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Circulation: Heart Failure

ORIGINAL ARTICLE

Contemporary Management of Cardiogenic Shock: A RAND Appropriateness Panel Approach

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BACKGROUND: Current practice in cardiogenic shock is guided by expert opinion in guidelines and scientific statements from professional societies with limited high quality randomized trial data to inform optimal patient management. An international panel conducted a modified Delphi process with the intent of identifying aspects of cardiogenic shock care where there was uncertainty regarding optimal patient management.

METHODS: An 18-person multidisciplinary panel comprising international experts was convened. A modified RAND/University of California Los Angeles appropriateness methodology was used. A survey comprising 70 statements was completed. Participants anonymously rated the appropriateness of each statement on a scale of 1 to 9: 1 to 3 inappropriate, 4 to 6 uncertain, and 7 to 9 appropriate. A summary of the results was discussed as a group, and the survey was iterated and completed again before final analysis.

RESULTS: There was broad alignment with current international guidelines and consensus statements. Overall, 44 statements were rated as appropriate, 19 as uncertain, and 7 as inappropriate. There was no disagreement with a disagreement index <1 for all statements. Routine fluid administration was deemed to be inappropriate. Areas of uncertainty focused panel on pre-PCI interventions, the use of right heart catheterization to guide management, routine use of left ventricular unloading strategies, and markers of futility when considering escalation to mechanical circulatory support.

CONCLUSIONS: While there was broad alignment with current guidance, an expert panel found several aspects of care where there was clinical equipoise, further highlighting the need for randomized controlled trials to better guide patient management and decision making in cardiogenic shock.

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Key Words: consensus ■ hemodynamics ■ myocardial infarction ■ percutaneous coronary intervention ■ shock, cardiogenic

Cardiogenic shock (CS) is a clinical syndrome of inadequate end-organ perfusion due to diminished cardiac output. CS is a leading cause of mortality associated with acute myocardial infarction (AMI) and acute decompensated heart failure.[1] Improved access to reperfusion therapies has had minimal impact on AMI CS mortality over the last decade,[2] and mortality from CS remains unacceptably high (30%–50%).[3,4] Outcomes in non-AMI CS patients, although less comprehensively studied, appear to be similarly disappointing.[5]

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WHAT IS NEW?

- This study uses established RAND methodology to explore and identify uncertainty regarding strategies proposed in current consensus guidance for the management of acute myocardial infarction cardiogenic shock.
- The panel comprised experts from a range of specialties involved in the care of cardiogenic shock patients across the globe, providing perspectives that reflect management across a range of practice and health systems.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Despite several consensus statements to guide practice, uncertainty in optimal management of acute myocardial infarction cardiogenic shock persists, and additional randomized controlled data are required to definitively guide clinical practice to resolve persisting uncertainty and improve patient outcomes.
- These uncertainties further highlight the need for randomized controlled trials in acute myocardial infarction cardiogenic shock specifically relating to the timing of mechanical circulatory support and the role of right heart catheterization and associated data to guide escalation to mechanical circulatory support.

Nonstandard Abbreviations and Acronyms

AMI	acute myocardial infarction
AMI CS	acute myocardial infarction cardiogenic shock
CICU	cardiac intensive care unit
CS	cardiogenic shock
MCS	mechanical circulatory support
PCI	percutaneous coronary intervention
RHC	right heart catheterization
VA ECMO	venoarterial extracorporeal membrane oxygenation

Technological advancements have driven improvements in mechanical circulatory support (MCS) including the development of percutaneous support devices as adjuncts to medical therapy to mitigate or reverse end-organ damage and potentially unload the heart. Regionalized systems of care and local team-based care analogous to that used in AMI and major trauma are evolving to improve early recognition, access to care, uniformity of escalation and consistency of care.[6–8] It is hoped that improved definitions of CS[9] coupled with comprehensive hemodynamic assessment of CS may improve patient selection for advanced therapies and ultimately mortality.[10]

The 2017 Scientific Statement from the American Heart Association[11] consolidated available evidence with expert opinion to define contemporary best management in CS. Since then, a number of International Committees have developed guidelines to inform the classification, diagnosis, and management of CS, with a focus on AMI CS.[7,9,12,13] These guidelines are limited by a paucity of randomized trial data to definitively guide many aspects of emergency care in CS. This reflects challenges in patient recruitment, informed consent, nonstandardized CS definitions and heterogeneity in presentation of a complex clinical syndrome.[14] Aside from early revascularization (SHOCK trial [Should We Emergently Revascularize Occluded Coronaries in Cardiogenic Shock?][15]), culprit lesion only revascularization (CULPRIT-SHOCK trial [Percutaneous Coronary Intervention Strategies with Acute Myocardial Infarction and Cardiogenic Shock][4]) and an absence of benefit from intraaortic balloon support in AMI CS (IABP-SHOCK II trial [Intra-aortic Balloon Pump Support for Myocardial Infarction with Cardiogenic Shock II][3]), best practices in CS are poorly defined, heterogenous, and often dictated by local resource as well as operator and institution specific clinical critical thinking.

