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Methods in Cardiovascular Research

The Multicenter Collaborative to Enhance Biologic Understanding, Quality, and Outcomes in Cardiogenic Shock (VANQUISH Shock): Rationale and Design

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ABSTRACT

Background: Despite efforts to advance therapies in cardiogenic shock (CS), outcomes remain poor. This is likely due to several factors, including major gaps in our understanding of the pathophysiology, phenotyping of patients, and challenges with conducting adequately powered clinical studies. An unmet need exists for a comprehensive multicentre "all-comers" prospective registry to facilitate characterising contemporary presentation, treatment (in a device-agnostic fashion), and short- and intermediate-term outcomes and quality of life (QOL) of CS patients.

RÉSUMÉ

Contexte : Malgré les efforts visant à faire progresser le traitement du choc cardiogénique (CC), les résultats cliniques demeurent médiocres. Cette situation tient probablement à plusieurs facteurs, notamment des lacunes importantes dans notre compréhension de la physiopathologie, le phénotypage incomplet des patients et les difficultés que pose la réalisation d'études cliniques ayant une puissance suffisante. La création d'un registre prospectif et multicentrique exhaustif « tout venant » répondrait à un besoin non satisfait puisque cela permettrait de caractériser plus facilement le tableau clinique et

Despite advances in coronary revascularisation and systems of care strategies, cardiogenic shock (CS) continues to pose a major challenge to health care systems worldwide. It remains the leading cause of in-hospital morbidity and mortality after acute myocardial infarction (AMI), with short-term mortality rates exceeding 40%.[1] Its prevalence is increasing: The number of hospitalisations attributed to CS have nearly tripled in the past 15 years.[2] It is also the second most common indication for admission to contemporary cardiac intensive care units (CICUs).[3] Moreover, CS is multifactorial; nearly 50% of cases stem from acutely decompensated heart failure (HF), a distinct etiology composed of varying disease states with equally suboptimal outcomes.[4]

While carefully conducted studies are ongoing in the shock field, eligible patients participating in shock trials constitute only one-third of the actual CS patient population, thus contributing to knowledge gaps and the current state of clinical equipoise and heterogeneity of treatment in the field.[5,6] The lack of progress in the field has also been attributed to gaps in our understanding of the pathophysiology and incomplete phenotyping of the heterogeneity of CS

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Methods: The Multicenter Collaborative to Enhance Biological Understanding, Quality and Outcomes in Cardiogenic Shock (VANQUISH Shock) registry is a prospective observational registry that will study unrestricted adult patients with a primary diagnosis of CS at 4 North American centres with multidisciplinary shock programs. Both acute myocardial infarction (AMI-CS) and acute heart failure (HF-CS) etiologies will be included, and the registry will be device agnostic and widely inclusive. The primary end point will be survival at 30 days after hospital discharge. Secondary outcomes will include in-hospital adverse events and survival to 6 and 12 months. Patients will also undergo neurologic and health-related QOL assessments with the Cerebral Performance Category (CPC) and Short-Form 36 (SF-36) health survey tools before discharge and during follow-up. Serial biospecimens will facilitate biomarker studies.

Conclusions: The VANQUISH Shock registry provides a unique opportunity to study the pathophysiology, contemporary management, clinical course, and outcomes of CS. By capturing detailed and high-quality longitudinal data, the registry will address existing knowledge gaps and serve as a springboard for future mechanistic clinical studies to advance the field.

Méthodologie : Le registre prospectif et observationnel VANQUISH Shock (*Multicenter Collaborative to Enhance Biological Understanding, Quality, and Outcomes in Cardiogenic Shock*) permettra d'étudier les cas de patients adultes ayant reçu un diagnostic primaire de CC au sein d'une population non restreinte dans quatre établissements nord-américains dotés de programmes multidisciplinaires de prise en charge du CC. Les caractéristiques étiologiques de l'infarctus aigu du myocarde et de l'insuffisance cardiaque aiguë avec choc cardiogénique (IAM-CC et ICA-CC) seront consignées dans le registre, qui comprendra en outre des données sur les traitements, sans égard aux dispositifs utilisés, et sera largement inclusif. Le paramètre d'évaluation principal sera la survie 30 jours après la sortie de l'hôpital. Les paramètres d'évaluation secondaires comprendront les effets indésirables survenus en cours d'hospitalisation et la survie à 6 et 12 mois. L'issue neurologique et la qualité de vie liée à la santé seront aussi évaluées au moyen du score CPC (*Cerebral Performance Category*) et du questionnaire abrégé sur la santé SF-36 (*Short-Form 36 Health Survey*) avant la sortie de l'hôpital et pendant la période de suivi des patients. Le prélèvement d'échantillons biologiques en série facilitera les études sur les biomarqueurs.

Conclusions : Le registre VANQUISH Shock nous offre une occasion unique d'étudier la physiopathologie ainsi que la prise en charge, l'évolution clinique et l'issue du CC chez les patients contemporains. En regroupant des données longitudinales détaillées et de haute qualité, le registre permettra de combler les lacunes actuelles et servira de tremplin à des études cliniques mécanistes ouvrant la voie à des avancées médicales dans ce domaine.

patients.[4,7] In the absence of randomised clinical trials to inform clinical decision making, data are emerging from dedicated North American CS registries supporting an algorithmic and team-based approach to management.[8-11] Although preliminary short-term results from these registries have been favourable, there remains uncertainty regarding a number of clinical domains across the severity spectrum of shock.[12] In addition, enrolling patients with CS in mechanistic studies and clinical trials is associated with inherent challenges. Therefore, there is a major unmet need for deep phenotyping within comprehensive multicentre registries to better characterise mutually exclusive groups of patients in this heterogenous disease state and to advance our biologic and clinical knowledge in CS (Table 1).[13,14]

