PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a multicenter randomized controlled trial evaluating the effects of moderate hypothermia versus normothermia on mortality in refractory cardiogenic shock patients rescued by veno-arterial Extracorporeal Membrane Oxygenation (ECMO) (HYPO-ECMO study)
AUTHORS	Jacquot, Audrey; Lepage, xavier; merckle, Ludovic; Girerd, Nicolas; Levy, Bruno

VERSION 1 – REVIEW

REVIEWER	Nuccia Morici Intensive Coronary Care Unit, ASST Grande Ospedale Metropolitano Niguarda Milan Italy
REVIEW RETURNED	28-May-2019

GENERAL COMMENTS	Jacquot et al present a very interesting protocol, which address patients at high risk of short term mortality and without any reference standard for therapy. The protocol is well-written and any part of it is accurately reported. Few aspects could be better defined: 1. Secondary endpoint include a composite of death, cardiac transplant, escalation to LVAD, stroke at days 30, 60, 180. However, therapies which are able to bridge patients to heart replacement therapy could be considered a success (Fried et al, IABP in ADHF). Authors should define if the patients were stabilized by study treatment and succesfully bridge to LAVD or HT. 2. cardiogenic shock is a heterogenous disorder. Hypothermia could induce different effects on cardiogenic shock due to acute myocardial infarction or to myocarditis or to decompensated heart failure. These aspects should be clarified. 3. Bleeding events will be adjudicated according to GUSTO classification. Even if the same classification was used in an other trial performed in cardiogenic shock patients (IABP shock trial), BARC classification is more current and I would suggest to introduce this instead of GUSTO.

REVIEWER	Werdan Karl Department of Medicine III, University Hospital Halle (Saale)
REVIEW RETURNED	04-Jun-2019

GENERAL COMMENTS	This is a well-planned RCT dealing with an important clinical topic: cooling in cardiogenic shock patients treated with VA-ECMO. 1. My main concern: This RCT will test the relevance of mild cooling in a patient population treated with a concept - VA-ECMO - which by

	no means has documented its prognostic benefit. Therefore, I cannot accept the sentence in "Introduction": "Unfortunately, there have been few recent advance in the treatment of cardiogenic shock on the exception of ExtraCorporeal Membrane Oxygenation (ECMO)." The authors should clearly describe the evidence for and the prognostic relevance of VA-ECMO including the guideline recommendations for this concept. Isn't this approach some kind of "step 2 first (hypothermia vs. normothermia in VA-ECMO" and step 1 second (VA-ECMO vs. control" second? (see also page 9 line 59: "clinical practice in post-MI-patients: VA-ECMO in cardiogenic shock patients is a class IIb recommendation in selected patients). Please discuss in detail. 2. Page 11/12: There a indeed very many secondary endpoints. With a p-value of 0.05 you will have a high probability of one false positive secondary endpoint. 3. Page 13 Table 2 Inclusion criteria: in comparison to studies with percutaneous left ventricular assist devices (IABP-II SHOCK study, Culprit Shock study) in cardiogenic shock complicating myocardial infarction, this study includes the very broad and heterogenous spectrium of cardigoenic shock patients in General, independent from the shock trigger. Further: why do the authors only include cardiogenic shock patients treated with VA-ECMO? VA-ECMO is not guideline-recommended as standard treatment. Please give the inclusion criteria for VA-ECMO treatment? What does mean "to ensure sufficient tissue perfusion.!? (see page 14). 4. The figures in page 23 should be included in the manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer number 1. Dr Nuccia Morici

1. Secondary endpoint include a composite of death, cardiac transplant, escalation to LVAD, stroke at days 30, 60, 180. However, therapies which are able to bridge patients to heart replacement therapy could be considered a success (Fried et al, IABP in ADHF). Authors should define if the patients were stabilized by study treatment and successfully bridge to LAVD or HT.

