Chlazení pacientů po CPR

- ano či ne?

OA Dr. Stibor B.

ICU, Landesklinikum Baden bei Wien, Austria

no conflict of interest

OA Dr. Stibor B.

ICU, Landesklinikum Baden bei Wien, Austria

přehled

1. jak to začalo
2. studie TTM a TTM2
3. máme přestat chladit?
4. guidelines
5. realita
6. současná doporučení
7. *future?*

jak to začalo

HACA trial

The New England Journal of Medicine

VOLUME 346 FEBRUARY 21, 2002 NUMBER 8

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

Conclusions In patients who have been successfully resuscitated after cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia increased the rate of a favorable neurologic outcome and reduced mortality. (N Engl J Med 2002;346:549-56.)

Bernard trial

The New England Journal of Medicine

VOLUME 346 FEBRUARY 21, 2002 NUMBER 8

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

STEPHEN A. BERNARD, M.B., B.S., TIMOTHY W. GRAY, M.B., B.S., MICHAEL D. BUIST, M.B., B.S., BRUCE M. JONES, M.B., B.S., WILLIAM SILVESTER, M.B., B.S., GEOFF GUTTERIDGE, M.B., B.S., AND KAREN SMITH, B.SC.

Conclusions Our preliminary observations suggest that treatment with moderate hypothermia appears to improve outcomes in patients with coma after resuscitation from out-of-hospital cardiac arrest. (N Engl J Med 2002;346:557-63.)

- in **2002**, two landmark **RCTs** were published simultaneously in **NEJM**

- they have found that **therapeutic hypothermia** (TH) is effective in **reducing the risk** of neurological disability in patients with **OHCA** due to an initial **shockable rhythm** who were comatose post-arrest

- a rapid adoption of TH into clinical practice in post-arrest patients (**revolution in therapy** after cardiac arrest)

- TH received a **class I recommendation** in resuscitation **guidelines**

- TH has since **expanded** to include patients with non-shockable rhythms and patients with IHCA

- **standard procedure** in the postresuscitation care

všichni chladili……

… až do studií TTM

TTM1 trial

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.,

N Engl J Med. 2013 Dec 5;369(23):2197-2206.

TTM1 trial

ORIGINAL ARTICLE

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

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.

CONCLUSIONS

In unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac cause, hypothermia at a targeted temperature of 33°C did not confer a benefit as compared with a targeted temperature of 36°C. (Funded by the Swedish Heart–Lung Foundation and others; TTM ClinicalTrials.gov number, NCT01020916.)

TTM2 trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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. Bělohlávek, 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*

N Engl J Med. 2021 Jun 17;384(24):2283-2294.

TTM2 trial

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

RESULTS

A total of 1850 patients were evaluated for the primary outcome. At 6 months, 465 of 925 patients (50%) in the hypothermia group had died, as compared with 446 of 925 (48%) in the normothermia group (relative risk with hypothermia, 1.04; 95% confidence interval [CI], 0.94 to 1.14; P=0.37). Of the 1747 patients in whom the functional outcome was assessed, 488 of 881 (55%) in the hypothermia group had moderately severe disability or worse (modified Rankin scale score ≥4), as compared with 479 of 866 (55%) in the normothermia group (relative risk with hypothermia, 1.00; 95% CI, 0.92 to 1.09). Outcomes were consistent in the prespecified subgroups. Arrhythmia resulting in hemodynamic compromise was more common in the hypothermia group than in the normothermia group (24% vs. 17%, P<0.001). The incidence of other adverse events did not differ significantly between the two groups.

CONCLUSIONS

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.

máme přestat chladit?

- výsledky **studií**

- **experimentální** modely

- klinické **zkušenosti**

- změna ***outcome*** po zavedení protokolu TTM1

- detaily studií **TTM1** a **TTM2**

what happened after TTM1?

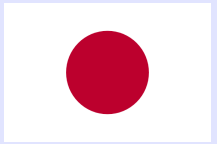
after TTM1

- ↑Mortalität ↓neurol. Outcome
  (Bray JE; Resuscitation 2017; 113:39)

- ↑Körpertemperatur ↑ Mortalität
  (Salter R; Crit Care Med 2018; 46:1722)

- ↓Adhärenz zur Hypothermie ↑Mortalität
  (Garfield B; Ther Hypothermia Temp Manag 2020; e-pub; Nolan JP; Resuscitation 2021; 162:304)

- ↑Mortalität
  (Nishikimi M; Crit Care Med 2021; 49:e741)



- ↓Mortalität 25% vs 44% (HACORE nach TTM1)
  (Akin M; JACC Cardiovasc Interv 2018; 11:1811)

Evidence set 3: real world experience

Changing target temperature from 33 °C to 36 °C in the ICU management of out-of-hospital cardiac arrest: A before and after study☆ *2017*

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]

Table 3
Comparison of temperatures and patient outcomes for patients admitted to ICU for the 33 °C and 36 °C TTM periods.

Outcome variables	33 °C N = 24	36 °C N = 52	Unadjusted p-value
Temperatures			
Temperature on arrival at ED, mean (SD)	34.5 (1.4)	35.2 (1.5)	0.07
Average temperature across first 24 h, median (IQR)	33.4 (33.1–33.5)	36.2 (36.1–36.5)	<0.001
Time at target temperature in first 24-h (%), mean (SD)	87 (15)	50 (31)	<0.001
All temperatures at or below target in first 24-h, n (%)			
Temperature ≥38.0 in first 24 h, n (%)	0 (0)	10 (19)	0.03
Temperature ≥38.0 in first 36 h, n (%)	2 (8)	16 (31)	0.04
Outcomes			
Discharge within 24 h of ICU, n (%)	0 (0)	2 (4)	0.99
Died within 24-h of ICU, n (%)	0 (0)	7 (14)	0.09
ICU survival, n (%)	17 (71)	30 (58)	0.32
Hospital survival, n (%)	17 (71)	30 (58)	0.32
Day treatment withdrawn, median (IQR)	3 (3-16)	4 (3-10)	0.99
CPC score 1–2, n (%)	17 (71)	29 (56)	0.31
Discharged home, n (%)	14 (58)	21 (40)	0.22
Discharged to rehabilitation, n (%)	3 (18)	8 (27)	0.48
Survivors CPC 1, n (%)	<16 (94)	19 (63)	
Survivors CPC 2, n (%)	1 (6)	10 (33)	0.02
Survivors CPC 3, n (%)	0 (0)	1 (3)	

After TTM1 trial of 33°C vs 36°C, some hospitals changed protocol – outcomes worsened

Bray JE et al, Resuscitation. 2017 Apr;113:39-43.

Evidence set 3: real world experience

2019

Targeted Temperature Management at 33 Versus 36 Degrees: A Retrospective Cohort Study

Nicholas J. Johnson, MD[1,2]; Kyle R. Danielson, MPH, ARNP[3]; Catherine R. Counts, PhD, MHA[1]; Katelyn Ruark, BS[4,5]; Sue Scruggs, RN[1]; Catherine L. Hough, MD, MS[2]; Charles Maynard, PhD[6]; Michael R. Sayre, MD[1,4]; David J. Carlbom, MD[2]

TABLE 2. Unadjusted Outcomes by Target Temperature 33°C and 36°C

Characteristic	TTM 33°C ($n = 258$)	TTM 36°C ($n = 195$)	p	Missing, n (%)
Survival to hospital discharge, n (%)	115 (44.6)	71 (36.4)	0.084	0
Neurologic status at discharge, n (%)			< 0.05	0
Favorable neurologic outcome, CPC 1–2	103 (39.9)	58 (29.7)		
Poor neurologic outcome, CPC 3–5	155 (60.1)	137 (70.3)		
Neurologic status at discharge, n (%)			< 0.05	0
CPC 1–Full neurologic recovery	91 (35.3)	42 (21.5)		
CPC 2–Mildly impaired	12 (4.7)	16 (8.2)		
CPC 3 –Awake with severely impaired neurologic status	7 (2.7)	8 (4.1)		
CPC 4–Comatose, vegetative, non-responsive	5 (1.9)	5 (2.6)		
CPC 5–Died in hospital	133 (55.4)	124 (63.6)		

CPC = Cerebral Performance Category, TTM = targeted temperature management.

After TTM1 trial of 33°C vs 36°C, some hospitals changed protocol – outcomes worsened

Johnson NJ et al. Crit Care Med. 2020 Mar;48(3):362-369.

