CRITICAL CARE AND RESUSCITATION

Online Appendix

This appendix was part of the submitted manuscript and has been peer reviewed.
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Appendix to: Nichol A, Bellomo R, Ady B, et al; TAME study and the Australia and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), the Irish Critical Care Clinical Trials Network (ICC-CTN), and the Australian Resuscitation Consortium (Aus-ROC). Protocol summary and statistical analysis plan for the targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest (TAME) trial. *Crit Care Resusc* 2021; doi: 10.51893/2021.4.OA2.

TABLES & FIGURES

Table 1. Baseline characteristics*		
Characteristic	**Targeted therapeutic mild hypercapnia (n=xxx)**	**Targeted normocapnia (n=xxx)**
Demographic characteristics		
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xx (xx)	xx (xx)
Medical history – no. (%)		
Coronary artery bypass grafting	xx (xx)	xx (xx)
COPDD	xx (xx)	xx (xx)
Diabetes	xx (xx)	xx (xx)
Hypertension	xx (xx)	xx (xx)
Myocardial infarction	xx (xx)	xx (xx)
PCI	xx (xx)	xx (xx)
Herat failure	xx (xx)	xx (xx)
NYHA III or IV heart failure	xx (xx)	xx (xx)
Median Charlson comorbidity index (IQR)	xx (xx)	xx (xx)
Characteristics of the cardiac arrest		
Location of cardiac arrest – no. (%)	xx (xx)	xx (xx)
Place of residence	xx (xx)	xx (xx)
Public place	xx (xx)	xx (xx)
Other	xx (xx)	xx (xx)
Bystander witnessed cardiac arrest – no. (%)	xx (xx)	xx (xx)
Bystander performed CPR – no. (%)	xx (xx)	xx (xx)
First monitored rhythm – no. (%)		
Shockable rhythm	xx (xx)	xx (xx)
Ventricular fibrillation	xx (xx)	xx (xx)
Non-perfusing ventricular tachycardia	xx (xx)	xx (xx)
ROSC after bystander-initiated defibrillation	xx (xx)	xx (xx)
Unknown rhythm, shock administered	xx (xx)	xx (xx)
Non-shockable rhythm		
Asystole	xx (xx)	xx (xx)
Pulseless electrical activity	xx (xx)	xx (xx)
Unknown, shock administered	xx (xx)	xx (xx)
Median time from cardiac arrest to sustained ROSC – minutes, median (IQR)	xx (xx)	xx (xx)
Median time from cardiac arrest to randomisation – minutes (IQR)	xx (xx)	xx (xx)
Clinical characteristic on hospital admission		
Tympanic temperature	xx (xx)	xx (xx)
FOUR motor score	xx (xx)	xx (xx)
Bilateral corneal reflexes present – no./total. (%)	xx (xx)	xx (xx)
Bilateral pupillary reflexes present – no./total. (%)	xx (xx)	xx (xx)
Arterial pH	xx (xx)	xx (xx)
Arterial lactate level – mmol/liter	xx (xx)	xx (xx)

First measured arterial carbon dioxide tension	xx (xx)	xx (xx)
Shock – no.(%)	xx (xx)	xx (xx)
ST-segment elevation myocardial infarction – no.(%)	xx (xx)	xx (xx)

Plus-minus values will be expressed as mean ± SD (where the distribution of the data is not normal, median [IQR] will be reported instead of mean ± SD).
* Statistically significant differences in baseline characteristics between groups will be indicated by * for $P < 0.05$, ** for $P < 0.01$, and *** for $P < 0.001$.
Abbreviations: AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease, CPR, cardiopulmonary resuscitation; ICU: Intensive Care Unit; $PaCO_2$: arterial partial pressure of carbon dioxide; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation..

New York Heart Association (NYHA) heart failure class was not assessed in X patients 9X in the normocapnia group and X in the mild hypercapnia group) who had a history of heart failure.

On the Charlson comorbidity index, each comorbidity category is weighted from 1 to 6 on the basis of adjusted risk of death or resource use, and the sum of the weights produces the score. A score of 0 indicates an absence of known coexisting conditions, and higher scores indicate higher risks of death and greater resource use.

For witnessed cardiac arrests, the time to ROSC was calculated from the time of the emergency call

Full Outline of Unresponsiveness (FOUR) motor score range from 0 to 4, with higher scores indicating better motor function. The FOUR motor score was assessed in XX patients.

Arterial pH was measured in XX patients.

Shock at admission was defined as a systolic blood pressure of less than 90 mm Hg for more than 30 minutes or end-organ hypoperfusion (cool extremities, a urine output of <30 ml per hour, and a heart rate of <60 beats per minute).

