OPTIMISATION DU CONTRÔLE THERMIQUE APRES ARRET CARDIAQUE: des ACSOS au CCT

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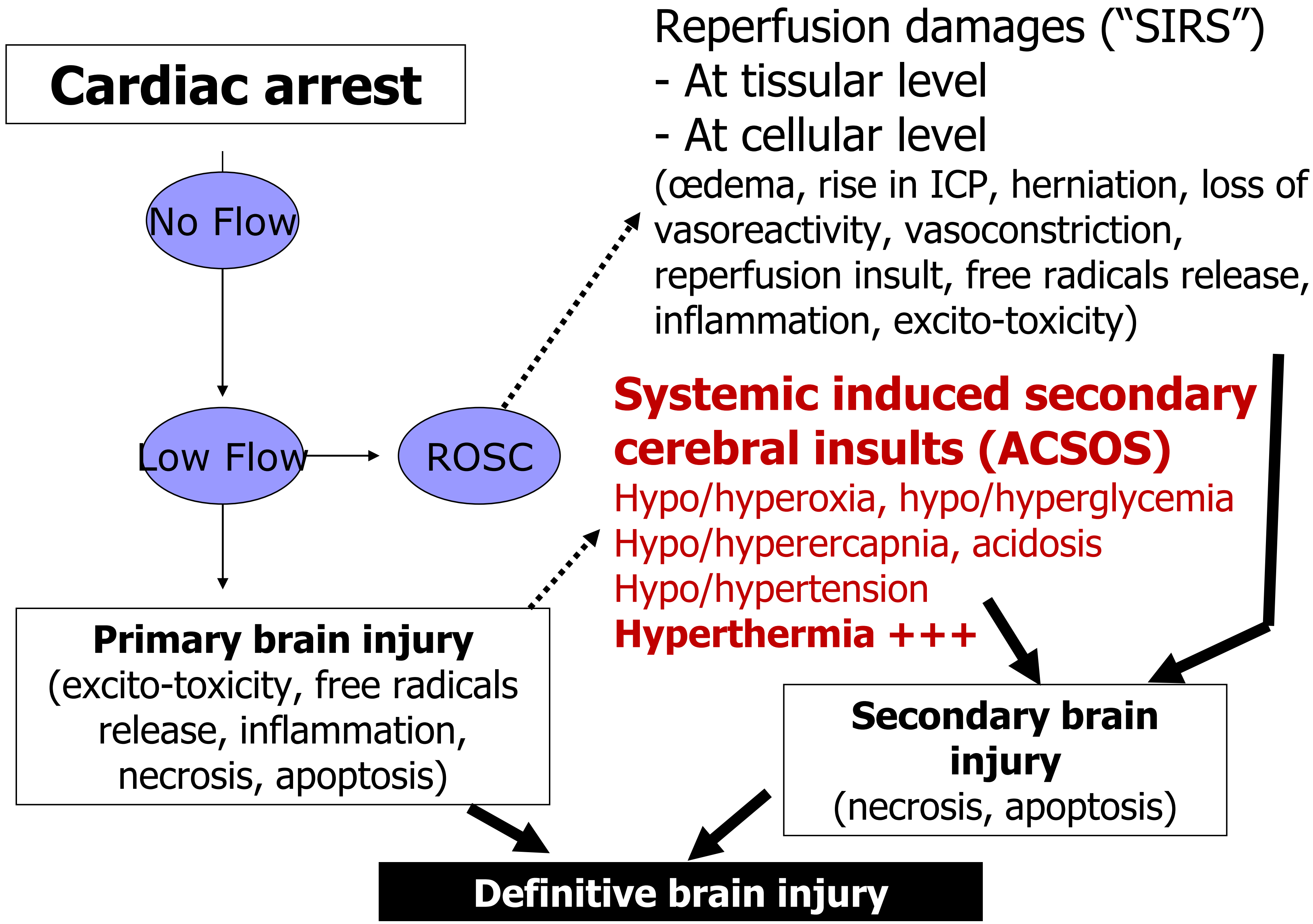
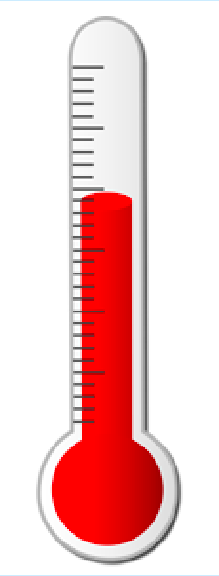

Cardiac arrest
No Flow
Low Flow
ROSC
Reperfusion damages ("SIRS")
- At tissular level
- At cellular level
(œdema, rise in ICP, herniation, loss of vasoreactivity, vasoconstriction, reperfusion insult, free radicals release, inflammation, excito-toxicity)
Systemic induced secondary cerebral insults (ACSOS)
Hypo/hyperoxia, hypo/hyperglycemia
Hypo/hyperercapnia, acidosis
Hypo/hypertension
Hyperthermia +++
Primary brain injury
(excito-toxicity, free radicals release, inflammation, necrosis, apoptosis)
Secondary brain injury
(necrosis, apoptosis)
Definitive brain injury

