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VIEWPOINT

Clinical Trials in Cardiogenic Shock

Challenges and Solutions for the Future

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Cardiogenic shock (CS) is a heterogeneous clinical syndrome precipitated by a primary cardiac pathology and marked by critical end-organ hypoperfusion leading to multiorgan failure and death.[1] Despite the numerous advances in percutaneous revascularization techniques and temporary mechanical circulatory support (MCS), in-hospital mortality due to CS remains unacceptably high. Given this, the need for appropriately designed and adequately powered randomized controlled trials (RCTs) within this space is dire. However, most existing studies are plagued by inadequate sample sizes, variable definitions of CS, acute myocardial infarction-related CS (AMI-CS)-focused data, nonprotocolized timing of mechanical hemodynamic support, and inconsistent clinical endpoints studied. Furthermore, RCTs in CS are fraught with various methodological, ethical, and operational challenges and are difficult to enroll in. Within this perspective, we identify challenges associated with the design and execution of CS RCTs and suggest solutions for future development of high-quality multicenter clinical trials to advance the field (Figure 1).

CHALLENGES WITH TRIALS IN CARDIOGENIC SHOCK

INFORMED CONSENT. CS trials pose difficult challenges with randomization and blinding due to their acuity and mortality. These patients are critically ill likely with compromised mental status, and often arrive at the emergency room without a legal representative. The short therapeutic window within which the investigational strategy must be applied, as early diagnosis and management are critical. Furthermore, the validity of informed consent may be limited in patients who have evidence of systemic and even partial cerebral hypoperfusion. For these reasons, obtaining informed consent can be practically difficult and of limited value. This is a significant issue in trials related to the use of investigational therapies and devices that are potentially beneficial but may be associated with increased risk of complications. Despite the federal regulations in the United States that allow for exceptions from standard informed consent requirements in "emergency research" settings on a study-by-study basis (21 CFR 50.24), all CS research may not qualify for exception from informed consent (EFIC) under these regulations, especially due to its varied spectrum of presentation.[2] Given the excessively high mortality rate associated with CS, the EFIC process needs to be expedited and made more efficient to enable desperately needed RCTs. Until then, clinicians are left with limited guidance. Moreover, informed consent requirements vary by country and are particularly stringent in the United States and some European countries, which explains the lack of major randomized data from the United States,

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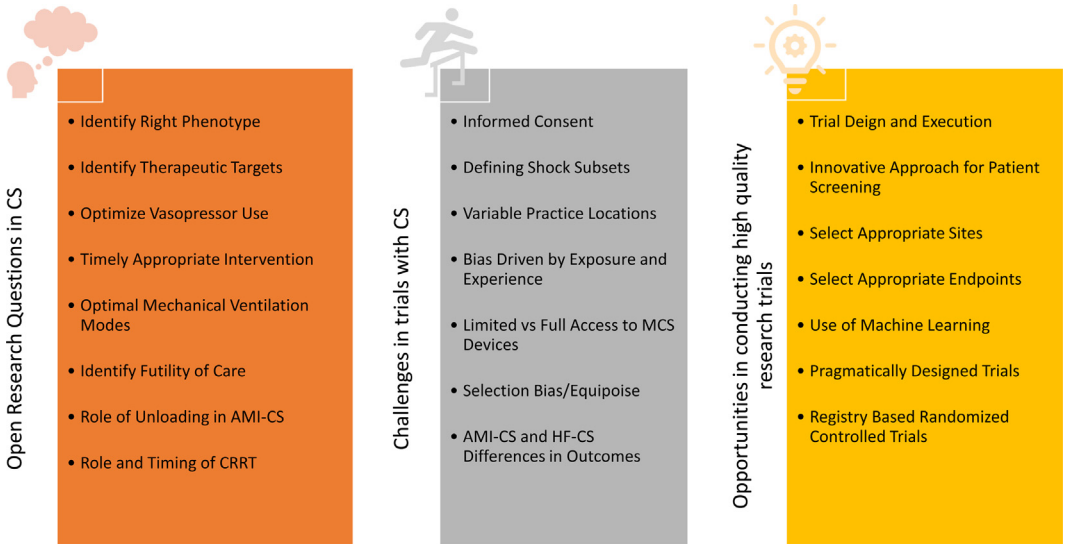
FIGURE 1 Open Research Questions, Challenges in Clinical Trials in Cardiogenic Shock, and Opportunities in Conducting High-Quality Research Trials



AMI-CS = acute myocardial infarction-related cardiogenic shock; CRRT = continuous renal replacement therapy; HF-CS = heart failure-related cardiogenic shock.

further highlighting the importance of international consensus and collaborations for CS research.

