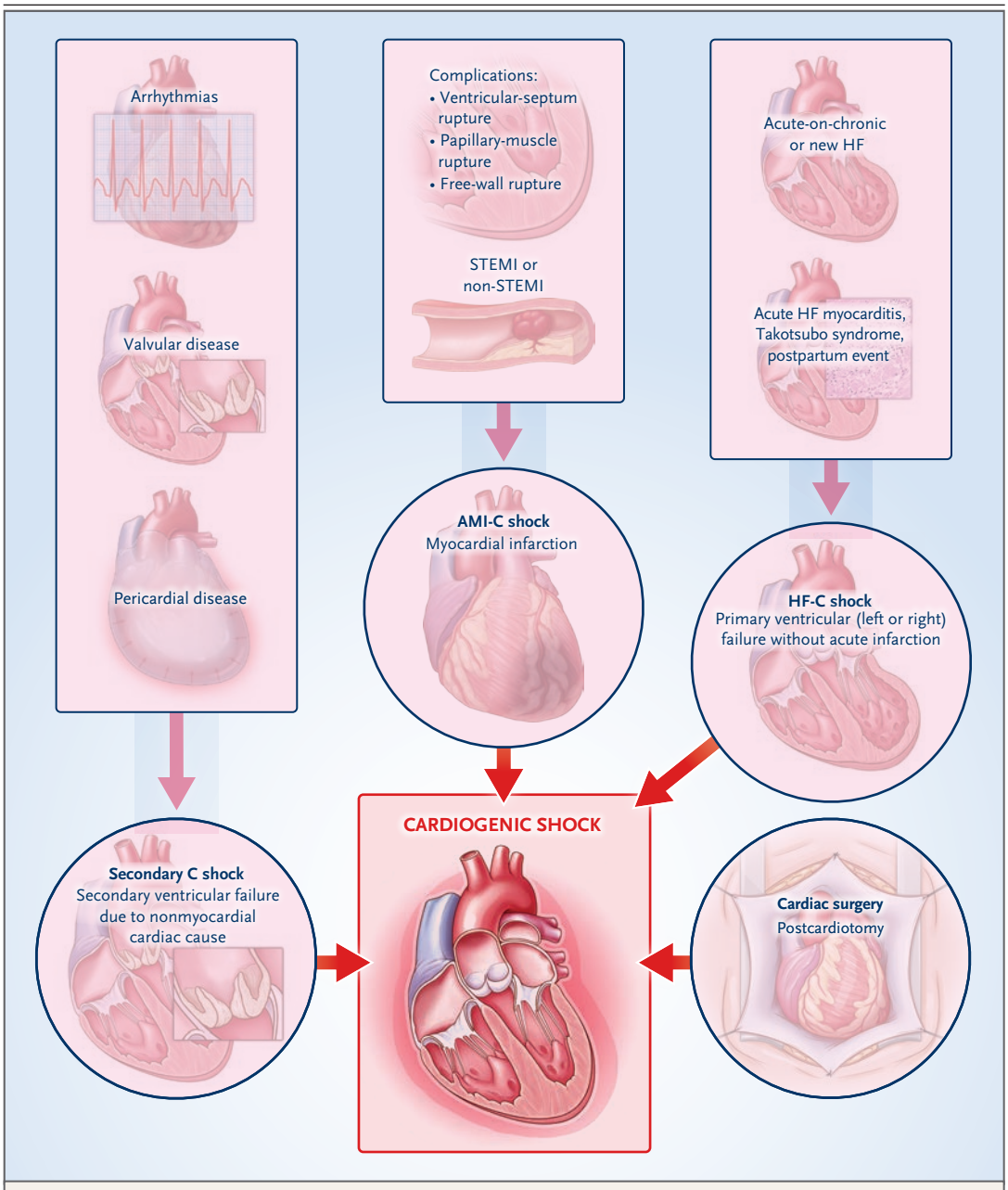


Figure 2. Causes of Cardiogenic Shock.

