GESTION DE LA TEMPERATURE APRES ARRET CARDIAQUE

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Historique
Pro TTM2
Pro TH
Conclusions « thermiques » en 2021

COI: lecture and travel fees for Bard / Zoll

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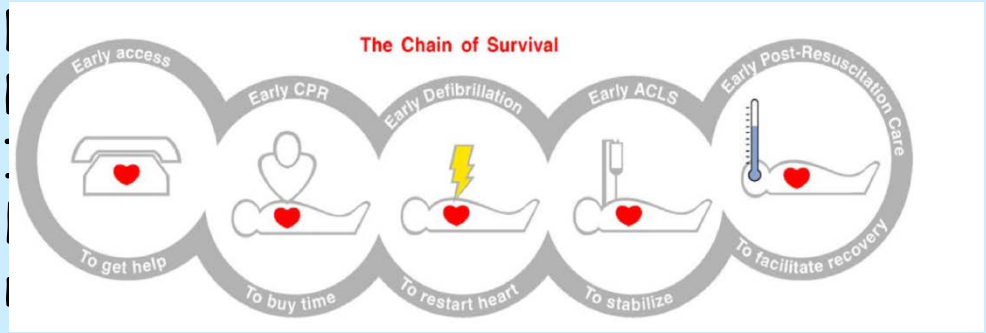


Historique

Pro TTM2

Pro TH

Conclusions « thermiques » en 2021

Background : Six Decades of TH/TTM History

Mild Resuscitative Hypothermia to Improve Neurological Outcome After Cardiac Arrest: A Clinical Feasibility Trial

Andrea Zeiner, Michael Holzer, Fritz Sterz, Wilhelm Behringer, Waltraud Schörkhuber, Marcus Müllner, Michael Frass, Peter Siostrzonek, Klaus Ratheiser, Alfred Kaff and Anton N. Laggner

Hyperthermia After Cardiac Arrest Is Associated With an Unfavorable Neurologic Outcome

Andrea Zeiner, MD; Michael Holzer, MD; Fritz Sterz, MD; Waltraud Schörkhuber, MD; Philip Eisenburger, MD; Christof Havel, MD; Andreas Kliegel, MD; Anton N. Laggner, MD

1961

2000

2003

2013

2021

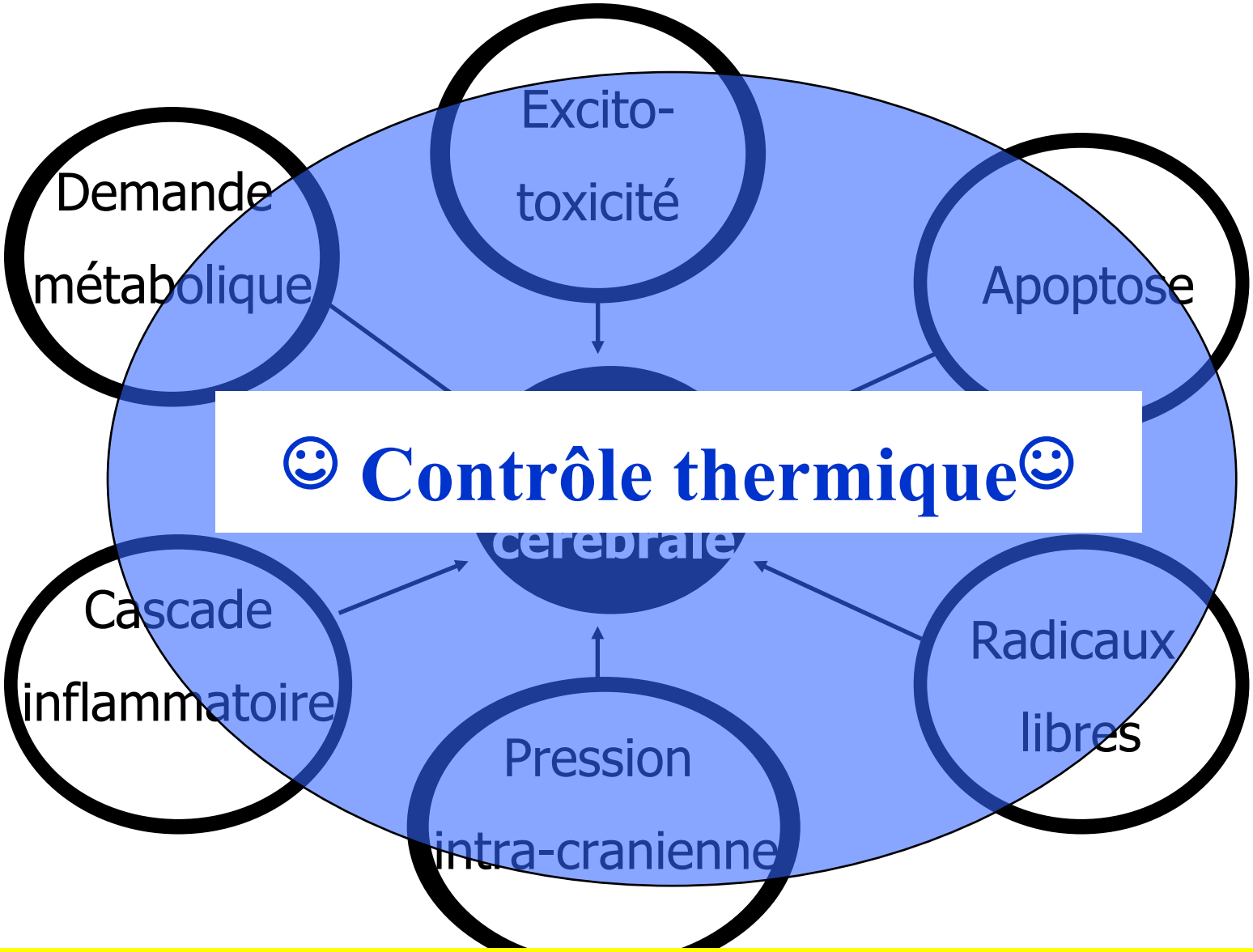
1960-90

2002

2006-2011

2019

Hypothermie efficace sur l'ensemble des lésions anoxo-ischémiques



Cascade biochimique des lésions d'ischémie / reperfusion

Meta-analysis of targeted temperature management in animal models of cardiac arrest

Olai H, et al. ICM Exp. 2020

N=17809 (after exclusion of duplicates) with 181 studies describing neurobehavioral outcome: 1787, brain histology: 6495, or mortality: 2945 animals

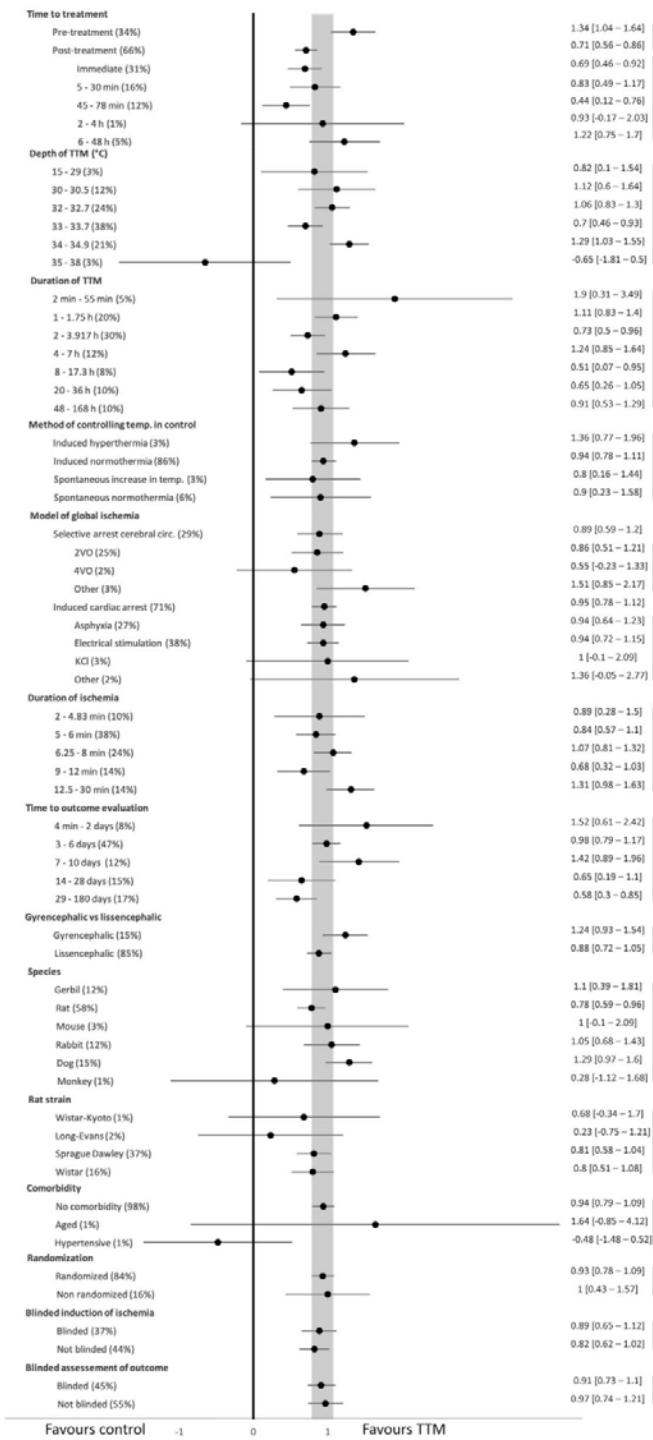
TTM was favoured vs. control for all outcomes.

TTM = beneficial using short and prolonged cooling, deep and moderate temperature reduction, early and delayed time to treatment.

Median (IQR) study quality = 4 (3-6); 18 studies: 7-8 quality items. No clear correlation between study quality and efficacy for all outcomes.

Conclusions: TTM is beneficial under most experimental conditions in animal models of cardiac arrest or global brain ischemia. However, research on gyrencephalic species and especially comorbid animals is uncommon and a possible translational gap. Also,

TTTM after CA. A review of animal studies. Arrich J, et al. Resuscitation. 2021
(in CA animals, consistent favourable effect of post-resuscitation TTM vs. normothermia on neurologic outcome increasing with lower temp)



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Nolan (2003)

1961 | 2000 | 2003 | 2013 | 2021

1960-90 | 2002 | 2006-2011 | 2019

2002, HACA & Bernard studies: benefits of TH (32-34°C) in post-CA

HT vs. control = normothermia or hyperthermia?

Limits of the 2 main RCTs in 2002

NEJM 2002

Bias. Patients in the control group slightly hyperthermic (37-38°C during the first 48 hours). No WLST guidelines.

The New England Journal of Medicine

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VOLUME 346 FEBRUARY 21, 2002 NUMBER 8

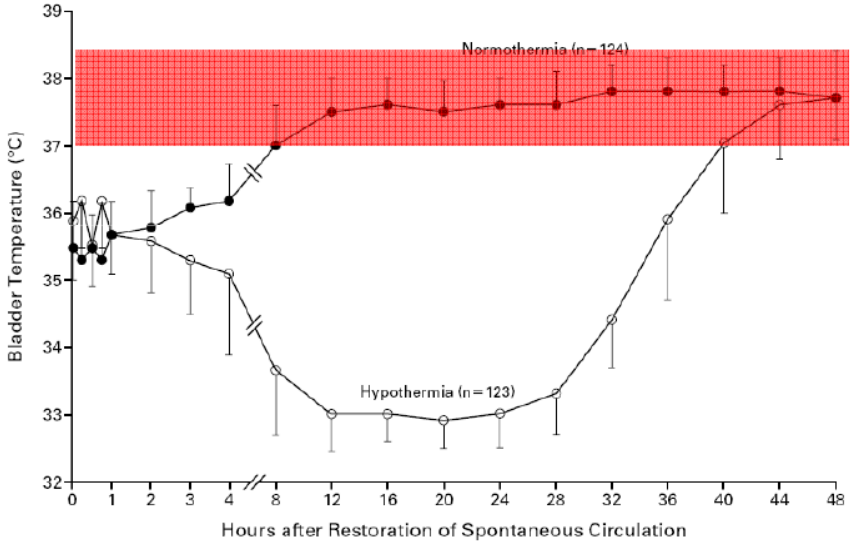
MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

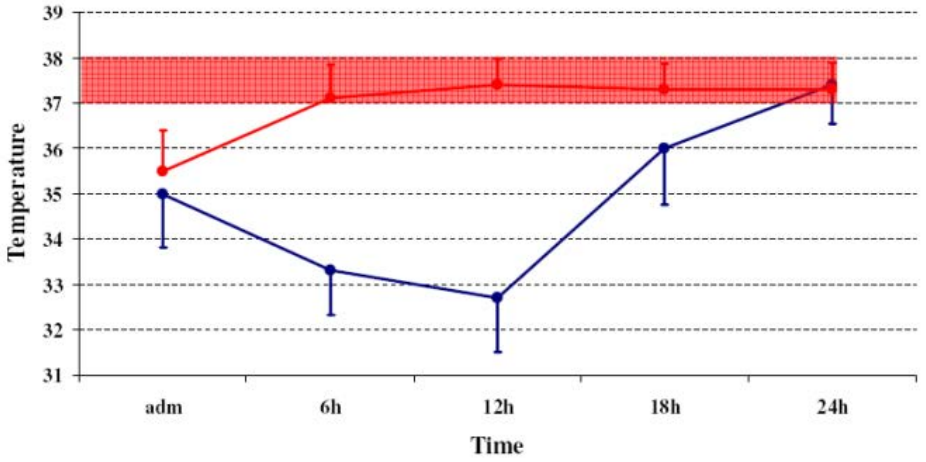
THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

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.

TH vs No TTM





Controversial metanalysis (NNT/NNH): Nielsen IJC 2010

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2003-2011, AHA upgraded to Class 2a → 1 recommendation to 32-34°C in (OH)CA patients (FV)

TTM > TH
after CA and NN-HIE
Nunally (2009-11)

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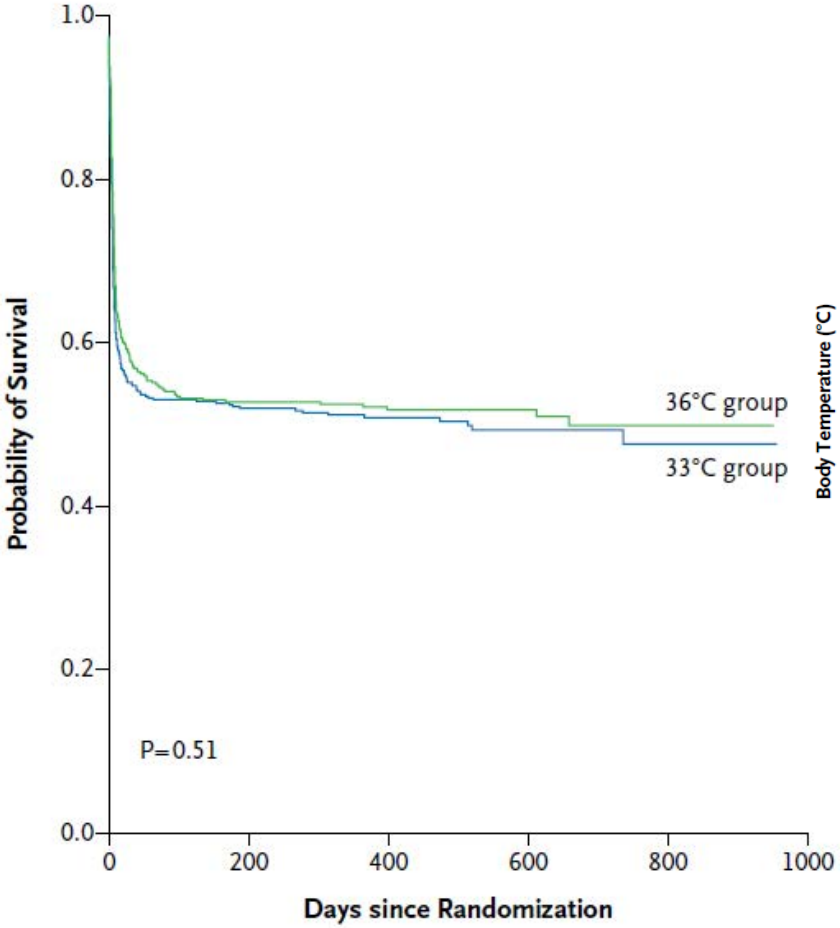
The NEW ENGLAND JOURNAL of MEDICINE

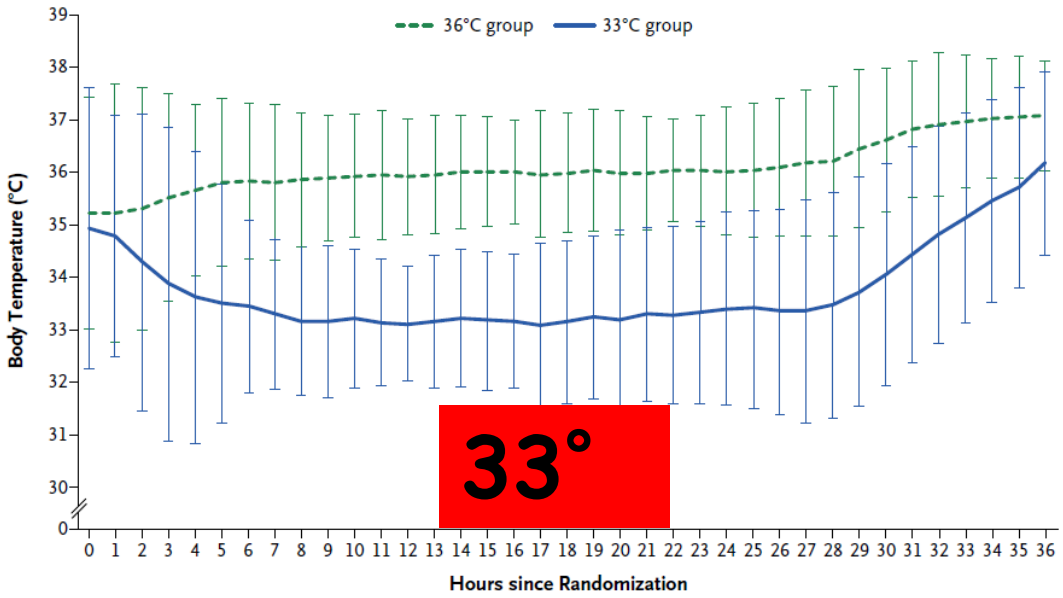
ORIGINAL ARTICLE

Nielsen et al, NEJM 2013
NS superiority large RCT
(469 vs 464 pts)

