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## Targeted Temperature Management after Cardiac Arrest REPLY

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forms of technology to ensure the safest delivery of the intervention.

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Since publication of their article, the authors report no further potential conflict of interest.

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## Targeted Temperature Management after Cardiac Arrest

**TO THE EDITOR:** Nielsen and coauthors (Dec. 5 issue)<sup>1</sup> show the importance of avoiding hyperthermia in patients who have had a cardiac arrest. However, if the clinical objective is to improve the neurologic outcome, it is important to define the expected neurologic outcome in individual patients. Studies have shown that the severity of neuronal lesions is dependent on the delay in initiation of cooling after reperfusion.<sup>2</sup>

In the article by Nielsen et al., the studied patients had a median return of spontaneous circulation of 25 minutes, with a wide interquartile range of 18 to 40 in the hypothermic group and 16 to 40 in the normothermic group. In prolonged cardiac arrest, we do not expect that a reduction of neurologic metabolism by hypothermia will have a real effect on already damaged structures.

We should not conclude, on the basis of this trial, that hypothermia is simply an antihyperthermic strategy. Not all cardiac arrests are equal in terms of the time to return of spontaneous circulation. We should identify the subgroups of patients who can benefit from this form of therapy.

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**TO THE EDITOR:** Nielsen et al. confirm that fever should be avoided in resuscitated patients. However, several unanswered questions remain before abandoning therapeutic hypothermia in patients after cardiac arrest. One key issue is the potential benefit of early cooling initiated during cardiopulmonary resuscitation (CPR).

Pathophysiological mechanisms<sup>1</sup> as well as experimental data suggest a benefit of early cooling, with intra-arrest cooling clearly superior to postresuscitation cooling.<sup>2</sup> Thus, when moving from very early cooling in the experimental setting to several hours of delay in clinical practice, we might miss the time window for the greatest effectiveness of hypothermia.<sup>3</sup>

Transnasal evaporative cooling can be induced in field conditions during CPR.<sup>4</sup> The method induces continuous cooling, primarily to the brain, without the hemodynamic side effects recently seen with cold saline. Ongoing and future studies may add important knowledge to this field of research.<sup>5</sup>

Nielsen et al. permitted a time to initiate cooling of 4 hours. We suggest that this time window may be crucial to influence outcome.

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may have brought a great deal of benefits to numerous patients during the past decade.

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**TO THE EDITOR:** The study by Nielsen et al. revealed no significant difference between hypothermic and near-normothermic treatment groups in patients after cardiac arrest and CPR in terms of their survival and neurologic outcome. This striking finding contradicts the previous understanding of the benefits of this form of therapy, and the next question seems to be whether there is any need to induce hypothermia in these patients.

However, the neurologic evaluation in Nielsen et al. was based on the Cerebral Performance Category (CPC) scale and a modified Rankin scale. These are simple tests devised for assessing patients' independent daily living and are inadequate for assessing cognitive prognosis, when mild cognitive impairment is a real concern in survivors of cardiac arrest.<sup>1-3</sup> Thus, the findings of Nielsen et al. should not lead to changes in practice before the long-term prognosis of hypothermic versus near-normothermic treatments and the patients' recovery of cognitive function are investigated by means of recent advancements in neurologic assessment.<sup>4</sup> We ask for more clarification on this topic, which has to precede the decision to "drop the old habit" that

**TO THE EDITOR:** Data from the study by Nielsen et al. showing that maintaining temperature at 33°C and at 36°C have similar benefits in comatose survivors of cardiac arrest originate from patients with an impressively short time to CPR and a higher percentage of bystander-initiated CPR (73%) than in previous clinical trials (49 to 58%).<sup>1,2</sup> Thus, whether such results could be widely applied to communities with a longer time to resuscitation remains to be clarified. Moreover, both midazolam and propofol provide additional neuroprotective effects<sup>3</sup>; however, doses of agents used were not specifically recorded. Finally, no specific guidelines for management of the postresuscitation syndrome were provided, yet it is known that early hemodynamic optimization may improve neurologic outcome after cardiac arrest.<sup>4</sup> Because patients in the 33°C group more frequently had severe cardiovascular impairment than those in the 36°C group (76% vs. 70% on day 2 and 67% vs. 54% on day 3), inadequate organ perfusion may account for potentially harmful effects of a lower target temperature; this was suggested by the higher proportion of deaths before prognostication from cardiac

causes or multiple organ failure observed in the 33°C group.

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**TO THE EDITOR:** The large, randomized trial by Nielsen et al. showed no significant difference in survival between two strategies of targeted temperature management (33°C vs. 36°C) in comatose survivors of out-of-hospital cardiac arrest and therefore cast doubt on the results of earlier trials that evaluated induced hypothermia in this population. The investigators are to be commended for their rigorous trial with concurrent high rates of coronary angiography and structured, deferred approaches to prognostication and withdrawal of care. Before abandoning 33°C as a treatment target, we should consider whether the benefit of this strategy may have been attenuated in this trial.