OPTIMIZING TTM/TH PROTOCOL

OPTIMAL LEVEL OF TEMPERATURE



Normal temperature? Abnormal damages

Holtzclaw. Sessler. 2000 37,0 ± 0,6°C

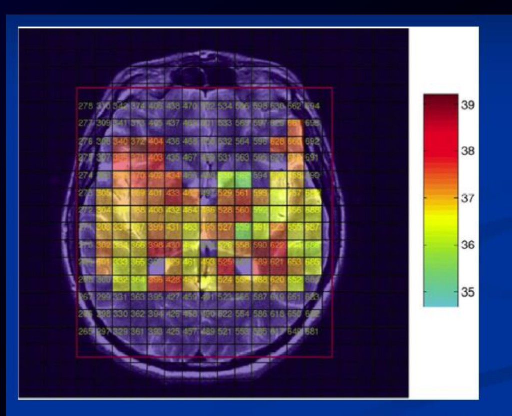
Villers. 2003 36,6 ± 0,4°C

Central compartments "core" (trunk, head) ≈ 2 to 4°C above periph. (surface: skin)

Precise thermoregulation (hypothalamus: intact or not)

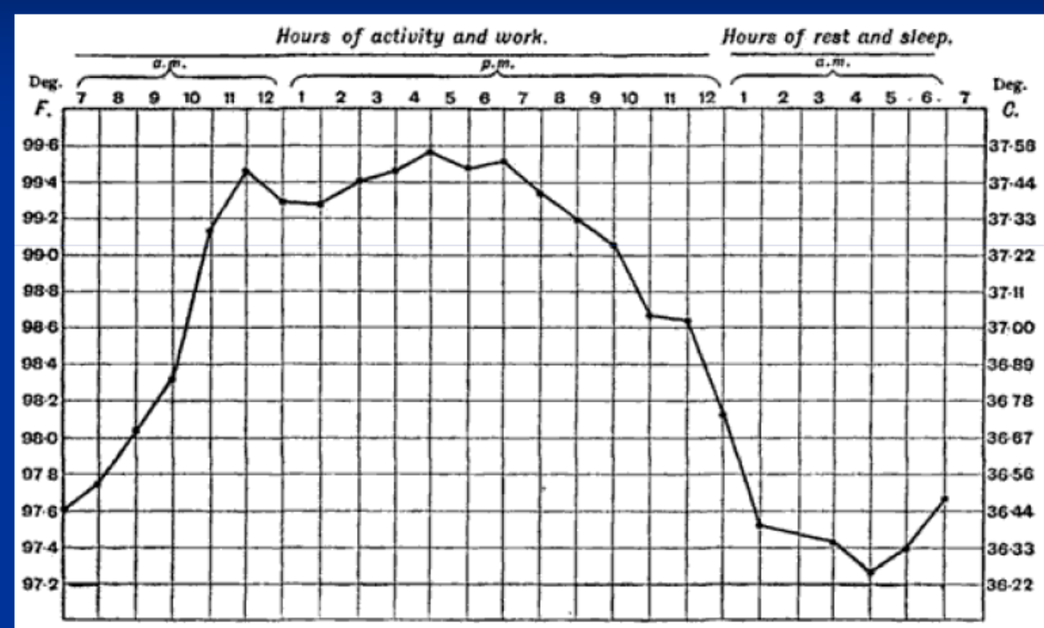
Variations (day, month…)

« Cerebral thermo-pooling »



