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The influence of prolonged temperature management on acute kidney injury after out-of-hospital cardiac arrest

A post-hoc analysis of the TTH48 trial

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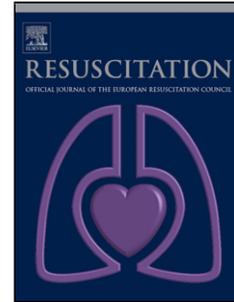
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The influence of prolonged temperature management on acute kidney injury after out-of-hospital cardiac arrest: A post-hoc analysis of the TTH48 trial

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1 **The influence of prolonged temperature management on acute**
2 **kidney injury after out-of-hospital cardiac arrest: A post-hoc**
3 **analysis of the TTH48 trial**

4
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45 Abstract

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47 Background

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49 Acute kidney injury (AKI) is common after cardiac arrest and targeted temperature
50 management (TTM). The impact of different lengths of cooling on the development of AKI
51 has not been well studied. In this study of patients included in a randomised controlled trial of
52 TTM at 33°C for 24 versus 48 hours after cardiac arrest (TTH48 trial), we examined the
53 influence of prolonged TTM on AKI and the incidence and factors associated with the
54 development of AKI. We also examined the impact of AKI on survival.

55

56 Methods

57

58 This study was a sub-study of the TTH48 trial, which included patients cooled to $33\pm 1^\circ\text{C}$ after
59 out-of-hospital cardiac arrest for 24 versus 48 hours. AKI was classified according to the
60 KDIGO AKI criteria based on serum creatinine and urine output collected until ICU discharge
61 for a maximum of seven days. Survival was followed for up to six months. The association of
62 admission factors on AKI was analysed with multivariate analysis and the association of AKI
63 on mortality was analysed with Cox regression using the time to AKI as a time-dependent
64 covariate.

65

66 Results

67

68 Of the 349 patients included in the study, 159 (45.5%) developed AKI. There was no
69 significant difference in the incidence, severity or time to AKI between the 24- and 48-hour
70 groups. Serum creatinine values had significantly different trajectories for the two groups with
71 a sharp rise occurring during rewarming. Age, time to return of spontaneous circulation,
72 serum creatinine at admission and body mass index were independent predictors of AKI.
73 Patients with AKI had a higher mortality than patients without AKI (hospital mortality 36.5%
74 vs 12.5%, $p<0.001$), but only AKI stages 2 and 3 were independently associated with
75 mortality.

76

77

78 Conclusions

79

80 We did not find any association between prolonged TTM at 33°C and the risk of AKI during
81 the first seven days in the ICU. AKI is prevalent after cardiac arrest and TTM and occurs in
82 almost half of all ICU admitted patients and more commonly in the elderly, with an increasing
83 BMI and longer arrest duration. AKI after cardiac arrest is an independent predictor of time to
84 death.

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86

87 **Keywords**

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89 Cardiac arrest, Acute kidney injury, Targeted temperature management, Therapeutic
90 hypothermia

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94 **Trial registration**95 NCT01689077. Registered on www.ClinicalTrials.gov 20 September, 2012 (main trial).

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Background

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111 Acute kidney injury (AKI) is a well-known complication in post-cardiac arrest patients [1].

112 Recent studies have found an incidence of AKI of more than 40% when modern staging of

113 AKI was used and targeted temperature management (TTM) implemented as standard post-

114 resuscitation care [1, 2]. The development of renal dysfunction in this setting is most likely

115 due to local and whole body ischemia and reperfusion injury as well as circulatory failure in

116 the post-resuscitation period [3]. This post-cardiac arrest syndrome is characterised by

117 immunological, inflammatory and coagulation disturbances leading to perfusion disturbances

118 and organ dysfunction. Although prognosis after successful resuscitation is mainly linked to

119 the presence of hypoxic-ischemic brain injury, extra-cerebral organ dysfunction in the

120 immediate post-resuscitation period has been shown to have prognostic implications [4].

121 Baseline renal insufficiency and post-resuscitative AKI have both been recognised as
122 independent predictors of mortality and poor neurological outcome. The direct effect of AKI
123 on the central nervous system has not been fully elucidated, but increased inflammation and
124 oxidative stress in the brain have also been shown in experimental models of AKI [5].

125 Hypothermia preceding ischemia has an established role in organ protection, but the
126 impact of post-cardiac arrest TTM on renal outcomes is less clear. A meta-analysis of 19 trials
127 of TTM after cardiac arrest, brain injury or major cardiac surgery did not show a reduction in
128 AKI when TTM was performed [6]. Even if TTM has the potential for renal protection
129 through mechanisms such as the reduction of metabolic demand, oxidative stress and
130 apoptosis, some potentially disadvantageous effects of TTM are present. A frequent
131 observation is ‘cold diuresis’, which most likely occurs due to a combination of increased
132 venous return, hormonal changes and tubular dysfunction and may cause hypovolemia if
133 volume replacement is insufficient.