Tympanic temperature was assessed in XX patients.

Table 2. Primary outcome and key secondary outcomes

	Targeted therapeutic mild hypercapnia (n=x)	Targeted normocapnia (n=x)	Estimate (95% CI)		P value
Primary outcome					
Favourable Score of 5-8 on GOSE scale at 6-month follow-up no. (%)	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)		x.xx
GOSE of 5 – 8	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)		x.xx
Key secondary outcomes			**odds ratio**		
			unadjusted	**adjusted†**	
Median ICU length of stay [IQR] – days	xx.x ± xx	xx.x ± xx	xx (xx)	xx (xx)	x.xx
Median hospital length of stay (IQR) – days	xx.x ± xx	xx.x ± xx	xx (xx)	xx (xx)	x.xx
Survival until ICU discharge – no.(%)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	x.xx
Survival until hospital discharge – no.(%)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	x.xx
Day 180 mortality – no. (%)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	x.xx

Abbreviations: ICU, intensive care unit; IQR: Interquartile range; CI: Confidence Interval
Glasgow Outcome Scale Extend scores range from 1 to 8, with 1 dead, 2 vegetative state, 3 lower severe disability, 4 upper severe disability, 5 lower moderate disability, 6 upper moderate disability, 7 lower good recovery, 8 upper good recovery.

Dichotomised categorisation of GOSE was 1 – 4 unfavourable and 5 – 8 favourable.

The neurologic follow-up was specified in the protocol to be performed at 180 days ±2 weeks, but the time to follow-up was in some vases several weeks longer for logistic reasons. The Glasgow Outcome Scale Extended.

Table 3. Neurological outcomes		
Variable	**Targeted therapeutic mild hypercapnia**	**Targeted normocapnia**
GOSE at day 180		
Total no. of patients	**xx**	**xx**
Category – no. (%)		
Dead (1)	xx (xx)	xx (xx)
Vegetative state (2)	xx (xx)	xx (xx)
Lower severe disability (3)	xx (xx)	xx (xx)
Upper severe disability (4)	xx (xx)	xx (xx)
Lower moderate disability (5)	xx (xx)	xx (xx)
Upper moderate disability (6)	xx (xx)	xx (xx)
Lower good recovery (7)	xx (xx)	xx (xx)
Upper good recovery (8)	xx (xx)	xx (xx)
Modified Rankin scale score at day 30		
Total no. of patients	**xx**	**xx**
Score – no. (%)		
No symptoms (0)	xx (xx)	xx (xx)
No clinically significant disability (1)	xx (xx)	xx (xx)
Slight disability (2)	xx (xx)	xx (xx)
Moderate disability (3)	xx (xx)	xx (xx)
Moderately severe disability (4)	xx (xx)	xx (xx)
Severe disability (5)	xx (xx)	xx (xx)
Death (6)	xx (xx)	xx (xx)
Modified Rankin scale score at 180 day		
Total no. of patients	**xx**	**xx**
Score – no. (%)		
No symptoms (0)	xx (xx)	xx (xx)
No clinically significant disability (1)	xx (xx)	xx (xx)
Slight disability (2)	xx (xx)	xx (xx)
Moderate disability (3)	xx (xx)	xx (xx)
Moderately severe disability (4)	xx (xx)	xx (xx)
Severe disability (5)	xx (xx)	xx (xx)
Death (6)	xx (xx)	xx (xx)

Plus-minus values will be expressed as mean ± SD (where the distribution of the data is not normal, median [IQR] will be reported instead of mean ± SD).
* Statistically significant differences in baseline characteristics between groups will be indicated by * for $P < 0.05$, **
Abbreviations: GOSE, Glasgow outcome scale extended.

Scores on the GOSE range from 1 to 8, with 1 dead, 2 vegetative state, 3 lower severe disability, 4 upper severe disability, 5 lower moderate disability, 6 upper moderate disability, 7 lower good recovery, 8 upper good recovery.

Scores for the modified Rankin scale range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability despite some symptoms, 2 slight disability (patient is able to look after own affairs without assistance), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to own bodily needs), 5 severe disability (patient is bedridden), and 6 death.

The neurologic follow-up was specified in the protocol to be performed at 180 days ±2 weeks, but the time to follow-up was in some vases several weeks longer for logistic reasons.

