

# Prehospital initiation of mild therapeutic hypothermia for out-of-hospital cardiac arrest (OHCA): where are we now?

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Over the past decade, much research has been devoted to the field of mild therapeutic hypothermia (MTH) and targeted temperature management (TTM) for patients resuscitated from out-of-hospital cardiac arrest (OHCA). Two studies indicating benefit for MTH were simultaneously published in 2002, sparking a wave of global excitement and research in this field and subsequent widespread clinical implementation of this therapy. Despite questions of the true effect of subnormal temperatures on outcomes and whether the available evidence justified the endorsement by international resuscitation organizations,<sup>1</sup> the advent of MTH undoubtedly impacted survival and neurological outcomes, even if indirectly. Many observational studies, most often using historical controls, demonstrated benefits in mortality and neurological outcomes after incorporating MTH for OHCA management.<sup>2-22</sup>

Based on the success of animal models,<sup>23,24</sup> the two landmark prospective controlled clinical studies were based on the theory that post-arrest hypothermia mitigated the effects of cerebral reperfusion injury.<sup>25,26</sup> These trials enrolled unresponsive adult patients resuscitated from OHCA of presumed cardiac etiology with initial shockable rhythms, and compared the use of MTH at goal temperatures of 32°C–34°C (89.6°F–93.2°F) to usual care (unregulated temperature).<sup>25,26</sup> Bernard et al. included 77 patients, with MTH initiated by emergency medical services in the intervention group and continued for 12 hours.<sup>25</sup> At 2 hours, the group mean temperature was at 33.5°C (92.3°F). The hypothermia-after-cardiac-arrest group randomized 275 patients after witnessed OHCA.<sup>26</sup> MTH was commenced in the hospital, had a median

time to target temperature of 8 hours, and continued for 24 hours. Benefits in neurological outcomes were seen in both studies.

With evidence supporting the use of MTH, it is not surprising that the assumption was made that earlier MTH initiation and faster induction could provide even greater benefit, as was demonstrated in controlled animal studies.<sup>27-30</sup> Several observational studies were performed to investigate this hypothesis; however, results ranged from demonstrating benefit,<sup>31-34</sup> no benefit,<sup>35,36</sup> or even worse outcomes.<sup>37-40</sup> Observational studies have significant biases, however, because 1) patients with lower initial temperatures prior to MTH initiation appear to have worse outcomes than their comparators<sup>39,41,42</sup>; and 2) those with worse anoxic brain injuries may be “easier to cool”<sup>43</sup>; both of which may be due to impaired thermoregulation, a possible marker of more profound brain injury and therefore a reduced likelihood of survival.

Several randomized controlled trials (RCTs) were performed, enrolling consecutive patients in the pre-hospital setting to examine the effects of earlier MTH initiation.<sup>44-49</sup> While these studies demonstrated that modestly lower temperatures at hospital arrival can be achieved, there were no differences in patient outcomes. In the largest of these studies, Kim et al. randomized 1,359 patients in the prehospital environment to either MTH induction with large boluses of iced saline as soon as possible after initial return of spontaneous circulation (ROSC), or usual care.<sup>48</sup> The intervention group demonstrated a lower mean temperature upon hospital arrival and reduced times to therapeutic range; however, there was a higher incidence of prehospital re-arrests

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and pulmonary edema, possibly owing to the large fluid boluses used for induction. There was no difference in overall survival to hospital discharge.

In this *CJEM* issue, Schenfeld et al. report a pragmatic observational study examining the effectiveness of prehospital MTH in decreasing the time-to-target temperature among those who survived to intensive care unit (ICU) admission and were treated with a MTH protocol, in comparison to historical controls who had MTH initiated upon emergency department arrival.<sup>50</sup> Due to the study's restrictive and subjective inclusion criteria and observational design, conclusions of the intervention's effectiveness on survival and neurological outcomes cannot be drawn. However, this study provides insight into the real-world application of prehospital MTH. Similar to the controlled trial setting of Kim et al.,<sup>48</sup> the prehospital MTH group demonstrated longer times to hospital arrival. In contrast to several previous RCTs,<sup>47-49</sup> time to therapeutic range was not decreased. This study adds to the body of evidence, indicating the lack of benefit of prehospital MTH, when compared to MTH initiated upon hospital arrival.