Harris, 2008

normal core body temperature of a healthy, adult human being

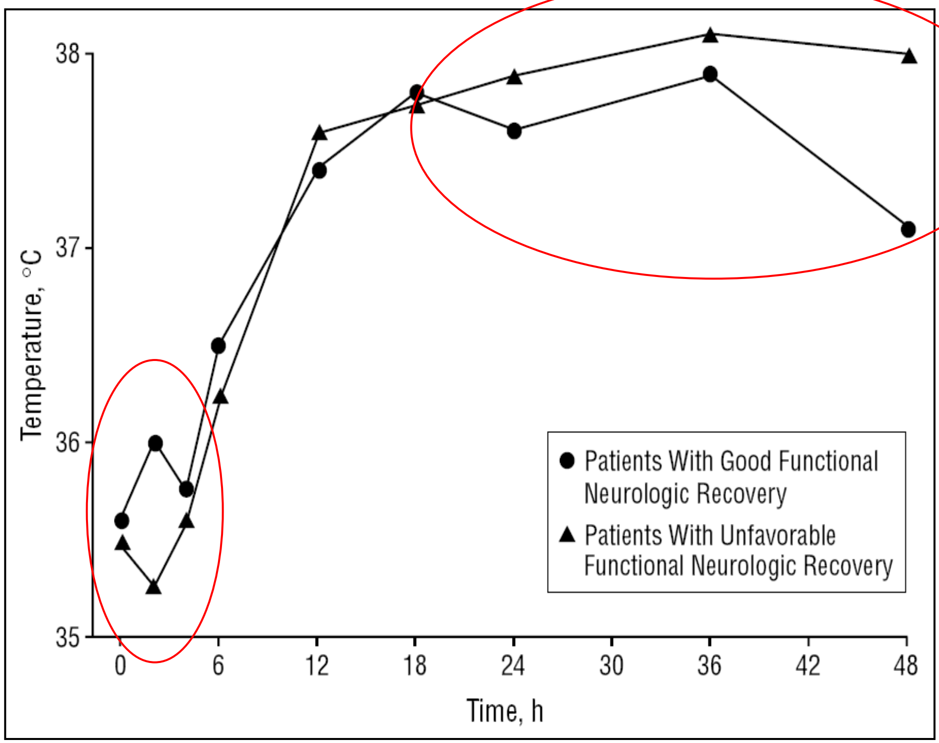


ORIGINAL INVESTIGATION

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

Arch Intern Med 2001



Body Temperature*	Functional Neurologic Recovery† Good (n = 89)	Unfavorable (n = 62)	*P*
On admission to the emergency department	35.6 (34.2-36.0)	35.3 (34.0-35.9)	.39
Minimum	36.0 (35.2-36.2)	35.2 (34.7-35.7)	.001
Maximum	37.7 (36.9-38.6)	38.3 (37.8-38.9)	<.001
Δ(+37)	0.25 (0.00-0.78)	0.66 (0.17-1.00)	.002

Variable	OR (95% CI)	p
No flow	1.34 (1.16-1.55)	<0.001
Low flow	1.05 (1.01-1.09)	.01
Maximal temp	2.26 (1.24-4.12)	.008

Survivors are less hypothermic on admission but less febrile thereafter

Benz-Woerner. Resuscitation 2012 | Lin. CCM 2014 | Lyon RM. Resuscitation 2010

Part 8: Advanced Life Support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations
Laurie J. Morrison, Charles D. Deakin, Peter T. Morley, Clifton W. Callaway, Richard E. Kerber, Steven L. Kronick, Eric J. Lavonas, Mark S. Link, Robert W. Neumar, Charles W. Otto, Michael Parr, Michael Shuster, Kjetil Sunde, Mary Ann Peberdy, Wanchun Tang, Terry L. Vanden Hoek, Bernd W. Böttiger, Saul Drajer, Swee Han Lim, Jerry P. Nolan and Advanced Life Support Chapter Collaborators
Circulation 2010;122;S345-S421

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.
Learn and Live.

From 2003-2010

Treatment Recommendations Related to Post–Cardiac Hypothermia

- Patient who develop hyperthermia after CA have worse prognosis. Despite lack of evidence, it is reasonable to treat hyperthermia.
- Comatose adult patients (not responding in a meaningful way to verbal commands) with spontaneous circulation after out-of-hospital VF CA should be cooled to 32 to 34°C for 12 to 24 hours.
- Induced hypothermia might also benefit comatose adult patients with spontaneous circulation after OHCA from an initial non-shockable rhythm, or IHCA (low level of evidence)

NNT using TH to save 1 patient = 6 ($IC_{95\%}$ [4-21])