Evidence set 4: better outcomes w TTM for some

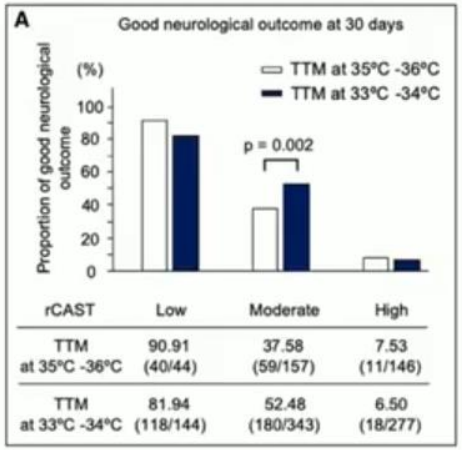
Outcome Related to Level of Targeted Temperature Management in Postcardiac Arrest Syndrome of Low, Moderate, and High Severities: A Nationwide Multicenter Prospective Registry

2021

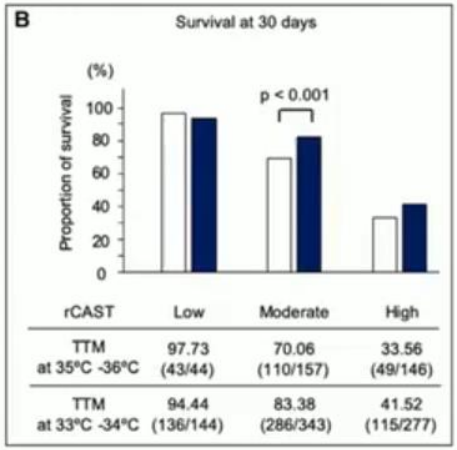
Mitsuaki Nishikimi, MD[1,2]
Takayuki Ogura, MD, PhD[3]

OBJECTIVES: The optimal target temperature during targeted temperature

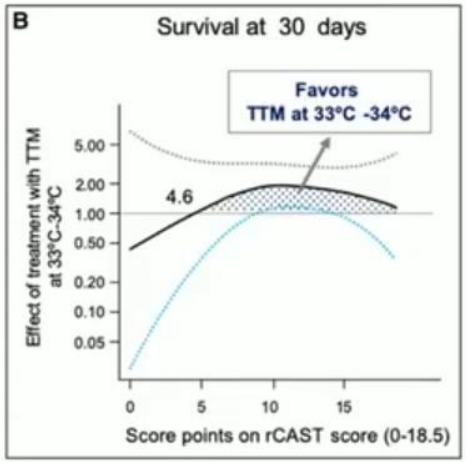
TTM more effective for more injured patients



rCAST	Low	Moderate	High
TTM at 35°C -36°C	90.91 (40/44)	37.58 (59/157)	7.53 (11/146)
TTM at 33°C -34°C	81.94 (118/144)	52.48 (180/343)	6.50 (18/277)



rCAST	Low	Moderate	High
TTM at 35°C -36°C	97.73 (43/44)	70.06 (110/157)	33.56 (49/146)
TTM at 33°C -34°C	94.44 (136/144)	83.38 (286/343)	41.52 (115/277)



Nishikimi, M 2021 *CCM* 49(8) e741-750(10)

Evidence set 4: better outcomes w TTM for some

JAMA Network | Open

Original Investigation | Critical Care Medicine

Association of Initial Illness Severity and Outcomes After Cardiac Arrest With Targeted Temperature Management at 36 °C or 33 °C

2020

Clifton W. Callaway, MD, PhD; Patrick J. Coppler, PA-C; John Faro, BS; Jacob S. Puyana, BS; Pawan Solanki, MD; Cameron Dezfulian, MD; Ankur A. Doshi, MD; Jonathan Elmer, MD, MS; Adam Frisch, MD; Francis X. Guyette, MD, MPH; Masashi Okubo, MD, MS; Jon C. Rittenberger, MD, MS; Alexandra Weissman, MD, MS, MPH

Table 4. Outcomes Stratified by Initial Illness Severity for Patients With Neither Severe Cerebral Edema nor Highly Malignant EEG Treated With TTM at 33 °C or 36 °C

Illness Severity	No./Total No. (%) TTM at 33 °C	TTM at 36 °C	Risk difference with 33 °C, % (95% CI)	RR (95% CI)	Adjusted RR (95% CI)[a]	RR in propensity matched sample (95% CI)[b]
Survival						
Overall	171/489 (35.0)	168/422 (39.8)	-4.8 (-11.1 to 1.5)	0.88 (0.74 to 1.04)	0.88 (0.76 to 1.01)	0.89 (0.74 to 1.08)
PCAC 2	86/134 (64.2)	110/141 (78.0)	-13.8 (-24.4 to -3.2)	0.82 (0.71 to 0.96)	0.79 (0.68 to 0.93)	0.84 (0.71 to 0.99)
PCAC 3	32/58 (55.1)	27/81 (33.3)	21.8 (5.4 to 38.2)	1.66 (1.13 to 2.43)	1.47 (1.01 to 2.13)	1.50 (0.90 to 2.51)
PCAC 4	39/259 (15.1)	8/148 (5.4)	9.7 (4.0 to 15.3)	2.79 (1.34 to 5.80)	1.89 (0.89 to 4.01)	1.50 (0.63 to 3.54)
CPC 1-3 at hospital discharge						
Overall	156/489 (31.9)	159/422 (37.8)	-5.8 (-12.0 to 0.4)	0.85 (0.71 to 1.01)	0.85 (0.73 to 0.99)	0.86 (0.70 to 1.05)
PCAC 2	82/134 (61.2)	105/141 (74.5)	-13.3 (-24.2 to -2.3)	0.82 (0.70 to 0.97)	0.80 (0.68 to 0.94)	0.83 (0.70 to 1.00)
PCAC 3	28/58 (48.3)	27/81 (33.3)	14.9 (-1.5 to 31.4)	1.45 (0.96 to 2.17)	1.37 (0.91 to 2.06)	1.36 (0.80 to 2.31)
PCAC 4	34/259 (13.1)	7/148 (4.7)	8.4 (3.0 to 13.7)	2.78 (1.26 to 6.10)	1.76 (0.78 to 3.97)	1.43 (0.56 to 3.63)

TTM more effective for more injured patients

Less injured patients:

More injured patients:

Callaway CW et al JAMA Open 2020 Jul 1;3(7):e208215.

Frequently asked questions – part 1

Temperature selection

When should we choose 33°C vs 36°C as a goal temperature?

- We recommend 33°C as goal for most patients
- 36°C acceptable, and may be safer in specific situations
- No RCT shows 36°C with improved outcomes or less side effects

Is 36°C an "easier" goal temperature with fewer side effects?

- No evidence that 36°C is easier to maintain
- No difference in shivering or bleeding adverse effects
- Both require active closed-loop cooling devices

FAQ

Is 36 degrees easier?

problémy studií TTM1 a TTM2

TTM2 trial

- study **protocol**: **90 min** from ROSC to 33°C

TTM2 trial

- study **protocol**: **90 min** from ROSC to 33°C
- time from **ROSC** to **randomisation**: **135 min**
- time from **randomisation** to **33°C**: **5 hours** (median)
- more than **50% of pts** needed **7 hours** from **ROSC** to **33°C**!
- only **few pts** with **intravascular** cooling (TTM1 24%, TTM 29%)
- **other studies** with more intravascular cooling had lower mortality (**25-35 %**)
- approximately **50%** of pts had **insufficient** control of **fever** at day 3
- 85% (88%) pts had propofol (0% in HACA, Bernard study)
- protocol for determination of the **neurologic prognosis** and withdrawal of life-supporting therapies