134 The potential modulating effect of various approaches to TTM on renal function has
135 not been well studied. In particular, the impact of the length of cooling on renal function has
136 not been addressed. In this study, we investigated the impact of 24 or 48 hours of TTM on the
137 incidence of AKI in patients suffering from out-of-hospital cardiac arrest (OHCA).
138 Secondly, we studied factors associated with the development of AKI and the impact of
139 AKI on survival using the KDIGO AKI classification as a time-dependent variable [7].

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142

143 **Methods**

144

145 *Study design*

146

147 The study is a preplanned explorative analysis of AKI in patients included in a multinational
148 randomised, controlled trial on the effect of 48 compared to 24 hours of TTM after OHCA of
149 a presumed cardiac origin (TTH48) . The details of the TTH48 study including inclusion and
150 exclusion criteria have previously been published elsewhere [8, 9]. In brief, TTM for 24
151 versus 48 hours with a target of $33\pm 1^{\circ}\text{C}$ was performed from hospital arrival as per local
152 protocol, utilising cold fluids, surface cooling and intravascular cooling devices.

153 Randomisation was performed during the first 24 hours of cooling.

154 The study was approved by the ethics committee in each participating centre or country. The
155 study was conducted according to the requirements of the Declaration of Helsinki; written
156 informed consent was obtained from the next of kin or a legal surrogate before randomisation
157 and from each patient who regained mental capacity, according to local ethical approval.

158

159 *Interventions*

160

161 Hypothermia at $33\pm 1^{\circ}\text{C}$ was maintained for either 24 or 48 hours according to randomisation
162 and rewarming performed at a maximum of 0.5°C/h . A urinary catheter with a thermistor
163 measured bladder temperature and provided feedback to the temperature management
164 systems. Sedation was maintained with propofol/midazolam and remifentanyl/fentanyl
165 infusions. Shivering was treated with increased sedation or cisatracurium. Noradrenaline was
166 the vasopressor of choice during hypothermia.

167

168 *Data*

169

170 From February 2013 to June 2016, 355 patients were randomised and included in the trial.
171 Study population characteristics included sex, age, body mass index (BMI) and previous
172 medical history as well as prehospital data followed the Utstein template recommendation.
173 Pre-ICU in-hospital data included data from admission to the emergency department and from
174 cardiac catheterisation laboratories. Data on serum creatinine (sCr), serum urea (sUr), urinary
175 output (UO) and the need for renal replacement therapy (RRT) were prospectively collected
176 for seven days or until ICU discharge, depending on which occurred first. Follow-up for
177 survival was a minimum of 180 days. Data were managed using REDCap electronic data
178 capture tools.

179

180

181 *AKI classification*

182

183 Due to the lack of hourly UO, we used a modified KDIGO AKI classification based on sCr
184 and daily UO averaged over 24 hours[2]. We estimated the baseline sCr using the MDRD
185 equation assuming a glomerular filtration rate (eGFR) of 75 for all patients [10]. The different
186 stages of AKI were defined as follows: Stage 1: A 1.5- to 1.9-fold increase in sCr compared to
187 the estimated baseline sCr or an absolute increase of more than $26.5\ \mu\text{mol/l}$ within 48 hours.

188 Stage 2: A 2.0- to 2.9-fold increase in sCr compared to the estimated baseline sCr or a UO of
189 less than 0.5 ml/kg/hour for the last 24 hours. Stage 3: A threefold increase in sCr compared
190 to the estimated baseline sCr, an increase in sCr to more than 353.6 $\mu\text{mol/l}$, a UO of less than
191 0.3 ml/kg/hour for the last 24 hours or the initiation of RRT.

192

193

194 *Statistical analysis*

195

196 Categorical variables were expressed as counts (percentages) and continuous variables as
197 means \pm SD or medians (IQR). Admission factors were compared using Student's t-test, chi-
198 square test and Fischer exact test as appropriate. Factors with a p-value < 0.1 in the univariate
199 analysis were included in the multivariate analysis. The difference in the time to AKI between
200 patients in the 24- and 48-hour cooling groups was assessed using the log-rank test. Cox
201 regression analysis was performed to assess independent predictors of the time to AKI.
202 Independent predictors of mortality at six months were performed using Cox regression
203 analysis with the time to AKI as a time-dependent covariate. The impact of the cooling length
204 on sCr levels was assessed using a mixed linear model. Statistical analysis was performed
205 with SPSS for Windows v.24.0 (IBM Corp., Armonk, NY) and SAS v. 9.4. (SAS Institute
206 Inc., Cary, NC).

207

208 **Results**

209

210 *Included patients and the incidence of AKI*

211

212 A total of 355 patients were randomised in the trial. Two patients withdrew consent, one
213 patient was lost to follow-up and one was incorrectly randomised. Of the 351 patients who
214 completed the trial, two were excluded due to chronic dialysis, leaving 349 patients for AKI
215 analysis (Fig. 1); 159 patients (45.5%) were classified as having AKI during their ICU stay
216 (KDIGO AKI 1-3), and 24 patients (6.9%) received RRT. Of the 159 patients who developed
217 AKI, 79 (49.7%) did not have AKI at ICU discharge or day 7 in the ICU.

