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*

ABSTRACT

BACKGROUND

Unconscious survivors of out-of-hospital cardiac arrest have a high risk of death or poor neurologic function. Therapeutic hypothermia is recommended by international guidelines, but the supporting evidence is limited, and the target temperature associated with the best outcome is unknown. Our objective was to compare two target temperatures, both intended to prevent fever.

METHODS

In an international trial, we randomly assigned 950 unconscious adults after out-of-hospital cardiac arrest of presumed cardiac cause to targeted temperature management at either 33°C or 36°C. The primary outcome was all-cause mortality through the end of the trial. Secondary outcomes included a composite of poor neurologic function or death at 180 days, as evaluated with the Cerebral Performance Category (CPC) scale and the modified Rankin scale.

RESULTS

In total, 939 patients were included in the primary analysis. At the end of the trial, 50% of the patients in the 33°C group (235 of 473 patients) had died, as compared with 48% of the patients in the 36°C group (225 of 466 patients) (hazard ratio with a temperature of 33°C, 1.06; 95% confidence interval [CI], 0.89 to 1.28; P=0.51). At the 180-day follow-up, 54% of the patients in the 33°C group had died or had poor neurologic function according to the CPC, as compared with 52% of patients in the 36°C group (risk ratio, 1.02; 95% CI, 0.88 to 1.16; P=0.78). In the analysis using the modified Rankin scale, the comparable rate was 52% in both groups (risk ratio, 1.01; 95% CI, 0.89 to 1.14; P=0.87). The results of analyses adjusted for known prognostic factors were similar.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Nielsen at the Department of Anesthesia and Intensive Care, Intensive Care Unit, Helsingborg Hospital, S Vallgatan 5, 251 87, Helsingborg, Sweden, or at niklas.nielsen@med.lu.se.

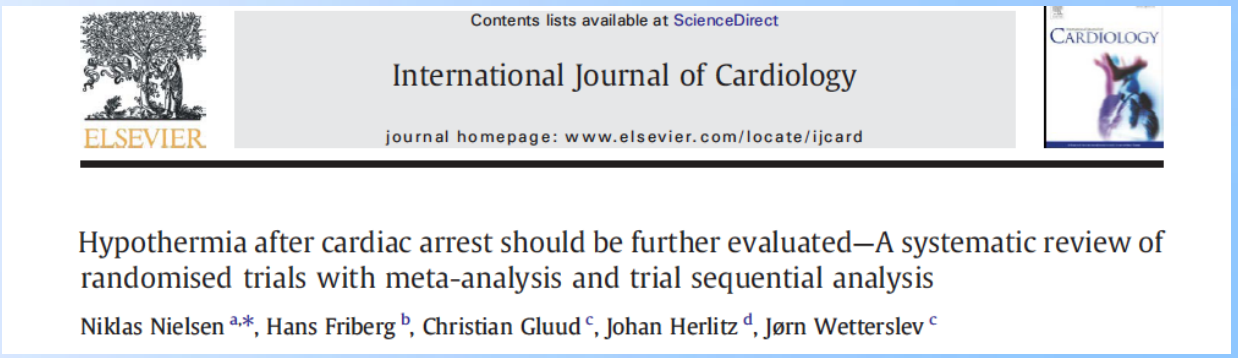
*A complete list of investigators participating in the Target Temperature Management 33°C versus 36°C after Out-of-Hospital Cardiac Arrest (TTM) trial is provided listed in the Supplementary Appendix, available at NEJM.org.

