

IRC 2021

CONGRESSO
NAZIONALE

16•17•18 DICEMBRE

NUOVE LINEE GUIDA 2021:
RIANIMAZIONE CARDIOPOLMONARE
POST-LOCKDOWN



Italian
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TTM 2021

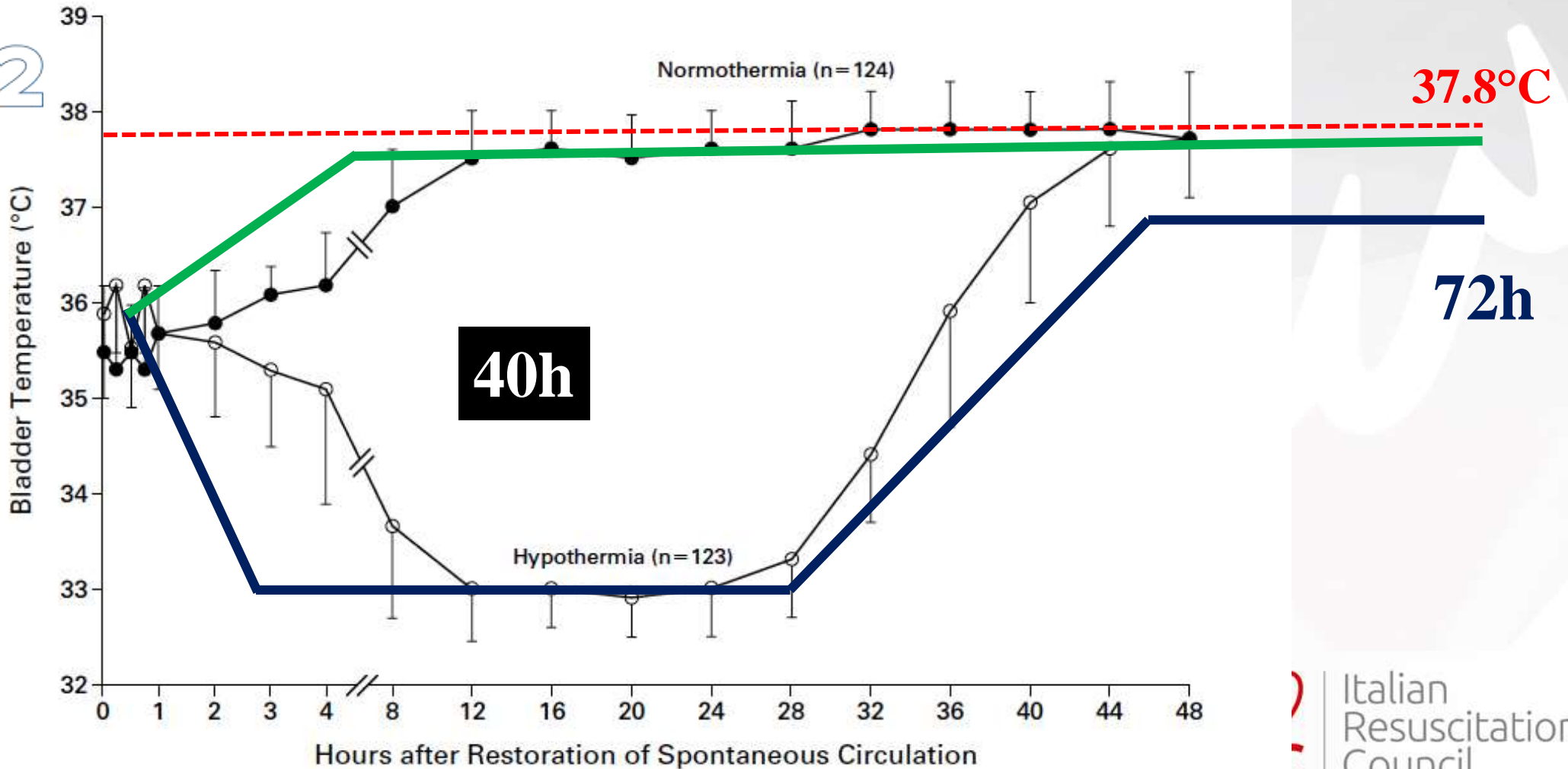
Dr. Tommaso Pellis – SOC Anestesia, Rianimazione e 118 – AS Friuli Occidentale

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

J. Dankiewicz, T. Cronberg, G. Lilja, J.C. Jakobsen, H. Levin, S. Ullén, C. Rylander, M.P. Wise, M. Oddo, A. Cariou, J. Bělohávek, J. Hovdenes, M. Saxena, H. Kirkegaard, P.J. Young, P. Pelosi, C. Storm, F.S. Taccone, M. Joannidis, C. Callaway, G.M. Eastwood, M.P.G. Morgan, P. Nordberg, D. Erlinge, A.D. Nichol, M.S. Chew, J. Hollenberg, M. Thomas, J. Bewley, K. Sweet, A.M. Grejs, S. Christensen, M. Haenggi, A. Levis, A. Lundin, J. Düring, S. Schmidbauer, T.R. Keeble, G.V. Karamasis, C. Schrag, E. Faessler, O. Smid, M. Otáhal, M. Maggiorini, P.D. Wendel Garcia, P. Jaubert, J.M. Cole, M. Solar, O. Borgquist, C. Leithner, S. Abed-Maillard, L. Navarra, M. Annborn, J. Undén, I. Brunetti, A. Awad, P. McGuigan, R. Bjørkholt Olsen, T. Cassina, P. Vignon, H. Langeland, T. Lange, H. Friberg, and N. Nielsen, for the TTM2 Trial Investigators*



Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest





Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest



Characteristic	Hypothermia (N=930)	Normothermia (N=931)
Demographic characteristics		
Age — yr	64±13	63±14
Male sex — no. (%)	742 (80)	735 (79)
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)
First monitored rhythm — no. (%)		
Shockable rhythm	671 (72)	700 (75)
Nonshockable rhythm	259 (28)	231 (25)
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)
Unknown rhythm, shock administered	40 (4)	45 (5)
Bilateral pupillary reflexes present — no./total no. (%)	535/761 (70)	529/776 (68)
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)

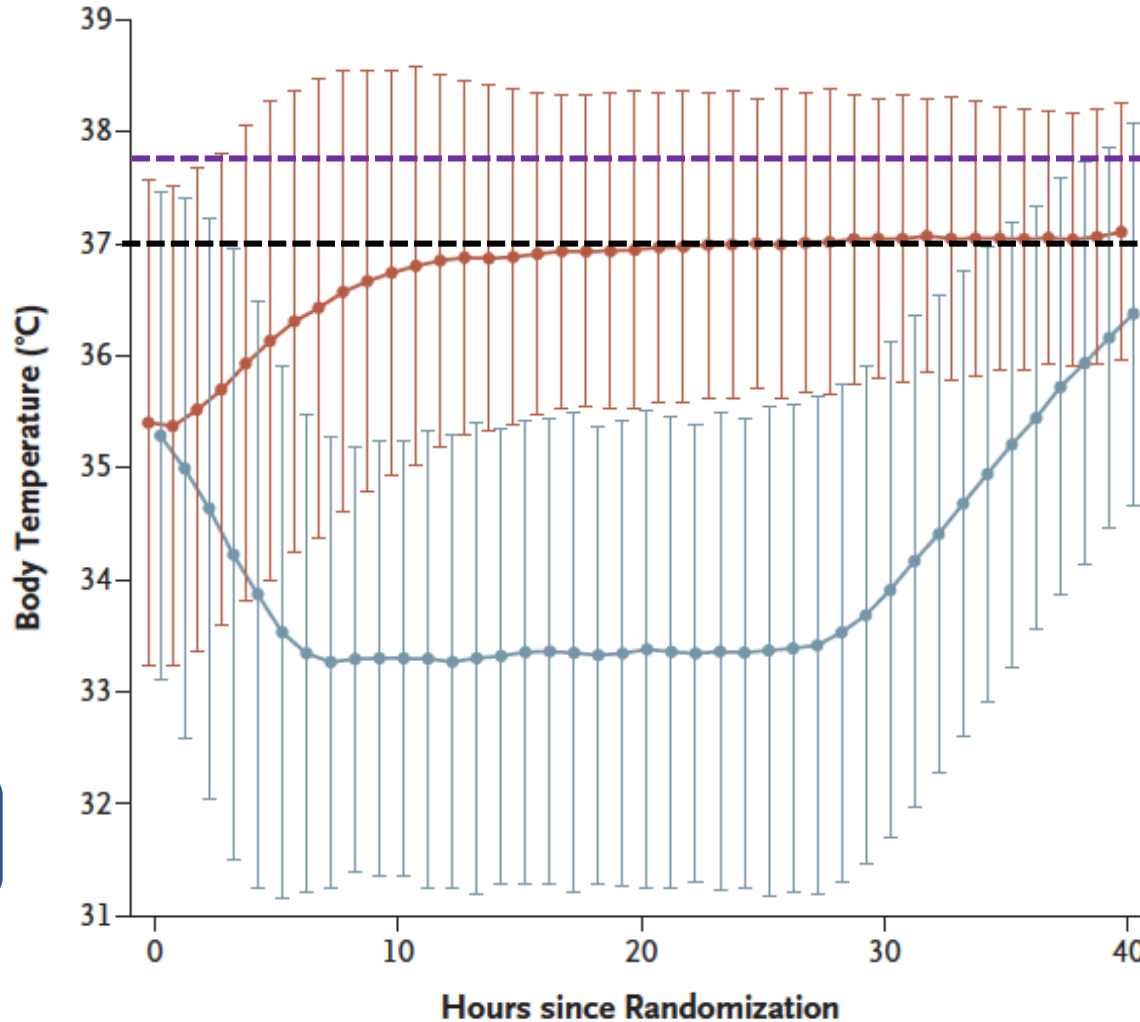




Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest



— Normothermia group — Hypothermia group



HACA

46% in the NT group

<10% had BT > 37.7°C

3h



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SEDATION

All participants were sedated for 40 hours.

