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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

Background

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

Methods

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

Results

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

Conclusions

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

Keywords

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

Trial registration

NCT01689077. Registered on www.ClinicalTrials.gov 20 September, 2012 (main trial).

Background

Acute kidney injury (AKI) is a well-known complication in post-cardiac arrest patients [1]. Recent studies have found an incidence of AKI of more than 40% when modern staging of AKI was used and targeted temperature management (TTM) implemented as standard post-resuscitation care [1, 2]. The development of renal dysfunction in this setting is most likely due to local and whole body ischemia and reperfusion injury as well as circulatory failure in the post-resuscitation period [3]. This post-cardiac arrest syndrome is characterised by immunological, inflammatory and coagulation disturbances leading to perfusion disturbances and organ dysfunction. Although prognosis after successful resuscitation is mainly linked to the presence of hypoxic-ischemic brain injury, extra-cerebral organ dysfunction in the immediate post-resuscitation period has been shown to have prognostic implications [4].

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

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

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

Methods

Study design

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

Randomisation was performed during the first 24 hours of cooling.

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

Interventions

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

Data

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

AKI classification

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

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

Statistical analysis

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

Results

Included patients and the incidence of AKI

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

Difference between 48- and 24-hour cooling

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

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

Admission factors for AKI

There were several differences in patient characteristics, factors at resuscitation and admission between the patients that developed AKI compared to those who did not develop AKI. Notably, AKI patients were older, had a higher BMI, more commonly had diabetes and had a higher sCr level at ICU admission (Table 1). Regarding factors at resuscitation, patients who developed AKI had a longer time to return of spontaneous circulation (ROSC) and more commonly received both adrenaline and amiodarone (Table 1). In a multivariate analysis of risk factors at ICU admission for the development of AKI, we found age, BMI, sCr at ICU admission and time to ROSC to be independent predictors of AKI (Table 2).

Association between AKI and outcome

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

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

Discussion

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

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

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-

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

Strengths and limitations

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

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

Conclusions

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

List of abbreviations

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

Declarations

Ethics approval and consent to participate:

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

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

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

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

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Authors' contributions

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

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Not applicable

References

1. Sandroni, C., et al., *Acute kidney injury after cardiac arrest: a systematic review and meta-analysis of clinical studies*. Minerva Anesthesiol, 2016. **82**(9): p. 989-99.
2. Rundgren, M., et al., *Renal function after out-of-hospital cardiac arrest; the influence of temperature management and coronary angiography, a post hoc study of the target temperature management trial*. Crit Care, 2019. **23**(1): p. 163.
3. Chua, H.R., N. Glassford, and R. Bellomo, *Acute kidney injury after cardiac arrest*. Resuscitation, 2012. **83**(6): p. 721-7.
4. Nobile, L., et al., *The impact of extracerebral organ failure on outcome of patients after cardiac arrest: an observational study from the ICON database*. Crit Care, 2016. **20**(1): p. 368.
5. Lu, R., et al., *Kidney-brain crosstalk in the acute and chronic setting*. Nat Rev Nephrol, 2015. **11**(12): p. 707-19.
6. Susantitaphong, P., et al., *Therapeutic hypothermia and prevention of acute kidney injury: a meta-analysis of randomized controlled trials*. Resuscitation, 2012. **83**(2): p. 159-67.
7. Khwaja, A., *KDIGO clinical practice guidelines for acute kidney injury*. Nephron Clin Pract, 2012. **120**(4): p. c179-84.
8. Kirkegaard, H., et al., *Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial*. JAMA, 2017. **318**(4): p. 341-350.
9. Kirkegaard, H., et al., *A statistical analysis protocol for the time-differentiated target temperature management after out-of-hospital cardiac arrest (TTH48) clinical trial*. Scand J Trauma Resusc Emerg Med, 2016. **24**(1): p. 138.
10. Levey, A.S., et al., *A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group*. Ann Intern Med, 1999. **130**(6): p. 461-70.
11. Waked, K. and M. Schepens, *State-of-the-art review on the renal and visceral protection during open thoracoabdominal aortic aneurysm repair*. J Vis Surg, 2018. **4**: p. 31.
12. Niemann, C.U. and D. Malinoski, *Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function*. N Engl J Med, 2015. **373**(27): p. 2687.
13. De Rosa, S., et al., *The effect of whole-body cooling on renal function in post-cardiac arrest patients*. BMC Nephrol, 2017. **18**(1): p. 376.
14. Luszczek, E.R., et al., *Prolonged induced hypothermia in hemorrhagic shock is associated with decreased muscle metabolism: a nuclear magnetic resonance-based metabolomics study*. Shock, 2014. **41**(1): p. 79-84.
15. Koeze, J., et al., *Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria*. BMC Nephrol, 2017. **18**(1): p. 70.
16. Winther-Jensen, M., et al., *Use of renal replacement therapy after out-of-hospital cardiac arrest in Denmark 2005-2013*. Scand Cardiovasc J, 2018. **52**(5): p. 238-243.
17. Beitland, S., et al., *Impact of acute kidney injury on patient outcome in out-of-hospital cardiac arrest: a prospective observational study*. Acta Anaesthesiol Scand, 2016. **60**(8): p. 1170-81.
18. Beitland, S. and K. Sunde, *Guidelines for post-resuscitation care should include management of acute kidney injury and use of renal replacement therapy*. Resuscitation, 2018. **126**: p. e14.
19. Gaudry, S., et al., *Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit*. N Engl J Med, 2016. **375**(2): p. 122-33.

20. Geri, G., et al., *Acute kidney injury after out-of-hospital cardiac arrest: risk factors and prognosis in a large cohort*. Intensive Care Med, 2015. **41**(7): p. 1273-80.
21. Tujjar, O., et al., *Acute kidney injury after cardiac arrest*. Crit Care, 2015. **19**: p. 169.
22. Danziger, J., et al., *Obesity, Acute Kidney Injury, and Mortality in Critical Illness*. Crit Care Med, 2016. **44**(2): p. 328-34.
23. Gameiro, J., et al., *Obesity, acute kidney injury and mortality in patients with sepsis: a cohort analysis*. Ren Fail, 2018. **40**(1): p. 120-126.
24. Nie, S., et al., *Are There Modifiable Risk Factors to Improve AKI?* Biomed Res Int, 2017. **2017**: p. 5605634.
25. Storm, C., et al., *Impact of acute kidney injury on neurological outcome and long-term survival after cardiac arrest - A 10year observational follow up*. J Crit Care, 2018. **47**: p. 254-259.
26. Kim, Y.W., et al., *Shock duration after resuscitation is associated with occurrence of post-cardiac arrest acute kidney injury*. J Korean Med Sci, 2015. **30**(6): p. 802-7.
27. Park, Y.S., et al., *Recovery from acute kidney injury as a potent predictor of survival and good neurological outcome at discharge after out-of-hospital cardiac arrest*. Crit Care, 2019. **23**(1): p. 256.
28. De Rosa, S., S. Samoni, and C. Ronco, *Creatinine-based definitions: from baseline creatinine to serum creatinine adjustment in intensive care*. Crit Care, 2016. **20**: p. 69.

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

AKI: AKI according to modified KDIGO criteria.

513
514
515
516

Table 1
Patient characteristics split into no AKI or AKI.

	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			
Bystander	161 (84.7)	137 (86.2)	0.894
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

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

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

	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

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

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

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

*First available serum creatine from hospital to ICU admission

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

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.

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

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)

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

Conflict of interest

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