Letter to the Editor

Prolonged targeted temperature management in patients suffering from out-of-hospital cardiac arrest

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We are very thankful for all the comments and interest that our publication (1) has generated. Overall, we agree with most of the issues raised in the editorials (2-4); however, we would like to make further comments on some of them.

We agree that our power calculation may seem optimistic, but we would like to point out that it is in line with other targeted temperature management (TTM) studies on neurocritical interventions (5-7). The lack of power is clearly reflected in the main conclusion of the study, where we have underlined that, "*the study may have limited power to detect clinically important differences.*" Thus, larger more randomized trials are needed in this setting, and the ongoing Targeted Temperature Management (TTM-2, NCT02908308) and Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest (TAME, NCT03114033) studies, which include 1,900 and 1,700 patients, respectively, will add new insights on the optimal management of cardiac arrest (CA) patients when they are completed. Such large studies need many recruiting centers to participate (ideally, 40–60). This number of participation was one of the limitations of the Time-Differentiated Therapeutic Hypothermia (TTH48) trial; it was due to an insufficient research network, such as that of the ANZICS Clinical Trial Group for the TAME study, as well as a lack of funding. A larger study verifying or refuting the 5% difference between the 24- and 48-hour cooling groups would require approximately 3,000 patients, making it much larger than the planned TTM-2 and TAME studies. Importantly, the TTH48 trial provides safety data, that indeed prolong cooling after OHCA is not only feasible, but it is also safe.

Another important point is whether a prolonged cooling period might benefit a specific subgroup of patients. One important aspect in this research, is age. The TTH48 study only included patients younger than 80 years, and in a preplanned subgroup analysis, patients younger than 60 years had higher survival rates, and favorable neurological outcome rates (11%), as assessed with the cerebral performance category (CPC) scale: 1–2 at 6 months after arrest with cooling for 48 hours. However, this should be interpreted with caution, since the P value of the interaction was not significant. Nevertheless,

it is possible that in the younger patients, the lack of comorbidities and frailty may reduce mortality rate, and increase the TTM signal. Rather than including all of the OHCA patients in a larger trial, we may need to try to identify which subgroups, such as younger adults, benefit from cooling, and especially, prolonged cooling. Such a study would also require a smaller number of patients, which would make the study more feasible and possible to complete within a few years.

The primary outcome in the TTH-48 trial was neurological, which we assessed using the CPC scale. Other TTM studies have also used neurological outcomes (8,9), and some have used mortality (10), which is objective and more straightforward for power calculations. The CPC scale is a crude measure for evaluating functional neurological outcomes, and future studies should use more accurate evaluation methods of cognitive and neuropsychological function, memory capacity, and quality of life. Within the TTH-48 trial, we have conducted sub-studies on cognitive tests at the 6-month mark, but they have yet to be published.

The overall survival rate in the TTH-48 study was high, when compared to the three landmark TTM studies (8-10), where a survival rate of approximately 50% was observed in the hypothermia group, and there are several explanations for this. Since informed consent was required from the family and a general practitioner, patients were screened and randomized during the first 24 hours of ICU care, it is possible that some patients who developed fulminant shock during the first 10–20 hours were not included, thereby increasing survival rates. Because of this bias, future studies evaluating the duration of cooling and featuring a longer window of time for inclusion should consider the possibility of a higher than expected survival rate when calculating sample size. Generalizability concerning survival rate should also consider the high rates of bystander cardiopulmonary resuscitation (CPR), which is more frequent in Northern Europe than in Southern Europe and North America, and of initial shockable rhythms, which does not reflect the standard CA population in many countries.

We observed some differences between the two study arms despite the randomization process. The occurrence of hypotension, and the number of patients who rewarmed before the end of study was higher in the 48-hour group. Most of these differences can be explained by the longer exposure time to cooling and sedation. With regard to hypotension, a stricter therapeutic protocol including hemodynamic end-points might have solved this problem, although the study was pragmatic (i.e., no change in local practices except for duration of cooling was considered) and few data on the most effective hemodynamic monitoring and targets to optimize therapy are available.

One of the editorials (4) stated that a prolonged cooling might be more effective in patients with a longer period of "no-flow". Indeed, patients with very short resuscitation attempts might show good neurological recovery even in the absence of temperature management. In contrast, patients with a very long no-flow time may present with severe post cardiac arrest syndrome, and extended brain injury, and they will die, regardless of how initiation and cooling duration procedures were handled. As such, future studies should help to identify those patients with a significant, but not irreversible post-anoxic brain injury, as they might benefit from neuroprotective strategies including TTM. Nevertheless, it remains unknown whether serum biomarkers, electroencephalography, or clinical signs might be effective in patient selection.

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Footnote

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