218

219 *Difference between 48- and 24-hour cooling*

220

221 The duration of hypothermia did not affect the incidence or severity of AKI. Seventy-eight
222 (44.3%) patients in the 24-hour cooling group developed AKI versus 81 (46.8%) in the 48-
223 hour cooling group, ($p=0.639$). In addition, there was no difference in the time to AKI in
224 patients treated with 48 compared to 24 hours of cooling in either univariate (HR 0.97, 95%
225 CI 0.71-1.32, $p=0.85$) or multivariate analysis (HR 1.02 95% CI 0.74-1.41, $p=0.89$).

226

227 Among the patients with AKI, there was no significant difference in the severity of AKI (2.0
228 vs 2.2, $p=0.13$) or the time to development of AKI between the two groups. The time to AKI
229 was 1.5 (1.3–1.7) days in the 24-hour cooling group and 1.8 (1.5–2.1) days in the 48-hour
230 cooling group ($p=0.66$). The cumulative number of AKI is shown in Fig. 2. The length of
231 cooling had a significant impact on the development of sCr values during the observation
232 period ($p<0.05$) (Fig 3). Data on the sCr, sUr, daily UO and fluid balance for the first 72 hours
233 of the ICU stay are provided in Supplemental Table 1.

234

235 *Admission factors for AKI*

236 There were several differences in patient characteristics, factors at resuscitation and admission
237 between the patients that developed AKI compared to those who did not develop AKI.

238 Notably, AKI patients were older, had a higher BMI, more commonly had diabetes and had a
239 higher sCr level at ICU admission (Table 1). Regarding factors at resuscitation, patients who
240 developed AKI had a longer time to return of spontaneous circulation (ROSC) and more
241 commonly received both adrenaline and amiodarone (Table 1). In a multivariate analysis of
242 risk factors at ICU admission for the development of AKI, we found age, BMI, sCr at ICU
243 admission and time to ROSC to be independent predictors of AKI (Table 2).

244

245 *Association between AKI and outcome*

246

247 Patients who developed AKI had a higher ICU- (25.2% vs 7.9%, $p<0.001$), hospital- (36.5%
248 vs 12.5%, $p<0.001$) and six-month mortality (45.9% vs 16.8%, $p<0.001$), than those who did
249 not develop AKI. Survival curves are provided in Supplemental Figure 1. In a Cox regression
250 model including KDIGO AKI as a time-dependent covariate, AKI was a significant predictor
251 of mortality. However, patients with KDIGO AKI 1 did not have significantly greater risk
252 than patients without kidney injury (Table 3). Other significant predictors of mortality were
253 age, time to ROSC and non-shockable rhythm.

254 Patients with AKI also had a longer ICU but not hospital stay compared to patients without
255 AKI. Patients with AKI were also treated longer with mechanical ventilation (Table 4).

256

257

258

259

260 **Discussion**

261

262 In this study of 349 patients from the TTH-48 randomised controlled trial with data
263 collection of creatinine levels and UO over the first seven days, we found that AKI was
264 common after cardiac arrest and associated with a higher age, a higher BMI and a longer time
265 to ROSC.

266 We did not find a significant effect of the length of cooling after cardiac arrest on AKI
267 evaluated by the KDIGO AKI criteria. The lack of effect is supported by existing evidence
268 from human clinical trials on the effect of hypothermia on kidney function [2], even though
269 the nephroprotective effects of pre-ischemic, locally applied hypothermia are well established
270 [11, 12]. Compared to isolated renal hypothermia, the physiological and biochemical effects
271 of systemic hypothermia on renal function are more complex, and increased systemic
272 vasoconstriction and volume depletion may reduce renal blood flow in a way that offsets the
273 positive effects of hypothermia on metabolic demand and oxygen consumption. Even if there
274 is equipoise on the effects of TTM on renal function after cardiac arrest, there is some
275 evidence that it may be influenced by how TTM is performed. A recent observational trial
276 found that prolonging the rewarming phase from 33 to 36 C to over 600 minutes resulted in
277 less AKI and a lower release of the pro-inflammatory cytokine uIL-18, which is an early
278 biomarker of AKI [13]. We found a significant difference in sCr trajectories for the two
279 groups. After 24 hours of TTM (Day 1), there was sharp increase in sCr in the 24-hour
280 cooling group during the rewarming phase. A similar increase in sCr was observed between
281 days 2 and 3 during the rewarming phase of the 48-hour cooling group, suggesting that the
282 reduced sCr observed during TTM is temporary and is reversed as patients become
283 normothermic. The cause of the reduced sCr frequently observed during TTM is not clear,
284 although a temporary reduction in creatinine production has been proposed [14]. Fluid
285 administration may also dilute sCr, but the sharp increases in sCr during the rewarming phase
286 were found despite daily positive fluid balances in both groups.