When considering HACA, australian (Bernard) and Hachimi-Idrissi trials

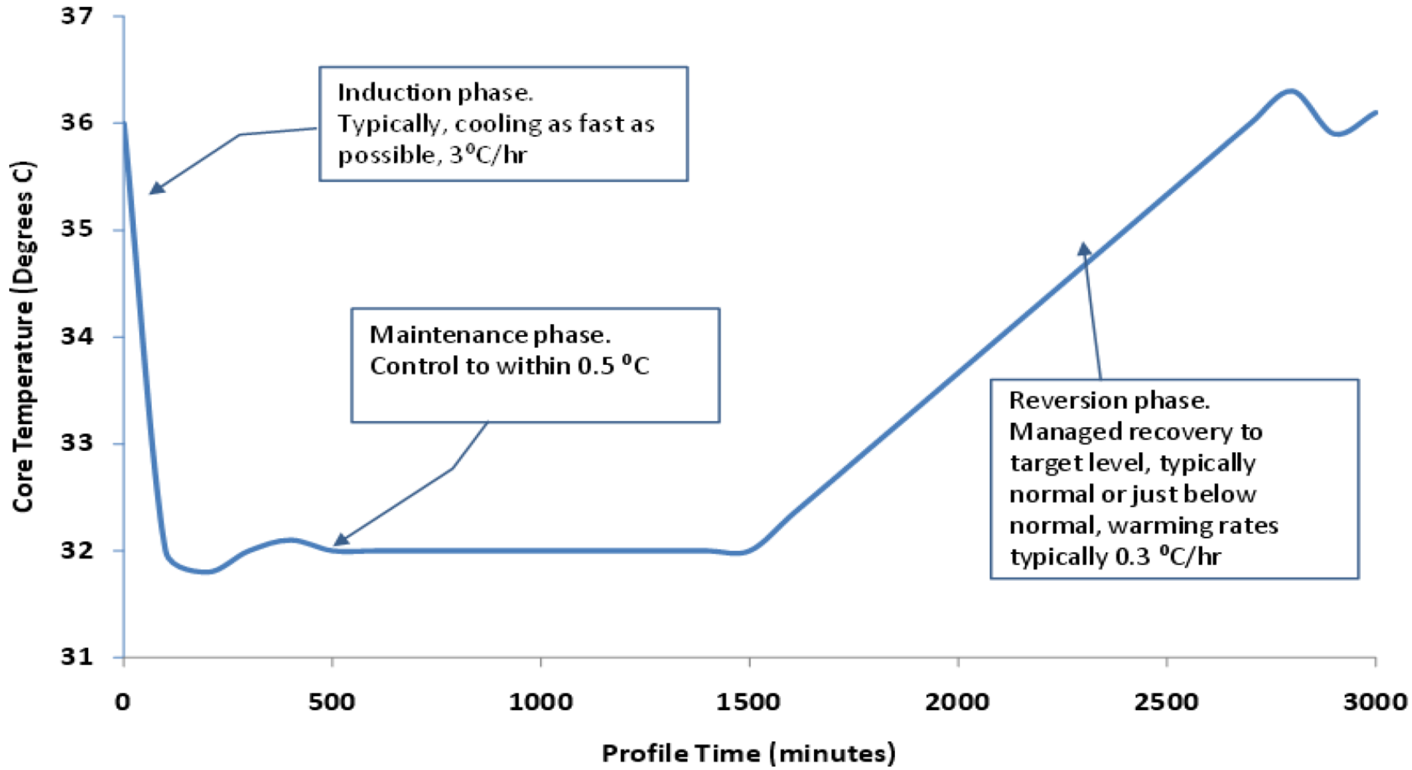
Nunnally
CCM 2011

ATS | ERS European Respiratory Society – every breath counts | ESICM European Society of Intensive Care Medicine | Society of Critical Care Medicine – The Intensive Care Professionals | Société de Réanimation de Langue Française

International Consensus Conference 2009

Targeted Temperature Management in Critical Care

A Report and Recommendations from Five Professional Societies



11th
International
Consensus
Conference

Therapeutic Hypothermia – To Cool or Not To Cool?

Condado Plaza Hotel and Casino
San Juan, Puerto Rico
April 23-24, 2009

TTM vs noTTM in HIE (neonates): weak recommendation (32.5-35.5°C, 72H)
TTM vs noTTM in CA (VF): strong recommendation (32-34°C, 24H)

Control = normothermia or hyperthermia?
Limit of the 2 main RCTs in 2002

Patients in the control group slightly hyperthermic
(37-38°C during the first 48 hours)

The New England Journal of Medicine

VOLUME 346 FEBRUARY 21, 2002 NUMBER 8

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

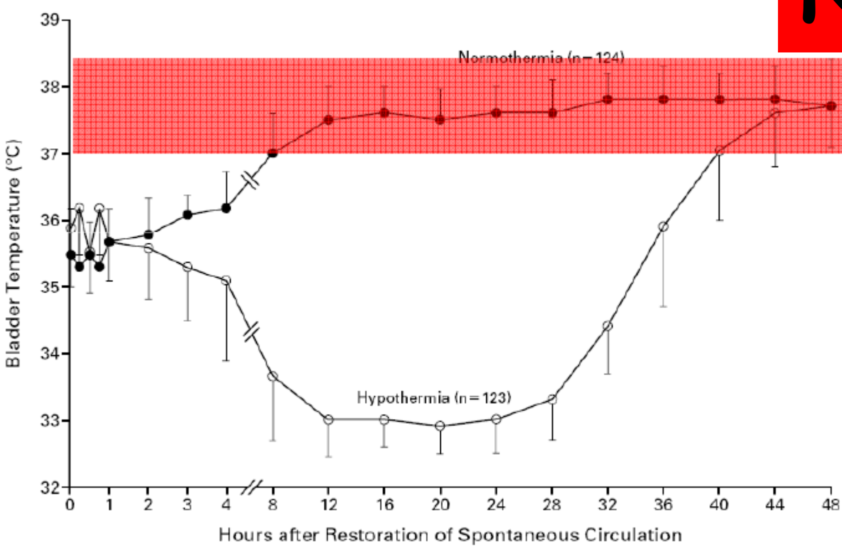
THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