DEFINING SHOCK SUBSETS. CS patients are a heterogenous population based on etiology, severity, and associated comorbidities. Various CS trials have used a variety of inclusion criteria, where "splitters" emphasize the heterogeneity within the diagnostic criteria and "lumpers" argue that the similarities justify the creation of a broader definition. This heterogeneity of inclusion criteria in different trials diminishes the validity of the data generated, potentially making it difficult to apply results to larger patient populations.[2]

Until recently, the lack of consensus across CS definitions was recently addressed by the development of the Society for Cardiovascular Angiography and Interventions (SCAI) classification of CS[3,4] by recommending a more granular classification structure for CS severity. However, adoption of SCAI staging in RCTs remains limited to date.[5]

Multiple elements within the current SCAI SHOCK classification remain subject to variable interpretations, as universal thresholds for MCS use across institutions are sorely lacking. In addition, the dynamic nature of the SCAI definition poses challenges since often randomization needs to be performed immediately in the cath lab or at the cardiac intensive care unit, not allowing one to wait for the dynamic process of the shock evolution. Thereby, we need precise research definitions of the different stages of SCAI classification for clinical trial enrollment.

VARIABLE PRACTICE LOCATIONS. Even though centers of excellence are paramount for successful CS research, CS patients are often present in community hospitals, thereby making it difficult to diagnose and manage at low-volume centers. This inability of many centers to diagnose CS in a timely manner may delay transfer to appropriate quaternary centers, which not only affects clinical short- and long-term outcomes but may also pose barriers to trial enrollment.

USE OF PULMONARY ARTERY CATHETER. There is clinical equipoise regarding use of invasive hemodynamic monitoring with pulmonary artery catheters (PAC) and no prospective RCT data on hemodynamic assessment in CS exists. The ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial[6] suggested no overall mortality or rehospitalization benefit from routine invasive assessment of hemodynamics compared with rigorous clinical assessment and noted no difference in the primary outcome. Even though most PAC studies, including ESCAPE, did not enroll CS patients, these results have been inaccurately extrapolated to these patients, and use of PAC has decreased significantly over the past decade.

Institutional differences may also play a role here. Most recently, the Cardiogenic Shock Working Group (CSWG) evaluated retrospective data from 8 tertiary care centers and demonstrated that use of complete PAC-derived hemodynamic data prior to MCS initiation was associated with improved survival in CS.[7] However, this is only hypothesis-generating data. Currently, a prospective RCT is underway to evaluate the use of PAC in patients with CS (NCT05485376).

BIAS DRIVEN BY EXPOSURE AND EXPERIENCE. With the accelerating pace of innovation in the percutaneous MCS device arena, its use has increased rapidly in patients with CS. Albeit, the evidence available for or against its use remains sparse, and its use is riddled with complications. The lack of evidence has led to variable practice patterns and institutional biases, where smaller centers with little experience tend to underutilize MCS and academic centers with high expertise may overuse MCS.[8] This is also driven by reimbursement patterns in different countries leading to high variability of MCS depending not only on institutional practice but also on reimbursement issues. Moreover, significant gaps in identifying the right device for the right patient and timing of intervention persist.[8] Use of MCS later in the course may not improve mortality in CS; hence, delayed MCS use may affect the outcomes in clinical trials. On the other hand, use of MCS in an earlier phase may expose many patients to an invasive strategy with inherent complications who would not need MCS.

AVAILABILITY BIAS AND OPERATOR/INSTITUTIONAL EXPERIENCE WITH TEMPORARY MCS DEVICES. The risk/benefit of centralizing vs decentralizing shock management remains unknown. The cost and complexity of employing MCS may require specialized shock centers depending on the severity of clinical presentation. This may limit access to MCS at smaller hospitals.[9] Few centers in United States have adequate resources, support personnel, and shock teams required to manage advanced MCS. This difference in timing and utilization of MCS in hub and spoke centers may lead to variable outcomes across centers. This is particularly important for the prevention of device-related complications such as bleeding, iatrogenic limb ischemia, and related infections, which may all negatively affect outcome.

AMI-CS VS HF-CS DIFFERENCES IN OUTCOMES. All shock is not equal. There has been a paradigm shift in the CS realm with incidence of AMI-CS decreasing over the last 2 decades. However, most of the CS research to date has been conducted on patients with AMI-CS. Heart failure-related cardiogenic shock (HF-CS) patients are more resource-intensive and may have a greater burden of disease. Although their in-hospital survival is significantly better than that of AMI-CS, HF-CS patients remain vulnerable after discharge, and single-center reports suggest significant morbidity and mortality in the first year after discharge.[10] Substantial heterogeneity exists with use of MCS in HF-CS, and thus more research is needed.[10]

SELECTION BIAS/EQUIPOISE. The different phenotypes of CS make rapid screening and randomization of patients for a clinical trial complicated. Most RCTs tend to exclude certain types of shock, and these result in extrapolation of their results to patients in the excluded population. Selection bias among the clinician investigators as they enroll patients may also impact trial recruitment. Most MCS trials have limited statistical power and tend to have lot of crossover, which may affect the outcomes of these trials. Timing of the insertion of the device is left to the discretion of the treating physician, which is another major limitation in MCS trials that requires protocolization.