AMI-C shock denotes acute myocardial infarction–related cardiogenic shock, C shock cardiogenic shock, HF heart failure, HF-C shock heart failure–related cardiogenic shock, and STEMI ST-segment elevation myocardial infarction.

effects on the cardiac index, but the effects of epinephrine on heart rate and metabolic changes, including lactic acidosis, were unfavorable.[47] These findings suggest that norepinephrine probably is the vasoconstrictor of choice when blood pressure is low and tissue perfusion pressure is insufficient.[40] Studies of vasopressin in cardiogenic shock are lacking. The target mean arterial blood pressure with vasopressor therapy has not been well defined. A mean arterial pressure greater than 65 mm Hg is usually considered adequate.[22,30] An ongoing trial is testing a mean arterial blood-

pressure target of 55 mm Hg as compared with 65 mm Hg in infarct-related cardiogenic shock (Table 2). The hemodynamic effects of inodilators and vasopressors are shown in Figure 3.

MECHANICAL CIRCULATORY SUPPORT DEVICES

Temporary percutaneous mechanical circulatory support can stabilize hemodynamics and enhance end-organ perfusion in cardiogenic shock.[13] General mechanical circulatory support concepts include bridge to decision, bridge to recovery, bridge to durable left ventricular assist device, or bridge to heart transplantation. Various modes of mechanical circulatory support offer partial or complete circulatory support, with or without oxygenation, and these devices operate through distinct mechanisms, delivering different levels of hemodynamic support, and each type is associated with specific potential benefits and complications (Fig. S1).[13] A thorough comprehension of the risk–benefit profile of each device is paramount for determining its role in managing cardiogenic shock of different causes and at different stages. In addition to single devices, combinations of devices are feasible for addressing specific needs, such as pulmonary support.[48,49]