First, patients in the current study underwent randomization up to 4 hours after cardiac arrest and had a further 4 hours to achieve mean temperatures below 34°C.<sup>1</sup> A briefer time to the target temperature after cardiac arrest<sup>2</sup> or in patients with ST-segment elevation myocardial infarction<sup>3</sup> may be required to modify reperfusion injury. Second, patients were sedated for 36 hours. Although details were not provided, it is plausible that sedation with propofol may have attenuated the effect of temperature management on the reduction of reperfusion injury.<sup>4,5</sup>

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**TO THE EDITOR:** Nielsen and collaborators report that therapeutic hypothermia (33°C) conferred no outcome benefits after cardiac arrest, as compared with strict fever control. This directly contradicts the findings of two randomized, controlled trials previously published in the *Journal* and other data supporting the use of therapeutic hypothermia after hypoxic injury.<sup>1-3</sup> How do we explain this? Should current guidelines be changed? The current study is large and well conducted but has potential limitations. One is a rapid rate of rewarming, from 33°C to 36°C in 6 hours — a much faster rate than in previous trials. Rapid warming is harmful and can negate the benefits of therapeutic hypothermia.<sup>4,5</sup> In addition, were all consecutive patients with cardiac arrest and return of spontaneous circulation screened for this study, or did physicians pre-assess potential eligibility? Participating centers routinely used therapeutic hypothermia before this study and continued to treat nonstudy patients with it. Physicians could have subconsciously selected patients with potential benefit for “routine” therapeutic hypothermia rather than refer for screening. The study enrolled an average of only one patient per center per month, possibly indicating preselection.

These results could be misconstrued to advocate abandoning temperature management after cardiac arrest altogether. We agree with the au-

thors that the question should be what temperature to maintain, not whether temperature control is needed.

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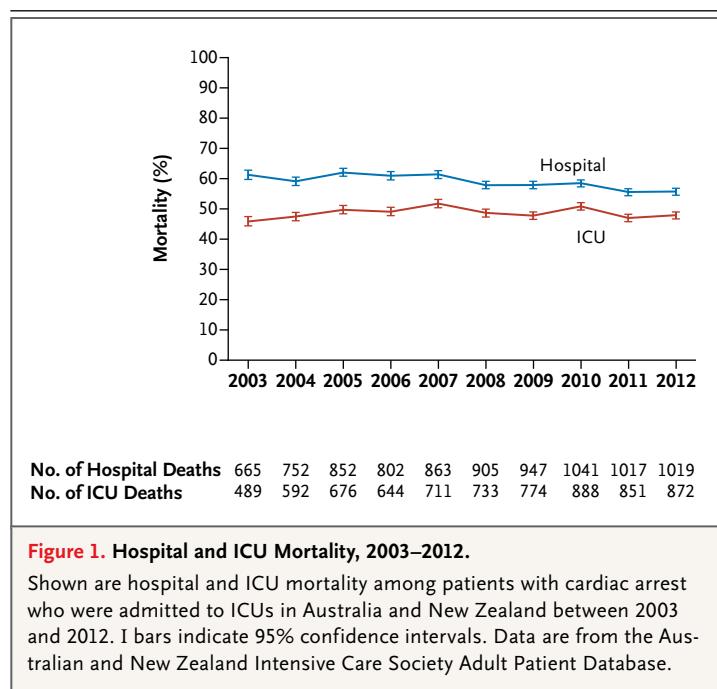
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**TO THE EDITOR:** With regard to the editorial accompanying the article by Nielsen and colleagues: we reflect on a key assertion that, “In contrast to a decade ago, one half instead of one third of patients with return of spontaneous circulation after CPR can expect to survive hospitalization.”<sup>1</sup> In fact, in 2002, the Hypothermia after Cardiac Arrest Study Group<sup>2</sup> reported a hospital mortality of 43% (119 of 275 participants). The investigators participating in the Target Temperature Management 33°C versus 36°C after Out-of-Hospital Cardiac Arrest (TTM) trial now report a nearly identical hospital mortality of 44% (411 of 939 participants).

Using the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD), which includes data on more than 1.4 million intensive care unit (ICU) admissions and more than 17,000 cardiac arrests, we determined the hospital mortality among patients with out-of-hospital cardiac arrest in Australia and New Zealand from 2003 to 2012. We found a hospital mortality of 61% in 2003 and 56% in 2012 and an ICU mortality of 46% in



**Figure 1. Hospital and ICU Mortality, 2003–2012.**

Shown are hospital and ICU mortality among patients with cardiac arrest who were admitted to ICUs in Australia and New Zealand between 2003 and 2012. I bars indicate 95% confidence intervals. Data are from the Australian and New Zealand Intensive Care Society Adult Patient Database.

2003 and 48% in 2012 (Fig. 1). These findings and those mentioned above indicate that hospital mortality in Australia and New Zealand and in the European trial sites has not improved over time. Investigators must now seek new therapeutic interventions that protect the brain and improve mortality and neurologic outcomes after out-of-hospital cardiac arrest.<sup>3</sup>

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No potential conflict of interest relevant to this letter was reported.