There was no mandated protocol for sedation, but short-acting drugs or volatile anaesthesia was recommended.

Sedation was titrated to a Richmond Agitation-Sedation Scale (RASS) of minus 4 (No response to voice, but any movement to physical stimulation.)

SHIVERING

Shivering was assessed according to the Bedside Shivering Assessment Scale (BSAS).

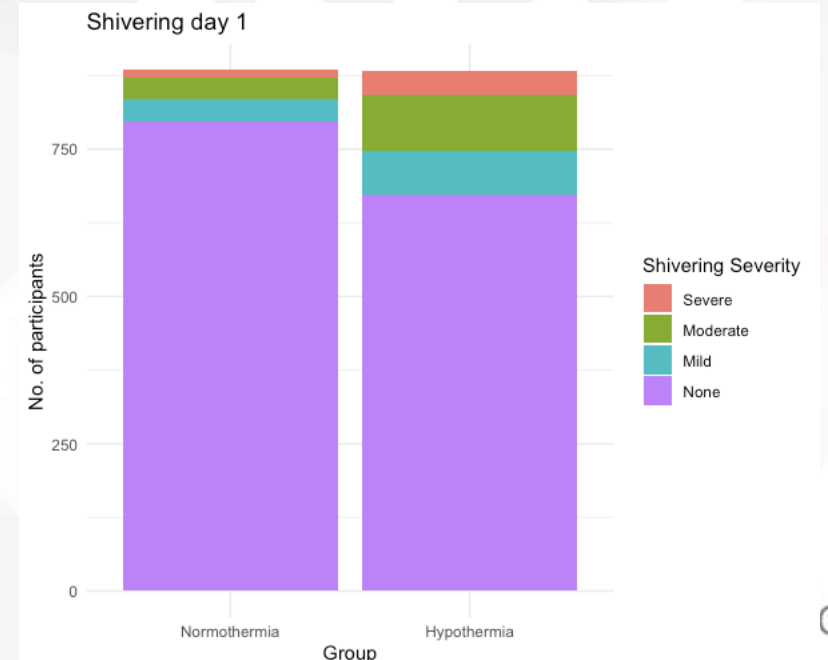
The treatment goal for shivering was to maintain a BSAS score of 0 or 1.

To ensure adequate control of shivering the following was recommended:

- 1) Adherence to local protocols for management of shivering and administration of acetaminophen for all patients.
- 2) Increased sedation with propofol/dexmedetomidine and/or opiate. If the participant was hemodynamically unstable midazolam could be used instead of propofol.
- 3) Administration of a neuromuscular blocking agent.

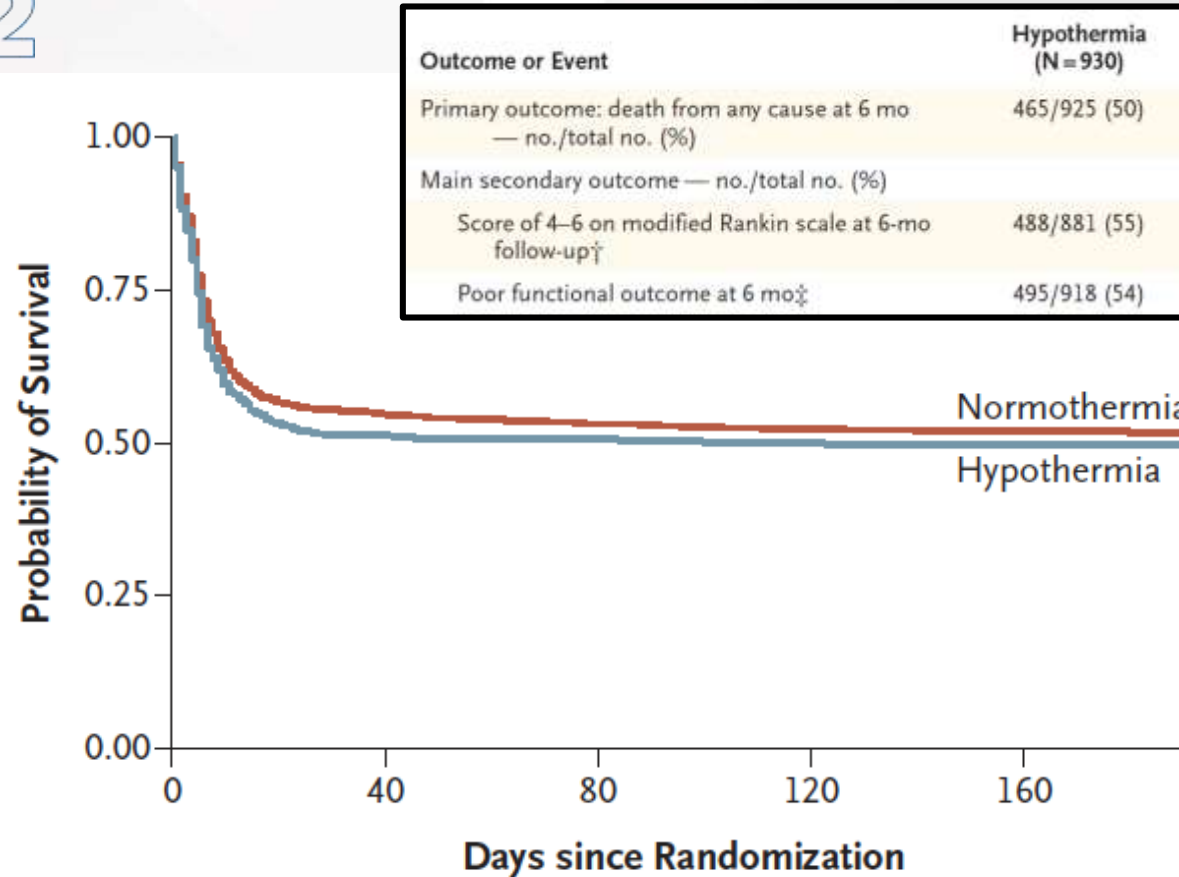
The Bedside Shivering Assessment Scale (BSAS)

Score	Severity	Description
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





Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest



Outcome or Event	Hypothermia (N = 930)	Normothermia (N = 931)	Relative Risk (95% CI) ^a	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 ^b	488/881 (55)	479/866 (55)	1.00 (0.92–1.09)	
Poor functional outcome at 6 mo ^c	495/918 (54)	493/911 (54)	1.00 (0.91–1.08)	

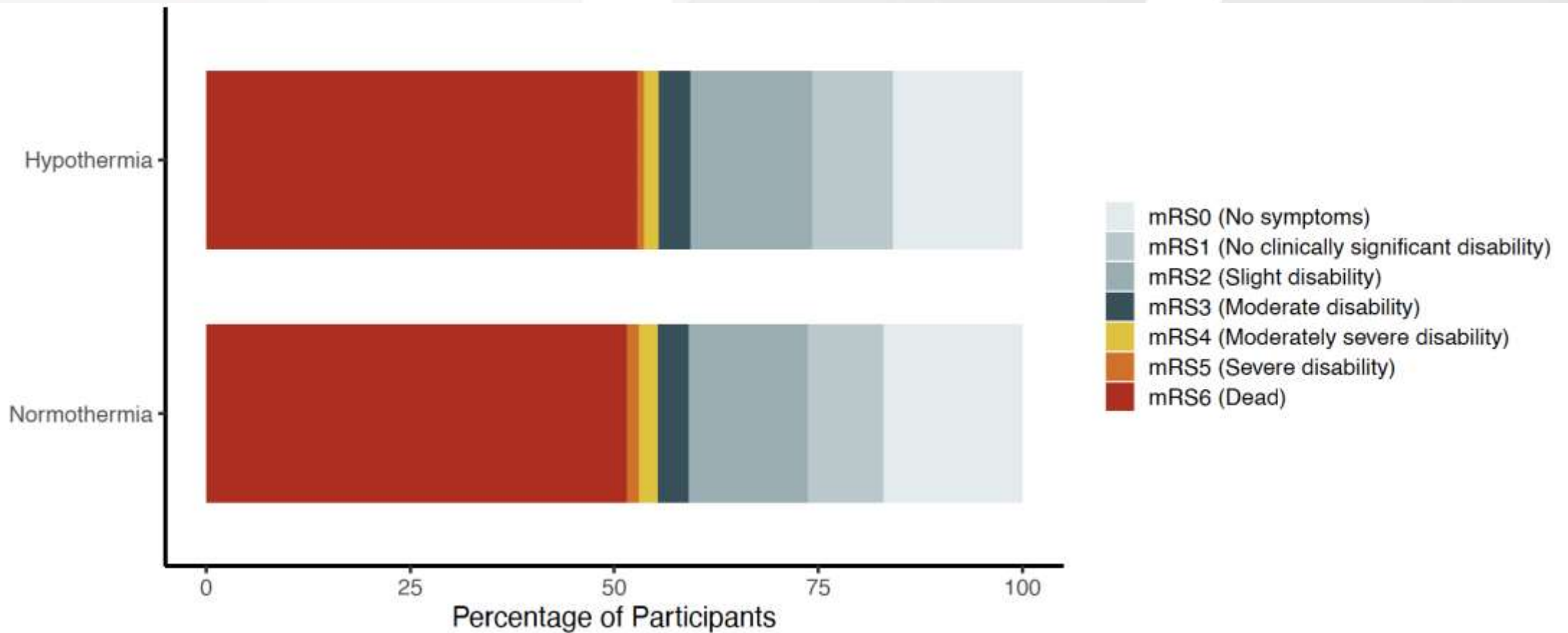
No. at Risk						
Normothermia	925	506	491	484	480	
Hypothermia	925	474	468	462	461	



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Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