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



36°



33°

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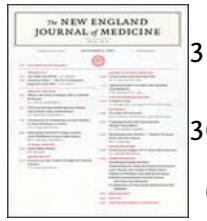
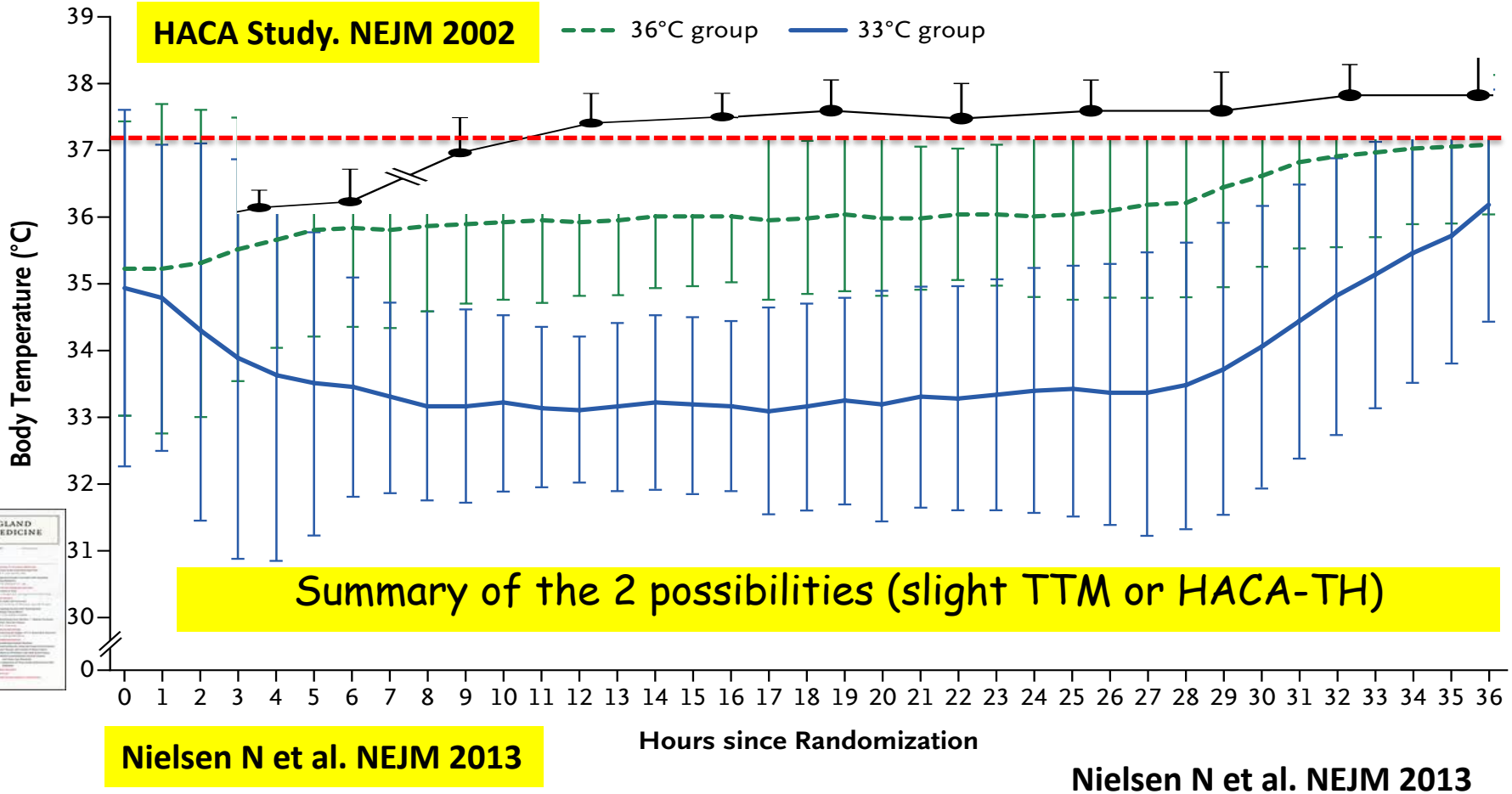
TTM trial: no difference between 33 vs 36°C

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

In-hospital low TTM effect = slight TTM > no TTM





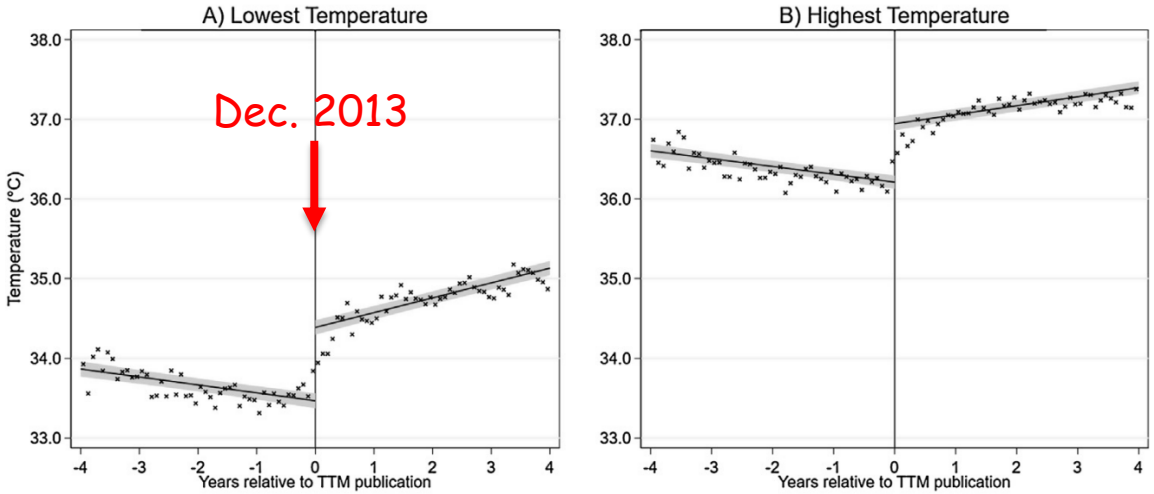
Nielsen N et al. NEJM 2013

- 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).

Guidelines: 2015 changes

Changes in temperature management and outcome after out-of-hospital cardiac arrest in United Kingdom intensive care units following publication of the targeted temperature management trial

Nolan JP et al. Resuscitation 2020



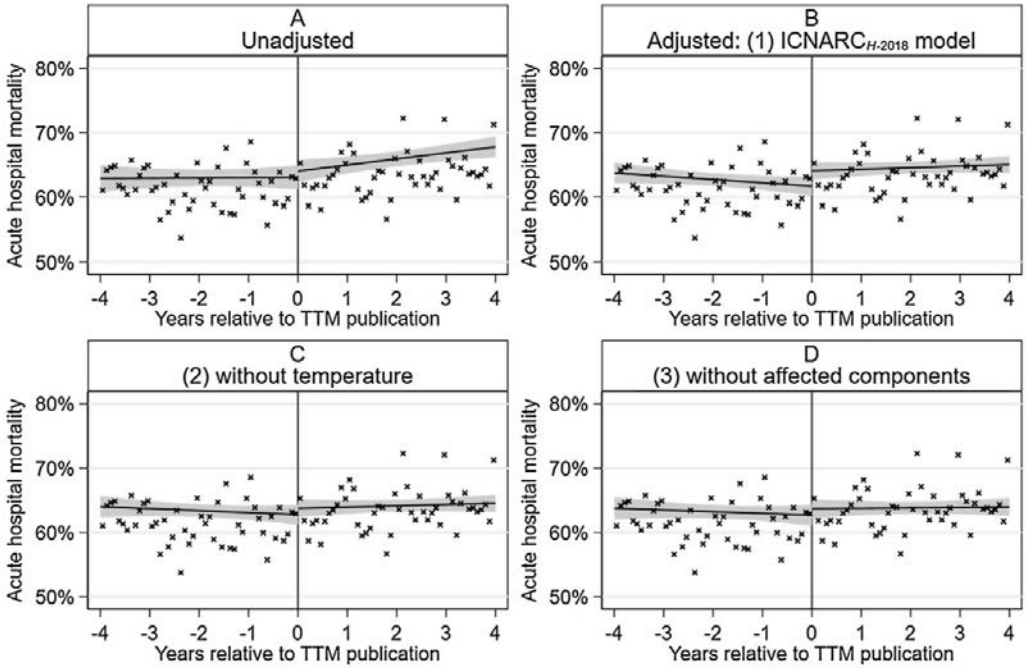
N=1.181.405 admissions in 235 ICUs.

Lowest temp. during the first 24h = lower in the preTTM1 era.

PostTTM cohort = more temp. >38°C (25 vs. 15%)

Highest unadjusted in-hospital mortality (63.7 vs. 61.6%)

Multivariate: step change in death, change in slope = NS



Similar results in

Australia/ New Zealand (Bray/Salter)

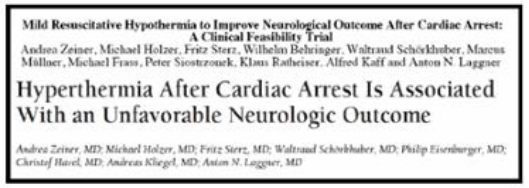
Sweden (Abazi),

USA (Bradley), and in

France (Lascarrou, CEMS)

Background : Six Decades of TH/TTM History

1961



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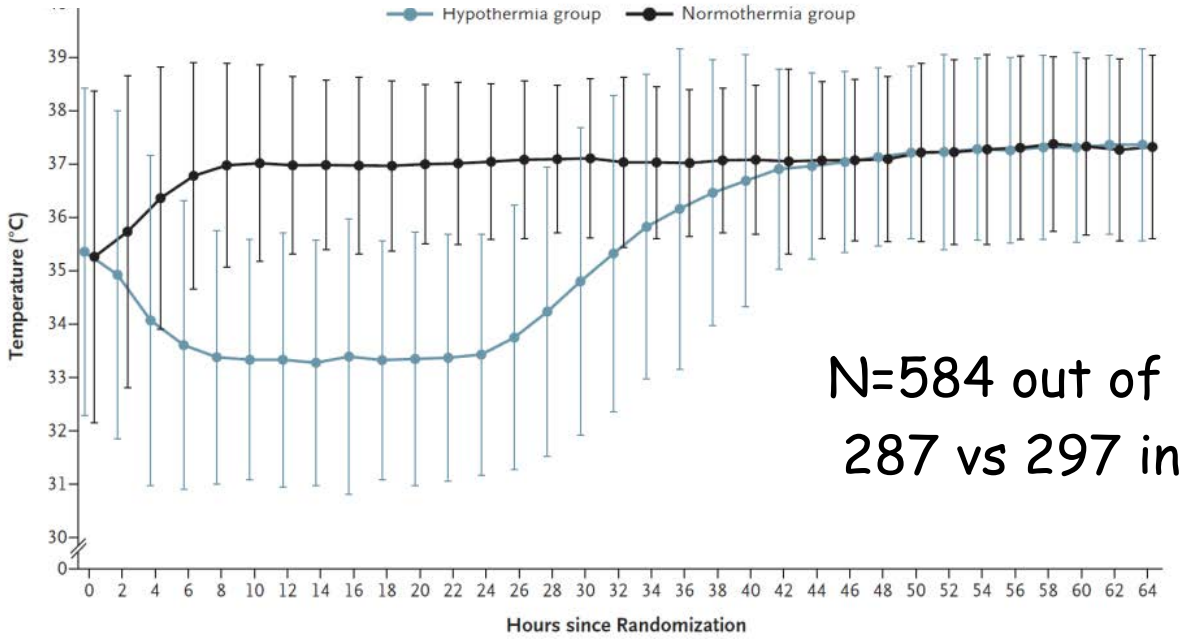
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

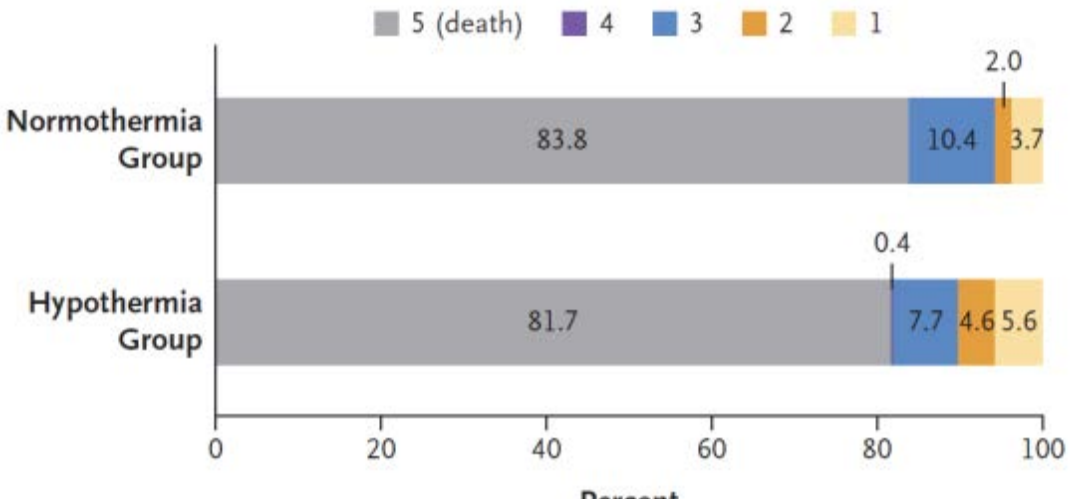
confusion, misinterpretations?
Post TTM trial publications:
Changes in clinical practice, TTM non-compliance, and worsened patient outcome?

Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm

Lascarrou et al, NEJM, 2019



N=584 out of 27723
287 vs 297 included



On D90, CPC 1-2:
TH: 29/284 (10.2%)
vs NT: 17/297 (5.7%);
Diff = 4.5% (CI 0.1-8.9); P=0.04
Mortality: NS (81.3 vs 83.2%)
Subgroups: NS

Circulation

Part 3: Adult Basic and Advanced Life Support

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

2020

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.

Recommendations for Performance of TTM

COR	LOE	Recommendations
1	B-R	1. We recommend selecting and maintaining a constant temperature between 32°C and 36°C during TTM.
2a	B-NR	2. It is reasonable that TTM be maintained for at least 24 h after achieving target temperature.
2b	C-LD	3. It may be reasonable to actively prevent fever in comatose patients after TTM.
3: No Benefit	A	4. We do not recommend the routine use of rapid infusion of cold IV fluids for prehospital cooling of patients after ROSC.

ILCOR et ERC/ESICM :

- **Contrôle thermique recommandé pour tous les rythmes d'AC adultes +++**
- **Cibler une température entre 32 et 36°C au moins 24h**
- **Eviter la fièvre > 37.7°C pdt 72h (si coma)**

CONFERENCE REPORTS AND EXPERT PANEL

European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care

Nolan et al. ICM 2021

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1961

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2003-2010, AHA upgraded to Class 2a → 1 recommendation to 32-34°C in (OH)CA patients (FV)

2015, AHA/ILCOR Expanded recommendation to 32-36°C

2020, AHA/ILCOR expanded Class 1 recommendation to IHCA/OHCA, 32-36°C, same for pregnancy

TTM > TH after CA and NN-HIE Nunally (2009-11)

Nolan (2003)

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?

1960-90

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2002, HACA & Bernard studies: benefits of TH (32-34°C) in post-CA

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confusion, misinterpretations?
Post TTM trial publications: Changes in clinical practice, TTM non-compliance, worsened patient outcome?

2019

Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm

2019, Hyperion: 33°C-TTM > in nonshockable CA

ttm2

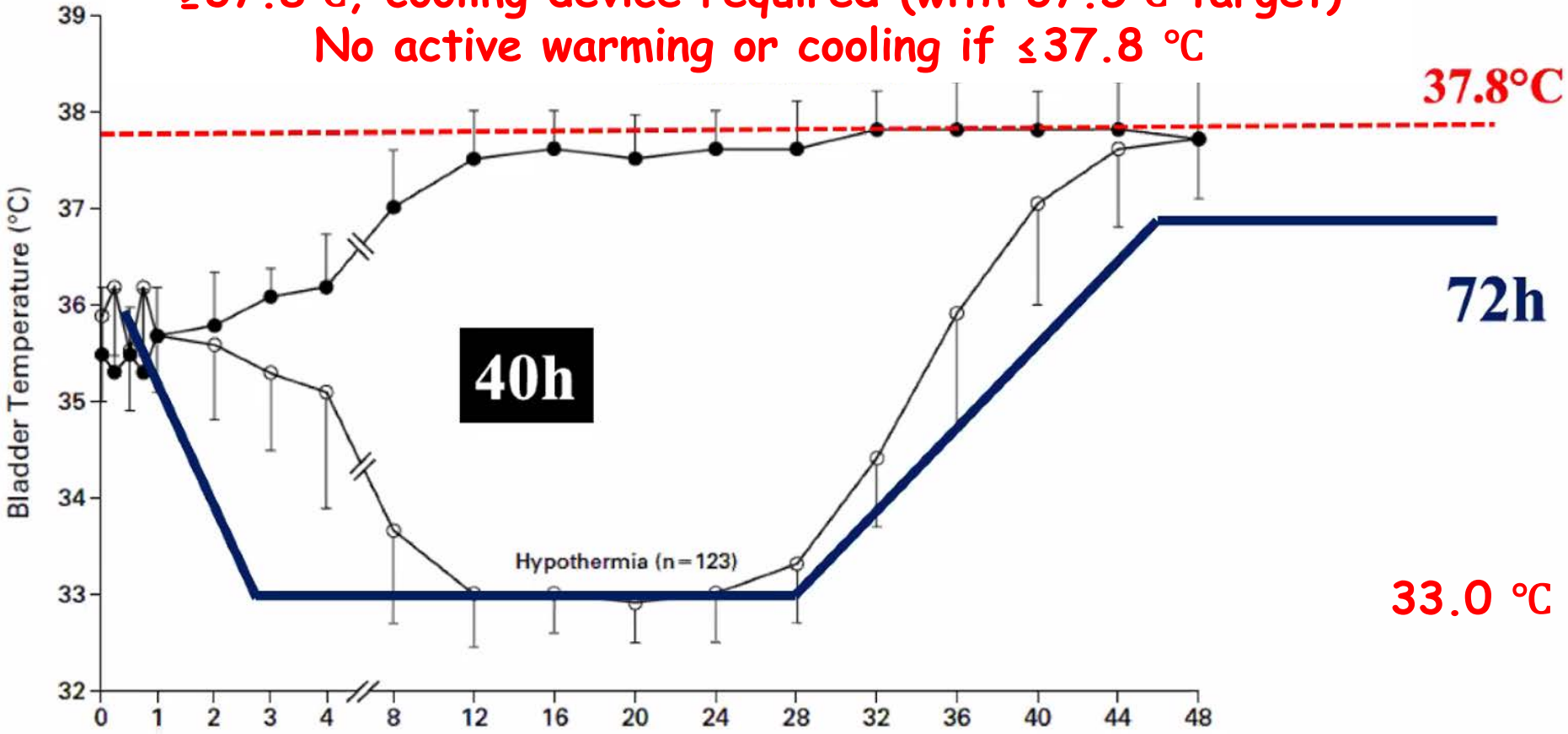
Hypothermia or Early Treatment of Fever

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

NT: aim of temperature ≤37.5°C

If conservative & pharmacologic ttt insufficient + temp. ≥37.8°C, cooling device required (with 37.5°C target)