EJA European Journal of Anaesthesiology

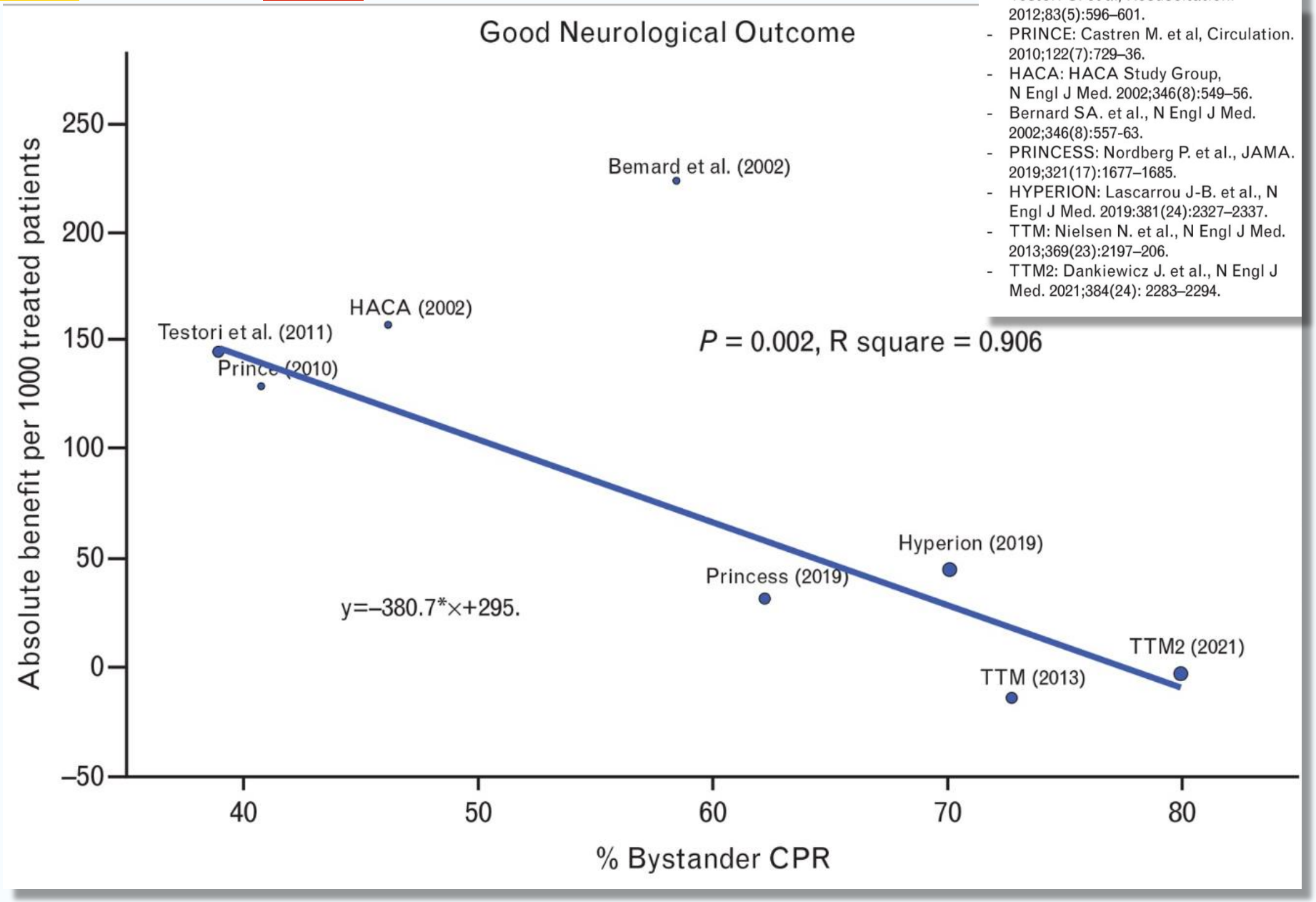
The effectiveness of targeted temperature management following cardiac arrest may depend on bystander cardiopulmonary resuscitation rates

Böttiger, Bernd W.; Hellmich, Martin; Wetsch, Wolfgang A.

Author Information

European Journal of Anaesthesiology 39(4):p 401-402, April 2022. | **DOI:** 10.1097/EJA.0000000000001663

40% 57%



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- TTM2: Dankiewicz J. et al., N Engl J Med. 2021;384(24): 2283–2294.

guidelines?

RESUSCITATION 161 (2021) 220 –269

Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care☆

Jerry P. Nolan[a,b,1,*], *Claudio Sandroni*[c,d,1], *Bernd W. Böttiger*[e], *Alain Cariou*[f], *Tobias Cronberg*[g], *Hans Friberg*[h], *Cornelia Genbrugge*[i,j], *Kirstie Haywood*[k], *Gisela Lilja*[l], *Véronique R.M. Moulaert*[m], *Nikolaos Nikolaou*[n], *Theresa Mariero Olasveengen*[o], *Markus B. Skrifvars*[p], *Fabio Taccone*[q], *Jasmeet Soar*[r]

POST RESUSCITATION CARE 2021
5 TOP MESSAGES

EUROPEAN RESUSCITATION COUNCIL

1. After ROSC use ABC approach

- Insert an advanced airway (tracheal intubation when skills available)
- Titrate inspired oxygen to an SpO_2 of 94-98% and ventilate lungs to achieve normocapnia
- Obtain reliable intravenous access, restore normovolaemia, avoid hypotension (aim for systolic BP > 100mmHg)

2. Emergent cardiac catheterisation +/- immediate PCI after cardiac arrest of suspected cardiac origin and ST-elevation on the ECG

3. Use targeted temperature management (TTM) for adults after either OHCA or IHCA (with any initial rhythm) who remain unresponsive after ROSC

4. Use multimodal neurological prognostication using clinical examination, electrophysiology, biomarkers, and imaging

5. Assess physical and non-physical impairments before and after discharge from the hospital and refer for rehabilitation if necessary

Table 1 – Summary of changes since the 2015 Guidelines on Post-resuscitation care.

2015 Guidelines	2021 Guidelines	Rationale for change
Temperature control • Maintain a constant, target temperature between 32 °C and 36 °C for those patients in whom temperature control is used (strong recommendation, moderate-quality evidence). • Whether certain subpopulations of cardiac arrest patients may benefit from lower (32–34 °C) or higher (36 °C) temperatures remains unknown, and further research may help elucidate this. • TTM is recommended for adults after OHCA with an initial shockable rhythm who remain unresponsive after ROSC (strong recommendation, low-quality evidence). • TTM is suggested for adults after OHCA with an initial non-shockable rhythm who remain unresponsive after ROSC (weak recommendation, very low-quality evidence). • TTM is suggested for adults after IHCA with any initial rhythm who remain unresponsive after ROSC (weak recommendation, very low-quality evidence). • If targeted temperature management is used, it is suggested that the duration is at least 24 h (weak recommendation, very low-quality evidence).	• We recommend TTM for adults after either OHCA or 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.	A recent randomised controlled trial of both IHCA and OHCA patients with initial non-shockable rhythms showed a higher percentage of patients survived with a favourable neurological outcome when treated with TTM at 33 °C versus 37 °C.[13] This has enabled the recommendation to be extended to all rhythms and locations. The definition of fever (>37.7 °C) is consistent with that used in the TTM2 trial.[14]

- We recommend TTM for adults after either OHCA or 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.

RESUSCITATION 172 (2022) 229–236

Available online at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

ERC-ESICM guidelines on temperature control after cardiac arrest in adults ☆

Table 2 – ERC-ESICM Recommendations for temperature control after cardiac arrest in adults.

We recommend continuous monitoring of core temperature in patients who remain comatose after ROSC from cardiac arrest (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).
We recommend actively preventing fever for at least 72 hours in post-cardiac arrest patients who remain comatose (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).
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 not using prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC (strong recommendation; moderate certainty evidence).

guidelines

vs.

reality

Roedl *et al. Critical Care* (2023) 27:35
https://doi.org/10.1186/s13054-023-04319-7

