Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

TTM2 Trial

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- Study Overview
- Background
- Methods
- Results
- Discussion & Conclusion
- Appraisal

Study Overview

- **Title**
  - Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest
- **Authors**
  - J. Dankiewicz, et al. TTM2 Trial Investigators
- **Journal**
  - The New England Journal of Medicine
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European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care☆

Temperature control

- We recommend targeted temperature management (TTM) for adults after either OHCA or in-hospital cardiac arrest (IHCA) (with any initial rhythm) who remain unresponsive after ROSC.
- Maintain a target temperature at a constant value between 32 °C and 36 °C for at least 24 h.
- Avoid fever (>37.7 °C) for at least 72 h after ROSC in patients who remain in coma.
- Do not use pre-hospital intravenous cold fluids to initiate hypothermia.

OHCA: out-of-hospital cardiac arrest
ROSC: return of spontaneous circulation

Part 3: Adult Basic and Advanced Life Support

2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Recommendations for Indications for TTM

COR	LOE	Recommendations
1	B-R	1. We recommend TTM for adults who do not follow commands after ROSC from OHCA with any initial rhythm.
1	B-R	2. We recommend TTM for adults who do not follow commands after ROSC from IHCA with initial nonshockable rhythm.
1	B-NR	3. We recommend TTM for adults who do not follow commands after ROSC from IHCA with initial shockable rhythm.

erformance of TTM

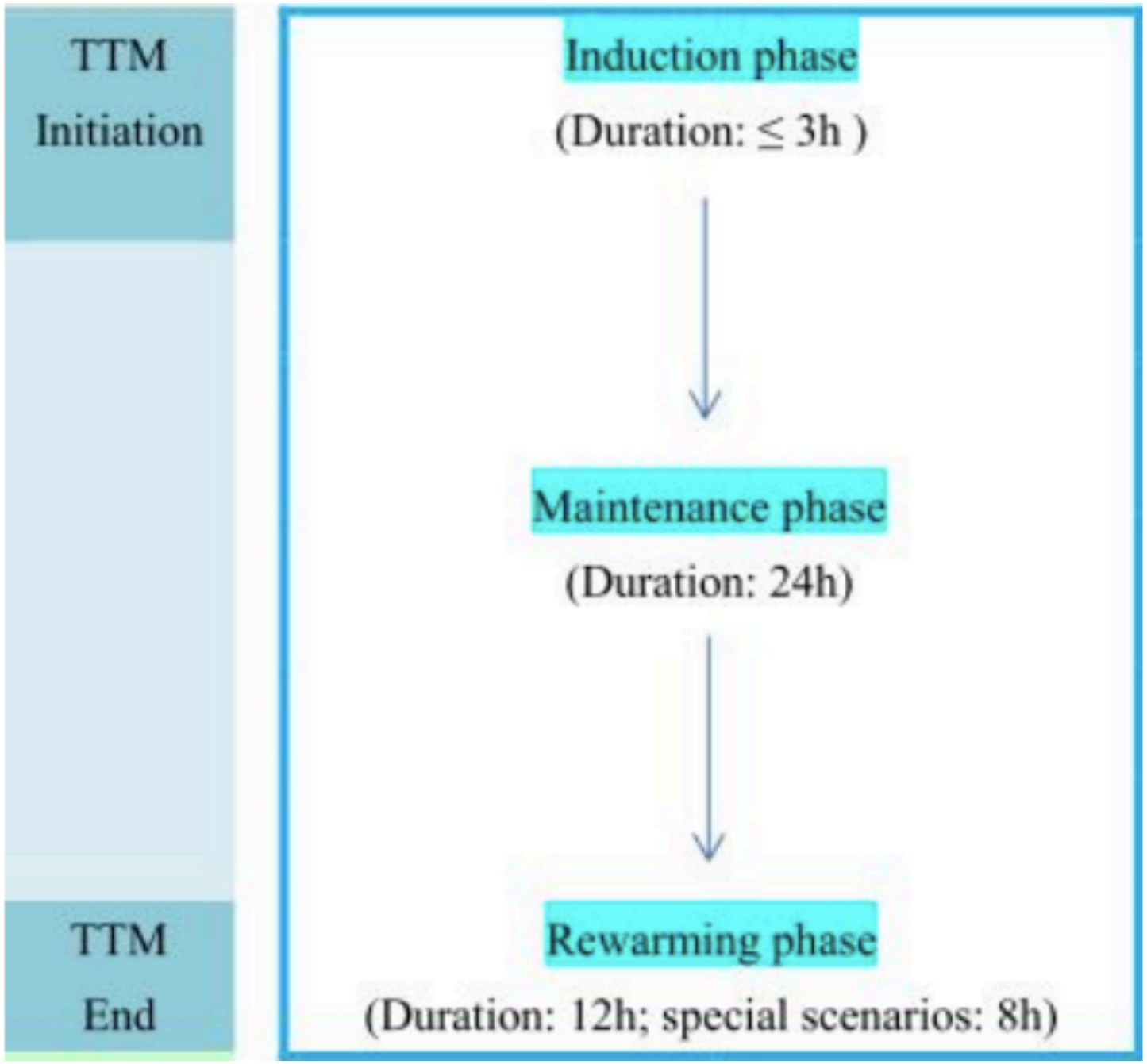
Recommendations
1. We recommend selecting and maintaining a constant temperature between 32°C and 36°C during TTM.
2. It is reasonable that TTM be maintained for at least 24 h after achieving target temperature.
3. It may be reasonable to actively prevent fever in comatose patients after TTM.
4. We do not recommend the routine use of rapid infusion of cold IV fluids for prehospital cooling of patients after ROSC.

2b	C-LD
3: No Benefit	A

Post-Cardiac Arrest Adult Targeted Temperature Management WanFang Hospital Protocol 08312021 V3

- **Purpose Statement**

Targeted Temperature Management (TTM) has become the standard of care in cardiac arrest of eligible adult survivors and the implementation of the TTM protocol at WanFang Hospital (WFH) is to improve long-term neurological outcomes. The goal core temperature is 33-36°C during the TTM phase at WFH.



Goal to reach the core body temperature as soon as possible

Maintain target core temperature at 33-36°C for at least 24 hrs with temperature check Q1H

over 12 hrs to 36.5-37°C
Rewarming at rate ≤ 0.5°C/hr

Ref. Post-Cardiac Arrest Adult Targeted Temperature Management WanFang Hospital Protocol 09162019 v2

- **Common Adverse Effects of TTM**
  - Shivering
  - Coagulopathy and bleeding
  - Arrhythmias
  - Fluid and electrolyte imbalances
  - Hyperglycemia
  - Increased risk of infection

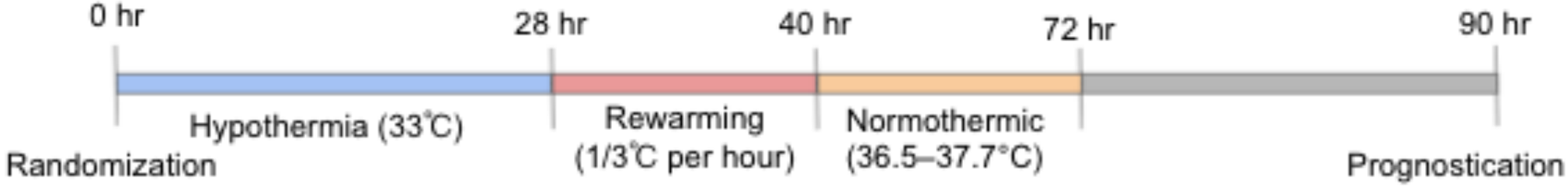
- Research Gap
  - Although guidelines strongly recommend TTM, they also state that the overall evidence is of low certainty
  - Available trials had high risks of bias and random errors

- Objective

  To assess the beneficial and harmful effects of hypothermia as compared with normothermia and early treatment of fever in patients after cardiac arrest.