No active warming or cooling if ≤37.8 °C



TTM: maintained 28 hours after randomization

Intervention (sedatives): 40h after randomization

ttm2

Hypothermia or Early Treatment of Fever

Inclusion

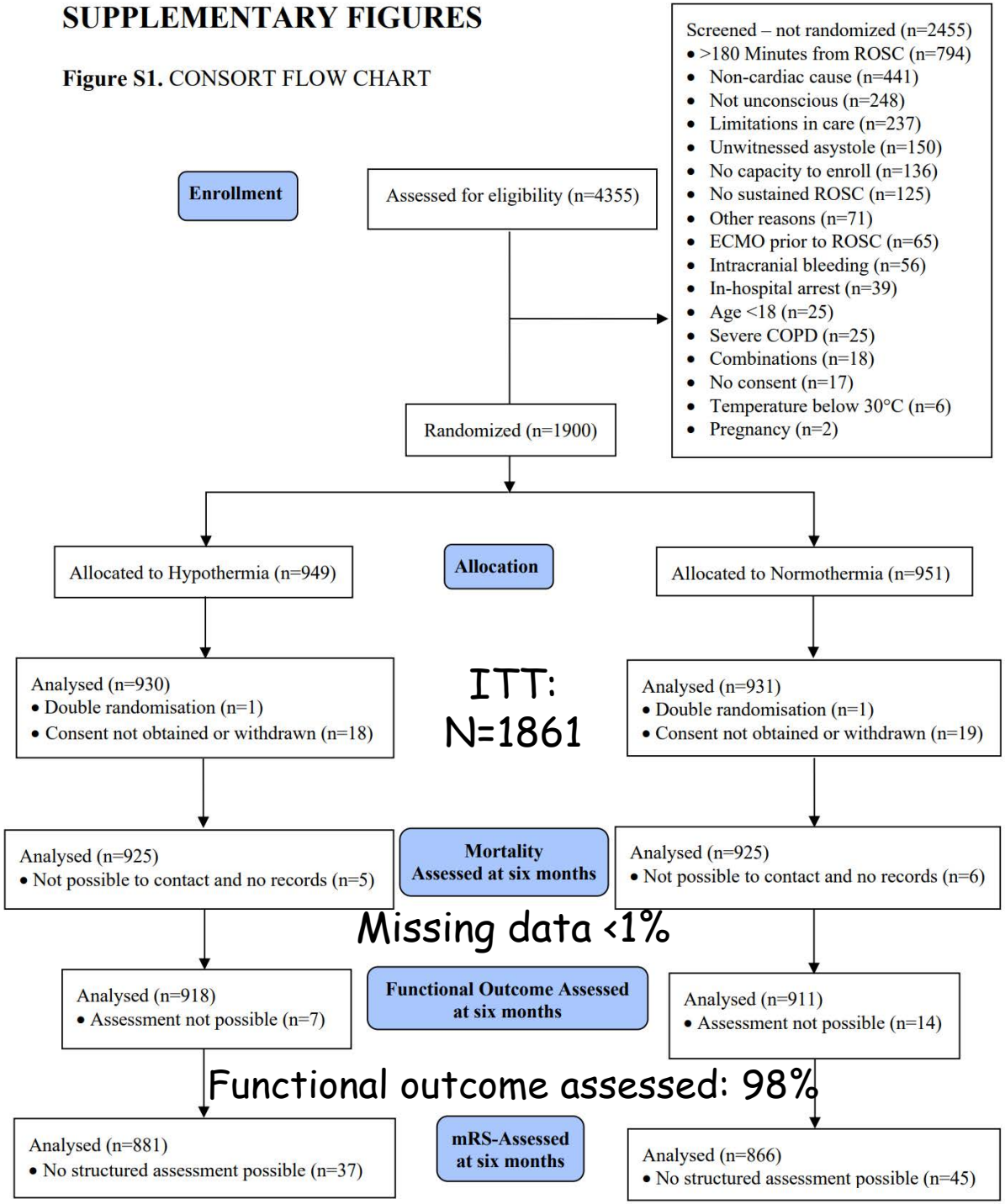
- ✓ Adult
- ✓ Comatose
- ✓ Presumed cardiac/unknown cause
- ✓ Stable ROSC
- ✓ No limitations in care
- ✓ ≤180 minutes from ROSC

Exclusion

- ✓ Unwitnessed asystole
- ✓ Temperature on admission <30°C
- ✓ ECPR
- ✓ Obvious or suspected pregnancy
- ✓ Intracranial bleeding
- ✓ Severe COPD on oxygen

SUPPLEMENTARY FIGURES

Figure S1. CONSORT FLOW CHART



ttm2
Hypothermia or Early Treatment of Fever

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)
Clinical characteristics on admission		
Tympanic temperature — °C¶	35.3±1.1	35.4±1.1
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)

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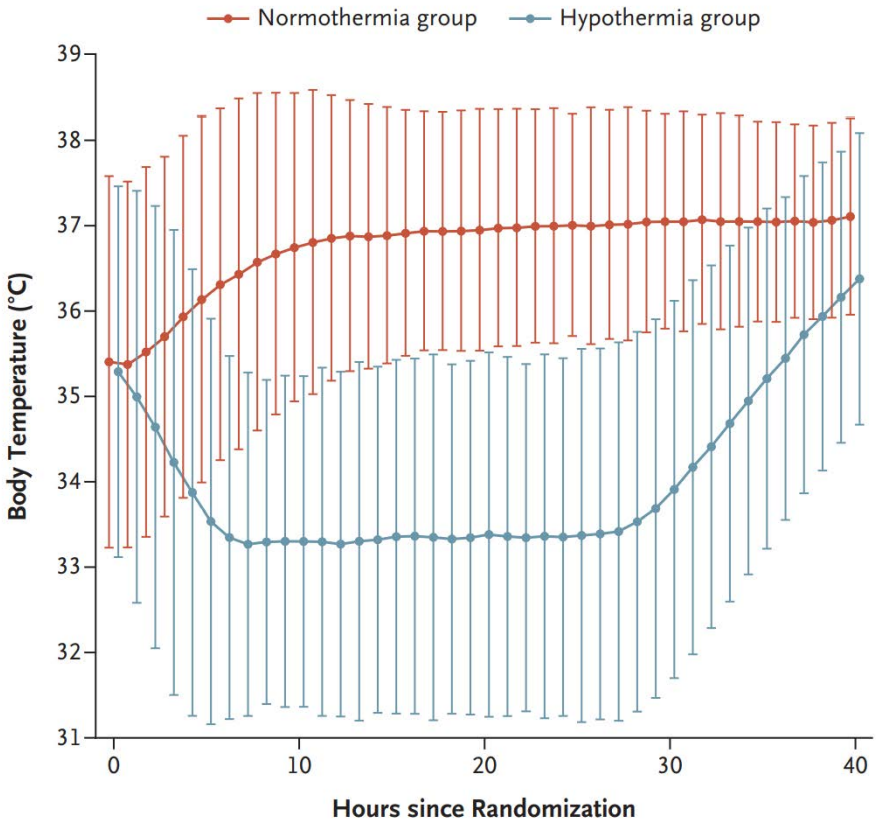
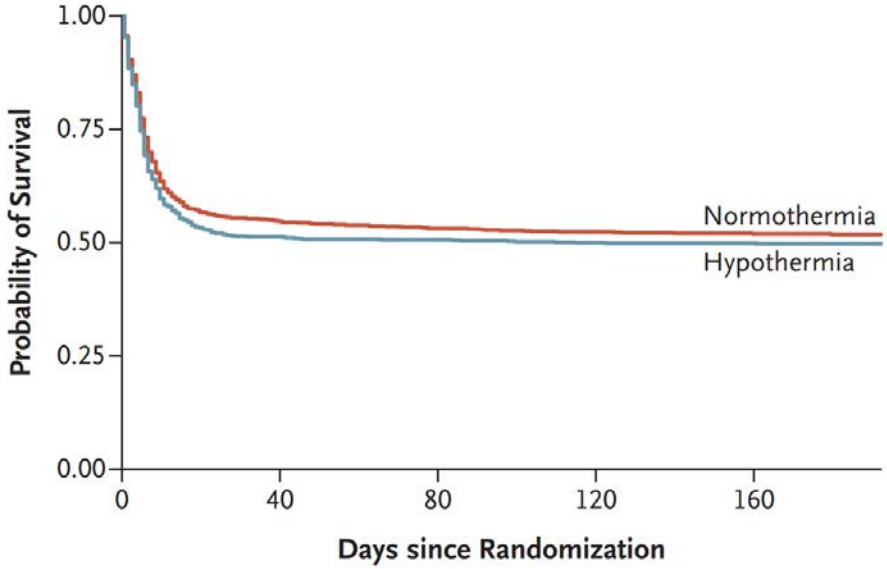




No. at Risk

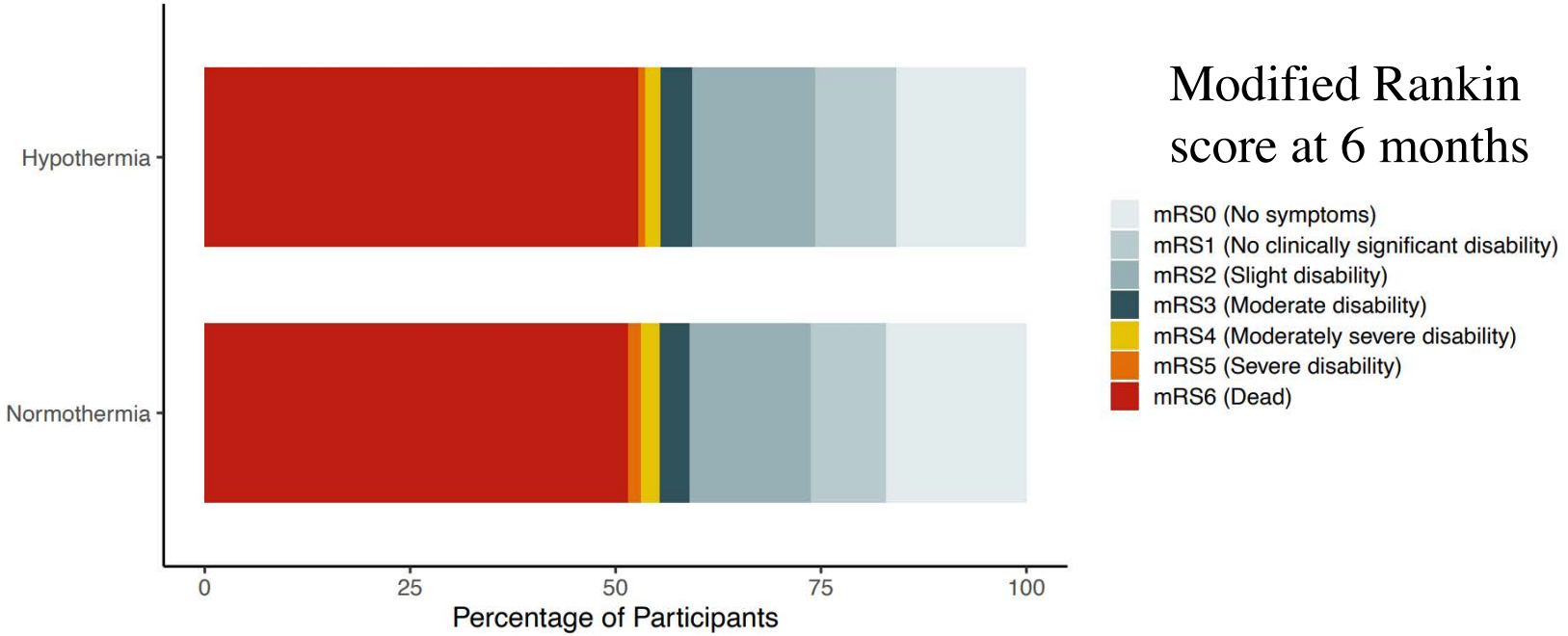
Normothermia	925	506	491	484	480
Hypothermia	925	474	468	462	461

Probability of survival until 180 days after randomization

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

Hypothermia or Early Treatment of Fever

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)	



No differences according to pre-specified subgroups for survival & neurological outcome

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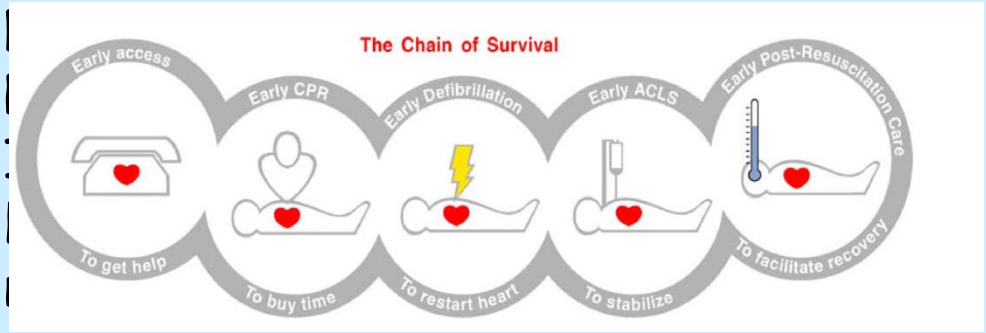


Historique

Pro TTM2

Pro TH

Conclusions « thermiques » en 2021

Human beings are animals (normal T°=37.0±0.5°C) but…

humans are different from animals !?

SUDATION

Different thermoregulation and basic temperature

POLYPNEA

EXPERIMENTAL-ANIMAL STUDIES

Homogeneous population & controlled experiment

Heterogeneous population & diseases

Experimental data: controversial?

Species (rat, swine… human ! Gyrencéphale…)
Quality of studies, parameter (neurologic, histologic, CPC)
Model (CA, asphyxia, carotid occlusion)
Co-morbidities (cerebral atherosclerosis…)
Type & severity of insult (multifactorial, predominant factor)
Degree of cooling, Duration of cooling (1, 3, 6, 12, 24, 72H…)
Post-ischemic delay before TH

Olai H, et al. ICM Exp. 2020

Conclusions: TTM is beneficial under most experimental conditions in animal models of cardiac arrest or global brain ischemia. However, research on gyrencephalic species and especially comorbid animals is uncommon and a possible translational gap. Also, low study quality suggests risk of bias within studies. Future animal research should focus on mimicking the clinical scenario and employ similar rigour in trial design to that of modern clinical trials.

Pathophysiology of post-anoxic (brain) damages

too complicated? individual variations? adverse effects?

Cerebral edema ↓

Apoptosis ↓

Brain pH ↑

PO_2 ↑

NOs activity ↓

Glycolysis ↑

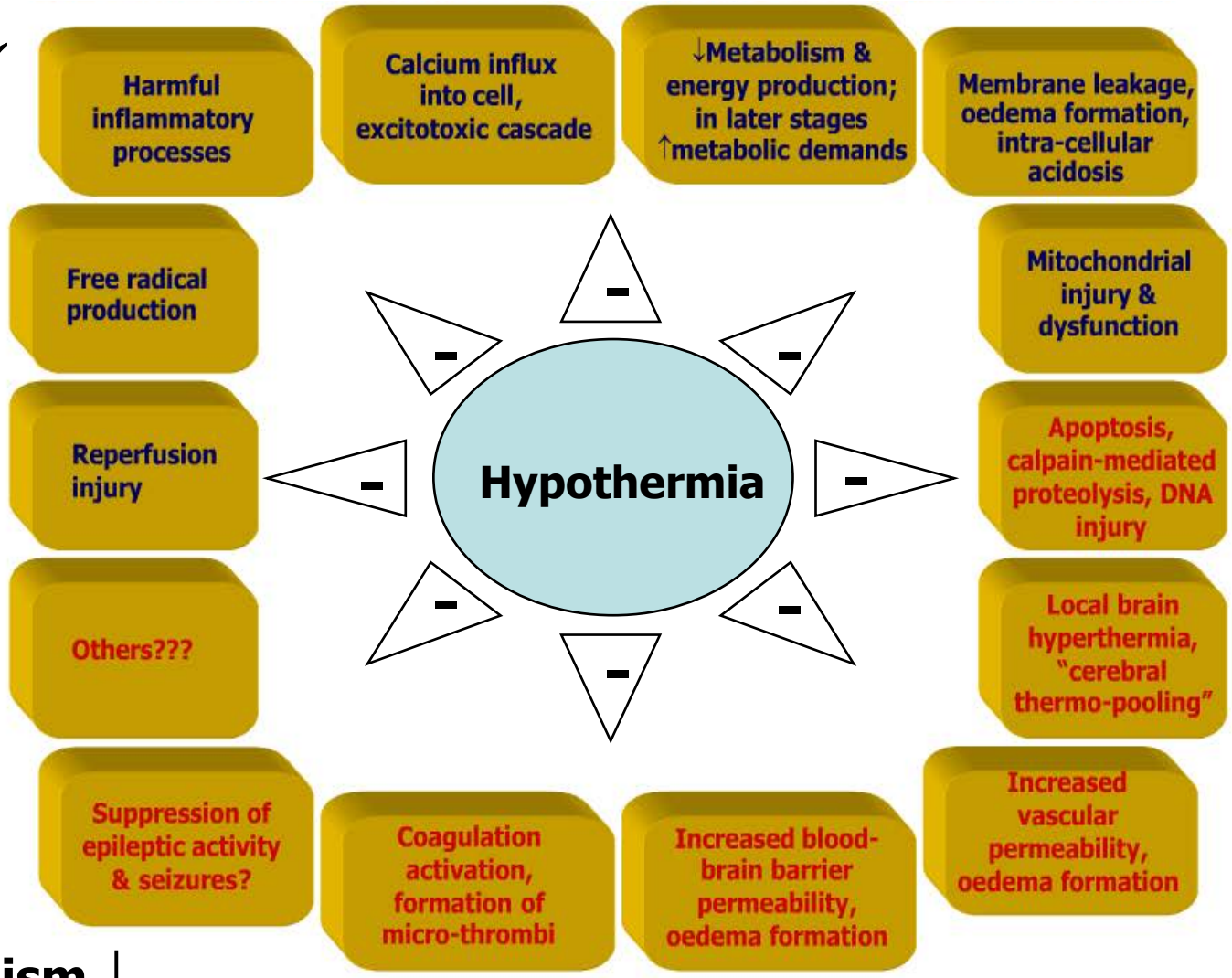
ICP ↓

ATP synthesis ↑

Jugular venous desaturation ↓

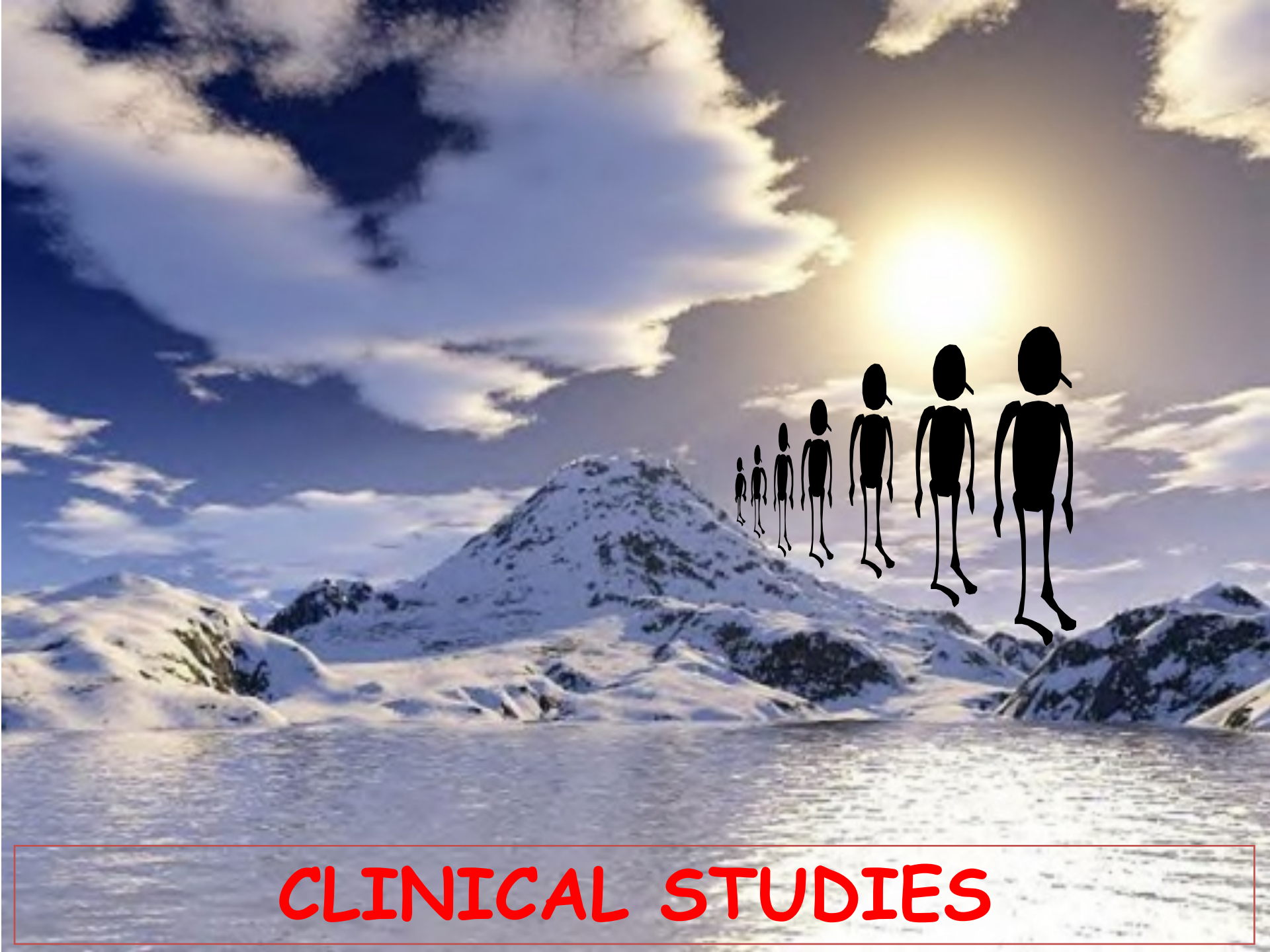
$CMRO_2$ ↓

Cerebral metabolism ↓



TTM is only delaying injuries? TTM dose?