An alternative theory emerged, that perhaps the apparent benefit of MTH was not in its subnormal temperatures but in its ability to mitigate the detrimental effects of hyperthermia,<sup>51</sup> a common occurrence in post-OHCA patients.<sup>52</sup> If this hypothesis were true, earlier MTH induction would be largely irrelevant because hyperthermia is rare in the early course of the post-arrest patient.<sup>26,53</sup> MTH was rebranded to the more general term, *targeted temperature management*, and a large multicentre randomized control trial was undertaken, randomizing 950 unresponsive patients after OHCA to the temperature goals of 33°C (91.4°F) and 36°C (96.8°F).<sup>53</sup> The only initial rhythm that was excluded was asystole in unwitnessed arrests. TTM was initiated within 240 minutes of ROSC, and measures to avoid hyperthermia continued for a total of 72 hours, with assessor-blinded, standardized neuroprognostication taking place at a minimum of 108 hours after TTM initiation. The results of this study were neutral, without demonstration of superiority in neurological outcomes or mortality of one target temperature over the other. This was the largest and most rigorously performed MTH/TTM study to date, and has led to practice changes in goal temperatures within critical care post-OHCA protocols, while ensuring continued attention to temperature regulation.<sup>54</sup>

Although the strategy of preventing hyperthermia in the days subsequent to an OHCA appears beneficial,

there may still be benefit with immediate post-arrest or intra-arrest hypothermia to reduce or prevent reperfusion injury, as has been demonstrated in multiple animal models.<sup>29,55</sup> With the exception of the original study by Bernard et al.,<sup>25</sup> the comparator groups in studies examining prehospital MTH induction have been in-hospital MTH, resulting in small differences in cooling time metrics, possibly the reason for neutral outcome results. Although likely a systematically different patient population, remarkable neurological outcomes with prolonged CPR have been reported in patients with pre-arrest hypothermia.<sup>56</sup> The ongoing RINSE<sup>57</sup> and PRINCESS<sup>58</sup> trials may provide insight into this question and into the safety of iced saline induction, randomizing patients to intra-arrest prehospital MTH using iced saline and a novel intra-nasal device, respectively. If harm is shown with the intervention groups, then this will likely be the last nail in the coffin for prehospital MTH. However, in the absence of this, because the comparator group in these studies is hospital-based MTH, a comparison to normothermic TTM may be required to detect a possible benefit of MTH in limiting early reperfusion injury.

Schenfeld et al. should be commended on their contribution to the field of resuscitation research. Acknowledging this and other data, at the current time, we are still lacking compelling evidence for a role of MTH/TTM in the prehospital environment. We will eagerly await the results of further studies to help determine the ideal initiation method and time, and patient populations for whom MTH and/or TTM therapies would be most beneficial.

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## REFERENCES

1. Nolan JP, Morley PT, Vanden Hoek TL, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation* 2003; 108(1):118-21, doi:10.1161/01.CIR.0000079019.02601.90.
2. Reinikainen M, Oksanen T, Leppänen P, et al. Mortality in out-of-hospital cardiac arrest patients has decreased in the era of therapeutic hypothermia. *Acta Anaesthesiol Scand* 2012;56(1):110-5, doi:10.1111/j.1399-6576.2011.02543.x.
3. Storm C, Nee J, Krueger A, et al. 2-year survival of patients undergoing mild hypothermia treatment after ventricular fibrillation cardiac arrest is significantly improved compared

