



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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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.

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*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.

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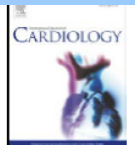
- Hypothermia to 32-34°C after out-of-hospital cardiac arrest is recommended in guidelines
- The overall quality of evidence for temperature management is low according to GRADE
- The optimal target temperature has not yet been determined



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

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

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Main objective

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



TTM-trial – 2010-2013

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



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Swedish Heart Lung Foundation

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Swedish Research Council

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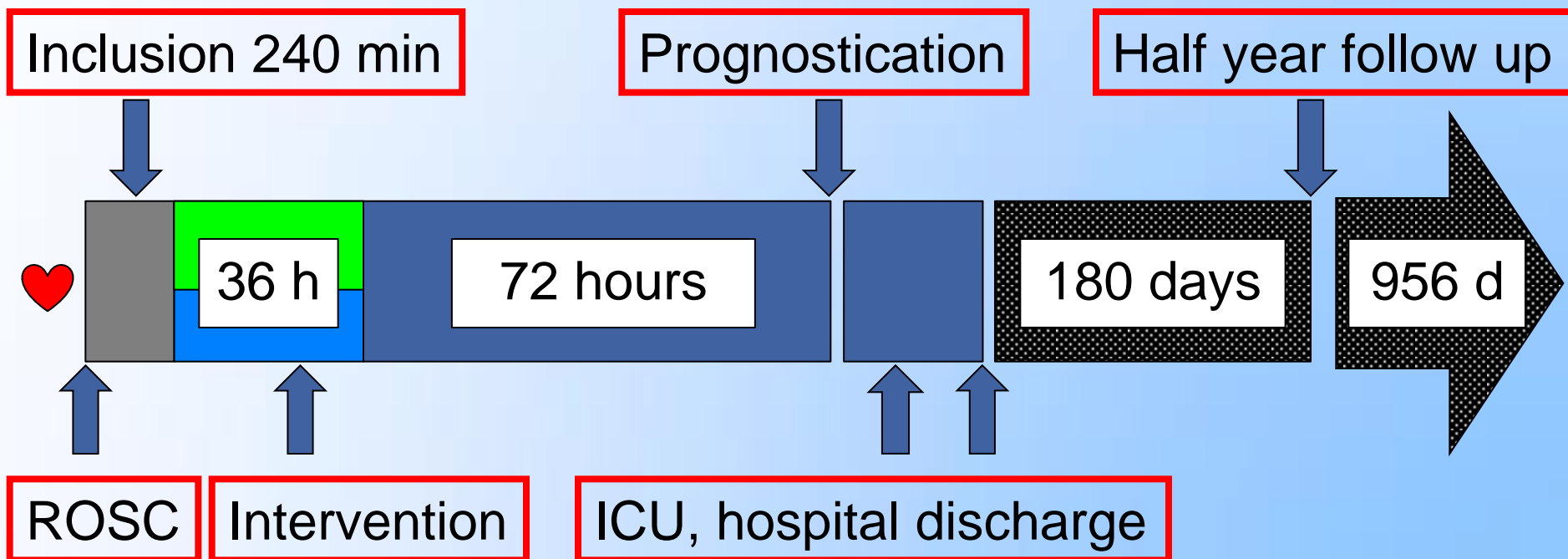
TrygFoundation, Denmark

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



Design and timeline

- Temperature intervention 36 hours
- Both groups sedated and ventilated during intervention
- 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 and 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)



Main exclusion criteria

- Unwitnessed arrest with initial rhythm asystole
- >240 minutes from Return of Circulation
- Body temperature below 30°C