Response: Thank you very much for this very accurate comment. In the present topic, this point is indeed a crucial question. In the context of refractory cardiogenic shock which is the current indication for VA-ECMO, the expected mortality is high. Therefore, for alive patients, the opportunity to reach LVAD and heart transplantation might be considered as a success.
In light of the above, we have added the following sentence in the manuscript: “Considering the secondary endpoints “escalation to LVAD or heart transplantation” and given the high expected mortality, the opportunity to reach LVAD and heart transplantation will also be considered as a success.”

2. Cardiogenic shock is a heterogenous disorder. Hypothermia could induce different effects on cardiogenic shock due to acute myocardial infarction or to myocarditis or to decompensated heart failure. These aspects should be clarified.

Response: It should be recognized that hypothermia might theoretically have different effects according to the origin of the cardiac shock. This point is underlined in the chapter “statistical analysis for secondary endpoint” : “An interaction analysis will be performed using the following list of possible

predictive markers: postcardiotomy setting, prior cardiac arrest, and prior myocardial infarction", which are likely the three main etiologies of cardiogenic shock that will be encountered in our study. We hope that the study of these sub-groups will allow us to better define the best use of moderate hypothermia in the present indication.

3. Bleeding events will be adjudicated according to GUSTO classification. Even if the same classification was used in an other trial performed in cardiogenic shock patients (IABP shock trial), BARC classification is more current and I would suggest to introduce this instead of GUSTO.
Response: The above has been done and stated accordingly in the manuscript

Reviewer 2

1. My main concern: This RCT will test the relevance of mild cooling in a patient population treated with a concept - VA-ECMO - which by no means has documented its prognostic benefit. Therefore, I cannot accept the sentence in "Introduction": "Unfortunately, there have been few recent advance in the treatment of cardiogenic shock on the exception of ExtraCorporeal Membrane Oxygenation (ECMO)." The authors should clearly describe the evidence for and the prognostic relevance of VA-ECMO including the guideline recommendations for this concept. Isn't this approach some kind of "step 2 first (hypothermia vs. normothermia in VA-ECMO" and step 1 second (VA-ECMO vs. control" second? (see also page 9 line 59: "clinical practice in post-MI-patients: VA-ECMO in cardiogenic shock patients is a class IIb recommendation in selected patients). Please discuss in detail.

Response: Thank you very much for this important comment. The following answer will be divided into two parts. First, we fully agree with Prof. Werdan that the place of ECMO in cardiogenic shock management is not fully established. The current ESC grading is 2bC (https://doi.org/10.1093/eurheartj/ehy394) (may be considered in selected patients). Three multicenter studies are currently ongoing to evaluate the place of ECMO in non refractory cardiogenic shock (earlier use when compared to the current commonly accepted indications). The AHA consensus is in favor of temporary ECLS when: « temporary over durable MCS as a first-line device should be considered when immediate stabilization is needed to enable recovery of the heart and other organ systems, when surgical risk is prohibitive support is required to facilitate a definitive procedure or intervention (such as revascularization or arrhythmia ablation), or when time is required to allow a full transplantation or durable MCS evaluation. » Moreover, they suggest that « veno-arterial ECMO may be the preferred temporary MCS option when there is poor oxygenation that is not expected to rapidly improve with an alternative temporary MCS device or during cardiopulmonary resuscitation. » Lastly, expert opinions are in favor of ECMO use and interest in cardiogenic shock management « TCS have become the cornerstone of the management of patients with cardiogenic shock, although the evidence supporting their efficacy is limited. VA-ECMO is considered the first-line option, with a growing number of accepted and emerging indications. Randomized clinical trials are now needed to determine the place VA-ECMO in cardiogenic shock treatment strategies. »

Considering step 1 versus step 2, we respectfully slightly disagree with Prof. Werdan. The HYPO-ECMO study is a pragmatic study aimed at evaluating a TTM strategy in patients with CS treated with VA-ECMO according to the current recommendations and clinical use. This issue is important because ECMO use during cardiogenic shock management is still increasing worldwide and it is now urgent to determine the best approach to optimize such promising therapy. Recent publication have demonstrated that the use of ECMO has increased rapidly, whereas rates of in-hospital mortality have decreased. These changes have taken place in the context of declining hospital costs associated with ECMO. Finally, comparatively to drug/new device research, hypothermia is inexpensive and very simple to implement in real life. Therefore, the only cost for society will be the grant for the study. Finally, in order to reconcile the 2 paradigms, it is crucial to perform a RCT aimed at demonstrating the efficiency of ECMO when compared to the classical strategy. Moreover, this RCT will be highly

informative given the increasing use of ECMO, so as to determine the best approach to optimize such promising therapy in its current use.