CCM 2009 Polderman



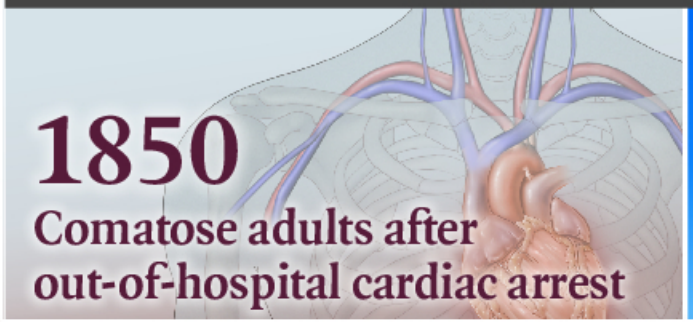
CLINICAL STUDIES

ttm2
Hypothermia or Early Treatment of Fever

The NEW ENGLAND JOURNAL of MEDICINE

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

	Hypothermia	Normothermia
Death from any cause at 6 mo	50%	48%
	RR, 1.04; 95% CI, 0.94 to 1.14; P=0.37	
Modified Rankin scale score ≥4 at 6 mo	55%	55%
	RR, 1.00; 95% CI, 0.92 to 1.09	
Arrhythmia with hemodynamic compromise	24%	17%

Hypothermia did not lead to a lower 6-mo incidence of death than normothermia.

J. Dankiewicz et al. 10.1056/NEJMoa2100591

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

ttm2
Hypothermia or Early Treatment of Fever

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

Intravascular device-related thrombosis: 1 (TH) vs. 2 (NT)

Kaliemia?

	Hypothermia	Normothermia
Days from randomization to hospital discharge (median (IQR))	9.4 (4.0–17.0)	9.8 (5.0–17.4)
- *Survivors*	15.4 (10.4–25.4)	14.6 (9.7–23.6)
- *Died in hospital*	4.0 (2.0–7.0)	5.0 (2.0–8.0)
Days from randomization to ICU-discharge (median (IQR))	4.9 (3.0-8.3)	4.8 (2.9-8.0)
- *Survivors*	5.9 (3.9–9.6)	5.4 (3.2–8.9)
- *Died in the ICU*	3.8 (1.2–5.8)	3.9 (1.4–6.2)
Days from randomization to extubation or death (n=1759) (median (IQR))	3.7 (1.9–6.0)	3.2 (1.8–5.7)
Survivors	3.8 (2.0–6.4)	2.9 (1.9–5.5)

Nielsen N, et al. TTM1. NEJM 2013

	33°C	36°C	Total
	473	466	939
Mechanical ventilation** Days receiving mechanical ventilation/days in ICU median [IQR]	0.83 [0.67-1.00]	0.76 [0.60-1.00]	0.80 [0.60-1.00]
Sedation Days with sedation affecting neurological evaluation median [IQR]	2 [2-3]	2 [1-3]	2 [1-3]

(P=0.006)

More hypoK+ if 33° C
Trend for pneumonia

Targeted Temperature Management after Cardiac Arrest: A Systematic Review and Meta-Analysis with Trial Sequential Analysis

2021

Filippo Sanfilippo [1,*,†], Luigi La Via [1,2,†], Bruno Lanzafame [1,2], Veronica Dezio [1,2], Diana Busalacchi Antonio Messina [3,4], Giuseppe Ristagno [5], Paolo Pelosi [6,7] and Marinella Astuto [1,2]

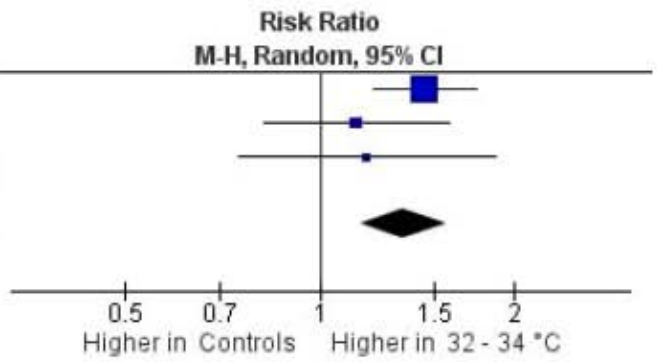
Journal of *Clinical Medicine*

N=8 trials (77 assessed for eligibility)

Study or Subgroup	TTM 32 - 34 °C Events	Total	TTM Controls Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dankiewicz, New Engl J Med 2021	222	927	152	921	67.6%	1.45 [1.21, 1.75]
Holzer, New Engl J Med 2002	49	135	44	138	21.2%	1.14 [0.82, 1.58]
Lascarrou, New Engl J Med 2019	35	284	31	297	11.2%	1.18 [0.75, 1.86]
Total (95% CI)		**1346**		**1356**	**100.0%**	**1.35 [1.16, 1.57]**
Total events	306		227			

Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 2 (P = 0.38); I² = 0%

Test for overall effect: Z = 3.83 (P = 0.0001)



Arrhythmias

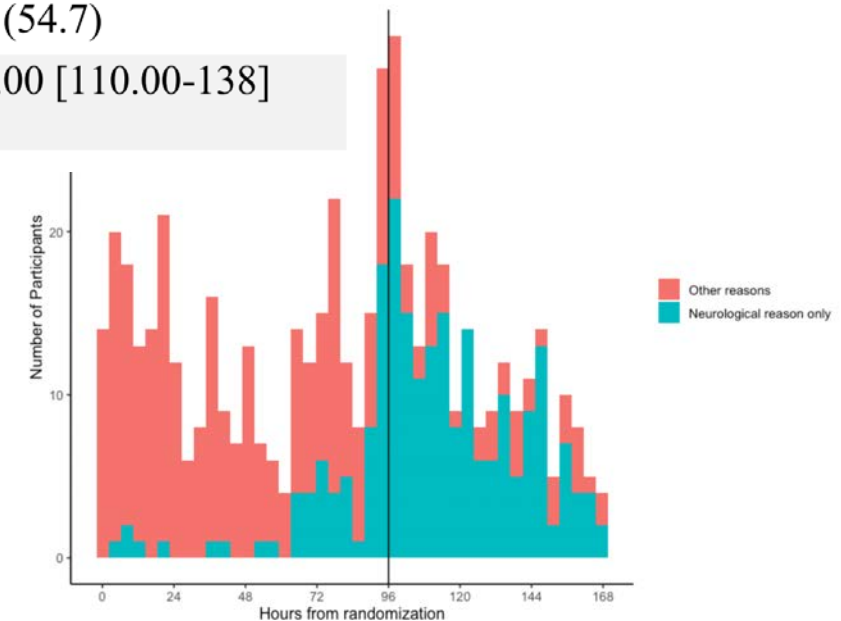
Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

ttm2
Hypothermia or Early Treatment of Fever

PROGNOSTICATION VARIABLES

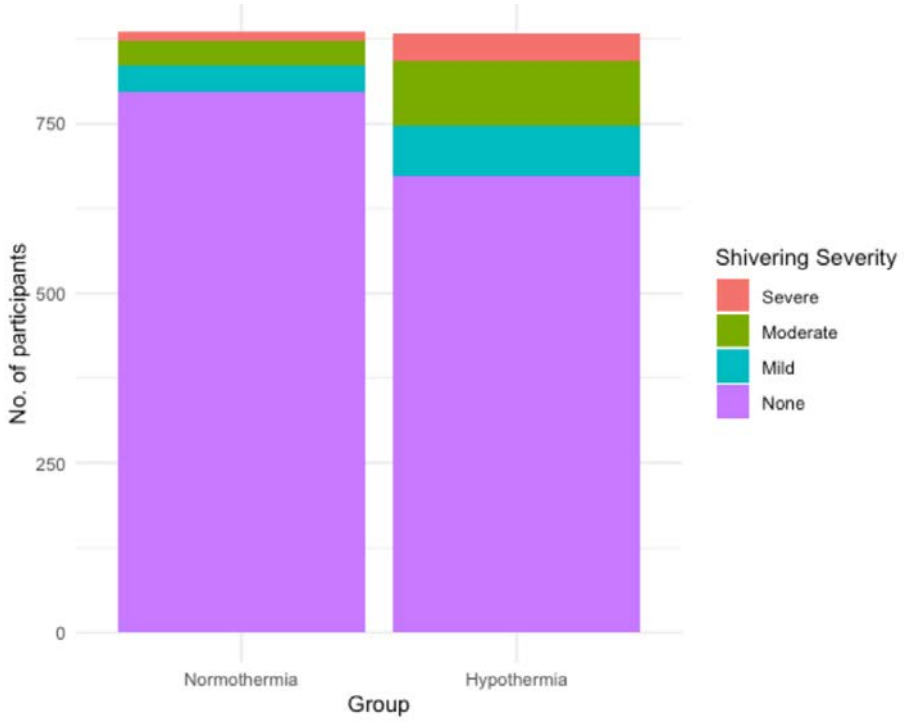
	HYPOTHERMIA	NORMOTHERMIA
PROGNOSTICATION PERFORMED	441 (47.4)	442 (47.6)
POOR PROGNOSIS LIKELY	131 (29.5)	133 (29.6)
EEG PERFORMED	484 (52.1)	445 (47.9)
CT PERFORMED	625 (67.3)	622 (67.0)
MRI PERFORMED	80 (8.6)	86 (9.3)
SSEP PERFORMED	159 (17.1)	165 (17.8)
NSE ANALYSED	510 (54.9)	508 (54.7)
HOURS TO PROGNOSTICATION	129.00 [110.00-137]	118.00 [110.00-138]

WLST: NT/TH = similar repartition during time



Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

ttm2
Hypothermia or Early Treatment of Fever

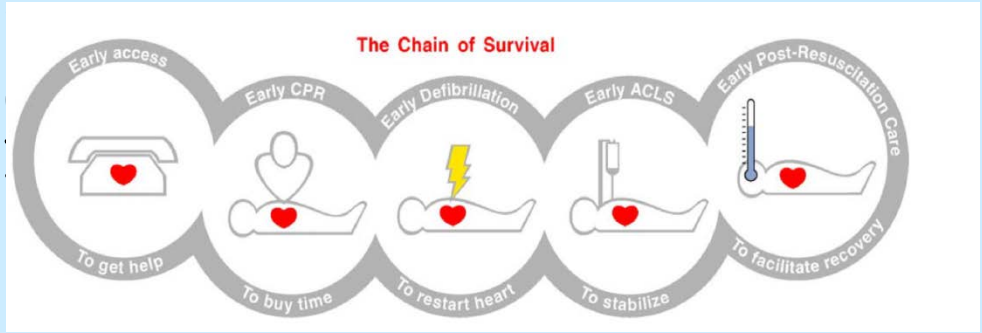


More shivering and paralyzers

DRUG	HYPOTHERMIA	NORMOTHERMIA
ATRACURIUM	156 (17%)	120 (13%)
CISATRACURIUM	164 (18%)	100 (11%)
ROCURONIUM	286 (31%)	207 (22%)
VECURONIUM	7 (1%)	11 (1%)
OTHER NMBA	47 (5%)	36 (4%)
ANY NMBA	614 (66%)	418 (45%)

TTM2: une des études les plus robustes en post-AC avec peu de biais et une conclusion peu discutable :
33-HT = NT/pas de fièvre en suivant un protocole strict (monitoring/cooling pharmacologique + device si besoin/sedation/LAT…)

GESTION DE LA TEMPERATURE APRES ARRET CARDIAQUE



Historique

Pro TTM2

Pro TH

Conclusions « thermiques » en 2021

ttm2
Hypothermia or Early Treatment of Fever

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

Reasons for rewarming in the hypothermia group

53/930 patients rewarmed before H40 (6%)

	No. of participants (% of total rewarmed)
Hemodynamic compromise	17 (32%)
Bradycardia	12 (23%)
Ventricular Fibrillation or Ventricular Tachycardia	6 (11%)
Intracranial hemorrhage	5 (9%)
Bleeding	3 (6%)
Brain death diagnosis	2 (4%)
Cardiac surgery	2 (4%)
ECMO	2 (4%)
Compartment syndrome	1 (2%)
Tachyarrhythmia	1 (2%)
Skin complications	1 (2%)
Unclear reasons	1 (2%)

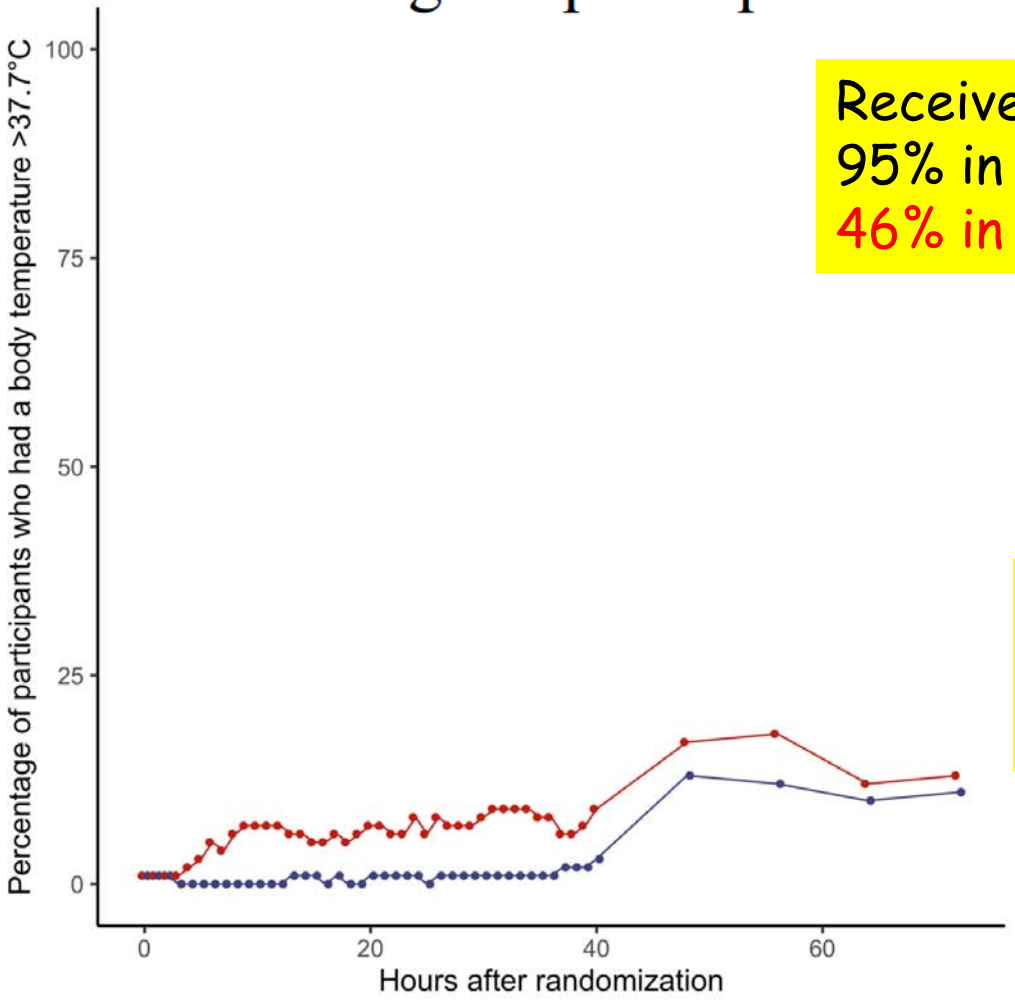
130 protocol deviations in 126 participants (63 for HT group vs. 63 for NT

Early awakening (before 40 hours) occurred in 29 cases

ttm2
Hypothermia or Early Treatment of Fever

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

Percentage of participants who were febrile per hour



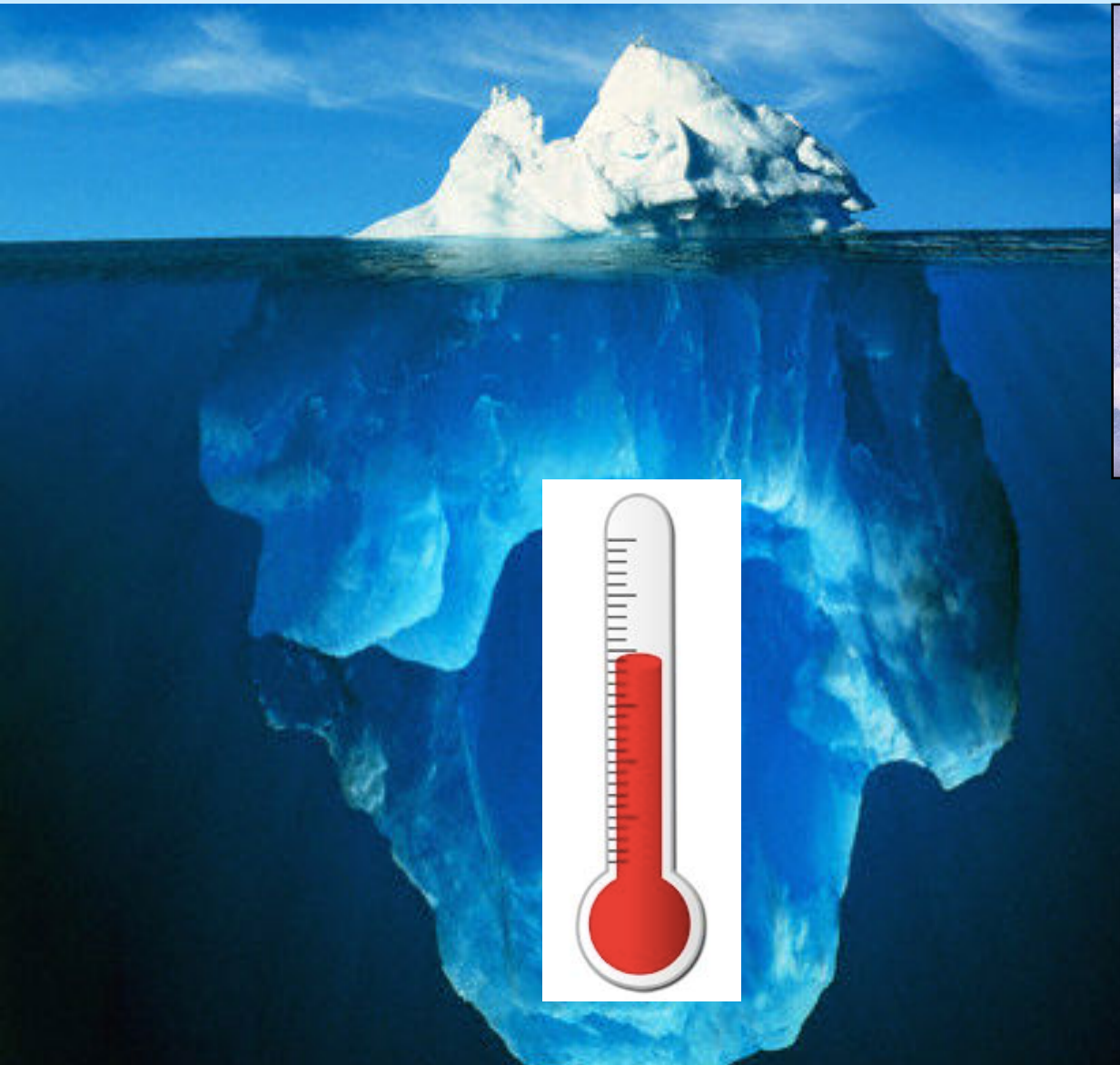
Received cooling with a device:
95% in the TH group (882/930)
46% in the NT group (428/931)

Cooling devices:
Endovascular: 30% TH ~ 31% NT
Surface: 70% TH ~ 69% NT

10-20% patients with temp. ≥37.7°C within first 72h (Morrison, NEJM 2021)

TH vs. TTM

Délai TT? Durée TTM? Sédation?

