

Evolution, safety and efficacy of targeted temperature management after pediatric cardiac arrest

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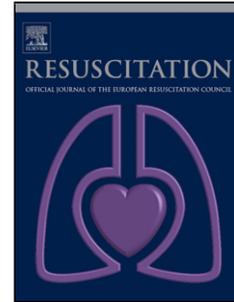
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23 **Short title:** Targeted temperature management after cardiac arrest.
24

25 **Key Words:** paediatric critical care, therapeutic hypothermia, targeted temperature
26 management, observational study, out-of-hospital cardiac arrest
27

28 **Define all nonstandard abbreviations:**

29 OHCA: Out-of-hospital cardiac arrest

30 PICU: Paediatric intensive care unit

31 ROSC: Return of spontaneous circulation

32 TTM: Targeted temperature management

33 STM: Standard temperature management
34

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40

41 **Contributors statement**

42 Dr Scholefield designed the current study protocol, data collection tool and database with
43 substantial intellectual input from Prof Gao & Perkins, and Drs Morris and Duncan. Data
44 collection was performed by Dr Scholefield, Dr Gosney, Dr Sanders and Dr Skone. Data
45 cleaning, validation and queries were performed by Dr Scholefield. All statistical analysis
46 was performed by Dr Scholefield with advice from Dr P Davies. Contributions to

47 interpretation of data were received from all authors. First draft of manuscript was written by
48 Dr Scholefield with intellectual input from Drs Morris & Duncan and Prof Gao & Perkins. In
49 addition, critical review and contributions of subsequent drafts were received from Drs
50 Gosney, Sanders and Skone. All authors reviewed and approved the final draft of the
51 manuscript prior to submission. All authors agree to be accountable for the accuracy and
52 integrity of the piece of work.

53

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55 **ABSTRACT**

56

57 **Background**

58 It is unknown whether targeted temperature management (TTM) improves survival after
59 paediatric out-of-hospital cardiac arrest (OHCA). The aim of this study was to assess the

60 evolution, safety and efficacy of TTM (32-34⁰C) compared to standard temperature

61 management (STM) (<38⁰C).

62 **Methods**

63 Retrospective, single centre cohort study. Patients aged >one day up to 16 years, admitted to
64 a UK Paediatric Intensive Care Unit (PICU) after OHCA (January 2004 to December 2010).
65 Primary outcome was survival to hospital discharge; efficacy and safety outcomes included:
66 application of TTM, physiological, haematological and biochemical side effects.

67 **Results**

68 Seventy three patients were included. Thirty eight patients (52%) received TTM (32-34⁰C).

69 Prior to ILCOR guidance adoption in January 2007, TTM was used infrequently (4/25; 16%).

70 Following adoption, TTM (32-34⁰C) use increased significantly (34/48; 71% Chi² p<0.0001).

71 TTM (32-34⁰C) and STM (<38⁰C) groups were similar at baseline. TTM (32-34⁰C) was

72 associated with bradycardia and hypotension compared to STM (<38⁰C). TTM (32-34⁰C)

73 reduced episodes of hyperthermia ($>38^{\circ}\text{C}$) in the 1st 24 hours; however, excessive
74 hypothermia ($<32^{\circ}\text{C}$) and hyperthermia ($>38^{\circ}\text{C}$) occurred in both groups upto 72 hours, and
75 all patients (n=11) experiencing temperature $<32^{\circ}\text{C}$ died. The study was underpowered to
76 determine a difference in hospital survival (34% (TTM ($32\text{-}34^{\circ}\text{C}$)) vs. 23% (STM ($<38^{\circ}\text{C}$));
77 $p=0.284$). However, the TTM ($32\text{-}34^{\circ}\text{C}$) group had a significantly longer PICU length of
78 stay.

79 **Conclusions**

80 TTM ($32\text{-}34^{\circ}\text{C}$) was feasible but associated with bradycardia, hypotension, and increased
81 length of stay in PICU. Temperature $<32^{\circ}\text{C}$ had a universally grave prognosis. Larger studies
82 are required to assess effect on survival.

83

83 **INTRODUCTION**

84 It is unknown whether targeted temperature management (TTM) (32-34°C) improves
85 survival and reduces brain injury for infants and children after out-of-hospital cardiac arrest
86 (OHCA) (1). TTM is the active treatment of inducing and maintaining a specific body
87 temperature for a specific duration of time attempting to improve health outcomes (2).
88 Randomized controlled trials in the 2000s renewed interest in 12-24 hours of TTM (32-34°C)
89 as a therapeutic intervention in adult survivors of OHCA (3, 4) and for 72 hours in neonates
90 after birth asphyxia (5). The International Liaison Committee on Resuscitation (ILCOR)
91 introduced guidance in April 2006 that TTM (32-34°C) may be: 1) *beneficial* for adolescents
92 who remain comatose following resuscitation from sudden, witnessed, ventricular fibrillation
93 OHCA and 2) *considered* for infants and children who remain comatose following
94 resuscitation from cardiac arrest (6). More recent adult studies confirm a role for 24 hours of
95 TTM but show that a higher temperature target (TTM 36°C) produces similar results to a
96 lower target (TTM 33°C) (7). The randomized control trials of Therapeutic Hypothermia
97 after Pediatric Cardiac Arrest (THAPCA studies) of OHCA (NCT00878644) and in-hospital
98 cardiac arrest (NCT00880087) investigating TTM at 33°C for 48 hours versus TTM at
99 36.7°C are on-going (8, 9).