- Hypothesis

  At 6 months, the incidence of death would be lower in the hypothermia group than in the normothermia group.

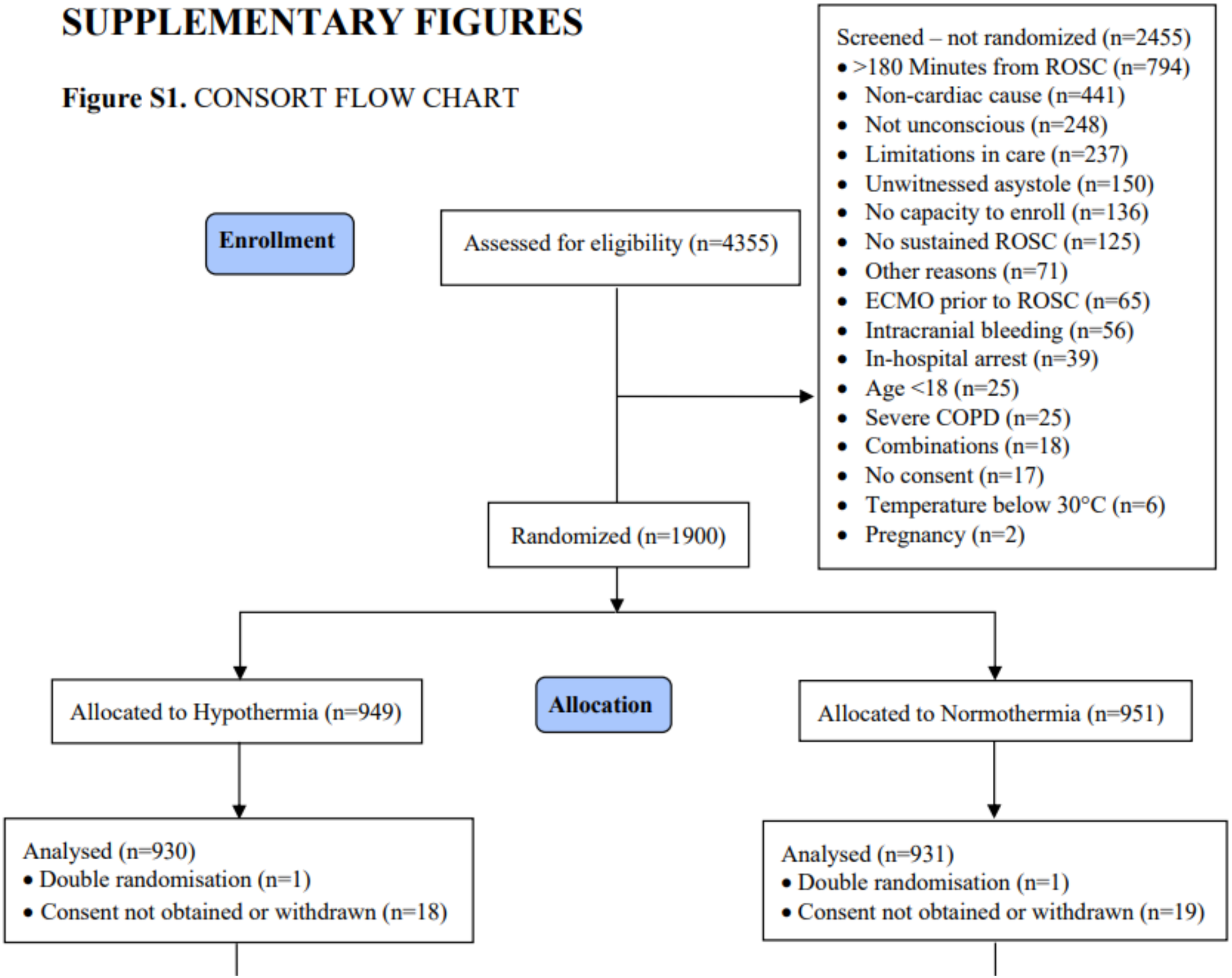
Study Design	International, multicenter, parallel group, investigator-initiated, randomized, superiority trial
Population	Inclusion criteria Adult (18 years or older) Out-of-hospital arrest of cardiac or unknown cause. Stable ROSC (20 minutes without the need for chest compressions) Unconscious (FOUR motor score <4 and does not obey verbal commands) Eligible for intensive care without restrictions Exclusion criteria Pregnancy Known or suspected intracranial bleeding Extracorporeal membrane oxygenation required before ROSC Initial body temperature <30°C Severe chronic obstructive pulmonary disorder (COPD) with home oxygen therapy. Unwitnessed cardiac arrest with an initial rhythm of asystole
Intervention	
Control	Maintain temperature ≤37.5°C Cooling management if ≥37.8°C

Outcomes	Primary	Death from any cause at 6 months
	Secondary	1. Poor functional outcome at 6 months: 4-6 on the modified Rankin Scale(mRS), dichotomized modified Rankin scale was alternative 2. Number of days the patient was alive and out of the hospital until day 180 3. Survival determined in a time-to-death analysis 4. Health-related quality of life: visual-analogue EQ-5D-5L questionnaire
Safety Outcomes	pneumonia, sepsis, bleeding, arrhythmia resulting in hemodynamic compromise, and skin complications related to the device used for targeted temperature management	
Statistical Analysis	1. Estimated 1862 patients would provide 90% power to detect a absolute risk reduction of 7.5% in the risk of death at a two-sided alpha level of 0.05 2. Principal analyses were performed in the intention-to-treat population 3. Dichotomous outcomes: mixed-effects generalized linear model, reported as population-level (marginal) relative risks derived by G-computation 4. Survival data: Cox regression 5. Statistical significance: Primary outcome: *P* value <0.05 Secondary outcome: 95% confidence intervals 6.All analyses were performed with the use of R: A Language and Environment for Statistical Computing	