We assembled an interdisciplinary panel of international experts and conducted a modified Delphi consensus process using modified RAND/University of California Los Angeles appropriateness methodology with the intent of identifying aspects of CS care where equipoise or clinical uncertainty persists despite societal guidance. Assessment was also made of the appropriateness of other interventions that were either outside the scope of guidelines and pervade clinical practice.

METHODS

The RAND/University of California Los Angeles (University of California, Los Angeles) appropriateness method uses a modified Delphi panel approach, combining expert opinion with the best available evidence and clinical guidance to determine the appropriateness of specific practices in defined clinical situations (https://www.rand.org/topics/methodology.html).[16] The RAND method is validated as a means of determining the benefit versus harm of a given intervention irrespective of cost or resources. It is particularly useful for areas of uncertainty in which evidence may be insufficient to guide clinical practice, such as in the management of CS. All data relevant to this study are contained within this article and are, therefore, freely available.

A web-based questionnaire designed and iterated by a core group (Dr Proudfoot, A. Kalakoutas, Dr Truesdell, Dr Morrow, Dr Fan, S. Meade, P.M. Irving, and Dr Griffiths) to address key challenges and uncertainties in the management of CS; this was further iterated at the panel meeting as described below. A bibliography on CS published after the American Heart Association Scientific Statement 2017[11] (search strategy in Figure S1) and a link to a web-based questionnaire was sent to an 17-person panel comprising specialties involved in the management of CS, namely: interventional cardiology, advanced heart failure cardiology) cardiac nursing, cardiac intensive care unit (CICU), and cardiac surgery. The RAND manual suggests a panel size of 7 to 15 participants to balance the breadth of expertise with the ability to facilitate flowing discussion.[16] We increased this to

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ensure adequate representation across specialities and geographic region and to account for the possibility of no-shows for the panel. There was no requirement for the bibliography to be used on completion of the questionnaire. Experts were identified through international meetings and societal membership and selected from a range of countries to encapsulate potential variable practice in CS globally. Institutional review board approval was waived given the nature of the study. Panellists were asked to grade the appropriateness of specific interventions through the course of admission for AMI CS on a scale of 1 to 9 (where 1–3 is inappropriate, 4–6 is uncertain, and 7–9 is appropriate) via an online survey. These responses were summarized, anonymized, and presented at a virtual meeting in January 2021. Ambiguity in the questionnaire was resolved and areas of disagreement within responses were discussed; achieving or forcing or consensus was not the objective of discussion. The moderators (S. Meade, P.M. Irving, and M.A. Samaan) provided expertise in RAND methodology but did not express opinions on management or vote. After the meeting, and based on panellist feedback, a second online survey comprising 69 questions was devised and completed (n=17). The final survey was subdivided into 3 categories: interventions before primary coronary intervention (22 questions), clinical markers to guide management and escalation (29 questions), and CS service provision (19 questions).

Several assumptions were made. First, CS was defined by historical trial entry criteria with severity based on the recent 2019 Society for Cardiovascular Angiography and Interventions classification of CS.[9] Second, all patients were assumed to have de novo CS and not decompensated heart failure with decompensation. Where appropriate, the questionnaire specified AMI CS as the cause if logistical decisions around percutaneous coronary intervention (PCI) required consideration. Third, other than those areas addressed in the survey, the management of CS was assumed to be in line with current guideline recommendations. Finally, vasoactive drugs were not prespecified in recognition of the level of evidence to guide choice beyond norepinephrine as the first line vasopressor (class IIB, level B).[17]

For each scenario, median scores were calculated with a score of <3.5 being considered inappropriate, ≥3.5 and <6.5 uncertain, and ≥6.5 appropriate. We used the validated RAND disagreement index to define disagreement (disagreement index ≥1) among panellists using the equation below and the interpercentile range, defined as the difference in the scores that lie on the 30th and 70th percentile. Any scenario in which disagreement was found was $DI = \frac{70\%ile - 30\%ile}{2.35 + \left(1.5 \times \mathrm{abs}\left(5 - \frac{70\%ile + 30\%ile}{2}\right)\right)}$ scored as uncertain, regardless of the median score.

