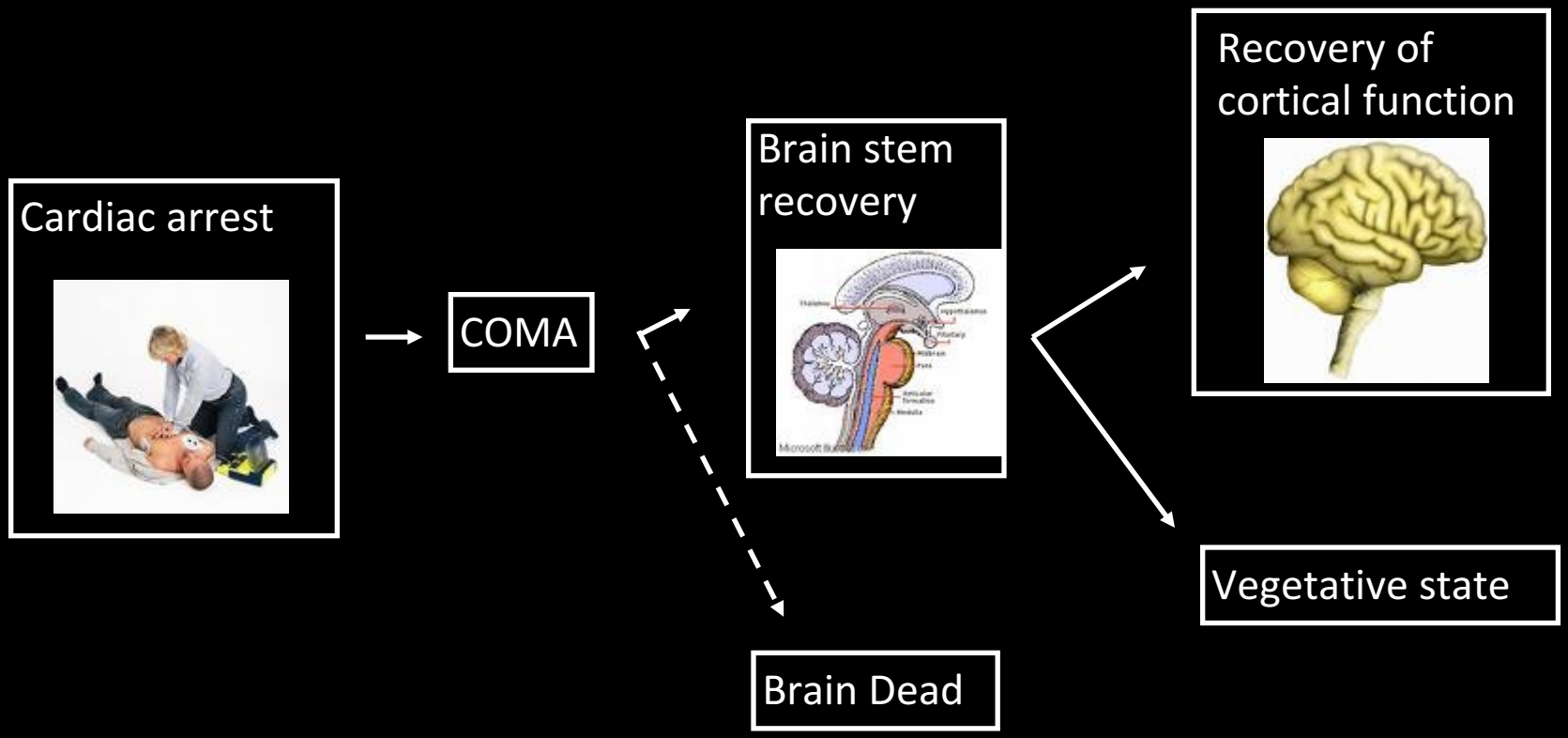
Ipotermia terapeutica controversie e TTM 2 Trial

Iole Brunetti

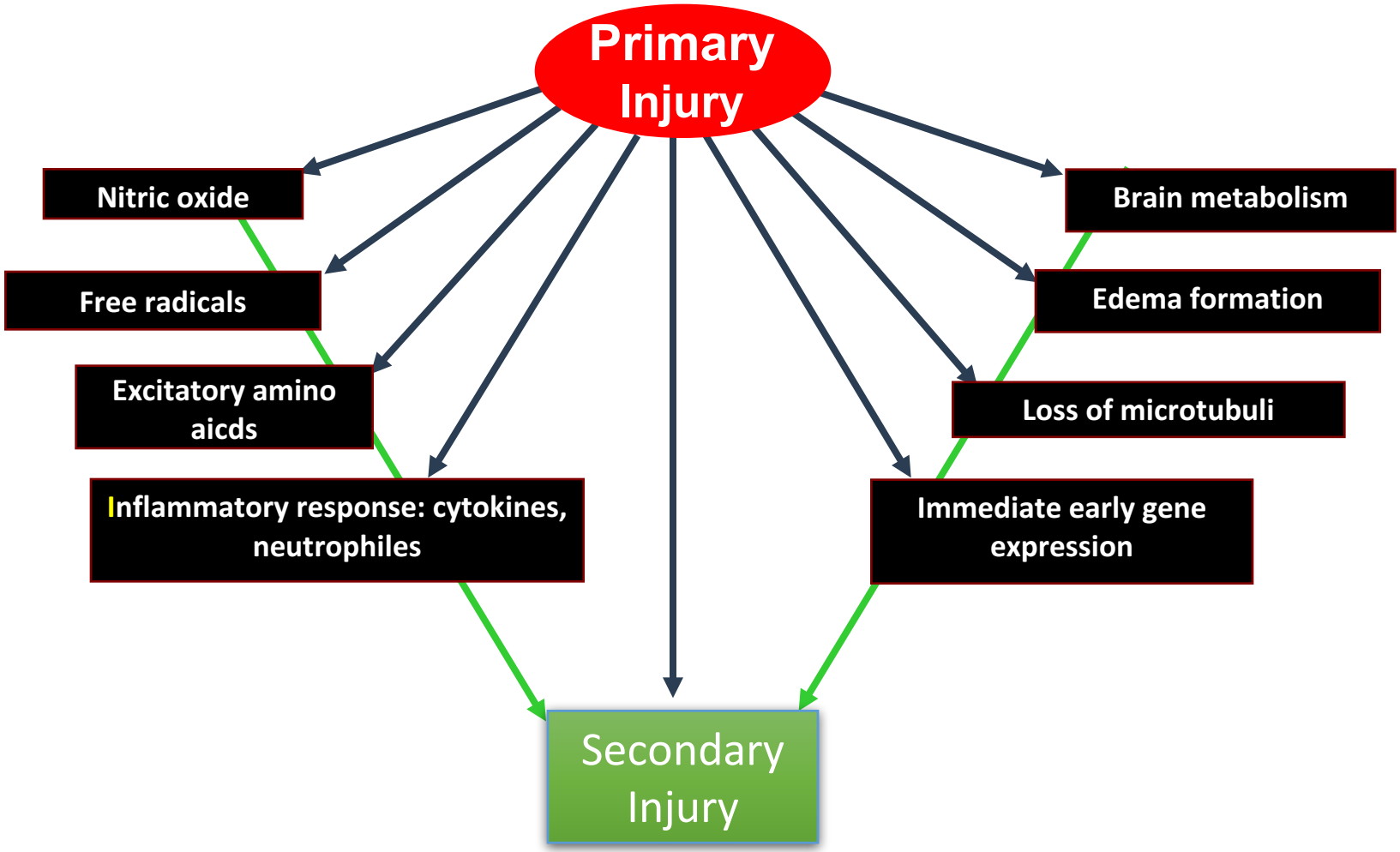
U.O.C Anestesia e Terapia Intensiva
Policlinico San Martino - GENOVA

Natural Course of Neurological Recovery Following Cardiac Arrest

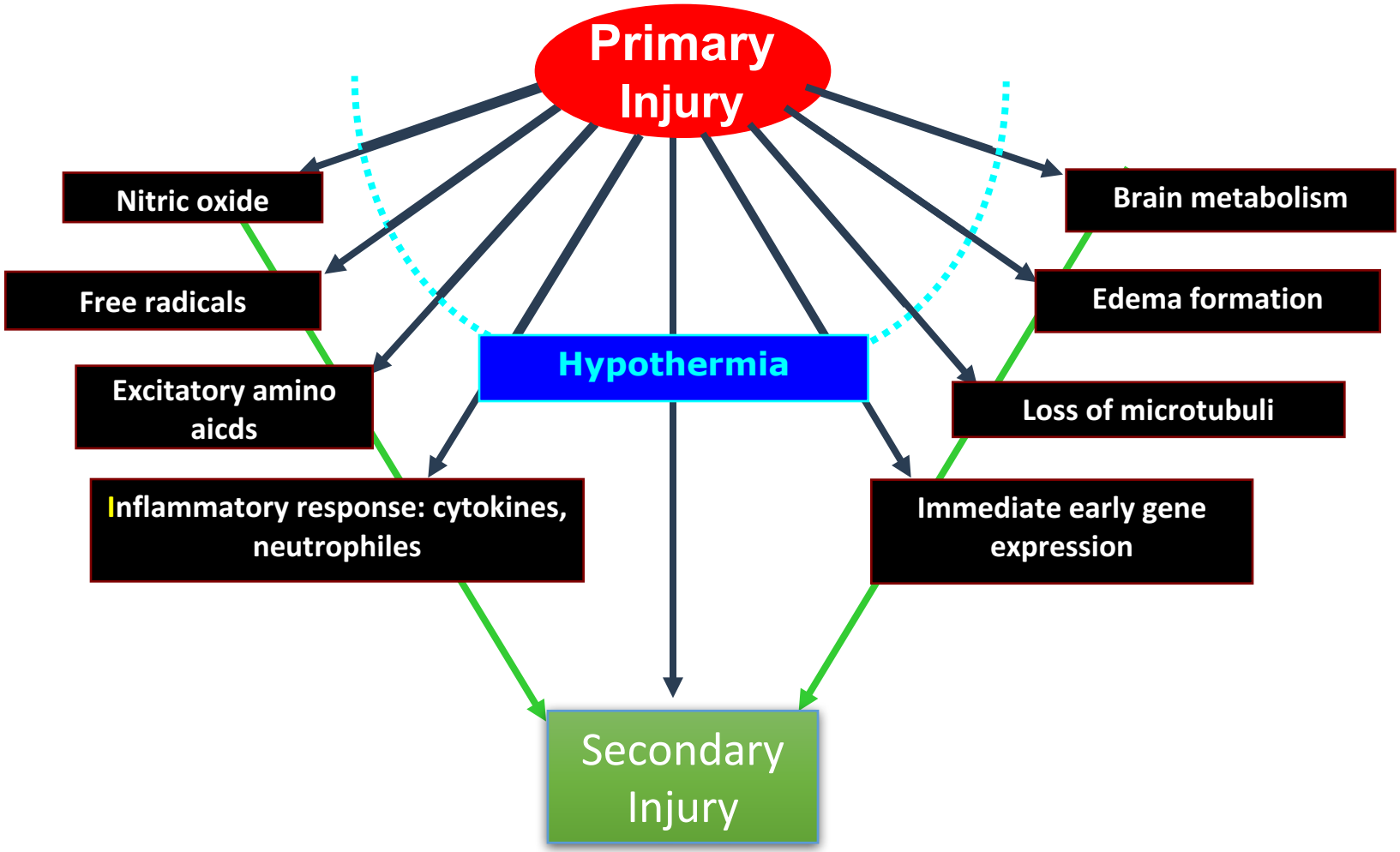


Xiong, 2009, Jorgensen 1987

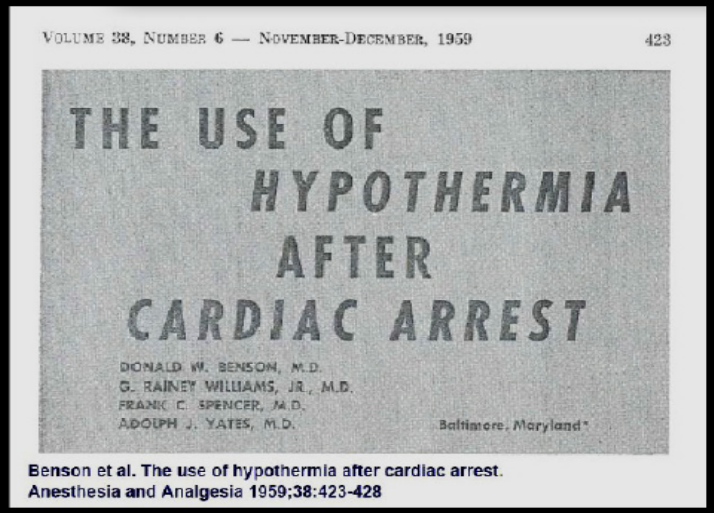
Effects of Hypothermia on Brain Damage



Effects of Hypothermia on Brain Damage



Background

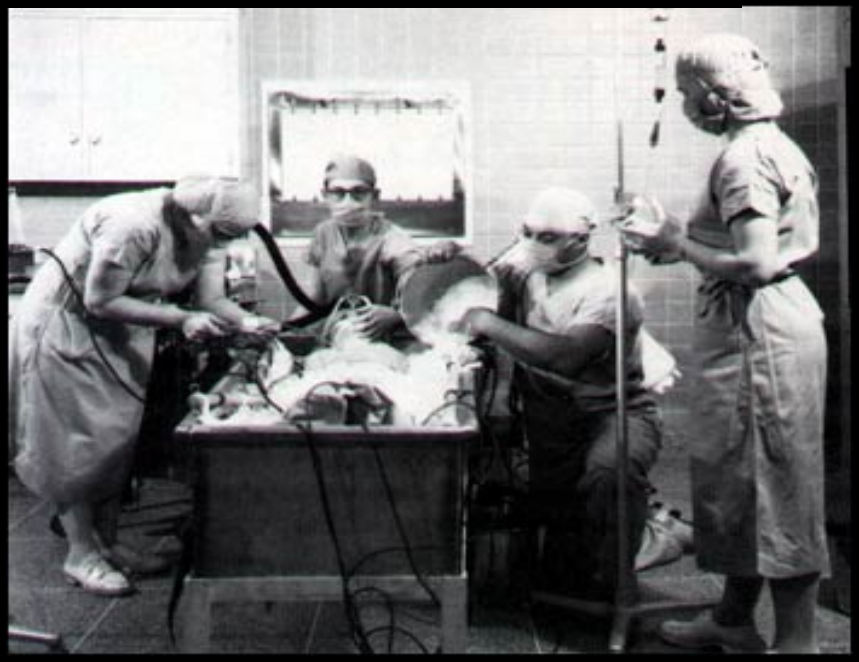


VOLUME 38, NUMBER 6 — NOVEMBER-DECEMBER, 1959 423

THE USE OF HYPOTHERMIA AFTER CARDIAC ARREST

DONALD W. BENSON, M.D.
G. RAINEY WILLIAMS, JR., M.D.
FRANK C. SPENCER, M.D.
ADOLPH J. YATES, M.D. Baltimore, Maryland

Benson et al. The use of hypothermia after cardiac arrest. Anesthesia and Analgesia 1959;38:423-428