Methods

Study design

The Multicenter Collaborative to Enhance Biological Understanding, Quality and Outcomes in Cardiogenic Shock (VANQUISH Shock) registry (ClinicalTrials.gov NCT05185492) is composed of 4 high-volume North American quaternary centres of care with dedicated multidisciplinary shock teams.[8,9,15] This prospective observational registry will study all patients with the primary diagnosis of CS who are evaluated by each institution's respective shock teams. Patients will be enrolled from the Inova Heart and Vascular Institute, Peter Munk Cardiac Centre, Cleveland Clinic Heart, Vascular, and Thoracic Institute, and the University of Utah. All 4 centres offer the full range of mechanical cardiac support modalities for cardiac support and replacement therapies, including durable mechanical circulatory support and heart transplantation. Deidentified clinical variables will be collected from the electronic medical records and stored in a central registry. Serial biospecimens will be prospectively collected and processed at all 4 centres and processed centrally (University of Utah or Peter Munk Cardiac Centre). All patients will be followed to 1 year after hospital discharge (Fig. 1).

Mission statement and governance

The mission of the VANQUISH Shock registry is to advance our understanding of the management and outcomes of CS in the real world through the longitudinal collection of granular clinical, molecular, and quality-of-life data in an unrestricted patient cohort and to collectively formulate research questions that address existing gaps in knowledge. The registry governance will operate through an executive committee comprised of 1 lead physician from each of the 4 sites (Table 2).

Study participants and follow-up

The study population eligible for inclusion in this registry will consist of consecutive adults ($\geq$ 18 years) with the primary diagnosis of suspected or confirmed CS who are triaged and managed by each institution's respective shock team.

Table 1. Opportunities for research in CS through prospective multicentre registries

Clinical domain	Gaps in knowledge
I. Diagnosis	1. Comprehensive hemodynamic phenotyping in CS 2. Prospective validation of SCAI shock and other risk stratification scores 3. Clinical and hemodynamic predictors of mortality in patients with pre-shock (SCAI stage B) 4. Machine learning and artificial intelligence to enhance disease recognition
II. Treatment	1. Optimal targets for fluid management and vasopressors 2. Patient selection for MCS 3. Best practices for vascular access and closure following deployment of MCS 4. MCS escalation and weaning strategies 5. Decongestion in CS complicated by cardiorenal syndrome 6. Anticoagulation targets for MCS (TEG, aPTT, ACT) 7. Left ventricular venting in patients supported with VA-ECMO
III. Molecular profiling	1. Discovery of biomarkers and "omics" with diagnostic, prognostic, and therapeutic value in CS
IV. Care delivery models	1. Multidisciplinary shock team 2. Regionalised systems of care networks for CS 3. Staffing models in contemporary CICUs
V. Prognosis	1. Risk prediction scores 2. Short- and long-term quality of life and neurologic assessments 3. Recognition of futility in CS 4. Integration of palliative care into clinical decision making

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CS, cardiogenic shock; CICU, cardiac intensive care unit; MCS, mechanical circulatory support; SCAI, Society for Cardiovascular Angiography and Intervention; TEG, thromboelastography; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Activation of the shock team is at the discretion of the local clinicians and will not require definitive evidence of CS before initiation. Inherent in this approach is that some patients referred to the shock team will not have cardiogenic shock (even of mild severity), and those patients will not be included.

The Society for Cardiovascular Angiography and Intervention (SCAI) CS stage will be assigned by prospective local team consensus at the time of index shock team evaluation and 24 hours later.[16] The SCAI staging will be complemented by application of the 2017 American Heart Association Scientific Statement on CS and the seminal **Sh**ould We Emergently Revascularize **O**ccluded **C**oronaries for Cardiogenic Sho**k** (SHOCK) trial definitions.[17,18] These clinical criteria include systolic blood pressure (SBP) < 90 mm Hg for ≥ 30 minutes (or the need for vasoactive infusions to maintain a SBP ≥ 90 mm Hg), and evidence of end-organ hypoperfusion. Examples of the latter include cool extremities, urinary output < 30 mL/h, and lactic acid > 2 mmol/L. Hemodynamic criteria will include Fick or thermodilution cardiac index ≤ 1.8 L/min/m^2 without vasopressors (or ≤ 2.2 L/min/m^2 with vasopressors). Additional hemodynamic correlates of CS will include cardiac power output (CPO) < 0.6 W or pulmonary arterial pulsatility index < 1.0.[19,20] Some patients may not meet the SHOCK trial definition of CS but may manifest SCAI stage B or early stage C shock, and their course will be captured in the registry. Patients with both AMI-CS and HF-CS etiologies will be studied (Table 3). Clinical follow-up will include the following time points: 30 days, 6 months, and 12 months after hospital discharge. A waiver of informed consent at the time of hospital admission will permit broad inclusion in the registry. The patient or their legally authorised representative, however, will provide informed consent as soon as possible after admission to allow storage and future analysis of biospecimens.

Management

All patients in the VANQUISH Shock registry will be managed in American Heart Association Level 1 CICUs equipped with "high intensity" and 24-hour 7-days-a-week staffing with cardiologists and intensivists.[18] They will all undergo initial evaluation and management by each institution's respective shock team, consisting of interventional cardiologists, cardiac surgeons, intensivists, and advanced HF specialists. Right heart catheterization will be recommended for all patients at the time of the index CS diagnosis for comprehensive shock phenotyping and to guide therapy. Variables that will be collected at the time of right heart catheterisation are outlined in Table 4. Additional variables that will be collected during each patient's hospital course will include markers of end-organ malperfusion, including lactate, renal, and hepatic function, as well as ventilator support for patients with acute respiratory failure. All baseline comorbidities and medication profiles will also be recorded longitudinally (Table 5). Specific vasopressor doses will not be captured.

Given the comprehensive nature of this registry, the treatment plan will be per discretion of the local shock team. Management strategies will include vasopressors, inotropes, and mechanical circulatory support (MCS) devices. Currently available hemodynamic assist platforms are outlined in Table 2.

