IRWAYS 3

IN-HOSPITAL CARDIAC ARREST CPD WEBINAR

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Temperature control after cardiac arrest

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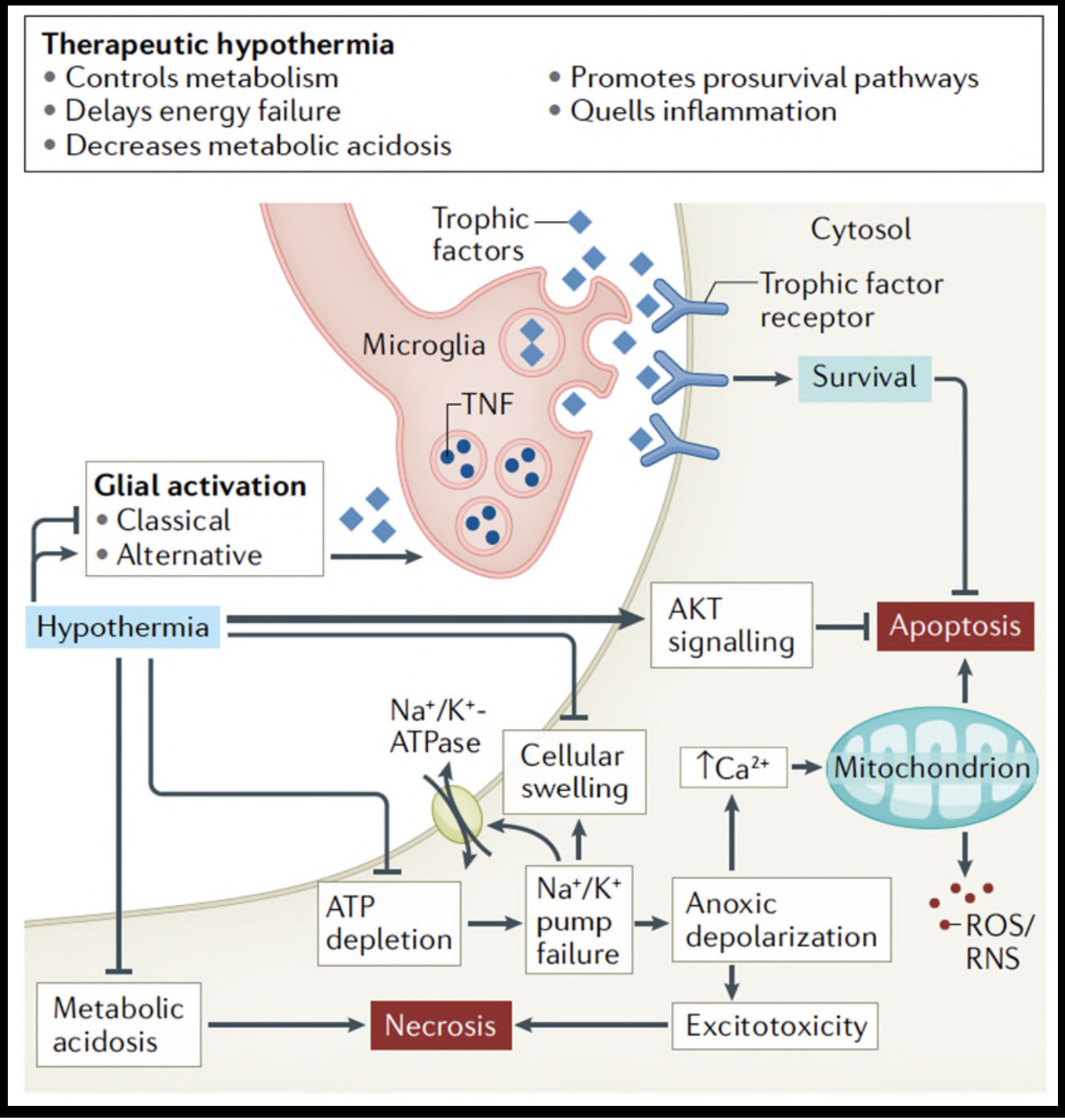


