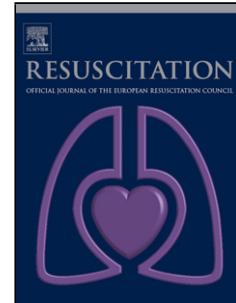# Journal Pre-proof

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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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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Abstract

46

47 Background

48

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℃ 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.

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56 Methods

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58 This study was a sub-study of the TTH48 trial, which included patients cooled to 33±1˚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.

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78 Conclusions
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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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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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109   **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 Secondarily, 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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141

142

143 **Methods**

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145 *Study design*

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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±1°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 $33\pm1°C$ 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 remifentanil/fentanyl

165 infusions. Shivering was treated with increased sedation or cisatracurium. Noradrenaline was

166 the vasopressor of choice during hypothermia.

167

168 *Data*

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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 catherisation 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*

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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 μmol/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 µmol/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*

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196   Categorical variables were expressed as counts (percentages) and continuous variables as

197   means ± 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).
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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

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

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

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

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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Fig 1. Patients analysed for AKI and outcomes in the TTH48 trial.
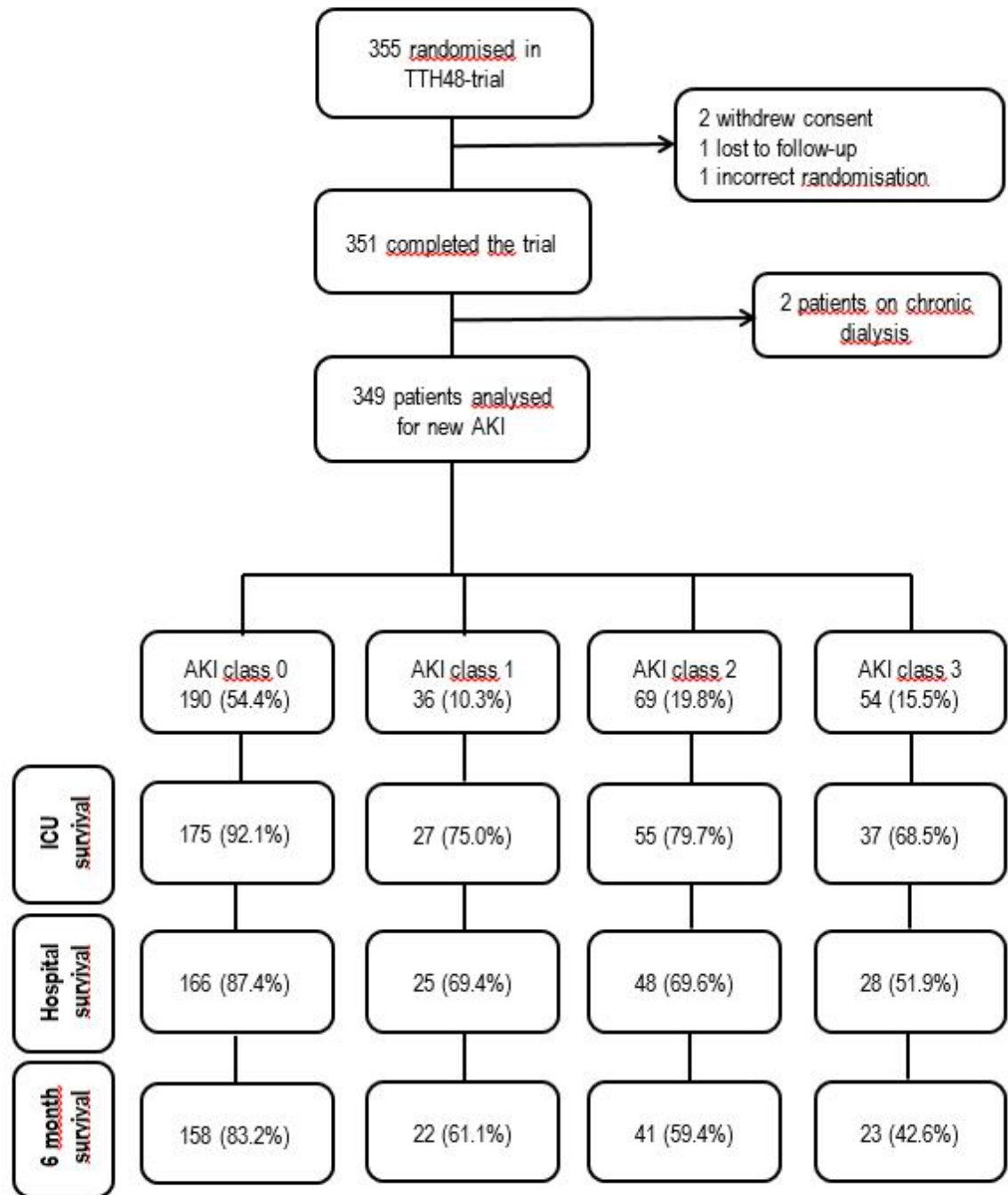
AKI: AKI according to modified KDIGO criteria.