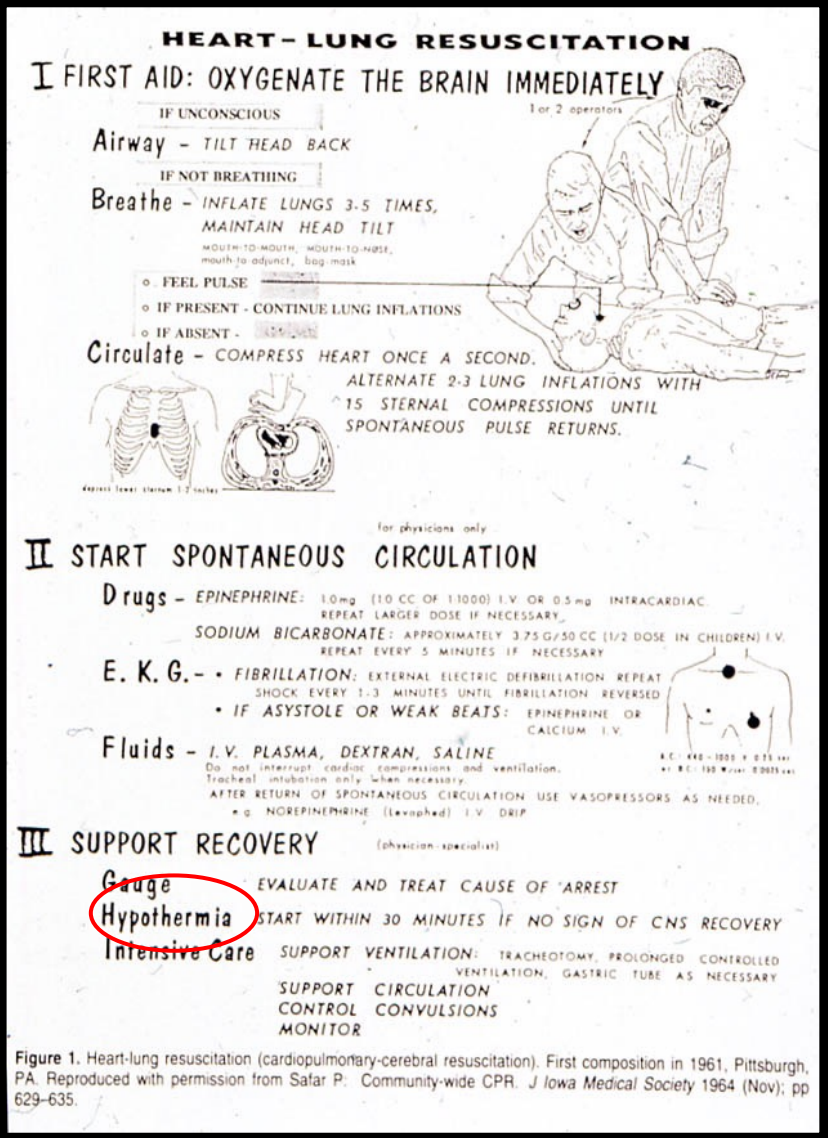
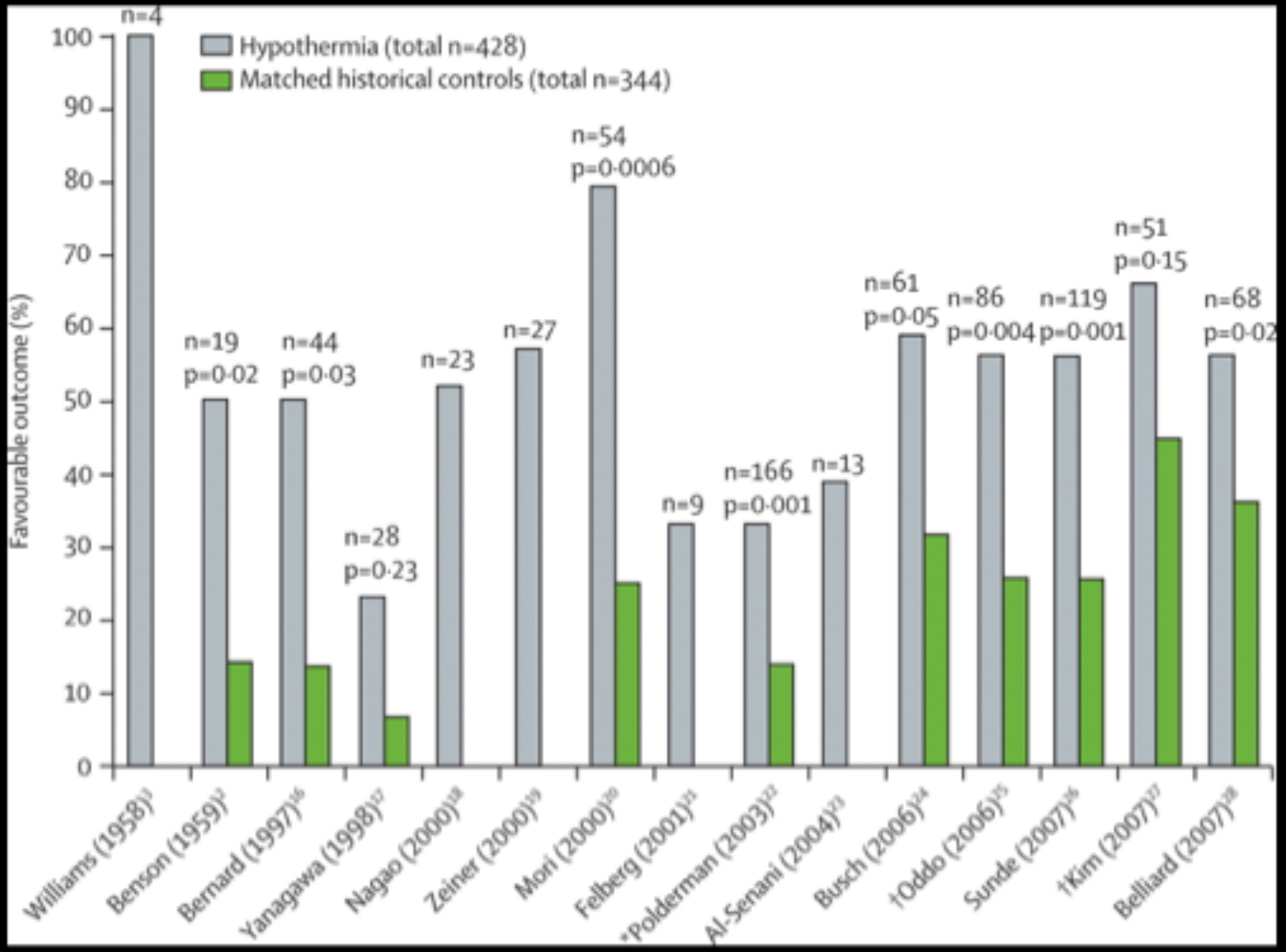


Figure 1. Heart-lung resuscitation (cardiopulmonary-cerebral resuscitation). First composition in 1961, Pittsburgh, PA. Reproduced with permission from Safar P: Community-wide CPR. *J Iowa Medical Society* 1964 (Nov); pp 629–635.

Literature



The Lancet 2008 371, 1955-1969DOI: (10.1016/S0140-6736(08)60837-5)

Background

Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest

The Hypothermia after Cardiac Arrest Study Group

N Engl J Med 2002; 346:549-556 | February 21, 2002

ORIGINAL ARTICLE

Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia

Stephen A. Bernard, M.B., B.S., Timothy W. Gray, M.B., B.S., Michael D. Buist, M.B., B.S., Bruce M. Jones, M.B., B.S., William Silvester, M.B., B.S., Geoff Gutteridge, M.B., B.S., and Karen Smith, B.Sc.

N Engl J Med 2002; 346:557-563 | February 21, 2002

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

STEPHEN A. BERNARD, M.B., B.S., TIMOTHY W. GRAY, M.B., B.S., MICHAEL D. BUIST, M.B., B.S., BRUCE M. JONES, M.B., B.S., WILLIAM SILVESTER, M.B., B.S., GEOFF GUTTERIDGE, M.B., B.S., AND KAREN SMITH, B.SC.

N Engl J Med. 2002 Feb 21;346(8):557-63.

- Quasi-randomised, odd and even days
- 84 eligible patients, 77 included
- Unscheduled interim analysis after 62 patients
- Unusual outcome measure
- Uneven groups (43 vs 34)
- Temperature in control group (37.1 -37.3 °C)
- Hospital discharge as outcome

Good outcome:
normal or with minimal or moderate disability

TABLE 5. OUTCOME OF PATIENTS AT DISCHARGE FROM THE HOSPITAL.

OUTCOME*	HYPOTHERMIA (N=43)	NORMOTHERMIA (N=34)
	number of patients	
Normal or minimal disability (able to care for self, discharged directly to home)	15	7
Moderate disability (discharged to a rehabilitation facility)	6	2
Severe disability, awake but completely dependent (discharged to a long-term nursing facility)	0	1
Severe disability, unconscious (discharged to a long-term nursing facility)	0	1
Death	22	23

N Engl J Med. 2002 Feb 21;346(8):557-63.

The New England
Journal of Medicine

VOLUME 346 FEBRUARY 21, 2002 NUMBER 8

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

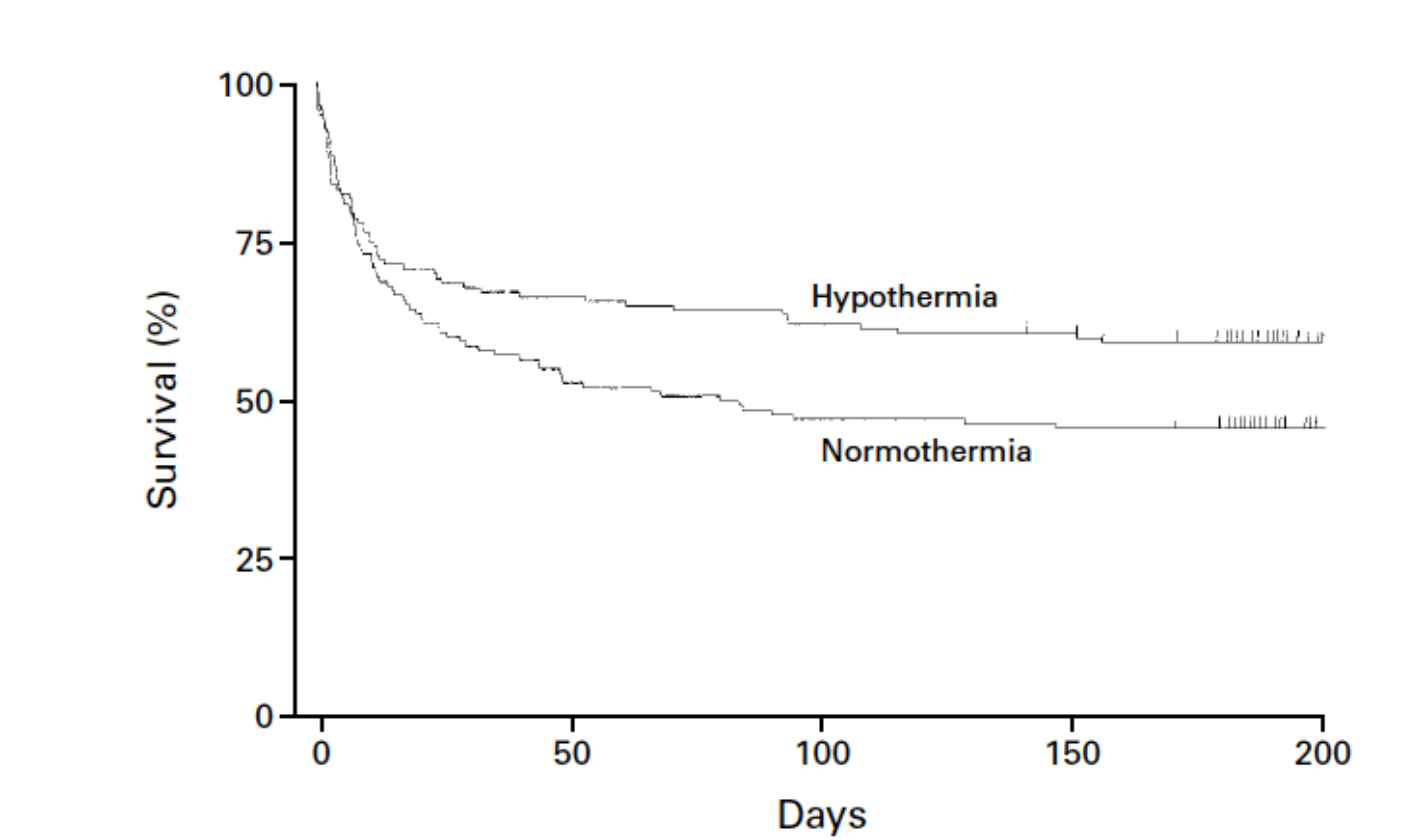
HACA-trial

Less risk of bias/systematic errors!

Included only 8 % of patients with ROSC

N Engl J Med 2002;346:549-56

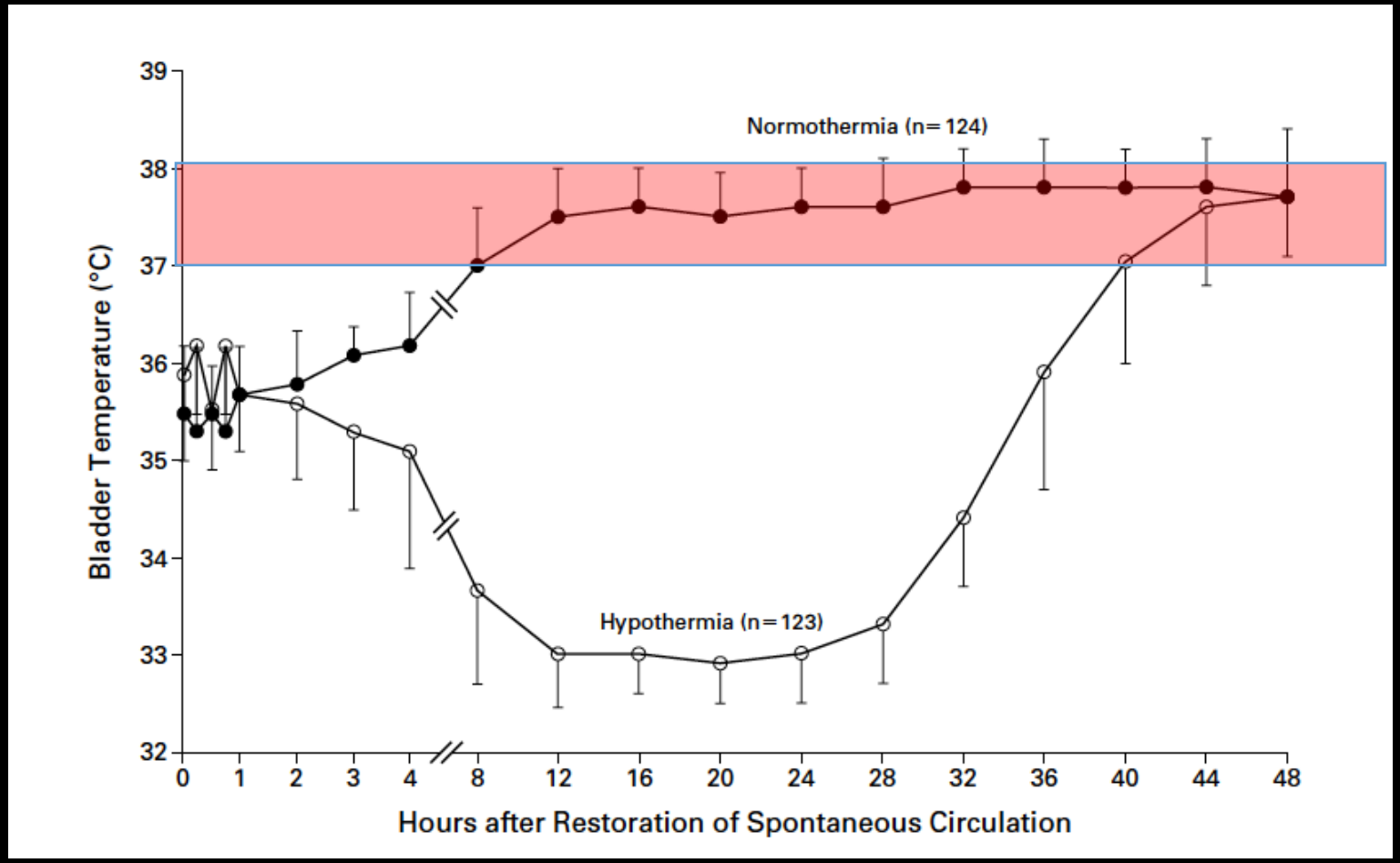
HACA-trial: Hypothermia Improves Survival !



No. at Risk					
Hypothermia	137	92	86	83	11
Normothermia	138	74	66	64	9

N Engl J Med 2002;346:549-56

HACA-trial: Hypothermia Compared with No Temperature Control = Fever!



N Engl J Med 2002;346:549-56

ELSEVIER

Resuscitation 57 (2003) 231–235

RESUSCITATION

www.elsevier.com/locate/resuscitation

Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation☆

Jerry P. Nolan[a,*], Peter T. Morley[b], Terry L. Vanden Hoek[c], Robert W. Hickey[d,1], ALS Task Force[2]

- Pz adulti non coscienti che abbiano sofferto un arresto cardiaco extraospedaliero andrebbero raffreddati a 32-34 °C per 12-24 h in caso di FV.
- Il raffreddamento potrebbe essere utile anche per altri ritmi di presentazione e per gli arresti intraospedalieri.