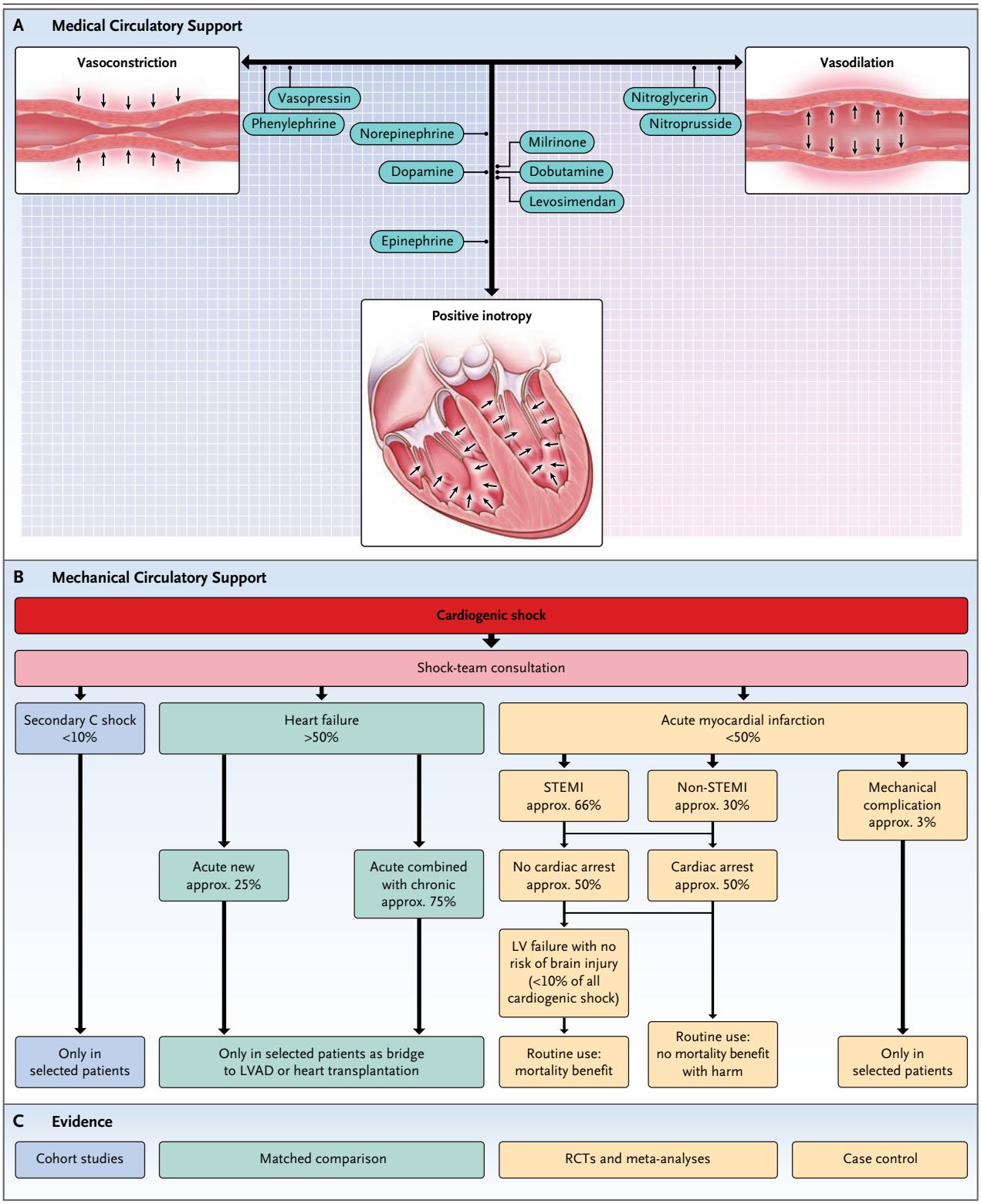
INTRAAORTIC BALLOON PUMP

Owing to its ease of insertion, cost, and favorable adverse-event profile, the intraaortic balloon pump (IABP) is still widely used.[50] An IABP placed in the descending aorta enhances coronary perfusion during diastole and reduces afterload during systole. As compared with medical therapy, IABPs did not augment cardiac index or any other hemodynamic variable, and a large-scale randomized trial in infarct-related cardiogenic shock did not show a survival benefit as compared with medical therapy.[7,51,52] Furthermore, the use of IABPs did not improve survival or successful bridging to heart replacement therapy in heart failure–related cardiogenic shock in the randomized Altshock-2 (Study on Early Intra-aortic Balloon Pump Placement in Acute Decompensated Heart Failure Complicated by Cardiogenic Shock).[53] On the basis of these data, routine use of IABPs in infarct-related cardiogenic shock is not recommended, although such devices are recommended for patients with infarct-related mechanical complications in European guidelines (but not U.S. guidelines).[54,55]

VENOARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION

Venoarterial ECMO, which delivers flow support of up to 6 liters per minute, can provide full respiratory and circulatory assistance for the right and left ventricles.[13] Peripheral venoarterial ECMO involves venous cannulation with the end of the cannula in the right atrium, directing blood to an extracorporeal pump and membrane oxygenator, with blood returned in a retrograde manner into the descending aorta.[56] Venoarterial ECMO is increasingly used in patients with cardiogenic shock.[56] The recent ECLS-SHOCK trial, which enrolled patients with severe infarct-related cardiogenic shock, assessed early routine venoarterial ECMO as compared with standard treatment. The trial showed no difference in death from any cause at 30 days between patients assigned to the group that received venoarterial ECMO (47.8%) and those in the control group (49.0%) (relative risk, 0.98; 95% confidence interval [CI], 0.80 to 1.19; P=0.81),[4] with similar mortality in the two groups at 1-year follow-up.[57] A substantial number of patients enrolled in the trial had a cardiac-arrest phenotype, which possibly explained the neutral results. These data are in line with a meta-analysis of individual-patient data from four randomized venoarterial ECMO trials that did not show a mortality benefit in patients with infarct-related cardiogenic shock but did identify more complications with device use.[58] Currently, routine use of venoarterial ECMO in cardiogenic shock is not recommended in U.S. guidelines.[55]

The venoarterial ECMO device itself may even harm the heart, owing to an increase in afterload caused by generation of retrograde blood flow in the aorta.[59] Active unloading of the left ventricle with microaxial flow pumps or an IABP aims to mitigate these adverse hemodynamic effects, and observational studies suggest mortality is lower when these devices are used.[60,61] However, a recent randomized trial comparing routine left ventricular unloading by a transseptal left atrial cannula as compared with venoarterial ECMO alone showed no effect on mortality.[62] Additional evidence from randomized trials is currently in development (Table 2).



MICROAXIAL FLOW PUMPS

Microaxial flow pumps provide a peak flow of approximately 4.3 liters per minute with a percutaneously placed catheter and are used to treat cardiogenic shock with predominant left ventricular dysfunction. Microaxial flow pumps have

Figure 3 (facing page). Medical and Mechanical Circulatory Support.