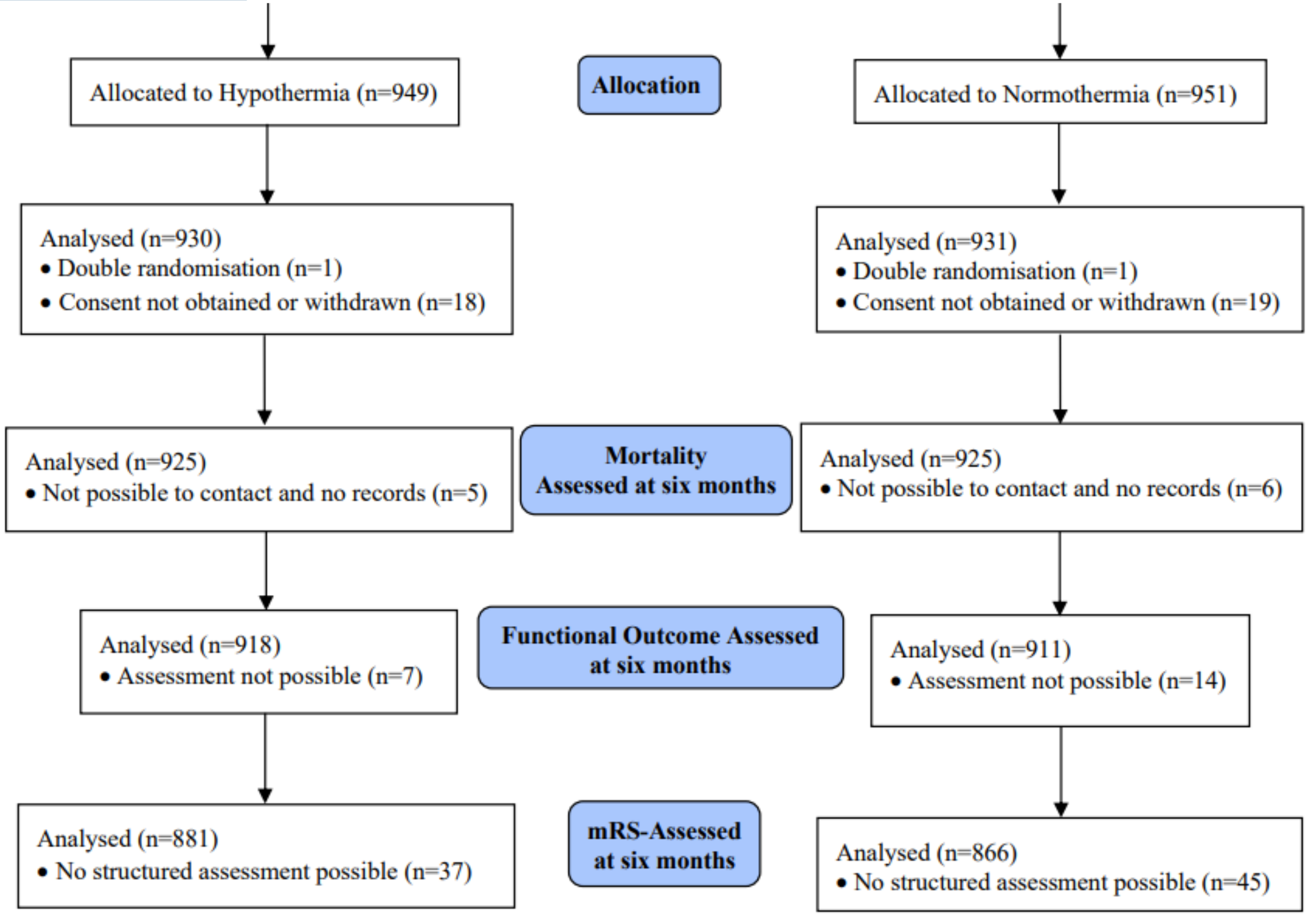
EQ-5D-5L: European Quality of Life–5-Dimension–5-Level questionnaire

SUPPLEMENTARY FIGURES

Figure S1. CONSORT FLOW CHART



Study Flowchart



Baseline Characteristic

Table 1. Baseline Characteristics of the Intention-to-Treat Population.*

Characteristic	Hypothermia (N=930)	Normothermia (N=931)
Demographic characteristics		
Age — yr	64±13	63±14
Male sex — no. (%)	742 (80)	735 (79)
Medical history		
Hypertension — no. (%)	345 (37)	298 (32)
Diabetes — no. (%)	173 (19)	167 (18)
Myocardial infarction — no. (%)	139 (15)	154 (17)
PCI — no. (%)	130 (14)	140 (15)
Coronary-artery bypass grafting — no. (%)	73 (8)	76 (8)
Heart failure — no. (%)	90 (10)	93 (10)
NYHA III or IV heart failure — no./total no. (%)†	20/906 (2)	23/904 (3)
Median Charlson comorbidity index (IQR)‡	3 (2–4)	3 (1–4)
Characteristics of the cardiac arrest — no. (%)		
Location at cardiac arrest		
Place of residence	487 (52)	491 (53)
Public place	338 (36)	320 (34)
Other	105 (11)	120 (13)
Bystander-witnessed cardiac arrest	850 (91)	852 (92)
Bystander-performed CPR	759 (82)	728 (78)

Baseline Characteristic

Characteristic	Hypothermia (N=930)	Normothermia (N=931)
First monitored rhythm — no. (%)		
Shockable rhythm	671 (72)	700 (75)
Ventricular fibrillation	576 (62)	585 (63)
Nonperfusing ventricular tachycardia	31 (3)	29 (3)
ROSC after bystander-initiated defibrillation	24 (3)	41 (4)
Unknown rhythm, shock administered	40 (4)	45 (5)
Nonshockable rhythm	259 (28)	231 (25)
Pulseless electrical activity	117 (13)	113 (12)
Asystole	124 (13)	100 (11)
Unknown rhythm, no shock administered	18 (2)	18 (2)
Median time from cardiac arrest to sustained ROSC (IQR) — min§	25 (16–40)	25 (17–40)
Median time from cardiac arrest to randomization — min (IQR)	136 (103–170)	133 (99–173)
Clinical characteristics on admission		
Tympanic temperature — °C¶	35.3±1.1	35.4±1.1
FOUR motor score‖	0	0
Bilateral corneal reflexes present — no./total no. (%)	168/511 (33)	194/537 (36)
Bilateral pupillary reflexes present — no./total no. (%)	535/761 (70)	529/776 (68)
Arterial pH**	7.2±0.2	7.2±0.2
Arterial lactate level — mmol/liter††	5.9±4.4	5.8±4.2
Shock — no. (%)‡‡	261 (28)	275 (30)
ST-segment elevation myocardial infarction — no./total no. (%)	379/918 (41)	370/921 (40)