This article was published on November 17, 2013, at NEJM.org.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1310519

- Hypothermia to 32-34˚ C after out-of-hospital cardiac arrest is recommended in guidelines
- The overall quality of evidence for temperature management is low according to GRADE
- The optimal target temperature has not yet been determined

Nielsen et al.
***Int J Card* 2010**



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]

Main objective

- To assess the benefits and harms of a targeted temperature management at 33° C versus 36° C
- Avoiding fever in post-cardiac arrest patients in both groups

TTM-trial – 2010-2013

- 950 patients randomized
- 36 hospitals
- 10 countries
- Europe and Australia

Funded by:

Swedish Heart Lung Foundation

AFA-insurance Foundation, Sweden

Swedish Research Council

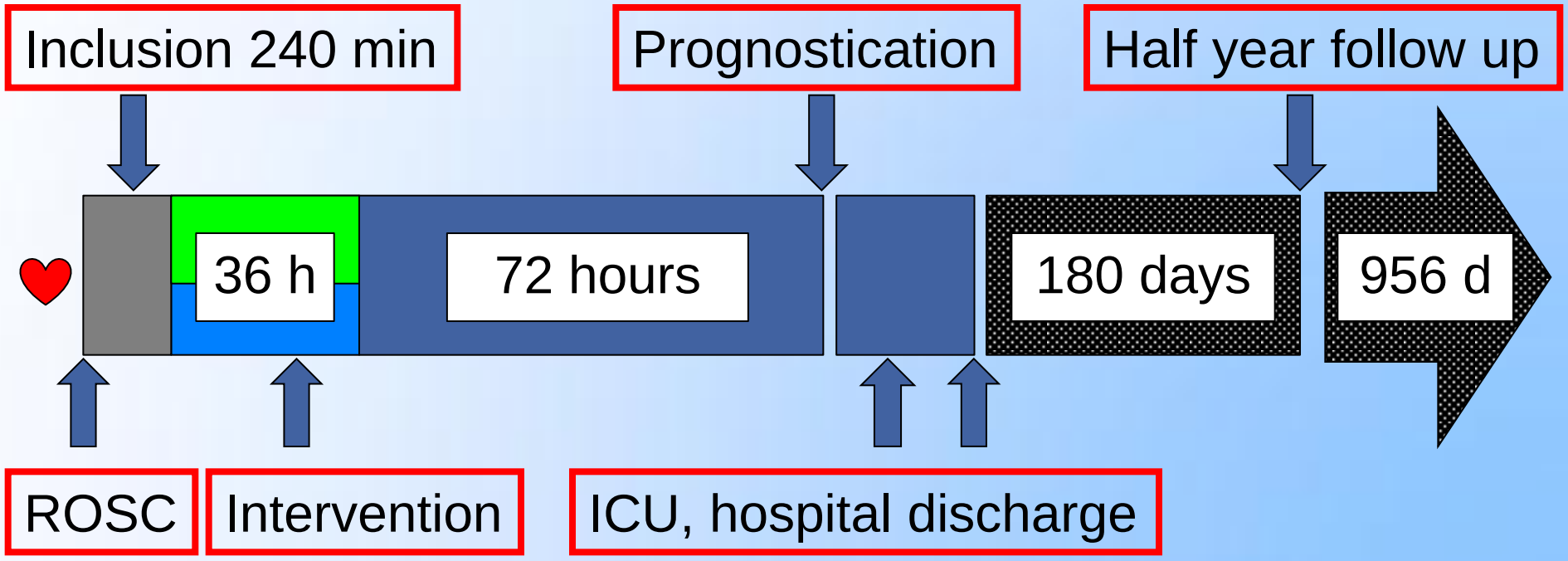
Governmental and Regional funding within the Swedish National Health System

TrygFoundation, Denmark

Zoega, Krapperup, Thure Carlsson, Trolle-Wachtmeister foundations, Sweden

Design and timeline

- Temperature intervention 36 hours
- All patients sedated and ventilated minimum 36 hours
- Feed-back controlled cooling devices in all patients
- Intravascular or surface devices



Methodological design

- 20% Hazard ratio reduction
- 5% α, 90% predicted power
- Standardized rules for prognostication
- Standardized rules for withdrawal of life support
- Blinded prognostication
- Blinded outcome assessment
- External monitoring

Inclusion criteria

- Out-of-hospital cardiac arrest
- Adult (18 years and over)
- Presumed cardiac cause
- All initial rhythms
- Unconscious (Glasgow Coma Scale < 8)
- Stable Return of Spontaneous Circulation