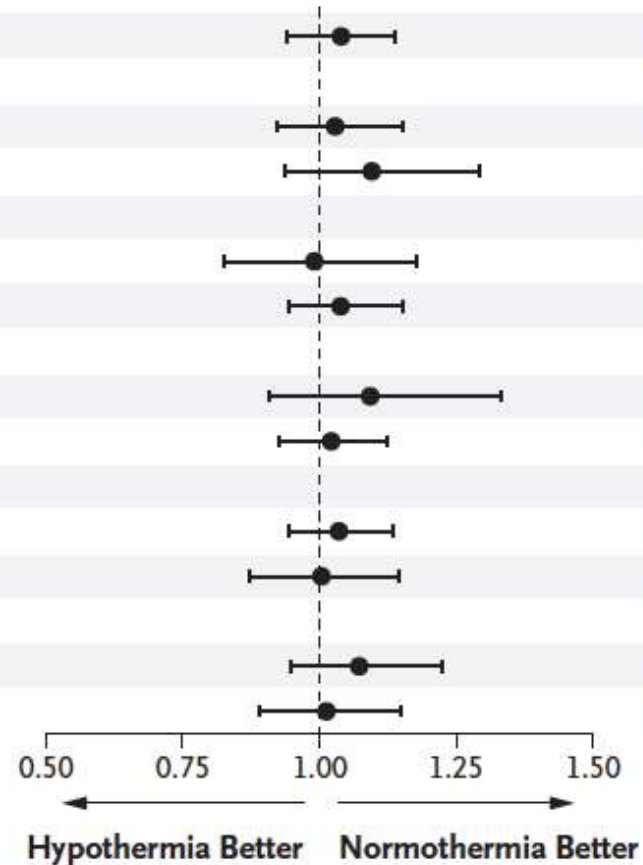




Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

A Death at 6 Months

Subgroup	Hypothermia no. of patients	Normothermia no. of patients	Relative Risk of Death (95% CI)
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)





Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest



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



Hypothermia vs. Normothermia after Out-of-Hospital Cardiac Arrest

OPEN-LABEL TRIAL WITH BLINDED OUTCOME ASSESSMENT

1850 Comatose adults after out-of-hospital cardiac arrest	Hypothermia (target body temperature, 33°C) N=925	Normothermia (target body temperature, ≤37.5°C) N=925
Death from any cause at 6 mo	50% RR, 1.04; 95% CI, 0.94 to 1.14; P=0.37	48%
Modified Rankin scale score ≥4 at 6 mo	55% RR, 1.00; 95% CI, 0.92 to 1.09	55%
Arrhythmia with hemodynamic compromise	24%	17%
Hypothermia did not lead to a lower 6-mo incidence of death than normothermia.		



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TTM 1 – Adverse events, 30 subtypes...

33°C

36°C

	33°C	36°C	
Bleeding from insertion sites (n=901)	42 (9.2)	27 (6.1)	0.076
Infection			
Pneumonia (n=932)	245 (52)	214 (46)	0.089
Severe sepsis (n=925)	46 (10)	46 (10)	0.92
Septic shock (n=922)	22 (4.8)	25 (5.4)	0.63
Other serious infection (n=923)	10 (2.2)	13 (2.8)	0.52
Arrhythmia			
Atrial fibrillation (n=929)	123 (26)	130 (28)	0.51
Atrial flutter (n=923)	17 (3.6)	19 (4.2)	0.68
Tachycardia (n=924)	65 (14)	71 (16)	0.49
Bradycardia needing pacing (n=922)	24 (5.2)	29 (6.4)	0.43
Ventricular tachycardia (n=922)	86 (18)	70 (15)	0.21
Ventricular fibrillation (n=921)	39 (8.4)	34 (7.4)	0.59
Recurrent CA mandating CPR (n=913)	42 (9.1)	46 (10)	0.60
Electrolyte and metabolic disorder			
Hypokalemia (n=911)	86 (19)	60 (13)	0.018
Any of the above events (n=936)	439 (93)	417 (90)	0.086



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2000

1800

1600

1400

1200

1000

800

600

400

200

0

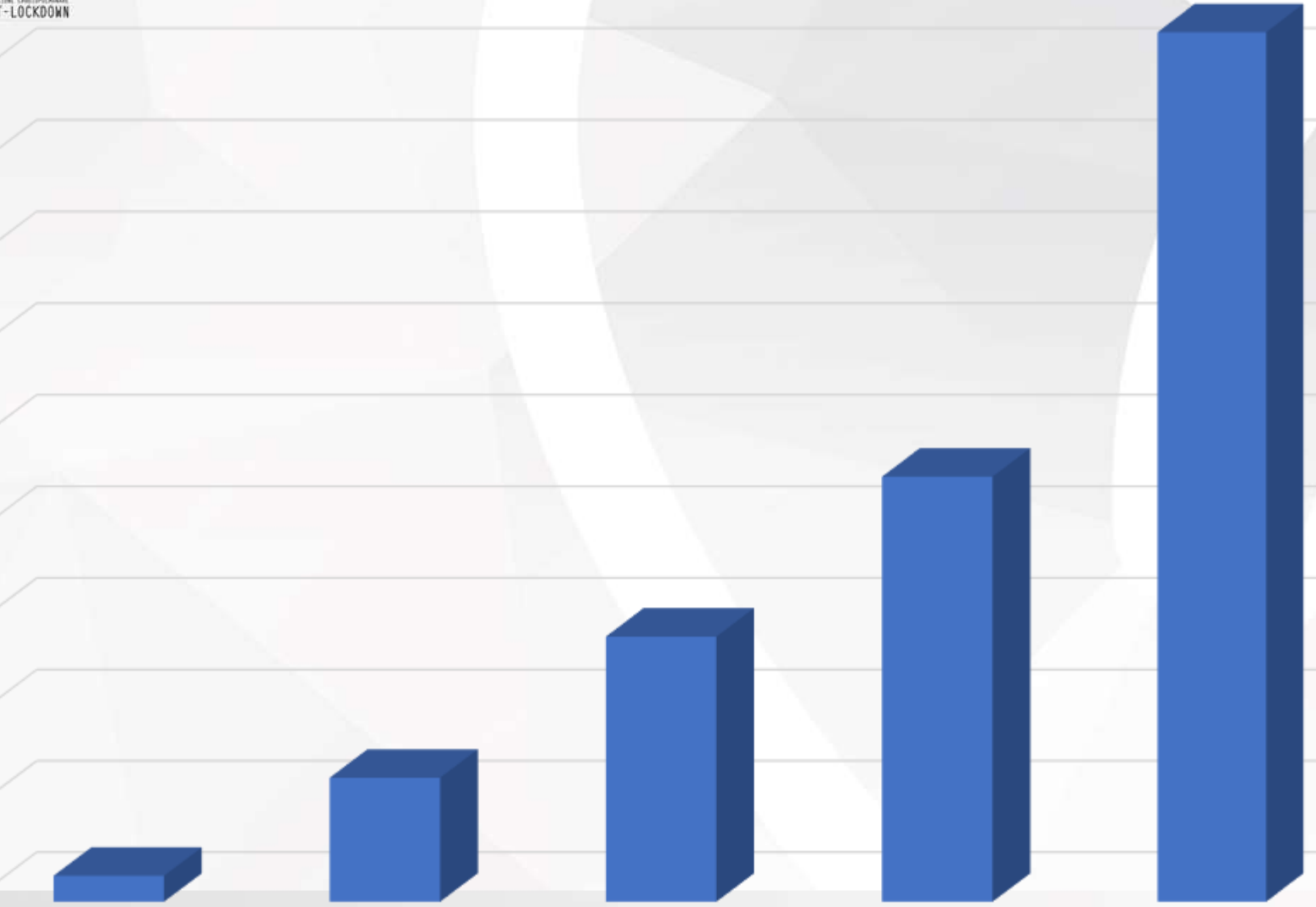
Bernard

HACA

Hyperion

TTM

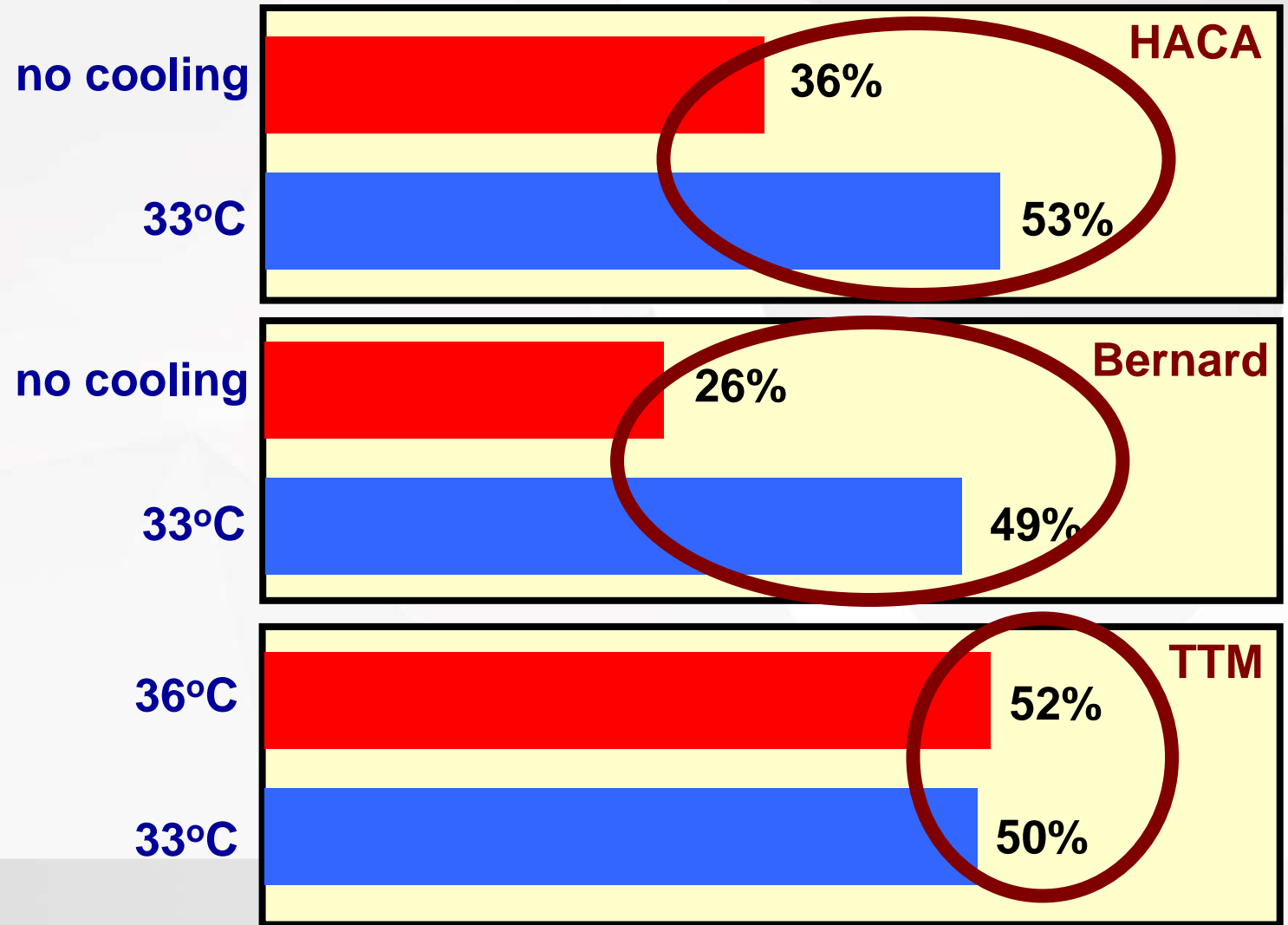
TTM2



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Making sense of the post-arrest trials