Invasive hemodynamic assessments will be performed daily in patients requiring temporary MCS. Patients with CS refractory to aggressive medical and device-based therapies will undergo evaluation for cardiac replacement therapies, such as durable ventricular assist devices and orthotopic heart transplantation. The individual CS algorithms for each center are included in Supplemental Figures S1-S4.[1] These function as a guide but do not restrict care by clinicians.

Clinical end points and follow-up

The primary end point will be survival at 30 days after hospital discharge. Secondary outcome measures will include survival to 6 and 12 months after discharge. Patients who are lost to follow-up will be censored at the date of last medical contact. Other secondary end points will include major bleeding, defined as Bleeding Academic Research Consortium

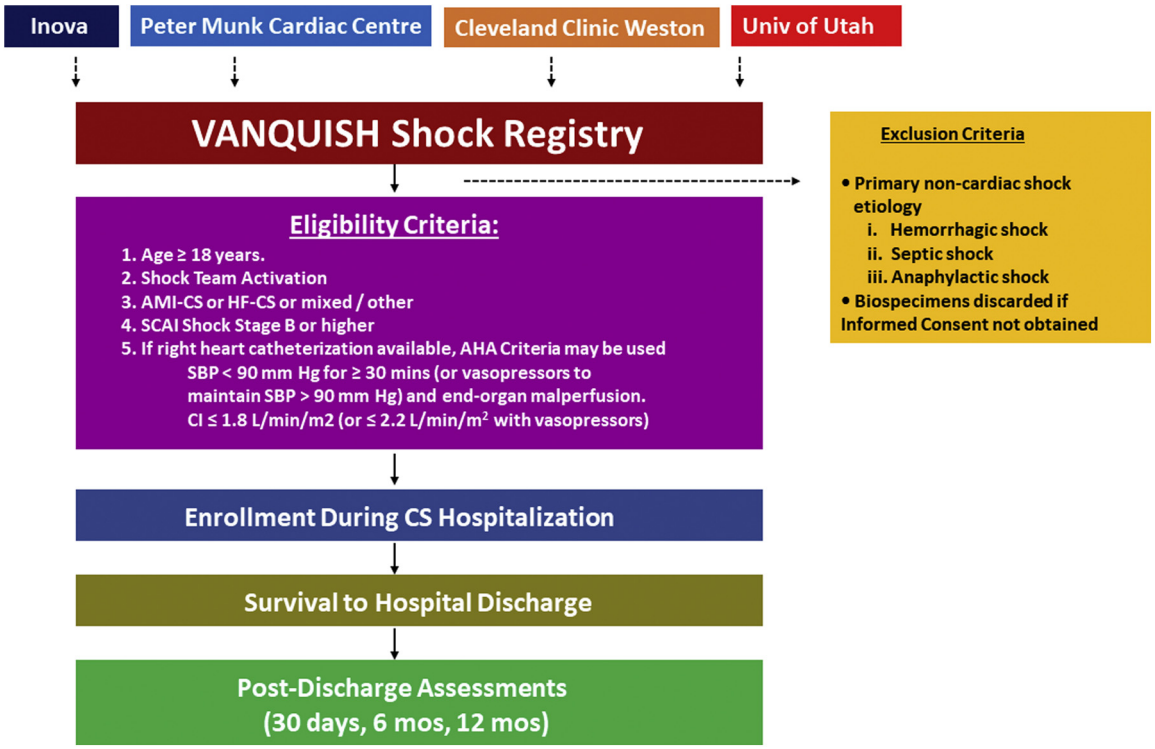

Figure 1. Multicenter Collaborative to Enhance Biological Understanding, Quality and Outcomes in Cardiogenic Shock (VANQUISH Shock) Consort diagram. AMI-CS, acute myocardial infarction complicated by cardiogenic shock; CI, cardiac index; CPO, cardiac power output; CS, cardiogenic shock; HF-CS, heart failure complicated by cardiogenic shock; PAPi, pulmonary arterial pulsatility index; SBP, systolic blood pressure; SCAI, Society for Cardiovascular Angiography and Intervention.

types 3 and 5 bleeds, Valve Academic Research Consortium 2 major vascular complications, acute kidney injury requiring renal replacement therapy, clinically significant hemolysis resulting in the need for transfusions or dialysis, stroke, and major adverse cardiac and cerebrovascular events, defined as a composite of 30-day mortality after hospital discharge, stroke, or HF rehospitalisation.[21,22] Patients surviving the index hospitalisation will also undergo neurologic and health-related quality-of-life outcome assessments with the Cerebral Performance Category (CPC) and Rand 36-Item Short-Form Survey tools before discharge and at 30 days and 6 and 12 months after hospital discharge.[23,24] These assessments will occur either in person or via telephone between a cardiology practitioner and either the patient or their legally authorised representative. Institutional language service lines with licensed medical translators will be used as necessary. A data-monitoring committee consisting of 1 steering committee member from each institution will adjudicate the primary and secondary outcome measures.

Data collection

Clinical and hemodynamic variables will be collected prospectively in real time from the electronic medical record during the hospitalisation. Clinical outcomes at 30 days and 6 and 12 months after hospital discharge will be collected prospectively via follow-up telephone calls (Table 3). All deidentified information will be entered into a comprehensive case report form and stored in a centralised **R**esearch **E**lectronic **D**ata **Cap**ture (REDCap) database at the University of Utah. An internal audit will be performed quarterly to ensure the accuracy and scientific integrity of the data. The Peter Munk Cardiac Centre and the University of Utah have existing infrastructure to allow for collection and storage of biospecimens in patients who consent to blood draws for research. With the use of standardised protocols, samples will be collected within 24 hours of CS diagnosis, on the second day after CS diagnosis, at the time of cannulation with MCS, and on the day of discharge. These samples will provide a rich repository of biospecimens from which biomarker studies will be performed. Both Inova and Cleveland Clinic will obtain and process biospecimens from consented patients and ship these frozen biospecimens in batches to the University of Utah for storage and future analysis.

