Can Escalation Reduce Acute Myocardial Infarction Mortality in Cardiogenic Shock (CERAMICS Study)

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1. **Introduction**

Acute myocardial infarction complicated by cardiogenic shock (AMICS) is a deadly condition with an in-hospital survival rate of ~50%[1-3]. To date, the only therapy proven to benefit patients in AMICS has been early revascularization[3]. Accordingly, American and European guidelines confer a class IB indication for early revascularization in the setting of AMICS[4]. Unfortunately, little progress has been made on improving survival with subsequent therapies, including intra-aortic balloon pump counter-pulsation (IABP) [5]. This lack of progress is worrisome as the incidence of AMICS is increasing[6-7].

Mechanical circulatory support (MCS) devices improve hemodynamics in patients with AMICS and use of such devices as adjunctive therapy is supported in US guidelines (Class II a/b recommendations). It has been hypothesized that robust MCS devices such as extracorporeal membrane oxygenation (ECMO) or transvalvular pumps may improve outcomes further. Despite being available for many decades, ECMO is infrequently used because of limited availability and a high level of expertise needed for use. ECMO has historically been used by surgeons in the operating room with few cardiac catheterization laboratories having access to ECMO. Transvalvular MCS devices however are available in over 90% of cardiac catheterization laboratories in the United States and have been approved by the FDA for use in AMICS. Clinicians have variable experiences and expertise with MCS devices. A retrospective analysis of 15,259 patients treated with a MCS between 2009 and 2017 revealed a wide variety of outcomes associated with the use of MCS in AMICS.

Within this context the National Cardiogenic Shock Initiative (NCSI) (NCT03677180) was conceived and implemented. The aim of the study was to evaluate outcomes of patients treated with MCS using a protocolized approach emphasizing best practices. The best practices included (1) to diagnose and treat patients with AMICS as quickly as possible thereby decreasing

the duration patients remain in cardiogenic shock and attempt to decrease use and duration of vasopressors and inotropes. (2) To rapidly deliver MCS, reversing end organ hypoperfusion and preventing the neuro-hormonal cascade associated with cardiogenic shock. (3) Routine use of invasive hemodynamic monitoring with pulmonary artery catheters to guide therapy.

The final results of the NCSI study were presented at the annual SCAI scientific sessions in 2021. Between July 2016 and December 2020, a total of 406 patients were enrolled in the study across 73 sites. Patients' average age was 64±12 years, 24% were female and 67% were admitted in shock. 85% of patients were on vasopressors or inotropes, 17% had a witnessed out-of-hospital cardiac arrest, 27% had in-hospital cardiac arrest, and 9% were under active cardiopulmonary resuscitation during MCS implantation. 73% of patients presented in SCAI stage C/D shock and 27% in stage E. Patients presented with an average blood pressure of 77/50, lactate of 4.8 mmol/dL and cardiac power output (CPO) of 0.67W. In accordance with the NCSI treatment algorithm, 71% of patients had MCS implanted prior to PCI. Pulmonary artery catheters were used in 93% of patients. 82% of patients presented with ST-elevation myocardial infarction with a median door to support time of 78 (IQR 54-116) mins and door to balloon time of 82 (IQR 57-114) mins. Procedural survival, survival to discharge, survival to 30-days, and survival to 1-year were 99%, 79%, 77%, 62% for patients presenting in stage C/D shock and 98%, 49%, 46%, 32% for patients in stage E shock ($p<0.01$). When compared to previously conducted studies in AMICS early use of MCS guided by invasive hemodynamics was associated with improved outcomes. Given the promising results, a randomized control trial is being formulated to further validate these results (RECOVIER IV).

The NCSI was an initial step in protocolizing care in AMICS. Over the past 5 years, further learnings have helped identify additional best practices that may contribute to further improving outcomes. Approximately 30-40% of patients with AMICS have concomitant right

ventricular failure (RVF), which is associated with worse morality and may therefore benefit from consideration of early right ventricular mechanical circulatory support (RV-MCS) devices. Vasopressors have been identified as being independently associated with worse outcomes and MCS escalation may lead to further improvement in outcomes. While sites participating in the NCSI were early adopters of MCS in AMICS, MCS escalation was open ended and dictated by variable local practice patterns. This contributed to the overall low rate of MCS escalation which occurred in NCSI.

In the CERAMICS study, we aim to more clearly delineate care of AMICS regarding MCS escalation and ICU management. Our goal is to enroll sites with significant experience in MCS, all of whom have the capability of MCS escalation and evaluate outcomes on ~120 patients focusing on MCS escalation decision making and ICU level management.