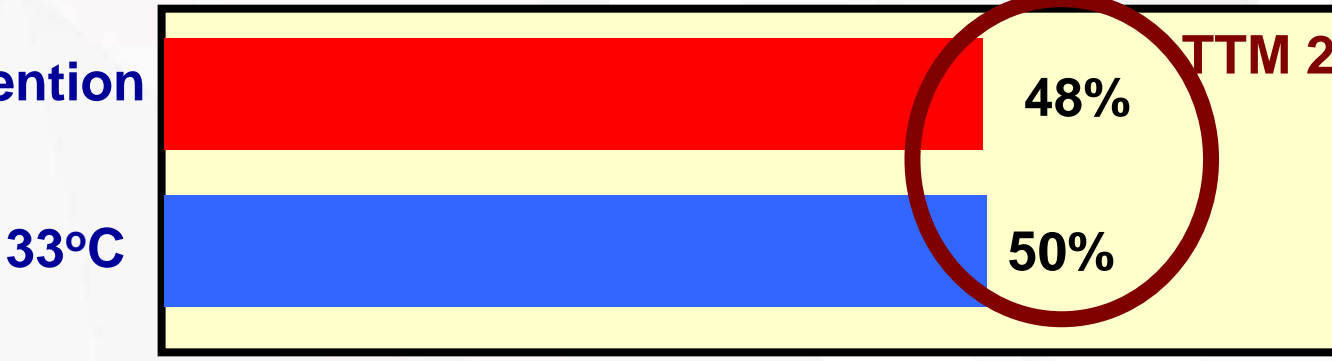
How can this be?



Making sense of the post-arrest trials




Fever prevention





Targeted temperature management following out-of-hospital cardiac arrest: a systematic review and network meta-analysis of temperature targets



Shannon M. Fernando^{1,2*} , Pietro Di Santo^{3,4}, Behnam Sadeghirad^{5,6}, Jean-Baptiste Lascarrou⁷, Bram Rochweg^{6,8}, Rebecca Mathew^{1,3}, Mypinder S. Sekhon⁹, Laveena Munshi^{10,11,12}, Eddy Fan^{10,11,12,13}, Daniel Brodie^{14,15}, Kathryn M. Rowan¹⁶, Catherine L. Hough¹⁷, Shelley L. McLeod^{6,18,19}, Christian Vaillancourt^{2,4,20}, Sheldon Cheskes^{19,21}, Niall D. Ferguson^{10,11,12,13}, Damon C. Scales^{10,11,21,22}, Claudio Sandroni^{23,24}, Jerry P. Nolan^{25,26} and Benjamin Hibbert^{3,4}

Received: 29 June 2021 Accepted: 5 August 2021
Published online: 13 August 2021

Intensive Care Med
<https://doi.org/10.1007/s00134-021-06505-z>

Conclusioni

- L'uso di routine del TTM non è associato a miglioramenti degli outcome importanti per il paziente, con potenziale danno
- L'uso di routine dell'ipotermia moderata non appare associata a beneficio, e si associa ad una incidenza maggiore di eventi avversi (es. aritmie)



Consensus on Science with Treatment Recommendations (CoSTR)



SR

Temperature Management in Adult Cardiac Arrest: Advanced Life Support Systematic Review

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ILCOR staff

Created: August 30, 2021 · Updated: August 31, 2021

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Raccomandazioni al trattamento

- Sugeriamo di prevenire attivamente la febbre avendo come target una temperatura ≤ 37.5 nei pazienti in coma dopo ROSC
 - Raccomandazione debole, basso livello di certezza dell'evidenza
- Che sottopopolazioni di pazienti con arresto cardiaco possano beneficiare di una temperatura target di 32-34°C rimane incerto.



Raccomandazioni al trattamento

- Pazienti in coma con ipotermia lieve dopo ROSC non andrebbero riscaldati attivamente per ottenere la normotermia
 - Good practice statement
- Raccomandiamo contro il raffreddamento preospedaliero mediante infusioni rapide di grandi volumi di liquidi freddi EV immediatamente dopo ROSC
 - Raccomandazione forte, certezza dell'evidenza moderata



Raccomandazioni al trattamento



- Suggeriamo tecniche di controllo della temperatura di superficie o endovascolari quando viene usato il controllo della temperatura in pazienti in coma dopo ROSC
 - Raccomandazione debole, bassa qualità dell'evidenza
- Qualora venga usato un presidio per il raffreddamento, per mantenere il target di temperatura suggeriamo di ricorrere a un presidio di controllo della temperatura che comprenda un sistema di feedback basato su rilevazioni continue della temperatura
 - good practice statement

Raccomandazioni al trattamento

- Sugeriamo di prevenire attivamente la febbre per almeno 72 ore dopo arresto cardiaco nei pazienti che permangono in coma
 - good practice statement



Justification and evidence to decision framework highlights

- Tutti i membri della Task Force concordano che **si continui a raccomandare il controllo attivo della temperatura** in pazienti dopo arresto cardiaco, sebbene l'evidenza sia limitata
- Siamo preoccupati che la scadente implementazione del controllo della temperatura possa nuocere ai pazienti



Justification and evidence to decision framework highlights

- Si è discusso sulla definizione dei normotermia e febbre
- In una coorte varia di 35.488 pazienti ospedalizzati il range del 99% di temperatura normale era di 35.3-37.7°C, e il range del 95% era di 35.7-37.3 C
- Il paragone tra 33 vs 36 C è stato incluso in un'analisi di sensibilità dei 33 C vs normotermia/prevenzione della febbre, dato che il 36 C cadono all'interno del range di normotermia – ciò non ha modificato i risultati a favore di nessuno dei due gruppi

Definizioni di strategie di controllo della temperatura

- Il termine TTM di per sé non è di aiuto
- Per essere più chiari vengono proposti:
 - Hypothermic Temperature Control: controllo attivo della temperatura con target di temperatura sotto il range di normalità
 - Normothermic Temperature Control: controllo attivo della temperatura con target di temperatura nel range di normalità
 - Fever Prevention Temperature Control: monitoraggio della temperatura e prevenzione attiva, nonché il trattamento attivo di temperature al di sopra della norma.
 - No Temperature Control: nessuna strategia protocollata di trattamento attivo della temperatura

Ipotermia vs normotermia o prevenzione della febbre

- La maggioranza della Task Force si è espressa in favore della prevenzione della febbre invece che dell'ipotermia:
 - L'evidenza a supporto di revisioni sistematiche
 - Tale strategia richiede meno risorse
 - Minori effetti collaterali dell'ipotermia
- Nel TTM2 nel gruppo normotermia/prevenzione della febbre si è fatto ricorso a:
 - Per mantenere $T \leq 37.5$: paracetamolo, scoprire il paziente, ridurre la temperatura ambientale
 - Un presidio per il controllo della temperatura se questa diveniva $\geq 37.7^{\circ}\text{C}$
 - Il presidio è stato usato nel 46% dei pazienti
 - La temperatura impostata era di 37.5°C