Panel A shows the hemodynamic effects of vasoactive drugs, such as vasopressors and inodilators on vasoconstriction, vasodilation, and inotropy. Panel B shows possible indications for mechanical circulatory support with respect to different causes of cardiogenic shock based on current evidence. No risk of hypoxic brain injury relates to the DanGer Shock trial criteria. LV denotes left ventricular, LVAD left ventricular assist device, and RCT randomized, controlled trial.

been investigated in few randomized trials involving patients with cardiogenic shock[63] and in large-scale propensity-matched studies including more than 100,000 patients; the studies consistently have shown no survival benefit and higher complication rates.[64-66] The recent DanGer Shock trial, which enrolled 360 patients with ST-segment elevation myocardial infarction who were not at risk for hypoxic brain injury, evaluated outcomes among patients treated with the microaxial flow pump as compared with those among patients who received standard (i.e., no microaxial flow pump but mechanical circulatory support for specific situations); in that trial, the pump led to lower all-cause mortality at 180 days (hazard ratio, 0.74; 95% CI, 0.55 to 0.99; P=0.04).[9] The survival benefit was sustained for up to 10 years, with proportional-hazards ratios over time suggesting a lasting effect.[67] This trial also reported a greater incidence of bleeding and limb ischemia as well as renal replacement therapy in the microaxial flow pump group than in the control group.[38] Even though this trial showed a benefit of the microaxial flow pump among selected patients with left ventricular–dominant cardiogenic shock,[9,68] further discussion regarding appropriate patient selection and complication avoidance is ongoing.[69,70] Current U.S. guidelines recommend use of the microaxial flow pump in selected patients with a class IIa indication.[55] Two other trials have started to investigate microaxial flow pumps in infarct-related cardiogenic shock; however, one was suspended by a data and safety monitoring board after the results of the DanGer Shock trial were published (Table 2).

LEFT ATRIAL-TO-FEMORAL ARTERIAL DEVICES

The TandemHeart mechanical circulatory support device, which directs flow from the left atrium to a femoral artery, is rarely used in clinical practice as compared with venoarterial ECMO or microaxial flow pumps. This device unloads the left ventricle and can support the heart with pump flow rates of up to 4 liters per minute, and has been investigated in two small trials that predominantly enrolled patients with infarct-related cardiogenic shock and did not show conclusive evidence on clinical outcome.[63]

GENERAL REFLECTIONS ON MECHANICAL CIRCULATORY SUPPORT

Patient selection for temporary mechanical circulatory support in cardiogenic shock is key to identifying a possible benefit with regard to clinical outcomes.[71] The use of mechanical circulatory support varies and is influenced by expert opinions, practitioner experience, and health care reimbursement, among other factors.[71] Appropriate patient and device selection is also influenced by a balance among efficacy, institutional experience, and device-related complications.

Currently, approximately 50 to 60% of patients with infarct-related cardiogenic shock survive without the use of any mechanical circulatory support device.[4,7-9,71] In these patients, use of these devices has the potential to lead to device-associated complications that may include death. Among the 40 to 50% of patients who do not survive cardiogenic shock without mechanical circulatory support, there are circumstances in which the devices may not improve mortality, such as severe shock, older age, and frailty, and those in which even the best available device cannot change the outcome, such as anoxic brain injury. In a recent analysis of registry data, only 5% of all patients admitted for cardiogenic shock and 32% of patients with ST-segment elevation myocardial infarction cardiogenic shock were considered appropriate candidates for mechanical circulatory support on the basis of the DanGer Shock trial eligibility criteria.[72]

Additional evidence for the effect of mechanical circulatory support on outcomes in patients with infarct-related cardiogenic shock has been gathered from a meta-analysis of individual-level data from 1059 patients in nine trials of mechanical circulatory support as compared with control interventions with extended 6-month follow-up.[71] Overall, there was no difference in mortality between mechanical circulatory support and control interventions. However, there was a mortality benefit of temporary mechanical circulatory support among patients who had

Table 2. Ongoing (Still Recruiting or Completed but Not Published) Randomized Trials in Cardiogenic Shock.*