2. Site Selection Criteria & IRB Requirements

A total of 20 total sites will be accepted into the CERAMICS study with the goal of gathering data and outcomes of ~120 patients treated at participating centers. The study is expected to collect data for ~2 years. Prior to joining the study, each site must have broad adoption of the NCSI treatment algorithm as the standard of care for AMICS among at least 80% of the interventional cardiologists who take STEMI call, as confirmed by the site principal investigator (PI).

We are requesting a waiver of informed consent for the CERAMICS study. A Waiver of Informed consent is appropriate for the registry for multiple reasons: (1) Eligible patients are identified retrospectively after discharge from the index hospitalization, thus obtaining informed consent is not feasible. (2) Patients included in the CERAMICS registry are being treated with commercially available and FDA-approved devices, and all care is being delivered at the discretion

of their treating physicians according to standard local practice. (3) Enrolling only patients who provide informed consent would introduce substantial selection bias that reduces the validity of this research. It is critically important to track consecutive patients to assess outcomes. This is important to identify the total sample size treated and to help identify if there were particular biases on the use of MCS, escalation of MCS, etc. We will therefore also track outcomes of those not treated with MCS (i.e., exclusion form) as well as with patients treated with MCS including when care deviates from the study protocol. Clinicians will not be contacted about the care they deliver to patients at any time during the study, and the care will be delivered routinely at participating hospitals.

Patients presenting with AMICS are critically ill, with >40% of patients presenting in cardiac arrest, patients are frequently sedated, intubated and have cognitive dysfunction. Due to the critical nature and extremes of patients with AMICS, we are requesting a full waiver of informed consent and HIPAA authorization from the IRB for data collection and submission under the guidelines of 45 CFR 46.116(f) and 45 CFR 64.512(i)(2)(ii).

All study data collection is occurring retrospectively at each time-point only using EMR, and there will be no contact between study personnel and patients. Patients will be discharged or deceased at the time of study entry.

Sites seeking to join CERAMICS will need approval from their internal/local/system IRB, or the ability to either directly use WCG IRB or receive approval from their institutional/local/ system IRB to defer to WCG IRB as the IRB of record and oversight for the study. For sites choosing to defer study oversight to a national IRB, the study will be reviewed by WCG IRB (formerly known as “WIRB” - Puyallup, WA), an independent IRB with AAHRPP accreditation and ISO 9001 certification for quality management.

All data is being collected via retrospective EMR review only - no patient contact will be made, including screening form, case report form (CRF), and the 30-day and 1-year follow-up forms. A limited data set of PHI will be collected (patient age, date of admission, date of MCS implant/explant, date of discharge/death) for the CRF or exclusion form, but no direct patient identifiers (i.e., name, date of birth, SSN, etc.) other than date of death will be collected. Study data forms will be submitted only after hospital discharge.

3. Research Procedures

3.1 Records Screening

This registry will be undertaken at sites only after an IRB has given full approval for the final protocol, screening and data collection forms, and the approval of the site PI. During participation in the study, study sites will regularly screen all acute MI patient records (STEMI and NSTEMI) for patients who presented with cardiogenic shock (AMICS) using the screening form.

4. Data Collection

All study data will be collected retrospectively after patient discharge or death at each study time point (post-hospital discharge, 30-days, and 1-year), via chart review only, on all patients who present with AMICS regardless of survival to hospital discharge. If a patient meets the study inclusion criteria on the screening form, then the following data will be collected (see Appendix 3):

Retrospective Data (from their medical records)

- Medical history
- Admission characteristics
- Procedure dates and times
- Procedure characteristics

- Diagnostic values
- Post-procedure information

Survival Data (collected via EMR review only) (see Appendix 4 and Appendix 5)

- Mortality at 30 days
- Mortality at 12 months

5. Population and Eligibility Criteria

Due to the heterogeneous cohort of patients who present with AMICS, we have defined a specific subset of patients from whom outcomes are to be collected (based upon our inclusion and exclusion criteria). We anticipated collecting data on approximately 120 adult AMICS patients at 20 hospital sites in the United States. Data collection and entry will occur after a patient has been discharged or deceased. The duration of hospital participation in this research study is anticipated to be approximately 2 years.

5.1. Inclusion Criteria

AMICS patients who meet the following inclusion criteria, and none of the exclusion criteria, will have a case report form (CRF) completed and submitted within 45 days of hospital discharge:

1. Diagnosis of acute myocardial infarction (AMI) with ECG and/or biomarker evidence of S-T elevation myocardial infarction (STEMI) or non-S-T elevation myocardial infarction (NSTEMI).
2. Cardiogenic shock is defined as the presence of at least two of the following:
    a. Hypotension (systolic blood pressure ≤90 mm Hg, or inotropes/vasopressors to maintain systolic blood pressure ≥90 mmHg).

b. Evidence of end organ hypoperfusion: elevated serum lactate levels (venous or arterial), cool extremities, oliguria/anuria.
c. Hemodynamic criteria represented by a cardiac index of < 2.2 L/min/m^2 or a cardiac power output ≤ 0.6 watts.