Daniele SG.
Nature Reviews Neuroscience 2021

Therapeutic hypothermia after cardiac arrest

An Advisory Statement by the ALS Task Force of the International Liaison Committee on Resuscitation (ILCOR)

- Unconscious adult patients with spontaneous circulation after out of hospital cardiac arrest should be cooled to 32-34°C for 12-24 hours when the initial rhythm was VF
- For any other rhythm, or cardiac arrest in hospital, such cooling may also be beneficial

Nolan J. Circulation 2003; 108: 118-21

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.,

	33°C Group (n=473)	36°C Group (n=466)	Hazard ratio (95% CI)
Shockable rhythm n (%)	375 (79)	377 (81)	
Death at end of trial (%)	235 (50)	225 (48)	1.06 (0.89 -1.28)
CPC 1-2 at follow up n (%)	218 (47)	222 (47)	

N Engl J Med 2013;369:2197-206

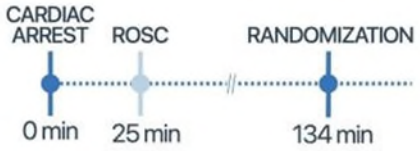
RANDOMIZED CLINICAL TRIAL

HYPOTHERMIA VERSUS NORMOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

POPULATION

1861 adults with coma after OHCA of presumed cardiac or unknown cause

64 mean age



RANDOMIZATION

HYPOTHERMIA

33°C
TARGET TEMPERATURE

for 28 h after randomization, followed by rewarming to 37°C in 1 h increments of 1/3 of a degree

NORMOTHERMIA

< 37.8°C
TARGET TEMPERATURE

If temperature ≥ 37.8°C, cooling was initiated with a target temperature of 37.5°C