100 Paediatric retrospective studies of TTM have been limited (10-12). Two studies showed no
101 difference in survival outcome with TTM (33-34°C) versus the institutions usual standard
102 temperature management (STM). The usual STM practice was to maintain normothermia by
103 avoiding hyperthermia (<38°C), but frequently did not involve using active temperature
104 control devices (4, 10). These studies included small numbers of OHCA patients and
105 contained very unbalanced groups with regards illness severity, with greater use of TTM (32-
106 34) in the more severe group. One recent study from Taiwan did show a statistically
107 significant increase in survival after 72 hours of TTM (33-34°C) (12). However, the OHCA

108 population was small and differences between healthcare systems may limit generalizability.
109 These studies identified that inadvertent overcooling ($<32^{\circ}\text{C}$) and hyperthermia ($>38^{\circ}\text{C}$)
110 increased the risk of worse outcome.

111 The ILCOR TTM ($32\text{-}34^{\circ}\text{C}$) guidance was adopted in our paediatric intensive care unit
112 (PICU) in 2007. TTM ($32\text{-}34^{\circ}\text{C}$) use has developed iteratively and culminated in the use of
113 servo-controlled temperature management devices and a standardized protocol. The aim of
114 this study was to assess evolution, safety and efficacy of TTM ($32\text{-}34^{\circ}\text{C}$) in a tertiary PICU
115 and compare to usual institutional standard temperature management (STM) (aiming to avoid
116 hyperthermia; $>38^{\circ}\text{C}$).

117 **PATIENTS AND METHODS**

118 The hospital research committee (Institutional Review Board) approved the study and waived
119 the need for consent given the observational nature of the study.

120 **Settings and participants**

121 This retrospective, single-centre, cohort study included infants and children admitted to the
122 PICU after OHCA between January 2004 and December 2010. Patients were included if aged
123 between at least one day and 16 years, admitted to PICU after an OHCA with return of
124 spontaneous circulation (ROSC). OHCA was defined as no cardiac output and pulseless for
125 greater than one minute as confirmed by a trained medical practitioner/paramedic prior to

126 arrival at an emergency department. Patients were identified via the Paediatric Intensive Care
127 Audit Network (PICANet) (13) and local admission databases.

128 **Data collection and assessment**

129 Case records were reviewed with data-verification at inputting and analysis stage. Patients
130 were divided into two groups, targeted temperature management (TTM 32-34°C) and
131 standard temperature management (STM). The use of TTM was defined *a priori* as
132 documented active TTM to maintain a core temperature between 32-34°C. STM group
133 included patients whose temperature was maintained at normothermia using rescue
134 temperature controlling measures to avoid hyperthermia (>38°C).

135 Data were collected on patient demographics, cardiac arrest resuscitation events, aetiology of
136 arrest, presence of chronic conditions and TTM dosing factors (start time, depth and duration
137 of hypothermia, and length of rewarming) using Utstein defined criteria where available (14).

138 Physiological variables were collected including; core temperature, heart rate, systolic blood
139 pressure, partial pressure of carbon dioxide (PaCO₂ measured at 37°C; alpha-stat

140 method(15)) in the blood, haematological and biochemical parameters. First, we compared
141 values up to four hours post PICU admission for TTM and STM groups to ascertain any
142 differences in risk of mortality. Secondly, the proportions with abnormal values or adverse
143 events within 72 hours of PICU admission were compared. Core temperatures were measured
144 as either rectal, oesophageal or bladder. Episodes of excessive hypothermia were defined as

145 temperature less than 32°C and hyperthermia greater than 38°C. Adverse events included:
146 seizures, bradycardia (<10th centile for age and sex)(16), hypotension (<5th centile for age and
147 sex)(17), use of critical care organ support and monitoring. The primary outcome was
148 survival at hospital discharge.

149 **Targeted temperature management**

150

151 In January 2007, following ILCOR guidance in April 2006, the PICU clinical team
152 considered TTM(32-34°C) for OHCA patients on a case by case basis. TTM (32-34°C) was
153 initiated in the PICU with the use of servo-controlled water blanket cooling mattresses
154 (Blanketroll II, Cincinnati Sub Zero, Ohio, USA) to reduce temperature between 32 to 34°C

155 for 24 hours followed by controlled rewarming, by 0.5°C every 2 hours, to 37°C.

156 Neuromuscular blocking drugs were used to prevent or treat shivering in conjunction with
157 intravenous sedation and analgesia (morphine and midazolam). Patients were invasively
158 ventilated with arterial blood gases monitoring. Standard 'neuroprotective' PaCO₂ target
159 range was 4.5 to 5.0kPa. Inotropes were used to maintain age appropriate blood pressure.
160 Intracranial pressure monitoring was not used in this population. Clinical neurological
161 assessment and additional neurological monitoring or imaging was performed if required;

162 however, appropriate, active withdrawal of intensive care occurred following established UK
163 guidelines which do not always require formal ancillary neurological assessment (18). Prior
164 to January 2007, and in patients after 2007 not receiving TTM (32-34°C), STM practice
165 followed recommendations to avoid hyperthermia (>38°C). Initial treatment included
166 paracetamol and surface cooling with ice packs, followed by servo-controlled water blanket
167 cooling mattresses (Blanketroll II) if unsuccessful.