ILCOR Recommendations

On the basis of the published evidence to date, the Advanced Life Support (ALS) Task Force of the International Liaison Committee on Resuscitation (ILCOR) made the following recommendations in October 2002:

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF).
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.

Targeted temperature management in critical care: A report and recommendations from five professional societies*

Mark E. Nunnally, MD; Roman Jaeschke, MD; Geoffrey J. Bellingan, MD; Jacques Lacroix, MD; Bruno Mourvillier, MD; Gloria M. Rodriguez-Vega, MD, FCCM; Sten Rubertsson, MD, PhD, FCCM; Theodoros Vassilakopoulos, MD; Craig Weinert, MD; Sergio Zanotti-Cavazzoni, MD; Timothy G. Buchman, MD, PhD, FCCM

Sponsoring Organizations: American Thoracic Society (ATS) (http://www.thoracic.org), European Respiratory Society (ERS) (http://www.ersnet.org), European Society of Intensive Care Medicine (ESICM) (http://www.esicm.org), Society of Critical Care Medicine (SCCM) (http://www.sccm.org), Société de Réanimation de Langue Française (SRLF) (http://www.srlf.org).

Objective: **Representatives of five international critical care societies convened topic specialists and a nonexpert jury to review, assess, and report on studies of targeted temperature management and to provide clinical recommendations.**

Data Sources: **Questions were allocated to experts who reviewed their areas, made formal presentations, and responded to questions. Jurors also performed independent searches. Sources used for consensus derived exclusively from peer-reviewed reports of human and animal studies.**

Study Selection: **Question-specific studies were selected from literature searches; jurors independently determined the relevance of each study included in the synthesis.**

Conclusions and Recommendations: **1) The jury opines that the term "targeted temperature management" replace "therapeutic hypothermia."**

2) The jury opines that descriptors (e.g., "mild") be replaced with explicit targeted temperature management profiles.

3) The jury opines that each report of a targeted temperature management trial enumerate the physiologic effects anticipated by the investigators and actually observed and/or measured in subjects in each arm of the trial as a strategy for increasing knowledge of the dose/duration/response characteristics of temperature management. This enumeration should be kept separate from the body of the report, be organized by body systems, and be made without assertions about the impact of any specific effect on the clinical outcome.

4) The jury STRONGLY RECOMMENDS targeted temperature management to a target of 32°C–34°C as the preferred treatment (vs. unstructured temperature management) of *out-of-hospital* adult cardiac arrest victims with a first registered electrocardiography rhythm of ventricular fibrillation or pulseless ventricular tachycardia and still unconscious after restoration of spontaneous circulation (strong recommendation, moderate quality of evidence).

5) The jury WEAKLY RECOMMENDS the use of targeted temperature management to 33°C–35.5°C (vs. less structured management) in the treatment of term newborns who sustained asphyxia and exhibit acidosis and/or encephalopathy (weak recommendation, moderate quality of evidence). (Crit Care Med 2011; 39:1113–1125)

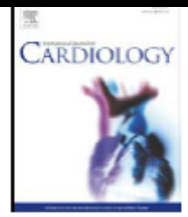
KEY WORDS: temperature; consensus; cardiac arrest; targeted temperature management; hypothermia

Hypothermia after Cardiac Arrest: A Metaanalysis

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Hypothermia after cardiac arrest should be further evaluated—A systematic review of randomised trials with meta-analysis and trial sequential analysis

Niklas Nielsen [a,*], Hans Friberg [b], Christian Gluud [c], Johan Herlitz [d], Jørn Wetterslev [c]

Earlier Trials:

- Possible risk of systematic errors
- Possible risk of being underpowered
- Investigated a selected group

Nielsen et al Int J Card 2010

Project

✓ There is a need for a sufficiently large clinical trial evaluating two target temperature management regimens

- both avoiding fever

✓ The study population should be inclusive and representative

N Engl J Med 2013;369:2197-206

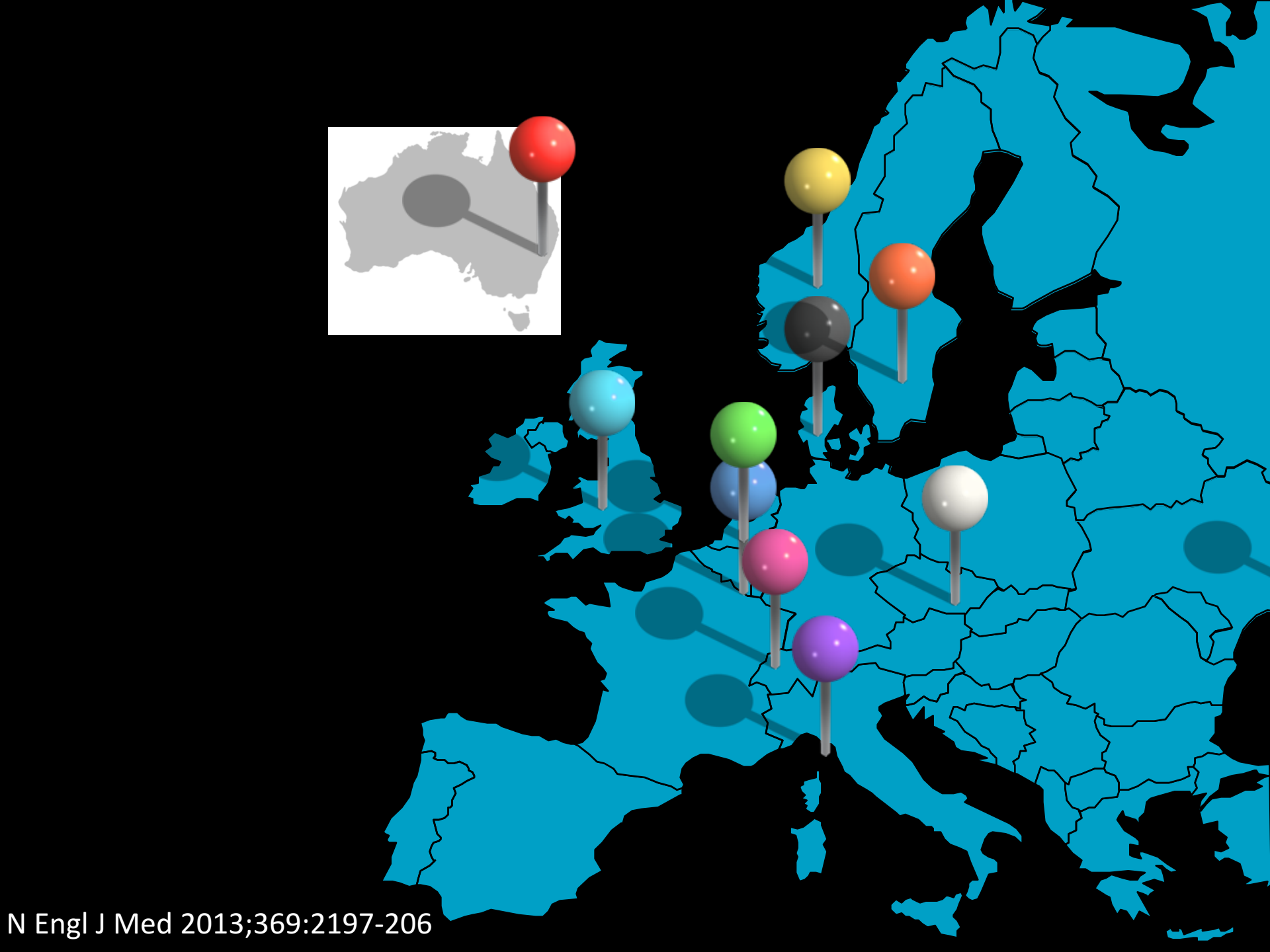
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

TTM 1 Trial

Main objective

To assess the efficacy and safety of a target temperature management of 33°C versus 36°C after resuscitation from out-of-hospital cardiac arrest of cardiac cause.

N Engl J Med 2013;369:2197-206



N Engl J Med 2013;369:2197-206

TTM1

- Enrolled 939 pts
- Open intervention
- Standardised rules for prognostication
- Standardised rules for withdrawal of life support
- Blinded outcome assessment

N Engl J Med 2013;369:2197-206

Design

- **INCLUSION CRITERIA**

- All cardiac arrest from cardiac cause
- All initial Rhythms
- Unconscious on admission to the hospital more than 20 min consecutive minutes of spontaneous circulation after ROSC

- **EXCLUSION CRITERIA**

- Time from ROSC to screening more than 240 min
- Unwitenessed asystolia
- Suspected or known acute intracranial hemorrhage or stroke

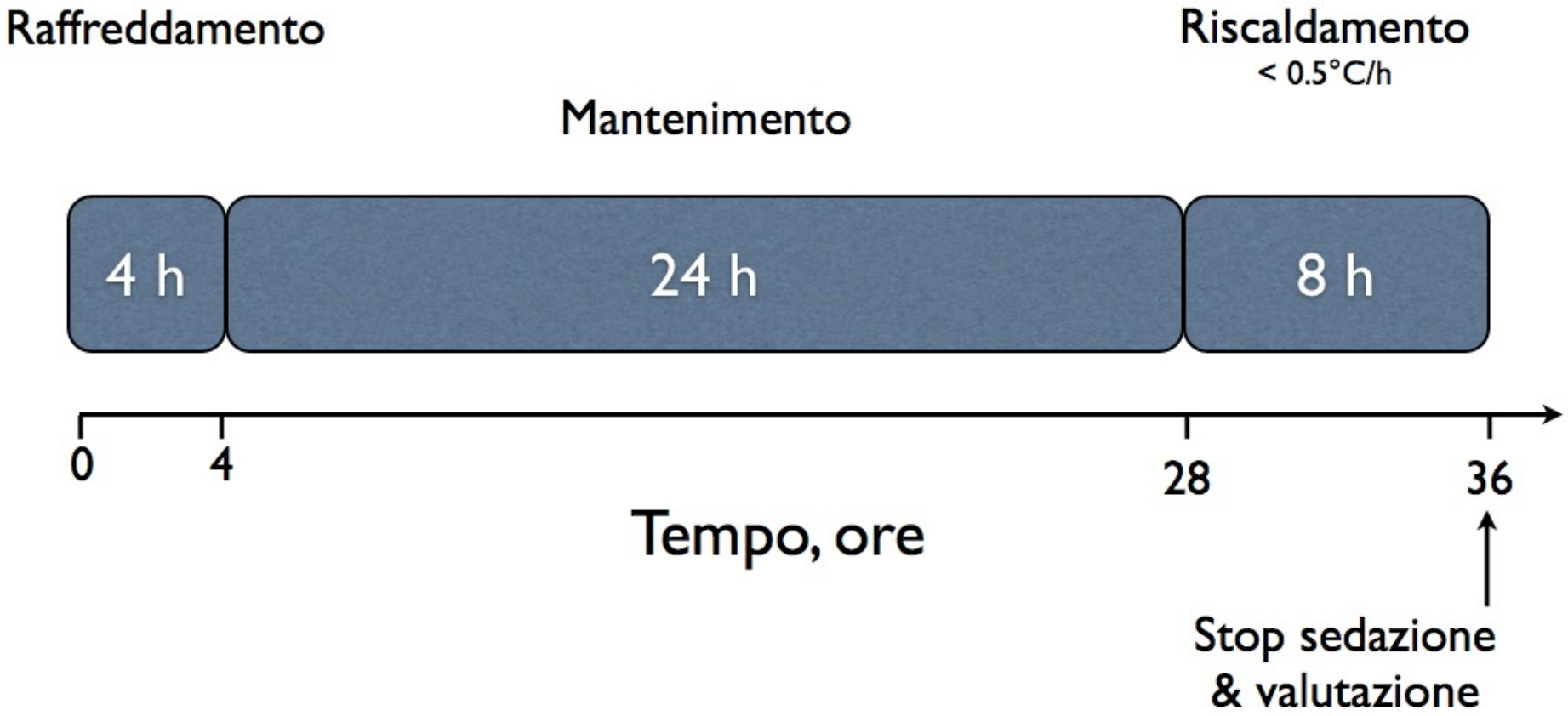
N Engl J Med 2013;369:2197-206

Endpoints

- ✓ **Primary endpoint:** Survival until the end of the trial
- ✓ **Secondary endpoints:**
- Landmark mortality and neurology 180 days
- Neurological function (CPC, mRS, MMSE, IQCODE)
- Safety aspects

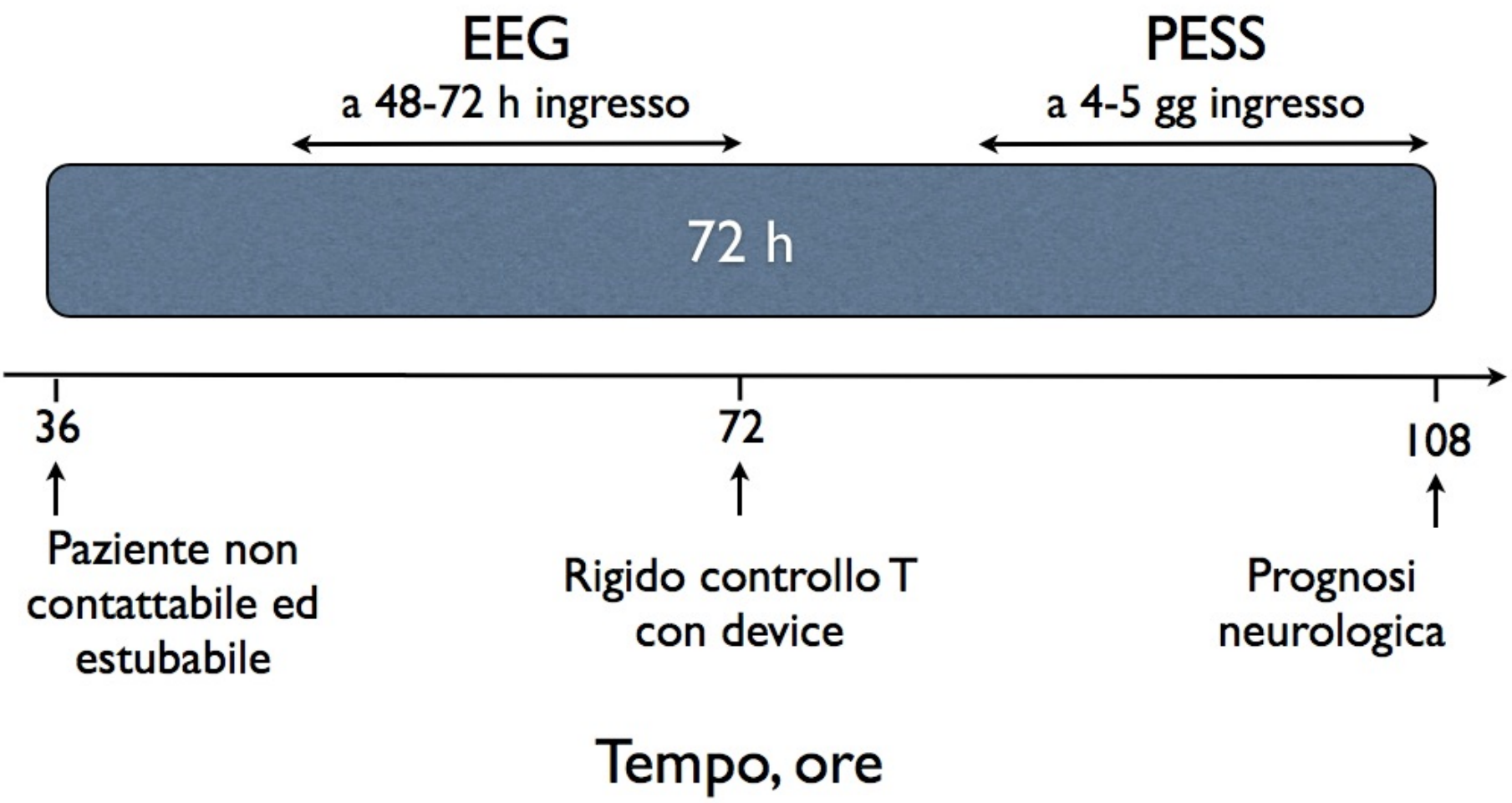
N Engl J Med 2013;369:2197-206

Fase di Trattamento



N Engl J Med 2013;369:2197-206

Fase di Gestione Attiva



N Engl J Med 2013;369:2197-206

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D., David Erlinge, M.D., Ph.D., Yvan Gasche, M.D., Christian Hassager, M.D., D.M.Sci., Janneke Horn, M.D., Ph.D., Jan Hovdenes, M.D., Ph.D., Jesper Kjaergaard, M.D., D.M.Sci., Michael Kuiper, M.D., Ph.D., Tommaso Pellis, M.D., Pascal Stammet, M.D., Michael Wanscher, M.D., Ph.D., Matt P. Wise, M.D., D.Phil., Anders Åneman, M.D., Ph.D., Nawaf Al-Subaie, M.D., Søren Boesgaard, M.D., D.M.Sci., John Bro-Jeppesen, M.D., Iole Brunetti, M.D., Jan Frederik Bugge, M.D., Ph.D., Christopher D. Hingston, M.D., Nicole P. Juffermans, M.D., Ph.D., Matty Koopmans, R.N., M.Sc., Lars Køber, M.D., D.M.Sci., Jørund Langørgen, M.D., Gisela Lilja, O.T., Jacob Eifer Møller, M.D., D.M.Sci., Malin Rundgren, M.D., Ph.D., Christian Rylander, M.D., Ph.D., Ondrej Smid, M.D., Christophe Werer, M.D., Per Winkel, M.D., D.M.Sci., and Hans Friberg, M.D., Ph.D., for the TTM Trial Investigators*