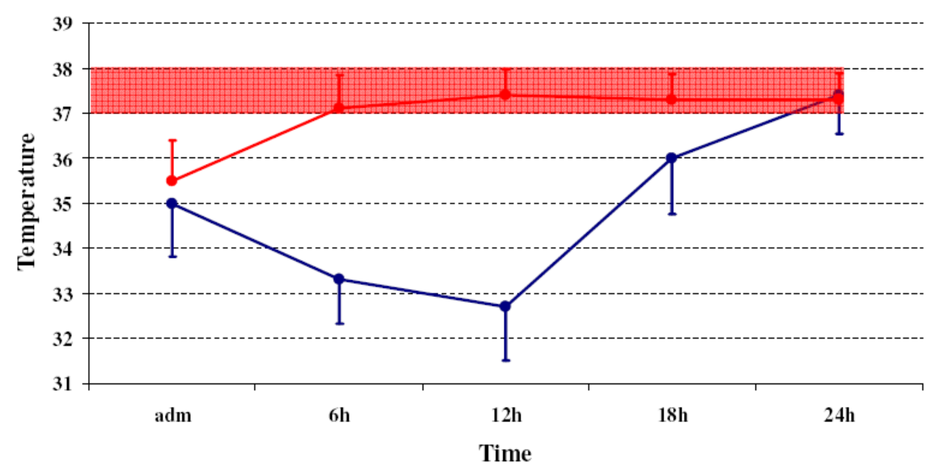
INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

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.

No TTM





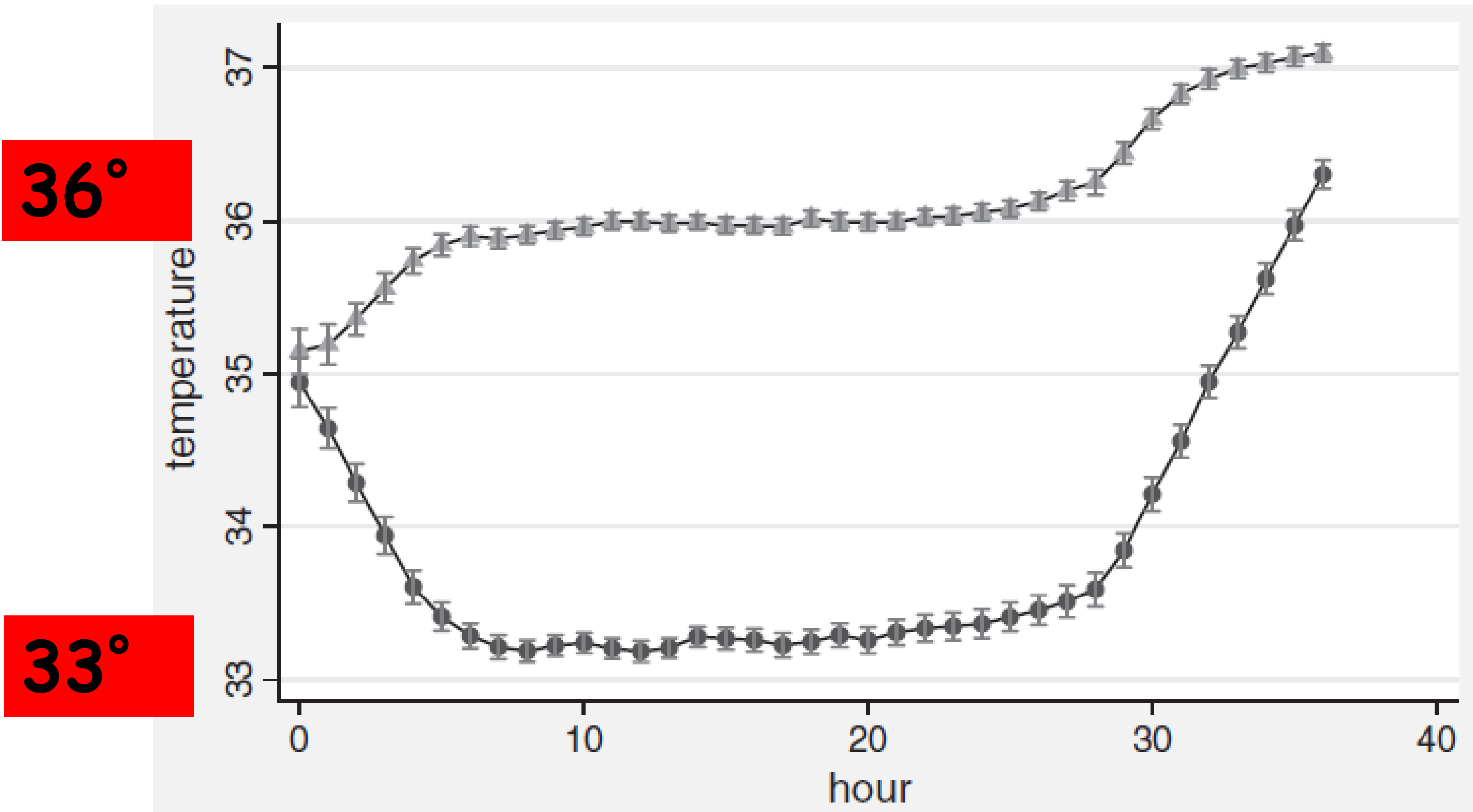
Controversial metanalysis (NNT/NNH): Nielsen IJC 2010