168 **Statistical Analysis**

169 Descriptive data were reported as median and interquartile range (IQR) or mean \pm 95%
170 confidence interval of the mean for continuous variables and as frequencies and percentages
171 for categorical variables. Parametric continuous data were analysed using the unpaired
172 Student t-test and non-parametric continuous data with the Mann Whitney U test or Kruskal-
173 Wallis, as appropriate. Categorical data were analysed using the Fisher's exact tests. Chi
174 squared trend test was used for change over time. Two sided p values of <0.05 are reported
175 here. Data analyses were performed using either IBM-SPSS Statistics version 19.0 software
176 (SPSS Inc, Chicago, USA) or Minitab 16 (USA).

177

178 **RESULTS**

179

180 **Evolution**

181 Seventy three patients were included, 38 (52%) received TTM (32-34°C) and 35 (48%) STM
182 (<38°C). Prior to ILCOR guidance adoption in January 2007, TTM (32-34°C) was used
183 infrequently (4/25; 16%). Following adoption, TTM (32-34°C) use increased significantly
184 and was initiated in 34/48; 71% of patients (p <0.0001, Fig. 1).

185

186 There were no differences in age, sex or weight in patients receiving either treatment (table
187 1). TTM (32-34°C) was used more frequently in patients whose cause of arrest was unknown
188 and less in patients presenting with cardiac arrest associated with trauma (including traumatic
189 brain injury). Prevalence of OHCA occurring in the home or being witnessed was similar for
190 patients receiving TTM (32-34°C) and STM (<38°C) (table 2). However, patients receiving
191 TTM (32-34°C) had significantly more reported episodes of bystander CPR. Only six patients
192 presented in a shockable rhythm (ventricular fibrillation or ventricular tachycardia) and 5 out
193 of 6 received TTM (32-34°C). Total duration of CPR was not significantly different (40
194 minutes (TTM 32-34°C) versus 29 minutes (STM); $p=0.23$) as was median duration of CPR
195 in the emergency department (12 versus 13 minutes; $p=0.98$). A small proportion of cases
196 (3% (TTM) vs. 9% (STM); $p=0.24$) had ROSC prior to arrival at the emergency department.

197

198

199 **Safety**

200 Hyperthermia (>38°C) in the first 24 hours after PICU admission was significantly less
201 frequent in patients receiving TTM (32-34°C) (1/35; 3%) versus STM (12/32; 38%,
202 $p<0.001$) (Supplementary APPENDIX tables A1). However, hyperthermia episodes at any
203 point in the first 72 hours post admission were not significantly different (TTM (15/28; 39%)
204 versus STM (14/35; 50%)) ($p = 0.46$). Five (7%) patients in the study presented to the ED
205 with a temperature below 30°C, of these patients one received TTM (32-34°C) and four STM
206 (<38°C). Four patients who received TTM (32-34°C) and two who received STM (<38°C)
207 experienced severe hypothermia (temperature <32°C) *after* arrival to PICU. All eleven
208 patients, with a recorded temperature <32°C from ED admission to 24 hours post PICU
209 admission died prior to PICU discharge.

210

211 More patients receiving TTM (32-34°C) experienced bradycardia (<10th centile for age) (42%
212 versus 19%; p=0.04) and systolic blood pressure (BP) hypotension (<5th centile for age) (63%
213 versus 28%; p=0.004) within 72 hours of admission. No patients required treatment for
214 bradycardia. There was also no statistically significant difference in the proportion of patients
215 receiving inotropic support. (74% vs. 54%; p=0.08). Only one patient in the TTM (32-34°C)
216 group received extra corporeal life support (ECLS) for refractory cardiac arrest and
217 rewarming due to profound hypothermia on admission (admission core temperature 14°C).

218

219 Lactate, pH, glucose, insulin use, base deficit and the Paediatric Index of Mortality 2 (PIM2)
220 score results were similar between the two treatment groups at PICU admission
221 (Supplementary APPENDIX tables A2). Sixty four percent (41/64) had bilateral
222 unresponsive pupils on PICU admission with no differences noted between treatment groups.
223 Similar proportion of patients experienced episodes of seizures (8% versus 14%),
224 thrombocytopenia (36% versus 36%), hypernatremia (24% versus 25%), hypokalaemia (66%
225 versus 46%) and hypomagnesaemia (57% versus 38%) in TTM (32-34°C) and STM (<38°C)
226 groups. Nearly 50% of patients in both groups experienced hypocarbia (<4.0kPa).

227

228 No patients received renal replacement therapy. MRI and EEG investigations were more
229 common in the TTM (32-34°C) group, although a greater number of MRIs (71%; 17/24) and
230 EEGs (89%; 17/19) were performed after 2007.