N Engl J Med 2013;369:2197-206

Results

Characteristic	33°C Group (N=473)	36°C Group (N=466)
Demographic characteristics		
Age — yr	64±12	64±13
Male sex — no. (%)	393 (83)	368 (79)
Location of cardiac arrest — no. (%)†		
Place of residence	245 (52)	255 (55)
Public place	197 (42)	188 (40)
Other	31 (7)	22 (5)
Bystander witnessed cardiac arrest — no. (%)	420 (89)	418 (90)
Bystander performed CPR — no. (%)	344 (73)	339 (73)
First monitored rhythm — no. (%)†		
Shockable rhythm	375 (79)	377 (81)
Ventricular fibrillation	349 (74)	356 (77)
Nonperfusing ventricular tachycardia	12 (3)	12 (3)
Unknown rhythm but responsive to shock	5 (1)	5 (1)
Perfusing rhythm after bystander-initiated defibrillation	9 (2)	4 (1)
Asystole	59 (12)	54 (12)
Pulseless electrical activity	37 (8)	28 (6)

Results

Characteristic	33°C Group (N=473)	36°C Group (N=466)
Time from cardiac arrest to event — min‡		
Start of basic life support		
Median	1	1
Interquartile range	0–2	0–2
Start of advanced life support		
Median	10	9
Interquartile range	6–13	5–13
Return of spontaneous circulation		
Median	25	25
Interquartile range	18–40	16–40

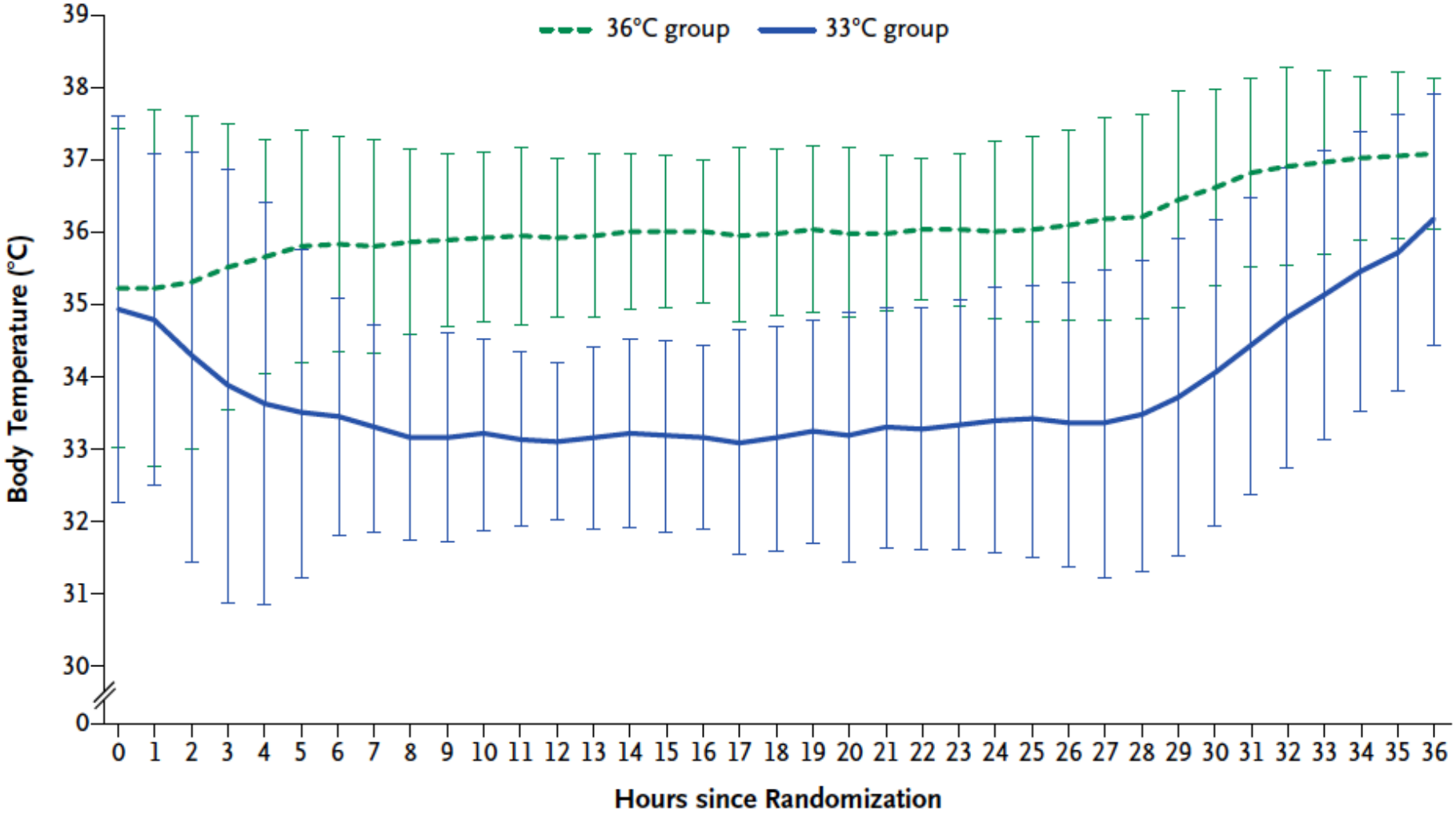
N Engl J Med 2013;369:2197-206

Results

Characteristic	33°C Group (N=473)	36°C Group (N=466)
Clinical characteristics on admission		
First measured body temperature — °C	35.2±1.3	35.3±1.1
Glasgow Coma Scale score§		
Median	3	3
Interquartile range	3–4	3–4
Corneal reflex present — no./total no. (%)	264/407 (65)	258/392 (66)
Pupillary reflex present — no./total no. (%)	344/460 (75)	363/458 (79)
Serum pH	7.2±0.2	7.2±0.2
Serum lactate — mmol/liter	6.7±4.5	6.7±4.5
Circulatory shock — no. (%)¶	70 (15)	67 (14)
ST-segment elevation myocardial infarction — no. (%)	190 (40)	194 (42)

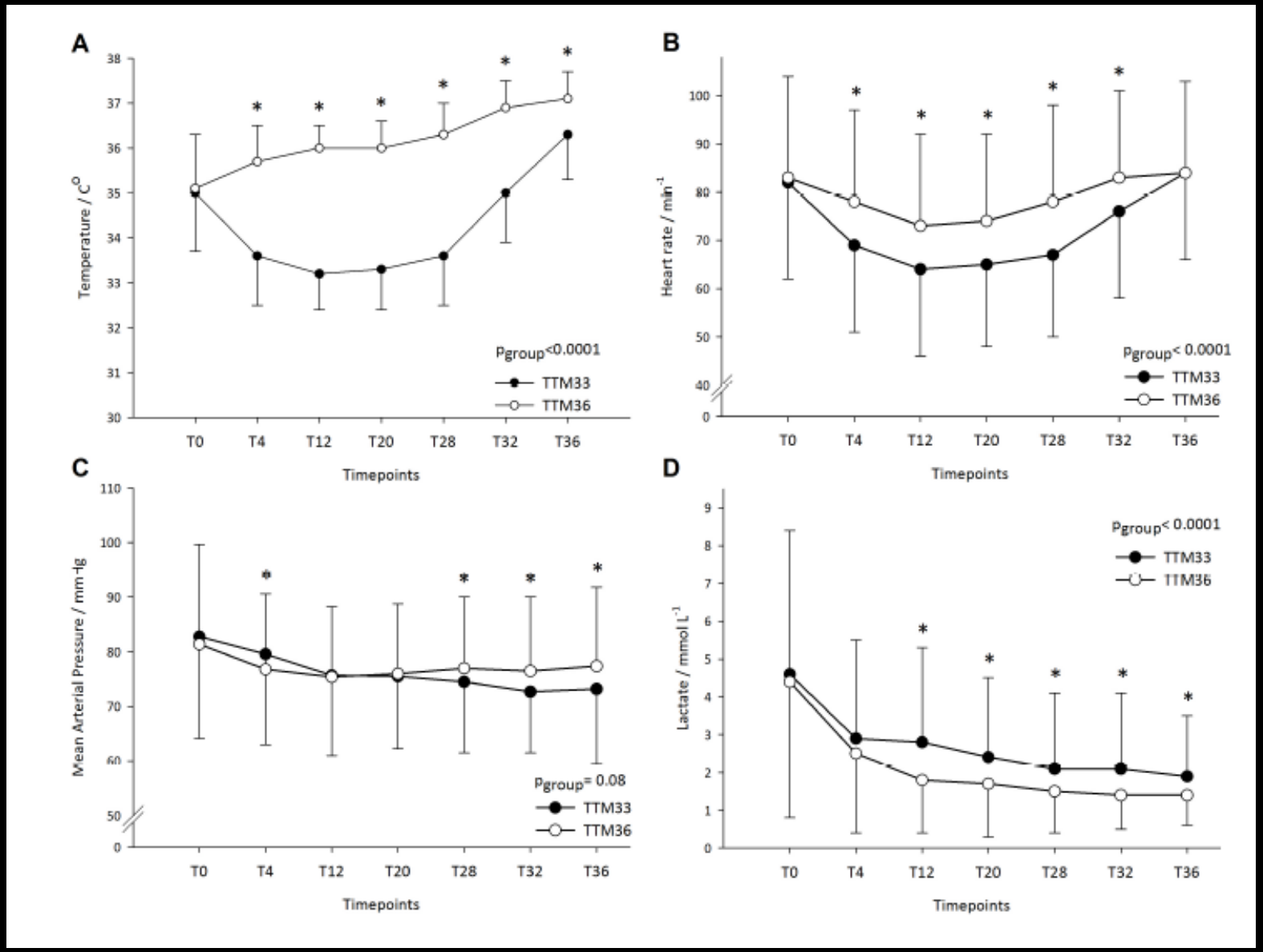
N Engl J Med 2013;369:2197-206

Results



N Engl J Med 2013;369:2197-206

Results



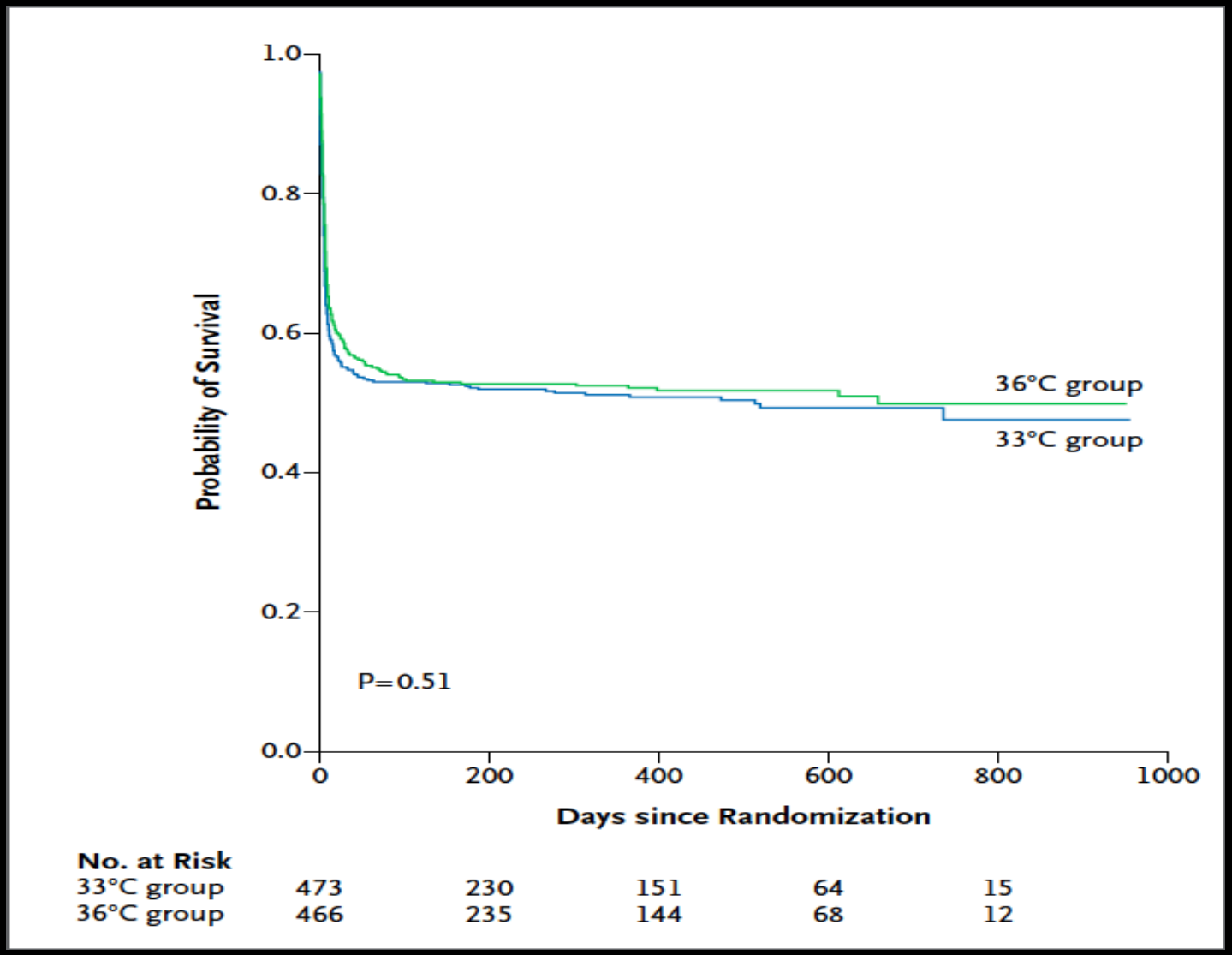
N Engl J Med 2013;369:2197-206

Results

Outcome	33°C Group	36°C Group	Hazard Ratio or Risk Ratio (95% CI)*	P Value
	no./total no. (%)			
Primary outcome: deaths at end of trial	235/473 (50)	225/466 (48)	1.06 (0.89–1.28)	0.51
Secondary outcomes				
Neurologic function at follow-up†				
CPC of 3–5	251/469 (54)	242/464 (52)	1.02 (0.88–1.16)	0.78
Modified Rankin scale score of 4–6	245/469 (52)	239/464 (52)	1.01 (0.89–1.14)	0.87
Deaths at 180 days	226/473 (48)	220/466 (47)	1.01 (0.87–1.15)	0.92