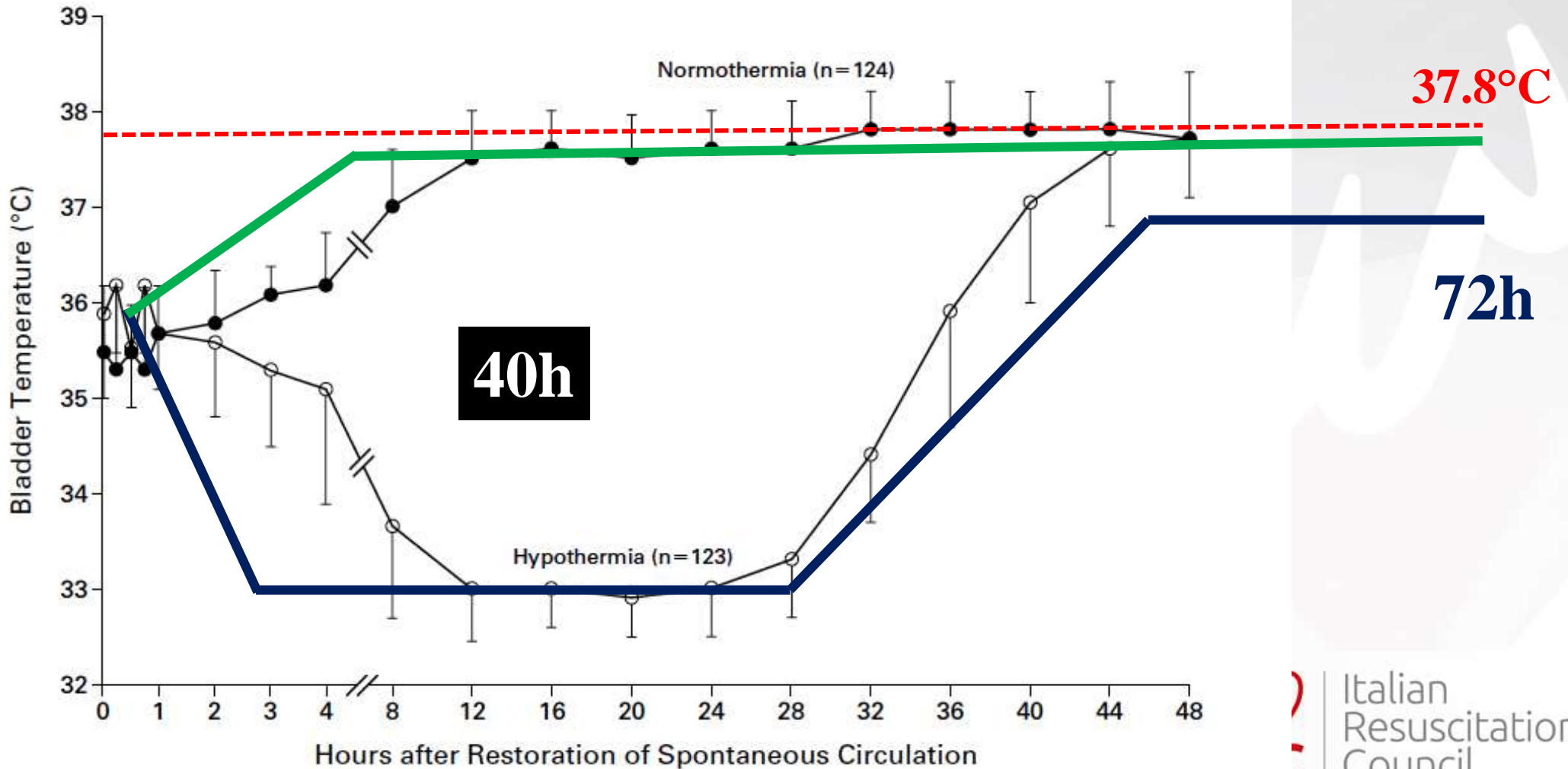
Ipotermia vs normotermia o prevenzione della febbre

- La Task Force ha scelto la prevenzione attiva della febbre invece della normotermia nelle raccomandazioni al trattamento
- La Task Force riconosce che le revisioni sistematiche non dimostrano una differenza di outcome tra i pazienti trattati con ipotermia, normotermia o prevenzione della febbre

Considerare attentamente le ricadute di qualsiasi cambiamento

- Problematiche possibili:
 - Pazienti non sottoposti a TC dopo AC già oggi risentono negativamente in termini di processo di cure
 - Perdita del volano nel garantire un trattamento post-rianimazione di elevata qualità
 - In assenza del TC come trattarsi da finestre neurologiche giornaliere/interruzioni della sedazione
 - Rittoia attenzione alla febbre

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest





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American Journal of Emergency Medicine 50 (2021) 202–206



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Passive antipyretic therapy is not as effective as invasive hypothermia for maintaining normothermia after cardiac arrest



Talal S. Alnabelsi, MD^{a,*}, Sarah P. Faulkner, MD^b, Matthew Cook, MD^b, Kalen Freeman, PharmD^b, Julie Shelton, MD^a, Marc Paranzino, MD^a, Sethabhisha Nerusu, PhD^c, Susan S. Smyth, MD^a, Vedant A. Gupta, MD^a



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Chain of survival



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Clinical paper

Changing target temperature from 33 °C to 36 °C in the ICU management of out-of-hospital cardiac arrest: A before and after study[☆]



Janet E. Bray^{a,b,c,*}, Dion Stub^{a,b,d,e,f}, Jason E. Bloom^b, Louise Segan^{a,b}, Biswadev Mitra^{a,b}, Karen Smith^{a,d,g,h}, Judith Finn^{a,c}, Stephen Bernard^{a,b,d}

J.E. Bray et al. / Resuscitation 113 (2017) 39–43

- VF-OHCA patients
- Tertiary referral hospital in Melbourne
- Before/after study
- 30 months (Jan 2013-Aug 2015)
 - 76 pts
 - 24 before
 - 52 after
- Compared to 33°C, during 36°C period:
 - less active cooling: 100% vs. 70%, $p < 0.001$
 - less time at target T: 87% vs. 50%, $p < 0.001$
 - fever rates increased: 0% vs. 19%, $p = 0.03$
 - Reduction in patients discharged:
 - Alive: 71% vs. 58%, $p = 0.31$
 - Home: 58% vs. 40%, $p = 0.08$



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J.E. Bray et al. / Resuscitation 113 (2017) 39–43

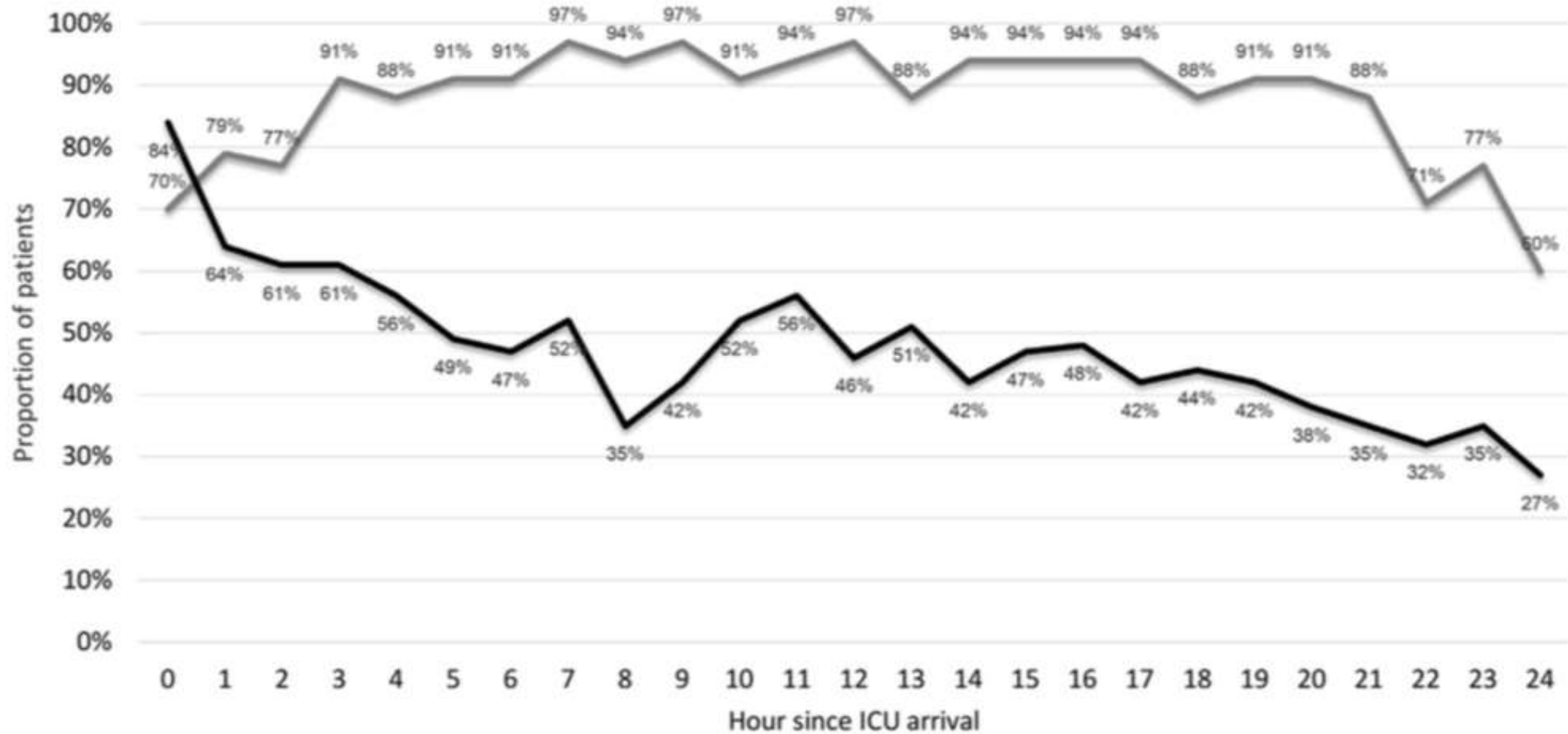


Fig. 1. The proportion of patients at target temperature for each hour of the first day of intensive care stay by the 33°C (grey line) and 36°C (black line) TTM periods.

Changes in Temperature Management of Cardiac Arrest Patients Following Publication of the Target Temperature Management Trial

Ryan Salter, FANZCA¹; Michael Bailey, PhD²⁻⁴; Rinaldo Bellomo, MD^{2,3,5}; Glenn Eastwood, PhD^{2,5}; Andrew Goodwin, BEng (Env)⁶; Niklas Nielsen, PhD^{7,8}; David Pilcher, FCICM^{2,9,10}; Alistair Nichol, PhD^{2,9,11}; Manoj Saxena, PhD¹²⁻¹⁴; Yahya Shehabi, PhD^{4,15}; Paul Young, PhD^{1,16}; on behalf of the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS-CORE)

January 2014 until December 2016 (change in slope 1.9 percentage points per year [99% CI, -0.6 to 4.4]). Fever occurred in 568 (12.8%) of 4,450 pretarget temperature management trial patients and 853 (16.5%) of 5,184 posttarget temperature management trial patients (odds ratio, 1.35 [99% CI, 1.16–1.57]).

Conclusions: The average lowest temperature of postcardiac arrest patients in the first 24 hours in ICU rose after publication of the target temperature management trial. This change was associated with an increased frequency of fever not seen in the target temperature management trial. (*Crit Care Med* 2018; XX:00–00)

Key Words: cardiac arrest; implementation science; intensive care medicine; knowledge translation; therapeutic hypothermia

Data analysed
n = 6618.

Data analysed
n = 4450.