231

232 **Efficacy**

233 Patients receiving TTM (32-34°C) were significantly colder during the 24 hours of TTM
234 therapy (Fig. 2). Median temperature at the start of TTM (32-34°C) was 35.0 (IQR [33.8 to
235 36.2])°C. Induction of temperature to target temperature took a median of 02:00

236 hours:minutes (IQR [0:00 to 03:15]). In those patients with a temperature $>35^{\circ}\text{C}$ at the start
237 of TTM ($32\text{-}34^{\circ}\text{C}$), induction of temperature to target temperature occurred at a median rate
238 of 0.91 (IQR [0.5 to 1.5]) $^{\circ}\text{C/hr}$. Four patients (11%) had overshoot hypothermia ($<32^{\circ}\text{C}$)
239 following induction. Median target temperature was 33.4°C and was maintained for a median
240 of 22:30 hours:minutes (IQR [16:37 to 24:44]). Rewarming occurred over a median of 10:30
241 hours:minutes (IQR [07:00 to 14:45]) at a rate of 0.3 (IQR [0.23 to 0.44]) $^{\circ}\text{C/hr}$. Three
242 patients receiving TTM ($32\text{-}34^{\circ}\text{C}$) died prior to rewarming.

243

244 Overall survival to hospital discharge of patients admitted to PICU after OHCA was 29%
245 (21/73) (Table 3). Survival was not significantly different between TTM ($32\text{-}34^{\circ}\text{C}$) and STM
246 ($<38^{\circ}\text{C}$) treatment groups (34% vs. 23%; $p=0.28$).

247 TTM ($32\text{-}34^{\circ}\text{C}$) patients stayed in PICU longer compared to STM ($<38^{\circ}\text{C}$) (Median 4.1 (IQR
248 [3.0 to 6.8] days vs. 1.3 (IQR [0.5 to 6.7]) days; $p < 0.001$). This difference was accounted for
249 by patients dying sooner in the STM ($<38^{\circ}\text{C}$) group compared with the TTM ($32\text{-}34^{\circ}\text{C}$)
250 group (Table 3). There were a similar proportion of patients in both groups who had
251 withdrawal of life sustaining intensive care support prior to death.

252

253

254

255

256 **DISCUSSION**

257

258 The aim of this study was to assess the evolution, efficacy and safety of TTM ($32\text{-}34^{\circ}\text{C}$) in
259 paediatric patients. TTM ($32\text{-}34^{\circ}\text{C}$) use was used frequently in post OHCA patients after the
260 2007 ILCOR guidance. Hospital survival rates were 11% higher in the TTM ($32\text{-}34^{\circ}\text{C}$) group

261 (34% v 23%; $p=0.284$) but did not reach statistical significance. The study included patients
262 over a seven year period; however, was underpowered to confirm this difference with
263 certainty. Overall the two groups were comparable across a range of known risk factors for
264 post cardiac arrest survival except bystander CPR and lower core temperature on PICU
265 admission (19). These results are similar to previous reported comparisons of TTM (32-34°C)
266 and usual institutional STM ($<38^{\circ}\text{C}$) in the paediatric population (10, 11). However, in these
267 studies in contrast to the current study, TTM (32-34°C) was used predominately in patients
268 with a higher predicted risk of mortality and included patients after in-hospital cardiac arrest.
269

270 This study confirms that TTM (32-34°C) is feasible in paediatric patients. TTM (32-34°C)
271 was successfully administered in 38 patients. Evidence suggests time to target temperature
272 should be as short as possible, whilst avoiding unintentional overshoot to temperature $<32^{\circ}\text{C}$
273 (20); however, rapid reduction in temperature has also been associated with worse
274 neurological injury (21). Unintentional overshoot in temperature to $<32^{\circ}\text{C}$ occurred in 11%
275 of patients, similar to the 15-17% rate in other retrospective studies (4, 10) but significantly
276 less than the 75% reported by Topjian et al (22). Increased mortality has been reported in
277 subgroups who are overcooled (6) although the causal association has not been established.
278 The use of servo-controlled cooling units, rather than manual temperature control (e.g. ice-
279 packs), may account for the reduction in unintentional overshoot.

280

281 Controlled rewarming and the avoidance of overshoot hyperthermia ($>38^{\circ}\text{C}$) are required to
282 prevent hemodynamic instability, rapid electrolyte changes and worsening of neurological
283 injury (23, 24). Patients were rewarmed at a median rate of $0.3^{\circ}\text{C}/\text{hour}$, but only 32% re-
284 warmed less than or equal to $0.25^{\circ}\text{C}/\text{hour}$ and of concern, 39% experienced hyperthermia.
285 The optimal rewarming rate after TTM (32-34°C) in humans has not been established with a

286 tendency to decrease rates over the last 10 years (25). Improvements to rewarming strategies
287 and prolonged active control of normothermia may be required to avoid rebound
288 hyperthermia as exposure to hyperthermia in the post-hypothermia phase has also been
289 associated with increased mortality and poor neurological outcome (26).