Outcomes

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

Mortality and poor neurological function at 180 days

- ✓ Cerebral Performance Category
- ✓ Modified Rankin Scale

Serious adverse events



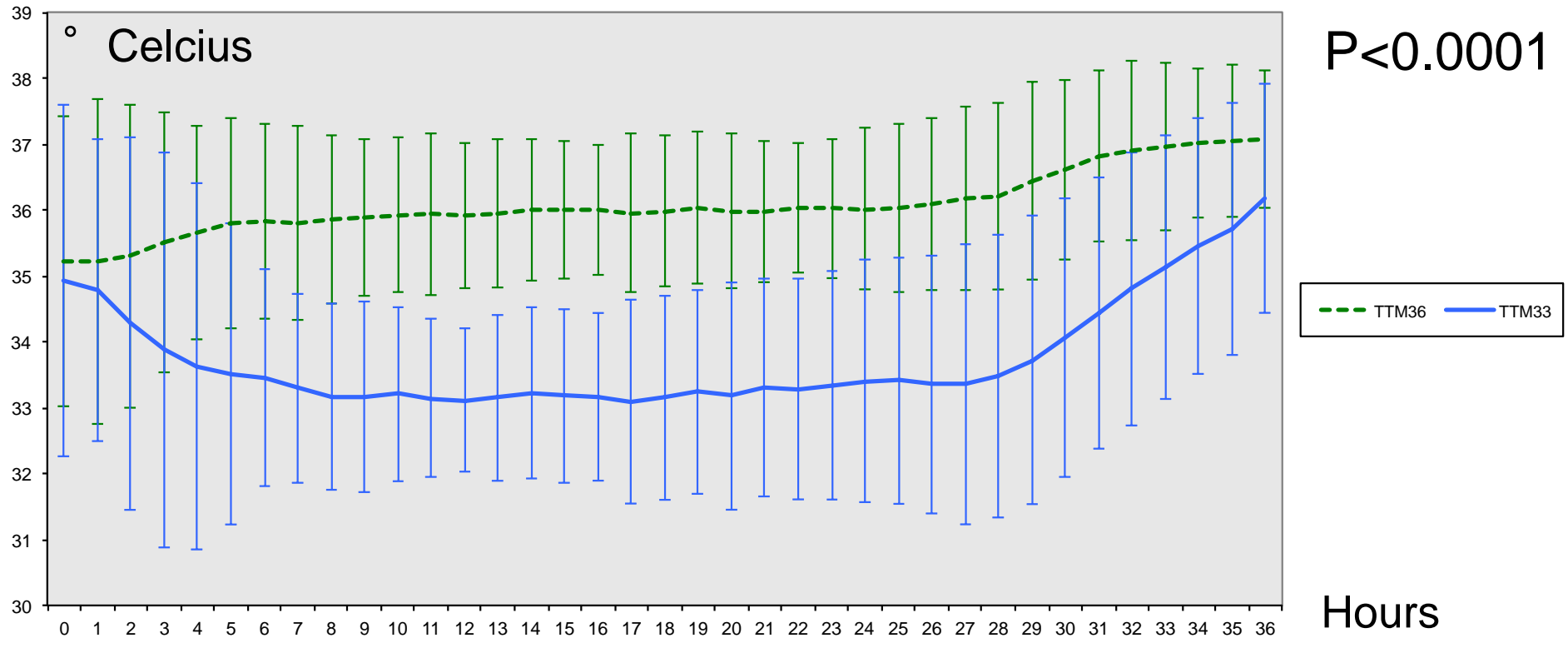
Baseline characteristics

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



Temperature profile

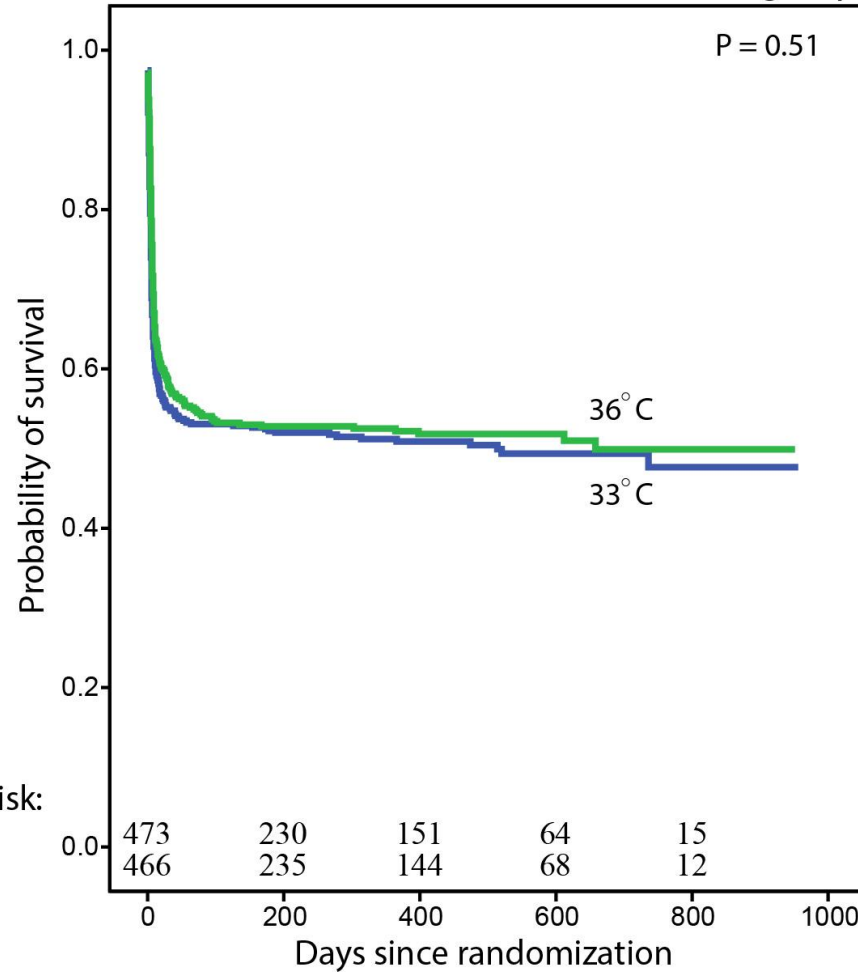
Mean \pm 2SD





Survival

Kaplan-Meier estimates for time to death in TTM-trial intervention groups



$P = 0.51$

No difference in survival



Outcomes

