PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impella vs. VA-ECMO for the treatment of Patients with Cardiogenic Shock. The Impella Network project: Observational Study Protocol for Cost-effectiveness and Budget Impact Analyses
AUTHORS	ARDITO, VITTORIA; ROGNONI, CARLA; Pieri, Marina; Barbone, Alessandro; Briguori, Carlo; Cigala, Emanuele; Gerosa, Gino; Iannaccone, Mario; Loforte, Antonio; Marini, Marco; Montalto, Andrea; Oreglia, Jacopo; Pacini, Davide; Pennacchi, Mauro; Pestrichella, Vincenzo; Porto, Italo; Stefano, Pierluigi; Tarantini, Giuseppe; Valente, Serafina; Vandoni, Pietro; Tarricone, Rosanna; Scandroglio, Anna

VERSION 1 – REVIEW

REVIEWER	Sharma, Kamal U.N. Mehta Institute of Cardiology & Research Centre
REVIEW RETURNED	30-Aug-2023

GENERAL COMMENTS	Hello, Thanks for submitting this manuscript to this journal. It is a well drafted manuscript however being a cost-effective analysis of 2 therapies , cost of which varies from subcontinent to subcontinent, it would be advisable to look into the same as well have statistical overview from that perspective. thanks

REVIEWER	Garan, Arthur Reshad Harvard Medical School
REVIEW RETURNED	24-Sep-2023

GENERAL COMMENTS	Thank you for the invitation to review “Impella versus VA-ECMO for treatment of patients with cardiogenic shock. The impella network project: observational study protocol for cost effectiveness and budget impact analyses”. The authors have provided an overview of the study planned to assess cost effectiveness and budget impact of the impella compared to VA ECMO for patients with cardiogenic shock. I have several questions/concerns for clarification: 1. The authors describe the patient population as one with severe cardiogenic shock. How is this actually defined? 2. Will the authors analyze any relationships between center volume of device use, and cost effectiveness? 3. The authors plan to study, patients supported by impella as the “study arm” and ECMO as the “control arm”. As data calling into

	question the benefits of these devices mounts, one question that arises is whether patients with cardiogenic shock who do not receive any device should be included as the true “control arm”. Do the authors have any thoughts regarding this? 4. As part of the inclusion criteria, patients will only be enrolled if support with a single device is planned. However, a subset of patients will likely require a second device placed even if the initial support was a single device strategy (eg for venting purposes if ECMO first or for additional hemodynamic support of impella is insufficient support). How will this population of patients be treated? 5. The authors indicate that the degree of shock will be incorporated into the analysis. Will this be assessed at device insertion or at the worst point during the entire hospitalization? 6. The authors plan to collect information regarding quality of life for patients at multiple time points. How will they handle scenarios where the patient is to ill to complete this questionnaire? 7. Similarly, how will patients who die during the hospitalization be treated with respect to the quality of life analysis?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Kamal Sharma, U.N. Mehta Institute of Cardiology & Research Centre
Comments to the Author:
Hello,
Thanks for submitting this manuscript to this journal. It is a well drafted manuscript however being a cost-effective analysis of 2 therapies , cost of which varies from subcontinent to subcontinent, it would be advisable to look into the same as well have statistical overview from that perspective. Thanks
R1. We thank the reviewer for this comment. The analysis will be focused only on the Italian setting, as data will be collected through a network of Italian centers. However, it is true that different countries might have different cost structures, and this has been clarified in the Manuscript. In particular, we have specified that the extension of the study results in other geographical contexts should be done with caution, in light of differences in costs structures, and adjustments might be needed to incorporate such differences in the analysis. These changes can be found in the “Budget Impact Analysis (BIA)” subparagraph (page 14), as follows:
As a final note, it has to be highlighted that the BIA will be conducted from an Italian perspective, based on the cost framework observed within Italian facilities. Therefore, extending the study results to other geographical contexts should be done with caution, and marginal adjustments might be needed to account for country-specific differences in the costs sustained at the local level.