Trial and ClincalTrials.gov No.	Type of Cardiogenic Shock	Experimental Intervention	Control	Sample Size	Primary End Point	Remarks
Mechanical circulatory support						
ECMO-RRT (NCT02870946)	AMI and HF	VA-ECMO plus RRT	VA-ECMO only	362	Mortality at 30 days	
HEMO-ECMO (NCT03729765)	AMI and HF	VA-ECMO plus hemoperfusion	VA-ECMO	60	Change in IL-6 level at 3 days	
ANCHOR (NCT04184635)	AMI	VA-ECMO plus IABP	Best medical therapy	400	Mortality or VA-ECMO at 30 days	
UNLOAD-ECMO (NCT05577195)	AMI and HF	VA-ECMO plus Impella CP	VA-ECMO	198	Mortality at 30 days	Lactate level >5 mmol/liter for inclusion
ULYSS (NCT05366452)	AMI	Impella CP	Best medical therapy	204	Either composite of all-cause death, ECMO, LVAD, or heart transplantation at 30 days	
RECOVER IV (NCT05506449)	AMI	Impella CP	Best medical therapy including IABP	558	Mortality at 30 days	Stopped early for safety
ICONE (NCT05699005)	AMI and HF	Individualized transfusion during VA-ECMO	Conventional transfusion during VA-ECMO	138	Total number of PRBCs transfused during support, adjusted for VA- ECMO duration	
REMAP ECMO (NCT05913622)	AMI and HF	VA-ECMO plus IABP	VA-ECMO	430	Successful weaning from VA-ECMO at 30 days	Bayesian analysis, adaptive design
Transcatheter interventions						
MINOS (NCT05298124)	AMI and HF	M-TEER	Best medical therapy	144	Composite of in-hospital death from any cause, cardiac transplantation, implantation of durable LVAD, or discharge with palliative inotropic therapy	Mitral regurgitation grade 3+ or 4+
RESCUE-SHOCK (NCT05527717)	AMI	Immediate multivessel PCI with VA-ECMO	Culprit-lesion only PCI with VA-ECMO	560	Composite of death from any cause, LVAD, or heart transplantation at 90 days	
Inotropes, vasopressors, and hemodynamic agents						
LevoHeartShock (NCT04020263)	AMI and HF	Levosimendan	Placebo	610	Composite of death from any cause, VA-ECMO, or dialysis at 30 days	

CAPITAL DOREMI-2 (NCT05267886)	AMI and HF	Dobutamine or milrinone	Placebo	346	Composite of in-hospital death from any cause and the occurrence of any of the following ≤12 hr after start of intervention: • Sustained hypotension (MAP ≤55 mm Hg) or sustained use of high-dose vasopressors • Lactate level >3.5 mmol/liter at 6 hr or thereafter • Need for MCS • Atrial or ventricular arrhythmia leading to emergent electrical cardioversion • Cardiac arrest	SCAI shock C or D
NorShock (NCT05168462)	AMI	MAP ≥55 mm Hg	MAP ≥65 mm Hg	776	Composite of death from any cause and severe renal failure leading to renal replacement therapy	
PACCS (NCT05485376)	HF	PAC	No PAC	400	In-hospital mortality	Lactate level >2 mmol/liter
Systemic approaches and antiplatelet agents						
DAPT-SHOCK (NCT03551964)	AMI	Cangrelor plus DAPT with ticagrelor	DAPT with ticagrelor	605	Laboratory end point, platelet reactivity index; clinical end point, MACE	Primary laboratory end point met; primary clinical end point not met
DOBERMANN (NCT05350592)	AMI preshock	Tocilizumab or dobutamine (or both)	Placebo		Pro–B-type natriuretic peptide plasma concentration <48 hr	2×2 factorial design; patients with preshock, no overt cardiogenic shock; double-blind
COCCOA (NCT03773822) — Completed	AMI and HF	Combination of hydrocortisone and fludrocortisone	Placebo	380	Free of corticosteroid therapy at day 7	

* DAPT denotes dual antiplatelet therapy, ECMO extracorporeal membrane oxygenation, HF heart failure, IABP intraaortic balloon pump, IL-6 interleukin-6, LVAD left ventricular assist device, M-TEER mitral transcatheter edge-to-edge repair, MACE major adverse cardiac event, MAP mean arterial blood pressure, MCS mechanical circulatory support, PAC pulmonary artery catheter, RRT renal replacement therapy, SCAI Society for Cardiovascular Angiography and Interventions, and VA-ECMO venoarterial ECMO.

the left ventricular dysfunction–dominant phenotype and who were at low risk for hypoxic brain injury (hazard ratio, 0.77; 95% CI, 0.61 to 0.97; P=0.024). Complication rates were consistently higher among patients in the mechanical circulatory support group, independent of the device used.