Main exclusion criteria

- Unwitnessed arrest with initial rhythm asystole
- >240 minutes from Return of Circulation
- Body temperature below 30° C
- Known or suspected intracranial hemorrhage and stroke

Outcomes

- **Primary outcome:** Survival
- **Secondary outcomes:**

  Mortality and poor neurological function at 180 days

  - ✓ Cerebral Performance Category
  - ✓ Modified Rankin Scale

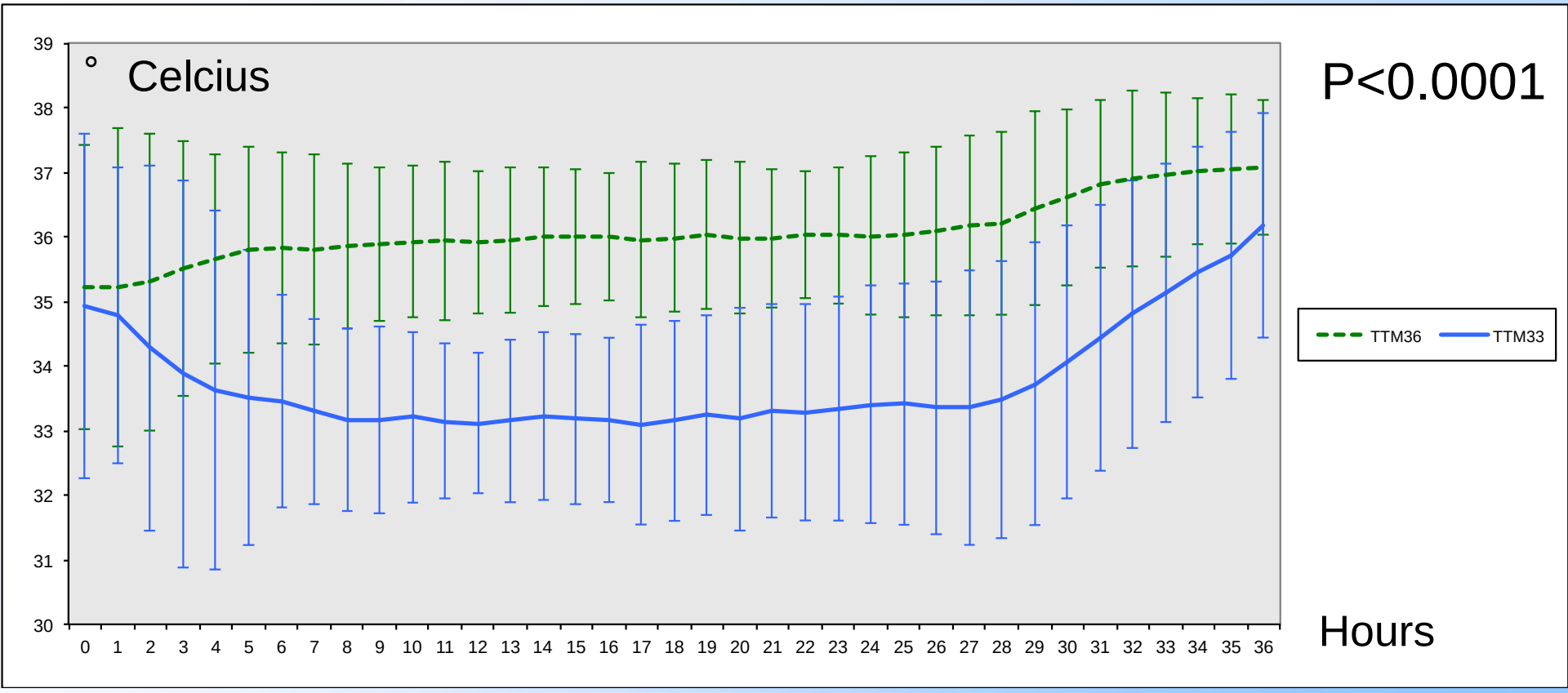
  Serious adverse events