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

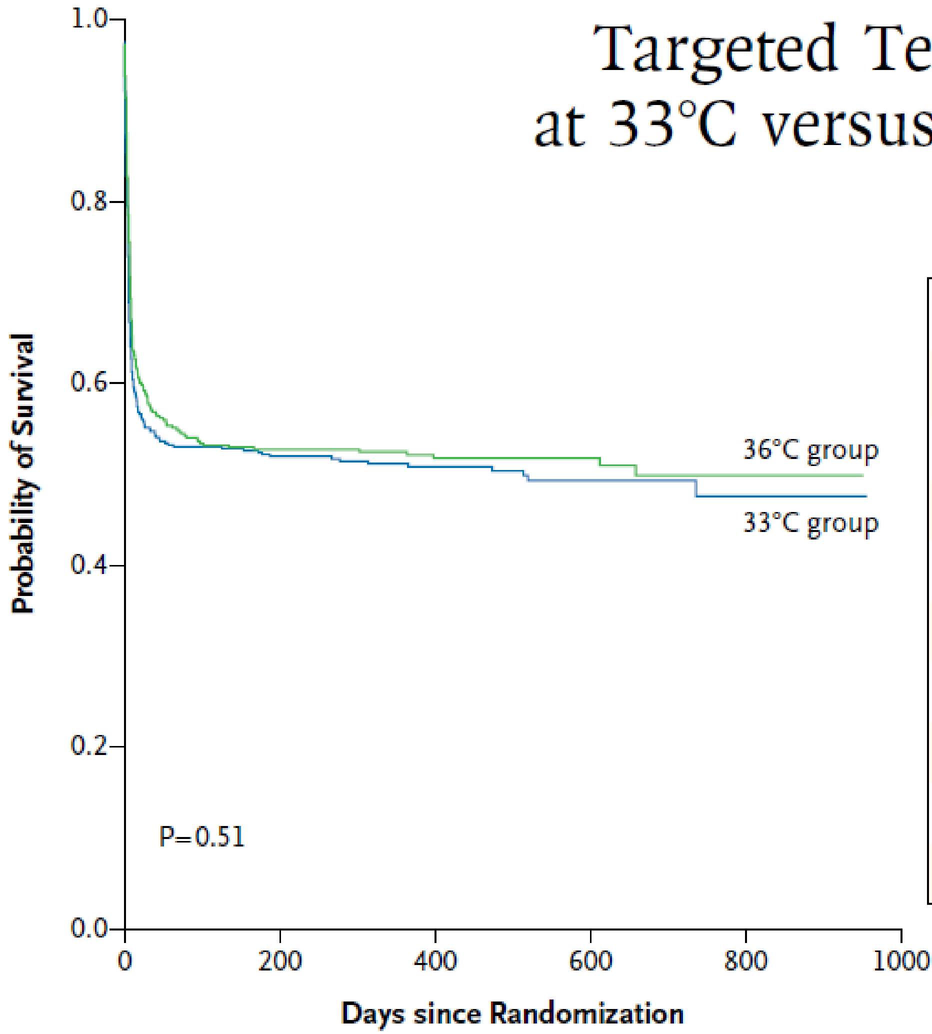


The NEW ENGLAND JOURNAL of MEDICINE

Nielsen Niklas
NEJM 2013

ORIGINAL ARTICLE

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

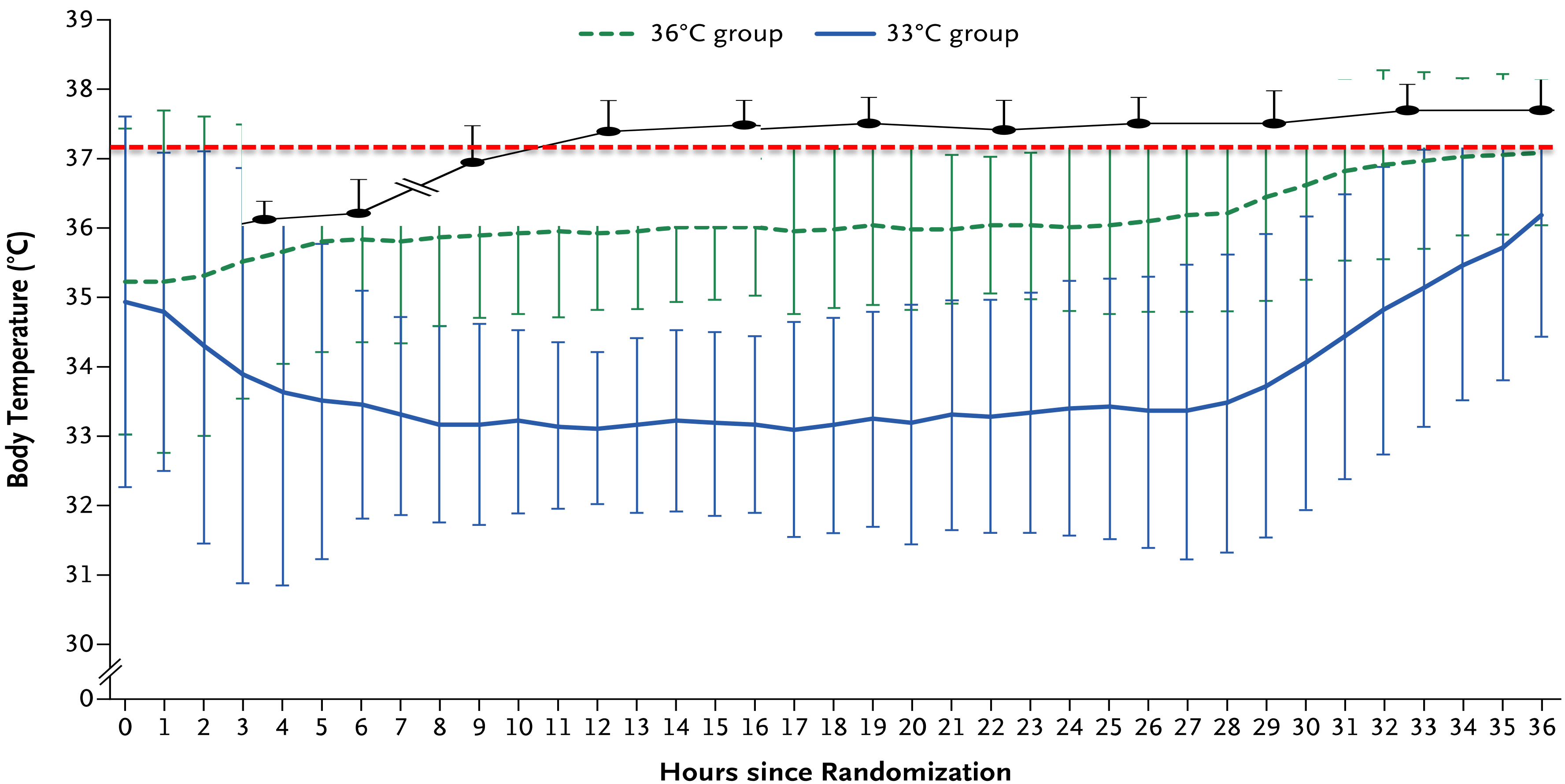


No. at Risk					
33°C group	473	230	151	64	15
36°C group	466	235	144	68	12

Variable	33°C Group	36°C Group
CPC at follow-up† D180		
Total no. of patients	469	464
Category — no. (%)		
1	195 (42)	183 (39)
2	23 (5)	39 (8)
3	17 (4)	20 (4)
4	6 (1)	2 (0.5)
5	228 (49)	220 (47)
P value for trend	0.85	

Summary of the 2 possibilities (slight TTM or HACA-TH)

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



Nielsen N et al. NEJM 2013
HACA Study. NEJM 2002

In-hospital low TTM effect vs slight TTM or vs no TTM ?

Vargas M. Resu 2015