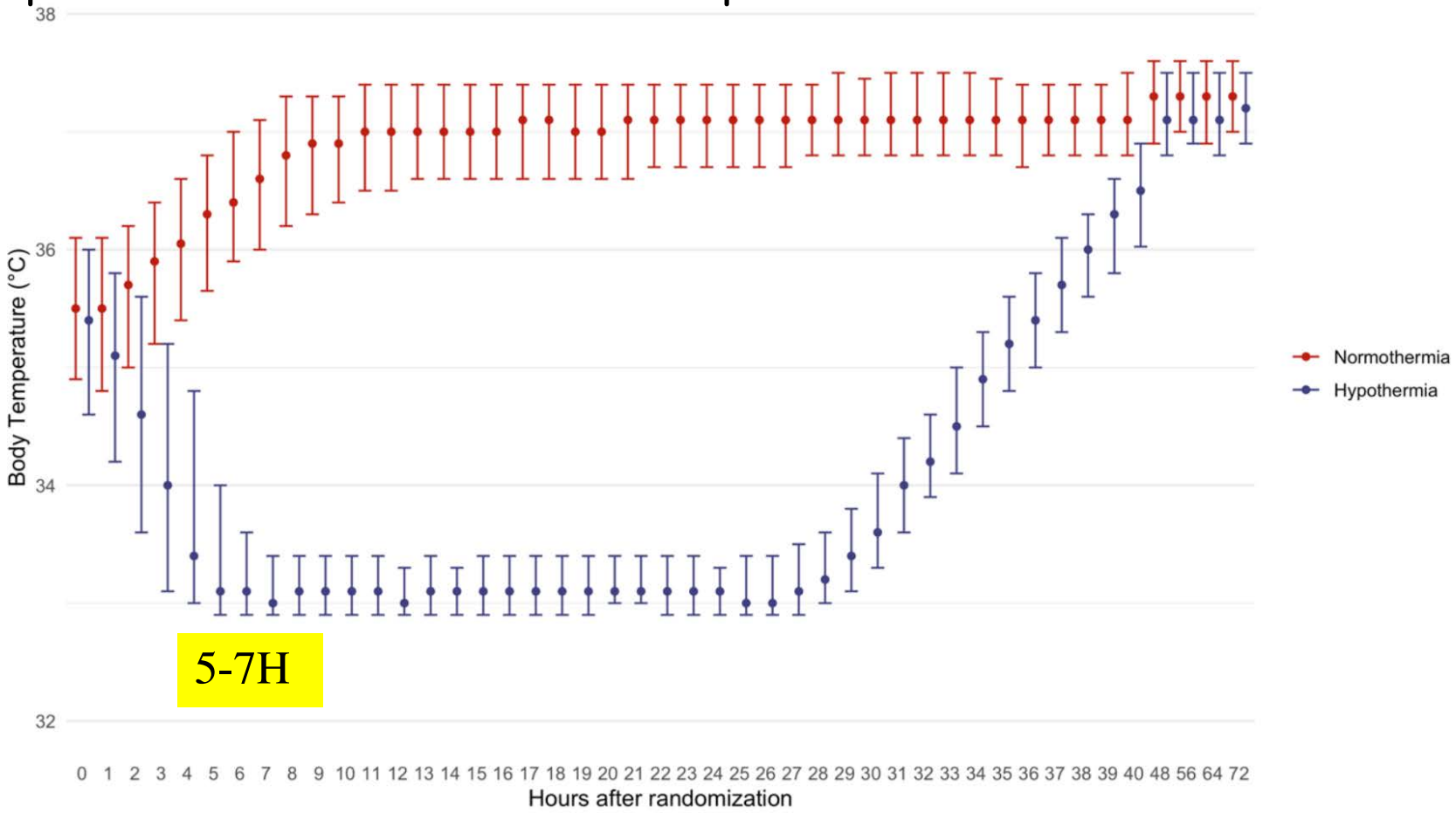


ttm2

Hypothermia or Early Treatment of Fever

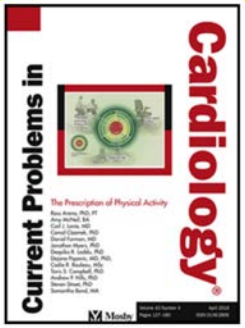
Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

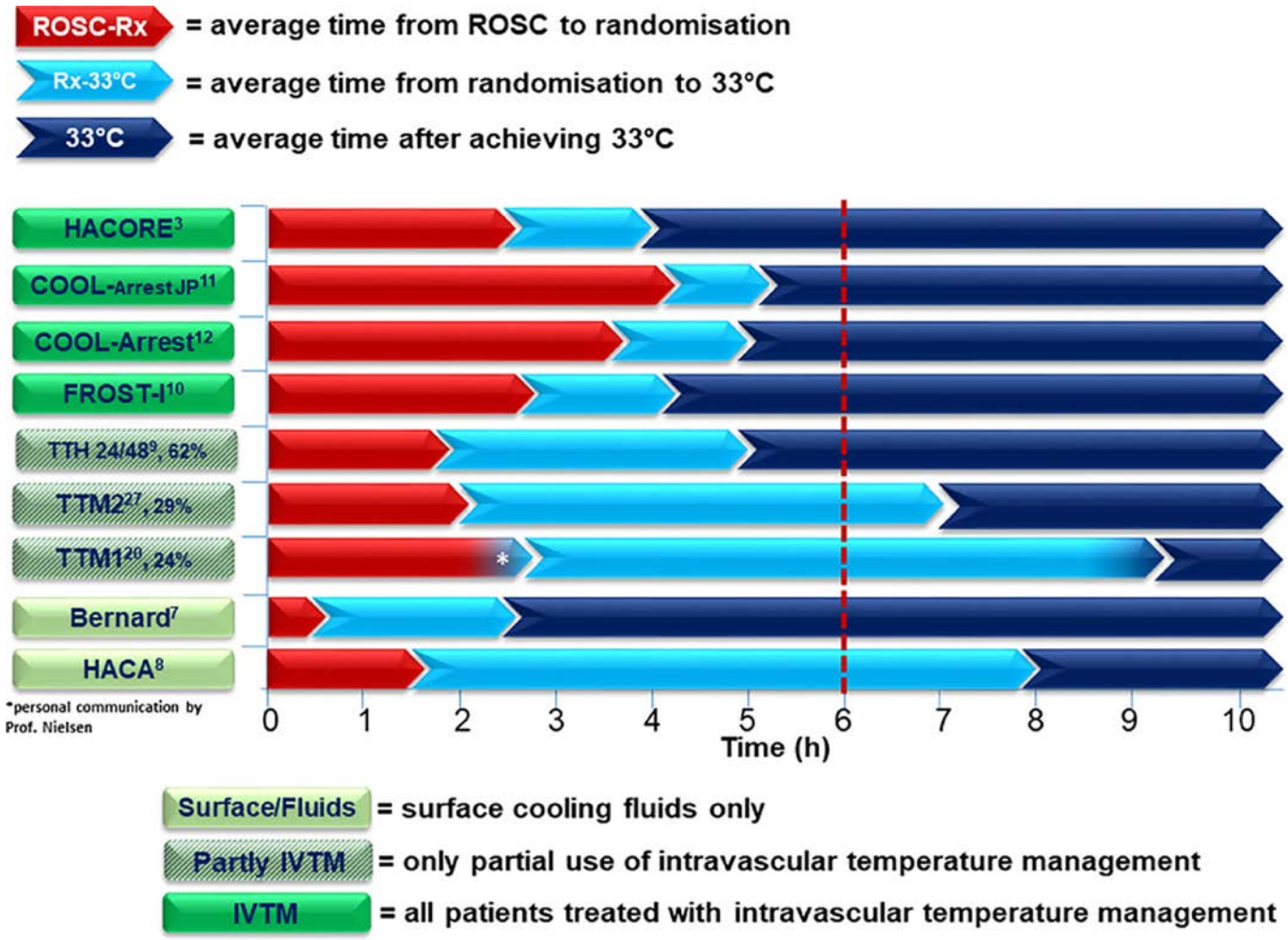
Time from CA to randomization: 135 min (ROSC-rando. ~ 110 min)
Time from Randomization to ≤34°C ~ 3h (TTM2)
Time from Randomization to ~33°C: 5h post-randomization (figure TTM2)
50% of patients reached 33°C ≥9 hours post CA for the first time



Therapeutic Hypothermia following Cardiac Arrest after the TTM2 trial – more Questions Raised than Answered

Schäfer A, Bauersachs J, Akin M. Current Problems in Cardiology. 2021





Time To Target Temperature: possiblement lié au prognostic

Uribarri et al. EHJ ACC. 2015

ttm2
Hypothermia or Early Treatment of Fever

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

Sedatives: 40 hours for TTM2 protocol

	HYPOTHERMIA		NORMOTHERMIA	
DRUG	**Participants who received drug**	**Median cumulative dose if given (IQR)**	**Participants who received drug**	**Median cumulative dose if given (IQR)**
NORADRENALINE	824/914 (90%)	24 mg (10-52 mg)	793/914 (85%)	22 mg (9-48 mg)
PROPOFOL	791/914 (85%)	8768 mg (3683-13365 mg)	819/915 (88%)	7744 mg (3183-12595 mg)
MIDAZOLAM	364/915 (39%)	117 mg (16-309 mg)	346/916 (37%)	125 mg (16-283mg)
REMIFENTANIL	326/915 (35%)	21 mg (6-39 mg)	317/915 (34%)	22 mg (8-41mg)
FENTANYL	495/914 (53%)	5 mg (2-8 mg)	477/916 (51%)	4mg (2-8 mg)
DEXMEDETOMIDINE	66/915 (7%)	1 mg (0.4-2 mg)	78/916 (8%)	1 mg (0.6-2 mg)
ACETAMINOPHEN	540/915 (58%)	4875 mg (2000-8000 mg)	661/916 (71%)	6000 mg (3000-10000 mg)
OXYCODONE	50/915 (5%)	12 mg (6-37 mg)	63/917 (7%)	12 mg (5-27 mg)
MORPHINE	98/915 (11%)	20 mg (10-130 mg)	124/916 (13%)	20 mg (10-75 mg)

?!

!

Length of sedation: 40h = similar

Degree of sedation (RASS -4) = similar

No pharmacologic adaptation according to temperature!

Guidelines ILCOR 2003-2010

Circulation — Journal of the American Heart Association — American Heart Association. Learn and Live. — European Resuscitation Council

Optimal Duration 12 to 24H for 33°C-TH
+ Duration of normothermia ≤ 37.5°C = 72H

Guidelines ILCOR 2015-2020

Optimal Duration ≥ 24H for TTM ≤ 36°C
+ Duration of normothermia ≤ 37.5°C = 72H

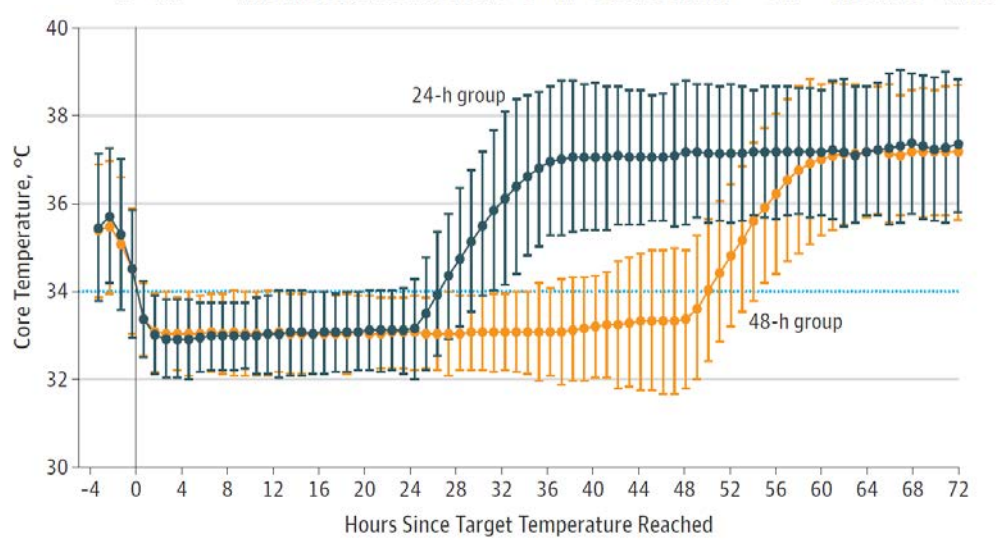
TTM2

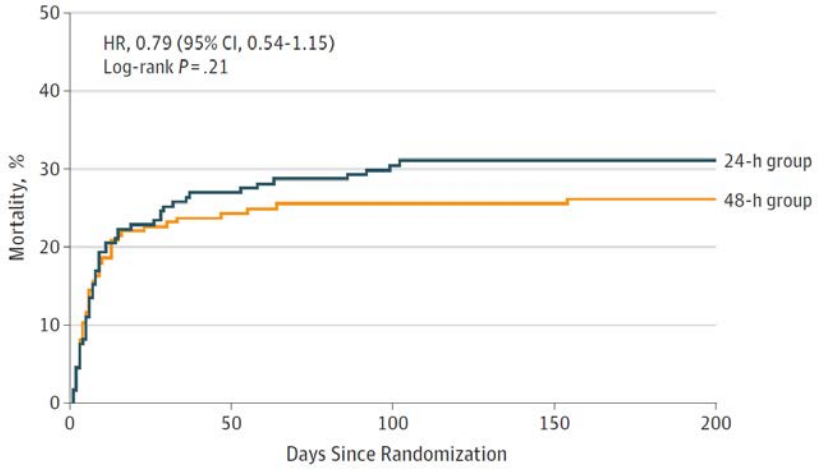
Optimal Duration 28H for TTM ≤ 33°C
+ Duration of normothermia ≤ 37.5°C = 72H

Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest
A Randomized Clinical Trial

Kikergaard
JAMA 2017

N=176 vs 179



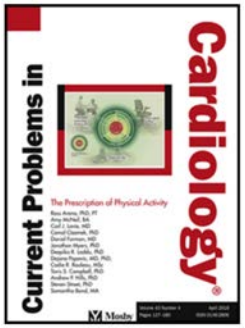


No. at risk

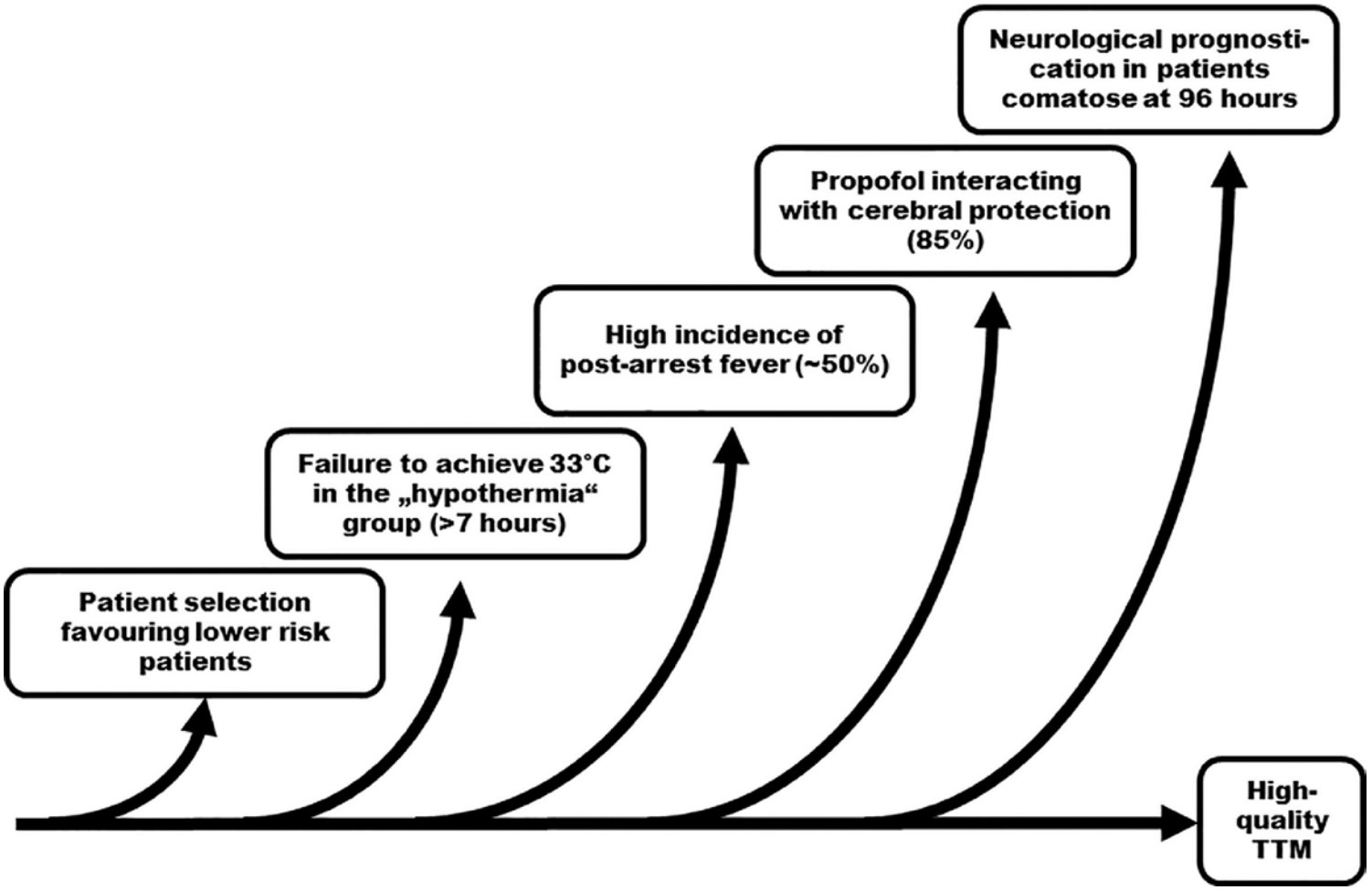
48-h group	175	131	128	128	127
24-h group	177	125	117	120	117