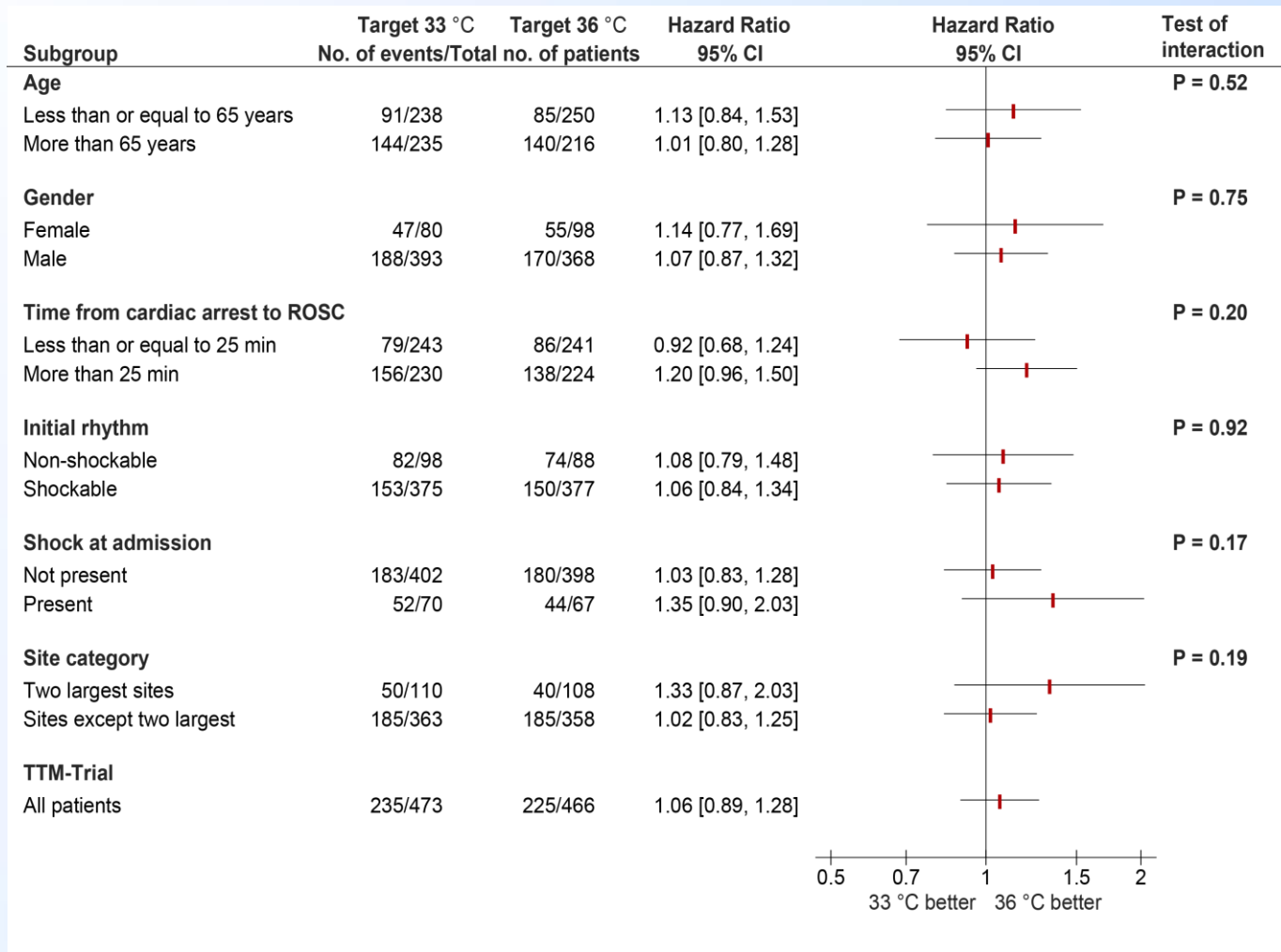
Outcome	33°C	36°C	HR or RR (95% CI)	P Value
PRIMARY OUTCOME				
Mortality at the end of trial				
Dead no./total no. (%)	235/473 (50)	225/466 (48)	HR=1.06 (0.89-1.28)	0.51
SECONDARY OUTCOMES				
Neurological function at follow-up				
CPC 3-5–no./total no. (%)	252/469 (54)	242/464 (52)	RR=1.02 (0.88-1.16)	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



Results consistent in pre-defined subgroups



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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