Statistical analysis

It is anticipated that each site's shock team will enroll a minimum of 125 patients annually with a primary diagnosis of CS. This will include patients who are admitted directly to the 4 quaternary care centres and who are transferred from a community "spoke" hospital. Patients who are deemed lost to follow-up at 30 days, 6 months, or 12 months after hospital discharge will be censored in the respective primary and secondary outcomes analyses. Conditional short- and intermediate-term cumulative survival rates of all patients in the registry will be determined with the use of the Kaplan-Meier method. In addition, Cox proportional hazards modelling will be used to identify the correlates of the primary and secondary outcomes. This will include not only

Table 2. VANQUISH Shock registry composition

	Cleveland Clinic Florida	Inova Fairfax Medical Campus	Peter Munk Cardiac Centre	University of Utah
Executive physician lead	David A. Baran, MD	Wayne B. Batchelor, MD, MHS	Filio Billia, MD, PhD	Stavros G. Drakos, MD, PhD
Shock team composition	1. Interventional Cardiology 2. Cardiac Surgery 3. Advanced Heart Failure 4. Cardiac Critical Care 5. Nursing	1. Interventional Cardiology 2. Cardiac Surgery 3. Advanced Heart Failure 4. Cardiac Critical Care 5. Nursing	1. Interventional Cardiology 2. Cardiac Surgery 3. Advanced Heart Failure 4. Cardiac Critical Care 5. Nursing	1. Interventional Cardiology 2. Cardiac Surgery 3. Advanced Heart Failure 4. Cardiac Critical Care 5. Nursing
Beds	230	923	417	425
Annual shock volume	$\geq$ 170	$\geq$ 170	$\geq$ 170	$\geq$ 170
MCS devices	1. IABP 2. Impella 2.5/CP/RP/5.0/5.5 (Abiomed) 3. VA-ECMO (Getinge; Medtronic) 4. Surgical Centrimag pump (Abbott Cardiovacular)	1. IABP 2. Impella 2.5/CP/RP/5.0/5.5 (Abiomed) 3. VA-ECMO (Abbott) 4. Surgical Centrimag pump (Abbott Cardiovacular)	1. IABP 2. Impella 2.5/CP/5.0/5.5 (Abiomed) 3. VA-ECMO (Getinge; Medtronic) 4. Surgical Centrimag pump (Abbott Cardiovacular)	1. IABP 2. Impella 2.5/CP/RP/5.0/5.5 (Abiomed) 3. VA-ECMO (TandemHeart; LivaNova) 4. Surgical Centrimag pump (Abbott Cardiovacular)
Cardiac replacement therapies	1. Durable LVAD 2. OHT	1. Durable LVAD 2. OHT	1. Durable LVAD 2. OHT	1. Durable LVAD 2. OHT

IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; MCS, mechanical circulatory support; OHT, orthotopic heart transplant; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VANQUISH Shock, Multicenter Collaborative to Enhance Biological Understanding, Quality and Outcomes in Cardiogenic Shock.

historically validated clinical variables currently used in clinical practice, but also potentially novel data points such as longitudinal assessments of hemodynamic and metabolic parameters, SCAI CS staging, and molecular profiling with the use of proteomics and biomarkers to predict outcomes.[16,25] Standard summary statistical presentations will be as mean $\pm$ SD, median (interquartile range [IQR]), or frequency and percentage as deemed appropriate. Comparisons between patient populations of clinical interest will be made via Student *t* test, Wilcoxon rank sum test, 1-way analysis of variance, chi-square, or Fisher exact test as appropriate. Data points that are missing at random will be imputed by means of multiple imputation with chained equations to avoid introduction of selection bias. The algorithmic management differences between each site will be accounted for in the primary end point analysis by adjusting for centre in a fixed-effect model, and differences in baseline composition between centres will be balanced by adjusting for baseline illness severity (ie, SCAI stage, invasive hemodynamics, lactate).

Ethical conduct and funding

The VANQUISH Shock registry has been approved by the institutional review boards of each individual institution. Participation in the registry will include a waiver of informed consent for clinical data and deferred consent for biospecimen use. All data will be deidentified and collected primarily for the purpose of clinical research. The registry is currently funded by the Peter Munk Cardiac Centre Innovation Fund. Because the study will be shock etiology and therapy agnostic, engagement with industry partners will be fully inclusive and solely for the purpose of clinical research. Supplemental financial support for statistical analysis will be provided by the Ted Rogers Centre for Heart Research. The executive and steering committee members of the consortium are responsible for the design and conduct of this registry, all study analyses, and the production of all manuscripts.

Discussion

The VANQUISH Shock registry will be the first international multicentre study to prospectively evaluate the clinical characteristics, hemodynamics, management, and both short-term and 1-year outcomes of consecutive CS patients presenting at 4 high-volume level 1 shock centres. Patients will be followed longitudinally and, unlike in other contemporary registries, comprehensive data will be collected in a multidisciplinary and device-agnostic manner. Variables of interest will include in-hospital clinical and hemodynamic data, major adverse events, and postdischarge survival and quality of life at 1 year. Together with the collection of biospecimens, the registry will provide unique holistic insights into the clinical and molecular signature of the dynamic shock state. Although current and ongoing research efforts have greatly informed our understanding of the hemometabolic complexities associated with CS, they have focused primarily on patients with AMI-CS, with a device-based approach. Alternatively, existing studies have been limited primarily to centres without dedicated shock teams, or the studies have not prospectively enrolled patients across the full spectrum of CS (Fig. 2).[10,26-28]

CS encompasses a wide spectrum of clinical presentations, yet most of the research has primarily been in patients with SCAI stages C-E shock.[27] These patients inevitably require pharmacologic and/or device-based circulatory support because they are both hypotensive and hypoperfused. Little is known, however, regarding the patients in preshock, who have early signs of end-organ malperfusion despite near normal SBPs because of catecholamine-mediated compensatory vasoconstriction.[29] Such patients, categorised as SCAI stage B CS, constituted only 5% of the SHOCK Trial registry but were a notably high-risk cohort. These patients had greater rates of anterior-wall MI compared with patients with