287

288 In our study, 45.5% of the patients developed AKI. Incidences of AKI 1–3 in recent
289 studies of OHCA patients admitted to the ICU ranges from 39 to 53% [1]. Although the
290 KDIGO AKI definitions are now almost universally accepted, there are still variations in how
291 AKI is defined since data on hourly UO are lacking in many studies including ours, leading to
292 a potential underreporting of actual AKI when UO is omitted [15]. In the present study, we
293 modified the UO criteria to be able to include daily UO and thereby increase the sensitivity of
294 our AKI staging. In contrast to several earlier studies, we did not exclude patients who died
295 within the first 48 hours, but in this period only five patients died, of which three developed
296 AKI. RRT was uncommon in our study, as it was only used in 6.9% of the patients. This is
297 low compared to the numbers reported in a 2016 systematic review where RRT utilisation
298 ranged from 18 to 60% in seven studies on general cardiac arrest patients [1]. However, in
299 two recent studies from Nordic countries, where most of the patients in our trial were
300 recruited, the use of RRT was between 6 and 9% [16, 17]. Several factors, such as decisions
301 to withhold RRT due to futility, local treatment preferences and the lack of consensus on RRT
302 initiation criteria, are likely to have an impact on the prevalence of RRT utilisation [18]. It is
303 worth noting that future studies might be influenced by the recent shift in evidence towards a
304 more conservative approach in RRT initiation [19].

305 Studies on risk factors of AKI after cardiac arrest have identified age, rhythm, time to
306 ROSC and higher doses of epinephrine as independent prognostic factors in the development
307 of AKI [1, 20, 21]. In our study, we also found BMI to have significant effect, which is in
308 accordance with several other studies that have identified obesity as an independent factor for
309 AKI in critically ill and post-operative patients [22, 23]. The pathophysiology behind obesity
310 related AKI still being explored. However, as obesity can be regarded as a state of low-grade
311 inflammation, pro-inflammatory cytokines and adipokines as well as endothelial dysfunction
312 may be involved. In addition, the direct physiological effects of overweight may include intra-
313 abdominal hypertension and cardiac dysfunction that might alter renal perfusion [24].

314 As in previous studies, we found AKI to have a negative impact on survival, although
315 this did not reach statistical significance in the group with AKI class 1 in the Cox regression
316 analysis. It is still unclear whether the presence of AKI either has an independent effect on
317 prognosis after cardiac arrest or this is due to unmeasured confounders [25]. Prolonged
318 hypoperfusion and subsequent reperfusion injury does cause organ injury, but even after
319 adjusting for classical markers of peri-arrest hypoperfusion, such as non-shockable rhythm,
320 prolonged resuscitation and lack of bystander CPR, AKI was still a strong predictor of short-

321 and long-term mortality. Post-resuscitation shock has been shown to be a strong predictor of
322 the development of AKI and mortality [21, 26, 27], but the present study does not include data
323 on the hemodynamic stability of the patients during the ICU stay, as we only considered
324 factors present on admission in our analysis.

325

326 *Strengths and limitations*

327 The multicentre design and data collection of creatinine and UO for up to seven days
328 within the context of a randomised controlled trial is a major strength of our study and
329 increases the validity of our findings. Nonetheless, several limitations are worth mentioning.
330 Since we did not have access to hourly UO data, using the original KDIGO AKI urine output
331 criteria was not possible. It may be that our ability to include UO criteria only in AKI classes
332 2 and 3 may have led to an underestimation of the number of patients in the AKI class 1
333 group, as this group was relatively small compared to another study where hourly urine data
334 were available [17].

335 We did not have preadmission creatinine available and estimated our baseline creatinine using
336 the MDRD equation as proposed by the KDIGO AKI guideline[7]. Since we did not have data
337 on chronic kidney disease (CKD) except chronic dialysis in our study, this may have led to an
338 overestimation of AKI. In a recent study of OHCA patients, 4% of the patients had previously
339 known CKD [17]. The question of whether to use admission creatinine or estimated creatinine
340 as a baseline has not been resolved, and studies have shown that up to 50% are misclassified
341 with both approaches [28]. However, in their study of cardiac arrest patients, Geri et al.
342 performed a sensitivity analysis of admission creatinine versus estimated creatinine and found
343 similar results [20]. In our study, admission creatinine was missing in a large number of
344 patients and in patients who did have an admission creatinine available, we saw a significant
345 increase to the first creatinine available in the ICU, leading us to conclude that the latter was
346 not a reasonable substitute for pre-morbid or admission creatinine. The validity of our
347 findings was strengthened by an analysis of the 144 patients who did have sCr available
348 before ICU admission. In this analysis, provided in Supplemental Table 2, there were only
349 small differences in AKI classifications based on admission sCr compared to the classification
350 based on estimated sCr. The patients cooled for 24 hours had a shorter length of stay than
351 those cooled for 48 hours. Since we did not collect creatinine or urinary data after ICU
352 discharge, it is possible that this could have influenced our results. However, it is likely that
353 only the most stable ICU patients were discharged early from the ICU.