N Engl J Med 2013;369:2197-206

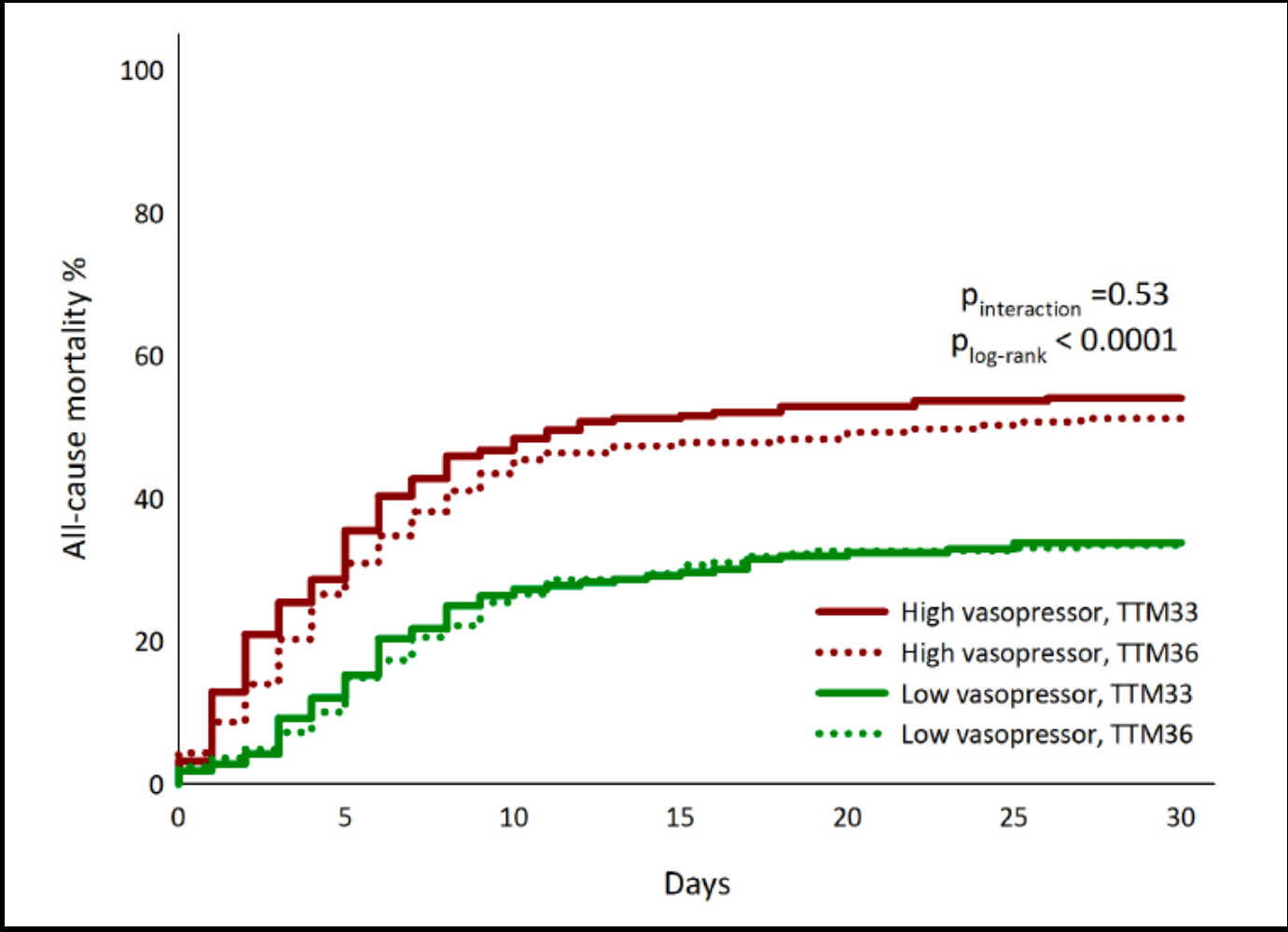
Results



N Engl J Med 2013;369:2197-206

Hemodynamics and Vasopressor Support At Two Target Temperatures After Cardiac Arrest

Bro-Jeppesen J, et al. (Intensive Care Med 2014)



Hemodynamics and vasopressor support at two target temperatures after cardiac arrest

Bro-Jeppesen J, et al. (Intensive Care Med 2014)

- Target temperature (TT) management at 33 °C compared to 36 °C was associated with:

✓ decreased heart rate
✓ elevated lactate levels
✓ need for increased vasopressor support

- Requirement for high doses of vasopressors and low MAP (< 65 mmHg) were both independent predictors of 30-day mortality independent of TT

Conclusions

In unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac cause:

- Hypothermia at a targeted temperature of 33°C did not confer a benefit as compared with a targeted temperature of 36°C.

N Engl J Med 2013;369:2197-206

ILCOR STATEMENT 2015

- We recommend targeted temperature management as opposed to no targeted temperature management for adults with OHCA with an initial shockable rhythm who remain unresponsive after ROSC (strong recommendation, low-quality evidence).

- We suggest targeted temperature management for adults with OHCA with an initial nonshockable rhythm who remain unresponsive after ROSC (weak recommendation, low-quality evidence).

- We suggest targeted temperature management for adults with IHCA with any initial rhythm who remain unresponsive after ROSC (weak recommendation, very low-quality evidence).

ILCOR STATEMENT 2015

We recommend selecting and maintaining a constant target temperature between 32°C and 36°C for those patients in whom targeted temperature management is used (strong recommendation, moderate-quality evidence).

- We recommend against routine use of prehospital cooling with rapid infusion of large volumes of cold intravenous fluid immediately after ROSC (strong recommendation, moderate-quality evidence).

- We suggest that if targeted temperature management is used, duration should be at least 24 hours as done in the 2 largest previous RCTs.

Deye et al. Ann. Intensive Care (2016) 6:4
DOI 10.1186/s13613-015-0104-6

Annals of Intensive Care
a SpringerOpen Journal

RESEARCH Open Access

Changes in cardiac arrest patients' temperature management after the 2013 "*TTM*" trial: results from an international survey

Nicolas Deye[1*], François Vincent[2], Philippe Michel[3], Stephan Ehrmann[4], Daniel da Silva[5], Michael Piagnerelli[6], Antoine Kimmoun[7], Olfa Hamzaoui[8], Jean-Claude Lacherade[9], Bernard de Jonghe[10], Florence Brouard[3], Corinne Audoin[11], Xavier Monnet[12], Pierre-François Laterre[13] and For the SRLF Trial Group

- Survey performed by the French Intensive Care Society
  - May 2014 - January 2015
- 518 respondents from 264 ICUs in 11 countries fulfilled the survey
  - 16% response

Deye *et al. Ann. Intensive Care (2016) 6:4*
DOI 10.1186/s13613-015-0104-6

Annals of Intensive Care
a SpringerOpen Journal

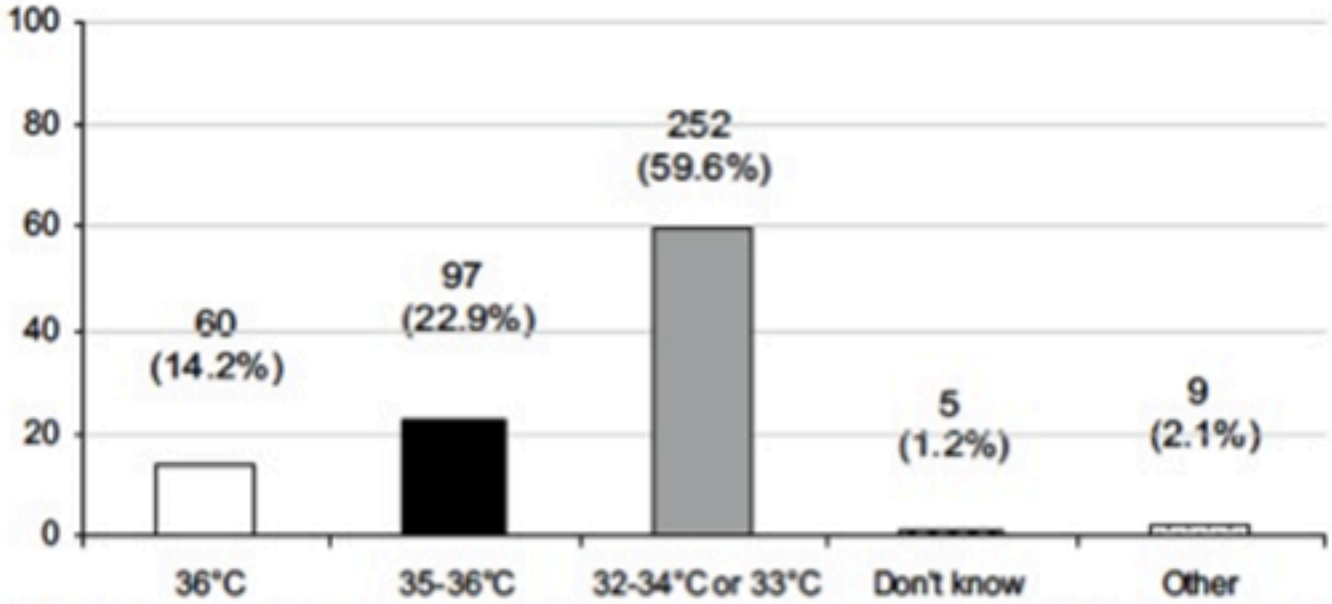


Fig. 1 Distribution of the new targets temperature expressed as absolute number (percentage) after the Nielsen's publication [6] ($n = 423$ respondents, expressed as percentage). Other targets ($n = 9$, 2.1 %) were documented as follows: 37 °C ($n = 4$, 0.9 %), 34 °C ($n = 3$, 0.7 %), and 35 °C ($n = 2$, 0.5 %)

Controversials (1)

- No comparison of hypothermia vs normothermia but of 33C°hypothermia versus 36C°hypothermia

Is fever control a sufficient measure to attenuate brain damage after cardiac arrest?

- Presence of numerous favor factors in both groups in TTM1 trial

Are there subgroups that would benefit from temperature management at a higher or lower level (for instance patients with longer arrests and more severe brain damage, or patients in circulatory shock)?

Controversials (2)

- Too long time interval between ROSC and target temperature achieve (screening time up to 4 hours)

Could faster and earlier induction hypothermia improve outcomes in the 33°C-group?

- Sample Size

- The results of the TTM1-trial are not definitive. Does it mean the need for larger sample sizes or meta-analytical approaches to better estimate effects.

Controversials (3)

Could a longer follow-up lead to identify which intervention is superior?

Open questions – Intervention period

- When to start cooling?
- Duration of hypothermia
- Depth of hypothermia or only not fever?

HYPOTHERMIA IN OUT OF HOSPITAL SETTING : WHY NOT ? …. IN MY OPINION ….

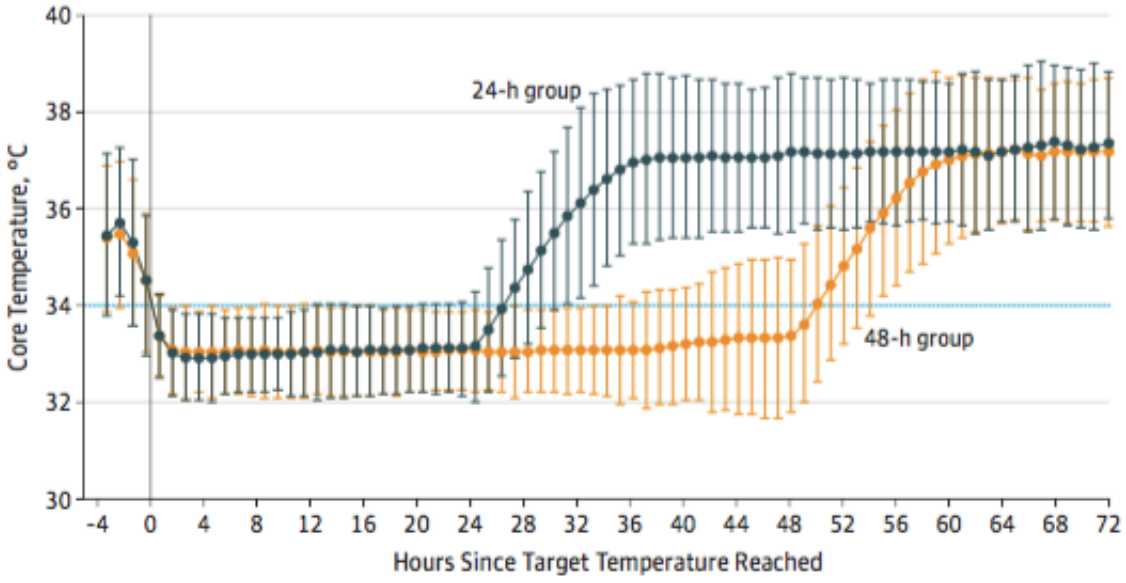
- The temperature normally decreases within the first hour
- It's necessary to use a temperature monitoring that avoids temperature fluctuations(and that includes continuous temperature feedback to achieve a set target temperature)
- Plasma electrolyte concentrations can change rapidly during cooling
- Effective intravascolar volume can change rapidly during cooling
- The patient needs neuromuscolar blockade and deep sedation to prevent shivering
- OH Inducing hypothermia means more time consuming for 118 staff

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest
A Randomized Clinical Trial

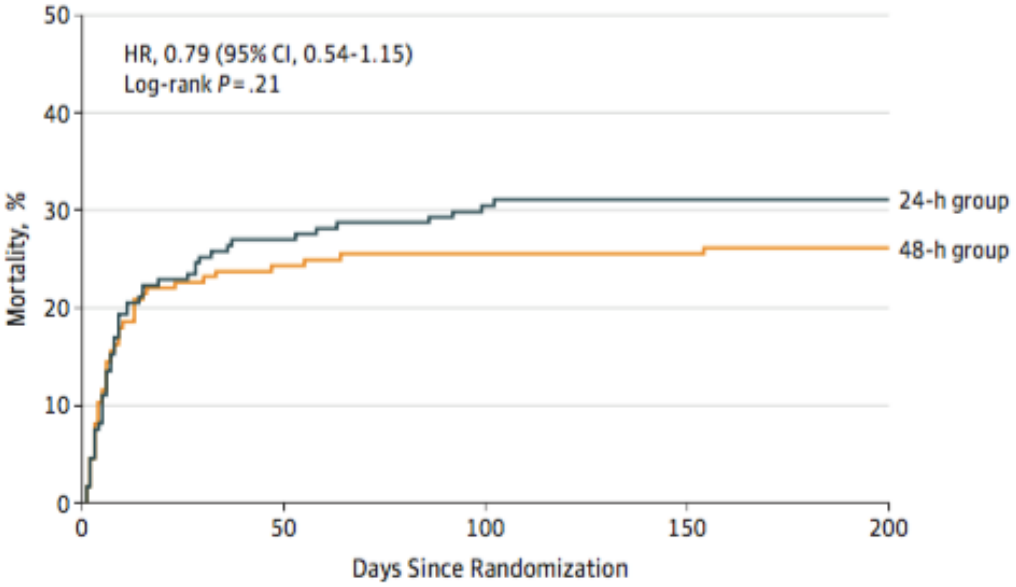
Hans Kirkegaard, MD, PhD, DMSci, DEAA, DLS; Eldar Søreide, MD, PhD, FERC; Inge de Haas, MD; Ville Pettilä, MD, PhD, EDIC; Fabio Silvio Taccone, MD, PhD; Urmet Arus, MD; Christian Storm, MD, PhD; Christian Hassager, MD, DMSc; Jørgen Feldbæk Nielsen, MD, DMSci; Christina Ankjær Sørensen, MD; Susanne Ilkjær, MD, PhD; Anni Nørgaard Jeppesen, MD; Anders Morten Grejs, MD, PhD; Christophe Henri Valdemar Duez, MD; Jakob Hjort, MPH; Alf Inge Larsen, MD, PhD, FESC; Valdo Toome, MD; Marjaana Tiainen, MD, PhD; Johanna Hästbacka, MD, PhD; Timo Laitio, MD, PhD; Markus B. Skrifvars, MD, PhD, EDIC, FCICM

Fi **Figure 2. Core Temperature of the Intervention Groups**



Temperatures in the study groups until 72 hours after achieving target temperature (≤34°C [dotted horizontal line]), with T0 defined as the time target temperature was reached. Temperature data were available for 347 of 352 patients and were recorded with variable frequency (median, 188; interquartile range, 61-798) during the depicted period, with no statistically significant difference in frequency between groups (P = .15). Values are presented as mean ±2 SDs.

Figure 3. Probability of Death With Standard and Prolonged Targeted Temperature Management.



No. at risk

48-h group	175	131	128	128	127
24-h group	177	125	117	120	117

Kaplan-Meier probability of death from randomization to 6 months (200 days) in the study groups. Median follow-up time was 184 days (IQR, 33-196 days) in the 48-hour group and 181 days (IQR, 15-193 days) in the 24-hour group.