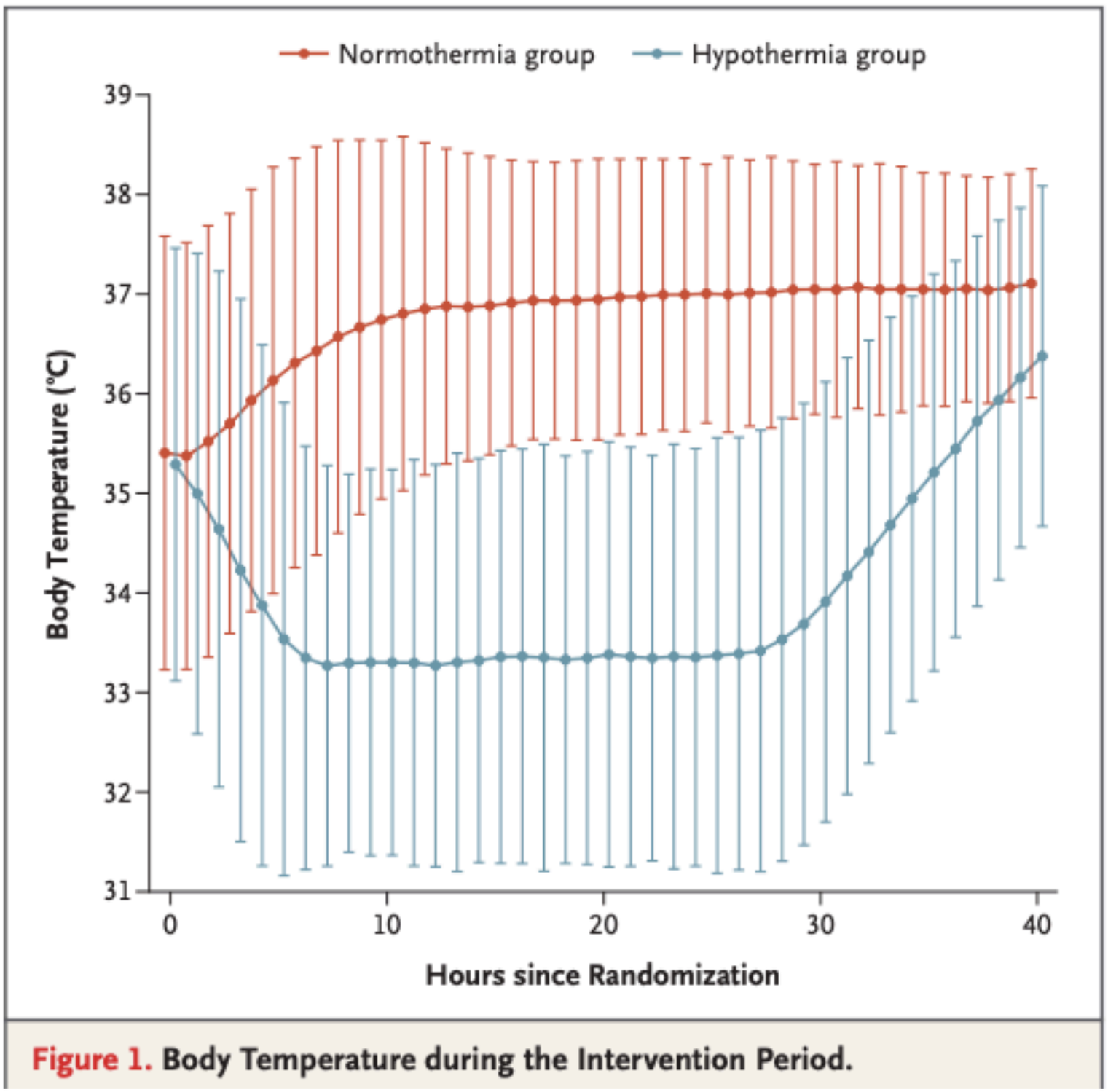


Figure 1. Body Temperature during the Intervention Period.

Hypothermia Group:

1.Medium time to 34°C is 3 hours

2. 53 of 930 patients (6%) were rewarmed before 40 hours after randomization

Received cooling with a device	
Hypothermia	Normothermia
882/930 (95%)	428/931 (46%)

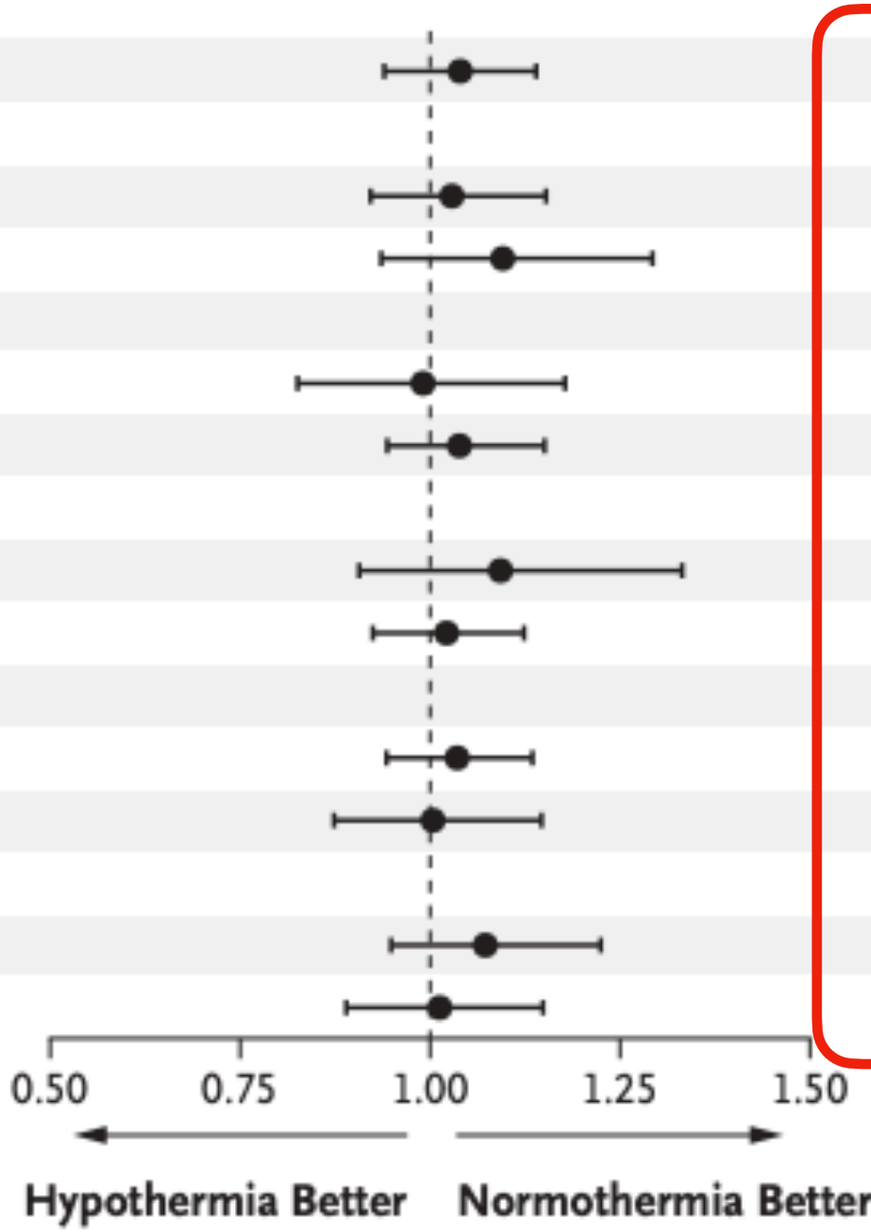
Table 2. Outcomes and Adverse Events.

Outcome or Event	Hypothermia (N=930)	Normothermia (N=931)	Relative Risk (95% CI)*	P Value
Primary outcome: death from any cause at 6 mo — no./total no. (%)	465/925 (50)	446/925 (48)	1.04 (0.94–1.14)	0.37
Main secondary outcome — no./total no. (%)				
Score of 4–6 on modified Rankin scale at 6-mo follow-up†	488/881 (55)	479/866 (55)	1.00 (0.92–1.09)	
Poor functional outcome at 6 mo‡	495/918 (54)	493/911 (54)	1.00 (0.91–1.08)	
Score on modified Rankin scale at 6-mo follow-up — no./total no. (%)†				
0	140/881 (16)	148/866 (17)		
1	87/881 (10)	80/866 (9)		
2	132/881 (15)	127/866 (15)		
3	34/881 (4)	32/866 (4)		
4	16/881 (2)	20/866 (2)		
5	7/881 (1)	13/866 (2)		
6	465/881 (53)	446/866 (52)		
Serious adverse events — no./total no. (%)				
Arrhythmia resulting in hemodynamic compromise	222/927 (24)	152/921 (16)	1.45 (1.21–1.75)	<0.001
Bleeding	44/927 (5)	46/922 (5)	0.95 (0.63–1.42)	0.81
Skin complication related to device used for targeted temperature management	10/927 (1)	5/922 (<1)	1.99 (0.71–6.37)	0.21
Pneumonia	330/927 (36)	322/921 (35)	1.02 (0.90–1.15)	0.75
Sepsis	99/926 (11)	83/922 (9)	1.19 (0.90–1.57)	0.23