Table 3. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• All consecutive patients will be enrolled under a waiver of informed consent for deidentified data collection. • Adult men and women (≥ 18 years) • Referral to the shock team for suspected or confirmed cardiogenic shock **AND/OR** primary diagnosis of shock due to cardiac etiology as determined by institutional shock teams based on clinical and/or hemodynamic criteria as defined in the 2017 AHA Scientific Statement on CS and the SHOCK trial[17]: ○ *Clinical criteria:* - SBP < 90 mm Hg for ≥ 30 minutes (or the need for vasoactive infusions to maintain a SBP ≥ 90 mm Hg), and - Evidence of end-organ hypoperfusion (cool extremities or urine output < 30 mL/h) ○ *Hemodynamic criteria:* - Fick or thermodilution cardiac index ≤ 1.8 L/min/m^2 without vasopressors (or ≤ 2.2 L/min/m^2) or - CPO < 0.6 W or PAPi < 1.0 - AMI-CS (STEMI, NSTEMI, unstable angina) • HF-CS - Valvular heart disease - Stress (takotsubo) cardiomyopathy - Myocarditis (including COVID-19) - Allograft rejection • CS complicated by cardiac arrest • Pulmonary embolism with right ventricular CS • CS due to post-MI mechanical complications: - Ventricular septal defect - Papillary muscle rupture with mitral regurgitation - Free wall rupture - Cardiac tamponade • Arrhythmia (AF, VF, VT, bradycardia, or heart block)	• Biospecimens will not be kept if consent is not later obtained from the patient or legally authorised representative. • Shock not due to primary cardiac etiology: - Septic shock - Anaphylactic shock - Hemorrhagic shock • Patients not evaluated by the shock team. • Postcardiotomy shock

AF, atrial fibrillation; AHA, American Heart Association; AMI-CS, acute myocardial infarction complicated by cardiogenic shock; CPO, cardiac power output; CS, cardiogenic shock; MI, myocardial infarction; NSTEMI, non–ST-segment elevation MI; PAPi, Pulmonary Arterial Pulsatility Index; SBP, systolic blood pressure; SHOCK, **Sh**ould We Emergently Revascularize **O**ccluded **C**oronaries for Cardiogenic Sho**k**; STEMI, ST-segment elevation MI; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 4. Invasive hemodynamic variables and calculations captured at time of right heart catheterisation

Invasive hemodynamics	Calculations
• Systemic systolic, diastolic, and mean arterial blood pressures (mm Hg) • Heart rate (beats/min) • Mean right atrial pressure (mm Hg) • Right ventricular systolic and diastolic pressures (mm Hg) • Systolic, diastolic, and mean pulmonary arterial pressures (mm Hg) • Pulmonary capillary wedge pressure (mm Hg) • Fick and/or thermodilution cardiac output (L/min) and cardiac index (L/min/m^2)	• Pulmonary and systemic vascular resistance (Woods units or dynes × sec/cm^{-5}) • Cardiac power output • Pulmonary arterial pulsatility index • Right ventricular stroke work index (g × m/m^2/beat)

classic CS, and they had a 43% in-hospital mortality rate.[30] SCAI B patients continue to be underrepresented even in contemporary registries: They have been only 7% of all CICU admissions in the Critical Care Cardiology Trials Network, and they have not been included in any of the National Cardiogenic Shock Initiative analyses.[31,32] Given the paucity of data to inform risk stratification of patients with preshock, an all-comer CS registry is needed to prospectively identify these patients. A recent prospective series of patients with uniform report of SCAI shock stage had 6% of patients initially assessed as SCAI B.[15] The mortality of such patients in this series was very low, but larger numbers will be needed to confirm this finding, as well as to define strategies to achieve this optimal survival. Through longitudinal assessment of a number of granular variables, such as vital signs, metabolic parameters, invasive hemodynamics, and SCAI staging, the VANQUISH Shock registry will study this patient population prospectively with the goal to develop prognostic models, similar to those in nonsevere sepsis, that may inform not only early disease recognition but also predict which of these patients are at highest risk for progressing to fulminant CS.[33]

Patients hospitalised with CS are at risk for several morbidities. There is a greater than 40% prevalence of acute respiratory failure requiring mechanical ventilation, nearly 30% will develop acute renal insufficiency, and up to 5% will suffer a cerebrovascular accident.[34,35] The post-hospital course in patients with CS is also associated with significant risk: 1 in 5 patients will be readmitted within 30 days, not only for recurrent HF but also for noncardiac issues, such as infection, bleeding, and respiratory failure.[36] These post-shock morbidities extend beyond the first month, with 59% of AMI-CS survivors experiencing a rehospitalisation or death at 1 year, a risk that may extend up to 5 years after discharge simply based on index severity of illness.[37,38] Patients with CS also encounter challenges with their daily quality of life, with 20% to 30% reporting impairment with daily activities, self-care, and chronic pain and anxiety up to 12 months after hospital discharge.[39] Little is known, however, regarding post-hospitalisation health outcomes outside of the constructs of payer databases and a limited number of randomised clinical trials conducted primarily in AMI-CS.[40] There is also a paucity of data on long-term cognitive function after CS. This is particularly important as nearly 50% of patients with CS experience cardiac arrest either at the time of clinical presentation or as a sequela of their illness.[41,42] Prognosis in these patients is determined primarily by the extent of anoxic brain injury, as predicted by the presence or absence of a shockable rhythm as well as duration and locale of resuscitation.[43] The VANQUISH Shock registry will seek to better understand the long-term health-related outcomes of unrestricted patients with CS through serial assessment of quality of life and neurologic status with the use of the Rand Short-Form 36 (SF-36) survey and CPC as well as Modified Rankin Scale (mRS) questionnaires, respectively. Both tools have been