- to historical controls. *Scand J Trauma Resusc Emerg Med* 2010;18:2, doi:[10.1186/1757-7241-18-2](https://doi.org/10.1186/1757-7241-18-2).
4. Takeuchi I, Takehana H, Satoh D, et al. Effect of hypothermia therapy after outpatient cardiac arrest due to ventricular fibrillation. *Circ J* 2009;73(10):1877-80.
  5. Belliard G, Catez E, Charron C, et al. Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. *Resuscitation* 2007;75(2):252-9, doi:[10.1016/j.resuscitation.2007.04.014](https://doi.org/10.1016/j.resuscitation.2007.04.014).
  6. Bro-Jeppesen J, Kjaergaard J, Horsted TI, et al. The impact of therapeutic hypothermia on neurological function and quality of life after cardiac arrest. *Resuscitation* 2009;80(2):171-6, doi:[10.1016/j.resuscitation.2008.09.009](https://doi.org/10.1016/j.resuscitation.2008.09.009).
  7. Lundbye JB, Rai M, Ramu B, et al. Therapeutic hypothermia is associated with improved neurologic outcome and survival in cardiac arrest survivors of non-shockable rhythms. *Resuscitation* 2012;83(2):202-7, doi:[10.1016/j.resuscitation.2011.08.005](https://doi.org/10.1016/j.resuscitation.2011.08.005).
  8. Testori C, Sterz F, Behringer W, et al. Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. *Resuscitation* 2011;82(9):1162-7, doi:[10.1016/j.resuscitation.2011.05.022](https://doi.org/10.1016/j.resuscitation.2011.05.022).
  9. Dumas F, Grimaldi D, Zuber B, et al. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients?: insights from a large registry. *Circulation* 2011;123(8):877-86, doi:[10.1161/CIRCULATIONAHA.110.987347](https://doi.org/10.1161/CIRCULATIONAHA.110.987347).
  10. Don CW, Longstreth WT, Maynard C, et al. Active surface cooling protocol to induce mild therapeutic hypothermia after out-of-hospital cardiac arrest: a retrospective before-and-after comparison in a single hospital. *Crit Care Med* 2009;37(12):3062-9, doi:[10.1097/CCM.0b013e3181b7f59c](https://doi.org/10.1097/CCM.0b013e3181b7f59c).
  11. Vaahersalo J, Hiltunen P, Tiainen M, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. *Intensive Care Med* 2013;39(5):826-37, doi:[10.1007/s00134-013-2868-1](https://doi.org/10.1007/s00134-013-2868-1).
  12. Storm C, Nee J, Roser M, et al. Mild hypothermia treatment in patients resuscitated from non-shockable cardiac arrest. *Emerg Med J* 2012;29(2):100-3, doi:[10.1136/emj.2010.105171](https://doi.org/10.1136/emj.2010.105171).
  13. Oddo M, Schaller MD, Feihl F, et al. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Crit Care Med* 2006;34(7):1865-73, doi:[10.1097/01.CCM.0000221922.08878.49](https://doi.org/10.1097/01.CCM.0000221922.08878.49).
  14. Martinell L, Larsson M, Bång A, et al. Survival in out-of-hospital cardiac arrest before and after use of advanced postresuscitation care: a survey focusing on incidence, patient characteristics, survival, and estimated cerebral function after postresuscitation care. *Am J Emerg Med* 2010;28(5):543-51, doi:[10.1016/j.ajem.2009.01.042](https://doi.org/10.1016/j.ajem.2009.01.042).
  15. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007;73(1):29-39, doi:[10.1016/j.resuscitation.2006.08.016](https://doi.org/10.1016/j.resuscitation.2006.08.016).
  16. Busch M, Soreide E, Lossius HM, et al. Rapid implementation of therapeutic hypothermia in comatose out-of-hospital cardiac arrest survivors. *Acta Anaesthesiol Scand* 2006;50(10):1277-83, doi:[10.1111/j.1399-6576.2006.01147.x](https://doi.org/10.1111/j.1399-6576.2006.01147.x).