Results

	No. (%) of Patients				
	48-Hour Group (n = 175)	24-Hour Group (n = 176)	Difference, % (95% CI)	RR (95% CI)	*P* Value
Primary outcome: CPC score of 1 or 2 at 6 mo	120 (69)	112 (64)	4.9 (−5 to 14.8)	1.08 (0.93 to 1.25)	.33
Secondary outcomes					
Mortality at 6 mo	48 (27)	60 (34)	−6.5 (−16.1 to 3.1)	0.81 (0.59 to 1.11)	.19
Any adverse event	169 (97)	161 (91)	5.6 (0.6 to 10.6)	1.06 (1.01 to 1.12)	.03

TTM2
Hypothermia or Normothermia –

Targeted Temperature Management after Out-of-hospital Cardiac Arrest, a randomised, parallell, groups, assessor blinded clinical trial

Main objective

To test the hypothesis that post –ischemic hypothermia, when compared
With normothermia and avoidance of fever, decreases mortality and improves neurologic function in unconscious adult after OHCA

Sample Size

Based on the results of the TTM1-trial and information in the International cardiac arrest registry, we calculate the sample size based on a total mortality of 45% and the possibility to demonstrate a relative risk of 0.8 with 90% power, giving 518 patients per group. In a conservative attempt to allow for a possible loss to follow-up, and in a scenario of low loss also gain power, we will recruit 1200 patients.

Population

Inclusion criteria

- Out-of-hospital CA or unknown cause
- Cardiac cause or unknown cause
- Sustained ROSC (<20 minutes without CPR)
- Unconscious (FOUR-score motor response of <4, not able to obey verbal commands) after sustained ROSC

Population

Exclusion criteria 1

- In-hospital cardiac arrest
- Cardiac arrest of non-cardiac cause
- Known bleeding diathesis
- Pregnancy
- Suspected or confirmed acute intracranial bleeding
- Unwitnessed asystole
- On ECMO prior to ROSC

Population

Exclusion criteria 2

- Temp <30°C at admission
- Known or current limitations in therapy
- 180 days survival unlikely
- > 3 hours (180 minutes) from ROSC to screening

Fever and normothermia

- Fever 37.8 and up
- Normothermia defined as the abscence of fever (From 36.5 to below 37.8)

LUND UNIVERSITY

Temperature Choice

- Diagrammatic data from the HACA-trial suggests a median temperature between 37.5°C and 37.8°C among patients in the control arm of the study. If a similar distribution is assumed in the current trial a substantial amount of patients will not require a device, thus making temperature management considerably less labour and resource intense.

- 37.7°C has been proposed as the upper limit of normal body temperature in healthy adults..

A Critical Appraisal of 98.6°F, the Upper Limit of the Normal Body Temperature, and Other Legacies of Carl Reinhold August Wunderlich

Philip A. Mackowiak, MD; Steven S. Wasserman, PhD; Myron M. Levine, MD

Objective.—To evaluate critically Carl Wunderlich's axioms on clinical thermometry.

Design.—Descriptive analysis of baseline oral temperature data from volunteers participating in *Shigella* vaccine trials conducted at the University of Maryland Center for Vaccine Development, Baltimore.

Setting.—Inpatient clinical research unit.

Participants.—One hundred forty-eight healthy men and women aged 18 through 40 years.

Main Measurements.—Oral temperatures were measured one to four times daily for 3 consecutive days using an electronic digital thermometer.

Results.—Our findings conflicted with Wunderlich's in that 36.8°C (98.2°F) rather than 37.0°C (98.6°F) was the mean oral temperature of our subjects; 37.7°C (99.9°F) rather than 38.0°C (100.4°F) was the upper limit of the normal temperature range; maximum temperatures, like mean temperatures, varied with time of day; and men and women exhibited comparable thermal variability. Our data corroborated Wunderlich's in that mean temperature varied diurnally, with a 6 AM nadir, a 4 to 6 PM zenith, and a mean amplitude of variability of 0.5°C (0.9°F); women had slightly higher normal temperatures than men; and there was a trend toward higher temperatures among black than among white subjects.

Conclusions.—Thirty-seven degrees centigrade (98.6°F) should be abandoned as a concept relevant to clinical thermometry; 37.2°C (98.9°F) in the early morning and 37.7°C (99.9°F) overall should be regarded as the upper limit of the normal oral temperature range in healthy adults aged 40 years or younger, and several of Wunderlich's other cherished dictums should be revised.

ple present a temperatu
less than younger pers

Only a few studies ha
appraise critically Wur
vations. Most were perf
years ago and involv
numbers of subjects[1,5]
bers of subjects from
gle temperature read
tained.[4,5] The presen
represents a more com
praisal than any yet pu
cepts promulgated
more than 120 years a

Subjects and Methods

Subjects.—One hund
subjects (aged 18 throug
ticipated in the investig
cluded 122 men (88 blac
Hispanic, and one Or
women (17 black and
were healthy volunteer
the community for nine
tient *Shigella* vaccine
at the Center for Vaccin

Primary Endpoint

The primary objective of this study is to determine if hypothermia (33°C) increases 180 day survival when compared to normothermia and avoidance of fever, in patients who are unconscious after OHCA.

Secondary Endpoints

- To evaluate if there is any difference in functional outcomes, using the Glasgow Outcome Scale-extended (GOS-E) between patients managed at 33°C compared to normothermia and avoidance of fever

- To evaluate potential differences in health-related quality of life (HRQoL) at follow up using EQ5D-5L

Tertiary explorative endpoints

- To evaluate functional outcomes using the mRS at 30 days and 180 days after CA
- To test leg strength and endurance, using the The 30-Second Chair Stand Test.
- Detailed neuro-cognitive function assessed by the Montreal Cognitive Assessment (MoCA) and the Symbol Digit Modalities Test (SDMT)
- Self and observer reported cognitive disability using Two Simple Questions (TSQ) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).
- Assessment at 24 months (Survival, GOS-E, EQ5D-5L, MoCA, SDMT, TSQ, IQCODE)

Prognostication in the TTM2-trial

- 96 hours after CA or later
- Based on the ERC/ESICM guidelines
- Prognosis *likely poor* – YES/NO

- EEG
  - All patients
  - Centralized blinded evaluation
  - Separate protocols

- Biobank

LUND UNIVERSITY

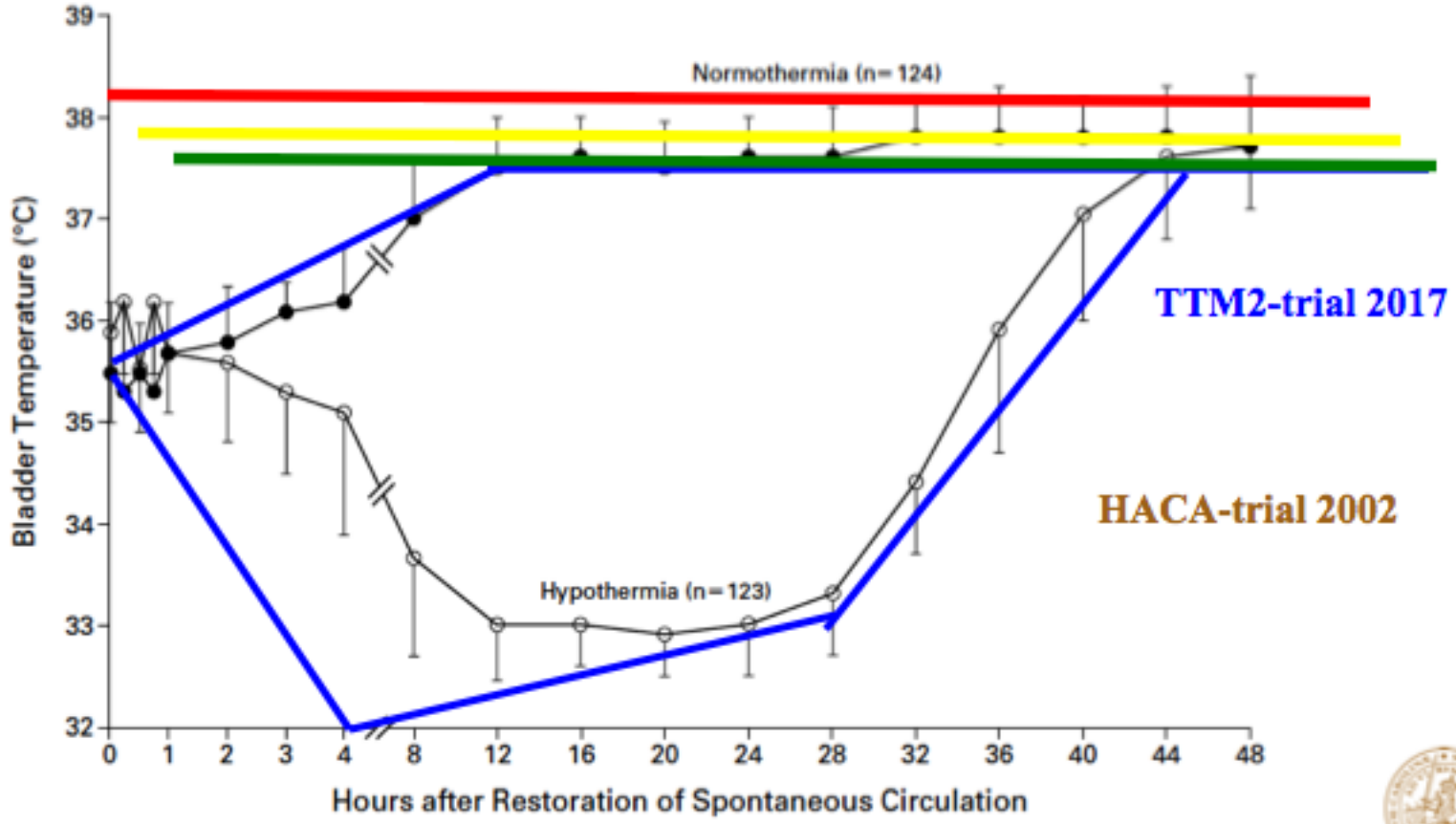
Why all initial rhythms?

- Possible neuroprotection should not depend on cardiac rhythm
- Increases generalisability
- PEA and witnessed asystole of cardiac cause have a fair prognosis (Hypothermia Network data)

Why all initial rhythms?

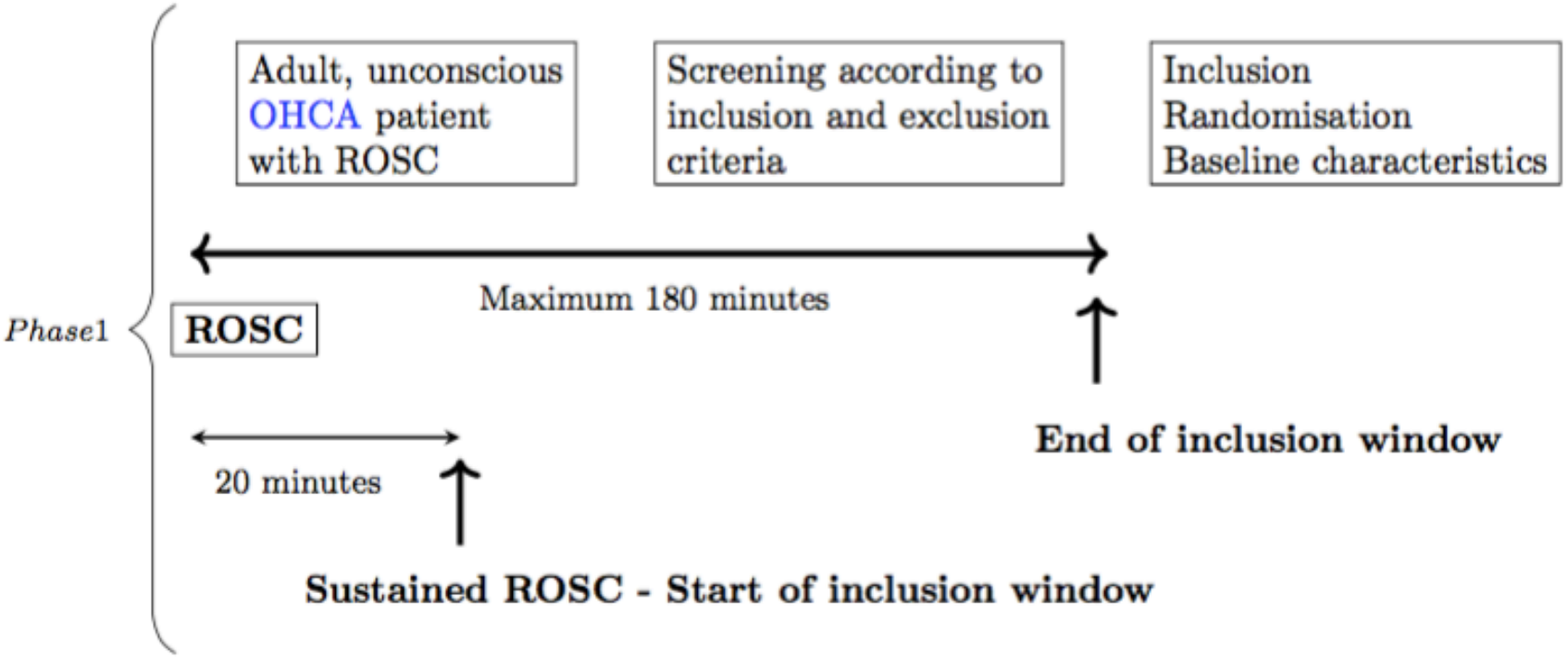
- Possible neuroprotection should not depend on cardiac rhythm
- Increases generalisability
- Asystole and PEA of cardiac cause- fair prognosis