Data analysed
n = 5184.

tation

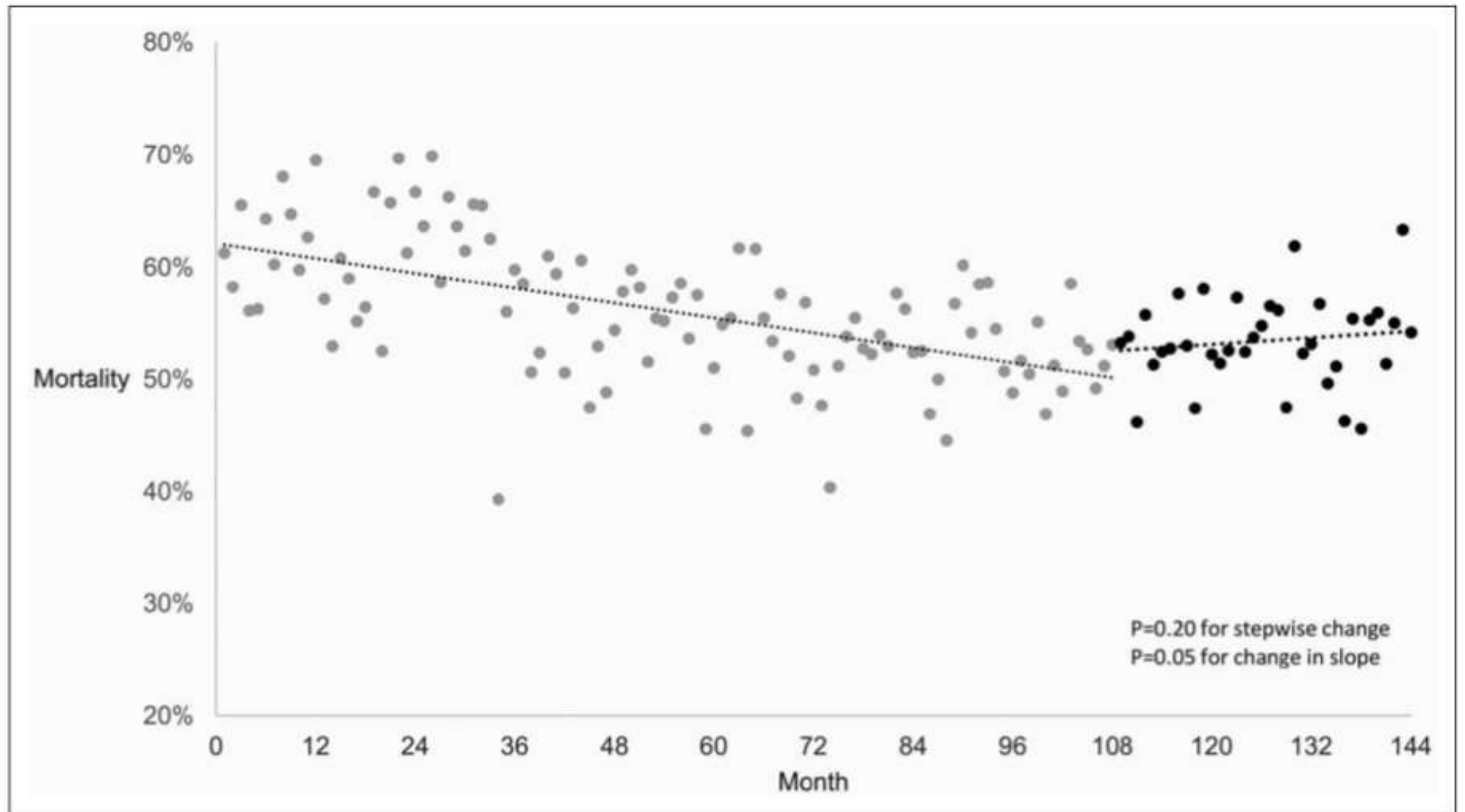


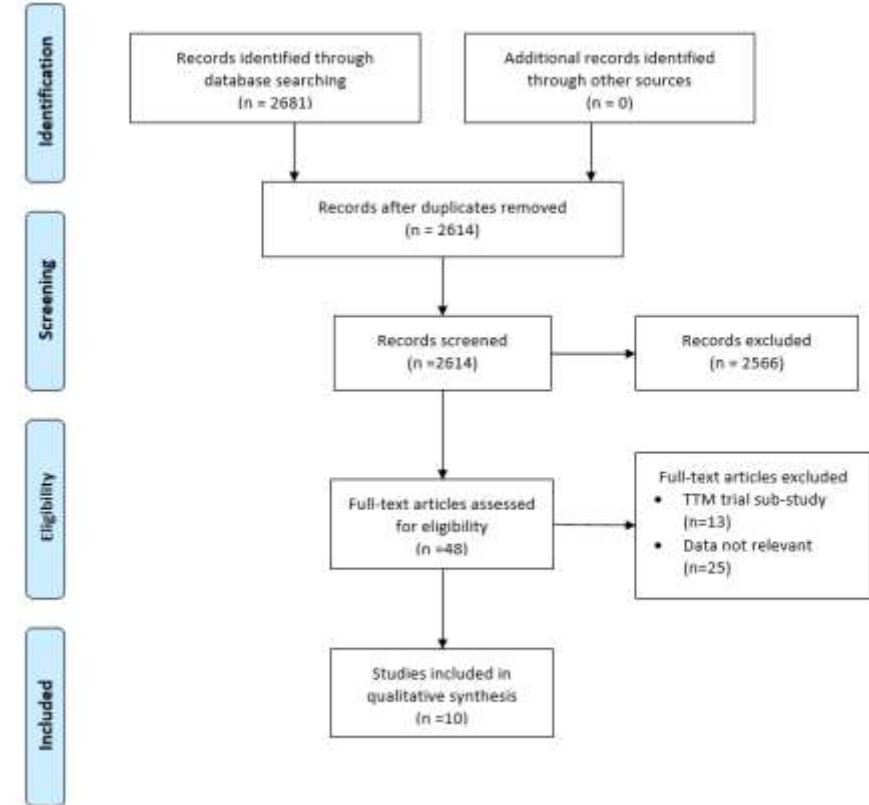
Figure 3. In-hospital mortality by month. The *gray dots* are for the months from January 2005 until December 2013 inclusive; the *black dots* are for the months from January 2014 until December 2016 inclusive. The targeted temperature management study was published online on November 17, 2013, and was published in print on December 5, 2013.

POOR TTM PROTOCOLS SHOULD BE AVOIDED

Review

Which Target Temperature for Post-Anoxic Brain Injury? A Systematic Review from "Real Life" Studies

Andrea Minini, Filippo Annoni , Lorenzo Peluso , Elisa Go and Fabio Silvio Taccone *



Study or Subgroup	Low TTM		High TTM		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
1.3.1 Poor Neurological Outcome						
Bray et al. [13]	7	24	23	52	1.2%	0.52 [0.18, 1.46]
Callaway et al [20]	685	728	554	591	6.0%	1.06 [0.68, 1.67]
Cragun et al. [21]	10	14	9	18	0.6%	2.50 [0.57, 11.01]
Düggelin et al. [22]	30	57	30	55	2.2%	0.93 [0.44, 1.95]
Johnson et al. [23]	155	258	137	195	7.9%	0.64 [0.43, 0.95]
Johnsson et al. [24]	853	1242	333	468	22.8%	0.89 [0.70, 1.12]
Kleissner et al. [25]	50	116	26	59	3.1%	0.96 [0.51, 1.81]
Okazaki et al. [26]	180	319	73	116	6.5%	0.76 [0.49, 1.18]
Subtotal (95% CI)		2758		1554	50.3%	0.85 [0.73, 0.99]

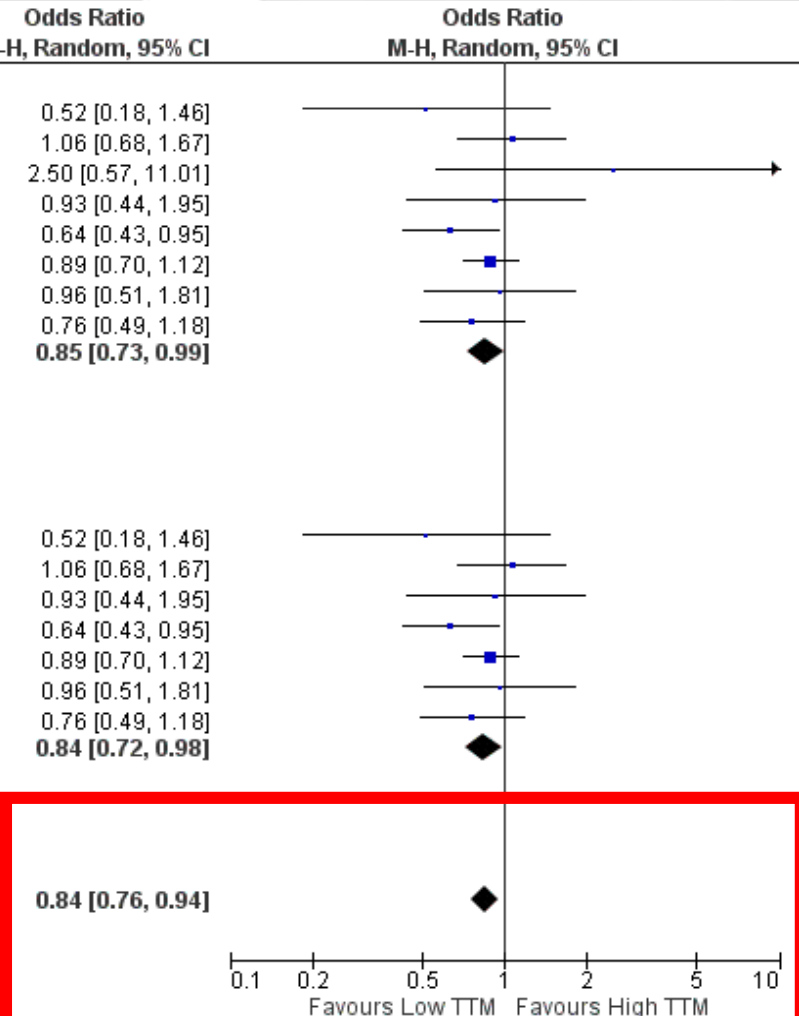
Total events 1970 1185
Heterogeneity: Tau² = 0.00; Chi² = 6.46, df = 7 (P = 0.49); I² = 0%
Test for overall effect: Z = 2.03 (P = 0.04)