354

355 **Conclusions**

356

357 We did not find any association between prolonged TTM at 33°C and the risk of AKI during
358 the first seven days in the ICU. AKI is prevalent after cardiac arrest and TTM and occurs in
359 almost half of all ICU admitted patients and more commonly in the elderly, with an increasing
360 BMI and longer arrest duration. AKI after cardiac arrest is an independent predictor of time to
361 death.

362

363 **List of abbreviations**

364 AKI: acute kidney injury, BMI: body mass index, CKD: chronic kidney disease, GFR:
365 glomerular filtration ratio, KDIGO: kidney disease improving global outcome, OHCA: out-
366 of-hospital cardiac arrest, ROSC: return of spontaneous circulation, RRT: renal replacement
367 therapy, sCr: serum creatinine, sUr: serum uread, TTM: targeted temperature management,
368 UO: urine output

369

370 **Declarations**

371

372 *Ethics approval and consent to participate:*

373 The study was approved by the ethics committee in each participating centre or country. The
374 study was conducted according to the requirements of the Declaration of Helsinki; written
375 informed consent was obtained from the next of kin or a legal surrogate before randomisation
376 and from each patient who regained mental capacity, according to local ethical approval.

377

378 *Consent for publication*

379 Not applicable

380

381 *Availability of data and materials*

382 The dataset used during the current study is available from the corresponding author upon
383 reasonable request.

384

385 *Competing interests*

386 MBS reports having received a research grant from GE Healthcare, travel reimbursements and
387 lecture fees from BARD Medical. CS reports having received travel reimbursements and

388 speaker fees from BD BARD and Zoll GmbH, as well as honorarium for consultancy from
389 BD BARD, Benechill and Sedana Medical. AMG and ANJ report having received lecture fees
390 from Novartis. All other authors report that they have no conflicts of interest.

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398

399 *Authors' contributions*

400 KS, HK and MBS planned the post-hoc study. KS and MBS provided the statistical analysis
401 and interpreted the data of the study. All authors contributed in writing the manuscript. All
402 authors read and approved the final manuscript.

403

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417 **References**

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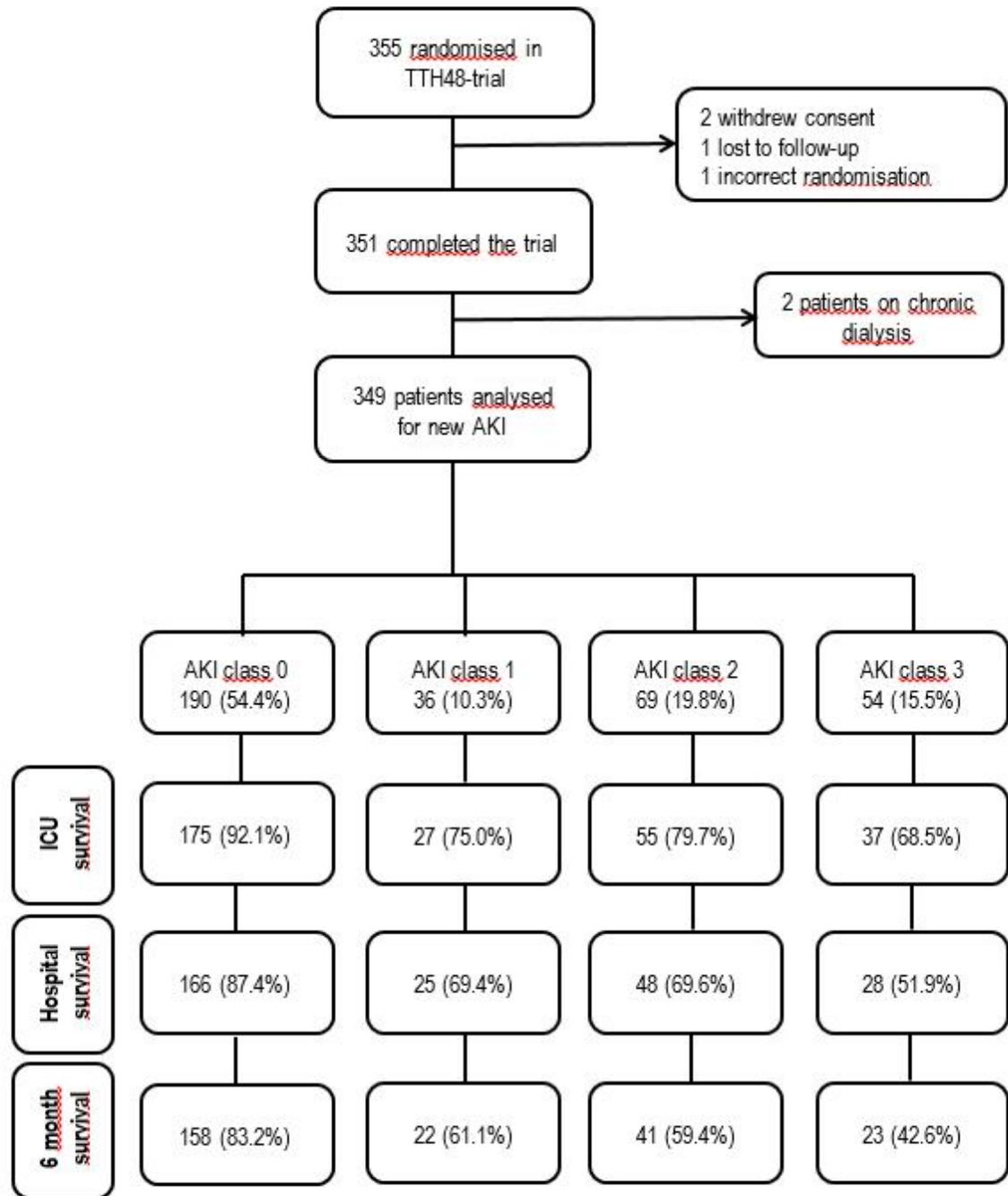
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Fig 1. Patients analysed for AKI and outcomes in the TTH48 trial.