Therapeutic Hypothermia following Cardiac Arrest after the TTM2 trial – more Questions Raised than Answered

Schäfer A, Bauersachs J, Akin M. Current Problems in Cardiology. 2021

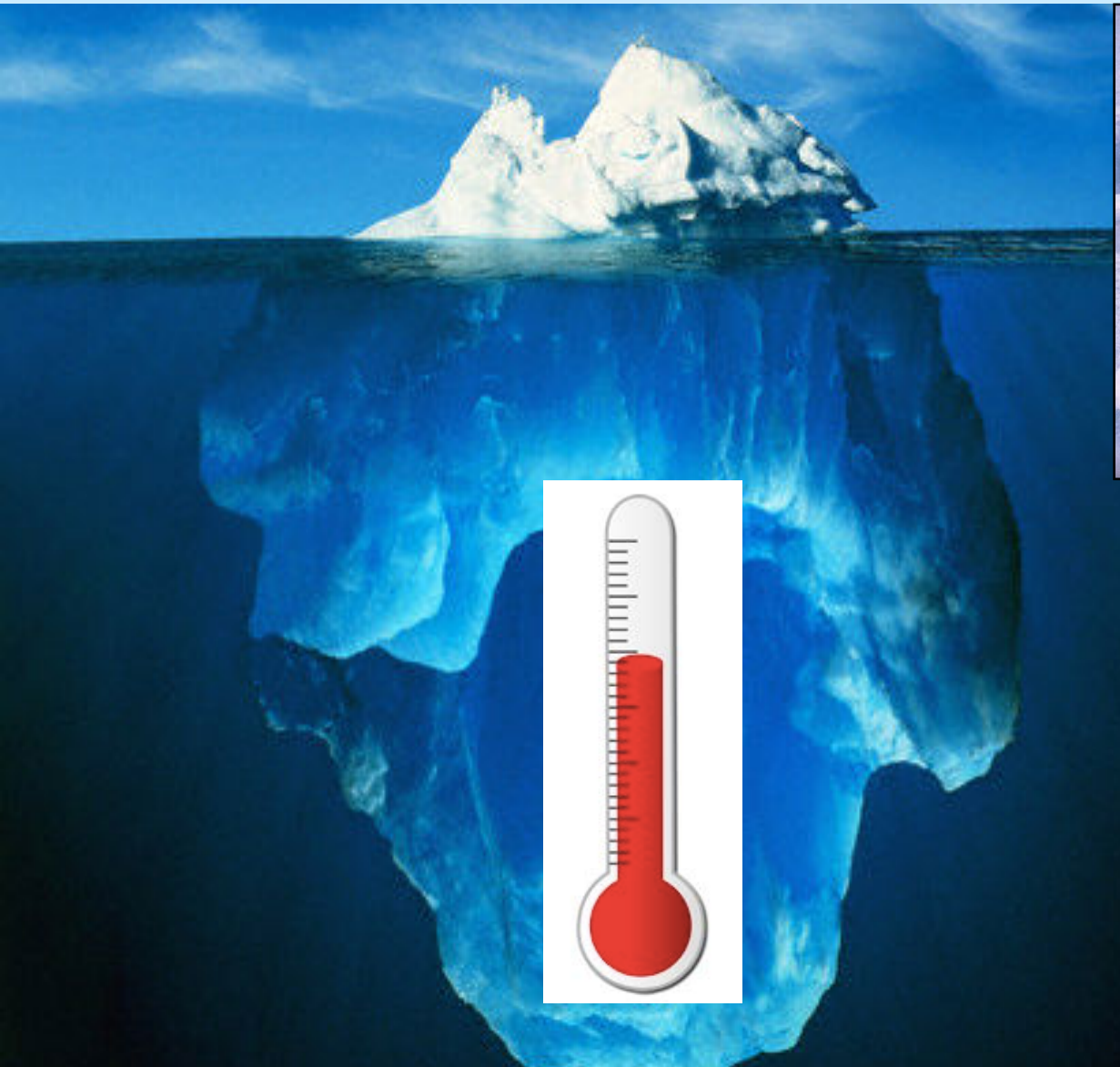


Diversion from high-quality TTM in the TTM2 trial



TH vs. TTM

Sélection: choquable-cardiaque? sévère?



	TTM-2	HACA	Bernard	TTM-1	HYPERION
Design	Multicentric	Multicentric	Single-center	Multicentric	Multicentric
N (HT group*)	1861 (930*)	275 (138*)	79 (43*)	939 (473*)	584 (284*)
Age	64±13	59 (49-67)	67 (49-89)	64±12	67 (57-76)
Male	80%	77%	58%	83%	65%
OHCA	100%	100%	100%	100%	74%

Adapted from Taccone FS, Lascarrou JB, Skrivars MB. Crit Care 2121

	TTM-2	HACA	Bernard	TTM-1	HYPERION
Design	Multicentric	Multicentric	Single-center	Multicentric	Multicentric
N (HT group*)	1861 (930*)	275 (138*)	79 (43*)	939 (473*)	584 (284*)
Age	64±13	59 (49-67)	67 (49-89)	64±12	67 (57-76)
Male	80%	77%	58%	83%	65%
OHCA	100%	100%	100%	100%	74%
CA Cause	presumed card.	presumed card.	unclear	presumed card.	asph.55% / card. 27%
Bystander CPR	82%*	49%	49%* vs. 71%	73%	70%
Shockable	72%*	96%	100%	79%	0%
Time to ROSC	25 (16-40)	22 (17-33*)	27±13	25 (18-40)	18 (10-25)
No Flow / Low Flow (min)	NR (yet)	5-15 / NR	10 / 15	1 /	<10 / <60
Shock on Admission	28%	49*	Unclear	15%	56%
STEMI	41%	NR	NR	40%	16%
Lactate	5.9±4.4	NR	8.3 (2.2-14.9)	6.7±4.5	5.8 (3.2-9.0)

Adapted from Taccone FS, Lascarrou JB, Skrivars MB. Crit Care 2121

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OHCA	100%	100%	100%	100%	74%
CA Cause	presumed card.	presumed card.	unclear	presumed card.	asph.55% / card. 27%
Bystander CPR	82%*	49%	49%*/71%	73%	70%
Shockable	72%*	96%	100%	79%	0%
Time to ROSC	25 (16-40)	22 (17-33*)	27±13	25 (18-40)	18 (10-25)
No Flow / Low Flow (min)	NR (yet)	5-15 / NR	10 / 15	1 /	<10 / <60
Shock on Admission	28%	49*	Unclear	15%	56%
STEMI	41%	NR	NR	40%	16%
Lactate	5.9±4.4	NR	8.3 (2.2-14.9)	6.7±4.5	5.8 (3.2-9.0)
Mortality	6 months	6 months	Hospital Discharge	6 months	3 months
Mortality, %	50	41	51	50	81
Unfavorable Outcome, % (assessment scale)	55 (mRS 4-6)	45* (CPC 3-5)	51* (CPC 3-5)	54 (CPC 3-5)	90* (CPC 3-5)
Prognostication Rule	Yes	No	No	Yes	Yes
Generalizability / Bias	High/Low	Low/High	Low/High	High/Low	High/Moderate

Adapted from Taccone FS, Lascarrou JB, Skrivars MB. Crit Care 2121

Therapeutic Hypothermia following Cardiac Arrest after the TTM2 trial – more Questions Raised than Answered

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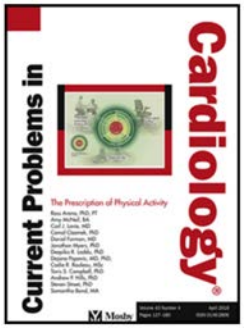
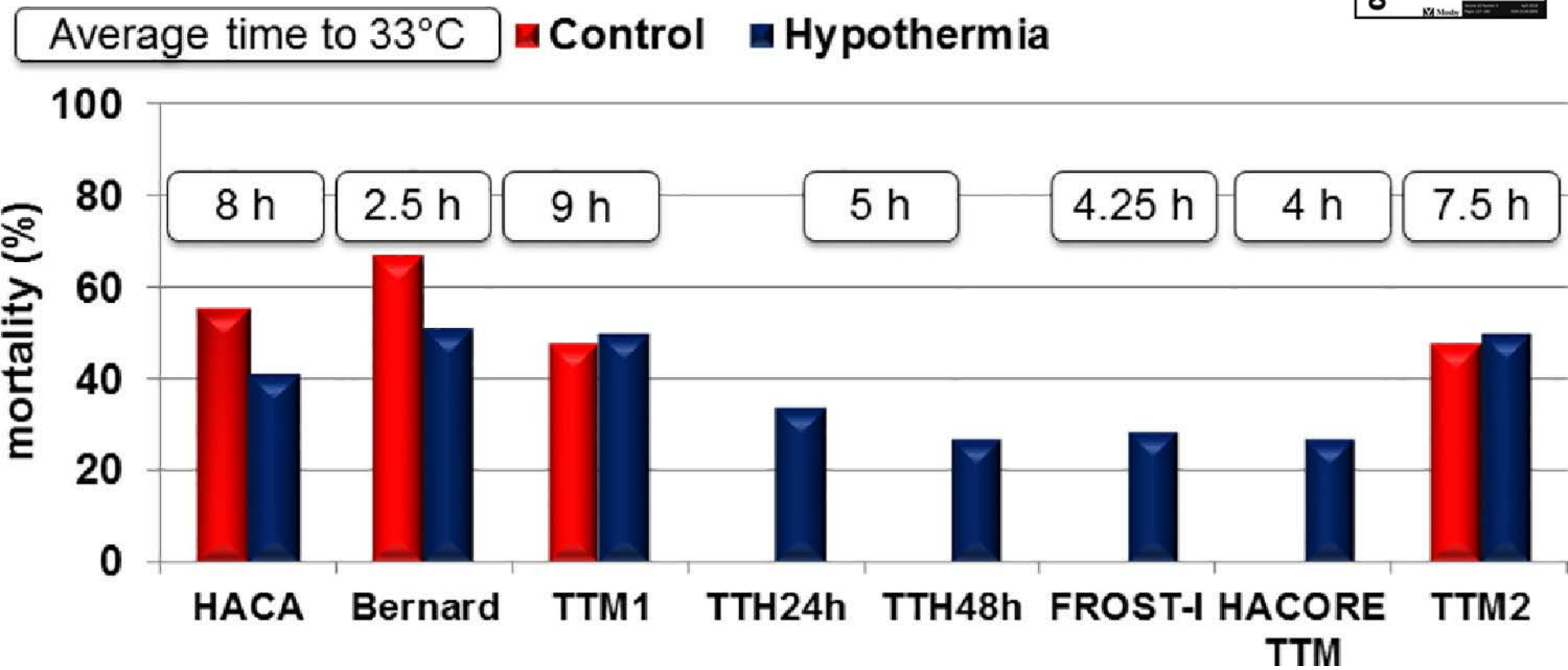




Population of TTM2 trial compared with other registries /studies

	OHCA Patient Characteristics Comparison Date		TTM2 Patient Characteristics
	2018 US Pennsylvania data [1]	2020 German Resus Registry [2]	2018-2020 TTM2
Gender, male, %	62%	66%	80%
Witnessed arrest	75.7%	49%	91%
Bystander CPR	39%	35.9%	82%
Presumed cardiac cause	55%	57.8%	100%
Initial shockable rhythm	26.8%	20.2%	72%
Shock	41.6%	---	28%
STEMI	12.4%	30.7%	41%

1. Fischer, M, et al. Öffentlicher Jahresbericht 2020 des Deutschen Reanimationsregisters: Außerklinische Reanimation 2020. www. Reanimationsregisters.de/beriche.html

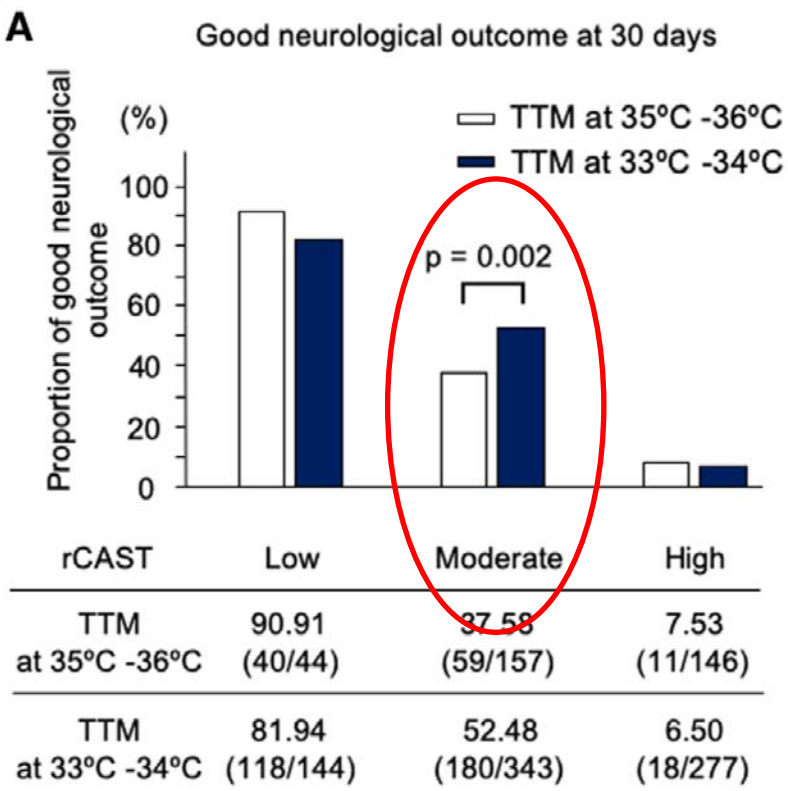
2. Callaway CW, et al. Association of Initial Illness Severity and Outcomes After Cardiac Arrest With Targeted Temperature Management at 36 ° C or 33 ° C. JAMA Network Open. 2020;3:e208215.

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

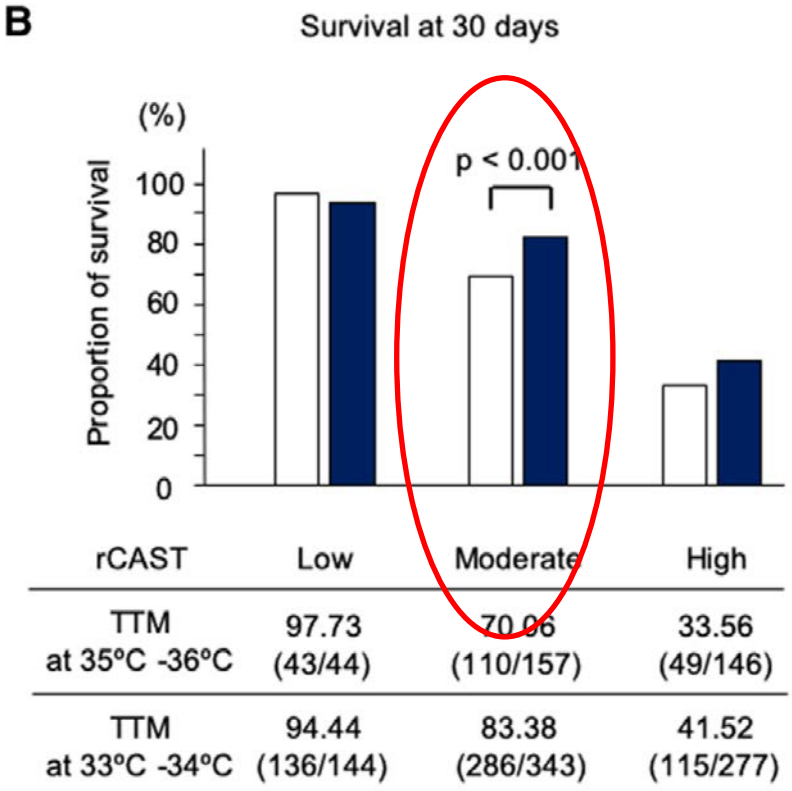
Critical Care Medicine 2021
Nishikimi N, et al.

N = 1111 OHCA with TTM in 125 ICUs
3 severity revised CAST categories (PCAS for TH: rhythm, witness, time to ROSC, pH, lactate, mGCS)

Multivariate analysis showed that targeted temperature management at 33–34°C was significantly associated with a good neurologic outcome and survival at 30 days in the moderate severity (odds ratio, 1.70 [95% CI, 1.03–2.83] and 1.90 [95% CI, 1.15–3.16], respectively), but not in the patients of low or high severity ($p_{interaction} = 0.033$). Propensity score analysis also showed that targeted temperature management at 33–34°C was associated with a good neurologic outcome in the moderate-severity group ($p = 0.022$).

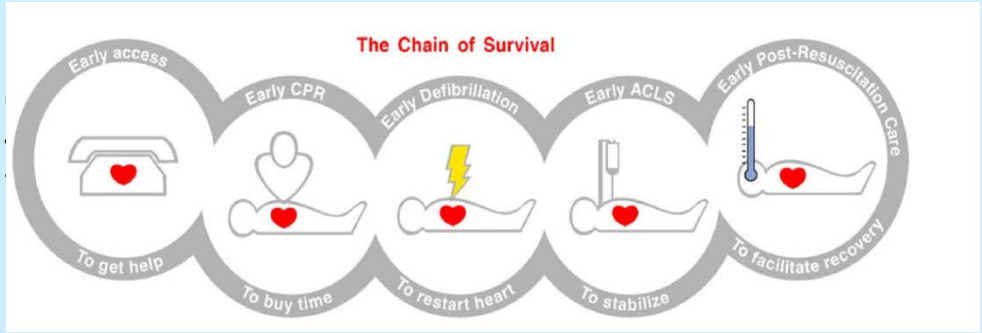


rCAST	Low	Moderate	High
TTM at 35°C -36°C	90.91 (40/44)	37.58 (59/157)	7.53 (11/146)
TTM at 33°C -34°C	81.94 (118/144)	52.48 (180/343)	6.50 (18/277)



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)

GESTION DE LA TEMPERATURE APRES ARRET CARDIAQUE



Historique
Pro TTM2
Con TTM2
Conclusions « thermiques » en 2021

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

Asger Granfeldt[a,1], Mathias J. Holmberg[b,c,1], Jerry P. Nolan[d,e], Jasmeet Soar[f], Lars W. Andersen[a,b,g,], for the International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force[2]*

EUROPEAN RESUSCITATION COUNCIL

Resuscitation 2021

N=32 trials (138 assessed for eligibility, 39 articles)

32-34 TTM vs. NT: 9 trials, 6 included in meta-analysis

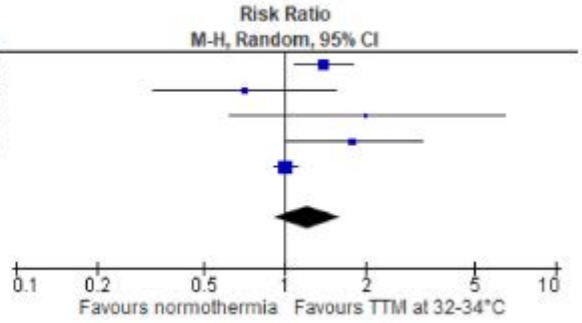
analyses. Targeted temperature management with a target of 32–34 °C did not result in an improvement in survival (risk ratio: 1.08 [95%CI: 0.89, 1.30]) or favorable neurologic outcome (risk ratio: 1.21 [95%CI: 0.91, 1.61]) at 90 to 180 days after the cardiac arrest (low certainty of evidence). Three trials assessed different hypothermic temperature targets and found no difference in outcomes (low certainty of evidence). Ten trials were identified comparing prehospital cooling vs. no prehospital cooling with no improvement in survival (risk ratio: 1.01 [95%CI: 0.92, 1.11]) or favorable neurologic outcome (risk ratio: 1.00 [95%CI: 0.90, 1.11]) at hospital discharge (moderate certainty of evidence).