Table 5. VANQUISH Shock Study schedule

	Shock team evaluation	24 h after shock team evaluation	Time of MCS implantation	Daily during CS hospitalisation	Hospital discharge	30-d follow-up	6-mo follow-up	1-y follow-up
Baseline demographics	X							
Coronary angiography findings (AMI-CS)	X							
Invasive hemodynamics and laboratory tests	X	X	X	X				
Transthoracic echocardiography	X		X		X			
SCAI CS staging	X	X	X					
Inotropes + vasopressor dosing	X	X	X	X				
Major bleeding, vascular complications, stroke, dialysis	X	X	X	X				
Primary end point						X		
MACCE						X		
Secondary survival end points							X	X
CPC + mRS					X	X	X	X
SF-36 questionnaire					X		X	X
Serum and plasma samples collection	X	X	X		X			

AMI-CS, acute myocardial infarction complicated by cardiogenic shock; CPC, Cerebral Performance Category; CS, cardiogenic shock; MACCE, major adverse cardiovascular and cerebrovascular events; MCS, mechanical circulatory support; mRS, Modified Rankin Scale; SCAI, Society for Cardiovascular Angiography and Intervention; SF-36, Short-Form 36 Health Survey; VANQUISH Shock, Multicenter Collaborative to Enh**a**nce Biological Understanding, **Q**ual**i**ty and Outcomes in Cardiogenic **Sh**ock.

validated as measures of health status in cardiovascular disease and may serve to inform prognosis after discharge across the severity and hemometabolic spectrum of CS.[44,45]

Despite contemporary efforts to enhance outcomes in CS through optimising clinical care pathways and restoring normal hemodynamics, gaps remain in knowledge regarding the pathophysiologic processes involved and the biochemical pathways that are dysregulated in this patient population.[10] While contemporary advances in "omics" have advanced knowledge regarding potential associations between gene products and clinical expression in other lethal syndromes, such a comprehensive and mechanistic understanding has been lacking in CS.[46] Two recent quantitative proteomic analyses, one from the Barcelona and CardShock registries and the other from the **Culprit** Lesion Only PCI Versus Multivessel PCI in Cardiogenic **Shock** (CULPRIT-SHOCK) trial with external validation with the use of the **I**ntra-**a**ortic **B**alloon **P**ump in Cardiogenic **Shock** (IABP-SHOCK) II trial, identified 2 candidate biomarker scores that were validated for predicting short-term mortality risk in CS: the CLIP (cystatin C, lactate, interleukin-6, and N-terminal pro−B-type natriuretic peptide) and the CS4P (liver-type fatty acid protein, beta-2-microglobulin, fructose-bisphosphate aldolase B, and serpin G1) classifiers.[25,47] The 2 assays incorporated proteins involved in inflammation and multiorgan system dysfunction. However, both analyses were derived from studies of patients predominantly with AMI-CS and the blood samples were collected within 24 hours of index shock diagnosis; it is unknown if dynamic changes in these biomarkers throughout the course of cardiogenic shock carry additional prognostic information.

The VANQUISH Shock registry will leverage the clinical volumes and breadth of disease acuity of 4 quaternary care shock centres by prospectively collecting longitudinal blood samples of participating shock patients across the spectrum of illness severity. The importance of longitudinal sampling related to CS admission agnostic to treatment strategy cannot be understated. Some of the current registries enroll patients once MCS is considered and implanted. This strategy leads to implicit selection bias at the outset. The collection of biospecimens for all patients presenting with CS presents us with the important unbiased phenotyping of patients through the assessment of changes in genetic expression profiling at the mRNA, miRNA, and protein levels We are keenly interested in defining the dysregulation of inflammation and cardioprotective signalling mechanisms in patients with varying severity of illness and etiologies of CS. The VANQUISH Shock registry will identify novel candidate biomarkers involved in the pathophysiology of cardiogenic shock. We think that these will include activation of the systemic inflammatory response, vasoplegia, microvascular leaking, alterations in metabolism, chemotaxis, coagulation, platelet function, and response to tissue hypoxia. We do not plan to focus on established panels such as CLIP and CS4P.

In addition to the extensive clinical longitudinal data that is being collected, a machine-learning approach will be applied to further inform our mechanistic understanding of cardiogenic shock. Several groups have used a variety of sophisticated approaches including techniques such as LogitBoost[48] and Extreme Gradient boost[49] algorithms, which facilitate computer detection of variables that associate with the outcome of