AKI: AKI according to modified KDIGO criteria.

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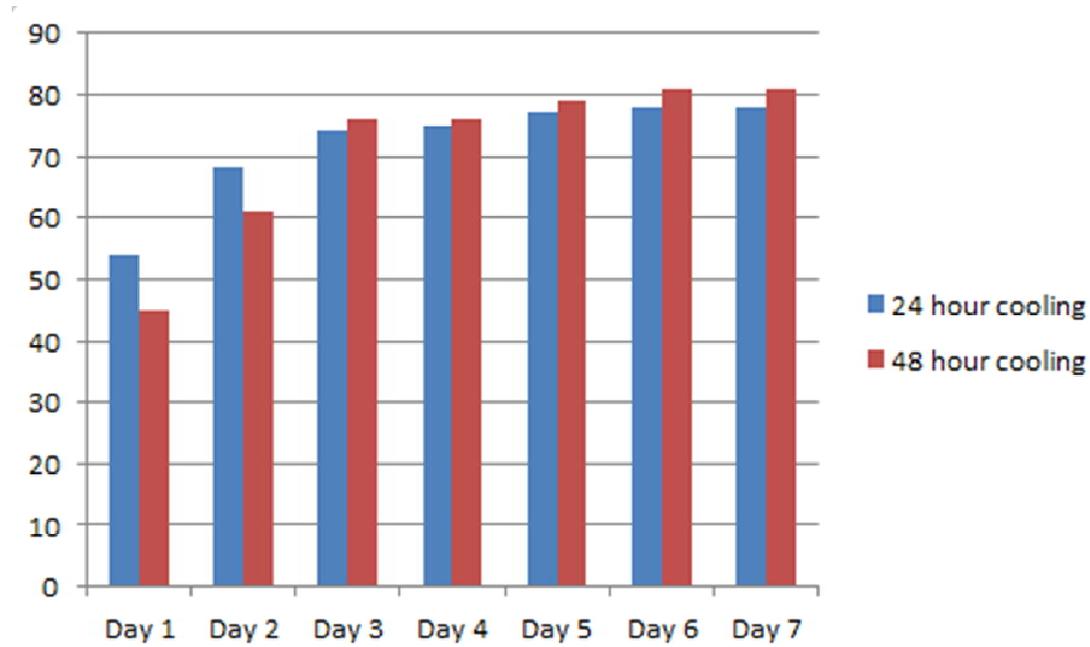
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 518 Table 1
 519 Patient characteristics split into no AKI or AKI.
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	No. (%) of Patients		
	No AKI	AKI	
Demographic characteristics			
Age (SD), y	58.0 (12.4)	63.0 (10.5)	<0.001
Male sex	157 (82.6)	133 (83.6)	0.801
BMI, mean (SD), kg/height ²	26.3 (3.7)	28.3 (5.3)	<0.001
Medical history			
Diabetes mellitus	23 (12.2)	39 (24.5)	0.003
Previous acute myocardial infarction	27 (14.3)	27 (17.2)	0.457
Chronic heart failure (NYHA class IV)	8 (4.2)	9 (5.7)	0.620
Liver cirrhosis	1 (0.5)	2 (1.3)	0.592
Arrest witnessed			0.894
Bystander	161 (84.7)	137 (86.2)	
Emergency medical services	12 (6.3)	10 (6.3)	
Unwitnessed	17 (8.9)	12 (7.5)	
Resuscitation factors			
Bystander-initiated CPR	162 (85.3)	130 (81.8)	0.378
Shockable rhythm	172 (90.9)	138 (87.1)	0.270
Time to basic life support, median (IQR), min	1 (2)	1 (1)	0.663
Time to advanced life support, median (IQR), min	8 (6)	8 (6)	0.333
Time to return of spontaneous circulation, median (IQR), min	19 (10)	22 (15)	<0.001
Epinephrine	106 (55.8)	112 (70.4)	0.005
Amiodarone	66 (34.7)	77 (48.4)	0.010
Immediate interventional cardiology			
Coronary angiography	160 (84.2)	128 (80.5)	0.364
Percutaneous intervention	81 (42.6)	63 (40.1)	0.637
Clinical status on ICU admission			
Temperature, mean (SD) °C	34.8 (0.9)	34.8 (1.1)	0.416
Lactate, median (IQR), mmol/l	1.7 (1.9)	3.1 (5.4)	0.006
Creatinine, mean (SD), μmol/l	92.0 (23.6)	117.0 (35.6)	0.003
pH, mean (SD)	7.28 (0.1)	7.24 (0.1)	0.025
Mean arterial pressure, mean (SD), mmHg	77.9 (14.5)	75.4 (17.5)	0.739
48-hour cooling	92 (53.2)	81 (45.6)	0.639