Mortality at hospital discharge

Studies	Estimate (95% C.I.)	Control	Hypothermia
Hachimi 2001	1.143 (0.867, 1.507)	13/14	13/16
Bernard 2002	1.322 (0.910, 1.920)	23/34	22/43
Holzer 2002	1.370 (1.039, 1.807)	69/138	50/137
Laurent 2005	1.008 (0.582, 1.748)	11/20	12/22
Nilesen 2013	0.991 (0.857, 1.145)	203/466	208/473
Overall (I^2=27% , P=0.239)	**1.127 (0.976, 1.302)**	**319/672**	**305/691**

Tau²=0.007, Q (df=4)=5.507, p=0.104

Good neurologic performance at hospital discharge

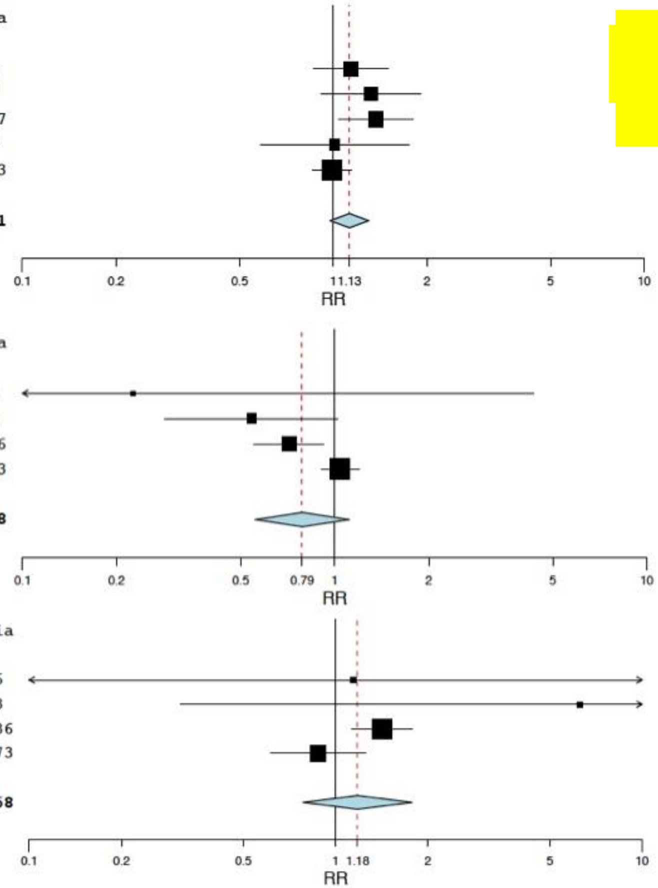
Studies	Estimate (95% C.I.)	Control	Hypothermia
Hachimi 2001	0.227 (0.012, 4.356)	0/14	2/16
Bernard 2002	0.542 (0.286, 1.026)	9/34	21/43
Holzer 2002	0.715 (0.553, 0.924)	54/137	75/136
Nielsen 2012	1.042 (0.903, 1.201)	212/465	207/473
Overall (I^2=70% , P=0.018)	**0.788 (0.556, 1.116)**	**275/650**	**305/668**