290

291 Reduction in core temperature in humans is known to be associated with a concomitant
292 reduction in heart rate in sedated patients (27). Bradycardia and hypotension is therefore a
293 consistent finding in studies of TTM (32-34°C), irrespective of underlying disease process
294 (10, 11, 27). Although bradycardia is believed to not require treatment, the management of
295 hypotension is more controversial. An increase in the proportion of patients with bradycardia
296 and hypotension in the TTM (32-34°C) group was observed. This was associated with
297 increased inotropic support though this did not reach significance. Recently, hypotension in
298 the 1st 6 hours after ROSC in children has been shown to be associated with higher in-
299 hospital mortality and worse neurological outcome (28). In the current study hypotension
300 episodes up to 72 hours after ROSC were included. It remains unclear whether the timing of
301 hypotension or the concomitant treatment is important in determining outcome. Certainly,
302 invasive, continuous monitoring of arterial blood pressure is recommended with TTM (32-
303 34°C).

304

305 A number of findings differed to previously published studies. Seizure frequency was low
306 (11%) with no difference between TTM (32-34°C) or STM (<38°C) groups. Abend et al
307 identified a higher rate of seizures (47%; 9/19) in a prospective study of therapeutic
308 hypothermia in paediatric cardiac arrest patients (29). Formal electroencephalography (EEG)
309 monitoring was performed in only 26% of our patients and may account for the lower rate.
310 Continuous EEG monitoring may allow improved identification and treatment in this

311 population (30, 31). Hypocarbia ($\text{PaCO}_2 < 4\text{kPa}$) occurred in nearly half of both TTM (32-
312 34°C) and STM ($< 38^\circ\text{C}$) patients in the first 24 hours of the study potentially exposing
313 patients to cerebral vasoconstriction and cerebral ischemia. Episodes of hypocarbia and/or
314 hypercarbia compared to normocarbia are associated with worse neurological outcome in
315 adult cardiac arrest survivors and should be avoided (32). Continuous end tidal CO_2
316 monitoring may therefore be beneficial.

317

318 TTM ($32\text{-}34^\circ\text{C}$) has changed the traditional timing of clinical, electrophysiological and
319 neuro-imaging investigation to predict outcome after hypoxic ischemic brain injury (33-36).
320 Delayed clearance of sedative drugs alters timing for neurological and brain death testing,
321 prolonging PICU length of stay (37). This effect was observed with a four-fold increase in
322 PICU length of stay for TTM ($32\text{-}34^\circ\text{C}$) patients who eventually died compared to STM non-
323 survivors. The inclusion of only OHCA patients may explain the comparative shorter length
324 of stay for STM patients (1.3 days) compared to Doherty et al (11) (9.0 days (IQR [5.0 to
325 22.3])) and Fink et al (10) (5 days (IQR [1 to 14])). A temporal trend of increasing time to
326 withdrawal of intensive care support and death along with an increased use of MRI and EEG
327 investigations was also noted. This may reflect a change in clinical practice when predicting
328 outcome with a delayed assessment and increased use of multi-modal methods of outcome
329 prediction occurring over time.

330

331 The prolonged duration of treatment associated with the TTM ($32\text{-}34^\circ\text{C}$) group may reflect
332 an optimistic view of paediatric intensivists for a good outcome following OHCA, influenced
333 in part by the positive findings of neonatal and adult TTM ($32\text{-}34^\circ\text{C}$) trials (3-5, 7). Twenty
334 four hours of TTM ($32\text{-}34^\circ\text{C}$) followed by 12-16 hours rewarming enables a period of active
335 PICU treatment, correction and titration of physiology variables and a delay to neurological

336 prognosis. This positive approach after OHCA contrasts the historic views of poor outcome
337 despite PICU management and may have positively effected patient outcome.

338

339 Neonatal studies after birth asphyxia have supported the recommendations of TTM (33°C)
340 for 72 hours (5). These study populations were carefully selected with a homogenous
341 pathology and severity assessed by predefined stratification criteria. However, the paediatric
342 OHCA population is heterogenous; variable aetiologies, co-morbidities and resuscitation
343 factors limit the ability to extrapolate the neonatal findings to paediatric OHCA.

344

345 This study has the following limitations. 1) This is a single centre study and is still relatively
346 small despite a seven year data collection period. 2) Data from a single centre may limit the
347 general applicability of the overall findings to other centres. 3) Owing to the retrospective
348 nature of this study we were unable to separate patients in the STM (<38°C) group who had
349 reactive hyperthermia (>38°C) treatment only and those initiated on an active normothermia
350 targeted temperature management. 4) Changes in clinical management of OHCA may have
351 changed over the study period. It was identified that the use of TTM (32-34°C), neuro-
352 imaging and neuro-electrophysiological monitoring increased in the second half of the study
353 and there may have been other confounding factors (e.g. new resuscitation guidelines in
354 2005) not identified. 5) The use of TTM (32-34°C) was not randomized with the potential for
355 case selection bias. 6) The primary outcome was hospital survival as neurological outcome
356 data was not available, but should be collected in future studies.

357

358 **CONCLUSION**

359 This study assessed the evolution, safety and efficacy of TTM (32-34°C) compared with
360 STM (<38°C) after OHCA. TTM (32-34°C) use increased significantly after ILCOR 2007

361 guidance. TTM (32-34°C) was effectively administered in the paediatric population but
362 resulted in bradycardia and hypotension. It did not significantly increase survival to hospital
363 discharge but increased PICU length of stay. Avoidance of excess hypothermia (<32°C) is
364 recommended. Further studies are required to demonstrate whether TTM (32-34°C) is cost-
365 effective, and improves the proportion of patients with good neurological survival after
366 OHCA.