OUTCOMES

PRIMARY OUTCOME

DEATH AT 6 MONTHS

Relative risk with hypothermia, 1.04; 95% CI, 0.94 to 1.14; P = 0.37

SECONDARY OUTCOME

POOR FUNCTIONAL OUTCOME AT 6 MONTHS

defined as a score of 4 to 6 on the modified Rankin scale

Relative risk with hypothermia, 1.00; 95% CI, 0.92 to 1.09

CONCLUSION

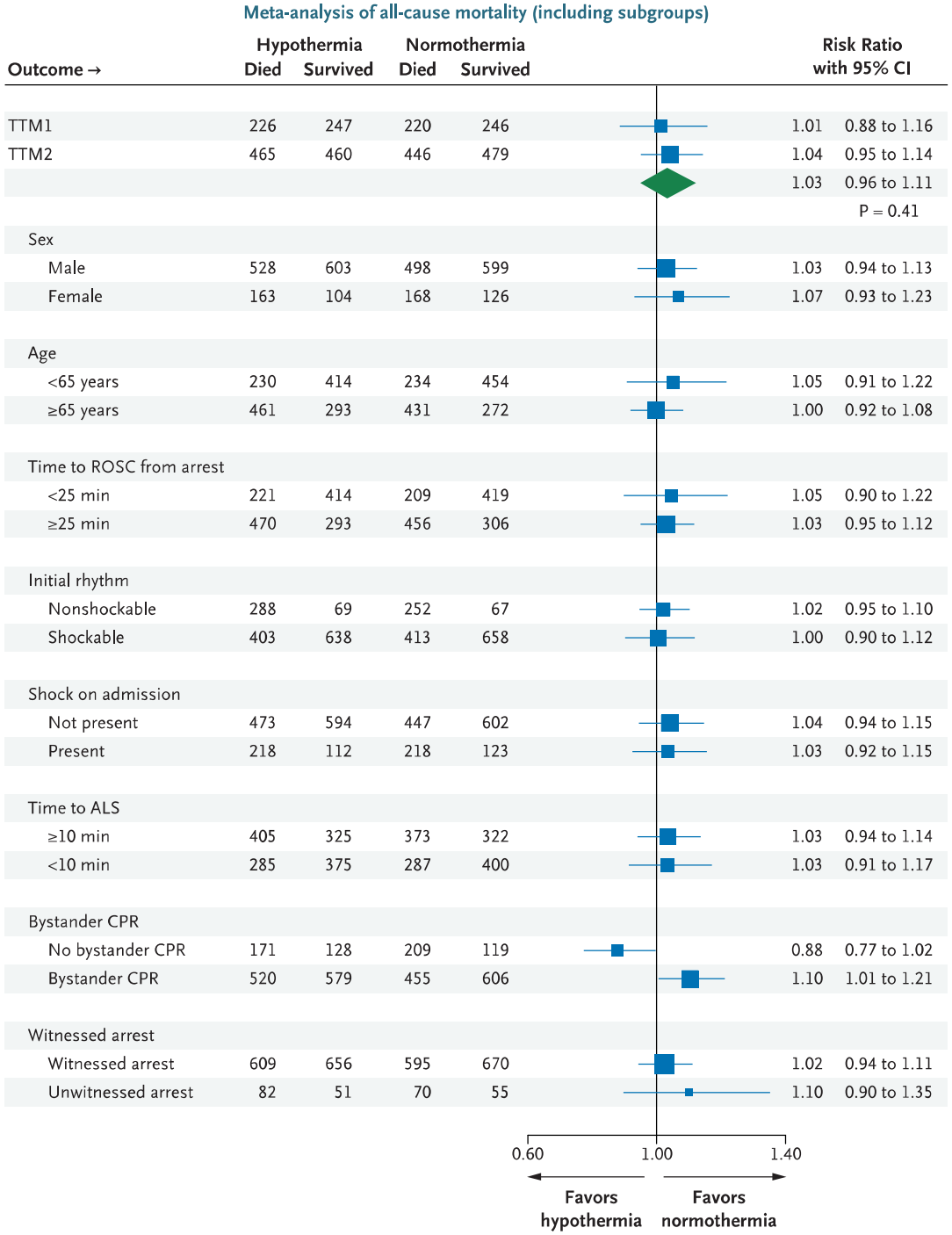
In patients with coma after out-of-hospital cardiac arrest, targeted HYPOTHERMIA did not lead to a lower incidence of death by 6 months than targeted NORMOTHERMIA

ttm2

Principal Investigator: Niklas Nielsen, MD PhD @nielsen_niklas @ttm2trial

Dankiewicz et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2100591

Infographic by
Tommaso Scquizzato
@tscquizzato



Individual patient meta-analysis of TTM1 and TTM 2

Holgersson J. NEJM Evidence 2022

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

Dankiewicz J. N Engl J Med 2021;384:2283-94

Adverse events TTM-2

Outcome or Event	Hypothermia (N=930)	Normothermia (N=931)	Relative Risk (95% CI)*	P Value
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

Time to target temperature 32–34°C

Trials assessing TTM at 32–34°C

Table courtesy of Lars Andersen

Trial	Target	Time to randomization from ROSC	Time to target from randomization	Time from ROSC to target
HACA, 2002[1]	32-34°C	105 min.*	NR	8 h
Bernard, 2002[2]	33°C	NR	NR	2 h
Nielsen, 2013[3]	33°C	NR	≈ 3 hours to 34°C***	NR
Moler, 2015[4]****	32-34°C	5.9 hours*	1.6 hours	≈ 7.5 h
Lascarrou, 2019[5]	33°C	≈ 216 min.	317 min	≈ 8.9 h
Lopez-de-Sa, 2018[6]	33°C	157 min.	≈ 1.5 hours***	≈ 4.1 h
Dankiewicz, 2021[7]	33°C	≈ 111 min.	3 hours to 34°C	≈ 4.9
COACT*****	34°C	≈ 184 min.	= 1-2 hours***	≈ 4-5 h