  17. Storm C, Steffen I, Schefold JC, et al. Mild therapeutic hypothermia shortens intensive care unit stay of survivors after out-of-hospital cardiac arrest compared to historical controls. *Crit Care* 2008;12(3):R78 doi:[10.1186/cc6925](https://doi.org/10.1186/cc6925).
  18. Knafelj R, Radsel P, Ploj T, Noc M. Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. *Resuscitation* 2007;74(2):227-34, doi:[10.1016/j.resuscitation.2007.01.016](https://doi.org/10.1016/j.resuscitation.2007.01.016).
  19. Hinchey PR, Myers JB, Lewis R, et al. Improved out-of-hospital cardiac arrest survival after the sequential implementation of 2005 AHA guidelines for compressions, ventilations, and induced hypothermia: the Wake County experience. *Ann Emerg Med* 2010;56(4):348-57, doi:[10.1016/j.annemergmed.2010.01.036](https://doi.org/10.1016/j.annemergmed.2010.01.036).
  20. Rittenberger JC, Guyette FX, Tisherman SA, et al. Outcomes of a hospital-wide plan to improve care of comatose survivors of cardiac arrest. *Resuscitation* 2008;79(2):198-204, doi:[10.1016/j.resuscitation.2008.08.014](https://doi.org/10.1016/j.resuscitation.2008.08.014).
  21. Holzer M, Müllner M, Sterz F, et al. Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. *Stroke* 2006;37(7):1792-7, doi:[10.1161/01.STR.0000227265.52763.16](https://doi.org/10.1161/01.STR.0000227265.52763.16).
  22. Granja C, Ferreira P, Ribeiro O, Pina J. Improved survival with therapeutic hypothermia after cardiac arrest with cold saline and surfacing cooling: keep it simple. *Emerg Med Int* 2011;2011: article ID 395813, epub, doi:[10.1155/2011/395813](https://doi.org/10.1155/2011/395813).
  23. Weinrauch V, Safar P, Tisherman S, et al. Beneficial effect of mild hypothermia and detrimental effect of deep hypothermia after cardiac arrest in dogs. *Stroke* 1992;23(10):1454-62.
  24. Sterz F, Safar P, Tisherman S, et al. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. *Crit Care Med* 1991;19(3):379-89.
  25. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346(8):557-63, doi:[10.1056/NEJMoa003289](https://doi.org/10.1056/NEJMoa003289).
  26. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346(8):549-56, doi:[10.1056/NEJMoa012689](https://doi.org/10.1056/NEJMoa012689).
  27. Kuboyama K, Safar P, Radovsky A, et al. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. *Crit Care Med* 1993;21(9):1348-58.
  28. Colbourne F, Sutherland GR, Auer RN. Electron microscopic evidence against apoptosis as the mechanism of neuronal death in global ischemia. *J Neurosci* 1999;19(11):4200-10.
  29. Abella BS, Zhao D, Alvarado J, et al. Intra-arrest cooling improves outcomes in a murine cardiac arrest model. *Circulation* 2004;109(22):2786-91, doi:[10.1161/01.CIR.0000131940.19833.85](https://doi.org/10.1161/01.CIR.0000131940.19833.85).
  30. Jia X, Koenig MA, Shin HC, et al. Improving neurological outcomes post-cardiac arrest in a rat model: immediate hypothermia and quantitative EEG monitoring. *Resuscitation* 2008;76(3):431-42, doi:[10.1016/j.resuscitation.2007.08.014](https://doi.org/10.1016/j.resuscitation.2007.08.014).
  31. Wolff B, Machill K, Schumacher D, et al. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. *Int J Cardiol* 2009;133(2):223-8, doi:[10.1016/j.ijcard.2007.12.039](https://doi.org/10.1016/j.ijcard.2007.12.039).