RESULTS

Overall, 44 statements were rated as appropriate, 19 as uncertain and 7 as inappropriate. The disagreement index was <1 for all statements (Tables 1 through 3), indicating no disagreement. Individual panellist scoring is outlined in Tables S1 through S3. This held when responses were divided by geographic region (N America or Europe) and specialty (interventional cardiology, heart failure cardiology, or CICU; Table S4).

Interventions Before Primary Coronary Intervention and the Institution of MCS

As soon as was feasible in the context of PCI, it was deemed appropriate to perform a bedside echocardiogram and activate the local multidisciplinary shock team to guide optimal patient management (Table 1). A fluid challenge was judged inappropriate in the context of AMI CS, aside from right ventricular CS. Other interventions including central venous access, arterial access, initiation of inopressors and right heart catheterization (RHC) before PCI were considered uncertain due to the risk of delaying revascularization. Regarding PCI in AMI CS, culprit vessel only PCI was considered appropriate. Where it had not been performed pre-PCI, it was deemed appropriate to insert central venous and arterial access and echocardiography following culprit vessel only PCI and before CICU transfer.

In the event of deteriorating hemodynamics despite inopressor support, it was considered appropriate that the decision to escalate to MCS should be discussed with the local shock team and conform to a local escalation algorithm. It was rated uncertain whether RHC data should guide escalation to MCS. In moderate to severe AMI CS (Society for Cardiovascular Angiography and Interventions Stage ≥C [9]) it was uncertain whether MCS should be instituted before PCI. Univentricular support was deemed preferable in situations where available data suggested univentricular failure or an absence of significant right ventricular failure. It was considered appropriate that routine insertion of percutaneous MCS should involve the use of ultrasound and angiography, micropuncture for vascular access and, in the context of venoarterial extracorporeal membrane oxygenation (VA ECMO), distal perfusion catheters. The routine use of left ventricular unloading strategies in patients on VA ECMO, to include an Impella/ECPella or IABP strategy were all judged as uncertain.

Clinical Markers to Guide Management and Escalation

Clinical examination, serial serum lactate, echocardiography (if not already performed), hemodynamic assessment using pulmonary capillary wedge pressure, pulmonary artery saturation, cardiac output/index, cardiac power output as well as assessment and reassessment of Society for Cardiovascular Angiography and Interventions CS stage were all considered appropriate post-PCI (Table 2). The use of pulmonary artery pulsatility index in CS, specifically in the context of congestion or raised right heart pressures, was considered uncertain.

Regarding hemodynamic or biochemical targets for patients with CS (both in the presence and absence of MCS), maintaining a mean arterial pressure of 65 mm Hg and reducing inopressors to maintain this

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Table 1. Interventions Before Primary Coronary Intervention and the Institution of Mechanical Circulatory Support

Statements	Median	DI	IPR	RAND panel outcome
In a patient presenting with AMI cardiogenic shock manifest with; a systolic BP of ≤85 mm Hg, cool peripheries, a lactate of ≥4 mmol/L and evidence of pulmonary oedema, please rate the appropriateness of the following investigations/interventions on admission and pre-PCI:				
Fluid challenge	3	0.04	0.2	Inappropriate
Echocardiography	7	0.22	1.0	Appropriate
Arterial line insertion	4	0.55	2.2	Uncertain
Central venous access	4	0.27	1.2	Uncertain
Hemodynamic stabilization with inopressors	6	0.97	3.0	Uncertain
Right heart catheterization	4	0.52	2.0	Uncertain
Shock team activation	7	0.30	1.2	Appropriate
Regarding percutaneous coronary intervention in AMI CS and management in the catheter lab, please rate the appropriateness of the following:				
Culprit vessel only PCI	9	0.16	1.2	Appropriate
Central venous and arterial access before CICU transfer	8	0.19	1.2	Appropriate
Right heart catheterization before CICU transfer to guide MCS strategy	7	0.16	1.0	Appropriate
Echocardiography before CICU transfer if not already performed	7	0.52	2.0	Appropriate
Regarding institution of mechanical circulatory support in AMI CS, please rate the appropriateness of the following:				
Institute before PCI in AMI CS SCAI ≥stage C where feasible	5.5	0.52	2.0	Uncertain
Should be guided by right heart catheter data	6	0.27	1.2	Uncertain
Should be guided by a local escalation algorithm	7	0.22	1.0	Appropriate
Ideally should occur after discussion with a local or regional shock team	8	0.16	1.0	Appropriate
Univentricular support is preferred where physiology allows (ie, data is available from RHC or echo)	8	0.16	1.0	Appropriate
Regarding the insertion of percutaneous mechanical circulatory support, please rate the appropriateness of the following				
Routine use of ultrasound and angiography if patients are sufficiently stable to move to the cardiac catheter lab or hybrid theatre	8	0.29	2.0	Appropriate
Use of micropuncture	7	0.27	1.2	Appropriate
Routine use of a distal limb/retrograde perfusion catheter for peripheral VA ECMO	8	0.29	2.0	Appropriate
Regarding routine left ventricular unloading in patients supported with venoarterial ECMO, please rate the appropriateness of the following:				
Use of an LV unloading strategy only where data support its use (LVEDP, echo, refractory pulmonary oedema)	6	0.52	2.0	Uncertain
Impella strategy	6	0.32	1.0	Uncertain
IABP strategy	5	0.32	1.0	Uncertain