Other post-arrest trials

Trial	Target	Time to randomization from ROSC	Time to target from randomization	Time from ROSC to target
Deye, 2015[8]	32-34°C	≈ 3.8 hours*	NR	Internal: 5.5 h External: 8.5 h
Kirkegaard, 2017[9]	32-34°C	NA	NA	≈ 5 h
Lemkes, 2019[10]	NR	NA	NA	≈ 5 h
François, 2019[11]	32-34°C	NA	NA	≈ 5-6 h

Defining post-cardiac arrest temperature control strategies

ILCOR ALS Task Force chose to avoid the term ‘TTM’ because of close linkage to the TTM studies – proposed:

- **Hypothermic Temperature Control** = active temperature control with target temperature below normal range.
- **Normothermic Temperature Control** = active temperature control with target temperature in normal range.
- **Fever Prevention Temperature Control** = monitoring temperature and actively preventing and treating temperature above the normal range
- **No Temperature Control** = no protocolised active temperature control strategy

www.costr.ilcor.org

Targeted temperature management in adult cardiac arrest: Systematic review and meta-analysis

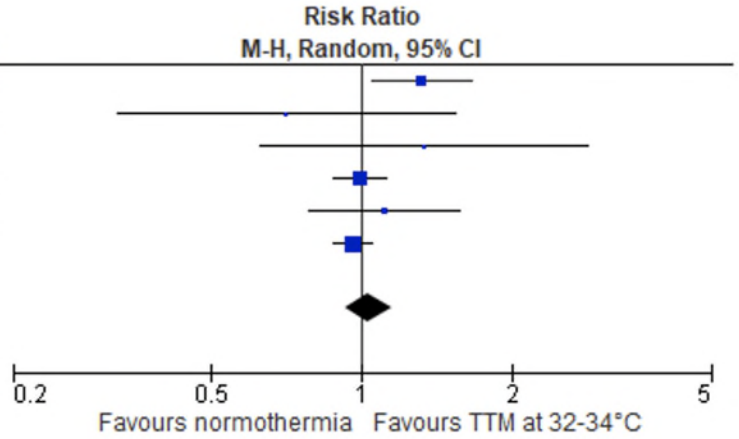
Granfeldt A, ILCOR ALS TF
Resuscitation 2021;167:160–172

Sensitivity analysis including TTM at 36ºC as normothermia

Survival to 90 or 180 days

Study or Subgroup	TTM at 32-34°C Events	Total	Normothermia Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
HACA, 2002	81	137	62	138	15.8%	1.32 [1.04, 1.66]	2002
Laurent, 2005	7	22	9	20	1.9%	0.71 [0.32, 1.54]	2005
Hachimi-Idrissi, 2005	8	14	6	14	2.0%	1.33 [0.63, 2.84]	2005
Nielsen, 2013	247	473	246	466	32.4%	0.99 [0.88, 1.12]	2013
Lascarrou, 2019	53	284	50	297	8.2%	1.11 [0.78, 1.57]	2019
Dankiewicz, 2021	460	925	479	925	39.6%	0.96 [0.88, 1.05]	2021
Total (95% CI)		**1855**		**1860**	**100.0%**	**1.03 [0.93, 1.15]**	
Total events	856		852				

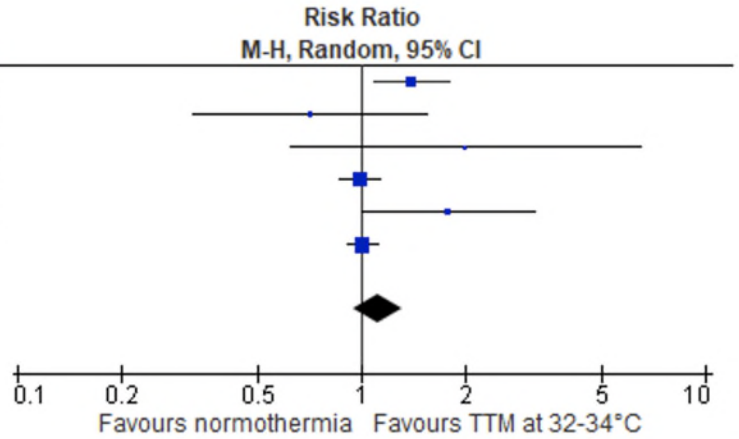
Heterogeneity: Tau² = 0.01; Chi² = 7.87, df = 5 (P = 0.16); I² = 36%
Test for overall effect: Z = 0.57 (P = 0.57)