Primary Outcome Subgroup Analysis

A Death at 6 Months

Subgroup	Hypothermia	Normothermia	Relative Risk of Death (95% CI)
	no. of patients		
All patients	925	925	1.04 (0.94–1.14)
Sex			
Male	738	729	1.03 (0.92–1.15)
Female	187	196	1.10 (0.94–1.29)
Age			
<65 yr	421	457	0.99 (0.83–1.18)
≥65 yr	504	468	1.04 (0.94–1.15)
Time to ROSC from cardiac arrest			
<25 min	419	416	1.09 (0.91–1.33)
≥25 min	506	509	1.02 (0.92–1.12)
Initial rhythm			
Nonshockable	259	231	1.04 (0.94–1.14)
Shockable	666	694	1.00 (0.87–1.15)
Shock on admission			
Not present	665	651	1.07 (0.95–1.23)
Present	260	274	1.01 (0.89–1.15)



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Poor functional outcome at 6 mo‡	495/918 (54)	493/911 (54)	1.00 (0.91–1.08)	
Score on modified Rankin scale at 6-mo follow-up — no./total no. (%)†				
0	140/881 (16)	148/866 (17)		
1	87/881 (10)	80/866 (9)		
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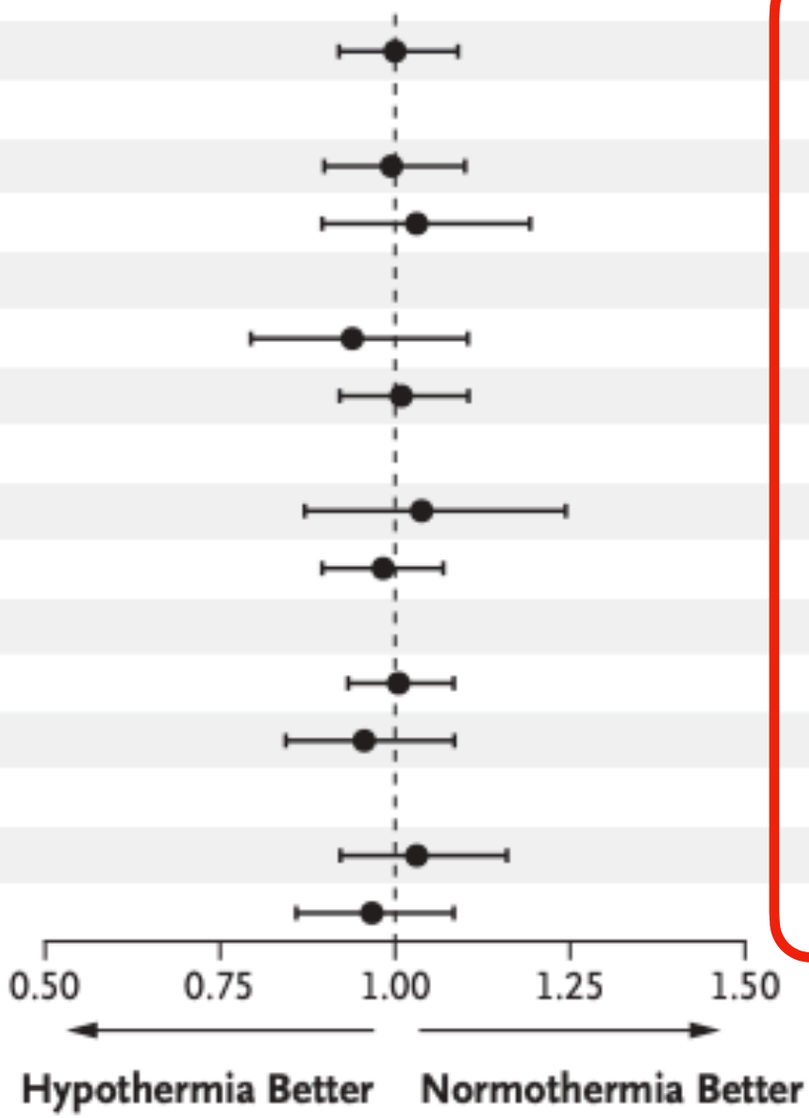
Sepsis	99/926 (11)	83/922 (9)	1.19 (0.90–1.57)	0.23

Secondary Outcome Subgroup Analysis

B Modified Rankin Scale Score of 4–6 at 6 Months

Subgroup	Hypothermia	Normothermia	Relative Risk of Score of 4–6 (95% CI)
	no. of patients		
All patients	881	866	1.00 (0.92–1.09)
Sex			
Male	701	679	1.00 (0.90–1.10)
Female	180	187	1.03 (0.90–1.19)
Age			
<65 yr	391	429	0.94 (0.79–1.10)
≥65 yr	490	437	1.01 (0.92–1.10)
Time to ROSC from cardiac arrest			
<25 min	395	389	1.04 (0.87–1.24)
≥25 min	486	477	0.98 (0.90–1.07)
Initial rhythm			
Nonshockable	252	218	1.00 (0.93–1.08)
Shockable	629	648	0.96 (0.84–1.08)
Shock on admission			
Not present	629	606	1.03 (0.92–1.16)
Present	252	260	0.97 (0.86–1.08)