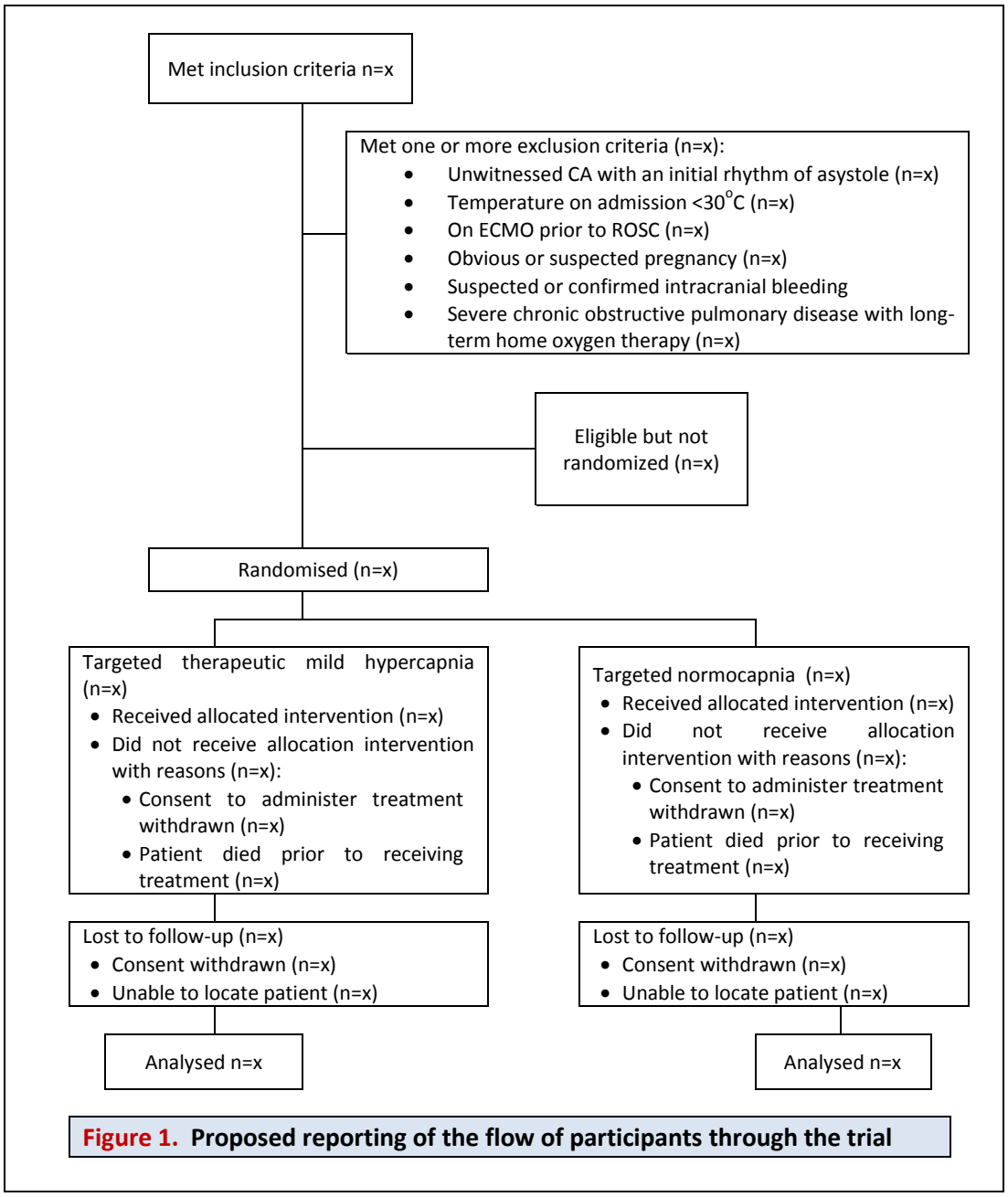

Figure 1. Proposed reporting of the flow of participants through the trial

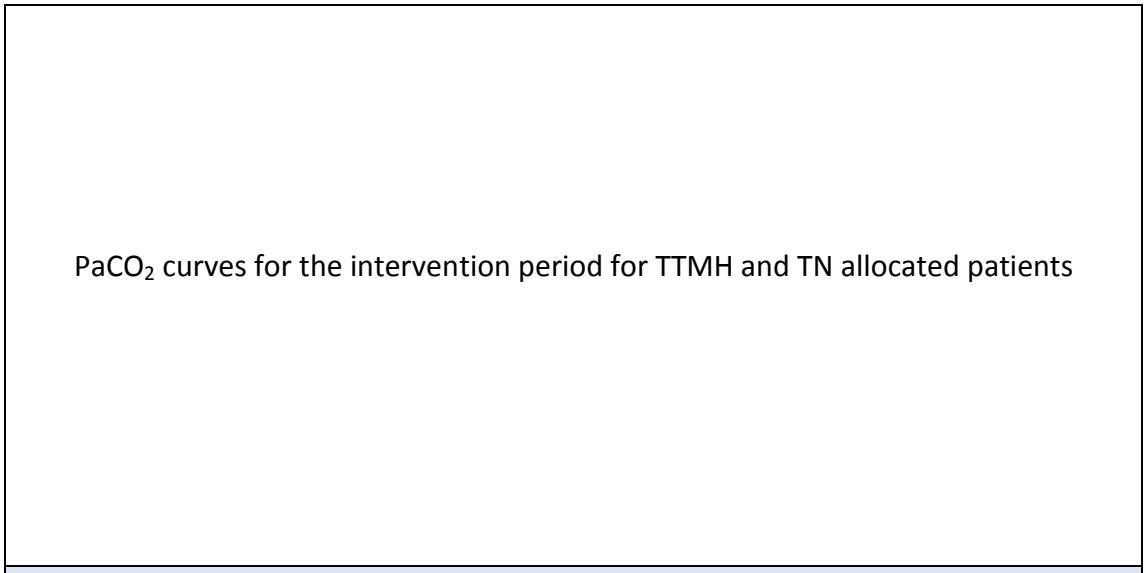

Figure 2. Arterial carbon dioxide tension values during intervention period

Shown are arterial carbon dioxide ($PaCO_2$) curves in the targeted therapeutic mild hypercapnia (TTMH) group and targeted normocapnia (TN) group for the X patients in who $PaCO_2$ was recorded. In the remaining X patients, the $PaCO_2$ was recorded XX. Targeting of normocapnia or targeting of mild hypercapnia commenced at the time of randomization and continued for 24 hours. The $PaCO_2$ curse display the means, and the I bars indicate $\pm$2 SD (95% of the observations are in the error bars).

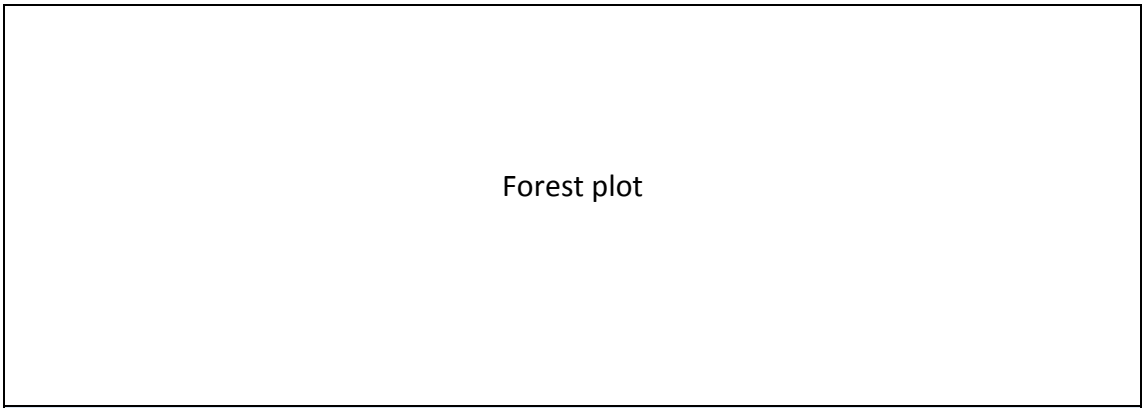

Figure 3. Subgroup analysis of death from any cause and the GOSE score at 6 months

Shown are the results of the analyses of death from any cause (Panel A) and a score of 5 to 8 on the GOSE in prespecified subgroups. Glasgow Outcome Scale Extend (GOSE) scores range from 1 to 8, with 1 dead, 2 vegetative state, 3 lower severe disability, 4 upper severe disability, 5 lower moderate disability, 6 upper moderate disability, 7 lower good recovery, 8 upper good recovery. Relative risks are derived from a stratified generalized linear model with trial site as a random intercept. The forest plot shows the relative risks for five prespecified subgroups. The horizontal bars represent 95% confidence intervals. The events are the total events 6 months after randomization.