Therefore we have modified the introduction as follows: Unfortunately, there have been few recent advances in the treatment of cardiogenic shock with the exception of ExtraCorporeal Membrane Oxygenation (ECMO) for refractory cardiogenic shock. Refractory cardiogenic shock is generally defined as cardiogenic shock associated with refractory hypotension and an increased need for vasopressor and inotrope support, along with lactic acidosis and organ failure. Of importance, three randomized controlled studies are currently ongoing aimed at defining the place of VA-ECMO in the management of non-refractory cardiogenic shock (NCT03813134, NCT03637205 and the ANCHOR study in France)
Finally, in all occurrences, we have replaced cardiogenic shock by refractory cardiogenic shock.

2. Page 11/12: There are indeed very many secondary endpoints. With a p-value of 0.05 you will have a high probability of one false positive secondary endpoint.
Response: We agree that the 0.05 threshold is associated with a higher risk for false positive results in secondary analyses. We systematically acknowledge this major limitation in all secondary articles we publish. However, we believe it is difficult to mention this important point in a design paper. If deemed necessary, we could nonetheless add a sentence proposed by the reviewer/editor in the design paper if deemed necessary by the editorial board.

2. Page 13 Table 2 Inclusion criteria: in comparison to studies with percutaneous left ventricular assist devices (IABP-II SHOCK study, Culprit Shock study) in cardiogenic shock complicating myocardial infarction, this study includes the very broad and heterogenous spectrium of cardigoenic shock patients in General, independent from the shock trigger.
Response: We thank you for the comment. We have to recognize that hypothermia might theoretically have different effects according to origin of the cardiac shock. This is the reason why we have scheduled to adjust our statistical analysis. This point is underlined in the chapter “statistical analysis for secondary end point” : “An interaction analysis will be performed using the following list of possible predictive markers: post cardiotomy setting, prior cardiac arrest, and prior myocardial infarction which are likely the three main aetiologies of cardiogenic shock that will be encountered in our study. We hope that this study of these sub-group will allow us to better define the best use of moderate hypothermia in the present indication."

3. Further: why do the authors only include cardiogenic shock patients treated with VA-ECMO? VA-ECMO is not guideline-recommended as standard treatment. Please give the inclusion criteria for VA-ECMO treatment? What does mean "to ensure sufficient tissue perfusion.!? (see page 14).

Response: As previously discussed, the study is designed to include patients that are actually treated according to current clinical practice. Once the patient is placed on VA-ECMO for refractory cardiogenic shock according to the center criteria, we consider that this patient is eligible for the study. Finally, a recent paper from Thiele et al. (in patients without ECMO) did not find any hemodynamic effects of moderate hypothermia in CS post myocardial infarction patients.
Therefore, given the above, we are not collecting the data pertaining to the inclusion criteria for VA-ECMO treatment.

4. The figures in page 23 should be included in the manuscript.
Response: The figure is already included in the manuscript submitted to BMJ Open (figure 1).

VERSION 2 – REVIEW

REVIEWER	Nuccia Morici ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
REVIEW RETURNED	31-Jul-2019

GENERAL COMMENTS	All the comments have been addressed. Accordingly, I recommend manuscript acceptance without any further revision.

REVIEWER	Werdan Karl Department of Medicine III, University Hospital Halle (Saale), Martin-Luther-University HalleWittenberg, Germany
REVIEW RETURNED	01-Aug-2019

GENERAL COMMENTS	Thank your for your response I agree with. Good luck for your study!