Baseline characteristics

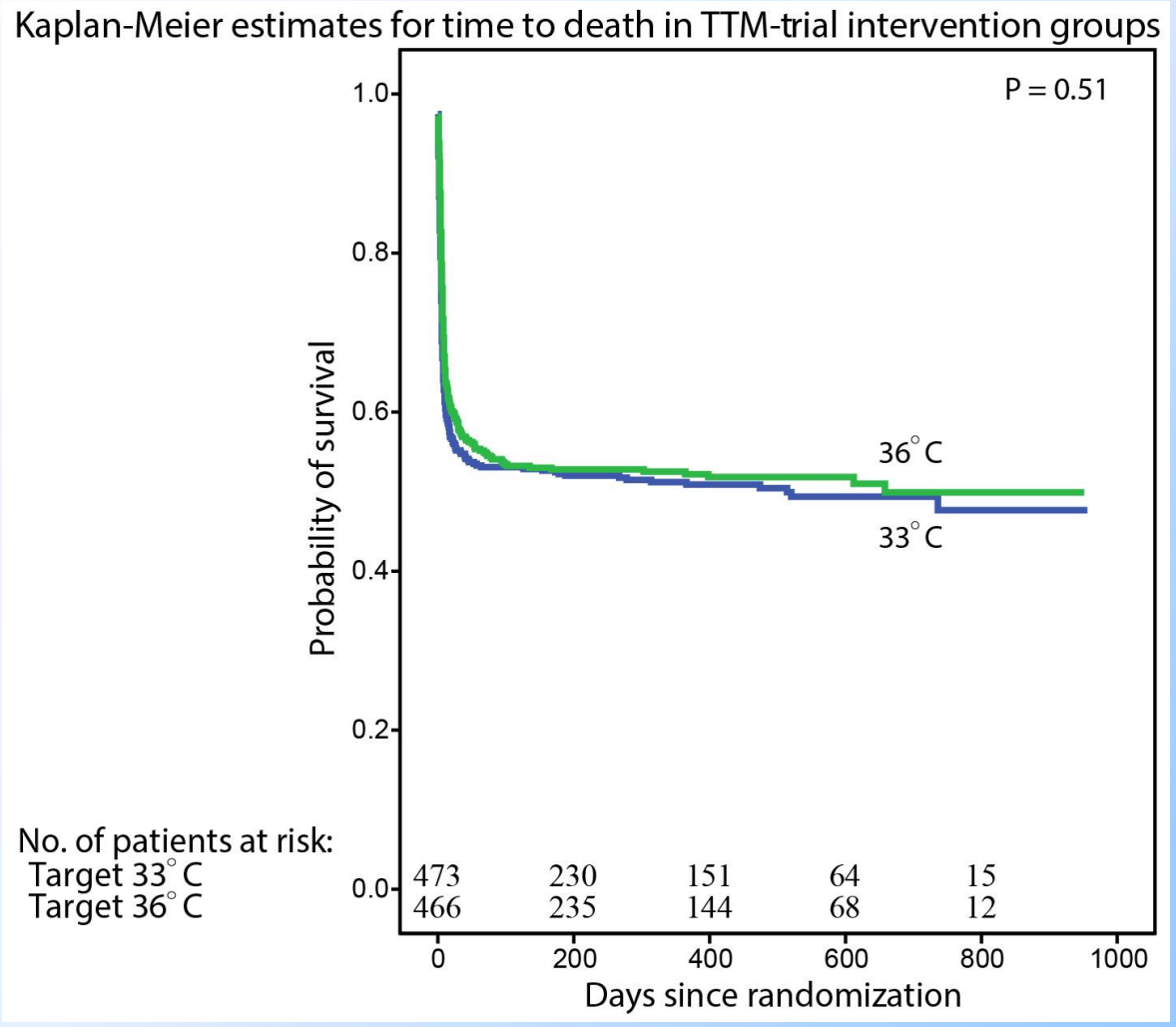
	33° C	36° C
No.	473	466
Age Male sex	64+/-12 83 %	64+/-13 79 %
Arrest in place of residence Arrest in public place Bystander witnessed Bystander CPR **Shockable rhythm**	52 % 42 % 89 % 73 % **79 %**	55 % 40 % 90 % 73 % **81 %**
Arrest to ROSC (min)	**25 [18-40]**	**25 [16-40]**
Circulatory shock on adm. Lactate mmol/L	15 % 6.7±4.5	14 % 6.7±4.5
ST-elevation infarction	40 %	42 %
GCS	3 [3-4]	3 [3-4]