SUPPLEMENTAL TABLES

Table S1: Additional baseline characteristics

Table S1. Additional baseline characteristics		
Characteristic	**Targeted therapeutic mild hypercapnia (n=xxx)**	**Targeted normocapnia (n=xxx)**
Demographic characteristics		
Height - cm	xx (xx)	xx (xx)
Weight – kg	xx (xx)	xx (xx)
Medical history – no. (%)		
Previous atrial fibrillation or flutter	xx (xx)	xx (xx)
Previous cardiac arrhythmia or flutter	xx (xx)	xx (xx)
Previous known cardiomyopathy	xx (xx)	xx (xx)
Previous ICD	xx (xx)	xx (xx)
Clinical physiology on admission		
Arterial oxygen tension	xx (xx)	xx (xx)
Fraction of inspired oxygen	xx (xx)	xx (xx)
Serum base excess	xx (xx)	xx (xx)
Serum creatinine	xx (xx)	xx (xx)
Serum glucose	xx (xx)	xx (xx)
Serum platelet count	xx (xx)	xx (xx)
HbA1c	xx (xx)	xx (xx)
Neurology on admission, no. (%)		
Corneal reflex present	xx (xx)	xx (xx)
Cough reflex present	xx (xx)	xx (xx)
Myoclonus		
Myoclonus present	xx (xx)	xx (xx)
Generalised myoclonus	xx (xx)	xx (xx)
Modified Rankin scale score, pre-arrest, no. (%)		
Total	xx (xx)	xx (xx)
Score		
No symptoms (0)	xx (xx)	xx (xx)
No clinically significant disability (1)	xx (xx)	xx (xx)
Slight disability (2)	xx (xx)	xx (xx)
Moderate disability (3)	xx (xx)	xx (xx)
Moderately severe disability (4)	xx (xx)	xx (xx)
Severe disability (5)	xx (xx)	xx (xx)
Death (6)	xx (xx)	xx (xx)

Abbreviations: CABG, coronary artery bypass graft; cm, centimetres; ICD, implantable cardioverter defibrillator; ICU: Intensive Care Unit; kg, kilogram; PCI, percutaneous coronary angiography.

Table S2. Diagnostic procedures, interventions, and service utilisation

Table S2. Diagnostic procedures, interventions, and service utilisation			
Variable	**All (n=xx)**	**Targeted therapeutic mild hypercapnia (n=xx)**	**Targeted normocapnia (n=xx)**
Time to enrolment, min [IQR]			
Minutes from CA to enrolment	xx.x ± xx	xx.x ± xx	xx.x ± xx
Pre-hospital characteristic, no. %			
Active mechanical CPR device	xx (xx)	xx (xx)	xx (xx)
Number of defibrillations	xx (xx)	xx (xx)	xx (xx)
Artificial airway inserted	xx (xx)	xx (xx)	xx (xx)
Adrenaline dose, - total, mg	xx (xx)	xx (xx)	xx (xx)
On admission, no. %			
Coronary angiography	xx (xx)	xx (xx)	xx (xx)
CT	xx (xx)	xx (xx)	xx (xx)
Time to intervention, no. %			
Hours from CA to coronary angiography [IQR]	xx (xx)	xx (xx)	xx (xx)
Hours from CA to PCI [IQR]	xx (xx)	xx (xx)	xx (xx)
Diagnostic procedures during ICU admission, no. %			
CT	xx (xx)	xx (xx)	xx (xx)
EEG	xx (xx)	xx (xx)	xx (xx)
NSE	xx (xx)	xx (xx)	xx (xx)
MRI	xx (xx)	xx (xx)	xx (xx)
SSEP	xx (xx)	xx (xx)	xx (xx)
Interventions during ICU admission, no. %			
CABG	xx (xx)	xx (xx)	xx (xx)
Coronary angiography	xx (xx)	xx (xx)	xx (xx)
ICD	xx (xx)	xx (xx)	xx (xx)
PCI	xx (xx)	xx (xx)	xx (xx)
Targeted therapeutic hypothermia	xx (xx)	xx (xx)	xx (xx)
Thrombolysis	xx (xx)	xx (xx)	xx (xx)
Mechanical ventilation, h [IQR]			
Hours from intubation to 1st extubation or death	xx (xx)	xx (xx)	xx (xx)
Sedation, no. (%)			
Hours from time of enrolment to ICU discharge, [IQR]	xx (xx)	xx (xx)	xx (xx)
Drugs, cumulative dose over 72 hours following randomisation, mg			
Noradrenaline	xx.x ± xx	xx.x ± xx	xx.x ± xx
Propofol	xx.x ± xx	xx.x ± xx	xx.x ± xx
Midazolam	xx.x ± xx	xx.x ± xx	xx.x ± xx
Remifentanil	xx.x ± xx	xx.x ± xx	xx.x ± xx
Fentanyl	xx.x ± xx	xx.x ± xx	xx.x ± xx
Buspirone	xx.x ± xx	xx.x ± xx	xx.x ± xx