3. Patient is supported with a transvalvular MCS as the initial MCS device.
4. Patient undergoes PCI within 12 hours of hospital presentation.

5.2. Registry Exclusion Criteria

AMICS patients who meet any of the following study exclusion criteria will have a limited set of data collected via a single-page Patient Exclusion Form completed and submitted within 45 days of hospital discharge, which includes the reason for exclusion, date of index PCI, and assessment of patient survival to hospital discharge:

1. Evidence of Anoxic Brain Injury
2. Unwitnessed out of hospital cardiac arrest or any cardiac arrest in which return of spontaneous circulation (ROSC) is not achieved within 30 minutes
3. IABP placed prior to MCS
4. Septic, anaphylactic, hemorrhagic, and neurologic causes of shock
5. Non-ischemic causes of shock/hypotension (pulmonary embolism, pneumothorax, myocarditis, tamponade, etc.)
6. Active bleeding for which MCS is contraindicated
7. Recent major surgery for which MCS is contraindicated
8. Mechanical complications of AMI (acute ventricular septal defect (VSD) or acute papillary muscle rupture)
9. Known left ventricular thrombus for which MCS is contraindicated

10. Mechanical aortic prosthetic valve
11. Contraindication to intravenous systemic anticoagulation which precludes placement of MCS.

6. Risks/Benefits of and Alternatives to Patient Participation

This is not a treatment study. This is a single-arm registry that captures data generated during procedures which are considered standard of care using FDA-approved technologies. There are no risks other than breach of confidentiality. To mitigate this risk, only a limited set of data directly related to the research will be captured, and all data will be stored in a secure REDCap database (please see below).

7. Data Management

Data collected from the participating sites will be securely stored and managed at Henry Ford Hospital in Detroit, Michigan. Electronic data will be stored and managed in a secure REDCap study database hosted through the Henry Ford Health System Department of Public Health Sciences in Detroit, Michigan. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. A study-specific database was created solely for CERAMICS study that includes only the specific data fields that pertain to the data points collected on the case report form (CRF) or Patient Exclusion Form (PEF) (see Appendix 3).

For patients who present to affiliated hospitals with AMICS but are excluded from a CRF (see section 5.2), a Patient Exclusion Form will be submitted to track the reasons for exclusion (see Appendix 3).

The CRFs and Patient Exclusion Forms from an individual site will be transmitted to the lead site, Henry Ford Hospital, via secure email and accessed only on hospital-approved, password-protected computers and stored on a password-protected and encrypted OneDrive system by Microsoft. Access to the OneDrive system and the REDCap database will be managed at Henry Ford Hospital by the NCSI coordinator and the investigators of the study via hospital-approved, password-protected computers inside locked offices in Henry Ford Hospital.

8. Access to Patient Information

The following will have access to the de-identified patient medical information, and any necessary research contracts and Data Use Agreements will be completed for each participating site.

Henry Ford Hospital – Detroit, Michigan CERAMICS team:

- Principal Investigators
- Co-Investigators
- Study Research Coordinator(s)
- Research Nurse(s)
- Research Assistant(s)
- Data Coordinator(s)
- Statistician, based at Henry Ford Hospital

9. Analysis and Publication of Data

There will be planned interim analysis of the data for the purpose of presentations, as well as a final analysis and submission for publication of all data at the end of the study. Demographics, admission characteristics, procedural characteristics, clinical characteristics, procedural outcomes, in-hospital outcomes, disposition, 30-day survival and 1-year survival will

be analyzed. The primary outcome of the study will be to assess mortality in AMICS at study sites with the ability to implant, and if needed, escalate MCS. The CERAMICS study is an observational study and as such prone to bias, confounding and thus causality should not be inferred. However, research in AMICS is difficult to perform and there is significant heterogeneity in care. Thus, even observational data, despite its limitations, can be practice changing and valuable to the care of this high-risk cohort.[10]

Statistical methods used for analysis will vary, however, continuous variables will be described using the mean and standard deviation. Categorical variables will be described are frequency and percentage. Student t test will be used for continuous variables. Chi square test or Fisher's exact tests will be used for categorical variables, as appropriate. All statistical tests and/or confidence intervals, as appropriate, will be performed using a 2-sided p value = 0.05. Univariate and multivariate logistical regression models will be used to assess the effect of variables on outcomes.

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