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Cardiac safety research consortium "shock II" think tank report: Advancing practical approaches to generating evidence for the treatment of cardiogenic shock

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(See Tables I and II.)

The Cardiac Safety Research Consortium (CSRC) Think Tank "Defining the Clinical and Regulatory Landscape for Cardiogenic Shock", held in September 2018, convened physicians, government regulators, and industry leaders to address the increasing use of mechanical circulatory support (MCS) devices for treatment of cardiogenic shock (CS) despite the absence of consistent evidence of a mortality benefit.[1] Think Tank participants identified common barriers to generating evidence including delays in CS diagnosis, variability of data collection and quality, non-uniform event definitions, variable international regulatory requirements for informed consent in emergency research, and a lack of clinical equipoise among some physicians when considering randomizing patients to MCS devices versus routine care. Other discussions focused on novel trial design options including registry-based trials, adaptive, and factorial designs as strategies to increase enrollment efficiency and maximize data interpretability.

The follow-up CSRC "Shock II" Think Tank on "Advancing Practical Approaches to Generating Evidence for the Treatment of Cardiogenic Shock" reconvened physicians, government regulators, and industry leaders on June 10, 2019, to crystallize initiatives and pragmatic solutions to these aforementioned challenges to determining optimal MCS use. At the conclusion of this Think Tank, the attendees agreed that CSRC efforts should focus ongoing Working Groups on four main themes. First, to create a network of "centers of excellence" committed to uniform and high-quality data capture and prospective clinical research collaboration and efficient approaches to informed consent for patients enrolled in cardiogenic shock studies. Second, to identify and develop in-kind and fiscal resources supporting collaborative efforts to advance evidence generation on the benefit/risk of MCS devices used in CS. Third, to develop consensus minimum core definitions for data elements critical to ongoing and future CS

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Table I. Cardiac Safety Research Consortium Working Groups for Cardiogenic Shock

Group name	Assignment
Shock network	Establish a cardiogenic shock network in order to conduct future research with a key emphasis on reliable data collection and reporting
Resources	Identify entities already conducting cardiogenic shock research and to identify potential financial and non-financial resources to support future research
SHARC	Create fit for purpose definitions to be used in future cardiogenic shock research
First clinical question	Develop a set of feasible research questions that would lead to pragmatic randomized trials of interest to a broad range of cardiogenic shock stakeholders

evidence development across case report forms, registries and electronic health records. Finally, to consider where unmet clinical needs, practical opportunity and resources, and equipoise for randomization point to priority areas for clinical trials.

Standardizing cardiogenic shock care

"Centers of Excellence" for medical devices are frequently defined by procedural volumes. Cardiovascular procedural volumes are consistently and positively associated with improved clinical outcomes including survival.[2-8] International practice guidelines recommend minimum procedural volumes for hospitals and operators for the maintenance of accreditation and competency.[9] Positive association between clinical volume and improved outcomes is not limited to procedural-based care. Increased hospital volumes of heart failure, community-acquired pneumonia, and critically ill patients requiring mechanical ventilation have all been positively associated with improved outcomes.[10-12]

As a result of these repeatedly demonstrated positive associations, regionalized systems of care have been implemented for time-critical scenarios. Transportation to level 1 trauma centers has reduced trauma-associated mortality by 15–20%.[13] Increased use of fibrinolytic therapy and improved survival has been associated with integrated and regionalized systems of care for patients with acute ischemic stroke.[14,15] Finally, coordination of ST elevation myocardial infarction (STEMI) care has served as the exemplar of operationalized systems of care. Emergency medical services, community hospitals, and tertiary referral centers seamlessly interact to form standardized "hub-and-spoke" STEMI networks to ensure timely reperfusion. Supported by the American Heart Association (AHA) and its Mission: Lifeline program, this system further provides quality assurance via real-time feedback and mechanisms for quality improvement via educational programs.[8,16-21]

Table II. Research ideas generated during CSRC Think Tank 2.

Concept	Randomization strategy
Anticoagulation management • Systemic vs purge/infusate algorithms • Dosing, target therapeutic ranges • Alternatives to heparin	Cluster randomized
MCS access site	Patient or cluster randomization
Device removal strategy	Patient randomization
Weaning protocols	Cluster randomization

The consensus of Think Tank participants is that systems of care for CS should mirror that of STEMI. Ideally, CS care would be incorporated into already established hub-and-spoke STEMI networks. However, attendees generally agreed that there are several significant limitations to this approach. Not all PCI-capable hospitals are fully staffed with the multidisciplinary resources needed to care for patients with CS. These resources include 24/7 in-house intensivists, cardiac surgeons, and the allied health specialties, specifically critical care nurses and perfusionists required to deploy and manage MCS and the range of organ support devices required in many patients with shock and multiorgan failure.