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**DR. NIELSEN AND COLLEAGUES REPLY:** Perchiazzi et al., Nordberg et al., and Stub suggest that a delay in the initiation of temperature management might influence outcome. The window of 240 minutes from return of spontaneous circulation to randomization was based on a study of data from the Hypothermia Network Registry, in which there was no association between time to the initiation of temperature management and 6-month neurologic outcome.<sup>1</sup> Other large observational studies have given similar signals.<sup>2</sup> Data from a recent randomized trial showed that early initiation of temperature management does not improve outcome.<sup>3</sup> Intra-arrest cooling is, however, compelling, and we look forward to results from ongoing trials.

Perchiazzi et al. call for subgroup analyses to elucidate which patients might benefit from one of the interventions. The forest plot in Figure S2 in the Supplementary Appendix (available with the full text of our article at NEJM.org) indicates a homogeneous intervention effect in five pre-defined subgroups. Further multivariate analysis may give signals in any direction, but we would not recommend basing practice on inferences that at best could be hypothesis-generating.

Oh and colleagues ask for more detailed neurologic assessment at follow-up, and we agree that the CPC scale and the modified Rankin scale represent crude measures. However, the CPC scale was used in trials introducing temperature management in clinical practice. Data from more detailed assessment were collected but have not yet been published.<sup>4</sup> Survival being the primary outcome, it is important to acknowledge that the TTM trial was not powered to conclusively assess these measures.

Taccone and Dell'Anna comment on the high rate of bystander-initiated CPR in the TTM trial. During the past decade, there has been a continuous rise in bystander-initiated CPR, with positive consequences on overall outcome.<sup>5</sup> The time to bystander-initiated CPR is naturally relevant only for patients receiving such help and should be short. The time to bystander-initiated CPR was, to our knowledge, not reported in earlier trials on temperature management.

In response to Varon and Polderman: we confirm that sites consecutively screened all patients meeting inclusion criteria and randomly assigned every patient not meeting exclusion criteria. The

baseline characteristics, active care (60% early angiography and 40% coronary intervention), and survival rates strongly contradict a selection of patients with a presumed poor outcome.

Whether goal-directed changes in post-cardiac arrest care, sedatives, or the rewarming rate influence outcome is to our knowledge unknown and remains to be investigated in future randomized clinical trials.

We disagree that our trial showed a benefit of avoiding fever; to do so, a no-intervention group would have been necessary. That said, we definitely would not advocate abandoning any temperature management on the basis of the results of the TTM trial.

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Since publication of their article, the authors report no further potential conflict of interest.

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**THE EDITORIALISTS REPLY:** The data from ANZICS APD are a welcome addition to the longitudinal data on survival after cardiac arrest. We urge three points of caution regarding interpretation of these data. First, we wonder whether partici-

pating ICUs adopted the use of a standard care plan including temperature management soon after the seminal articles,<sup>1,2</sup> making the excellent survival rates depicted in this graph representative of the “temperature-management era.” Second, the relevant comparison group for baseline survival from the Hypothermia after Cardiac Arrest Study Group trial<sup>1</sup> is the control group, which received no regimented care with respect to temperature management. Although control patients were highly selected from a group with a high likelihood of survival, hospital mortality was 50% (69 of 138 patients), substantially higher than the hospital mortality of 44% (411 of 939 patients) in the TTM trial involving less selected patients. Third, if the ANZICS APD includes patients admitted to the ICU, it may not capture deaths that

occur in the emergency department or during pre-ICU procedures. Despite this limitation, we do appreciate a modest decline in hospital deaths over the decade from more than 60% to its current level.

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## BMI and Mortality among Adults with Incident Type 2 Diabetes

**TO THE EDITOR:** Tobias et al. (Jan. 16 issue)<sup>1</sup> found no evidence of lower mortality among obese patients with incident type 2 diabetes, as compared with their normal-weight counterparts. An “obesity paradox” (i.e., an association between obesity and reduced mortality) had been reported, in particular in patient populations with a short survival time, whereas obesity by its nature is a risk factor for increased long-term mortality. Our earlier results show that short follow-up and the advanced age of populations with chronic diseases are major limitations of such studies: over short periods, a high body-mass index (BMI) was not associated with increased mortality among patients with end-stage renal disease, but it was also not associated with increased mortality in the general population of equal age.<sup>2</sup> Moreover, different underlying causes of the disease and coexisting illnesses impede a valid comparison between patients with a high BMI and those with a low BMI. Because of these limitations, it is not possible to translate such observations into causal interpretations — for example, to advise a high body weight in these patients. The findings by Tobias et al. are a timely reminder of the many biases that need to be taken into account before a causal interpretation of population data is possible.

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**TO THE EDITOR:** Although Carnethon et al.<sup>1</sup> found a better prognosis in obese patients with type 2 diabetes as compared with patients of “normal” weight, Tobias and colleagues did not find an obesity paradox. They explained that prior analyses were limited by short follow-up, a small number of deaths, and a lack of data on smoking or undiagnosed diseases.

We are concerned, however, that neither study mentioned above accounted for fitness, especially because obese but fit persons with type 2 diabetes have a considerably better prognosis