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373

374

374 **TABLES & FIGURES**

375

376 **Table 1** Demographics and relationship to treatment groups

377

378 **Table 2** Cardiac arrest resuscitation factors, PICU interventions and relationship to treatment
379 groups

380 **Table 3** Survival outcomes in relationship to treatment groups

381

382 **FIGURES**

383

384 **Figure 1** Percentage of patients receiving targeted temperature management (TTM) and
385 standard temperature therapy (STM)

386 Dashed red line indicates first publication date of ILCOR guidelines for paediatric TTM use:
387 Published on-line April 17th 2006 - "Induction of hypothermia (32 to 34°C) for 12 to 24
388 hours should be considered in children who remain comatose after resuscitation from cardiac
389 arrest." (38)

390

391 **Figure 2** Temperature profiles of patients receiving targeted temperature management and
392 standard temperature therapy.

393 Mean temperature (with 95% confidence intervals for the mean). TTM: targeted temperature
394 management. STM: Standard temperature management.

395

396

397 **SUPPLEMENTARY APPENDIX**

398 **Table A1** Adverse events within 72 hours of admission

399 **Table A2** Physiological variables available between ROSC to four hours after PICU

400 admission and relationship to treatment groups

401

Accepted Manuscript

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489

490

491

491 Table 1 Demographics and relationship to treatment groups

	Total Group n = 73	TTM n=38	STM n = 35	p
Age (years)	1.0 (0-5.0)	1.5 (0-5.8)	1.0 (0-4.0)	0.74
Weight (kg)	8 (4-15)	10 (6-20)	6 (4-12)	0.06
Age category (Utstein ^a)				0.57
1-30 days	7 (10%)	5 (13%)	2 (6%)	
31 days to < 1 yr	23 (32%)	10 (26%)	13 (38%)	
1yr to < 4yrs	21 (29%)	11 (29%)	10 (29%)	
4yrs to < 12yrs	9 (13)	4 (11%)	5 (15%)	
12yrs to < 16yrs	12 (17%)	8 (21%)	4 (12%)	
Male	25 (34%)	17 (45%)	8 (23%)	0.08
Any Chronic Condition	33 (45%)	15 (39%)	18 (51%)	0.30
Neurological	17 (23%)	9 (24%)	8 (23%)	0.93
Respiratory	13 (18%)	7 (18%)	6 (17%)	0.89
Cardiac	4 (5%)	1 (3%)	3 (9%)	0.27
Prematurity	3 (4%)	1(3%)	2 (6%)	0.60
Metabolic	4 (5%)	2 (4%)	2 (3%)	0.71
Gastrointestinal	1 (1%)	1 (3%)	0	1.00
Renal	1 (1%)	0	1 (3%)	1.00
Transported from different admitting hospital	37 (51%)	21 (55%)	16 (47%)	0.49
Etiology of arrest				
Not Known	12 (16%)	9 (23%)	3 (9%)	0.12
Pulmonary	16 (22%)	9 (24%)	7 (20%)	0.78
Cardiac	5 (7%)	4 (11%)	1 (3%)	0.19
Trauma (including traumatic brain injury)	11 (14%)	3 (8%)	8 (23%)	0.10
Drowning/Submersion	6 (8%)	3 (7%)	3 (9%)	1.00
Neurological (non-trauma)	7 (10%)	2 (5%)	5 (14%)	0.25
Sepsis	5 (7%)	2 (5%)	3 (9%)	0.67
Strangulation	3 (4%)	2 (5%)	1 (3%)	1.00
Sudden infant death syndrome	2 (3%)	0	2 (5%)	0.23
Other	6 (8%)	4 (11%)	2 (6%)	0.68

492 ^a Utstein pre-defined age groups with modified upper age limit to less than 16 years (13)(14). Results expressed
493 as Median (Inter-quartile range) or number (percent). Allocation to multiple chronic conditions was permitted.
494 Fisher's exact test was used for categorical variable and Mann Whitney U test for continuous variables.