Temperature profile

Mean ± 2SD



Survival



P=0.51

No difference in survival

Outcomes

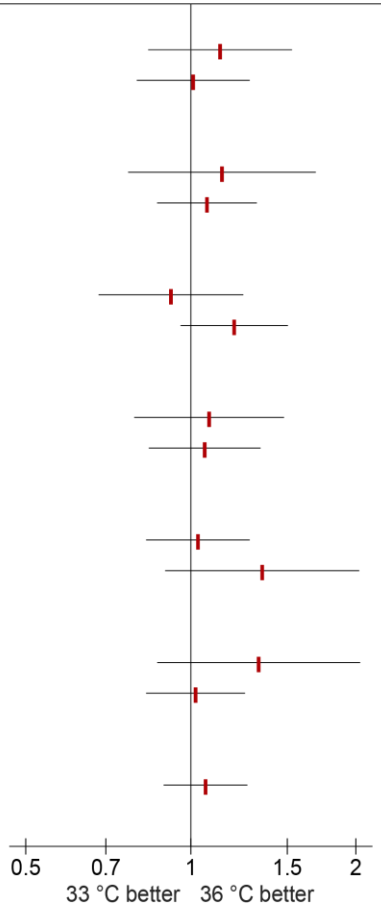
Outcome	TTM33	TTM36	HR or RR (95% CI)	P Value
PRIMARY OUTCOME				
Mortality at the end of trial				
Dead no./total no. (%)	235/473 **(50)**	225/466 (**48**)	HR=1.06 (0.89-1.28)	0.51
SECONDARY OUTCOMES				
Neurological function at follow-up				
CPC 3-5–no./total no. (%)	252/469 **(54)**	242/464 **(52)**	RR=1.02 (0.88-1.16)	0.78
mRS 4-6–no./total no. (%)	245/469 **(52)**	239/464 **(52)**	RR=1.01 (0.89-1.14)	0.87
Serious adverse events				
Any event–no./total no. (%)	439/472 **(93)**	417/464 **(90)**	RR=1.03 (1.00-1.08)	0.09

100% follow-up

99% follow-up

Subgroups

Subgroup	Target 33 °C No. of events/Total	Target 36 °C no. of patients	Hazard Ratio 95% CI	Test of interaction
Age				P = 0.52
Less than or equal to 65 years	91/238	85/250	1.13 [0.84, 1.53]	
More than 65 years	144/235	140/216	1.01 [0.80, 1.28]	
Gender				P = 0.75
Female	47/80	55/98	1.14 [0.77, 1.69]	
Male	188/393	170/368	1.07 [0.87, 1.32]	
Time from cardiac arrest to ROSC				P = 0.20
Less than or equal to 25 min	79/243	86/241	0.92 [0.68, 1.24]	
More than 25 min	156/230	138/224	1.20 [0.96, 1.50]	
Initial rhythm				P = 0.92
Non-shockable	82/98	74/88	1.08 [0.79, 1.48]	
Shockable	153/375	150/377	1.06 [0.84, 1.34]	
Shock at admission				P = 0.17
Not present	183/402	180/398	1.03 [0.83, 1.28]	
Present	52/70	44/67	1.35 [0.90, 2.03]	
Site category				P = 0.19
Two largest sites	50/110	40/108	1.33 [0.87, 2.03]	
Sites except two largest	185/363	185/358	1.02 [0.83, 1.25]	
TTM-Trial				
All patients	235/473	225/466	1.06 [0.89, 1.28]	



Results consistent in pre-defined subgroups

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Conclusion

In unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac cause targeting a temperature of 33° C did not confer any benefit compared to targeting a temperature of 36° C