For each survey question, median scores were calculated with a score of <3.5 being considered inappropriate, ≥3.5 and <6.5 uncertain, and ≥6.5 appropriate. DI was calculated using the validated RAND DI to define disagreement (DI ≥1) among panellists. AMI indicates acute myocardial infarction; BP, blood pressure; CICU, cardiac intensive care unit; CS, cardiogenic shock; DI, disagreement index; echo, echocardiogram; IABP, intraaortic balloon pump; IPR, interpercentile range; LV, left ventricular; LVEDP, left ventricular diastolic pressure; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; RHC, right heart catheterization; SCAI, Society for Cardiovascular Angiography and Interventions; and VA ECMO, venoarterial extracorporeal membrane oxygenation.

threshold were deemed appropriate. It was also considered appropriate to target a serum lactate <2 mmol/L. The use of a cardiac index of >2.2 L/(min·m^2), cardiac power output >0.6 W or a pulmonary capillary wedge pressure <15 mm Hg as treatment thresholds were deemed uncertain.

Panellists subsequently rated the appropriateness of a trial of MCS for CS in the presence of putative markers of futility. It was deemed inappropriate to institute MCS in cases where there was unequivocal evidence of anoxic brain injury, active or uncontrolled bleeding, prohibitive vascular access or shock team consensus of futility. The institution of short-term MCS was considered uncertain in patients with a serum lactate >8 mmoml/L, >30 minutes of cardiopulmonary resuscitation before return of spontaneous circulation or in patients ineligible for advanced heart failure therapies.

It was considered appropriate for patients with CS requiring inopressor and MCS to be managed on a unit with the requisite expertise including cardiology, cardiac intensive care, and cardiac surgery. Additionally, it was considered appropriate to use continuous mixed venous oxygen saturations ($ScVO_2$) and either continuous or intermittent cardiac output monitoring to guide titration and escalation of medical therapies and MCS. Early consultation with the advanced heart failure team was recommended in patients failing to demonstrate clinical or physiological improvements within 72 hours of admission. Failure to improve by this juncture should trigger transfer to a center with durable ventricular assist device or transplant capacity in eligible patients.

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Table 2. Clinical Markers to Guide Management and Escalation

Statements	Median	DI	IPR	RAND panel outcome
In patients with cardiogenic shock requiring inopressor and MCS support the following investigations/interventions should be performed routinely during the first 24–48 h:				
Clinical examination	9	0.00	0.0	Appropriate
Serum lactate	9	0.02	0.2	Appropriate
Echocardiography if not already performed	9	0.16	1.2	Appropriate
PCWP measurement	7	0.37	2.0	Appropriate
Pulmonary artery saturations	7	0.19	1.2	Appropriate
Continuous $ScVO_2$ and CO measurement	7	0.25	1.2	Appropriate
Assessment and re-assessment of SCAI CS stage	7	0.00	0.0	Appropriate
Assessment of cardiac power output	7.0	0.27	1.2	Appropriate
Assessment of pulmonary artery pulsatility index in the context of congestion or elevated right heart pressures	6	0.27	1.2	Uncertain
Please rate the appropriateness of the following hemodynamic/biochemical targets for patients with CS managed with or without MCS:				
Mean arterial pressure >65 mm Hg	7	0.42	2.2	Appropriate
Minimize inopressors to maintain a mean arterial pressure >65	7	0.16	1.0	Appropriate
Lactate <2 mmol/L	8	0.16	1.0	Appropriate
PCWP <15 mm Hg	6	0.52	2.0	Uncertain
CI >2.2 L/min/m^2	6	0.22	1.0	Uncertain
Cardiac power output >0.6 W	6	0.32	1.0	Uncertain
Please rate the appropriateness of initiation of a trial of mechanical circulatory support for cardiogenic shock in the presence of the following:				
Lactate >8 mmol/L	6	0.52	2.0	Uncertain
Prolonged (>30 min) CPR before ROSC	5	0.15	0.4	Uncertain
Evidence of anoxic brain injury (clinical or imaging)	2	0.29	2.0	Inappropriate
Active/uncontrolled bleeding	2	0.16	1.0	Inappropriate
Prohibitive vascular access	2	0.16	1.0	Inappropriate
Age >80 y	3	0.22	1.0	Inappropriate
Ineligibility for advanced heart failure therapies	5	0.37	1.2	Uncertain
Shock team consensus of futility	2	0.9	1.0	Inappropriate
Regarding the management of patients with cardiogenic shock requiring inopressor and MCS on the CICU please rate the appropriateness of the following:				
Should be managed on a unit with the relevant expertise with input from cardiology, cardiac surgery and intensive care (eg, cardiac intensive care unit)	8	0.13	1.0	Appropriate
Right heart catheter guided management of MCS and/or inopressors	7	0.20	1.2	Appropriate
Early consultation with advanced heart failure team in patients who fail to improve within 72 h	8	0.03	0.2	Appropriate
Eligible patients who fail to improve within 72–96 h should be transferred to a center with durable VAD/transplant capability	7	0.20	1.2	Appropriate