Favorable neurologic outcome at 90 or 180 days

Study or Subgroup	TTM at 32-34°C Events	Total	Normothermia Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
HACA, 2002	75	136	54	137	20.3%	1.40 [1.08, 1.81]	2002
Laurent, 2005	7	22	9	20	4.0%	0.71 [0.32, 1.54]	2005
Hachimi-Idrissi, 2005	6	14	3	14	1.9%	2.00 [0.62, 6.45]	2005
Nielsen, 2013	224	469	225	464	31.9%	0.98 [0.86, 1.13]	2013
Lascarrou, 2019	29	284	17	297	6.8%	1.78 [1.00, 3.17]	2019
Dankiewicz, 2021	423	918	418	911	35.2%	1.00 [0.91, 1.11]	2021
Total (95% CI)		**1843**		**1843**	**100.0%**	**1.11 [0.94, 1.31]**	
Total events	764		726				

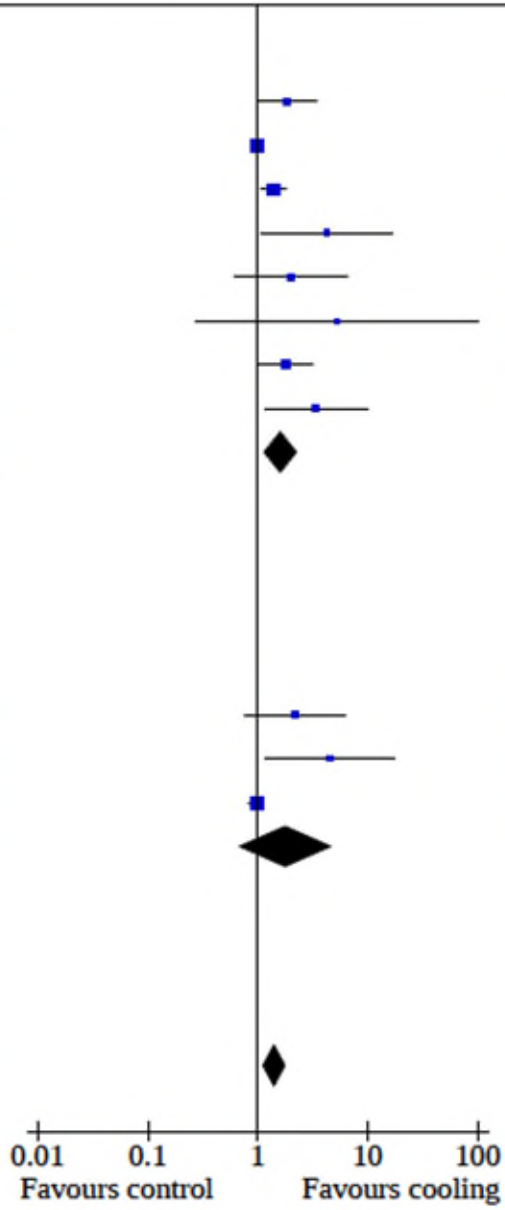
Heterogeneity: Tau² = 0.02; Chi² = 11.78, df = 5 (P = 0.04); I² = 58%
Test for overall effect: Z = 1.23 (P = 0.22)