Secondary Outcome

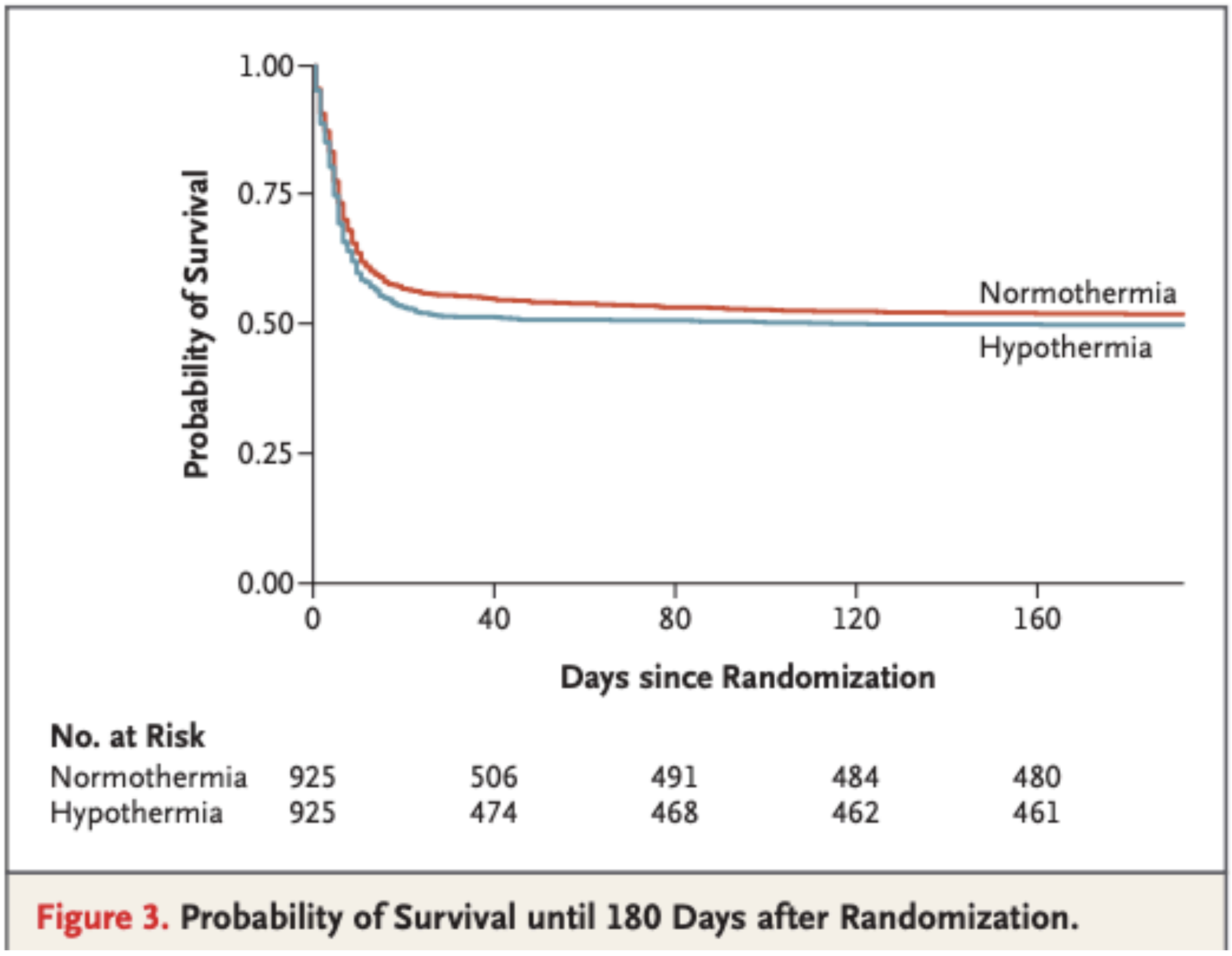
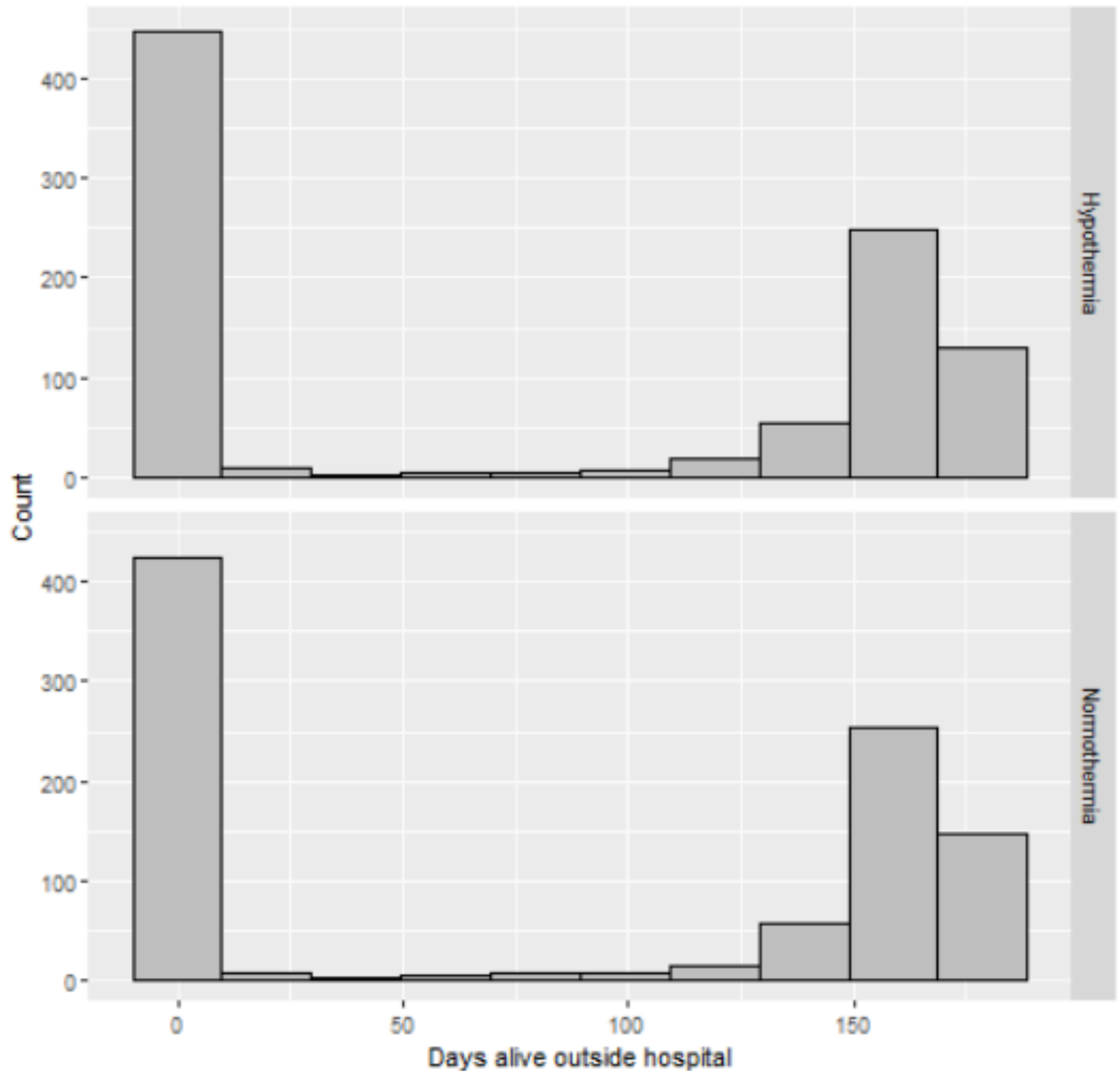


Figure 3. Probability of Survival until 180 Days after Randomization.

Time-to-event analysis:

hazard ratio in the hypothermia group, 1.08; 95% CI, 0.95 to 1.23)

Secondary Outcome



Distribution of days alive outside hospital after the first hospitalization within 180 days

Secondary Outcome

Table S9. Health-related quality of life at six months.

EQ-VAS	Hypothermia	Normothermia	Mean difference (95% CI)
All participants*	Median score: 0 (IQR: 0 – 80)	Median score: 0 (IQR: 0 – 80)	
Participants alive at six months	Mean score: 74 (SD: 20)	Mean score: 75 (SD: 20)	-0.8 points (-3.6 to +2.0 points)

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Sepsis	99/926 (11)	83/922 (9)	1.19 (0.90–1.57)	0.23

Table S8. Shivering by group, day 1 to 3 after randomization.

	Day 1		Day 2		Day 3	
	Hypothermia	**Normothermia**	**Hypothermia**	**Normothermia**	**Hypothermia**	**Normothermia**
None	673 (76%)	798 (90%)	618 (73%)	720 (83%)	606 (76%)	650 (82%)
Mild	75 (8%)	37 (4%)	93 (11%)	59 (7%)	74 (9%)	49 (6%)
Moderate	95 (11%)	36 (4%)	103 (12%)	58 (7%)	77 (10%)	60 (8%)
Severe	40 (5%)	13 (1%)	33 (4%)	27 (3%)	36 (4%)	34 (4%)

Shivering according to the Bedside shivering assessment scale (BSAS).

Discussion

- **Contrast Results with practice-changing trials[1,2]**
  - Changes in standards of intensive care
  - Five times larger sample size→lower risk of bias and random error

- **Consistent Results with recent trial[3,4]**
  - Hypothermia was not shown to reduce mortality

Ref.
1. Treatment of comatose survivors of out- of-hospital cardiac arrest with induced hypothermia. Bernard SA, Gray TW, Buist MD, et al. NEnglJMed2002;346:557- 63.
2. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest.(HACA trial) N Engl J Med 2002; 346:549-56.
3. Targeted temperature management at 33°C versus 36°C after cardiac arrest.(TTM trial) Nielsen N, Wetterslev J, Cronberg T, et al. N Engl J Med 2013;369:2197-206.
4.Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm(HYPERION trial) Lascarrou J-B, Merdji H, Le Gouge A, et al. N Engl J Med 2019;381:2327-37.