495

495

496 Table 2 Cardiac arrest resuscitation factors, PICU interventions and relationship to treatment groups

Cardiac arrest resuscitation events	Total Group n=73	TTM n=38	STM n= 35	p
Location own home (versus public place or other)	45 (68%)	23 (70%)	22 (67%)	0.79
Witnessed arrest	45 (65%)	23 (62%)	22 (69%)	0.57
Bystander CPR	45 (65%)	30 (81%)	15 (47%)	0.003
VF/VT ^a (vs. PEA/bradycardia/asystole)	6 (9%)	5 (14%)	1 (3%)	0.20
Pulseless electrical activity (PEA)	10 (15%)	6 (17%)	4 (13%)	
Bradycardia	7 (6%)	2 (16%)	5 (11%)	
Asystole	43 (65%)	22 (63%)	21 (67%)	
Ventricular fibrillation (VF)	5 (8%)	5 (14%)	0 (0)	
Pulseless Ventricular tachycardia (VT)	1 (2%)	0 (0)	1 (3%)	
Defibrillation attempted	10 (14%)	7 (18%)	3 (10%)	0.28
Epinephrine doses during resuscitation ^b	3 (1-4)	3 (1-4)	3 (1-4)	0.83
No epinephrine given during resuscitation	6 (9%)	2 (5%)	4 (13%)	0.40
Time duration from cardiac arrest onset to ROSC (mins)	38 (24-49)	40 (26-56)	29 (21-46)	0.23
ROSC prior to ED admission	8 (6%)	2 (3%)	6 (9%)	0.24
Time from ED admission to ROSC (mins) ^c	12 (5-19)	12 (4-20)	13 (8-18)	0.98
Time duration from ROSC to PICU admission (hrs:mins)	02:57 (01:13-04:34)	02:50 (01:24-04:51)	03:20 (00:50-04:29)	0.67
PICU interventions				
Mechanical ventilation	73 (100%)	38 (100%)	35 (100%)	1.00
Inotropes after resuscitation	47 (64%)	28 (74%)	19 (54%)	0.08
Two or more inotropes	11 (15%)	8 (21%)	3 (9%)	0.19
HFOV	2 (3%)	2 (3%)	2 (3%)	1.00
ECMO	1 (1%)	1 (3%)	0	1.00
Renal replacement therapy	0	0	0	
Insulin therapy	19 (26%)	13 (34%)	6 (17%)	0.10
Neuromuscular blockade after PICU admission	31 (42%)	16 (42%)	15 (43%)	0.95
Anti-seizure therapy	10 (14%)	6 (16%)	4 (11%)	0.74

497 CPR denotes cardiopulmonary resuscitation. ROSC denotes return of spontaneous circulation. ED: emergency
498 department, PICU Paediatric intensive care unit. ^aFirst recorded rhythm after cardiac arrest. VF: ventricular
499 fibrillation, VT: ventricular tachycardia, PEA: pulseless electrical activity. Unavailable (missing) values were
500 excluded from calculations of summary statistics. Data was missing for location (7), witnessed status (4),
501 Bystander (4), presenting electrical rhythm (7), Defibrillation attempt (6), Epinephrine dose (4), duration from
502 cardiac arrest (5), ROSC prior to Ed admission (4), Time from ED admission (4), time duration ROSC to PICU (5).
503 Results expressed as Median (Inter-quartile range) or number (percent). Chi² test or Fishers exact test was
504 used for categorical variable. ^b median value rounded up to nearest whole value. ^c Only patients receiving CPR
505 at ED admission were included in calculation, Fishers exact test was used for categorical variable and Mann
506 Whitney U test for continuous variables. ** p value < 0.05 comparing treatment groups
507
508

508 Table 3 Survival outcomes in relationship to treatment groups

	Total Group n = 73	TTM n=38	STM n = 35	p
Outcome				
Survival to PICU discharge	22 (30%)	14 (37%)	8 (23%)	0.19
Survival to Hospital discharge	21 (29%)	13 (34%)	8 (23%)	0.28
PICU Length of stay (LOS) (days)	3.1 (1.3-6.6)	4.1 (3.0-6.8)	1.3 (0.5-6.7)	<0.001
PICU LOS for survivors (days)	6.5 (2.9-7.6)	6.2 (3.0-7.8)	6.7 (0.9-8.1)	0.81
PICU LOS for non-survivors (days)	2.4 (0.8-4.7)	4.1 (2.6-5.2)	1.2 (0.4-2.4)	<0.001
Withdrawal of intensive care support (proportion of patients who died in PICU [n=51])	46 (90%)	24 (100%)	22 (81%)	0.31
Fulfilled brain death criteria (proportion of patients who died in PICU [n=51])	9 (18)	5 (21%)	4 (15%)	0.73