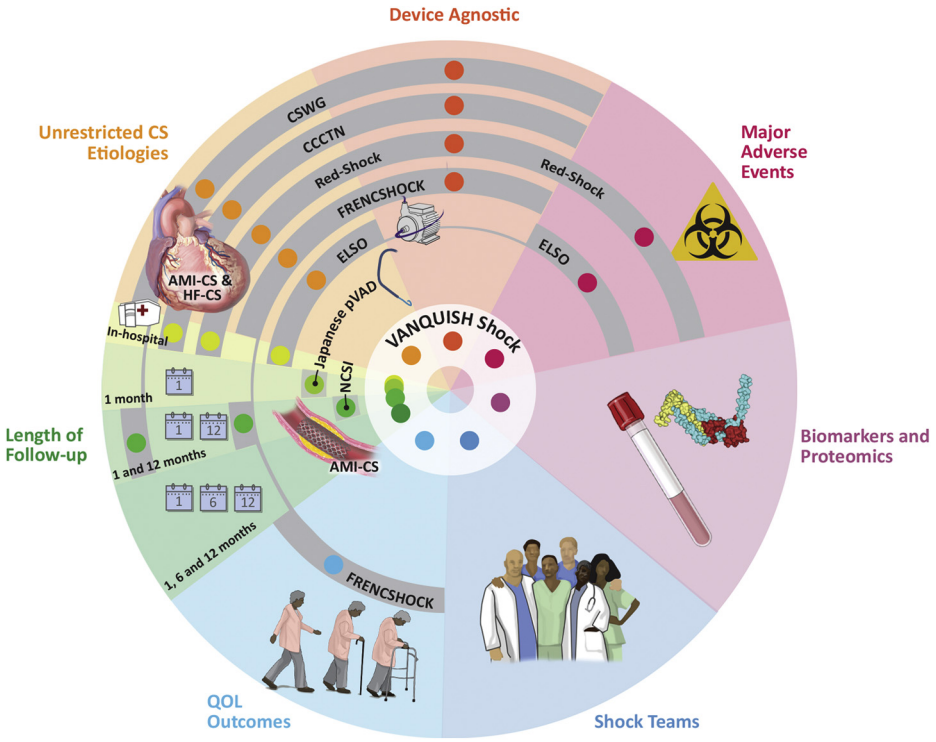

Figure 2. Current landscape of cardiogenic shock registries. The Multicenter Collaborative to Enhance Biological Understanding, Quality and Outcomes in Cardiogenic Shock (VANQUISH Shock) Collaborative will consist of 4 high-volume cardiogenic shock centres. It will address translational and clinical gaps in knowledge through its deep phenotyping and treatment-agnostic approach. In complementary fashion to other contemporary registries listed in this diagram, which are either prespecified regarding their patient populations or study outcomes, VANQUISH Shock will be composed of centres with dedicated shock teams, will study all cardiogenic shock etiologies, will be device agnostic, and will capture all in-hospital adverse events and short-term and 1-year follow-up of QOL measures. It will also study the mechanisms of shock by examining how longitudinal changes in biomarkers and proteomics may be correlated with clinical outcomes. AMI-CS, acute myocardial infarction complicated by cardiogenic shock; CCCTN, Critical Care Cardiology Trials Network; CS, cardiogenic shock; CSWG, Cardiogenic Shock Working Group; ELSO, Extracorporeal Life Support Organization; HF, heart failure complicated by cardiogenic shock; NCSI, National Cardiogenic Shock Initiative; QOL, quality of life.

interest. A recent systematic review covers the field in further detail.[50] A key aspect is to define the outcome of interest, and most reports have focused on mortality,[14] but other end points, such as cognitive function and quality of life, could also be investigated with the VANQUISH Shock data set.

Conclusion

The VANQUISH Shock registry will provide a unique opportunity to comprehensively study the contemporary management, clinical course, and short-term as well as 1-year outcomes of consecutive patients presenting with CS at 4 high-volume dedicated shock care centres. Combining prospective biospecimen collection, detailed and systematic assessment of complications and device utilisation, and serial quality of life assessments and cerebral performance measures, the registry will be distinct from current multicentre efforts. The information garnered from this registry will serve as a springboard for future mechanistic clinical studies and trials with other like-minded centres interested in collaborating regarding standardised multidisciplinary efforts to advance the CS field.