32. Sendelbach S, Hearst MO, Johnson PJ, et al. Effects of variation in temperature management on cerebral performance category scores in patients who received therapeutic hypothermia post cardiac arrest. *Resuscitation* 2012;83(7):829-34, doi:[10.1016/j.resuscitation.2011.12.026](https://doi.org/10.1016/j.resuscitation.2011.12.026).
33. Chiota NA, Freeman WD, Barrett K. Earlier hypothermia attainment is associated with improved outcomes after cardiac arrest. *J Vasc Interv Neurol* 2011;4(1):14-7.
34. Mooney MR, Unger BT, Boland LL, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: evaluation of a regional system to increase access to cooling. *Circulation* 2011;124(2):206-14, doi:[10.1161/CIRCULATIONAHA.110.986257](https://doi.org/10.1161/CIRCULATIONAHA.110.986257).
35. Nielsen N, Hovdenes J, Nilsson F, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. *Acta Anaesthesiol Scand* 2009;53(7):926-34, doi:[10.1111/j.1399-6576.2009.02021.x](https://doi.org/10.1111/j.1399-6576.2009.02021.x).
36. Larsen LP, Kristensen KV, Kirkegaard H. Therapeutic hypothermia after cardiac arrest. *Ugeskr Laeger* 2009;171(17):1392-6.
37. Italian Cooling Experience Study Group. Early- versus late-initiation of therapeutic hypothermia after cardiac arrest: preliminary observations from the experience of 17 Italian intensive care units. *Resuscitation* 2012;83(7):823-8, doi:[10.1016/j.resuscitation.2011.12.002](https://doi.org/10.1016/j.resuscitation.2011.12.002).
38. Haugk M, Testori C, Sterz F, et al. Relationship between time to target temperature and outcome in patients treated with therapeutic hypothermia after cardiac arrest. *Crit Care* 2011;15(2):R101 doi:[10.1186/cc10116](https://doi.org/10.1186/cc10116).
39. Benz-Woerner J, Delodder F, Benz R, et al. Body temperature regulation and outcome after cardiac arrest and therapeutic hypothermia. *Resuscitation* 2012;83(3):338-42, doi:[10.1016/j.resuscitation.2011.10.026](https://doi.org/10.1016/j.resuscitation.2011.10.026).
40. Vanston VJ, Lawhon-Triano M, Getts R, et al. Predictors of poor neurologic outcome in patients undergoing therapeutic hypothermia after cardiac arrest. *South Med J* 2010;103(4):301-6.
41. Den Hartog AW, de Pont A-CJM, Robillard LBM, et al. Spontaneous hypothermia on intensive care unit admission is a predictor of unfavorable neurological outcome in patients after resuscitation: an observational cohort study. *Crit Care* 2010;14(3):R121 doi:[10.1186/cc9077](https://doi.org/10.1186/cc9077).
42. Lyon RM, Richardson SE, Hay AW, et al. Esophageal temperature after out-of-hospital cardiac arrest: an observational study. *Resuscitation* 2010;81(7):867-71, doi:[10.1016/j.resuscitation.2010.03.017](https://doi.org/10.1016/j.resuscitation.2010.03.017).
43. Perman SM, Ellenberg JH, Grossestreuer AV, et al. Shorter time to target temperature is associated with poor neurologic outcome in post-arrest patients treated with targeted temperature management. *Resuscitation* 2015;88:114-9, doi:[10.1016/j.resuscitation.2014.10.018](https://doi.org/10.1016/j.resuscitation.2014.10.018).
44. Bernard SA, Smith K, Cameron P, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. *Circulation* 2010;122(7):737-42, doi:[10.1161/CIRCULATIONAHA.109.906859](https://doi.org/10.1161/CIRCULATIONAHA.109.906859).
45. Kim F, Olsufka M, Longstreth WT, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. *Circulation* 2007;115(24):3064-3070, doi:[10.1161/CIRCULATIONAHA.106.655480](https://doi.org/10.1161/CIRCULATIONAHA.106.655480).
46. Kämäräinen A, Virkkunen I, Tenhunen J, et al. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial. *Acta Anaesthesiol Scand* 2009;53(7):900-7, doi:[10.1111/j.1399-6576.2009.02015.x](https://doi.org/10.1111/j.1399-6576.2009.02015.x).
47. Bernard SA, Smith K, Cameron P, et al. Induction of prehospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest\*. *Crit Care Med* 2012;40(3):747-53, doi:[10.1097/CCM.0b013e3182377038](https://doi.org/10.1097/CCM.0b013e3182377038).
48. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA* 2014;311(1):45-52, doi:[10.1001/jama.2013.282173](https://doi.org/10.1001/jama.2013.282173).
49. Castrén M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). *Circulation* 2010;122(7):729-36, doi:[10.1161/CIRCULATIONAHA.109.931691](https://doi.org/10.1161/CIRCULATIONAHA.109.931691).
50. Schenfeld EM, Studnek J, Heffner AC, et al. Effect of prehospital initiation of therapeutic hypothermia in adults with cardiac arrest on time-to-target temperature. *CJEM* 2015;17(3):240-7.
51. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. *Arch Intern Med* 2001;161(16):2007-12.
52. Nielsen N, Wetterslev J, al-Subaie N, et al. Target Temperature Management after out-of-hospital cardiac arrest—a randomized, parallel-group, assessor-blinded clinical trial—rationale and design. *Am Heart J* 2012;163(4):541-8, doi:[10.1016/j.ahj.2012.01.013](https://doi.org/10.1016/j.ahj.2012.01.013).
53. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013;369(23):2197-206, doi:[10.1056/NEJMoa1310519](https://doi.org/10.1056/NEJMoa1310519).
54. Bernard S. Inducing hypothermia after out of hospital cardiac arrest. *BMJ* 2014;348:g2735 doi:[10.1136/bmj.g2735](https://doi.org/10.1136/bmj.g2735).
55. Zhao D, Abella BS, Beiser DG, et al. Intra-arrest cooling with delayed reperfusion yields higher survival than earlier normothermic resuscitation in a mouse model of cardiac arrest. *Resuscitation* 2008;77(2):242-9, doi:[10.1016/j.resuscitation.2007.10.015](https://doi.org/10.1016/j.resuscitation.2007.10.015).
56. Silfvast T, Pettilä V. Outcome from severe accidental hypothermia in Southern Finland—a 10-year review. *Resuscitation* 2003;59(3):285-90, doi:[10.1016/S0300-9572\(03\)00237-5](https://doi.org/10.1016/S0300-9572(03)00237-5).
57. Deasy C, Bernard S, Cameron P, et al. Design of the RINSE trial: the rapid infusion of cold normal saline by paramedics during CPR. *BMC Emerg Med* 2011;11(1):17 doi:[10.1186/1471-227X-11-17](https://doi.org/10.1186/1471-227X-11-17).
58. *Prehospital Resuscitation Intra Nasal Cooling Effectiveness Survival Study (PRINCESS)*. Erasme Univ Hosp Stock Pre-hospital Centre, Karolinska Institutet Södersjukhuset: NCT01400373. Available at: <https://clinicaltrials.gov> (accessed January 15, 2015).