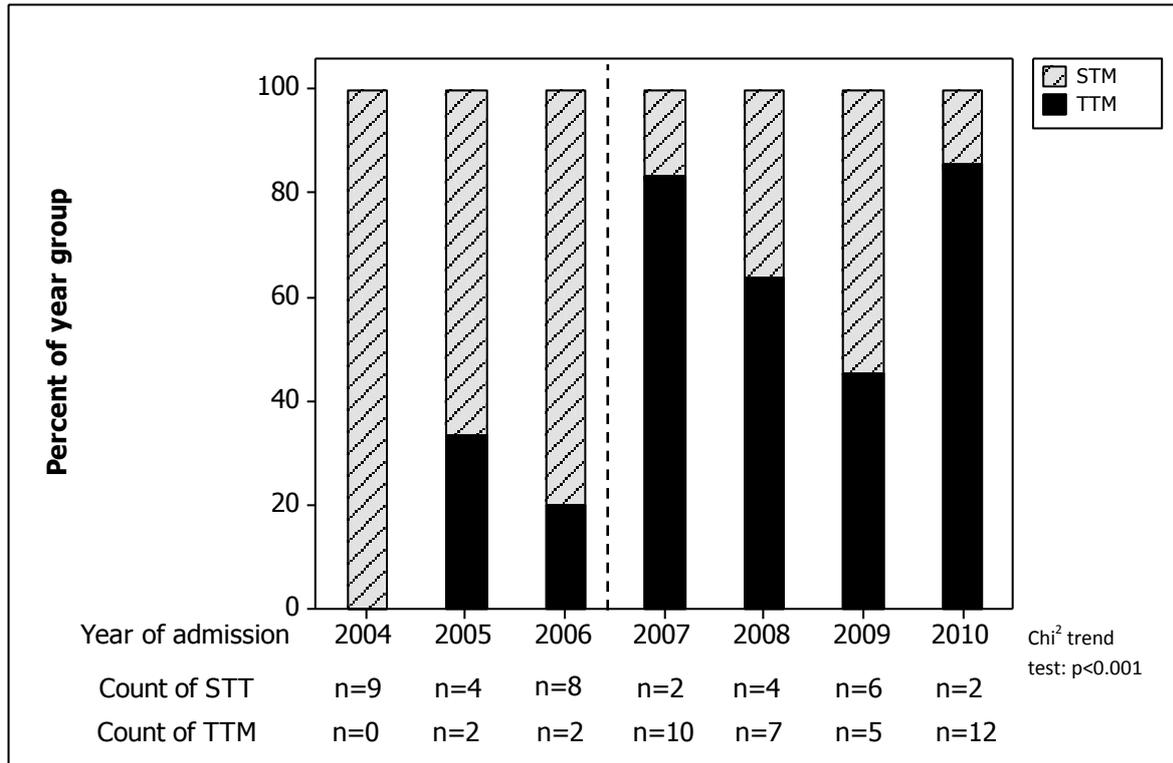
509 Results expressed as Median (Inter-quartile range) or number (percent). LOS: length of stay. Fisher's exact test
 510 was used for categorical variable and Mann Whitney U test for continuous variables.

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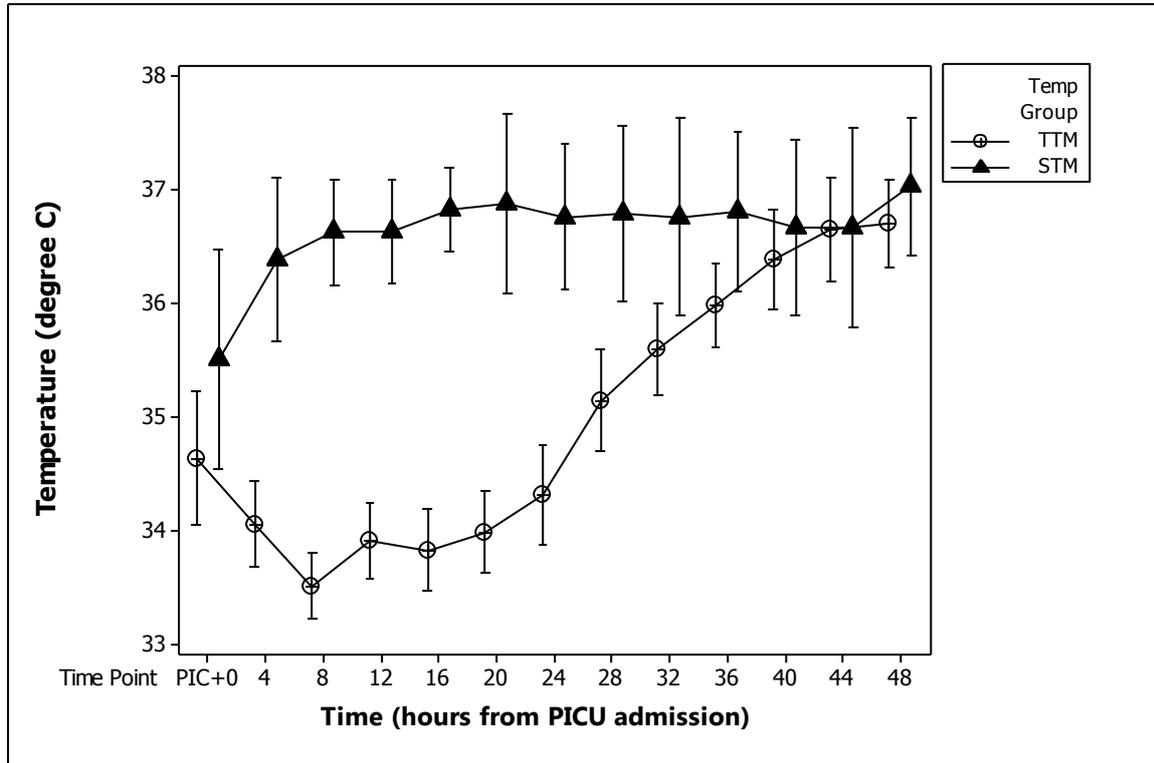
513

Figure 1 Percentage of patients receiving targeted temperature management (TTM) and standard temperature management (STM)



Dashed line indicates first publication date of ILCOR guidelines for paediatric TTM use: Published on-line April 17th 2006 - "Induction of hypothermia (32 to 34°C) for 12 to 24 hours should be considered in children who remain comatose after resuscitation from cardiac arrest." (37)

Figure 2 Temperature profiles of patients receiving targeted temperature management and standard temperature management.



Mean temperature (with 95% confidence intervals for the mean). TTM: targeted temperature management (32-34°C). STM: Standard temperature management (<38°C).