TTM2-temperature profile

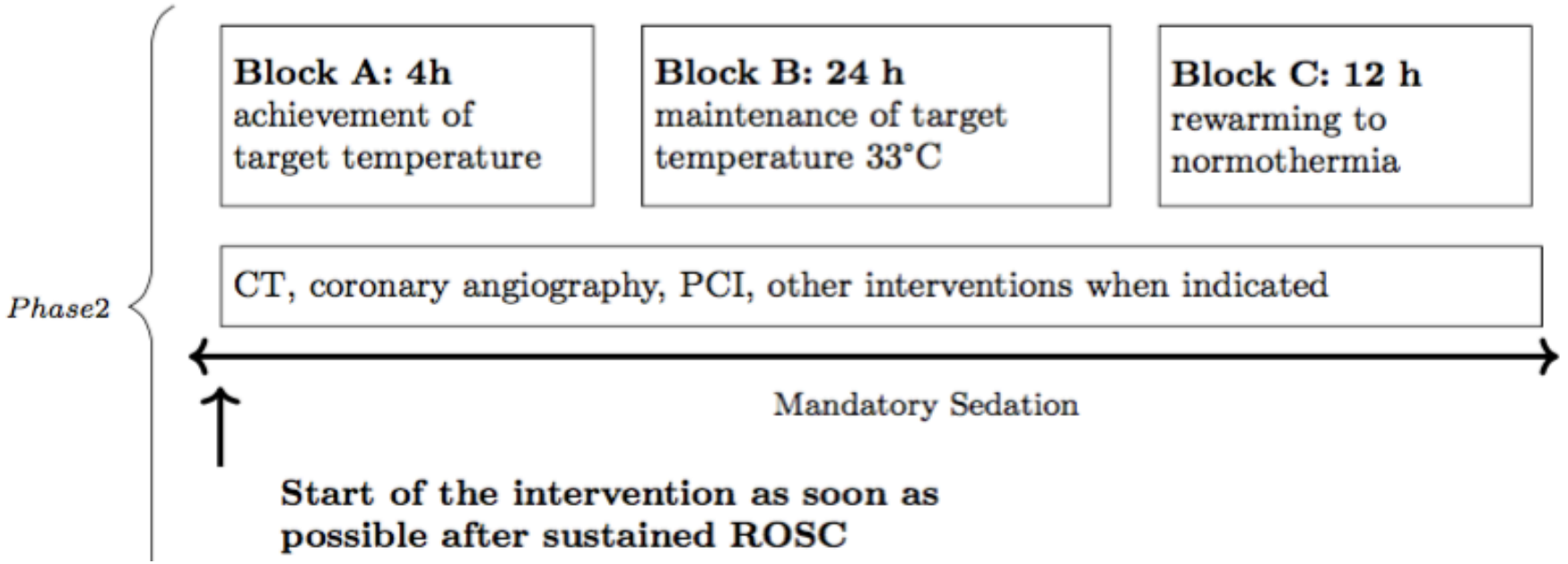


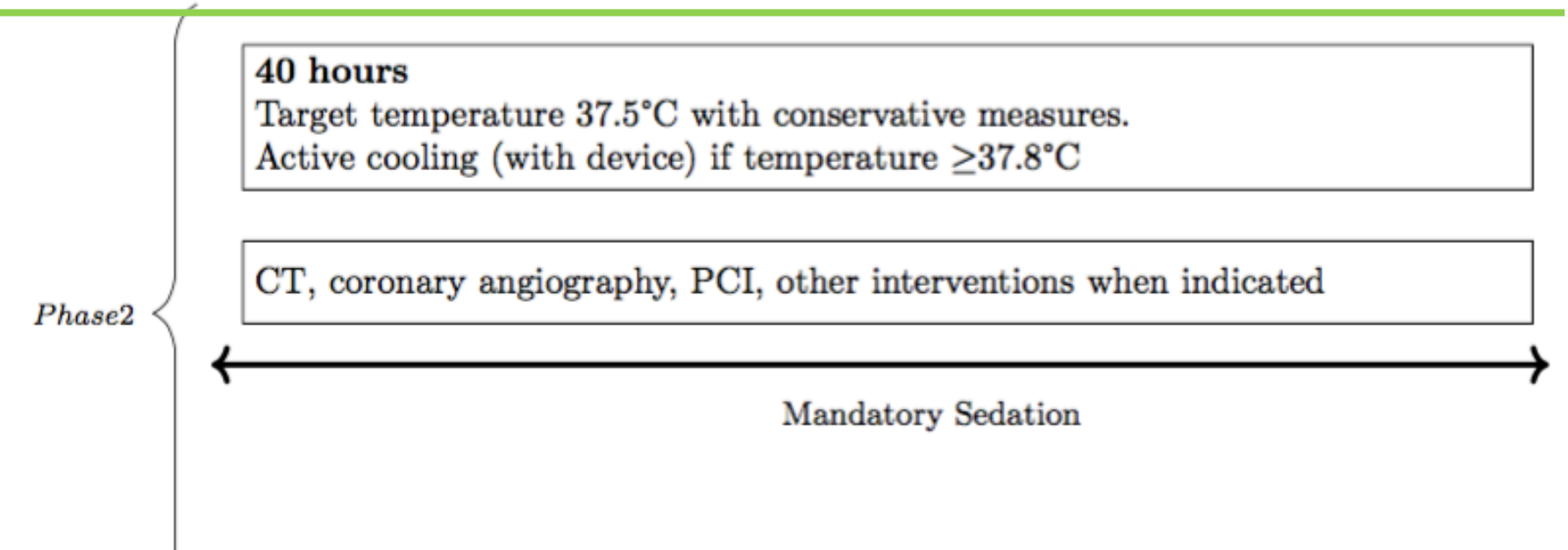
LUND UNIVERSITY

COOLING

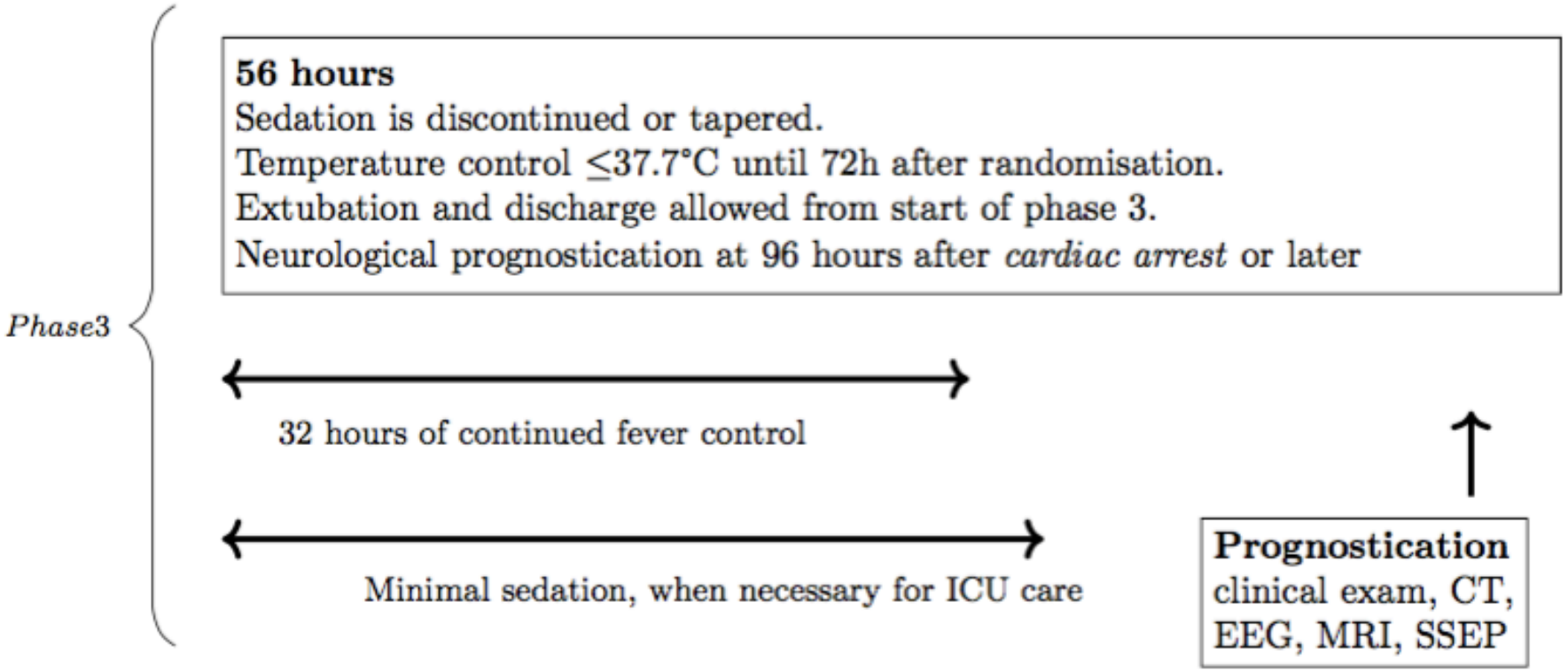

Adult, unconscious OHCA patient with ROSC
Screening according to inclusion and exclusion criteria
Inclusion Randomisation Baseline characteristics
Maximum 180 minutes
Phase1
ROSC
End of inclusion window
20 minutes
Sustained ROSC - Start of inclusion window

MAINTENANCE





Sedation discontinued



Timeline

- 2017 center recruitment -start patients enrollment
- Early 2018 most sites active, run-in period
- 2017 – 2019 Patient recruitment and interim analysis
- 2020 Presentation of result , long term follow up performed
- 2022 Presentation of long term outcomes

S. Martino Hospital - Intensive Care
(Prof. P. Pelosi)

- **National Coordinator center**
- **CE approval – 31 agosto 2017**
- **Start up enrollment TTM 2 trial : 15 november 2017**

Targeted Temperature Management After Cardiac Arrest
Finding the Right Dose for Critical Care Interventions

Opinion Editorial

Advancement in resuscitation requires identification of appropriate targets or monitors to guide titration of post arrest care to individual response. Advances may also require more sophisticated trial designs.

Clifton W. Callaway, MD

JAMA July 25, 2017 Volume 318, Number 4

Everyday is a new beginning …
look at what can be

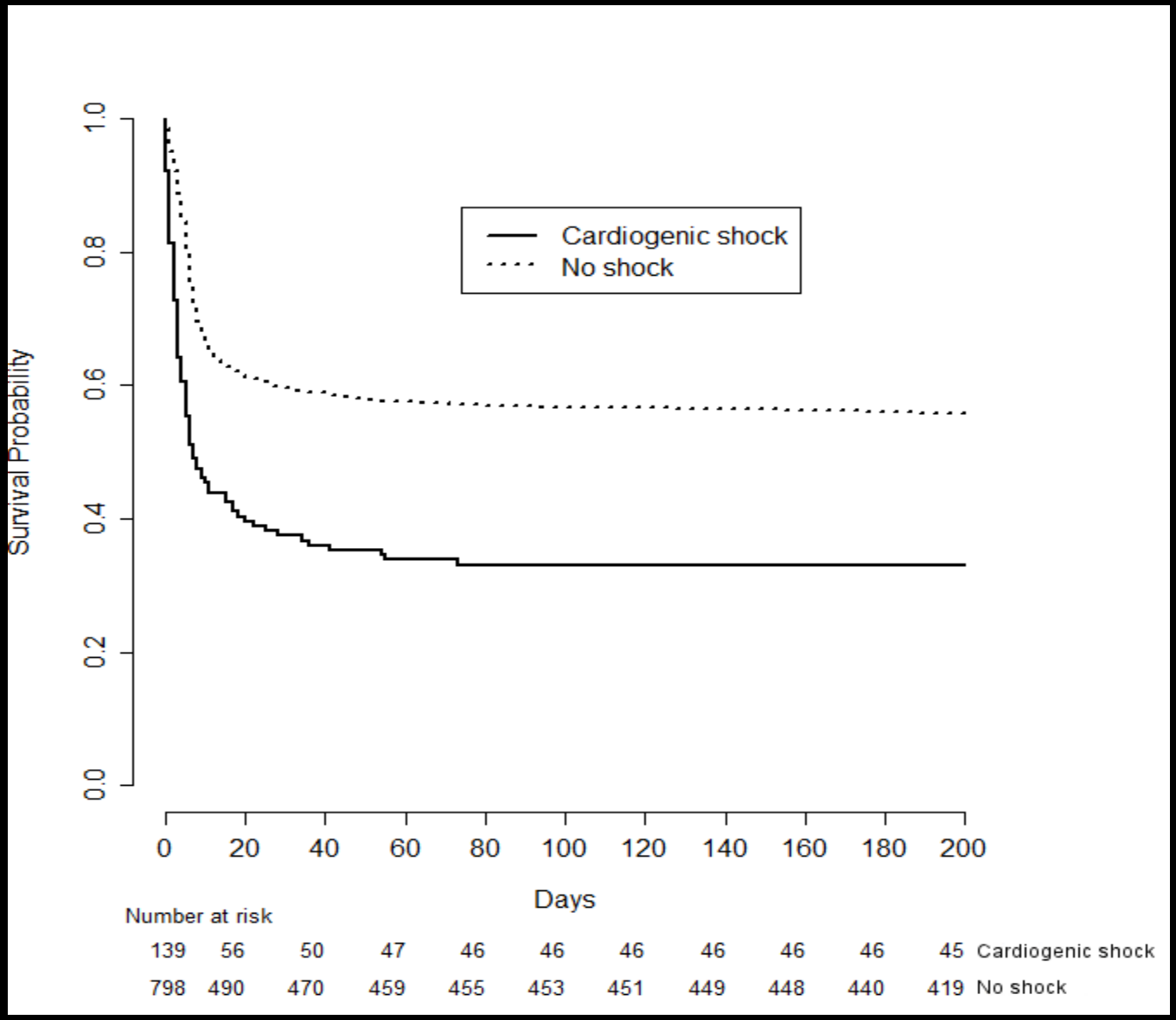
brunettimed@gmail.com

Effect of targeted temperature management at 33°C versus 36°C in patients with shock after out-of-hospital cardiac arrest

- A post-hoc analysis of the Target Temperature Management trial

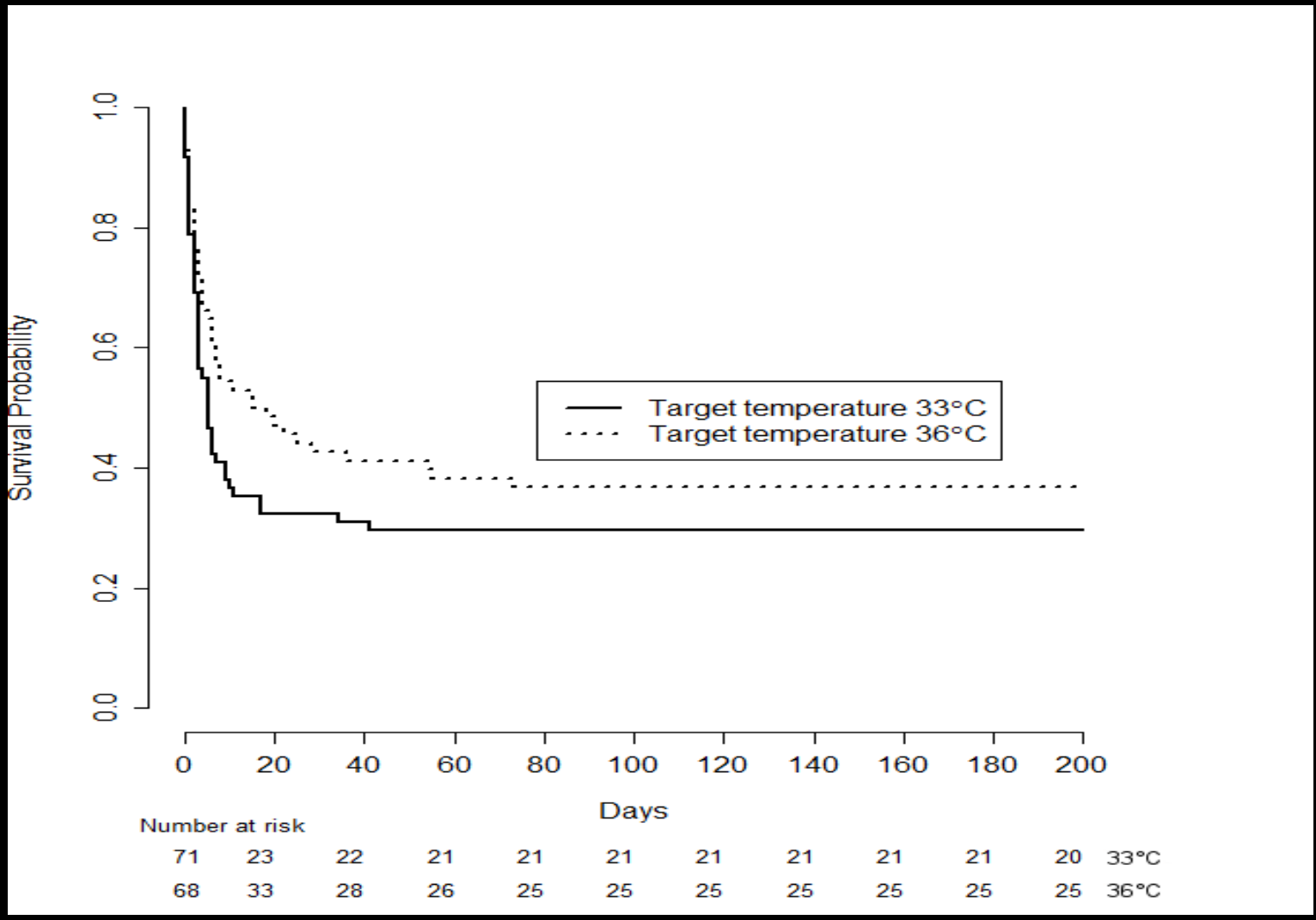
Martin Annborn [a], John Bro-Jeppesen [b], Niklas Nielsen [c], Susann Ullén [d], Jesper Kjaergaard [b], Christian Hassager [b], Michael Wanscher [e], Thomas Pellis [f], Paolo Pelosi [g], Matt P Wise [h], Tobias Cronberg [i], David Erlinge [j], Hans Friberg [a] on behalf of the TTM-trial investigators

Probability of survival through 180 days for patients with shock on admission compared to patients with no-shock