Cochrane Library

Arrich J. Cochrane 2023;5:CD004128

Study or Subgroup	Cooling to 33 °C Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.1.1 Neurological outcome: conventional cooling versus no cooling or fever control												
Bernard 2002	21	43	9	34	8.2%	1.84 [0.97 , 3.49]	−	?	+	+	+	−
Dankiewicz 2021	423	918	418	911	24.1%	1.00 [0.91 , 1.11]	+	?	+	+	+	?
HACA 2002	75	136	54	137	19.0%	1.40 [1.08 , 1.81]	+	?	+	+	+	?
Hachimi-Idrissi 2001	8	16	2	17	2.3%	4.25 [1.06 , 17.08]	+	?	+	+	+	?
Hachimi-Idrissi 2005 LSP	6	14	3	14	3.2%	2.00 [0.62 , 6.45]	?	?	+	+	+	?
Hachimi-Idrissi 2005 SSP	2	16	0	17	0.6%	5.29 [0.27 , 102.49]	?	?	+	+	+	?
Lascarrou 2019	29	284	17	297	9.4%	1.78 [1.00 , 3.17]	+	?	+	+	+	?
Zhang 2005	8	8	2	8	3.7%	3.40 [1.17 , 9.87]	?	?	+	?	?	?
Subtotal (95% CI)		**1435**		**1435**	**70.6%**	**1.60 [1.15 , 2.23]**						
Total events:	572		505									
Heterogeneity: Tau² = 0.10; Chi² = 22.12, df = 7 (P = 0.002); I² = 68%												
Test for overall effect: Z = 2.81 (P = 0.005)												
1.1.2 Neurological outcome: conventional cooling versus 36 °C												
Kwon 2021	9	29	4	28	3.8%	2.17 [0.75 , 6.25]	?	?	+	+	+	?
Mori 2000	18	36	2	18	2.5%	4.50 [1.17 , 17.30]	?	?	+	+	?	−
Nielsen 2013	218	469	222	464	23.2%	0.97 [0.85 , 1.11]	+	?	+	+	+	?
Subtotal (95% CI)		**534**		**510**	**29.4%**	**1.78 [0.70 , 4.53]**						
Total events:	245		228									
Heterogeneity: Tau² = 0.48; Chi² = 7.28, df = 2 (P = 0.03); I² = 73%												
Test for overall effect: Z = 1.20 (P = 0.23)												
Total (95% CI)		**1969**		**1945**	**100.0%**	**1.41 [1.12 , 1.76]**						
Total events:	817		733									
Heterogeneity: Tau² = 0.05; Chi² = 30.64, df = 10 (P = 0.0007); I² = 67%												
Test for overall effect: Z = 2.99 (P = 0.003)												
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%												



ERC–ESICM GUIDELINES

TEMPERATURE CONTROL AFTER CARDIAC ARREST IN ADULTS

EUROPEAN RESUSCITATION COUNCIL

ESICM

RECOMMENDATIONS

We recommend continuous monitoring of core temperature in patients who remain comatose after ROSC from cardiac arrest.

GOOD PRACTICE STATEMENT

Temperature control can be achieved by exposing the patient, using anti-pyretic drugs, or if this is insufficient, by using a cooling device with a target temperature of 37.5 °C.

GOOD PRACTICE STATEMENT

We recommend actively preventing fever (defined as a temperature > 37.7 °C) in post-cardiac arrest patients who remain comatose.

WEAK RECOMMENDATION

★★☆☆ LOW CERTAINTY EVIDENCE

There is currently insufficient evidence to recommend for or against temperature control at 32–36 °C in sub-populations of cardiac arrest patients or using early cooling, and future research may help elucidate this. We recommend not actively rewarming comatose patients with mild hypothermia after ROSC to achieve normothermia.

GOOD PRACTICE STATEMENT

We recommend actively preventing fever for at least 72 hours in post-cardiac arrest patients who remain comatose.

GOOD PRACTICE STATEMENT

We recommend not using prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC.