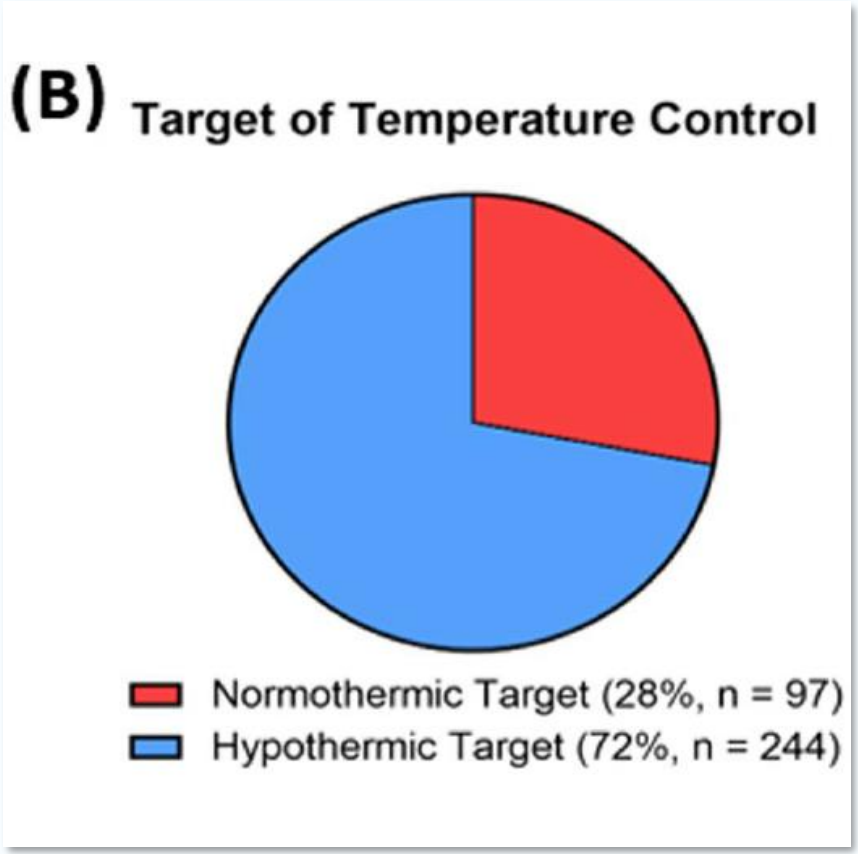
Critical Care

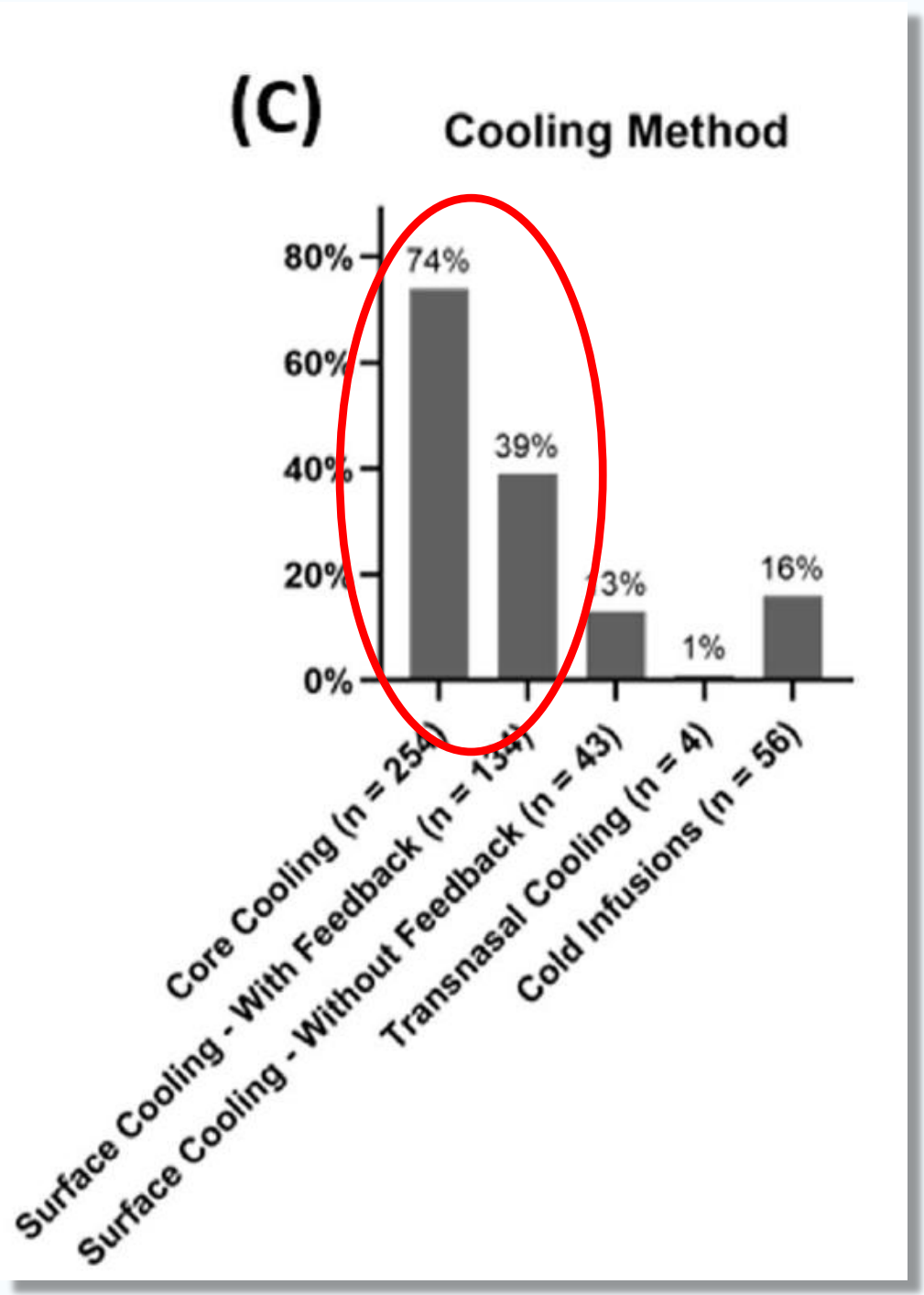
BRIEF REPORT Open Access

Temperature control in adults after cardiac arrest: a survey of current clinical practice in Germany

Kevin Roedl[1*], Sebastian Wolfrum[2], Guido Michels[3], Martin Pin[4], Gerold Söffker[1], Uwe Janssens[5] and Stefan Kluge[1]

Published online: 23 January 2023


(B)
Target of Temperature Control
Normothermic Target (28%, n = 97)
Hypothermic Target (72%, n = 244)


(C)
Cooling Method
80%
60%
40%
20%
0%
74%
39%
13%
1%
16%
Core Cooling (n = 254)
Surface Cooling - With Feedback (n = 134)
Surface Cooling - Without Feedback (n = 43)
Transnasal Cooling (n = 4)
Cold Infusions (n = 56)

Cochrane Library

Publication status and date: published in Issue 6, 2023.

Cochrane Database of Systematic Reviews

Hypothermia for neuroprotection in adults after cardiac arrest (Review)

Arrich J, Schütz N, Oppenauer J, Vendt J, Holzer M, Havel C, Herkner H

Data collection and analysis

We used standard Cochrane methods. Our primary outcome was 1. neurological recovery. Our secondary outcomes were 2. survival to hospital discharge, 3. quality of life, 4. cost-effectiveness and 5. adverse events. We used GRADE to assess certainty.

Main results

We found 12 studies with 3956 participants reporting the effects of therapeutic hypothermia on neurological outcome or survival. There were some concerns about the quality of all the studies, and two studies had high risk of bias overall. When we compared conventional cooling methods versus any type of standard treatment (including a body temperature of 36 °C), we found that participants in the therapeutic hypothermia group were more likely to reach a favourable neurological outcome (risk ratio (RR) 1.41, 95% confidence interval (CI) 1.12 to 1.76; 11 studies, 3914 participants). The certainty of the evidence was low.

When we compared therapeutic hypothermia with fever prevention or no cooling, we found that participants in the therapeutic hypothermia group were more likely to reach a favourable neurological outcome (RR 1.60, 95% CI 1.15 to 2.23; 8 studies, 2870 participants). The certainty of the evidence was low.

Authors' conclusions

Current evidence suggests that conventional cooling methods to induce therapeutic hypothermia may improve neurological outcomes after cardiac arrest. We obtained available evidence from studies in which the target temperature was 32 °C to 34 °C.