Limitation

- Conservative protocol for assessment of neurologic prognosis and guidance for withdrawal of life support
- Staff members in the ICU were aware of the assigned target temperature during the ICU stay
- Knowledge gap regarding whether any temperature management is better than no temperature management(about half the patients in the normothermia group were cooled with a device)
- Concomitant care was not part of the protocol and was left to the discretion of participating hospitals
- Results are not fully applicable to other presentations of cardiac arrest

Authors'Conclusion

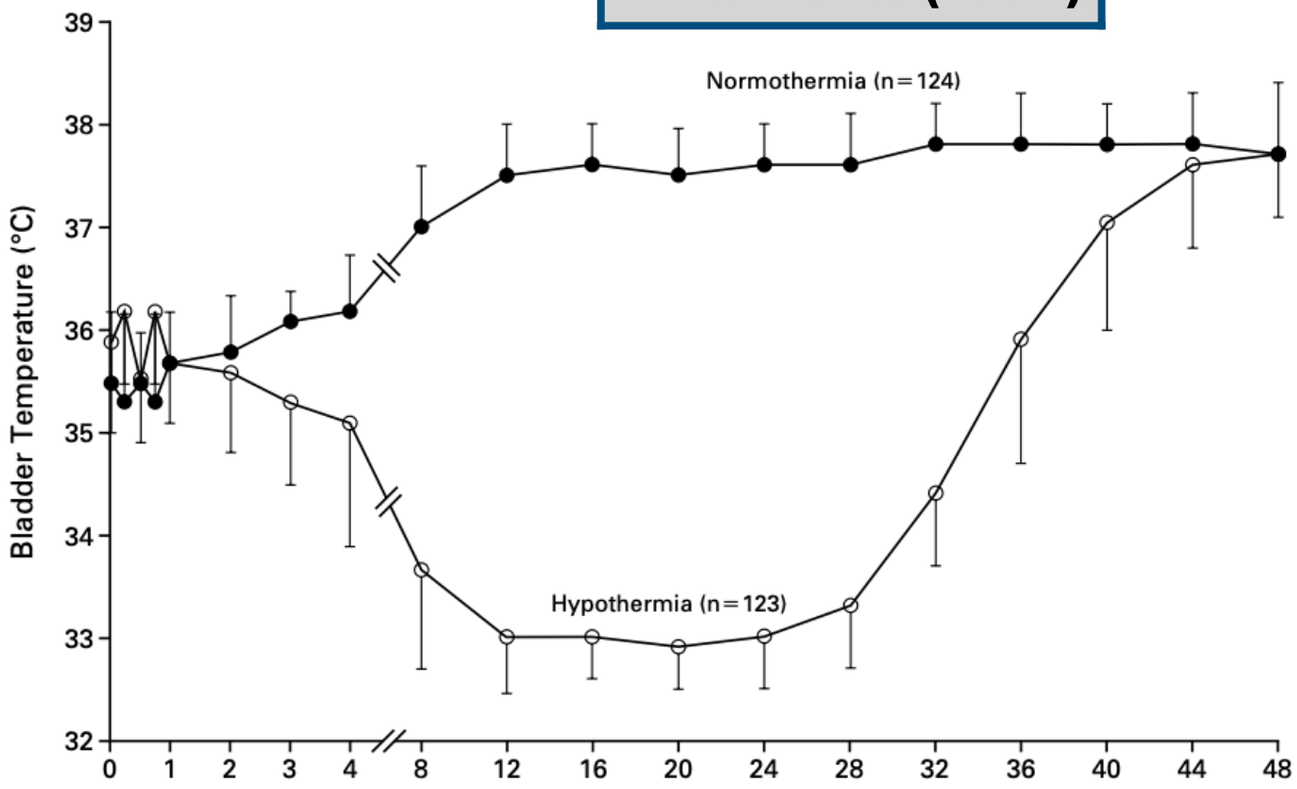
Patients with coma after out-of-hospital cardiac arrest who were treated with hypothermia did not have a lower incidence of death at 6 months than those who were treated with normothermia.

Appraisal

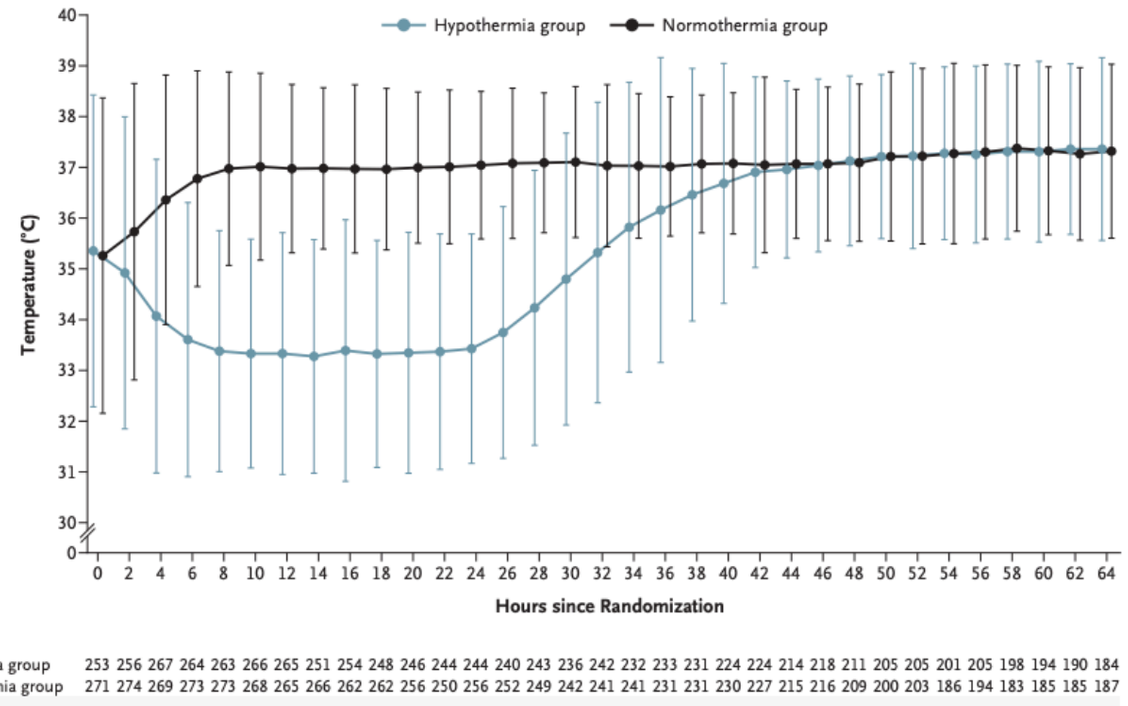
Study Design	Study Methodology
• International, multicenter • Clear research focus • Randomised controlled trial • Intention-to-treat analysis	• Blind to physicians assessing neurologic prognosis, assessors of functional outcome, statisticians and authors • No difference between baseline characteristics
Results	**Application**
• 1862 patients for 90% power (n=1861) • Missing data is relatively equal between groups • Relatively objective outcomes	• Results are applicable to our population but limited to OHCA patients • Extracorporeal membrane oxygenation required patients were excluded in this trial