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Reviewer: 2
Dr. Arthur Reshad Garan, Harvard Medical School

Comments to the Author:
Thank you for the invitation to review “Impella versus VA-ECMO for treatment of patients with cardiogenic shock. The impella network project: observational study protocol for cost effectiveness

and budget impact analyses". The authors have provided an overview of the study planned to assess cost effectiveness and budget impact of the impella compared to VA ECMO for patients with cardiogenic shock. I have several questions/concerns for clarification:

Q1. The authors describe the patient population as one with severe cardiogenic shock. How is this actually defined?
R1. We are grateful to the reviewer for this input and we totally agree that the definition of cardiogenic shock should be clear to readers, since different classifications exist and are applied in clinical studies. In line with contemporary clinical practice and recommendations and according to the aim of this study, we identified among the inclusion criteria the presence of shock of cardiac origin that requires pharmacologic therapy with inotropes or mechanical circulatory support (i.e INTERMACS class 1,2 or 3 and SCAI class C, D or E). We now better clarify this in the "Study population" paragraph of the methods, among inclusion criteria (page 9), as follows:
"The study population will include all patients suffering from CS, according to clinical relevant classifications (Interagency Registry for mechanically assisted circulatory support (INTERMACS) and International Society for Cardiovascular Angiography and Interventions (SCAI) treated with Impella 5.5, Impella 5.0 or Impella CP at the Impella Network institutions. To be included in the study group (i.e. Impella Intention To Treat group), patients must meet all the following inclusion criteria:
• CS at presentation (as defined by INTERMACS Class 1-2-3 or SCAI Class C-D-E);
• Support as single device strategy;
• Impella support duration of at least 24 hours;
• Patients treated in the last 3 years (2020-2022) (for retrospective data collection);
• Onset of CS from less than 12 hours.

The control group will include all patients treated at the Impella Network institutions for severe left ventricular failure with VA-ECMO. To be included in the control group (i.e. VA-ECMO intention to treat group), patients must fulfill ALL the following inclusion criteria:
• CS at presentation (as defined by INTERMACS Class 1-2-3 or SCAI Class C-D-E);
• VA-ECMO support as single device strategy;
• VA-ECMO support duration of at least 24 hours;
• Onset of CS from less than 12 hours."

Q2. Will the authors analyze any relationships between center volume of device use, and cost effectiveness?
R2. We thank the reviewer for this useful comment. As a matter of fact, we expect volumes of implanted Impella devices and patients treated to vary significantly across centers. Therefore, centers will be clustered based on the volume of implanted devices, and sub-group analysis will be conducted to investigate whether there is a relationship between cost-effectiveness and volume of devices implanted on an annual basis. This aspect has now been clarified also in the manuscript (page 13), as follows:
"In addition, if collected data will allow it, centers will be clustered based on the number of implanted Impella devices and patients treated, to investigate if there is a relationship between cost-effectiveness and the volumes of device use in each center. The definition of the clusters and conduct of sub-group analyses will depend on the data that will be actually collected."

Q3. The authors plan to study, patients supported by impella as the "study arm" and ECMO as the "control arm". As data calling into question the benefits of these devices mounts, one question that arises is whether patients with cardiogenic shock who do not receive any device should be included as the true "control arm". Do the authors have any thoughts regarding this?
R3. We thank the reviewer for this comment. We totally agree that addressing the issues of the treatment of cardiogenic shock is complex and a comprehensive approach, which encompasses all possible therapies, beyond MCS itself, should be adopted. However, the aim of the present study is

not to justify the use of MCS in cardiogenic shock, rather this work builds on the need to conduct more comparative studies in the field of MCS health technologies for the treatment of cardiogenic shock. We now better clarify our perspective and we modified as follows the “strengths and limitations section” (page 4):
“This study does not consider alternative therapeutic courses for the treatment of patients with cardiogenic shock (e.g., intra-aortic balloon pump, pharmacological therapy alone, ...) nor the combination of devices (e.g., ECPELLA), as primary therapeutic strategy.”