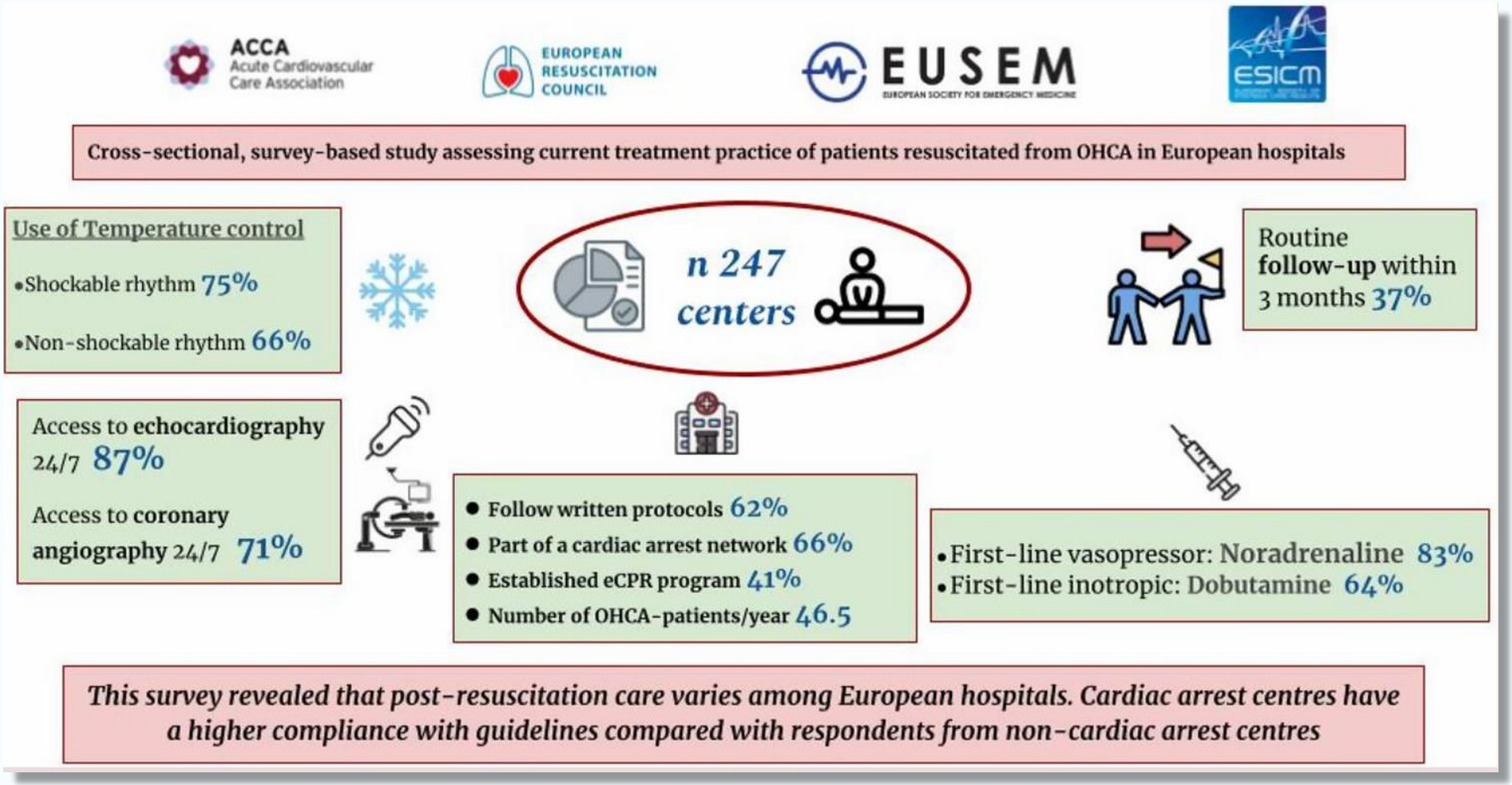
ESC European Society of Cardiology

European Heart Journal: Acute Cardiovascular Care (2023) **12**, 96–105
https://doi.org/10.1093/ehjacc/zuac153

ORIGINAL SCIENTIFIC PAPER

Management of comatose survivors of out-of-hospital cardiac arrest in Europe: current treatment practice and adherence to guidelines. A joint survey by the Association for Acute CardioVascular Care (ACVC) of the ESC, the European Resuscitation Council (ERC), the European Society for Emergency Medicine (EUSEM), and the European Society of Intensive Care Medicine (ESICM)

Received 26 June 2022; revised 15 October 2022; accepted 30 November 2022; online publish-ahead-of-print 2 December 2022



Received 26 June 2022; revised 15 October 2022; accepted 30 November 2022; online publish-ahead-of-print 2 December 2022

Table 3 General intensive care and targeted temperature management

	Overall $n = 237$	Cardiac arrest centre $n = 165$ (70%)	Not cardiac arrest centre $n = 72$ (30%)	*P*-value
Targeted temperature management				
routinely use of TTM for initial shockable rhythm	160 (75%)	123 (80%)	37 (60%)	0.006
routinely use of TTM for initial non-shockable rhythm	142 (66%)	108 (70%)	34 (57%)	0.06
Place of TTM induction				
ICU	141 (66%)	100 (65%)	41 (70%)	0.43
Emergency Department	32 (15%)	24 (15%)	8 (14%)	
Cath lab	10 (5%)	9 (6%)	1 (2%)	
Other	10 (4%)	9 (6%)	1 (2%)	
TTM-methods (more than one is possible)				
Antipyretic medication	104 (44%)	69 (42%)	35 (49%)	0.33
Cold fluids	99 (42%)	69 (42%)	30 (42%)	0.98
External cooling without feedback	109 (46%)	71 (43%)	38 (53%)	0.25
Invasive and external cooling with feedback	89 (38%)	72 (44%)	17 (24%)	0.0003

Level of target temperature	
< 32°C	1 (0.5%)
between 32–34°C	46 (21%)
Between 34–36°C	103 (52%)
< 37.5°C	35 (16%)
Duration of TTM including fever control after cooling	
24 h in total from start of TTM	28 (14%)
48 h in total from start of TTM	29 (14%)
72 h in total from start of TTM	64 (31%)
More than 72 h if patient has fever	25 (12%)
Other	60 (29%)

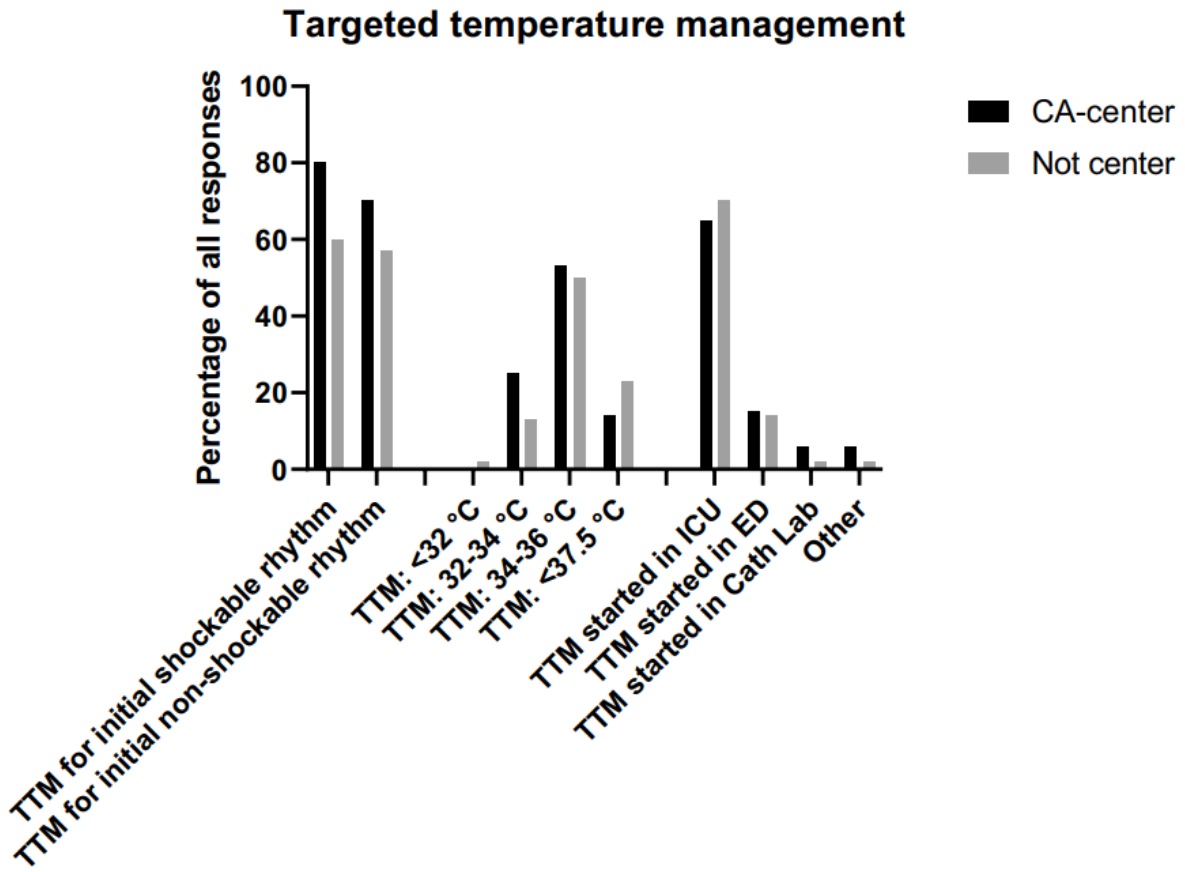


Figure 3 Temperature control practices following OHCA. TTM, targeted temperature management; ICU, intensive care unit; ED, Emergency Department; CA centre, cardiac arrest centre.

what

now?

Medizinische Klinik
Intensivmedizin und Notfallmedizin

Positionspapier

Med Klin Intensivmed Notfmed 2023 · 118 (Suppl 1):S59–S63
https://doi.org/10.1007/s00063-023-01092-x
Angenommen: 9. November 2023
Online publiziert: 5. Dezember 2023

Hypotherme Temperaturkontrolle nach erfolgreicher Wiederbelebung eines außerklinischen Herz-Kreislauf-Stillstands beim Erwachsenen

Statement der Arbeitsgruppen Reanimation und Post-Reanimationsbehandlung in der Deutschen Gesellschaft für Internistische Intensiv- und Notfallmedizin (DGIIN) und Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin (DIVI), der Deutschen Gesellschaft Interdisziplinäre Notfall- und Akutmedizin (DGINA) und der Österreichischen Gesellschaft für Notfallmedizin (AAEM)

Hans-Jörg Busch[1] · Wilhelm Behringer[2] · Paul Biever[3] · Bernd W. Böttiger[4] · Philip Eisenburger[5] · Katrin Fink[1] · Harald Herkner[2] · Uwe Kreimeier[6] · Martin Pin[7] · Sebastian Wolfrum[8]

Germany and Austria

- Germany 60.000 Austria 5.000 OHCA/year

  (Fischer M; 2022; Außerklinische Reanimation)

- pouze 10-15% pacientů bez neurologického deficitu

  (Gräsner JT; Resuscitation 2020; 148:218)

statement:

- Deutsche Gesellschaft für Internistische Intensiv- und Notfallmedizin **(DGIIN)**

- Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin **(DIVI)**

- Deutsche Gesellschaft Interdisziplinäre Notfall- und Akutmedizin **(DGINA)**

- Österreichische Gesellschaft für Notfallmedizin **(AAEM)**

TTM trials:

1) rate of **bystander CPR** in all groups was **73 to 82%,** which is **considerably higher** than the **average** rate in **Europe** of **58% (D 40%, A 57%)**

patients with a **short** cardiac arrest time, as it is in the case of **bystander CPR**, presumably have **less** brain damage and so might **not benefit** from hypothermia

2) both **TTM studies** allowed a **delay** of up to **3 to 4 h** between ROSC and **randomisation**, and the **targeted temperature** has taken up to **7 h after** cardiac arrest to achieve

reperfusion injury starts **immediately** following resuscitation from cardiac arrest, and all **pathophysiology shows** that **earlier cooling** is more **effective**

3) both TTM studies included **many centres** from various countries, with **each centre** enrolling only a **few patients**

this creates **potential** for considerable **heterogeneity** in all other aspects of **postresuscitation care**

guidelines ERC/ESICM:

1) are predominantly based on the **meta-analysis** by **Granfeld** *(Resuscitation 2021)*

- the selected studies were **separated** into **two** different analyses *(30ds vs 3-6ms)*
- both meta-analyses showed a risk ratio in **favour of hypothermia** at 32 to 34°C compared with normothermia; however, the 95% confidence interval crossed 1, and so the results of these two group analyses were **not statistically significant**
- why the data was split into these **underpowered groups** is **not clear**

2) new meta-analysis by **Granfeldt** *(Resuscitation 2023)*

- there were more, but still **not all available studies** are taken into account again **no statistically significant benefit** of therapeutic hypothermia at 32-34°C
- which is why there were **no subsequent changes** to the **recommendations** for post-resuscitation therapy by the ERC ESICM

Hypothermic temperature control after successful resuscitation of out-of-hospital cardiac arrest in adults. Statement from the resuscitation and postresuscitation treatment working groups of the German Society of Medical Intensive Care and Emergency Medicine (DGIIN) and the German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI), the German Society for Interdisciplinary Emergency and Acute Medicine (DGINA) and the Austrian Association of Emergency Medicine (AAEM)

Online publiziert: 5. Dezember 2023

Recommendation:

Based on current scientific evidence, it is **recommended** that comatose adult patients after out-of-hospital cardiac arrest and primarily successful **resuscitation** should be placed in **controlled hypothermia** with a **target temperature of 32 - 34 °C** for at least **24 hours as soon as possible**, unless there are contraindications

Med Klin Intensivmed Notfalmed. 2023;118:59-63

EJA

Eur J Anaesthesiol 2024; **41:**278–281

OPEN

STATEMENT

Temperature control after successful resuscitation from cardiac arrest in adults

A joint statement from the European Society for Emergency Medicine and the European Society of Anaesthesiology and Intensive Care

Wilhelm Behringer*†, Bernd W. Böttiger*‡, Daniele G. Biasucci‡, Athanasios Chalkias‡, Jim Connolly†, Christoph Dodt†, Abdo Khoury†, Said Laribi†, Robert Leach† and Giuseppe Ristagno‡

published 2024 Apr 1; e-published 2023 Dec 19

Summary of 2023 evidence

(1) Animal studies with cardiac arrest models show a remarkable benefit from hypothermia in the range of 32 to 34 °C on neuronal damage and neurological outcome when hypothermia is induced early after ROSC.

(2) Some RCT show a statistically significant benefit from hypothermia in the range of 32 to 34 °C compared with normothermia or no temperature control after cardiac arrest, though other randomised controlled trials do not confirm this beneficial effect. Which patients may benefit from lower (32 to 34 °C) or higher temperatures is still unknown.

(3) Earlier and more recent meta-analyses of RCT show a statistically nonsignificant effect in favour of hypothermia in the range of 32 to 34 °C compared to normothermia or no temperature control in patients after cardiac arrest. In the most recent and comprehensive Cochrane systematic review and meta-analyses including all RCT, the beneficial effect of hypothermia in the range of 32 to 34 °C compared with normothermia or no temperature control was statistically significant.

Summary of 2023 evidence

(1) Animal studies with cardiac arrest models show a remarkable benefit from hypothermia in the range of 32 to 34 °C on neuronal damage and neurological outcome when hypothermia is induced early after ROSC.

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Summary of 2023 evidence

(4) Several retrospective clinical studies indicate a beneficial effect of hypothermia in the range of 32 to 34 °C compared with normothermia, especially in subgroups with presumed moderate brain damage.

(5) There is no animal or human study showing that hypothermia in the range 32 to 34 °C results in worse neurological or overall outcome compared with normothermia or no temperature control.

Summary of 2023 evidence

(4) Several retrospective clinical studies indicate a beneficial effect of hypothermia in the range of 32 to 34 °C compared with normothermia, especially in subgroups with presumed moderate brain damage.

(5) There is no animal or human study showing that hypothermia in the range 32 to 34 °C results in worse neurological or overall outcome compared with normothermia or no temperature control.

Recommendation 2023

Some uncertainty exists as to whether hypothermia in the range of 32 to 34 °C compared with normothermia is beneficial in terms of improving neurological outcome in all patients after cardiac arrest. The current recommendations from the ERC and ESICM to merely prevent fever, in our view, neither take into account all current available evidence, nor consider the shortcomings of studies. Based on retrospective studies showing that a large proportion of patients with presumed moderate brain damage significantly benefit from hypothermia in the range of 32 to 34 °C, along with the most recent Cochrane systematic review and meta-analyses of RCT showing a statistically significant benefit of hypothermia in the range of 32 to 34 °C, and based on the fact that no study has shown a deleterious effect of hypothermia in the range of 32 to 34 °C on neurological or overall outcome, we suggest that international guidelines follow the current Cochrane analyses and in the interim period, clinicians should consider hypothermia in the range of 32 to 34 °C in all adults after cardiac arrest as soon as feasible, and to maintain this temperature range for at least 24 h. Active normothermia (36.5 to 37.7 °C) should be ensured after rewarming before and during neurological assessment, to avoid fever.

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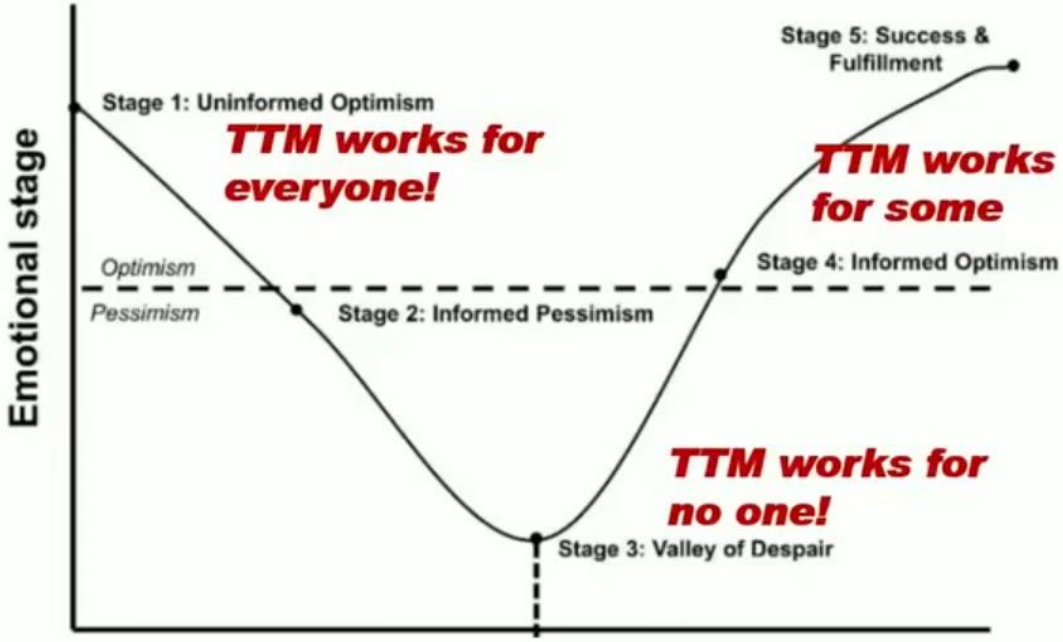
Reality of scientific progress