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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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528   Fig 2. Cumulative number of patients developing AKI according to the KDIGO criteria in
529   patients treated with either 24 or 48 hours of TTM.
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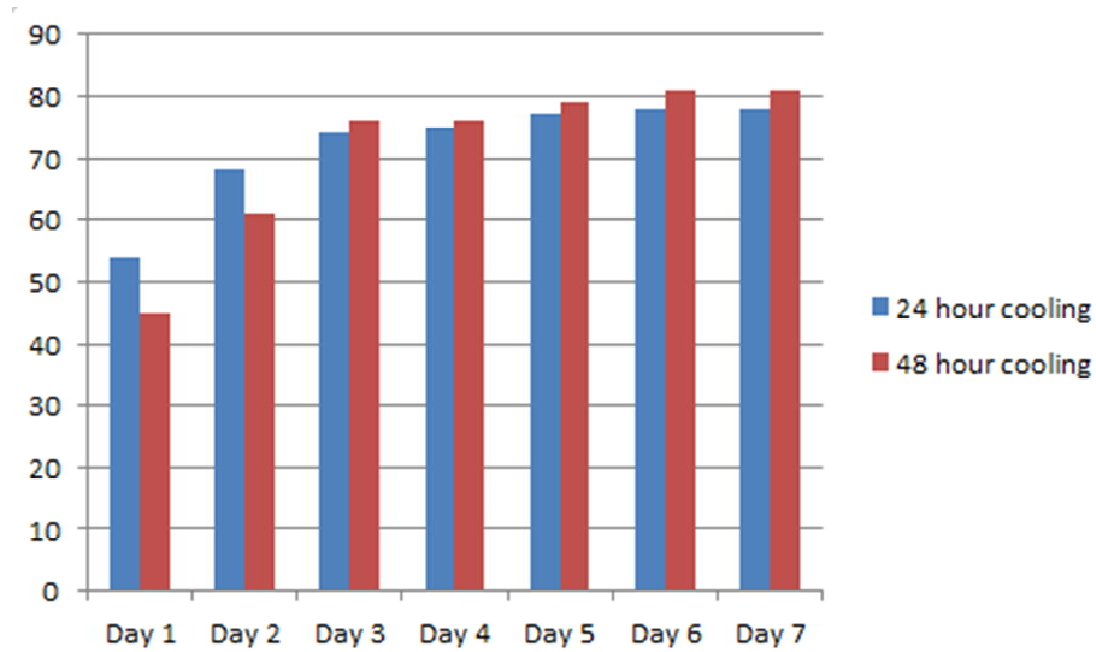
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553   Table 2 Results of the logistic regression analysis of admission factors predicting the

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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572   Table 3 Predictors of mortality including time to development and severity of AKI.
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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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583 Table 4 Outcome and resource use in patients with various degrees of AKI during their ICU
584 stay.
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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