Dexmedetomidine	xx.x ± xx	xx.x ± xx	xx.x ± xx
Paracetamol	xx.x ± xx	xx.x ± xx	xx.x ± xx
Oxycodone	xx.x ± xx	xx.x ± xx	xx.x ± xx
Morphine	xx.x ± xx	xx.x ± xx	xx.x ± xx
Neuromuscular blocking agent			
Received	xx (xx)	xx (xx)	xx (xx)
Cumulative dose over 72 h from randomisation, mg	xx (xx)	xx (xx)	xx (xx)
Mechanical assist device no. (%)			
IABP	xx (xx)	xx (xx)	xx (xx)
Renal replacement therapy during ICU admission no. (%)			
CRRT	xx (xx)	xx (xx)	xx (xx)
Length of time, [IQR]			
Hours from CA to ICU discharge	xx.x ± xx	xx.x ± xx	xx.x ± xx
Days from CA to hospital discharge	xx.x ± xx	xx.x ± xx	xx.x ± xx

Abbreviations: CA, cardiac arrest; CABG, coronary artery bypass graft surgery; CRRT, continuous renal replacement therapy; CT, computerized tomography, EEG, electroencephalogram; IABP, intra-aortic balloon pump; ICD, Implantable cardiac defibrillator; IQR, interquartile range; NSE, neuron specific enolase; MRI, magnetic resonance imaging; PCI, percutaneous coronary angiography; SSEP; somatosensory evoked potentials.

Table S3. Protocol violations and no intervention received

Table S3. Protocol deviations and no intervention received

Variable	All (n=xx)	Targeted therapeutic mild hypercapnia (n=xx)	Targeted normocapnia (n=xx)
Protocol deviation, no. (%)			
Carbon dioxide target abandoned	xx (xx)	xx (xx)	xx (xx)
Other	xx (xx)	xx (xx)	xx (xx)
No intervention received, no. (%)			
Transfer to another hospital	xx (xx)	xx (xx)	xx (xx)
Died before start of intervention	xx (xx)	xx (xx)	xx (xx)
Never received intervention	xx (xx)	xx (xx)	xx (xx)

Table S4. Reasons for early discontinuation of targeted arterial carbon dioxide range

Table S4. Reasons for early discontinuation of targeted arterial carbon dioxide range			
Variable, no. (%)	**All (n=xx)**	**Targeted therapeutic mild hypercapnia (n=xx)**	**Targeted normocapnia (n=xx)**
Withdrawal of life supporting therapies	xx (xx)	xx (xx)	xx (xx)
Early discharge from the ICU	xx (xx)	xx (xx)	xx (xx)
Death	xx (xx)	xx (xx)	xx (xx)
Withdrawn consent	xx (xx)	xx (xx)	xx (xx)
Treating clinical believes it is in the best interest of the patient	xx (xx)	xx (xx)	xx (xx)

Abbreviations: ICU, intensive care unit.

Table S5. Reasons for withdrawal of life sustaining therapy

Table S5. Reasons for withdrawal of life sustaining therapy							
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day5**	**Day 6**	**Day 7**
Total WLST, no. (%)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Reason for WLST, no. (%)							
Brain dead	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Neurological reasons	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
MOF and haemodynamic compromise	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Co-morbidity	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Ethical reasons	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)

Abbreviations MOF, multi-organ failure; WLST, withdrawal of life-sustaining therapy.

Table S6. Neurological prognostication

Table S6. Neurological prognostication			
Variable	**All (n=xx)**	**Targeted therapeutic mild hypercapnia (n=xx)**	**Targeted normocapnia (n=xx)**
Prognostication performed, no. (%)			
Prognostication recommendation, no. (%)			
Continue care	xx (xx)	xx (xx)	xx (xx)
Do not escalate	xx (xx)	xx (xx)	xx (xx)
Withdrawal care	xx (xx)	xx (xx)	xx (xx)
No recommendation recorded	xx (xx)	xx (xx)	xx (xx)
Prognostication not performed, no. (%)			
Regained consciousness before prognostication	xx (xx)	xx (xx)	xx (xx)
No reason given	xx (xx)	xx (xx)	xx (xx)
Transfer to other hospital	xx (xx)	xx (xx)	xx (xx)
On-going sedation	xx (xx)	xx (xx)	xx (xx)
WLST due to ethical reasons	xx (xx)	xx (xx)	xx (xx)
Ongoing MOF	xx (xx)	xx (xx)	xx (xx)
Died before prognostication performed, no. (%)			
Cerebral	xx (xx)	xx (xx)	xx (xx)
Cardiovascular	xx (xx)	xx (xx)	xx (xx)
Multi-organ failure	xx (xx)	xx (xx)	xx (xx)
Other	xx (xx)	xx (xx)	xx (xx)

Abbreviations: MOF, multi-organ failure; WLST, withdrawal of life-sustaining therapy.