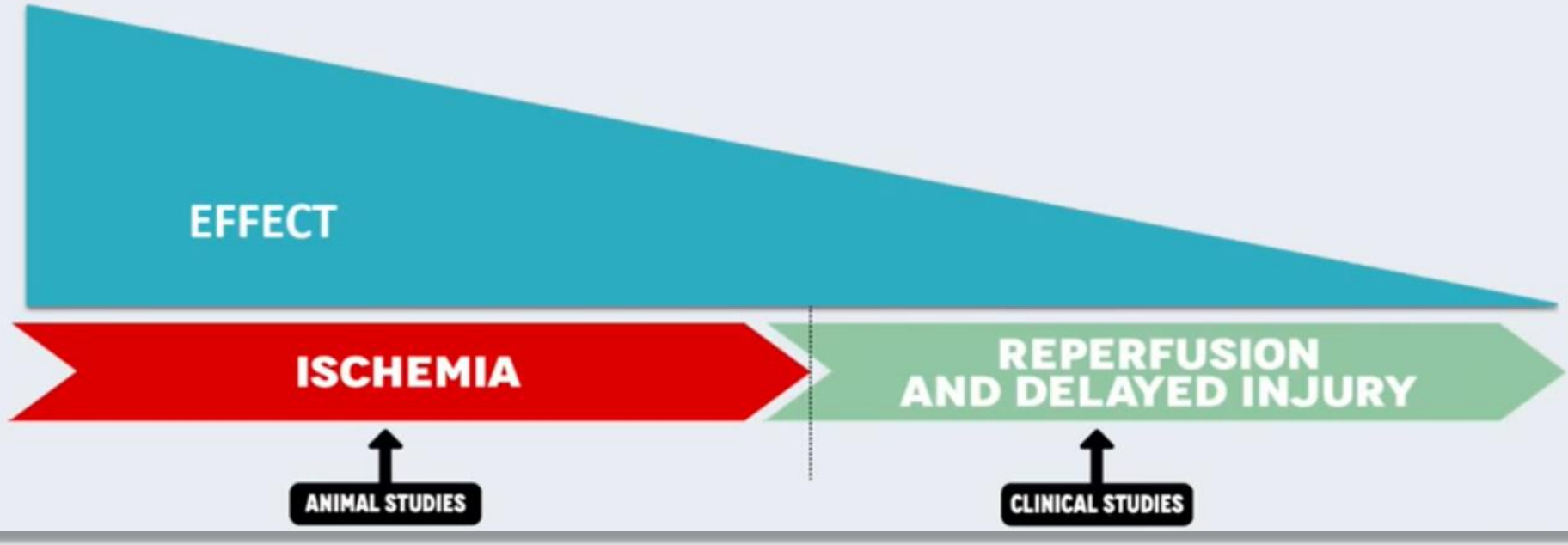


WHAT'S ONGOING AND WHAT'S UPCOMING?

- Dose of hypothermia and outcome - ICECAP
- Need for TTM device to control fever – STEPCARE
- Ultrafast cooling at the scene of the arrest– PRINCESS2

www.princess2.org

THE CONCEPT



INTERVENTION

ACLS and Cooling at the scene of the arrest.

Standardized post-resuscitation protocol

- Hypothermia to 33°C for 24 hours
- Fever control for 72 hours
- Standardized prognostication

CONTROL

ACLS at the scene of the arrest

Standardized post-resuscitation protocol

- Fever control for 72 hours
- Standardized prognostication

- Study start Q1 2024 in Sweden, Austria, Germany, Slovenia
- Expected full inclusion rate (20-25 sites) Q3-4 2024

Our Partners

Université Libre de Bruxelles

Policlinico di Milano

University Medical Centre, Ljubljana

Karolinska Sjukhuset, Stockholm

Södersjukhuset, Stockholm

Hospital Universitario La Paz, Madrid

Clinico San Carlos, Madrid

Universitätsklinik Freiburg

Medizinische Universität, Vienna

Martha Maria Hospital, Halle

St Elizabeth Hospital, Halle

University Hospital, Halle

Asklepios Südpfalzklinik, Kandel

Medical University, Graz

University Medical Center, Maribor

neue guidelines ERC 2025?

Chapter 9: Post Resuscitation Care

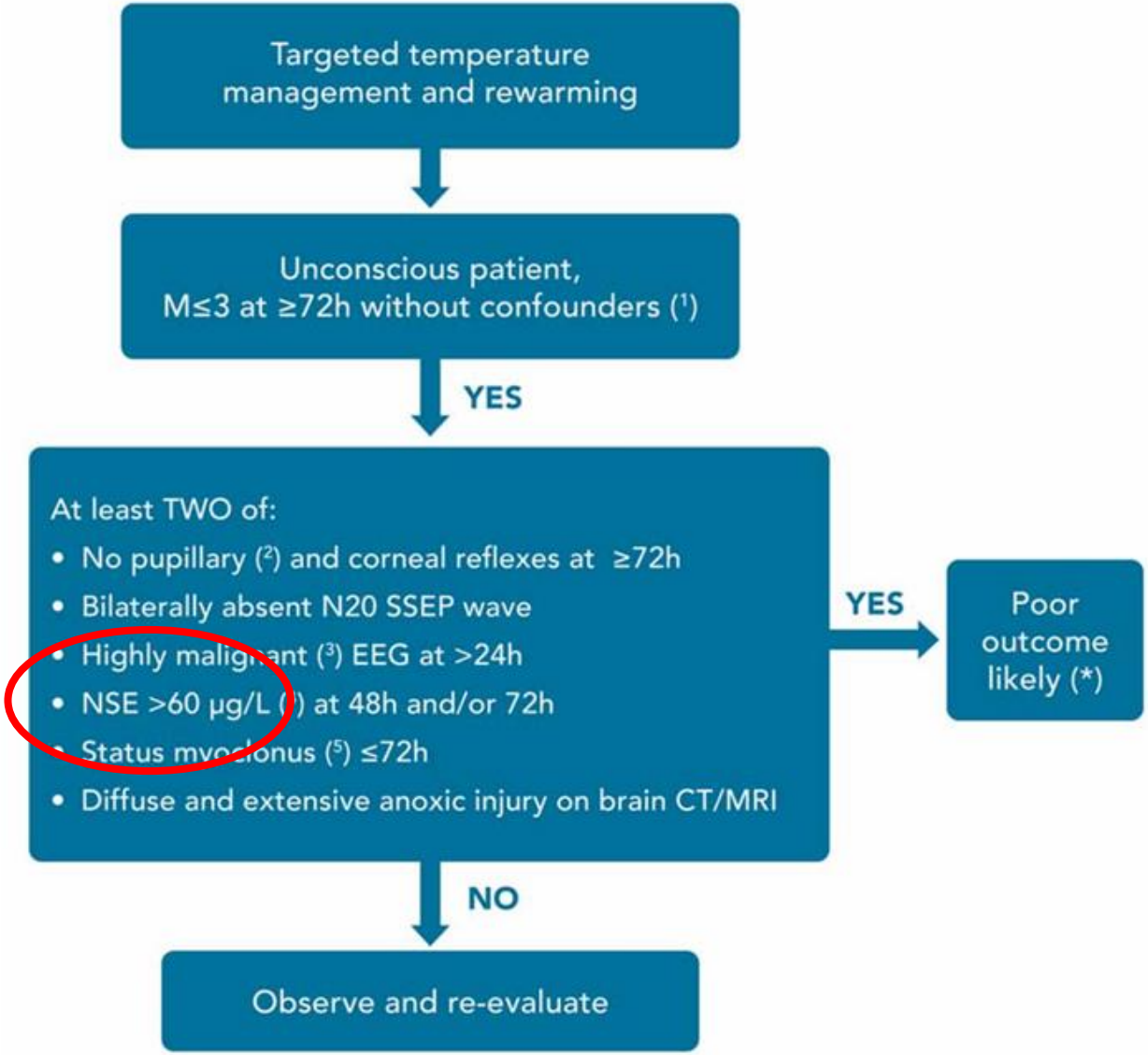
Jerry Nolan, Claudio Sandroni (co-chair), Alain Cariou, Tobias Cronberg, Sonia D'Arrigo, Kirstie Haywood, Astrid Hoedemaekers, Gisela Lilj, Nikolaos Nicolaou, Theresa Olasveengen, Chiara Robba, Markus B. Skrifvars, Jas Soar