In the Altshock-2 trial of heart failure–related cardiogenic shock, early placement of an IABP did not improve survival or the bridge to heart replacement therapy at 60 days, although the trial only enrolled 101 patients.[53] Other randomized trials of mechanical circulatory support in this patient population are lacking, and clinical practice is based on expert consensus opinion only. In this clinical setting, percutaneous mechanical circulatory support should only be considered in patients in whom there is a chance of myocardial recovery or in patients who are eligible for permanent ventricular assist devices or heart transplantation.

Although some data suggest that mechanical circulatory support improves outcomes in selected patient subgroups, further randomized trials including patients with specific cardiogenic-shock phenotypes are needed. The evidence is also insufficient regarding the risks and benefits of combined mechanical circulatory support strategies, the practices surrounding mechanical circulatory support escalation and de-escalation, management of complications, and costs.

TREATMENT OF CAUSES OF CARDIOGENIC SHOCK

REVASCULARIZATION IN ACUTE MYOCARDIAL INFARCTION

The SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial did not show a reduction in 30-day mortality with early revascularization as compared with initial medical stabilization.[5] However, longer-term results showed reduced mortality (by up to 6 years) with early revascularization.[73] Therefore, early revascularization is highly recommended in society guidelines.[54,74] Multiple registries have shown that a delay in revascularization in the clinical setting of cardiogenic shock is associated with worse clinical outcomes, a finding that has led to a call for more efforts to reduce the time from first medical contact to balloon inflation (door-to-balloon time) in this patient population.[39,40]

In an observational study, patients with ST-segment elevation myocardial infarction who presented with cardiogenic shock and prolonged interhospital transport times had a clinical benefit from a pharmacoinvasive approach with fibrinolysis as compared with primary percutaneous coronary intervention (PCI). The pharmacoinvasive approach was not associated with an increase in major bleeding.[75]

The vast majority (70 to 80%) of patients with infarct-related cardiogenic shock have multivessel coronary artery disease.[21] The CULPRIT-SHOCK (Culprit-Lesion-Only PCI versus Multivessel PCI in Cardiogenic Shock) trial showed a clinical benefit for culprit-lesion–only PCI as compared with immediate multivessel PCI.[8,76] The rate of death and renal replacement therapy in culprit-lesion–only PCI was 45.9%, as compared with 55.4% for immediate multivessel PCI (relative risk, 0.83; 95% CI, 0.71 to 0.96; P=0.01), which was driven by a significant reduction in mortality. Most surviving patients in the culprit-lesion–only PCI group in CULPRIT-SHOCK underwent staged, protocol-recommended revascularization during follow-up. Thus, the current preferred revascularization strategy is culprit-lesion–only PCI with subsequent staged revascularization after clinical stabilization.[54,55,74] If the patient's coronary anatomy is not amenable to PCI, coronary-artery bypass grafting may be considered.[54,55,74]

MECHANICAL AND VALVULAR COMPLICATIONS AND ACCESS-SITE CONSIDERATIONS

Mechanical complications after acute myocardial infarction, such as papillary muscle rupture or ventricular septal-wall and free-wall rupture or defects, are rare and of decreasing incidence; however, if these occur, the prognosis is dismal. Therefore, surgical or percutaneous correction is required for survival.[20] Further details regarding valvular causes of cardiogenic shock, myocarditis, and exploratory antiinflammatory treatments, along with details of access-site considerations, are provided in the Supplementary Appendix.

FUTURE PERSPECTIVES

In general, randomized trials in cardiogenic shock are difficult to perform, and only a few trials have

enrolled a sufficient number of patients to be adequately powered to detect differences in outcomes (Table 1). The diversity of cardiogenic-shock phenotypes complicates patient selection for trials, potentially causing variability in treatment responses, and may also explain neutral trial results. Therefore, advanced phenotyping of patients with cardiogenic shock to understand who might benefit from specific targeted therapeutic strategies should be taken into account in trial design. Ethical considerations, owing to the acuity and severity of the condition, present another issue that challenges informed-consent processes. Despite challenges associated with clinical trials in cardiogenic shock, it has been repeatedly shown that such trials can be performed successfully. International activities are therefore required to build large shock-research networks to answer the multiple open questions regarding treatment.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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