Table S7. Adverse events and severe unexpected serious adverse events

Table S7. Adverse events and suspected unexpected serious adverse events			
Variable	**All (n=xx)**	**Targeted therapeutic mild hypercapnia (n=xx)**	**Targeted normocapnia (n=xx)**
Seizures, no. (%)			
Myoclonic seizures	xx (xx)	xx (xx)	xx (xx)
Tonic-clonic seizures	xx (xx)	xx (xx)	xx (xx)
Bleeding, no. (%)			
Mild	xx (xx)	xx (xx)	xx (xx)
Moderate	xx (xx)	xx (xx)	xx (xx)
Severe	xx (xx)	xx (xx)	xx (xx)
Infection, no. (%)			
Pneumonia	xx (xx)	xx (xx)	xx (xx)
Sepsis	xx (xx)	xx (xx)	xx (xx)
Other	xx (xx)	xx (xx)	xx (xx)
Arrhythmia, no. (%)			
Bradycardia requiring pacing or CPR	xx (xx)	xx (xx)	xx (xx)
Ventricular fibrillation	xx (xx)	xx (xx)	xx (xx)
Ventricular tachycardia	xx (xx)	xx (xx)	xx (xx)
Rapid atrial fibrillation	xx (xx)	xx (xx)	xx (xx)
Supraventricular tachycardia	xx (xx)	xx (xx)	xx (xx)
Cooling device related skin complication, no. (%)			
Overall	xx (xx)	xx (xx)	xx (xx)
During intervention period	xx (xx)	xx (xx)	xx (xx)
Suspected unexpected serious adverse event, no. (%)			
Total	xx (xx)	xx (xx)	xx (xx)

Abbreviations: CPR, cardiopulmonary resuscitation.

Occurring in 1st 7 days following enrolment.

Table S8. Reported initial cause of cardiac arrest

Table S8. Reported initial cause of cardiac arrest			
Variable	**All (n=xx)**	**Targeted therapeutic mild hypercapnia (n=xx)**	**Targeted normocapnia (n=xx)**
Cardiac, no. (%)			
Total cardiac cause	xxx (xx)	xxx (xx)	xxx (xx)
Acute coronary syndrome – STEMI	xxx (xx)	xxx (xx)	xxx (xx)
Acute coronary syndrome – NSTEMI	xxx (xx)	xxx (xx)	xxx (xx)
Arrhythmia – due to cardiomyopathy	xxx (xx)	xxx (xx)	xxx (xx)
Arrhythmia – due to primary heart rhythm abnormalities (Brugada, long-QT)	xxx (xx)	xxx (xx)	xxx (xx)
Heart failure	xxx (xx)	xxx (xx)	xxx (xx)
Hypertrophic obstructive cardiomyopathy	xxx (xx)	xxx (xx)	xxx (xx)
Congenital heart disease	xxx (xx)	xxx (xx)	xxx (xx)
Myocarditis	xxx (xx)	xxx (xx)	xxx (xx)
Brady-arrhythmia	xxx (xx)	xxx (xx)	xxx (xx)
Idiopathic ventricular tachycardia	xxx (xx)	xxx (xx)	xxx (xx)
Idiopathic ventricular fibrillation	xxx (xx)	xxx (xx)	xxx (xx)
Other cardiac causes	xxx (xx)	xxx (xx)	xxx (xx)
Other medical, no. (%)			
Total other medical causes	xxx (xx)	xxx (xx)	xxx (xx)
Pulmonary embolism	xxx (xx)	xxx (xx)	xxx (xx)
Anaphylaxis	xxx (xx)	xxx (xx)	xxx (xx)
Electrolyte disorder	xxx (xx)	xxx (xx)	xxx (xx)
Hypoxia	xxx (xx)	xxx (xx)	xxx (xx)
Hypoglycaemia	xxx (xx)	xxx (xx)	xxx (xx)
Sepsis	xxx (xx)	xxx (xx)	xxx (xx)
Other medical cause	xxx (xx)	xxx (xx)	xxx (xx)
External, no. (%)			
Total external causes	xxx (xx)	xxx (xx)	xxx (xx)
Trauma	xxx (xx)	xxx (xx)	xxx (xx)
Overdose	xxx (xx)	xxx (xx)	xxx (xx)
Other, no. (%)			
Non-cardiac and non-medical	xxx (xx)	xxx (xx)	xxx (xx)

Abbreviations: STEMI, ST segment elevation myocardial infarction.