STRONG RECOMMENDATION

★★★☆ MODERATE CERTAINTY EVIDENCE

Nolan JP. Resuscitation 2022;172:229
Sandroni C. ICM 2022;48:261

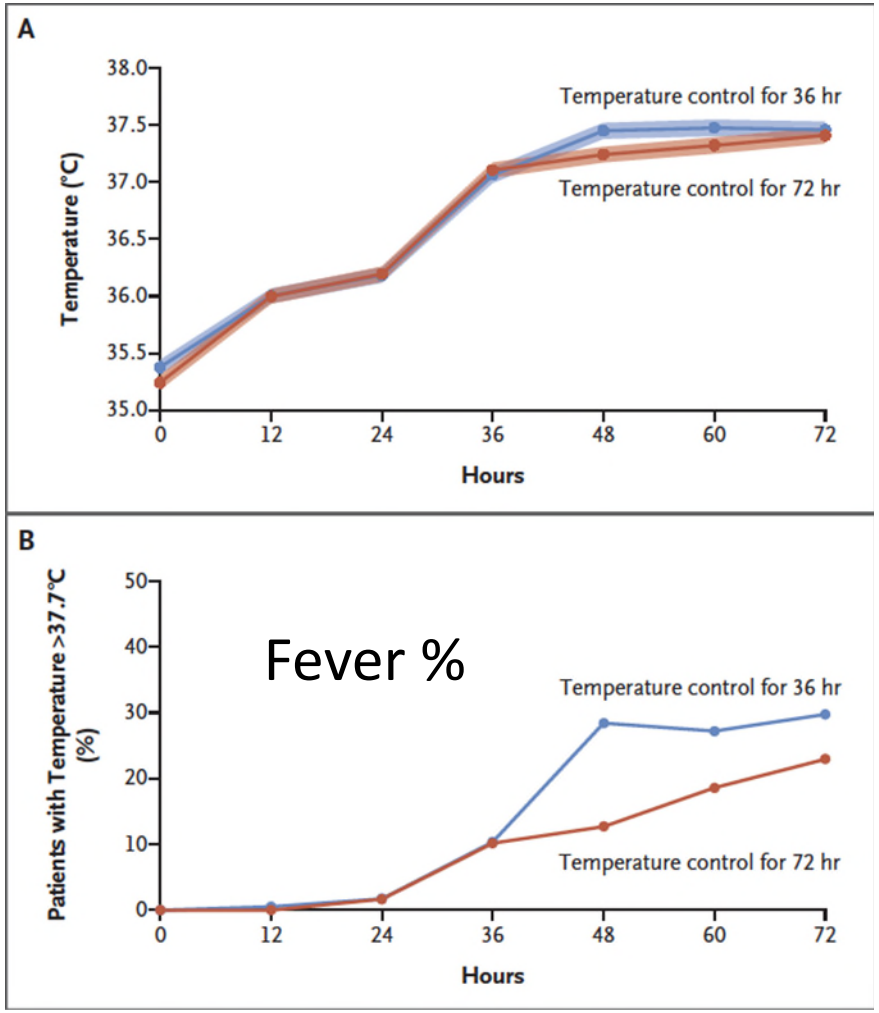
Temperature control in hypoxic-ischaemic brain injury stratified by severity

- Mild injury: likely to make good recovery regardless of temp control
- Severe injury: likely to have bad outcome regardless of temp control
- Temperature control at 33°C associated with better outcome in those with moderate injury

Nishikimi M. Crit Care Med 2021;49:e741–e750
Callaway CW. JAMA Open 2020;7:e208215