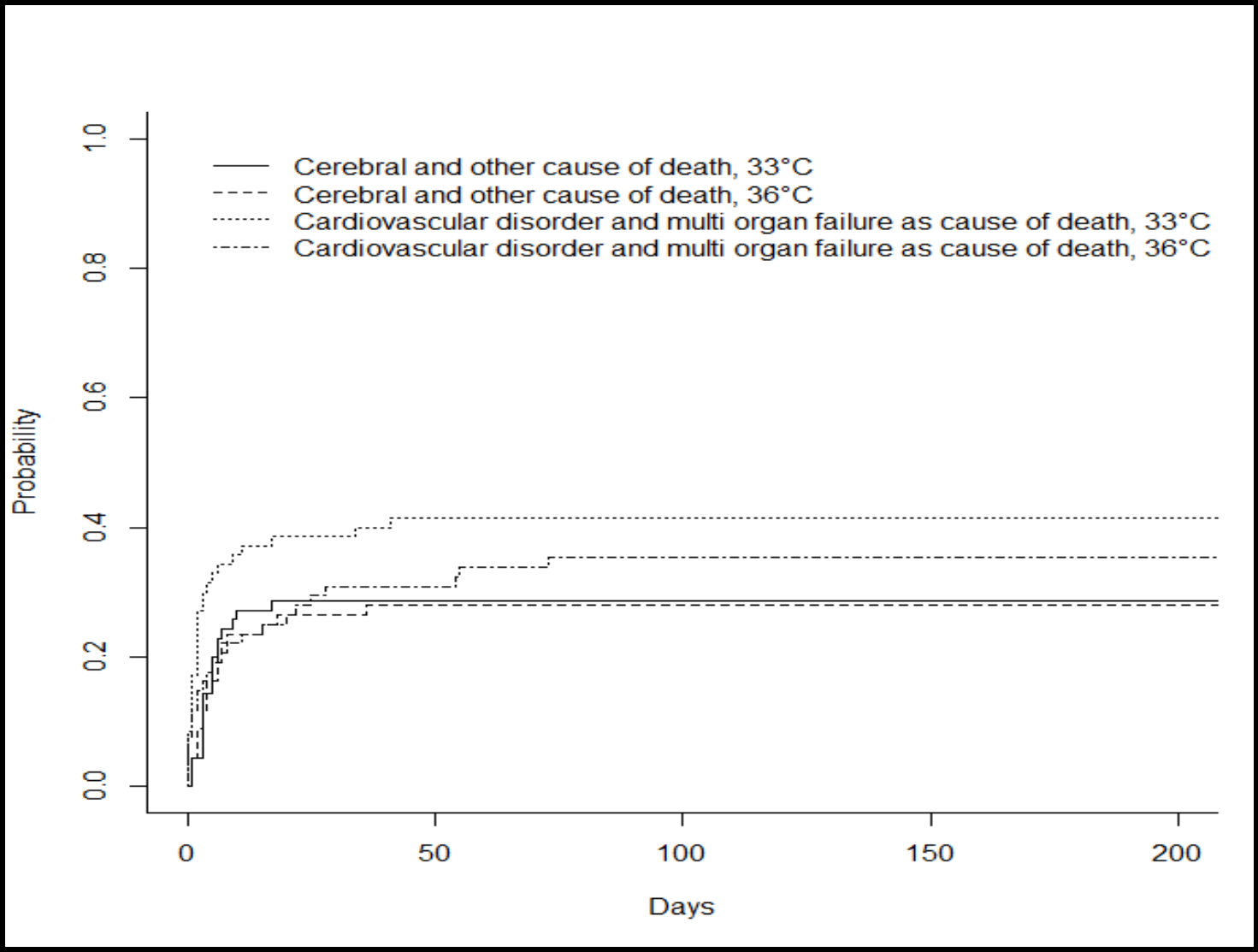
p<0.001

Probability of survival through 180 days for patients with shock on admission allocated to either 33°C or 36°C



p=0.155

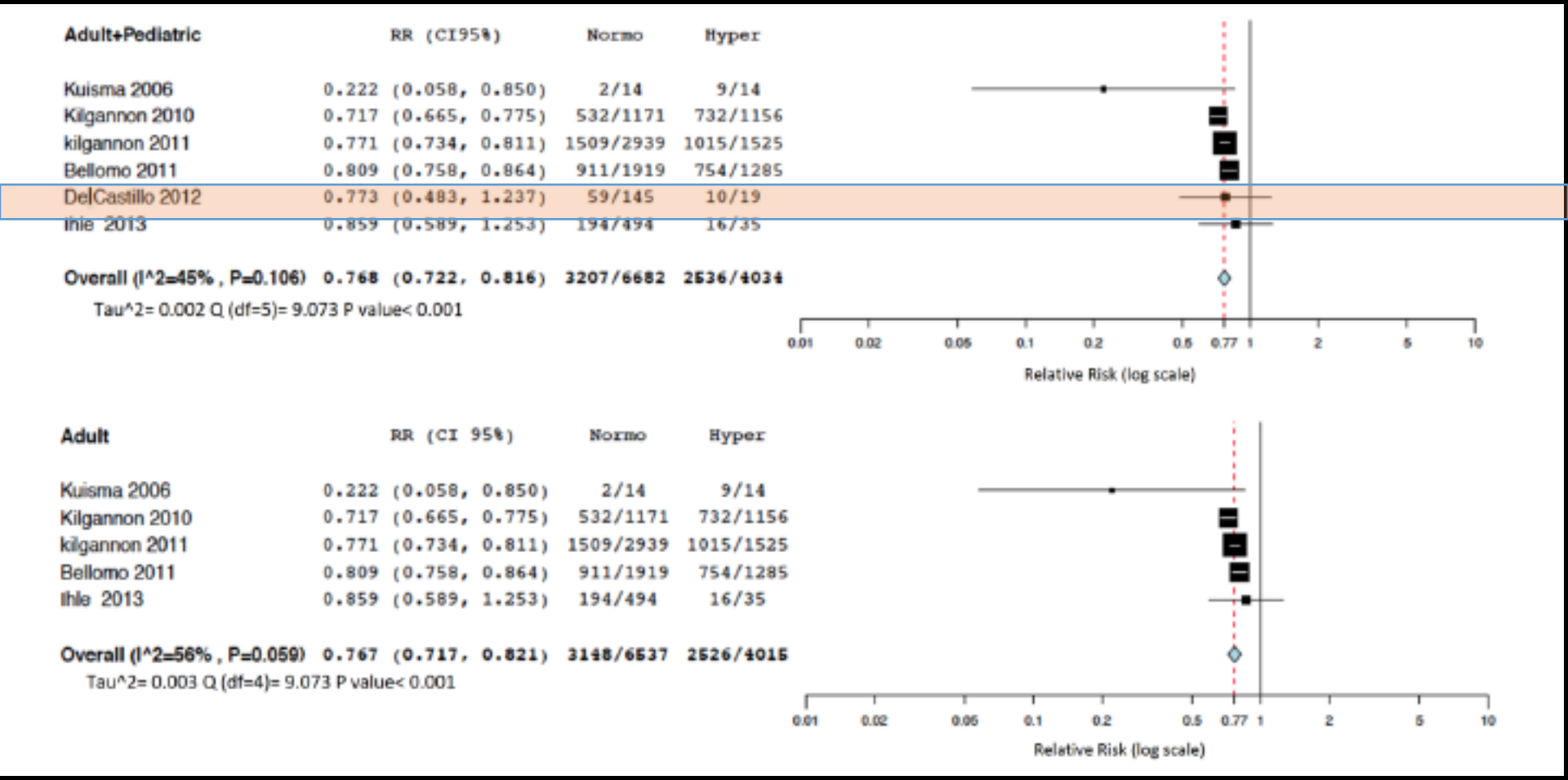
Probability of survival for patients with shock on admission allocated to either 33°C or 36°C.



p=0.04

Effect of normoxia vs. hyperoxia on mortality in adult and pediatric studies

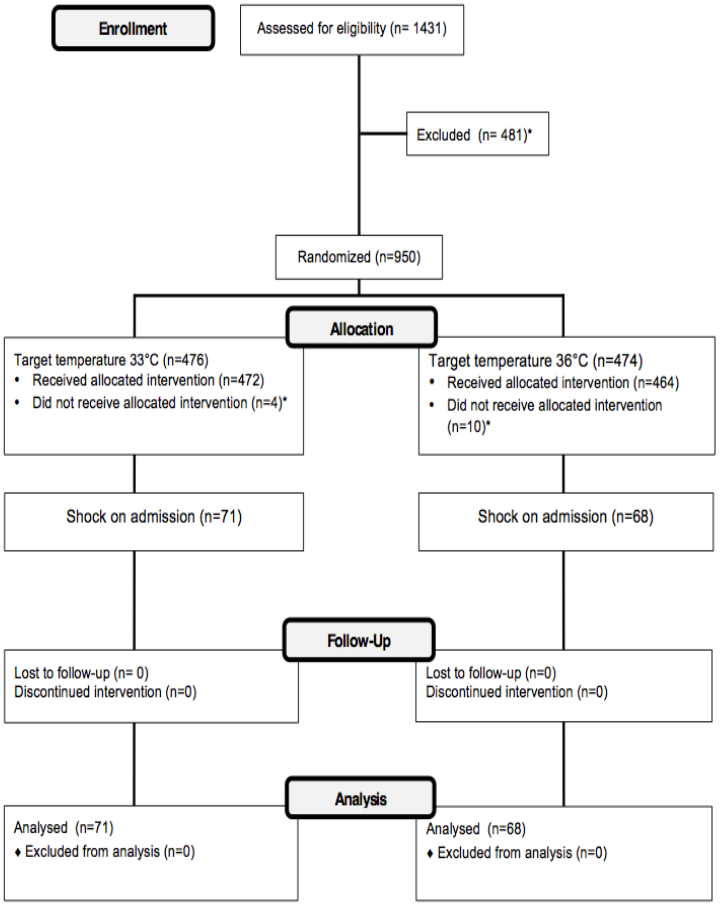
Sutherasan Y et al Minerva Anestesiol 2014 Mar 19 [Epub ahead of print]



Results

Variable	33°C Group	36°C Group
CPC at follow-up†		
Total no. of patients	469	464
Category — no. (%)		
1	195 (42)	183 (39)
2	23 (5)	39 (8)
3	17 (4)	20 (4)
4	6 (1)	2 (0.5)
5	228 (49)	220 (47)
P value for trend	0.85	

Consort statement flow chart: Assessment, randomization, analysis and follow up of patients

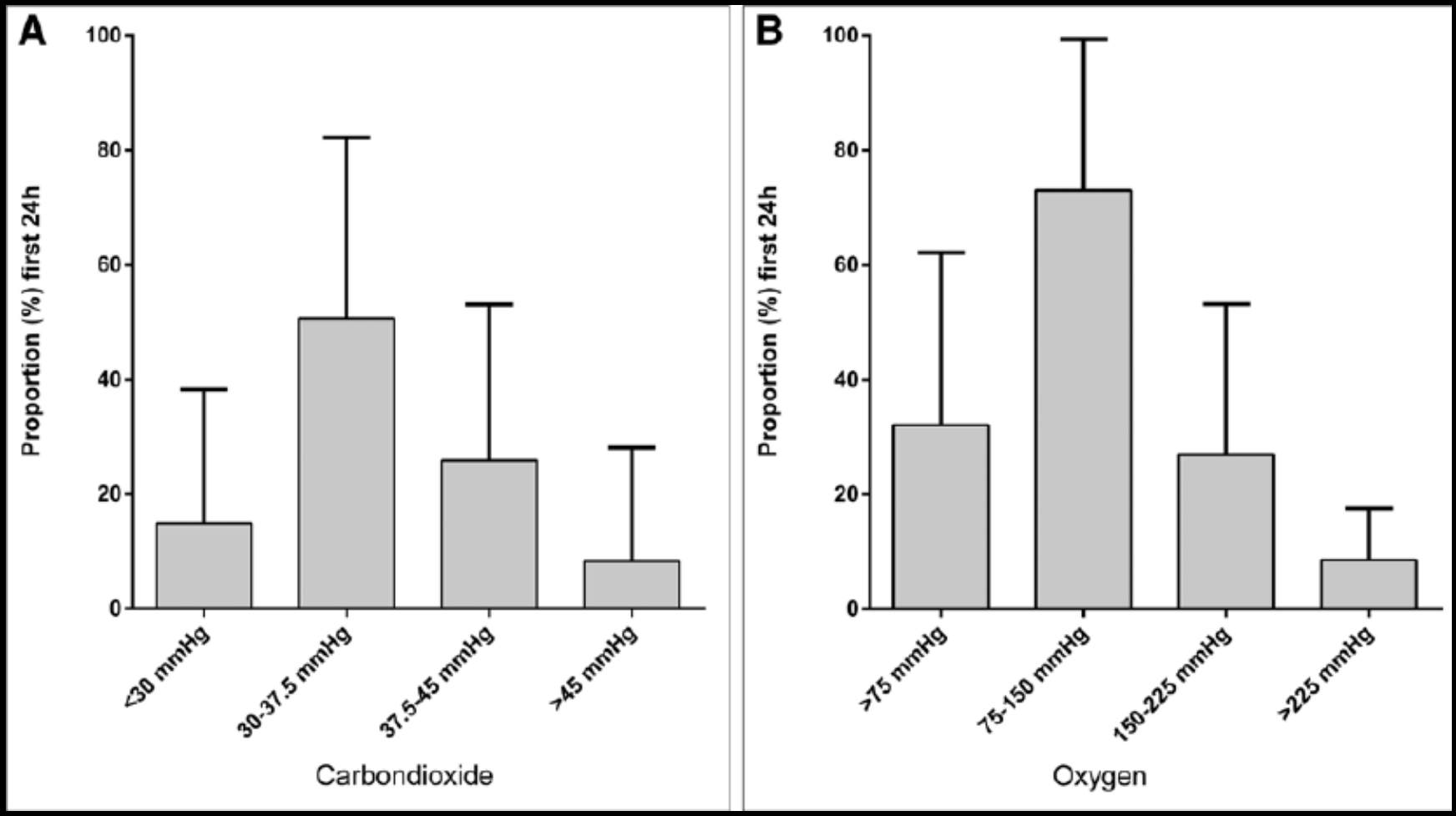


* Nielsen N et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. The New England journal of medicine 369: 2197-2206

Arterial Blood Gas Tensions After Resuscitation From Out-of-Hospital Cardiac Arrest: Associations With Long-Term Neurological Outcome

Vaahersalo J et al Crit Care Med 2014; XX:00–00

Proportion of time (mean and sd) during the first 24 hr



Arterial Blood Gas Tensions After Resuscitation From Out-of-Hospital Cardiac Arrest: Associations With Long-Term Neurological Outcome

Vaahersalo J et al Crit Care Med 2014; XX:00–00

Model/Exposure Variable		Good Outcome ($n = 168$)	Poor Outcome ($n = 241$)	OR for Good 12-Mo Outcome (95% CI)	p
Proportion of time (%) spent in oxygen range					
Low	< 75 mm Hg	0% (0–74%)	1% (0–83%)	0.99 (0.989–1.010)	0.85
Middle	75–150 mm Hg	79% (1–100%)	78% (0–100%)	1.001 (0.991–1.008)	0.93
Intermediate	150–225 mm Hg	7% (0–63%)	0% (0–85%)	1.000 (0.989–1.012)	0.99
High	> 225 mm Hg	0 (0–13%)	0% (0–10%)	1.019 (0.976–1.064)	0.40
Proportion of time (%) spent in carbon dioxide range					
Low	< 30 mm Hg	3% (0–59%)	0% (0–82%)	1.001 (0.990–1.012)	0.88
Middle	30–37.5 mm Hg	54% (0–91%)	51% (0–98%)	0.993 (0.985–1.002)	0.12
Intermediate	37.5–45 mm Hg	21% (0–85%)	15% (0–92%)	1.001 (0.992–1.0010)	0.82
High	> 45 mm Hg	0% (0–61%)	0% (0–59%)	1.015 (1.002–1.029)	0.024

How to assess prognosis after cardiac arrest and therapeutic hypothermia

Taccone FS et al. Critical Care 2014, 18:202

- The clinical examination is the gold standard for assessing prognosis in comatose survivors after CA;
- The use of sedatives and cooling procedures severely limit the early use of clinical findings in this setting.
- There is no optimal timing to assess prognosis after CA.
- The use of a multimodal approach, including full neurological examination with at least SSEPs and EEG, to help with coma prognostication after CA and TH.

General Care and Shivering

- Shivering medications
  - Paracetamol
  - Increased sedation
  - Neuromuscular blocking agent.
- Propofol // Short-acting opioid

5.4.3 The Bedside Shivering Assessment Scale (BSAS)

0	**None**	No shivering
1	**Mild**	Shivering localized to neck/thorax, may be seen only as artifact on ECG or felt by palpation
2	**Moderate**	Intermittent involvement of the upper extremities ±thorax
3	**Severe**	Generalized shivering or sustained upper/lower extremity shivering