Guideline title	**Chapter 9: Post Resuscitation Care**
Guideline objective	This section of the guidelines is a collaboration between the European Resuscitation Council and the European Society of Intensive Care Medicine. It will provide recommendations for the treatment of the cardiac arrest patient after return of spontaneous circulation has been achieved. It will include some aspects of treatment out of hospital but the main focus is on in-hospital management. It will include investigations and diagnosis of the cause of cardiac arrest and all aspects of the intensive care management of the post-cardiac arrest patient (temperature control, blood pressure targets, oxygenation and ventilation targets, and temperature control). The approach to prognostication will be discussed, as will rehabilitation, organ donation, long-term outcomes and investigation of sudden cardiac death.
Intended audience	All clinicians who treat post-cardiac arrest patients
Setting	Any setting after return of spontaneous circulation
Writing group members	Jerry Nolan, Claudio Sandroni, Alain Cariou, Tobias Cronberg, Sonia D'Arrigo, Kirstie Haywood, Astrid Hoedemaekers, Gisela Lilja, Nikolaos Nikolaou, Theresa Olasveengen, Chiara Robba, Markus B. Skrifvars, Jas Soar

poznámky k prognostifikaci

NEUROPROGNOSTICATION FOR THE COMATOSE PATIENT AFTER RESUSCITATION FROM CARDIAC ARREST

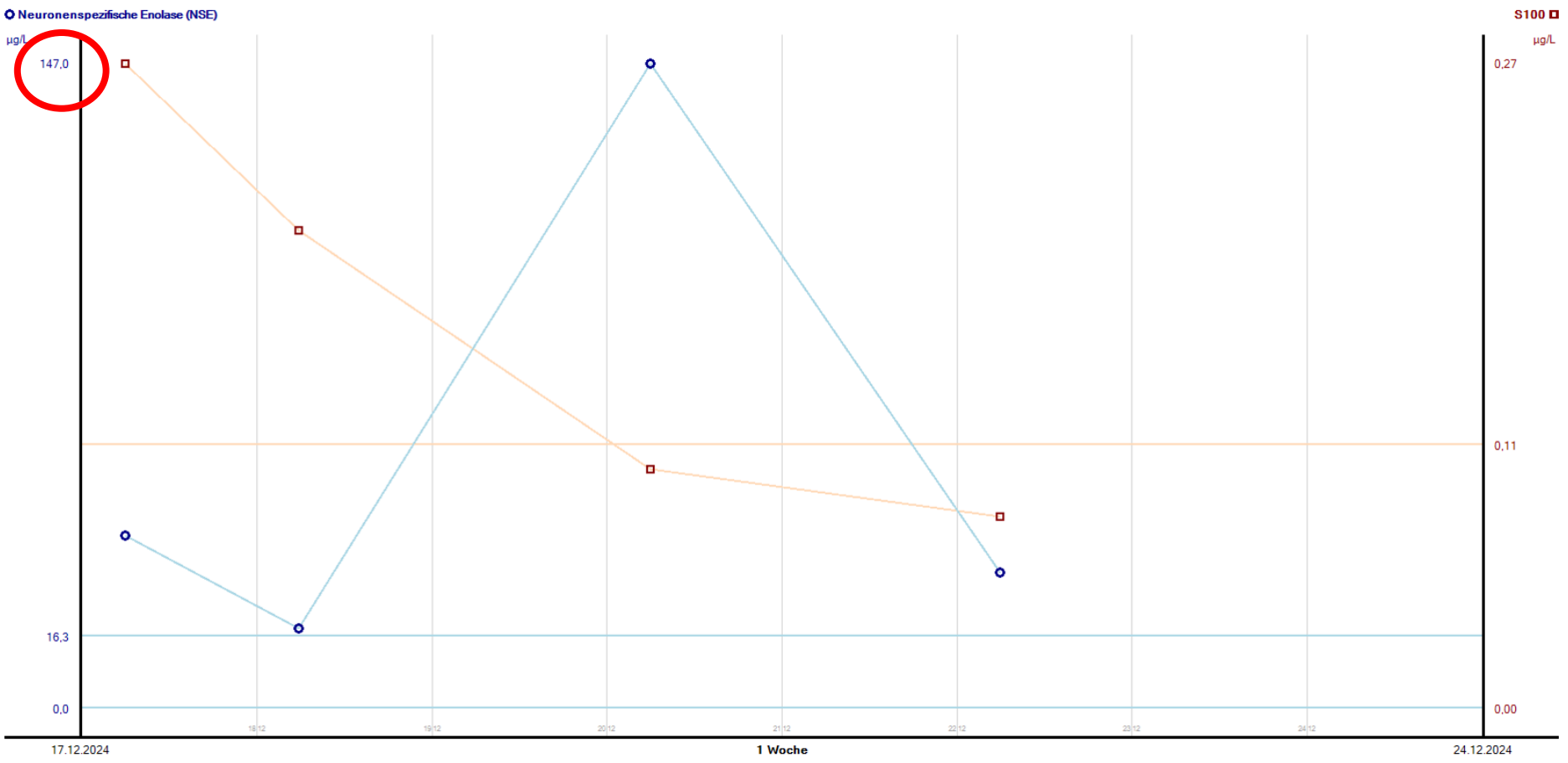
EUROPEAN RESUSCITATION COUNCIL GUIDELINES 2021



1961, M 63

Neuronenspezifische Enolase (NSE) - S100

Zeitraum: 1 Woche | Ab Datum: 17.12.2024 | Bis Datum: 24.12.2024 | Skalieren auf: Referenz | Aktualisieren



- We recommend that neuroprognostication always be undertaken using a multi-modal approach because no single test has sufficient specificity to eliminate false positives (strong recommendation, very-low-certainty evidence).
- We suggest using neuron specific enolase (NSE) within 72 h after ROSC, in combination with other tests, for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence). There is no consensus on a threshold value.
- We suggest against using S-100B protein for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, low-certainty evidence).
- We suggest against using serum levels of glial fibrillary acidic protein (GFAP), serum tau protein, or neurofilament light chain (Nfl) for predicting poor neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

ÜBERSICHT

Prädiktoren zur Prognoseabschätzung

Eine schlechte Prognose ist wahrscheinlich, wenn ≥ 2 der folgenden Prädiktoren vorliegen [1]:

- Reflextests: keine Pupillen- und Kornealreflexe nach ≥ 72 h,
- Biomarker: neuronenspezifische Enolase (NSE), steigende und hohe Werte (> 60 µg/l) 48 h und 72 h nach ROSC,
- EEG: hochmalignes EEG nach ≥ 24 h, Anfälle in den ersten 72 h,
- SSEP: bilaterales Fehlen SEEP (N20-Potenzial) nach ≥ 24 h,
- Status myoclonus ≤ 72 h oder diffuse axonale Schädigung im cCT/cMRT.

Summary
for
ICU Baden?

Schiewe R, Bein B. Post Resuscitation Care ... Anästhesiol Intensivmed Notfallmed Schmerzther 2024; 59: 237–250

Post Resuscitation Care – Postreanimationsbehandlung

Robert Schiewe, Berthold Bein

Phase 3: Optimierung der Erholung

SOP Baden

Gezieltes Temperaturmanagement

Das gezielte Temperaturmanagement (TTM, Targeted Temperature Management) im Rahmen der Postreanimationsbehandlung ist ein bereits seit Langem kontrovers diskutiertes Thema, das insbesondere seit Veröffentlichung der 2022 aktualisierten Empfehlung der ERC/ESICM wieder stärker in den Fokus gerückt ist.

PRAXIS

Mögliches Ablaufschema des TTM

- Alle Patienten mit einer vorangegangenen Reanimationsdauer von mehr als 15 min werden im Rahmen des TTM gekühlt. Ein TTM erfordert nicht unbedingt eine invasive Kühlung. Eine Temperaturkontrolle ist jedoch in jedem Fall durch geeignete Methoden sicherzustellen!
- Beträgt die gemessene Körpertemperatur nach ROSC bei Aufnahme in der Klinik bzw. auf Intensivstation ≥ 36 °C, so ist primär ein invasives Kühlverfahren zu etablieren. Bei einer Körpertemperatur < 36 °C können zunächst nichtinvasive Verfahren im Rahmen des TTM angewandt werden, um eine definierte Zieltemperatur von 34 °C konstant zu halten.

PRAXIS

Mögliches Ablaufschema des TTM

- Bis auf definierte Ausnahmen erfolgt ein TTM nach Stufenschema:
  - Konstante Zieltemperatur von 34 °C für ≥ 24 h.
  - Anschließend langsame kontrollierte Erwärmung (0,2 °C/h) über 24 h auf 37 °C, dann weitere 24 h Temperatur von max. 37 °C halten.
  - Ohne TTM/nach Abschluss des TTM bis mindestens 72 h nach ROSC strikte Verhinderung einer Temperatur > 37,5 °C!

nicht kühlen

PRAXIS

Mögliches Ablaufschema des TTM

- Erwäge ggf. alleinige Fieberverhinderung und möglichen Verzicht auf eine milde Hypothermie im Rahmen des TTM, wenn alles zutrifft:
  - beobachteter Kreislaufstillstand,
  - sofortiger Beginn der Reanimation, keine No-Flow-Zeit,
  - ROSC innerhalb weniger (max. 15) min, geringe Low-Flow-Zeit,
  - keine relevante hypoxisch-ischämische neuronale Schädigung zu erwarten,
  - Körperkerntemperatur ohne TTM jederzeit sicher < 37,5 °C.

ICU Baden:

1) chladit ***as sonn as possible***

2) cílová teplota **34ºC**

3) minimálně **24-48h** (přizpůsobit dennímu režimu)

4) primárně **Arctic Sun**, u některých **ThermoGard**

3) **Fieber** unbedingt **vermeiden**

4) měřit hladiny **NSE** + **S100 3** po sobě následující dny

...please keep cooling!

Antarctica 2024