Discussion

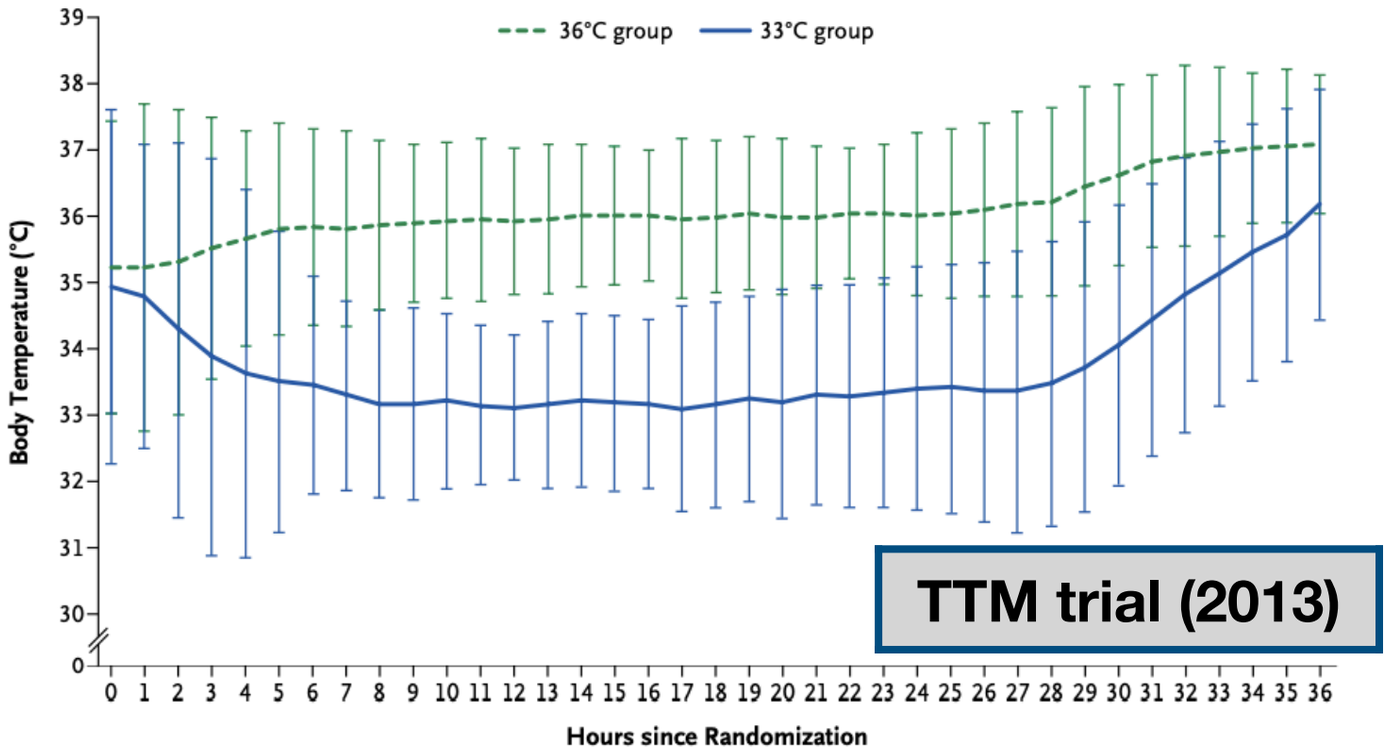
HACA trial (2002)



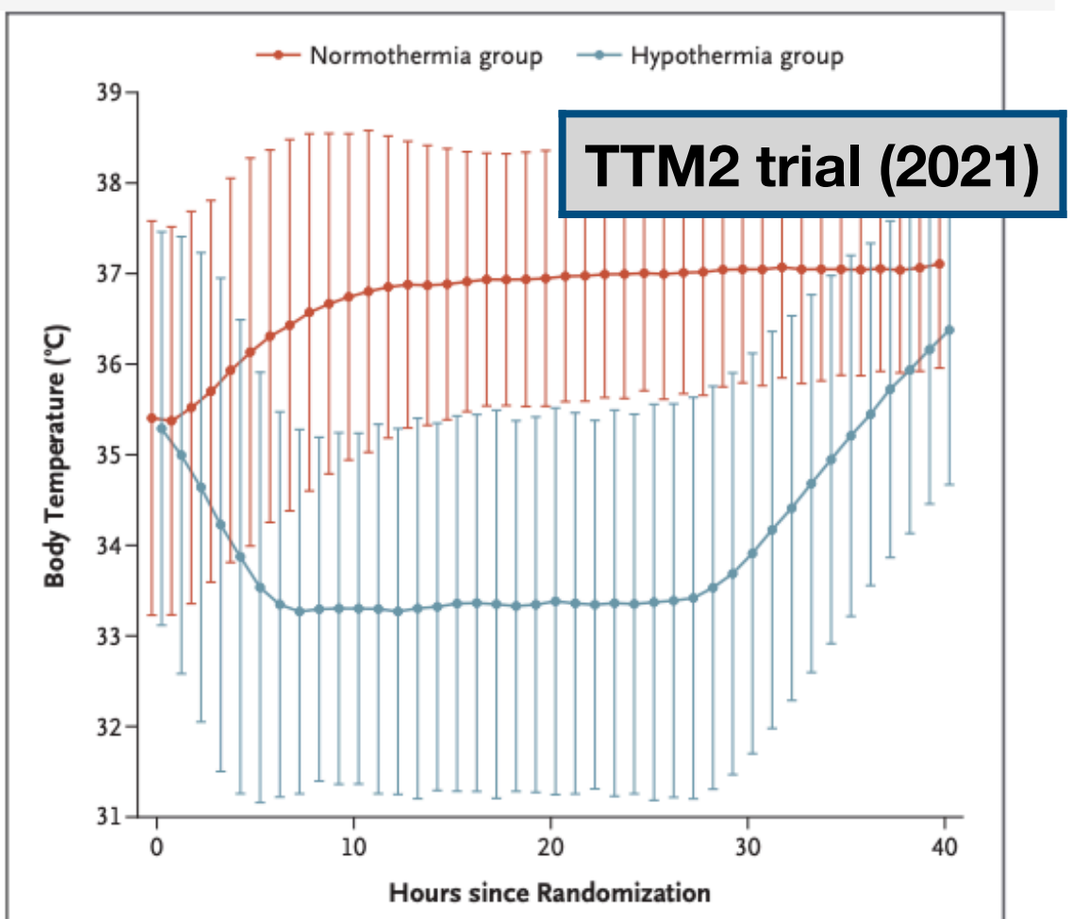
HYPERION trial (2019)



TTM trial (2013)



TTM2 trial (2021)



Hypothermia Treatment	HACA trial (2002)	Bernard trial (2002)	TTM trial (2013)	HYPERION trial (2019)	TTM2 trial (2021)
Mortality	Benefit	No benefit	No benefit	No benefit	No benefit
Neurologic Function	Benefit	Benefit	No benefit	Benefit	No benefit

- **Benefit versus Harm**
  - Meaningful clinical improvement?
  - Higher risk of adverse effect
- **Raised issue: Normotheramia versus No targeted temperature management**
  - Is hypothermia ‘therapeutic’?

Conclusion

A. Current guidelines recommend targeted temperature management(TTM) in either OHCA or IHCA patients

B. Higher targeted temperature goal may be considered in patients with high risk of adverse events and unstable heartbeat.

Thank you !