Q4. As part of the inclusion criteria, patients will only be enrolled if support with a single device is planned. However, a subset of patients will likely require a second device placed even if the initial support was a single device strategy (eg for venting purposes if ECMO first or for additional hemodynamic support of impella is insufficient support). How will this population of patients be treated?
R4. This is a key point and we are grateful to the reviewer for this question. As we write in the methods (page 10), patients will be treated according to the intention to treat (Impella vs VA ECMO). It is reasonable to expect that some patient nevertheless will later require a second device in the course of therapy (for LV venting, need for therapy escalation or descalation, ...). However, this possibility is present in both groups, it reflects the real clinical world scenario and, at the same time, excluding these patients from the study would lead to a substantial bias that may jeopardize the usefulness of this analysis for clinical practice. For this reason, we specify in the methods that patients are assigned to both treatment and control group according to the intention to treat and we modified as follows the “strengths and limitations section” (page 4):
“This study does not consider alternative therapeutic courses for the treatment of patients with cardiogenic shock (e.g., intra-aortic balloon pump, pharmacological therapy alone,..) nor the combination of devices (e.g., ECPELLA), as primary therapeutic strategy.”

Q5. The authors indicate that the degree of shock will be incorporated into the analysis. Will this be assessed at device insertion or at the worst point during the entire hospitalization?
R5. We appreciated this question, because it addresses a critical point. For this study, a large number of variables will be collected over the entire hospitalization and presented in details in the supplementary material. With reference to the degree of shock, the data collected at the time of device implantation are pivotal to the aim of this analysis. However, several hemodynamic, laboratory and clinical data will be assessed regularly during the treatment with Impella or VA ECMO to assess the evolution of the condition of shock during support. Indeed, patients in cardiogenic shock may present different clinical trajectories that should be detected to improve clinical outcomes. In the section on “clinical parameters” of the methods (page 11) we now write:
Clinical parameters
Data related to medical history, shock related hospitalization, mechanical circulatory support characteristics (for Impella or VA-ECMO), clinical and hospital outcomes will be collected from each center and included in a pre-specified structured data set. Short term MCS related adverse events will be defined according to most recent recommendations. In adjunct to data registered at specific time points (for example at baseline) and outcome measures, several hemodynamic, laboratory and clinical data will be assessed regularly during the treatment with Impella or VA ECMO to assess the evolution of the condition of shock during support. The detailed list of clinical parameters to be collected through the study is outlined in the Supplementary Materials.

Q6. The authors plan to collect information regarding quality of life for patients at multiple time points. How will they handle scenarios where the patient is too ill to complete this questionnaire?
R6. Thank you for this comment, which is very relevant. Quality of life questionnaires will be completed with the support of the clinicians who fill in paper-based questionnaires based on the verbal responses given by the patients. As such, we expect that the clinicians will choose an

appropriate moment to fill in the questionnaire, namely when the patient is awake, conscious, and able to respond. However, there might be cases in which patients do not recover from the cardiogenic shock or are too weak to answer the questionnaire. Such cases will be excluded from the quality of life analyses. This aspect has now been better specified in the sub-paragraph “Quality of life” of the manuscript (page 11-12), as follows:
“The clinicians will choose an appropriate timing to fill in the questionnaire, namely when patients are awake, conscious and willing to respond. However, should the patients be too weak to respond, or should they fail to recover from the shock, they will be excluded from the QoL analyses.”

Q7. Similarly, how will patients who die during the hospitalization be treated with respect to the quality of life analysis?
R7. Thank you for this very useful comment. As a premise, any data (clinical parameters, information on resource use and costs, and quality of life-QoL) will be collected as long as the patient is alive; furthermore, quality of life by definition is a metric that has an intrinsic sense as long as the patient lives. Having said that, each patient is included in the analyses until they die. Specifically, as for costs, any cost accrued until a patient dies are considered; as for quality of life, the most recent measurement of QoL is used through interpolation techniques, if available and if it can still be considered a reliable measurement. However, patients who have never measured QoL will be excluded from the QALYs analysis. This aspect has now been better specified in the “Cost-effectiveness analysis” sub-paragraph of the manuscript (page 13), as follows:
“It has to be specified that QoL will be measured as long as patients stay alive. Interpolation techniques might be used to manage missing data (e.g., to carry forward QoL measurements occurred prior to death); however, patients who never completed QoL measurements will be excluded from QALYs analyses.”

VERSION 2 – REVIEW

REVIEWER	Garan, Arthur Reshad Harvard Medical School
REVIEW RETURNED	11-Dec-2023

GENERAL COMMENTS	There authors have sufficiently addressed my comments and concerns. I have no further concerns.