In addition to developing regionalized systems of care, the concept of timely and coordinated multidisciplinary evaluation by an institutional "Shock Team" has been suggested as an approach to efficiently recognize, triage and manage CS patients.[22] In practice, centralized shock triage might also help overcome critical barriers to trial enrollment. Along with performing clinical care, members of the shock team would also identify patients for clinical trials in real-time and be the point of contact for informed consent. Thus, in addition to technical or procedural capabilities, these aspects of a shock team might also be incorporated as criteria for shock "Centers of Excellence."

Two contemporary examples of shock teams and standardized protocols for using invasive hemodynamic and biochemical metrics to identify and escalate to percutaneous MCS were presented at the Think Tank.[23,24] In these single-arm observational studies, compared to historical controls, standardized protocols were associated with higher survival rates among patients presenting with CS. In both examples, invasive hemodynamics and laboratory values such as lactate were predictive of outcomes, but it remains unclear which components of the protocol drove the clinical impact. Extension of the Detroit Cardiogenic Shock initiative to a nationwide network that uses protocols to assess responses to intervention demonstrates the feasibility of protocol-driven CS treatment.[23,24] Although encouraging, these observational studies require further validation with prospective randomized controlled trials.

Identification of research partners and resources support efficient evidence development for MCS in cardiogenic shock

The current climate of high volume MCS use, high reimbursement rates, and a need to better safety of device use was discussed as an impetus focus for rapid generation of more evidence. Furthermore, the absence of prospective randomized data was identified as an opportunity to form collaborative initiatives across industry, federal agencies, professional societies, and international stakeholders.

Ongoing international trials were discussed, including the DanGer shock[25] (NCT01633502), EuroShock (NCT03813134), and Extracorporeal Life Support in Cardiogenic Shock (ECLS-Shock) trials (NCT03637205). These European trials will provide much needed prospective randomized data regarding MCS device use in patients with CS associated with acute myocardial infarction. Despite interest in expanding these trials to include U.S. sites, Think Tank attendees agreed that current barriers to CS trial enrollment were problematic and that alternative strategies were both desirable and feasible.

The Cardiogenic Shock Working Group (CSWG) is a registry-based initiative with a focus on clinical CS phenotyping. CSWG investigators successfully identified clinical sub-phenotypes within Society for Cardiovascular Angiography and Interventions (SCAI) classification system using including invasive hemodynamics and MCS use which were associated with in-hospital mortality.[26,27]

Historically, systems developed for electronic health records and the infrastructure used to conduct clinical trials operate independently, requiring redundant data collection by sites resulting in increased trial costs. Participants agreed that registry-based randomized trials would be an ideal fit for more efficient CS research.[28-30] Similarly, informatics platforms incorporated into EHRs that automatically populate research protocol case-report forms extracted from clinical workflow could be a future model to optimize trial efficiency and reduce costs.[28,31] Additionally, ongoing registry data independent of RCTs could provide highly useful real-word practice information, temporal trends in outcomes, and improvements in performance measures.

Definitions of Cardiogenic Shock and the Academic Research Consortium: SHARC

Since the initial CSRC CS Think Tank in September 2018, multiple MCS RCTs have initiated enrollment or are planned to start.[32] CS is heterogeneous in etiology and presentation, and CS outcomes are likely related to the impact of patient characteristics, disease severity at time of CS diagnosis, underlying etiology, timing of evidence-based intervention (i.e. revascularization) where appropriate, and complications of therapy.

The recently published SCAI classification system provides a practical and useful characterization of the spectrum of CS from "at-risk" to end-stage.[33] The schema was developed to simplify and standardize terminology to facilitate professional staff communication regarding a patient's clinical status. The SCAI classification. It also could be applied to future trials to advance homogeneity of patient recruitment, poolability of data, and generalizability of outcomes. Retrospective cohort studies have shown associations between SCAI CS subgroups and clinical outcomes.[26,27,34] However, there was agreement among think tank participants that further data are required to assess the accuracy and prognostic and clinical utility of this classification system. For example, hemodynamic criteria are not central to the SCAI schema, despite being key prognostic markers in recent and current RCTs.

The heterogeneity of CS definitions used in practice and clinical research was repeatedly discussed as a barrier to comparisons across trials, which limits the knowledge about MCS benefit/risk in CS patients. Pragmatic consensus definitions with common data elements for future clinical research were recognized as key steps to advancing the CS research landscape. Professional societies may be helpful in developing such consensus definitions. However, a unique need for MCS device evidence development requires definitions that support clinical trial processes such as adverse event adjudication and safety monitoring. The Academic Research Consortium (ARC) was established in 2006 to "create a dynamic, open-ended, transparent, collaborative forum across stakeholders, whose objective is to develop consensus definitions and nomenclature and related processes, optimized for application in pivotal clinical trials of new medical devices, and to disseminate such definitions and recommended processes into the public domain."[35] Think Tank participants encouraged the creation of a shock-ARC (SHARC) initiative as a high priority for public health benefit, which would include patients, providers, industry sponsors, federal agencies, and regulators.