Table S9. Presumed cause of death and organ donation

Table S9. Presumed cause of death and organ donation			
Variable	**All (n=xx)**	**Targeted therapeutic mild hypercapnia (n=xx)**	**Targeted normocapnia (n=xx)**
Presumed cause of death, no. (%)			
Cerebral	xx (xx)	xx (xx)	xx (xx)
Cardiovascular	xx (xx)	xx (xx)	xx (xx)
Multi-organ failure	xx (xx)	xx (xx)	xx (xx)
Other	xx (xx)	xx (xx)	xx (xx)
Organ donation, no. (%)			
No	xx (xx)	xx (xx)	xx (xx)
Yes – after cardiac death	xx (xx)	xx (xx)	xx (xx)
Yes – after confirmed brain death	xx (xx)	xx (xx)	xx (xx)
Autopsy performed	xx (xx)	xx (xx)	xx (xx)

Table S10. Interaction analyses between trial group allocation and co-enrolment/allocation in the two groups of the TTM2-trial for the outcomes

Table S10. Assessment of treatment interaction between arterial carbon dioxide and temperature	
Outcome	**P for interaction (overall)**
All-cause mortality at 6 months	
GOSE 5-8 at 6 months	
Poor functional outcome at 6 months	
Time to event (survival)	
EQ-5D-VAS for participants alive at 6 months	

EQ-5D-VAS, European Quality of Life-5-Dimension-5 visual analogue scale.
GOSE, Glasgow outcome scale extended score

Table S11. Unadjusted analyses in the intention-to-treat population

Table S11. Unadjusted analyses in the intention-to-treat population		
	Relative risk	**95% confidence interval**
Mortality at 6 months		
GOSE 5-8 at 6 months		
mRS 4-6 at 6 months		
Binary function outcome at 6 months		

GOSE, Glasgow outcome scale extended
mRS, modified Rankin score

Table S12. Unadjusted analyses in participants of the intention-to-treat population where the 367 patients co-enrolled in the TTM2 trial were excluded

Table S12. Unadjusted analyses in participants of the intention-to-treat population where the 367 patients co-enrolled in the TTM2 trial were excluded		
	Relative risk	**95% confidence interval**
Mortality at 6 months		
GOSE 5-8 at 6 months		
mRS 4-6 at 6 months		
Binary function outcome at 6 months		

GOSE, Glasgow outcome scale extended
mRS, modified Rankin score

SUPPLEMENTAL FIGURES:

Figure S1. Consort diagram showing assessment of patient eligibility, random assignment of patients, analysis population, and flow of patients in the TAME trial

Figure S2. Forest plot for subgroup analysis of death from any cause and the score of 5 – 8 on the GOSE scale at 6 months

Figure S3. Glasgow outcome scale extended score (GOSE) at 6 months follow-up

Figure S4. Modified Rankin Score (mRS) at 6 months follow-up

Figure S5. Time-weighted mean $PaCO_2$ during intervention period by treatment group

Figure S6. Mean, lowest, and highest $PaCO_2$ during intervention period by treatment group

Figure S7. Time-weighted mean PaO_2 during intervention period by treatment group

Figure S8. Mean, lowest, and highest PaO_2 during intervention period by treatment group

Figure S9. Time-weighted mean pH during intervention period by treatment group

Figure S10. Mean, lowest, and highest pH during intervention period by treatment group

Figure S11. Time-weighted mean FiO2 during intervention period by treatment group

Figure S12. Mean, lowest, and highest FiO2 during intervention period by treatment group

Figure S13. Time-weighted mean PEEP during intervention period by treatment group

Figure S14. Mean, lowest, and highest PEEP during intervention period by treatment group

Figure S15. Histogram depicting the ventilator modes used during intervention period by treatment group

Figure S16. Time-weighted mean temperature during intervention period by treatment group

Figure S17. Mean, lowest, and highest temperature during intervention period by treatment group

Figure S18. Histogram depicting the motor response of the Full Outline of Unresponsiveness [FOUR] score from enrolment until ICU discharge by treatment group

Figure S19. Histogram depicting the number of participants from whom a decision to withdraw life-sustaining therapies (WLST) was made and the time of the decision

Figure S20. Withdrawal of life-sustaining therapies, by reason

Figure S21. Distribution of days alive outside hospital after first hospitalisation within 180 days.