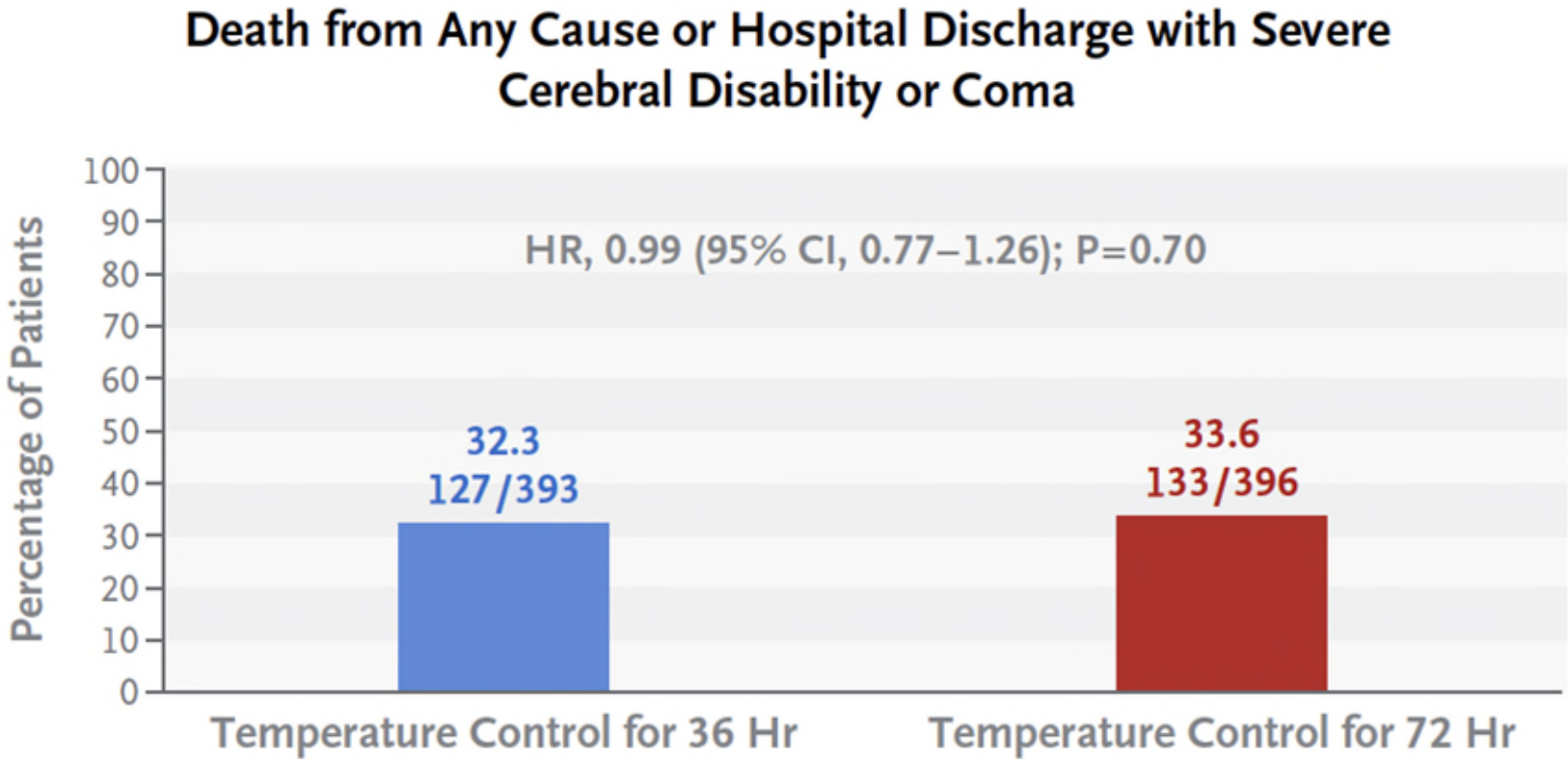
Duration of Device-Based Fever Prevention after Cardiac Arrest

Hassager C. NEJM 2023;388:888-97



789 OHCA patients

36°C for 24 h then 37°C for 12 h vs. 36°C for 24 h then 37°C for 48 h



Sedation, Temperature and Pressure After Cardiac Arrest and Resuscitation (STEPCARE)

- 3500 OHCA patients; 2x2x2 factorial design
- Continuous deep sedation 36 h or minimal sedation (SEDCARE)
- Fever (37.7°C) management with or without a feedback-controlled device (target 37.5°C) (TEMPCARE)
- Mean arterial pressure target >85mmHg or >65mmHg (MAPCARE)
- Primary outcome: 6-month survival

NCT05564754

Temperature control after cardiac arrest

- While comatose, prevent fever for 72 h
- Optimal method for achieving this is unknown
- Temperature control with feedback device to be evaluated in STEPCARE trial