For each survey question, median scores were calculated with a score of <3.5 being considered inappropriate, ≥3.5 and <6.5 uncertain, and ≥6.5 appropriate. DI was calculated using the validated RAND DI to define disagreement (DI ≥1) among panellists. CI indicates cardiac index; CICU, cardiac intensive care unit; CO, cardiac output; CPR, cardiopulmonary resuscitation; DI, disagreement index; IPR, interpercentile range; MCS, mechanical circulatory support; PCWP, pulmonary capillary wedge pressure; ROSC, return of spontaneous circulation; SCAI CS stage, Society for Cardiovascular Angiography and Interventions cardiogenic shock stage; $ScVO_2$, mixed venous oxygen saturations; and VAD, ventricular assist device.

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CS Service Provision

Panellists considered it highly important for a shock hub to have onsite access to a complement of allied specialties (Table 3). The importance of the need for onsite durable ventricular assist device/transplant capacity for centers managing CS was deemed uncertain. Regarding the requirements of a putative CS center of excellence, panellists considered it important to have onsite access to are range of ancillary services outlined in Table 3. The importance of the need for a retrieval service or CS coordinator were deemed uncertain.

DISCUSSION

The responses of a multidisciplinary, international panel of experts suggest there is broad alignment with current international guidelines and consensus statements, including the most contemporaneous American Heart Association guidance in AMI CS which was published subsequent to this process.[13] Nonetheless, there was uncertainty regarding the value of several interventions that pervade contemporary clinical practice, summarized in the Figure.

Contrary to the class 1C recommendation of the European Society of Cardiology guidance,[17] the

Table 3. Cardiogenic Shock Service Provision

Statements	Median	DI	IPR	RAND panel outcome
How important is it to have the following specialties present as the minimum clinical requirement of a cardiogenic shock hub				
Interventional cardiology	9	0.00	0.0	Appropriate
Advanced heart failure cardiology	9	0.02	0.2	Appropriate
Durable VAD service and heart transplantation	6	0.55	2.2	Uncertain
Cardiac surgery	9	0.02	0.2	Appropriate
Cardiac intensive care	9	0.00	0.0	Appropriate
Electrophysiology	7	0.23	1.4	Appropriate
Structural heart cardiology	7	0.23	1.4	Appropriate
Vascular surgery	7	0.04	0.2	Appropriate
Palliative care	7	0.40	2.2	Appropriate
How important is it to include the following as service requirements in a cardiogenic shock center of excellence?				
Multi-professional shock team	9	0.13	1.0	Appropriate
24/7 MCS capability	9	0.00	0.0	Appropriate
Routine use of escalation algorithms	7	0.20	1.2	Appropriate
Dedicated cardiogenic shock coordinator	6	0.27	1.2	Uncertain
Access to a range of short-term MCS devices (univentricular, biventricular, left and right)	8	0.13	1.0	Appropriate
Retrieval service to support regional referrals	6	0.27	1.2	Uncertain
Contribution to a local, regional or national registry	7	0.40	2.2	Appropriate
Established research infrastructure	7	0.37	2.0	Appropriate
Capability to recruit patients into clinical trials in CS	7	0.30	1.4	Appropriate
Regular network meetings with leads from referral sites	7	0.20	1.4	Appropriate
>20 short-term MCS cases per annum	8	0.29	2.0	Appropriate

For each survey question, median scores were calculated with a score of <3.5 being considered inappropriate, ≥3.5 and <6.5 uncertain, and ≥6.5 appropriate. Disagreement index was calculated using the validated RAND DI to define disagreement (DI ≥ 1) among panellists. CS indicates cardiogenic shock; DI, disagreement index; IPR, interpercentile range; MCS, mechanical circulatory support; and VAD, ventricular assist device.