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Fig 2. Cumulative number of patients developing AKI according to the KDIGO criteria in patients treated with either 24 or 48 hours of TTM.



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553 Table 2 Results of the logistic regression analysis of admission factors predicting the
554 development of AKI in post-cardiac arrest patients treated with TTM.

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	OR (95% CI)	p-value
Age	1.03 (1.01-1.06)	0.008
BMI	1.10 (1.04-1.17)	0.001
Diabetes mellitus	0.77 (0.40-1.50)	0.435
Time to ROSC	1.03 (1.01-1.06)	0.011
Adrenaline given	1.10 (0.63-1.97)	0.721
Amiodarone given	1.28 (0.74-2.21)	0.375
Lactate at admission	1.00 (0.91-1.11)	0.958
pH at admission	0.15 (0.06-3.75)	0.250
Creatinine at admission	1.02 (1.01-1.03)	0.000
48-hour cooling	1.14 (0.69-1.87)	0.615

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Table 3 Predictors of mortality including time to development and severity of AKI.

Variable	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Age	1.05 (1.03-1.07)	<0.001	1.04 (1.02-1.07)	<0.001
Male	1.55 (0.98-2.47)	0.06	1.56 (0.96-2.53)	0.07
Bystander CPR	1.88 (1.21-2.93)	0.01	1.50 (0.92-2.45)	<0.001
Time to ROSC	1.01 (1.01-1.02)	<0.001	1.01 (1.00-1.01)	0.02
Shockable rhythm	2.88 (1.81-4.58)	<0.001	2.52 (1.50-4.23)	<0.001
KDIGO AKI 1	1.47 (0.75-2.88)	<0.001	1.33 (0.66-2.66)	0.43
KDIGO AKI 2	3.07 (1.83-5.13)	<0.001	3.00 (1.73-5.19)	<0.001
KDIGO AKI 3	4.37 (2.61-7.33)	<0.001	2.34 (1.27-4.32)	0.01
24-hour cooling	1.52 (0.89-2.58)	0.13	1.09 (0.73-1.62)	0.68

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Table 4 Outcome and resource use in patients with various degrees of AKI during their ICU stay.

Outcome	No AKI (n=190)	KDIGO 1 (n=36)	KDIGO 2 (n=69)	KDIGO 3 (n=54)	p-value
Resource use					
Time on mechanical ventilation (hours)	86 (62-130)	75 (60-122)	114 (48-144)	130(80-189)	0.02
ICU length of stay (hours)	119 (78-178)	80 (64-128)	134 (72-229)	188(133-269)	0.013
Hospital length of stay (days)	14 (10-21)	13 (8-21)	16 (8-21)	21(11-31)	0.195

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590 Suppl. Table 1. Development of markers of renal function during the first 72 hours.

	All patients	24-hour cooling	48-hour cooling	p-value
First available creatinine*	101.8 (32.9)	104.2 (37.1)	99.5 (27.6)	0.193
Est. Baseline creatinine**	92.3 (8.9)	91.0 (9.5)	91.5 (8.3)	0.558
Creatinine				
24-hours	95.9 (54.1)	96.7 (50.6)	95.0 (57.5)	0.78
48-hours	107.4 (70.6)	115.3 (77.8)	100.3 (62.6)	0.059
72-hours	121.6 (87.5)	126.6 (96.1)	117.2 (79.2)	0.367
Urea				
24-hours	7.9 (5.2)	8.0 (4.5)	7.7 (5.9)	0.851
48-hours	7.7 (6.5)	7.8 (5.3)	7.5 (7.6)	0.761
72-hours	8.2 (7.2)	9.2 (8.0)	7.4 (6.4)	0.039
Urine output				
24-hours	2294 (1232)	2368 (1329)	2220 (1123)	0.262
48-hours	2154 (1070)	2182 (1769)	2128 (10699)	0.459
72-hours	2554 (1292)	2424 (1248)	2655 (1319)	0.145
Daily fluid balance				
24-hours	2294 (1232)	1585 (2106)	1667 (2033)	0.713
48-hours	1087 (1674)	888 (1769)	1276 (1562)	0.033
72-hours	333 (1768)	307 (1713)	354 (1814)	0.828