1.3.2 Poor Neurological Outcome CPC 3-5

Bray et al. [13]	7	24	23	52	1.2%	0.52 [0.18, 1.46]
Callaway et al [20]	685	728	554	591	6.0%	1.06 [0.68, 1.67]
Düggelin et al. [22]	30	57	30	55	2.2%	0.93 [0.44, 1.95]
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Kleissner et al. [25]	50	116	26	59	3.1%	0.96 [0.51, 1.81]
Okazaki et al. [26]	180	319	73	116	6.5%	0.76 [0.49, 1.18]
Subtotal (95% CI)		2744		1536	49.7%	0.84 [0.72, 0.98]

Total events 1960 1176
Heterogeneity: Tau² = 0.00; Chi² = 4.40, df = 6 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.17 (P = 0.03)

Total (95% CI) 5502 3090 100.0%
Total events 3930 2361
Heterogeneity: Tau² = 0.00; Chi² = 10.88, df = 14 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.97 (P = 0.003)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%



Conclusioni

- Nuovi termini: controllo della temperature (TC)
- **Abbandonare la gestione della temperature non è una opzione percorribile**
 - Prevenire attivamente la febbre avendo come target una temperatura ≤ 37.5 °C
 - Prevenire la febbre per almeno 72 ore
- Se introducete dei cambiamenti pianificate degli audit sugli esiti e processi di cure



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Cardiac Origin

Non-Cardiac Origin

Short No-Flow

Prolonged No-Flow

Short No-Flow

Prolonged No-Flow

NT



33



Italian Resuscitation Council

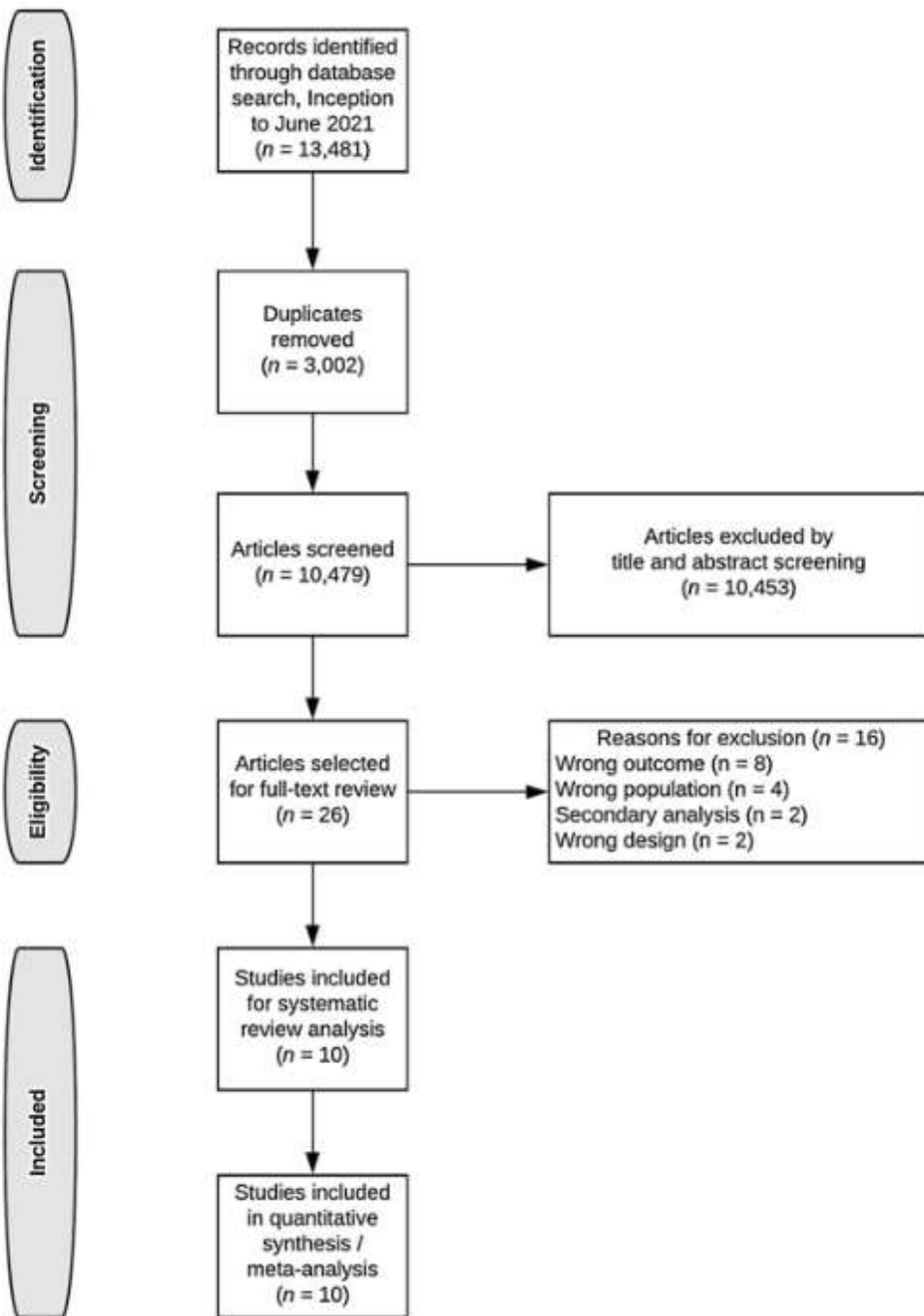
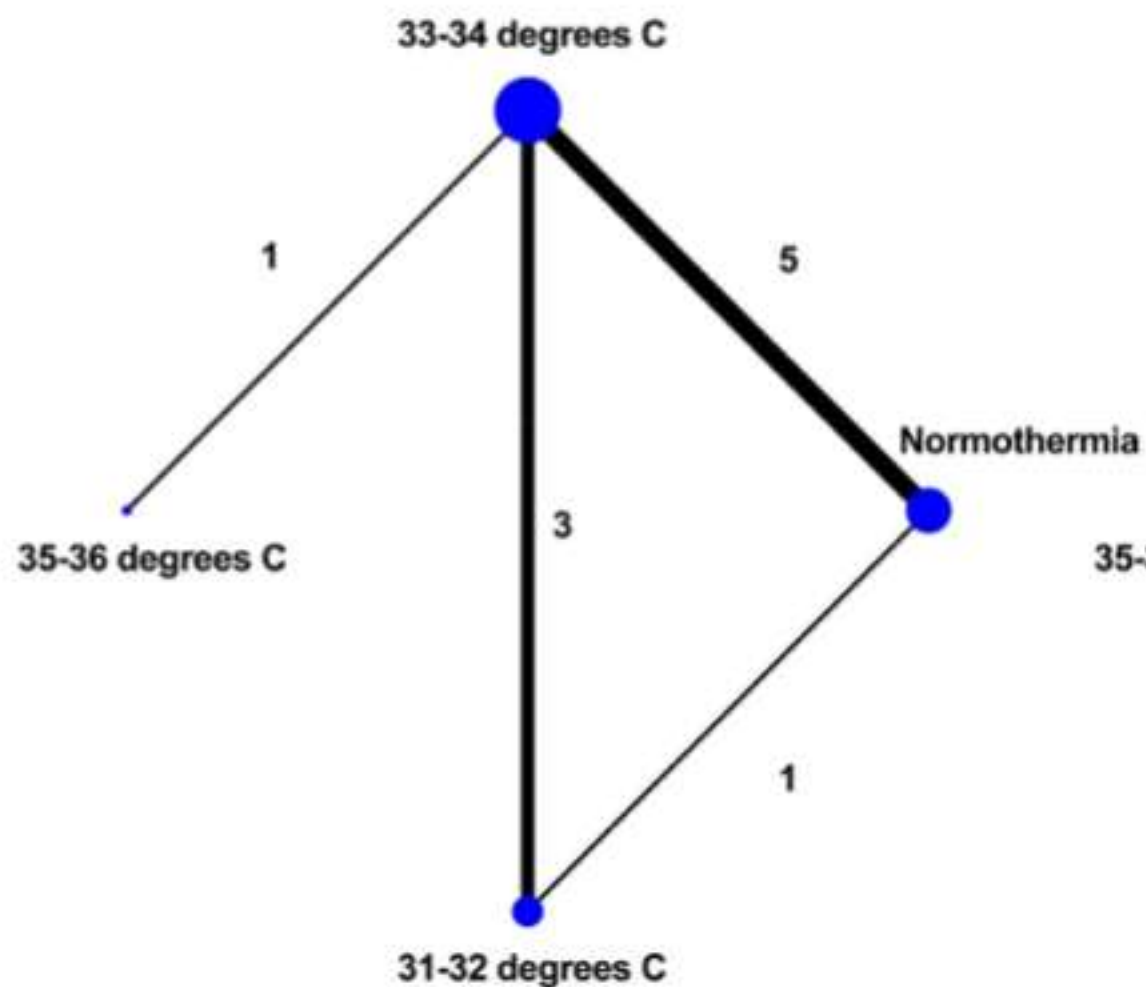