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institution of a fluid challenge before PCI or hemodynamic assessment was deemed inappropriate. Although one-third of CS patients are euvolemic and may increment stroke volume with fluid administration,[18] the panel felt that the absence of hypovolemia was a criterion of CS, and additional fluid administration may worsen hemodynamics before PCI. This statement was qualified with the view that fluid administration was appropriate in isolated right ventricle infarction and CS. The equipoise regarding the need for hemodynamic stabilization with continuous infusion vasopressors and associated arterial and venous access, before PCI was underpinned by the recognition that timely revascularization is one of few evidenced based interventions in CS.[15] PCI should occur without delay given the impact on mortality of even minor delays to revascularization.[19,20] Hence, hemodynamic stabilization with associated vascular access could occur concomitantly either in or en-route to the catheter lab.

There was agreement that echocardiography and shock team activation were appropriate as soon as was practicable without inappropriate delay to primary revascularization in accordance with consensus guidance.[7,11,12] Urgent echocardiography is essential to identify complications requiring intervention as well as to identify isolated left, right, or biventricular involvement.[10,21] Early consultation with a local shock team may incur a brief delay to revascularization; however, the panel felt that in cases where MCS was being considered, team-based decision making was essential to optimize device timing and selection and to begin planning longitudinal patient care including palliative care where intervention was likely to be futile.

There exists a weak evidence base for MCS in modifying outcome in CS overall. Recent observational data have suggested that early MCS implementation in CS may improve systemic and coronary perfusion and reduce cardiac work as well as mitigate the risks of multiorgan failure.[11,22] Consistent with concerns about delays to revascularization, in the absence of data from ongoing clinical trials, the panel highlighted concerns regarding delays to evidence-based reperfusion therapy with implementation of pre-PCI MCS. Although, left ventricular unloading in ST-segment elevation myocardial infarction without CS for 30 minutes pre-PCI may be safe, neither the use of percutaneous microaxial univentricular support or the intraaortic balloon pump pre-PCI confer clear clinical benefit.[23,24] Regardless of timing, there was consensus that institution of MCS should be guided by local escalation algorithms with input from the shock team and that a univentricular support strategy was preferable where hemodynamic data were supportive.