Key research question(s)

The purpose of the CSRC is to advance scientific knowledge on cardiac safety by facilitating pragmatic research. There was support from attendees for the creation of a working group tasked with generating a focused list of clinical questions to be discussed at the follow up CSRC Shock III meeting scheduled for February 2020. The aim of the Shock III meeting is reaching consensus on the first clinical question to be addressed in an initial pragmatic trial. The driving principles of the initiative will be an emphasis on feasibility, to showcase the capabilities of a collaborative research network including rapid identification of CS patients, high quality standardized data collection, and novel informed consent solution(s) to create a uniquely efficient avenue for

projects of interest to clinical, scientific, industry, federal and regulatory communities. Proposals included a more thorough safety analysis of temporary MCS devices, anticoagulation strategies for temporary MCS, MCS weaning algorithms, and vascular access approaches including device removal strategies.

Conclusions

The follow-up CSRC Think Tank focusing on CS "Practical Approaches to Generating Evidence for the Treatment of Cardiogenic Shock" began to crystallize a collaborative path for CS research. Four key initiatives were identified as the focus of future CSRC CS efforts. The first initiative is to establish a CS network to support and conduct research with an emphasis on reliable data collection and reporting. Second, to engage with existing CS research collaboratives and to identify potential financial and non-financial resources to support future CS research; third, to leverage the ARC and establish SHARC to create fit-for-purpose definitions to be used in CS research. Finally, to develop a set of feasible research questions that would lead to pragmatic randomized trials of interest to a broad range of CS stakeholders.

Conflicts of interest

Alexander G. Truesdell is a consultant and member of the Speakers Bureau of Abiomed Inc.

David A. Morrow reports no conflicts relevant to this work and reports grants from Anthos Therapeutics, grants and personal fees from AstraZeneca, personal fees from Bayer Pharma, grants from Daiichi Sankyo, grants from Eisai,grants from GlaxoSmithKline, personal fees from InCarda, grants from Medicines Company, grants and personal fees from Merck & Co, grants and personal fees from Novartis, grants from Pfizer, grants from Quark, grants from Regeneron, grants and personal fees from Roche Diagnostics, grants from Siemens, grants from Takeda, and grants from Zora Biosciences outside the submitted work; Dr. Morrow is also a member of the TIMI Study Group which has received institutional research grant support through Brigham and Women's Hospital from Abbott; Amgen; Aralez; AstraZeneca; Bayer HealthCare Pharmaceuticals, Inc.; BRAHMS, Daiichi-Sankyo; Eisai; GlaxoSmithKline; Intarcia; Janssen; MedImmune; Merck; Novartis; Pfizer; Poxel; Quark Pharmaceuticals; Regeneron; Roche; Siemens; Takeda; The Medicines Company; and Zora Biosciences.

E. Magnus Ohman mentions Chiesi (USA), Jansen Pharmaceutical, Xylocor, Cardinal Health, Milestone Pharmaceutical, Abiomed, and Cara Therapeutics.

Ian C. Gilchrist reports no conflicts relevant to this work and is a consultant for Terumo Medical, Inc.

Judith S. Hochman reports no conflicts relevant to this work; Dr. Hochman is PI for the ISCHEMIA trial for which, in addition to support by National Heart, Lung, and Blood Institute grant, there were in-kind donations for participating sites from Abbott Vascular; Medtronic, Inc.; St. Jude Medical, Inc.; Volcano Corporation; Arbor Pharmaceuticals, LLC; AstraZeneca Pharmaceuticals, LP; Merck Sharp & Dohme Corp.; Omron Healthcare, Inc.; and Amgen Inc.; and financial donations from Arbor Pharmaceuticals LLC and AstraZeneca Pharmaceuticals LP.

Navin K. Kapur is a consultant/receives speaker honoraria from Abbott, Abiomed, Boston Scientific, Medtronic, LivaNova, Getinge, MD Start, and Precardia as well as institutional research grants from Abiomed, Boston Scientific, and MD Start.

Ron Waksman is an advisory board/board member and consultant for Abbott Vascular, Amgen, Pi-Cardia LTD, Cardioset, Medtronic, Philips (Volcano), and Boston Scientific Corp; consultant for Biosensors, Biotronik; received grant support from Abbott Vascular, AstraZeneca, Biosensors, Biotronik, Chiesi, and Boston Scientific Corp; is on the Speaker Bureau of AstraZeneca and Chiesi; and is an investor in MedAlliance.

Eric Chen is an employee of Abbott.

Adam DeVore reports research funding through his institution from the American Heart Association; Amgen; AstraZeneca; Bayer; Intra-Cellular Therapies; American Regent, Inc; the NHLBI; Novartis; and PCORI. He also provides consulting services for Amgen, AstraZeneca, Bayer, CareDx, InnaMed, LivaNova, Mardil Medical, Novartis, Procyrion, scPharmaceuticals, Story Health and Zoll and has also received non-financial support from Abbott for educational activities.

William O'Neill is a consultant for Abiomed and Abbott and receives consulting fees for his services.

Charles A. Simonton is an employee of Abiomed.

Behram N. Tehrani is a consultant for Medtronic.

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