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	30.7%	1.40 [1.08, 1.81]	2002
Laurent, 2005	7	22	9	20	10.0%	0.71 [0.32, 1.54]	2005
Hachimi-Idrissi, 2005	6	14	3	14	5.1%	2.00 [0.62, 6.45]	2005
Lascarrou, 2019	29	284	17	297	15.2%	1.78 [1.00, 3.17]	2019
Dankiewicz, 2021	423	918	418	911	39.0%	1.00 [0.91, 1.11]	2021
Total (95% CI)		**1374**		**1379**	**100.0%**	**1.21 [0.91, 1.61]**	
Total events	540		501				

Heterogeneity: Tau² = 0.05; Chi² = 10.97, df = 4 (P = 0.03); I² = 64%

Test for overall effect: Z = 1.34 (P = 0.18)



Similar for survival

Conclusions: Among adult patients with cardiac arrest, the use of targeted temperature management at 32–34 °C, when compared to normothermia, did not result in improved outcomes in this meta-analysis. There was no effect of initiating targeted temperature management prior to hospital arrival. These findings warrant an update of international cardiac arrest guidelines.

Meta-analyses of targeted temperature management in adult cardiac arrest studies – The big picture is dependent on study selection

Behringer W, Abella B, Sunde K. Resuscitation 2021

EUROPEAN RESUSCITATION COUNCIL

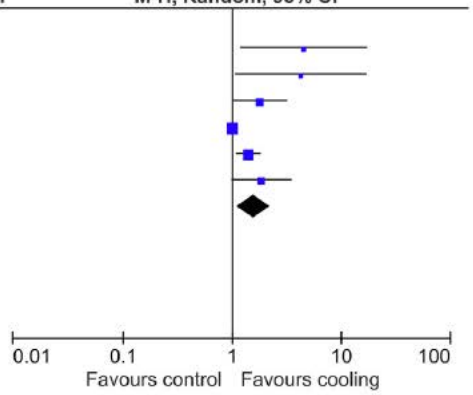
Letter to the Editor

Study or Subgroup	cooling to 33°C Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Cooling versus all else						
Mori 2000	18	36	2	18	5.6%	4.50 [1.17, 17.30]
Hachimi-Idrissi 2001	8	16	2	17	5.3%	4.25 [1.06, 17.08]
Lascarrou 2019	29	284	17	297	16.9%	1.78 [1.00, 3.17]
Dankiewicz 2021	423	918	418	911	30.2%	1.00 [0.91, 1.11]
HACA 2002	75	136	54	137	26.6%	1.40 [1.08, 1.81]
Bernard 2002	21	43	9	34	15.3%	1.84 [0.97, 3.49]
Subtotal (95% CI)		**1433**		**1414**	**100.0%**	**1.56 [1.10, 2.21]**
Total events	574		502			

Heterogeneity: Tau² = 0.10; Chi² = 19.99, df = 5 (P = 0.001); I² = 75%

Test for overall effect: Z = 2.47 (P = 0.01)

Test for subgroup differences: Not applicable

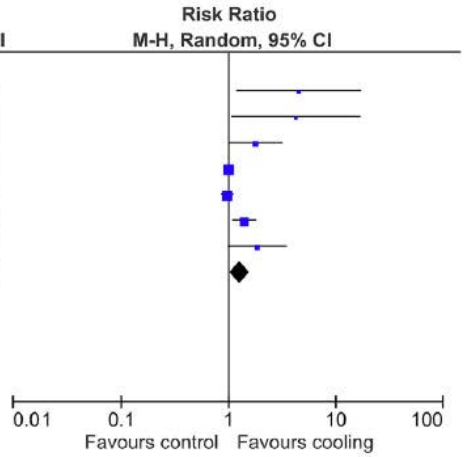


Study or Subgroup	cooling to 33°C Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Cooling versus all else						
Mori 2000	18	36	2	18	2.4%	4.50 [1.17, 17.30]
Hachimi-Idrissi 2001	8	16	2	17	2.3%	4.25 [1.06, 17.08]
Lascarrou 2019	29	284	17	297	9.7%	1.78 [1.00, 3.17]
Dankiewicz 2021	423	918	418	911	28.6%	1.00 [0.91, 1.11]
Nielsen 2013	218	469	222	464	27.2%	0.97 [0.85, 1.11]
HACA 2002	75	136	54	137	21.4%	1.40 [1.08, 1.81]
Bernard 2002	21	43	9	34	8.4%	1.84 [0.97, 3.49]
Subtotal (95% CI)		**1902**		**1878**	**100.0%**	**1.27 [1.02, 1.58]**
Total events	792		724			

Heterogeneity: Tau² = 0.04; Chi² = 21.76, df = 6 (P = 0.001); I² = 72%

Test for overall effect: Z = 2.18 (P = 0.03)

Test for subgroup differences: Not applicable



All available RCTs with outcome evaluation at 6 months after CA (random effects analyses of 32-34TTM compared to NT for good neurologic outcome; if Mori excluded, close results: OR 1.43 (CI 1.01-2.02), P=0.04; RR 1.21 (0.99-1.48, P=0.06)

ILCOR GUIDELINES - PROPOSAL 2021

Soar J, Nolan JP, Andersen LW, Böttinger BW, Couper K, Deakin CD, Drennan I, Hirsch KG, Nicholson TC, O'Neil BJ, Paiva EF, Parr MJ, Reynolds JC, Sandroni C, Wang TL, Callaway CW, Donnino MW, Granfeldt A, Holmberg MJ, Lavonas EJ, Morrisson LJ, Nation K, Neumar RW, Nikolaou, Skrifvars MB, Welsford M, Morley PT, Berg KM.

Defining Post-Cardiac Arrest Temperature Management Strategies

- *The term TTM on its own is not helpful and it is preferable to use the terms active temperature control, hypothermia, normothermia, or fever prevention. To provide additional clarity for interpreting future clinical trials, systematic reviews and CoSTRs we propose the following terms are used:*
  - *Hypothermic TTM (H-TTM) = active temperature control with the target temperature below the normal range.*
  - *Normothermic TTM = active temperature control with the target temperature in the normal range.*
  - *Fever prevention TTM (FP-TTM) = monitoring temperature and actively preventing and treating temperature above the normal range*
  - *No TTM = no protocolised active temperature control strategy.*

Recommendation

We suggest actively preventing fever by targeting a temperature ≤37.5 for those patients who remain comatose after ROSC from cardiac arrest (weak recommendation, low certainty evidence).

Whether subpopulations of cardiac arrest patients may benefit from targeting hypothermia at 32-34°C remains uncertain.

Comatose patients with mild hypothermia after ROSC should not be actively warmed to achieve normothermia (good practice statement).

Targeted Temperature Management after Cardiac Arrest: A Systematic Review and Meta-Analysis with Trial Sequential Analysis

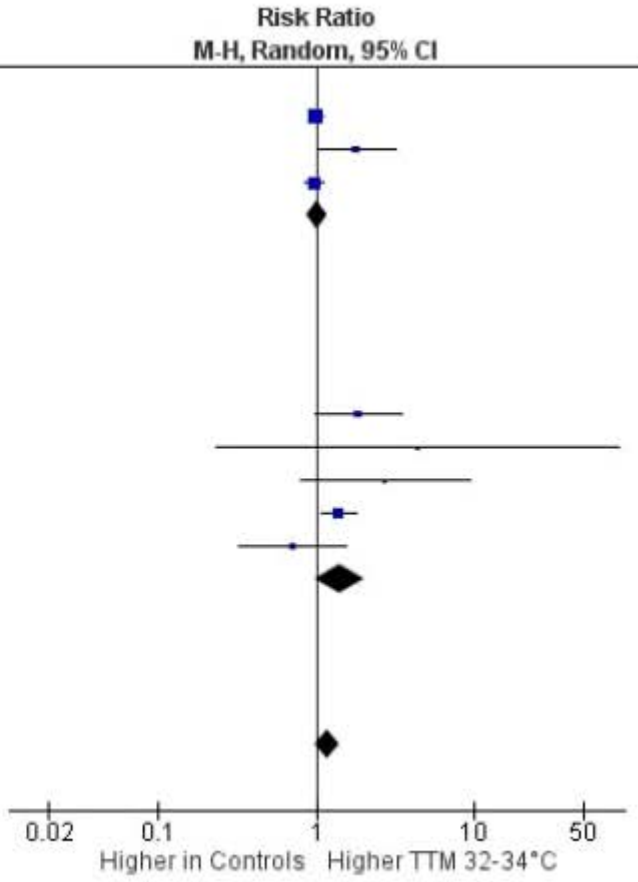
2021

Filippo Sanfilippo [1,*,†], Luigi La Via [1,2,†], Bruno Lanzafame [1,2], Veronica Dezio [1,2], Diana Busalacchi Antonio Messina [3,4], Giuseppe Ristagno [5], Paolo Pelosi [6,7] and Marinella Astuto [1,2]

Journal of *Clinical Medicine*

N=8 trials (77 assessed for eligibility)

Study or Subgroup	TTM 32-34°C Events	Total	TTM 36°C or SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Actively controlled normothermia						
Dankiewicz, New Engl J Med 2021	393	881	387	866	29.8%	1.00 [0.90, 1.11]
Lascarrou, New Engl J Med 2019	29	284	17	297	7.9%	1.78 [1.00, 3.17]
Nielsen, New Engl J Med 2013	218	469	222	464	28.0%	0.97 [0.85, 1.11]
Subtotal (95% CI)		**1634**		**1627**	**65.7%**	**1.02 [0.88, 1.18]**
Total events	640		626			
Heterogeneity: Tau² = 0.01; Chi² = 4.10, df = 2 (P = 0.13); I² = 51%						
Test for overall effect: Z = 0.27 (P = 0.79)						
1.2.2 Passively controlled normothermia						
Bernard, New Engl J Med 2002	21	43	9	34	6.7%	1.84 [0.97, 3.49]
Hachimi-idrissi, Resuscitation 2001	2	16	0	14	0.4%	4.41 [0.23, 84.79]
Hachimi-idrissi, Resuscitation 2005	8	30	3	31	2.1%	2.76 [0.81, 9.41]
Holzer, New Engl J Med 2002	75	136	54	137	20.2%	1.40 [1.08, 1.81]
Laurent, JACC 2005	7	22	9	20	4.8%	0.71 [0.32, 1.54]
Subtotal (95% CI)		**247**		**236**	**34.3%**	**1.42 [0.99, 2.04]**
Total events	113		75			
Heterogeneity: Tau² = 0.05; Chi² = 5.46, df = 4 (P = 0.24); I² = 27%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Total (95% CI)		**1881**		**1863**	**100.0%**	**1.17 [0.97, 1.41]**
Total events	753		701			
Heterogeneity: Tau² = 0.03; Chi² = 17.55, df = 7 (P = 0.01); I² = 60%						
Test for overall effect: Z = 1.66 (P = 0.10)						
Test for subgroup differences: Chi² = 2.87, df = 1 (P = 0.09), I² = 65.1%						

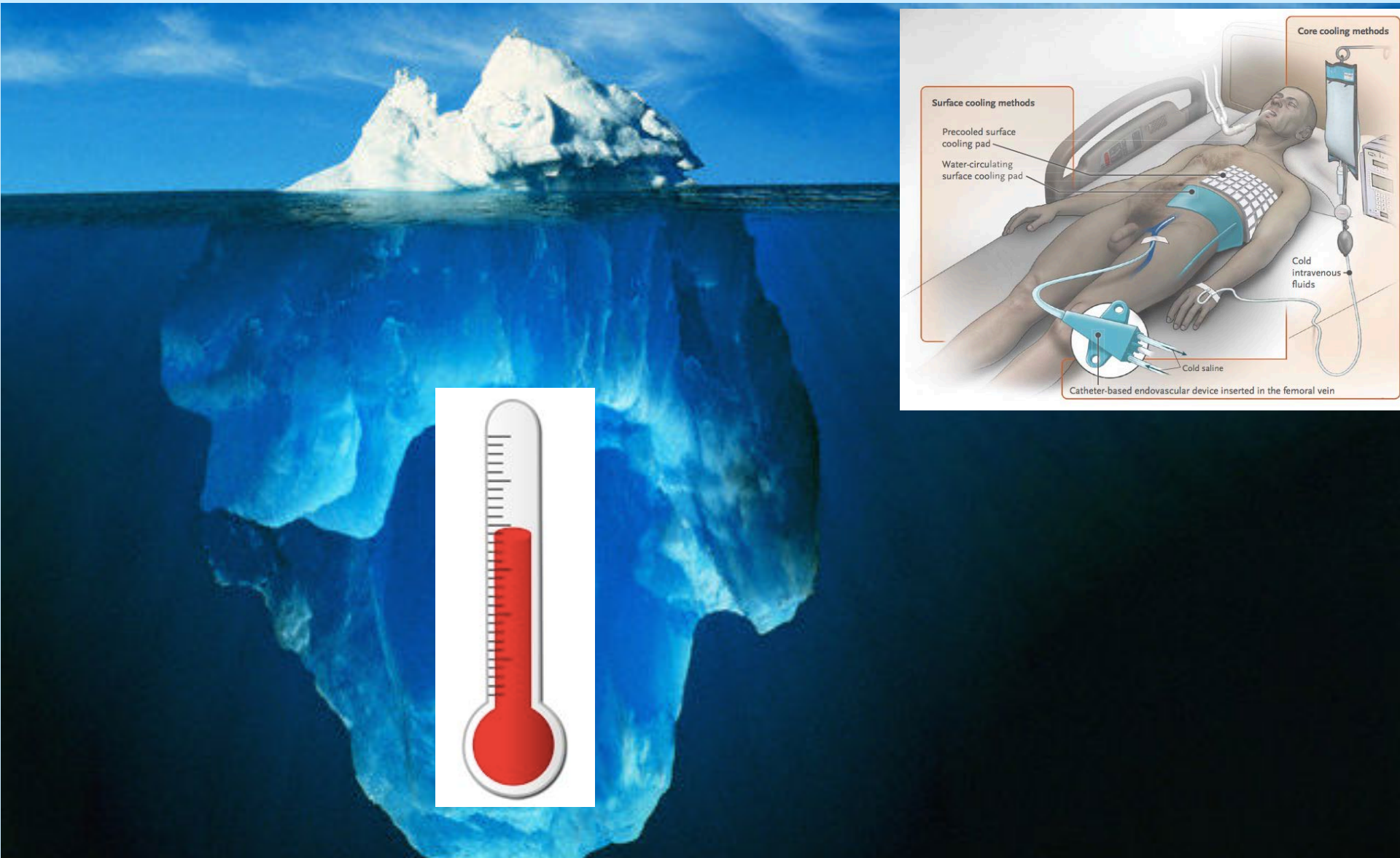


Similar for survival

Neurologic outcome

OPTIMIZING TTM/TH PROTOCOL

METHOD? Advanced (no basic)



CONTROLE CIBLE DE LA TEMPERATURE EN REANIMATION (HORS NOUVEAU-NES)

Recommandations Formalisées d'Experts commune SRLF- SFAR

En collaboration avec les Sociétés ANARLF, GFRUP, SFMU et SFNV

Association de Neuro Anesthésie Réanimation de Langue Française, Groupe Francophone de Réanimation et Urgences Pédiatriques, Société Française de Médecine d'Urgence, Société Française de Neuro-Vasculaire

Modalités de mise en œuvre et surveillance du CCT (question 6)

R6.1 - Chez les patients traités par CCT, il faut utiliser des méthodes asservies à la température corporelle par comparaison aux méthodes non asservies dans le but d'améliorer la qualité du CCT.

(Grade 1+) Accord FORT

Alain Cariou, JF Payen et al. AIC 2017

ILCOR GUIDELINES - PROPOSAL 2021

Soar J, Nolan JP, Andersen LW, Böttinger BW, Couper K, Deakin CD, Drennan I, Hirsch KG, Nicholson TC, O'Neil BJ, Paiva EF, Parr MJ, Reynolds JC, Sandroni C, Wang TL, Callaway CW, Donnino MW, Granfeldt A, Holmberg MJ, Lavonas EJ, Morrisson LJ, Nation K, Neumar RW, Nikolaou, Skrifvars MB, Welsford M, Morley PT, Berg KM.

Should endovascular cooling vs. surface cooling be used for cardiac arrest?

Recommendation

We suggest surface or endovascular temperature control techniques when temperature control is used in comatose patients after ROSC (weak recommendation, low certainty of evidence).

When a cooling device is used, we suggest using a temperature control device that includes a feedback system based on continuous temperature monitoring to maintain the target temperature (good practice statement).

We recommend against the routine use of prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC (strong recommendation, moderate certainty evidence)

Justification

Cooling devices

· Task Force members agreed that based on our SR either surface or endovascular cooling should be suggested.

· There is no consensus on whether a feedback surface cooling device should be routinely used so this was added as a good practice statement as there is no evidence this approach improves outcomes. There was consensus that temperature should be continually monitored by the cooling device in order to maintain a stable temperature.

There was a comment that endovascular cooling is superior – there are two recent SRs with conflicting conclusions: Bartlett ES (Resuscitation 2020 82) showed intravascular cooling is associated with improved neurological outcome, and Kim JG (Resuscitation 2020 14) found no associated with survival or neurological outcomes.