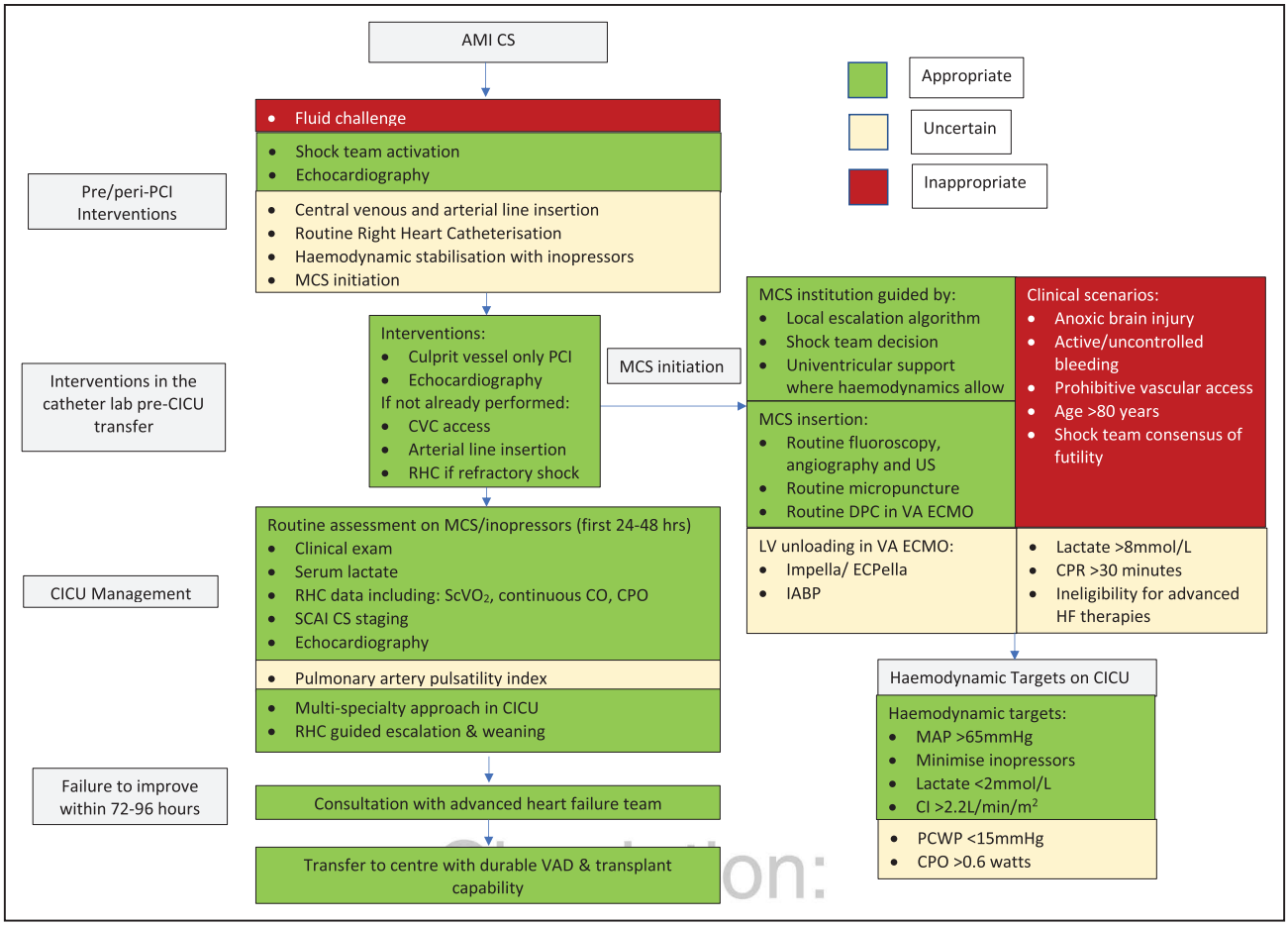

Figure. Management algorithm summarizing RAND panel recommendations in acute myocardial infarction cardiogenic shock (AMI CS).

CICU indicates cardiac intensive care unit; CPR, cardiopulmonary resuscitation; CI, cardiac index; CO, cardiac output; CPO, cardiac power output; CS, cardiogenic shock; CVC, central venous catheter; DPC, distal perfusion cannula; IABP, intra aortic balloon pump; HF, heart failure; LV, left ventricular; MAP, mean arterial pressure; MCS, mechanical circulatory support; PCI, primary percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterization; SCAI, Society for Cardiovascular Angiography and Interventions; $ScVO_2$, mixed venous oxygen saturations; US, ultrasound; VAD, ventricular assist device; and VA ECMO, venoarterial extracorporeal membrane oxygenation.

Observational data suggest that a RHC guided approach may improve survival in AMI CS[25,26] despite prior study suggesting no benefit.[27] Current guidelines and scientific statements propose RHC use in the management of CS patients unresponsive to initial therapy or where there is diagnostic or therapeutic uncertainty. While escalation algorithms focus on elevated left ventricular end-diastolic pressure in the context of low cardiac output as a trigger for MCS deployment,[25,26] panellists had equipoise regarding routine RHC use in the initial pre-PCI assessment of CS in the catheter lab to guide emergent MCS pre-PCI. RHC data may allow identification/confirmation of right heart dysfunction which can impact both MCS configuration and prognosis.[10,28] The use of RHC to guide management of refractory shock including fluid management, titration of inopressors, and escalation/de-escalation of MCS on the CICU was, however, advocated and the panel felt that RHC insertion immediately before CICU transfer or on CICU admission was appropriate. The utility of continuous $ScVO_2$ and either continuous or intermittent cardiac output to guide titration and escalation/de-escalation of both pharmacological and mechanical support therapies was highlighted. There was uncertainty regarding the value of pulmonary artery pulsatility index, specifically in the presence of elevated right-sided heart pressures. Despite a small attendant risk pulmonary artery perforation/hemorrhage with pulmonary capillary wedge pressure measurement, there was agreement that this should be serially performed daily and targeted according to local algorithms using pulmonary artery diastolic pressure used as a surrogate in the intervening period.

