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Therapeutic hypothermia in ST-elevation myocardial infarction (STEMI): targeting the appropriate STEMI

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We thank Drs. Liberale and Montecucco for their insightful commentary published in *Journal of Thoracic Disease*: "Therapeutic hypothermia in ST elevation myocardial infarction (STEMI): a long way to go".

We agree with their perspective, and in fact, their viewpoint incorporates many of the reasons for the limited success of therapeutic hypothermia (TH) shown in our meta-analysis.

Whilst timely myocardial reperfusion forms the cornerstone of therapy for STEMI patients, and prevention is by far the best strategy to limit the ravages of ischemic heart disease, novel strategies such as TH among others needs to be evaluated further. Paradoxically, although myocardial reperfusion is essential for myocardial salvage, it comes at a price, as it can in itself induce myocardial injury and cardiomyocyte death—a phenomenon termed 'myocardial reperfusion injury (MRI)'. There is currently no effective therapy for preventing MRI in reperfused-STEMI patients, making it an important residual target for cardioprotection.

Our study provides important information on the possible benefit in a subgroup of anterior MI. More importantly the Genova group point to the fact that adverse events were similar in the both groups.

Whilst TH has emerged as the standard of care in post-cardiac arrest patients (1), when we examine the evidence of TH specifically in STEMIs positive effects have been demonstrated in animal models of STEMI, but clinical application of TH has been extremely challenging in human studies.

In our meta-analysis (2), we provide an evidence-based review of TH in patients with STEMI and highlight potential therapeutic interventions of TH for preventing MRI, but these must be considered preliminary as pointed out by the Genova group, and the concept should not be abandoned based on prior studies and lack of efficacy in humans. As mentioned in their letter: (I) animal models may not fully reflect human studies; (II) smaller animals may achieve hypothermia more quickly; (III) animals may achieve target hypothermic temperature that is considered an "effective dose" to achieve a meaningful outcome, whereas the human studies thus far have a "sub-effective dose" to show therapeutic efficacy.

Given that the studies were underpowered to test for the effect of TH, we did a pooled analysis in order to arrive at more precise estimates of the efficacy and safety of the available evidence. What we found was no significant benefit from TH in preventing major adverse cardiac events, mortality, new myocardial infarction, heart failure and reduction of infarct size. However, we did find a significant reduction of infarct size TH utilization in anterior wall STEMIs. Our meta-analysis did analyze the safety concerns and found no harm with a TH strategy compared with standard of care, which is encouraging, however as further more robust studies are planned to a target lower TH, an increase in adverse events may occur. In fact, TH seems to be safe and does not increase the risk of life-threatening arrhythmias and bleeding complications at the temperatures achieved in the completed (underpowered) studies, which may indeed be underpowered to assess adverse events.

So why the observed differences in animal models *vs.*

human studies were not replicated in the RCTs and meta-analysis?

Animal models which are used to test potential cardioprotective strategies in the pre-clinical setting do not adequately represent the typical STEMI patient, in terms of patient age, co-morbidities, concomitant medication, and myocardial infarction pathophysiology, time to hypothermia: all factors which are known to attenuate the cardioprotective efficacy of many therapeutic interventions (3).

Another explanation for the lack of significant reduction in major adverse cardiovascular events was not only the small number of patients in the RCTs but also the design of the studies. The STEMI patients who are most likely to benefit from a therapeutic intervention targeting MRI are those with a complete occlusion in a large coronary artery territory, and in whom there is little coronary collateralization to the area at risk (4). By including patients without these characteristics, there is a risk of diluting any cardioprotective effect. The subgroup analysis of our paper indeed showed a significant trend in patients with anterior wall STEMI that at some point resembles the aforementioned characteristics of the patients that may benefit from novel therapeutics.

Furthermore, it is essential too, that the TH is applied prior to or at the onset of myocardial reperfusion and failure to do this may in part explain the negative findings of some RCTs. MRI occurs in the first few minutes of reflow, so delaying the implementation or failure to achieve target temperature could mitigate the effect of the intervention. Most of the trials showed that it is feasible to deliver efficient TH within the setting of a clinical trial to patients presenting with STEMI, without significant change of door-to-balloon time compared to standard control patient undergoing regular PCI. This can be achieved with a strict adherence to protocol, coordination of the team, and clearly defined roles. More importantly, this minor delay is well within the target 90-minute door-to-balloon time target that PCI centers are expected to meet. However, failure to achieve "effective" TH temperature remains an important goal. Multiple methods to establish hypothermia have been explored. To date only one RCT has compared different cooling methods (surface *vs.* endovascular), suggesting that endovascular cooling maintains target temperatures better than conventional surface cooling methods, with less temperature fluctuation and fewer complications, though no mortality difference (5). A small observational study reported that peritoneal hypothermia in patients with STEMI is feasible and results in rapid cooling too (6). There is a need to establish standardization in the future protocols to determine which is the best method to cool STEMI patients, as the correct rate to achieve TH and mechanism may also influence scar size.

We fully agree with the Genova group, that TH remains a promising strategy in patients with STEMI and that additional RCTs are needed to conclude and potentially provide recommendations on its efficacy against STEMI and MRI.

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Footnote

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