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References

1. Tehrani BN, Truesdell AG, Psotka MA, et al. A standardized and comprehensive approach to the management of cardiogenic shock. JACC Heart Fail 2020;8:879-91.
2. Osman M, Syed M, Patibandla S, et al. Fifteen-year trends in incidence of cardiogenic shock hospitalization and in-hospital mortality in the United States. J Am Heart Assoc 2021;10:e021061.
3. Berg DD, Bohula EA, Diepen Sv, et al. Epidemiology of Shock in Contemporary Cardiac Intensive Care Units. Circ Cardiovasc Qual Outcomes 2019;12:e005618.
4. Abraham J, Blumer V, Burkhoff DAN, et al. Heart failure—related cardiogenic shock: pathophysiology, evaluation and management considerations. J Card Fail 2021;27:1126-40.
5. Schrage B, Beer BN, Savarese G, et al. Eligibility for mechanical circulatory support devices based on current and past randomised cardiogenic shock trials. Eur J Heart Fail 2021.
6. Udesen NJ, Møller JE, Lindholm MG, et al. Rationale and design of DanGer Shock: Danish-German cardiogenic shock trial. Am Heart J 2019;214:60-8.
7. Bertini P, Guarracino F. Pathophysiology of cardiogenic shock. Curr Opin Crit Care 2021;27:409-15.
8. Tehrani BN, Truesdell AG, Sherwood MW, et al. Standardized team-based care for cardiogenic shock. J Am Coll Cardiol 2019;73:1659-69.
9. Taleb I, Koliopoulou AG, Tandar A, et al. Shock team approach in refractory cardiogenic shock requiring short-term mechanical circulatory support: a proof of concept. Circulation 2019;140:98-100.
10. Basir MB, Kapur NK, Patel K, et al. Improved outcomes associated with the use of shock protocols: updates from the National Cardiogenic Shock Initiative. Catheter Cardiovasc Interv 2019;93:1173-83.
11. Lee F, Hutson JH, Boodhwani M, et al. Multidisciplinary code shock team in cardiogenic shock: a Canadian centre experience. CJC Open 2020;2:249-57.
12. Moghaddam N, van Diepen S, So D, Lawler PR, Fordyce CB. Cardiogenic shock teams and centres: a contemporary review of multidisciplinary care for cardiogenic shock. ESC Heart Fail 2021;8:988-98.
13. van Diepen S, Morrow DA. Potential growth in cardiogenic shock research though an international registry collaboration: the merits and challenges of a Hub-of-Spokes model. Eur Heart J Acute Cardiovasc Care 2021;10:3-5.
14. Zweck E, Thayer KL, Helgestad OKL, et al. Phenotyping cardiogenic shock. J Am Heart Assoc 2021;10:e020085.
15. Baran DA, Long A, Badiye AP, Stelling K. Prospective validation of the SCAI shock classification: single center analysis. Catheter Cardiovasc Interv 2020;96:1339-47.
16. Baran DA, Grines CL, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Crit Care Med (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. Catheter Cardiovasc Interv 2019;94:29-37.
17. Hochman JS, Sleeper LA, Webb JG, et al. SHOCK Investigators. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625-34.
18. Diepen Sv, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation 2017;136:e232-68.
19. Fincke R, Hochman JS, Lowe AM, et al. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK Trial registry. J Am Coll Cardiol 2004;44:340-8.
20. Kochav SM, Flores RJ, Truby LK, Topkara VK. Prognostic impact of Pulmonary Artery Pulsatility Index (PAPi) in patients with advanced heart failure: insights from the ESCAPE trial. J Card Fail 2018;24:453-9.
21. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized end point definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg 2012;42:S45-60.
22. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.
23. Phelps R, Dumas F, Maynard C, Silver J, Rea T. Cerebral performance category and long-term prognosis following out-of-hospital cardiac arrest. Crit Care Med 2013;41:1252-7.
24. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: scoping review. SAGE Open Med 2016;4. 2050312116671725.
25. Ceglarek U, Schellong P, Rosolowski M, et al. The novel cystatin C, lactate, interleukin-6, and N-terminal pro—B-type natriuretic peptide (CLIP)—based mortality risk score in cardiogenic shock after acute myocardial infarction. Eur Heart J 2021;42:2344-52.
26. Hernandez-Montfort J, Sinha SS, Thayer KL, et al. Clinical outcomes associated with acute mechanical circulatory support utilization in heart failure related cardiogenic shock. Circ Heart Fail 2021;14:e007924.
27. Thayer KL, Zweck E, Ayouty M, et al. Invasive hemodynamic assessment and classification of in-hospital mortality risk among patients with cardiogenic shock. Circ Heart Fail 2020;13:e007099.
28. Papolos AI, Kenigsberg BB, Berg DD, et al. Management and outcomes of cardiogenic shock in cardiac ICUs with versus without shock teams. J Am Coll Cardiol 2021;78:1309-17.
29. Saxena A, Garan AR, Kapur NK, et al. Value of hemodynamic monitoring in patients with cardiogenic shock undergoing mechanical circulatory support. Circulation 2020;141:1184-97.
30. Menon V, Slater JN, White HD, et al. Acute myocardial infarction complicated by systemic hypoperfusion without hypotension: report of the SHOCK Trial registry. Am J Med 2000;108:374-80.
31. Hanson ID, Tagami T, Mando R, et al. SCAI shock classification in acute myocardial infarction: insights from the National Cardiogenic Shock Initiative. Catheter Cardiovasc Interv 2020;96:1137-42.
32. Lawler PR, Berg DD, Park J-G, et al. The range of cardiogenic shock survival by clinical stage: data from the Critical Care Cardiology Trials Network Registry. Crit Care Med 2021;49.
33. Holder AL, Gupta N, Lulaj E, et al. Predictors of early progression to severe sepsis or shock among emergency department patients with non-severe sepsis. Int J Emerg Med 2016;9:10.
34. Schrage B, Becher PM, Goßling A, et al. Temporal trends in incidence, causes, use of mechanical circulatory support and mortality in cardiogenic shock. ESC Heart Fail 2021;8:1295-303.
35. Pahuja M, Chehab O, Ranka S, et al. Incidence and clinical outcomes of stroke in ST-elevation myocardial infarction and cardiogenic shock. Catheter Cardiovasc Interv 2021;97:217-25.
36. Mahmoud AN, Elgendy IY, Mojadidi MK, et al. Prevalence, causes, and predictors of 30-day readmissions following hospitalization with acute myocardial infarction complicated by cardiogenic shock: findings from

the 2013-2014 National Readmissions Database. J Am Heart Assoc 2018;7:e008235.

37. Shah RU, de Lemos JA, Wang TY, et al. Post-hospital outcomes of patients with acute myocardial infarction with cardiogenic shock: findings from the NCDR. J Am Coll Cardiol 2016;67:739-47.

38. Jentzer JC, Baran DA, van Diepen S, et al. Admission Society for Cardiovascular Angiography and Intervention shock stage stratifies post-discharge mortality risk in cardiac intensive care unit patients. Am Heart J 2020;219:37-46.

39. Thiele H, Zeymer U, Neumann FJ, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. Lancet 2013;382:1638-45.

40. Ouweneel DM, Eriksen E, Sjauw KD, et al. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol 2017;69:278-87.

41. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med 2017;377:2419-32.

42. Omer MA, Tyler JM, Henry TD, et al. Clinical characteristics and outcomes of STEMI patients with cardiogenic shock and cardiac arrest. JACC Cardiovasc Interv 2020;13:1211-9.

43. Harhash AA, May TL, Hsu CH, et al. Risk stratification among survivors of cardiac arrest considered for coronary angiography. J Am Coll Cardiol 2021;77:360-71.

44. Munir H, Morais JA, Goldfarb M. Health-related quality of life in older adults with acute cardiovascular disease undergoing early mobilization. CJC Open 2021;3:888-95.

45. Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary angiography after cardiac arrest without ST-segment elevation. N Engl J Med 2019;380:1397-407.

46. Cao Z, Robinson RA. The role of proteomics in understanding biological mechanisms of sepsis. Proteomics Clin Appl 2014;8:35-52.

47. Rueda F, Borràs E, García-García C, et al. Protein-based cardiogenic shock patient classifier. Eur Heart J 2019;40:2684-94.

48. Calvillo-Argüelles O, Sierra-Fernández CR, Padilla-Ibarra J, et al. Integrating the STOP-BANG score and clinical data to predict cardiovascular events after infarction: a machine learning study. Chest 2020;158:1669-79.

49. Bai Z, Hu S, Wang Y, et al. Development of a machine learning model to predict the risk of late cardiogenic shock in patients with ST-segment elevation myocardial infarction. Ann Transl Med 2021;9:1162.

50. Aleman R, Patel S, Sleiman J, et al. Cardiogenic shock and machine learning: a systematic review on prediction through clinical decision support softwares. J Card Surg 2021;36:4153-9.

Supplementary Material

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