For the hemodynamic and clinical benefits of MCS to manifest, complications from large-bore vascular access, including bleeding, must be offset. Recent registry data have highlighted increased rates of vascular injury, major bleeding and in-hospital death in AMI CS patients.[29–33] Predicated by recognition for needed improved safety to

improve outcome in CS, the panel deemed it appropriate that percutaneous MCS insertion should be guided by a combination of micropuncture access guided by ultrasound, fluoroscopy, and angiography. Safety approaches, specifically bundles of vascular access care, require formative assessment through innovative randomized controlled trials. In the context of peripheral VA ECMO, which has a larger arterial cannula size than most percutaneous support devices, routine use of distal perfusion catheter was deemed appropriate, based on high rates of limb ischemia and observational data suggesting this can be minimized with distal perfusion catheter use.[34,35]

Panellists were uncertain regarding left ventricular unloading strategies in the context of peripheral VA ECMO. International practice is heterogenous regarding both timing and unloading device strategy with potential for increased complications associated with multiple MCS devices. Nonetheless, a recent meta-analysis of observational studies identified expedited weaning from VA ECMO and improved short-term mortality with a venting strategy, particularly if instituted in the first 12-hours.[36] Further, in propensity matched patients with predominantly AMI CS supported with VA ECMO, there was 21% absolute reduction in 30-day mortality in patients unloaded with an Impella device (Abiomed, Danvers, MA) compared with no unloading, despite increased complications in the unloaded cohort.[37]

Given the resource implications of MCS deployment, the development of prognostic markers and risk scores to identify futility is desirable and should be a priority for future research.[11] The use of a lactate >8 mmol/L and cardiopulmonary resuscitation duration of >30 minutes were deemed as uncertain metrics of futility. Lactate dynamics are likely to be more prognostically valuable than a single, point of entry measurement.[38] While anoxic brain injury was deemed to be an acceptable metric of futility, at least for escalation to interventional therapies, it was recognized that there are significant uncertainties around assessment and prognostication in the acute phases of shock and cardiac arrest. Similarly, duration of resuscitation presented uncertainty given that survival with good neurological outcome occurs in 8% of patients even after 30 minutes of resuscitation.[39] There was agreement that single parameters such as these in isolation are unlikely to define escalation decisions.

Recent observational data from North America have proposed benefit of protocolized escalation of care through the implementation of CS hubs within a network of care supporting referring spoke centers.[6,8,25] Panellists substantiated guideline-based recommendations to develop such systems of care with uncertainty regarding a mandate for durable MCS and transplantation to be located at a CS hub and the requirement for a CS coordinator. In many health care systems, access to advanced heart failure therapies is supra-regionalized. The panel deemed that geographically strategic CS hubs (without durable MCS and transplant) to optimize patient and referrer access was an unmet need whereas multiple small volume centers was less so, albeit that close collaboration between the 2 would be essential. Notably, research infrastructure and the capability to recruit patients into prospective clinical trials was accepted as a prerequisite of a CS center of excellence.

The current focus of current or planned randomized clinical trials in CS is the role of MCS devices to improve mortality. The data presented herein, suggest that there remains either uncertainty regarding aspects of AMI CS care such as the timing of RHC, translating hemodynamic parameters into optimal therapeutic intervention, left ventricle unloading strategies and markers of futility or clinician confidence in aspects of care where there is limited evidence base such as vascular access and the role of local shock teams and local escalation algorithms. While trials in CS remain challenging, efforts to address these knowledge gaps leveraging novel trial designs and collaborations with industry and regulators are required to better inform future consensus guidelines and clinical practice alike. The Cardiac Safety Research Consortium Think Tank[14] and Critical Care Clinical Trialists Workshop[40] are 2 such collaborations working to address these challenges.

The major strength of our study was engagement of specialists from a range of disciplines and from a broad scope of international practice using rigorous methodology to combine the best available evidence with the clinical expertise of the panel. We acknowledge several limitations. RAND panels interrogate the appropriateness of an intervention, regardless of available resources. Many of the proposed interventions and service developments within guidelines and substantiated herein are expensive and their use is restricted in resource-limited health care systems. The process was agnostic to MCS device reflecting the absence of evidence base for specific devices and the variable availability across health care systems of different MCS modalities. It was impossible to encompass all scenarios encountered in clinical practice. We focussed on AMI CS because it is the phenotype most comprehensively covered by consensus guidance with clear patient pathways that are broadly similar across health care systems. While there is overlap, the conclusions drawn here are of limited value in the management of acute decompensated heart failure. A RAND analysis of acute decompensated heart failure CS management may have future value to delineate uncertainties in the management of this important cohort. Finally, shared decision making in CS should always consider patient (and family) wishes which are not discussed herein.

To conclude, this RAND panel provides further real-world guidance on the perceived best practices for management of AMI CS. A multidisciplinary panel supported many of the recommendations of current guidelines and consensus statements. Nonetheless, the panel also identified areas of care where uncertainty persists,

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specifically in pre-PCI interventions, the role of RHC as a precursor to MCS pre-PCI, derived hemodynamic parameters to guide management and optimal left ventricle unloading strategies. Based on the results, several research priorities were identified that may be integrated into current and future clinical trials.

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Supplemental Material

Supplemental Methods
Figure S1
Tables S1–S4

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