OPPORTUNITIES IN CONDUCTING HIGH-QUALITY CLINICAL TRIALS IN CS

Various ways we can improve the design and quality of clinical trials in CS include the following.

TRIAL DESIGN AND EXECUTION. Very few trials in CS, revascularization strategies, and MCS are adequately powered. Implementation of the new SCAI classification with practical definitions for each stage may avoid variable interpretations of CS severity. Practical application of SCAI stages was recently enhanced by criteria proposed by the CSWG for rapid bedside assessment.[11] It is also crucial to consider more sophisticated clinical trial designs in this challenging population. A design that allows frequent interim analyses without compromising validity of the results may be beneficial.

INNOVATIVE APPROACHES FOR SCREENING PATIENTS FOR ENROLLMENT IN TRIALS. The goal of patient selection is to ensure those with the greatest potential for benefit from the investigational strategy are enrolled. Specific range of disease severity should be targeted. Our aim while enrolling patients in CS trials should be to enrich the study population without getting too far from real-world practice. Danish and German law allow for research without formal informed consent in situations where research can only be conducted in given acute situation, such as when the patient is incapable or surrogate is unavailable for informed consent, and if research

specifically involves the patient's current condition and is possible to benefit the patient. For this reason, the DanGer Shock trial[12] was able to enroll and randomize these patients. In the United States, the RECOVER IV (NCT03431467) RCT aims to deploy EFIC in most participating centers, thereby improving enrollment and randomization in patients with AMI-CS.

SELECT APPROPRIATE SITES. Ongoing data collection and feedback between physician and administrative champions at hub-and-spoke shock care centers is the key to ensuring adherence to best practices, appropriate use of resources, and refinement of system-wide strategies to sustain enhanced outcomes. Such local collaboration may then spur the development of larger multicenter registries and clinical trials on a national level to address clinical gaps in knowledge and assess innovative therapies and care models to inform clinical practice. Moreover, the sites selected should have necessary infrastructure, as undertaking CS and MCS trials is a mammoth task given the complexity and costs involved in these trials.

SELECTING APPROPRIATE ENDPOINTS. Most CS trials have focused on all-cause mortality as a primary endpoint, with a few focusing on parameters of hemodynamic stability, including but not limited to cardiac index, cardiac output, etc. Given the high mortality associated with CS, it may be prudent to identify endpoints that predict all-cause mortality. However, use of surrogate endpoints needs to be carefully vetted to establish clinical utility. Using the win-ratio and other adaptive designs for clinical trials may be of critical importance in future studies. Moreover, with the distinct phenotypes, we could identify parameters that are reflective of hemodynamic and hemometabolic compromise in order to increase the efficacy of therapeutic intervention targeting different components of CS.

USE OF MACHINE LEARNING. Appropriately phenotyping patients with CS upon admission is the most critical step in the design of prospective clinical studies to assess and eventually improve patient outcomes. We can obtain unique mechanistic insights by using an unbiased, algorithmic approach with machine learning to analyze data and better subclassify patients with CS.[13] Using machine learning, the CSWG identified and validated 3 distinct clusters of CS phenotypes in both AMI-CS and HF-CS from their data and tested the reproducibility in Danish registry of patients with AMI-CS.[14] These distinct phenotypes were directly associated with mortality and may allow for targeted patient enrollment in future clinical trials in CS, thereby helping to develop strategies tailored to treat each phenotype.

PRAGMATICALLY DESIGNED TRIALS. Compared to traditional 'explanatory' trial, CS can be better studied with a 'pragmatic' design trial, which tests the effectiveness of a treatment or intervention in a real-world scenario.[15] These pragmatic trials are characterized by a large sample size, a simple design with no special strategy to increase adherence to a specific protocol and include diverse settings with high external validity. These trials measure patient-centric outcomes and can help identify if a particular intervention can improve outcomes without controlling any confounders. All participants are included in an intention to treat fashion thereby avoiding ethical dilemma. No inclusion and exclusion criteria make the results generalizable and applicable in a routine clinical practice.

REGISTRY BASED RCTs. A RCT that is embedded into a large population-based or a small single-center registry is known as registry-based RCT.[16] Using these registries for CS trials allows collection of data from patients in a 'real world' clinical setting compared with traditional RCTs. These registries provide answers to clinical questions in a timely and cost-effective manner. These datasets include patients who may otherwise be excluded from RCTs and thereby have better external validity compared with traditional RCTs.

CONCLUSIONS

Clinical studies in CS are necessary to guide health care providers with data to improve mortality and outcomes. There are numerous challenges we face as we set out to design clinical trials in this space. The abovementioned suggestions may be helpful to conduct high-quality clinical trials, create real-world data, and use MCS in CS, thereby improving the outcomes of this fatal syndrome.

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