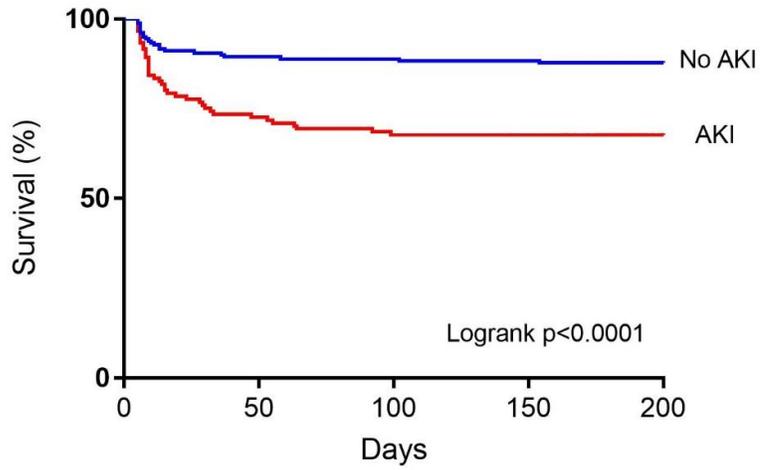
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*First available serum creatine from hospital to ICU admission

**Estimated baseline creatinine base on the MDRD equation assuming a GFR of 75

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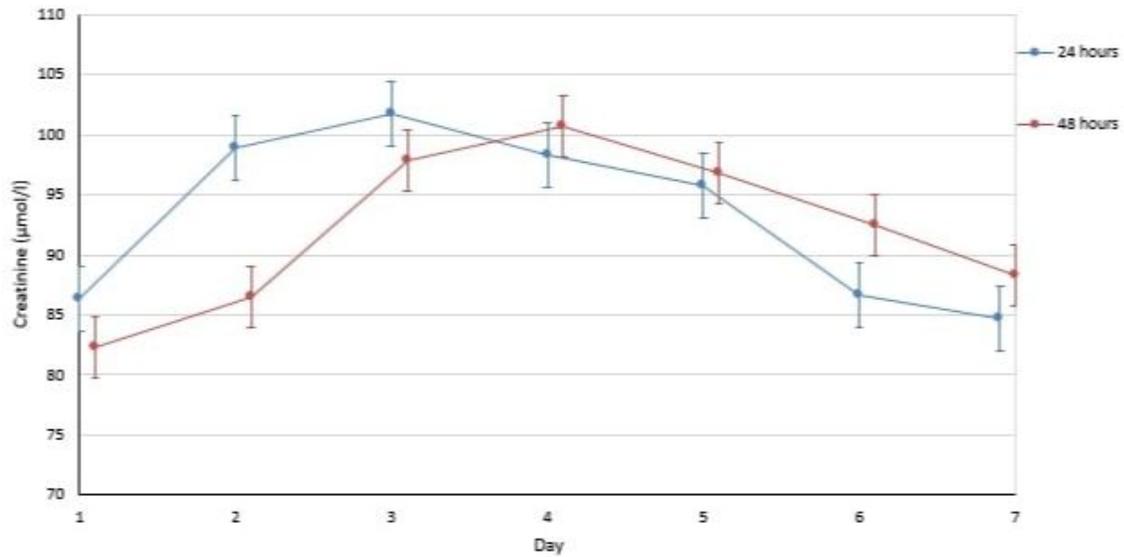
Suppl. Fig 1 Survival of patients alive at day 4 after cardiac arrest with or without AKI according to the KDIGO criteria prior to day 4.



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Fig 3. Serum creatinine over the first seven days in patients treated with either 24 or 48 hours of TTM.



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Suppl. Table 2. KDIGO AKI classification based on first available serum creatinine before ICU admission or estimated baseline serum creatinine at hospital admission.

KDIGI AKI	First sCr No.(%)	Est. sCr* No.(%)
0	78 (54.2)	77 (53.5)
1	15 (10.4)	9 (6.3)
2	19 (13.2)	25 (17.4)
3	32 (22.2)	33 (22.9)
Total	144 (100)	144 (100)

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*Estimated baseline creatinine based on the MDRD equation assuming an eGFR of 75

682 **Conflict of interest**

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684 MBS reports having received a research grant from GE Healthcare, travel reimbursements and
685 lecture fees from BARD Medical. CS reports having received travel reimbursements and
686 speaker fees from BD BARD and Zoll GmbH, as well as honorarium for consultancy from
687 BD BARD, Benechill and Sedana Medical. AMG and ANJ report having received lecture fees
688 from Novartis. All other authors report that they have no conflicts of interest.

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