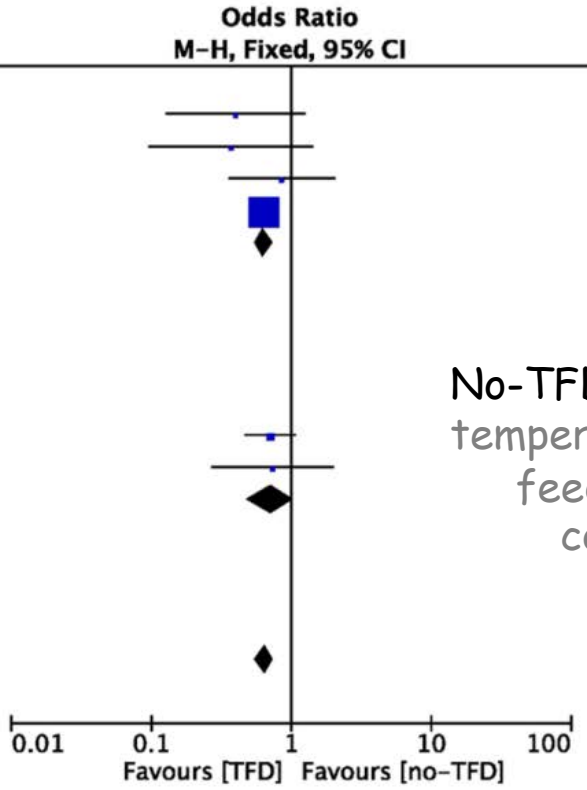
Effect of different methods of cooling for targeted temperature management on outcome after cardiac arrest: a systematic review and meta-analysis

Lorenzo Calabrò[1†], Wulfran Bougouin[2,3,4†], Alain Cariou[3,4,5], Chiara De Fazio[1], Markus Skrifvars[6], Eldar Soreide[7], Jacques Creteur[1], Hans Kirkegaard[8], Stéphane Legriel[9], Jean-Baptiste Lascarrou[10], Bruno Megarbane[11], Nicolas Deye[11†] and Fabio Silvio Taccone[1*†]

Critical Care 2019

22 studies among 46 elligible (out of 6686 screened)

Study or Subgroup	TFD Events	TFD Total	no-TFD Events	no-TFD Total	Weight	Odds Ratio M-H, Fixed, 95% CI
5.2.1 no RCT						
Ferreira et al.	9	24	15	25	1.9%	0.40 [0.13, 1.26]
Feutchel et al.	10	19	15	20	1.4%	0.37 [0.10, 1.44]
Gillies et al.	24	42	25	41	2.2%	0.85 [0.36, 2.05]
Kim et al.	1896	2483	1472	1763	82.3%	0.64 [0.55, 0.75]
Subtotal (95% CI)		**2568**		**1849**	**87.8%**	**0.63 [0.55, 0.74]**
Total events	1939		1527			
Heterogeneity: $Chi^2 = 1.67$, df = 3 (P = 0.64); $I^2 = 0\%$						
Test for overall effect: Z = 5.89 (P < 0.00001)						
5.2.2 RCT						
Deye et al.	130	203	141	197	10.4%	0.71 [0.46, 1.08]
Heard et al.	19	34	19	30	1.8%	0.73 [0.27, 2.00]
Subtotal (95% CI)		**237**		**227**	**12.2%**	**0.71 [0.48, 1.05]**
Total events	149		160			
Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.95); $I^2 = 0\%$						
Test for overall effect: Z = 1.72 (P = 0.09)						
Total (95% CI)		**2805**		**2076**	**100.0%**	**0.64 [0.56, 0.74]**
Total events	2088		1687			
Heterogeneity: $Chi^2 = 1.96$, df = 5 (P = 0.85); $I^2 = 0\%$						
Test for overall effect: Z = 6.12 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 0.29$, df = 1 (P = 0.59), $I^2 = 0\%$						



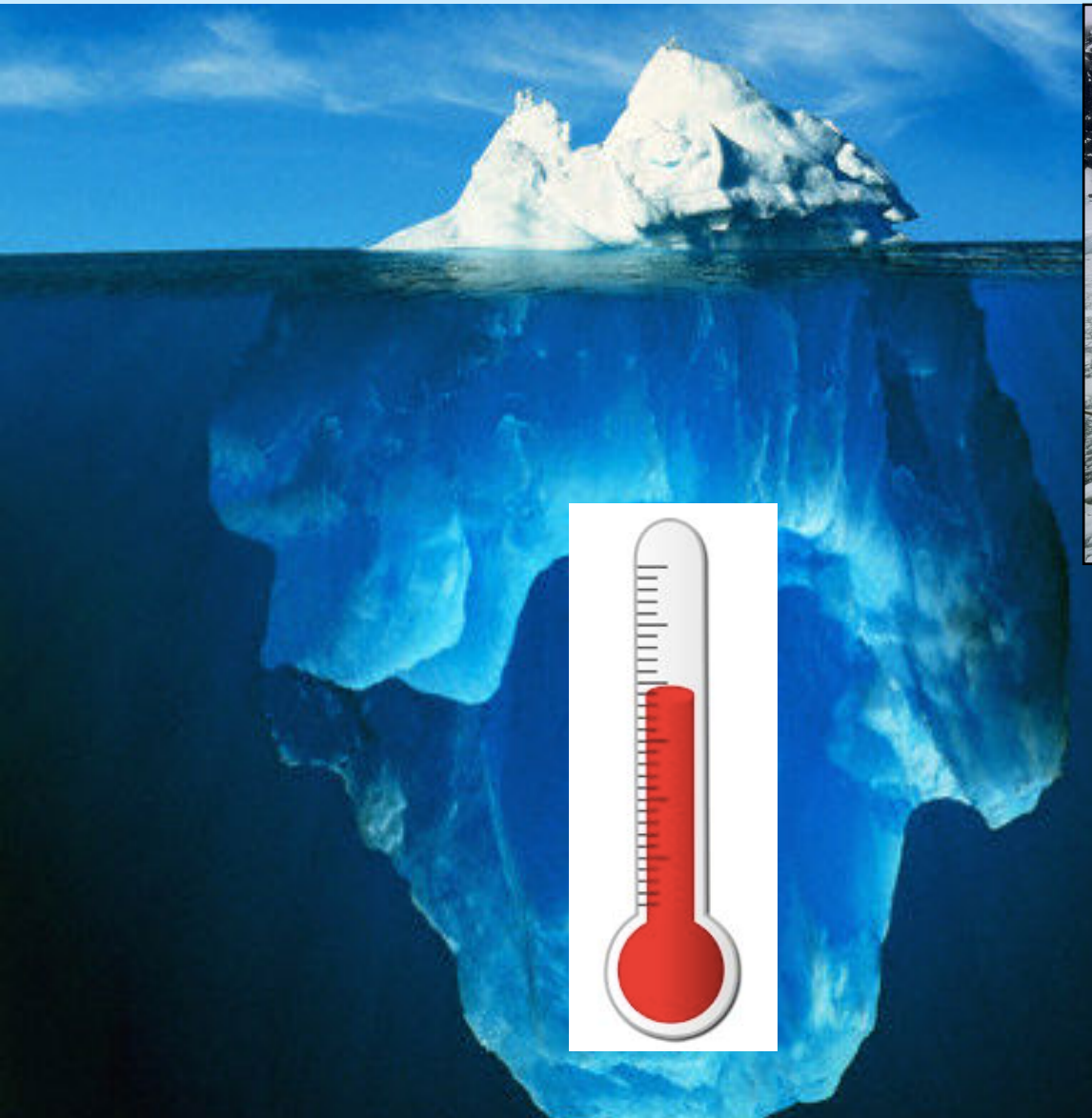
No-TFD = no temperature feedback control

Unfavorable outcome (Sign. for mortality in non-RCTs)

Conclusions: Although existing literature is mostly based on retrospective or prospective studies, specific TTM methods (i.e., core, invasive, and with TFD) were associated with a lower probability of poor neurological outcome when compared to other methods in adult CA survivors (CRD42019111021).

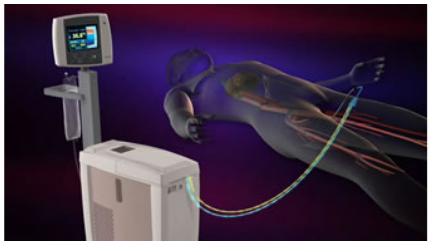
TH vs. TTM

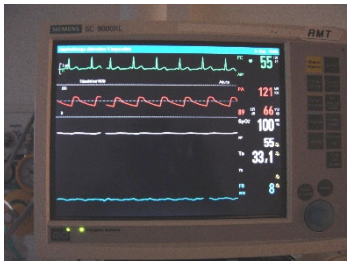
PROTOCOL, MONITORING, ACSOS



CONTROLE CIBLE DE LA TEMPERATURE EN REANIMATION (HORS NOUVEAU-NES)

Recommandations Formalisées d'Experts





Toutes les études publiées sur TH/TTM utilisent un monitorage continu (central)

Modalités de mise en œuvre et surveillance du CCT (question 6)

R6.3 - Chez les patients traités par CCT, il faut probablement privilégier des sites de mesure de température centrale.

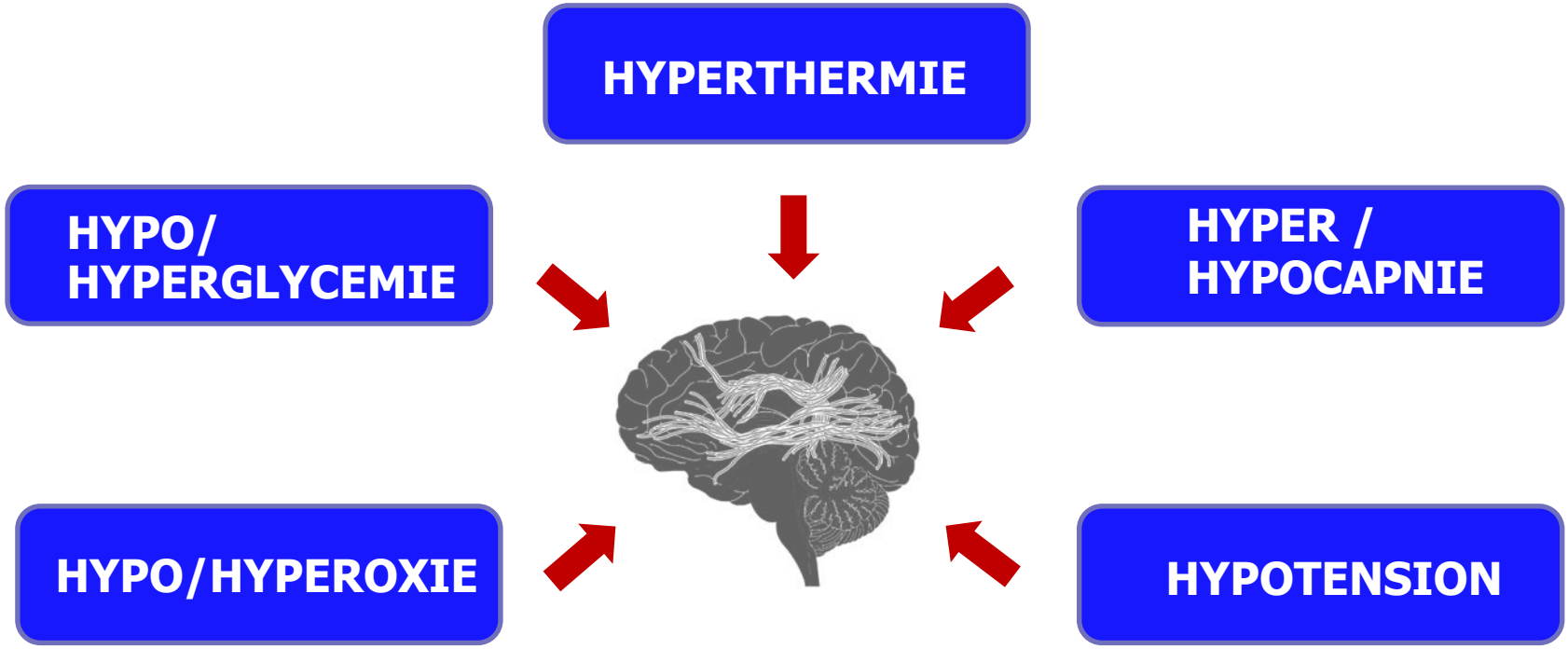
(Grade 2+) Accord FORT

Niven et al. Ann Med Int 2016

Alain Cariou, JF Payen et al. 2016

TTT DES AGRESSIONS CÉRÉBRALES SECONDAIRES D'ORIGINE SYSTÉMIQUE

Post-CA care (from 2000 to 2020):
Meilleure prise en charge en réanimation =
moins d'effet de la température sur le pronostic?



Treatments of potential secondary insults (reperfusion...): short acting sedatives & opioids, target blood glucose, shivering, seizures, antibiotics if needed

ERC & ESICM guidelines: post-CA care. Nolan et al. ICM 2021

Practical protocol for treatment of patients

Sedatives (propofol)
Analgesics (remifentanil…)
Neuromuscular blockers (if necessary)

Normoxia in controlled MV (PaO_2: 60-200mmHg)

Normocapnia (4.9-5.5 kPa = 37-42 mmHg)

Hemodynamic optimization (and cerebral perfusion pressure), euvolemia (SAP > 90 mmHg, MAP ≥ 70 mmHg, diuresis ≥ 1ml/kg/h)

No fever (temp. <37.5° C) / High-quality TTM

Normo-natremia, -kaliemia, -magnesemia, -phosphoremia, -calcemia

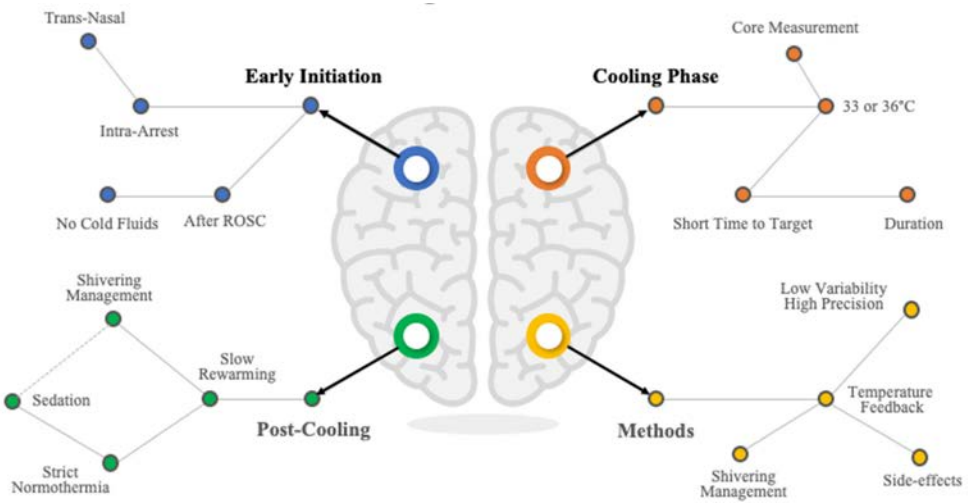
Normoglycemia (insuline protocol to treat hyperglycemia > 1.80 g/L (>10 mmol/L), hypoglycemia avoided, target within 12H after CA : 1.16-1.43 g/L**)**

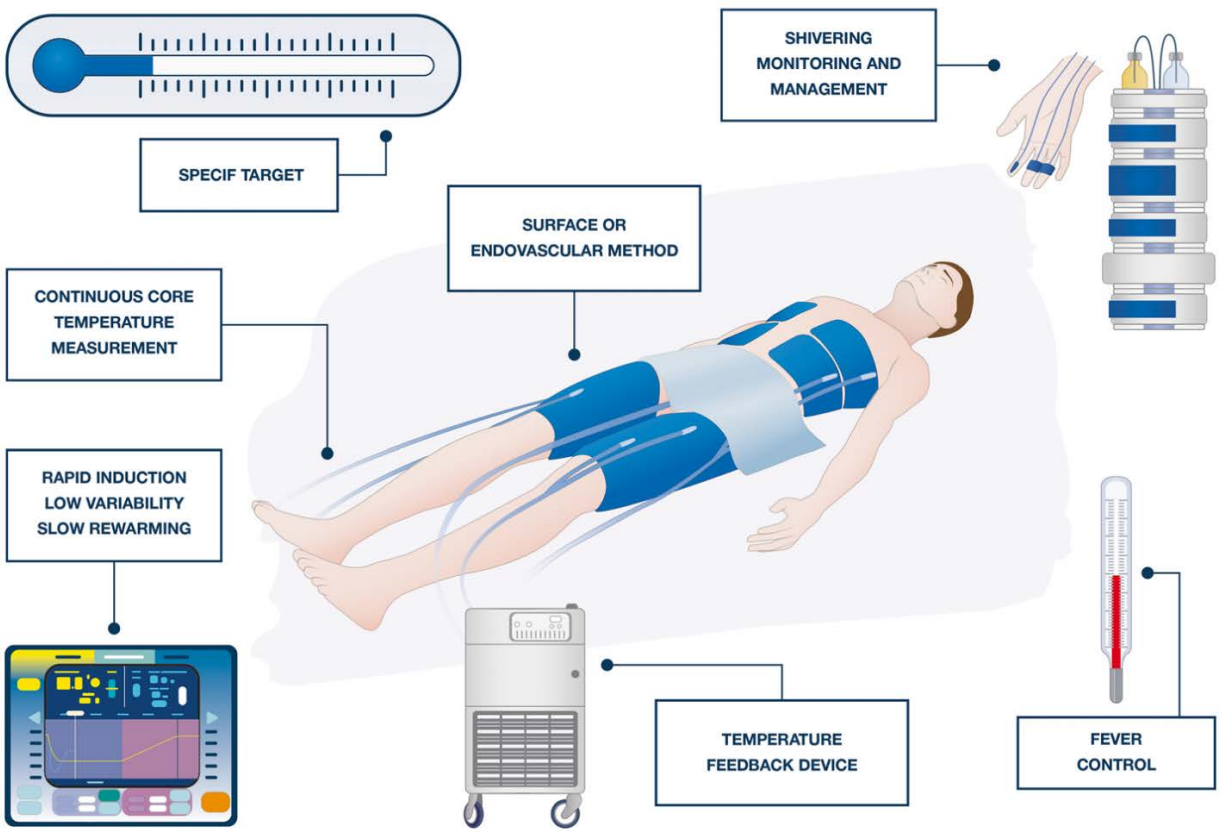
Semi-recumbent position in bed (30-45°)

Prophylactic treatments: heparin, anti-arrhythmics

STANDARDIZATION OF WLST

High quality TTM after CA
Taccone FS, et al.
Crit Care 2020





The NEW ENGLAND JOURNAL of MEDICINE

Translating Targeted Temperature Management Trials into Postarrest Care

Laurie J. Morrison, M.D., and Brent Thoma, M.D.

clinicians should be that targeted temperature management involving pharmacotherapy, device cooling, and timely neurologic prognostication is a crucial treatment strategy to improve outcomes in patients who have had a cardiac arrest. The target temperature, at the discretion of the clinician, could be 33°C, 36°C, or 37.5°C or less.

Other subgroups (excluded from trials)
TTM2 substudies waited:
comparaison des groupes NT + fièvre vs. NT sans fièvre +++


CONCLUSION
TEMPERATURE CONTROL
FOR ALL,
NO HYPERTHERMIA!
ANY
QUESTIONS?

ILCOR GUIDELINES - PROPOSAL 2021

Soar J, Nolan JP, Andersen LW, Böttinger BW, Couper K, Deakin CD, Drennan I, Hirsch KG, Nicholson TC, O'Neil BJ, Paiva EF, Parr MJ, Reynolds JC, Sandroni C, Wang TL, Callaway CW, Donnino MW, Granfeldt A, Holmberg MJ, Lavonas EJ, Morrisson LJ, Nation K, Neumar RW, Nikolaou, Skrifvars MB, Welsford M, Morley PT, Berg KM.

Research priorities

- *There are no RCTs of no TTM versus fever prevention TTM.*
- *There are few RCTs of TTM after eCPR.*
- *There are no large RCTs of TTM after in-hospital cardiac arrest.*
- *Is there a therapeutic window within which hypothermic TTM (H-TTM) is effective in the clinical setting?*
- *If a therapeutic window exists, are there clinically feasible cooling strategies that can rapidly achieve therapeutic target temperatures within the therapeutic window?*
- *Is the clinical effectiveness of hypothermia dependent on providing the appropriate dose (target temperature and duration) based on the severity of brain injury?*
- *Are there unidentified subsets of post-cardiac arrest patient who would benefit from H-TTM as currently practiced?*
- *Is TTM using a cooling device with feedback more effective than TTM without a feedback controlled cooling device?*

TTM2 SUBGROUP ANALYSES & ANCILLARY STUDIES MANDATORY

WHO ARE THESE FEBRILE PATIENTS = ???

PROGNOSIS ? ROLE OF FEVER ? CAUSES OF FEVER ?