Fig. 1 Flowchart summarizing evidence search and study selection

Description	Overall (10 studies, n = 4,218)	
	Number of studies (%)	Number of patients (%)
Continent of study		
Europe	6 (60)	974 (23.1)
North America	1 (10)	367 (8.7)
Australia	1 (10)	77 (1.8)
Multicontinental	2 (20)	2800 (66.3)
Year of publication		
2000–2004	3 (30)	382 (9.1)
2005–2009	1 (10)	61 (1.4)
2010–2014	2 (20)	975 (23.1)
2015–2019	2 (20)	572 (13.6)
2020–2021	2 (20)	2228 (52.8)
Sites		
Single center	3 (30)	433 (10.3)
Multicenter	7 (70)	3785 (89.7)
Initial rhythm		
Ventricular fibrillation/ventricular tachycardia	3 (30)	502 (11.9)
Pulseless electrical activity/asystole	2 (20)	452 (10.7)
Mixed	5 (50)	3264 (77.4)
Interventions studied		
31–32 °C Deep	4 (40)	276 (6.5)
33–34 °C Moderate	9 (90)	2086 (49.5)
35–36 °C Mild	1 (10)	466 (11.0)
Normothermia (37–37.8 °C)	6 (60)	1390 (33.0)

A Survival with Good Functional Outcome



B Overall Survival

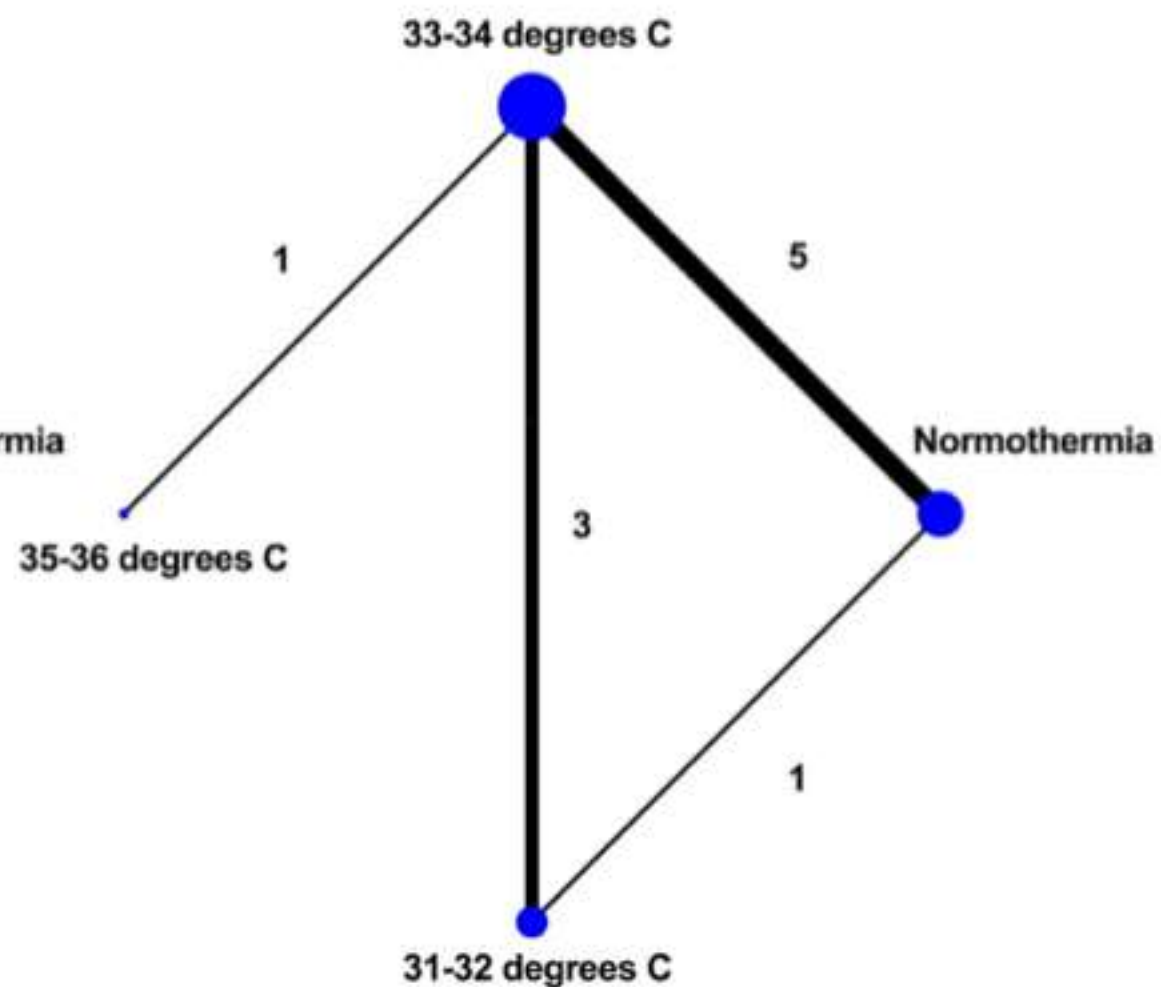


Fig. 2 Network plots for **A** survival with good functional outcome; and **B** overall survival. The size of the node corresponds to the number of patients randomized to that intervention. The thickness of the line and the associated numbers correspond to the number of studies comparing the two linked interventions

Sopravvivenza con buon recupero neurologici – Network estimates –

- Rispetto alla normotermia, potrebbe non esserci alcun effetto

Comparison	Direct estimate OR (95% CI)	Indirect estimate OR (95% CI)	Network estimate ¹ OR (95% CI)	GRADE	Narrative summary
31–32 °C vs. Normothermia	0.93 (0.31–2.85)	1.46 (0.71–2.99)	1.30 (0.73–2.30)	Low ²	There may be no difference between 31 and 32 °C and normothermia
33–34 °C vs. Normothermia	1.43 (0.94–2.16)	0.90 (0.23–3.50)	1.34 (0.92–1.94)	Low ²	There may be no difference between 33 and 34 °C and normothermia
35–36 °C vs. Normothermia	–	1.44 (0.74–2.80)	1.44 (0.74–2.80)	Low ²	There may be no difference between 35 and 36 °C and normothermia
31–32 °C vs. 33–34 °C	1.04 (0.61–1.79)	0.66 (0.18–2.49)	0.97 (0.61–1.54)	Low ²	There may be no difference between 31–32 and 33–34 °C
31–32 °C vs. 35–36 °C	–	0.90 (0.44–1.86)	0.90 (0.44–1.86)	Low ²	There may be no difference between 31–32 and 35–36 °C
35–36 °C vs. 33–34 °C	1.07 (0.83–1.39)	0.55 (0.00–∞)	1.07 (0.62–1.87)	Low ²	There may be no difference between 35–36 and 33–34 °C

GRADE Grading of Recommendations Assessment, Development, and Evaluation, OR odds ratio, CI confidence interval

¹ Imprecision only incorporated at network level not at direct or indirect

² Lowered two levels for very serious imprecision

Sopravvivenza complessiva – Network estimates –

- Rispetto alla normotermia, potrebbe non esserci alcun effetto

Comparison	Direct estimate OR (95% CI)	Indirect estimate OR (95% CI)	Network estimate OR (95% CI)	GRADE	Narrative summary
31–32 °C vs. Normothermia	1.33 (0.46–3.84)	1.29 (0.62–2.70)	1.27 (0.70–2.32)	Low ²	There may be no difference between 31 and 32 °C and normothermia
33–34 °C vs. Normothermia	1.25 (0.85–1.81)	1.29 (0.34–4.86)	1.23 (0.86–1.77)	Low ²	There may be no difference between 33 and 34 °C and normothermia
35–36 °C vs. Normothermia	–	1.26 (0.64–2.49)	1.26 (0.64–2.49)	Low ²	There may be no difference between 35 and 36 °C and normothermia
31–32 °C vs. 33–34 °C	1.13 (0.55–2.32)	1.07 (0.30–3.82)	1.03 (0.64–1.68)	Low ²	There may be no difference between 31–32 and 33–34 °C
31–32 °C vs. 35–36 °C	–	1.01 (0.47–2.14)	1.01 (0.47–2.14)	Low ²	There may be no difference between 31–32 and 35–36 °C
35–36 °C vs. 33–34 °C	1.02 (0.79–1.32)	0.65 (0.00–∞)	1.02 (0.79–1.32)	Low ²	There may be no difference between 35–36 and 33–34 °C

GRADE Grading of Recommendations Assessment, Development, and Evaluation, OR odds ratio, CI confidence interval

¹ Imprecision only incorporated at network level not at direct or indirect

² Lowered one level for imprecision

Eventi Avversi

- Le aritmie erano più frequenti in coloro trattati con ipotermia moderata o profonda

Comparison	Arrhythmia OR (95% CI)	Bleeding OR (95% CI)	Pneumonia OR (95% CI)	Sepsis ^a OR (95% CI)	Seizure ^a OR (95% CI)
31–32 °C vs. Normothermia	<i>3.58 (1.77–7.26)¹</i>	1.21 (0.68–2.15) ²	0.91 (0.42–2.09) ²	Not available	Not available
33–34 °C vs. Normothermia	<i>1.45 (1.08–1.94)¹</i>	1.10 (0.78–1.55) ²	1.24 (0.79–1.95) ²	1.36 (0.88–2.10) ²	0.95 (0.67–1.35) ²
35–36 °C vs. Normothermia	1.16 (0.76–1.78) ²	1.21 (0.66–2.21) ²	0.98 (0.41–2.33) ²	Not available	Not available
31–32 °C vs. 33–34 °C	<i>2.47 (1.25–4.88)¹</i>	1.10 (0.68–1.79) ³	0.75 (0.38–1.49) ³	Not available	1.55 (0.86–2.80) ²
31–32 °C vs. 35–36 °C	<i>3.09 (1.46–6.53)¹</i>	1.00 (0.50–2.01) ²	0.96 (0.35–2.60) ²	Not available	Not available
33–34 °C vs. 35–36 °C	1.25 (0.91–1.71) ²	0.91 (0.55–1.50) ²	1.27 (0.61–2.65) ²	Not available	Not available

Italics represent a statistically significant difference between groups

Superscripts reflect GRADE certainty

GRADE Grading of Recommendations Assessment, Development, and Evaluation, OR odds ratio, CI confidence interval

^a Comparison done through conventional meta-analysis, and not network meta-analysis

¹ High certainty in higher rates with intervention

² Low certainty in no difference between intervention and comparator, rated down for very serious imprecision

³ Very low certainty, rated down for very serious imprecision and inconsistency