591 *First available serum creatine from hospital to ICU admission

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

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602 Suppl. Fig 1 Survival of patients alive at day 4 after cardiac arrest with or without AKI
603 according to the KDIGO criteria prior to day 4.
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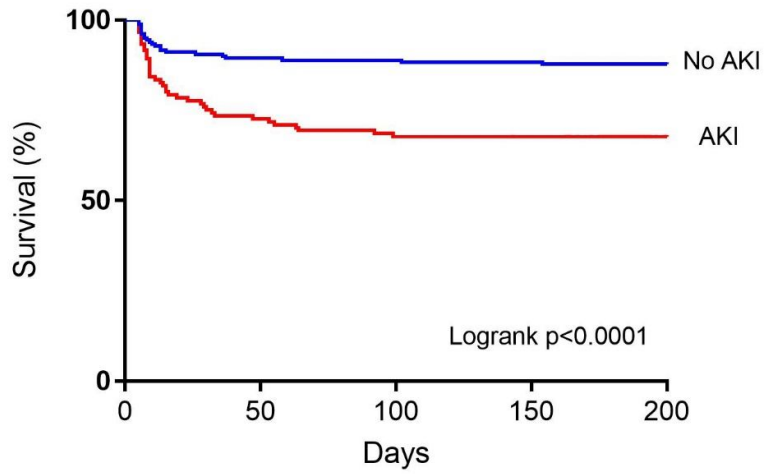
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639 Fig 3. Serum creatinine over the first seven days in patients treated with either 24 or 48 hours
640 of TTM.
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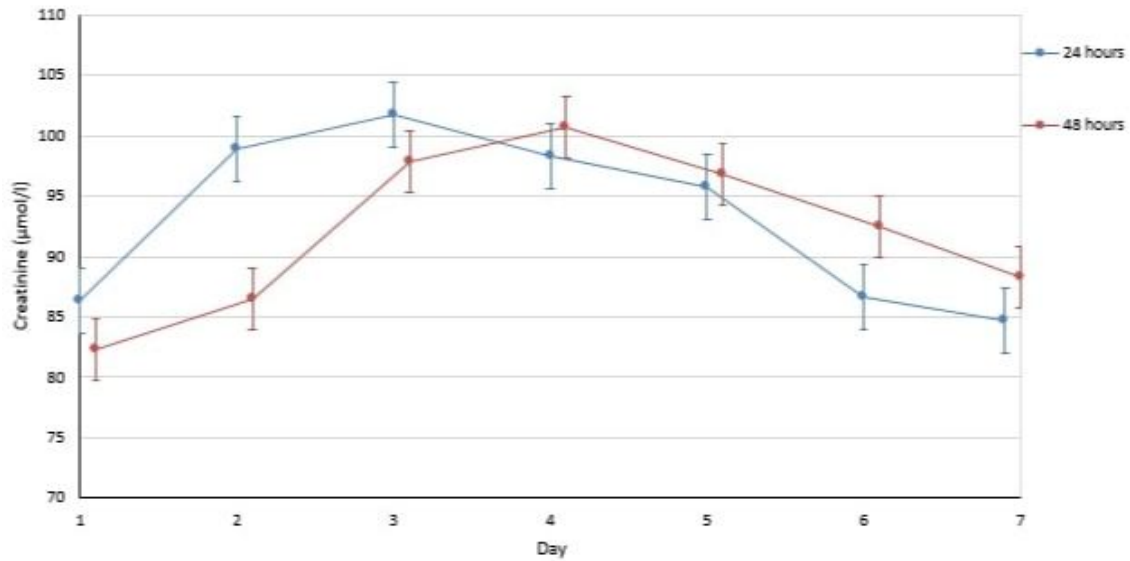
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674 Suppl. Table 2. KDIGO AKI classification based on first available serum creatinine before

675 ICU admission or estimated baseline serum creatinine at hospital admission.

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

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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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