Tau²=0.068, Q (df=3)=10.091, p=0.180

Poor neurologic performance at hospital discharge

Studies	Estimate (95% C.I.)	Control	Hypothermia
Hachimi 2001	1.143 (0.079, 16.625)	1/14	1/16
Bernard 2002	6.286 (0.312, 126.725)	2/34	0/43
Holzer 2002	1.416 (1.130, 1.774)	87/137	61/136
Nielsen 2013	0.877 (0.614, 1.252)	50/465	58/473
Overall (I^2=51% , P=0.107)	**1.179 (0.783, 1.776)**	**140/650**	**120/668**

Tau²=0.068 Q (df=3)=10.091, p=0.180



IH low TTM improved short and long term mortality compared with no TTM
Conversely low TTM outcome did not improve compared with slight TTM

More than 15 metanalyses: Cochrane, CCM, CMEJ, Resu, ACA, AMJ, CC, IC…
Remind Laurent RCT: JACC 2005 (No TTM vs HF±TH ~ 32-36°)
Remind Lopez-De-Sa RCT: Circulation 2012 (32 vs 34°)

European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015 Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015☆

Jerry P. Nolan[a,b,*], Jasmeet Soar[c], Alain Cariou[d], Tobias Cronberg[e], Véronique R.M. Moulaert[f], Charles D. Deakin[g], Bernd W. Bottiger[h], Hans Friberg[i], Kjetil Sunde[j], Claudio Sandroni[k]

EUROPEAN RESUSCITATION COUNCIL

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

Optimising recovery

ICU management

- Temperature control: constant temperature 32°C – 36°C for ≥ 24h; prevent fever for at least 72 h
- Maintain normoxia and normocapnia; protective ventilation
- Optimise haemodynamics (MAP, lactate, $ScvO_2$, CO/CI, urine output)
- Echocardiography
- Maintain normoglycaemia
- Diagnose/treat seizures (EEG, sedation, anticonvulsants)
- Delay prognostication for at least 72 h

2015 summary of changes since 2010 guidelines

- 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).

- Targeted temperature management remains important but there is now an option to target a temperature of 36 °C instead of the previously recommended 32–34 °C.

- 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.

LESSONS FROM TTM TRIAL

You can choose to treat at 36°C (1/3 of respondents) or keep 33°C

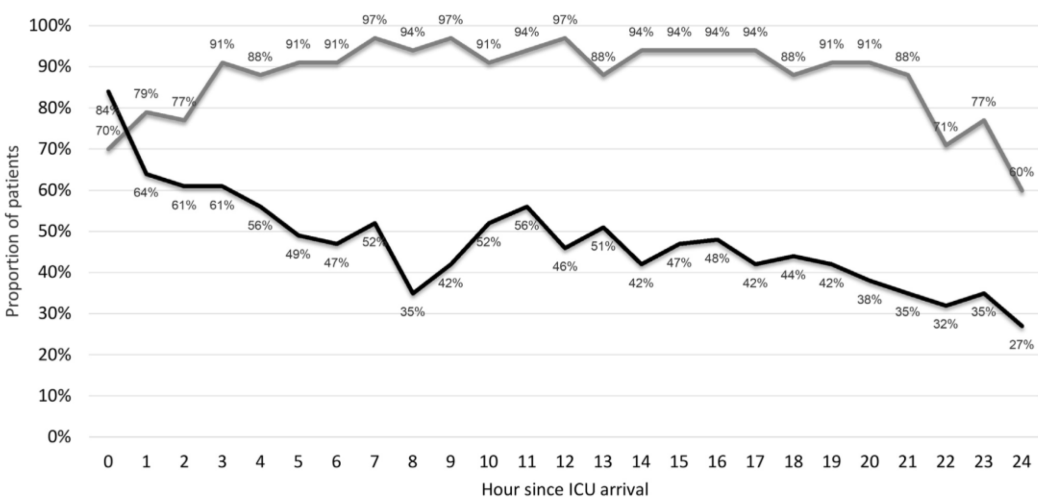
Deye et al, AIC,2016

We do not abandon TTM based on the TTM-trial
One size does not fit all ! Adaptative approach?

Storm et al. Resu.2017

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

Bray et al. Resuscitation 2017



After the change from TTM of 33 to 36° C, we report a low compliance with TT, higher fever rates and trends toward clinical worsening.

STRICT PROTOCOL!

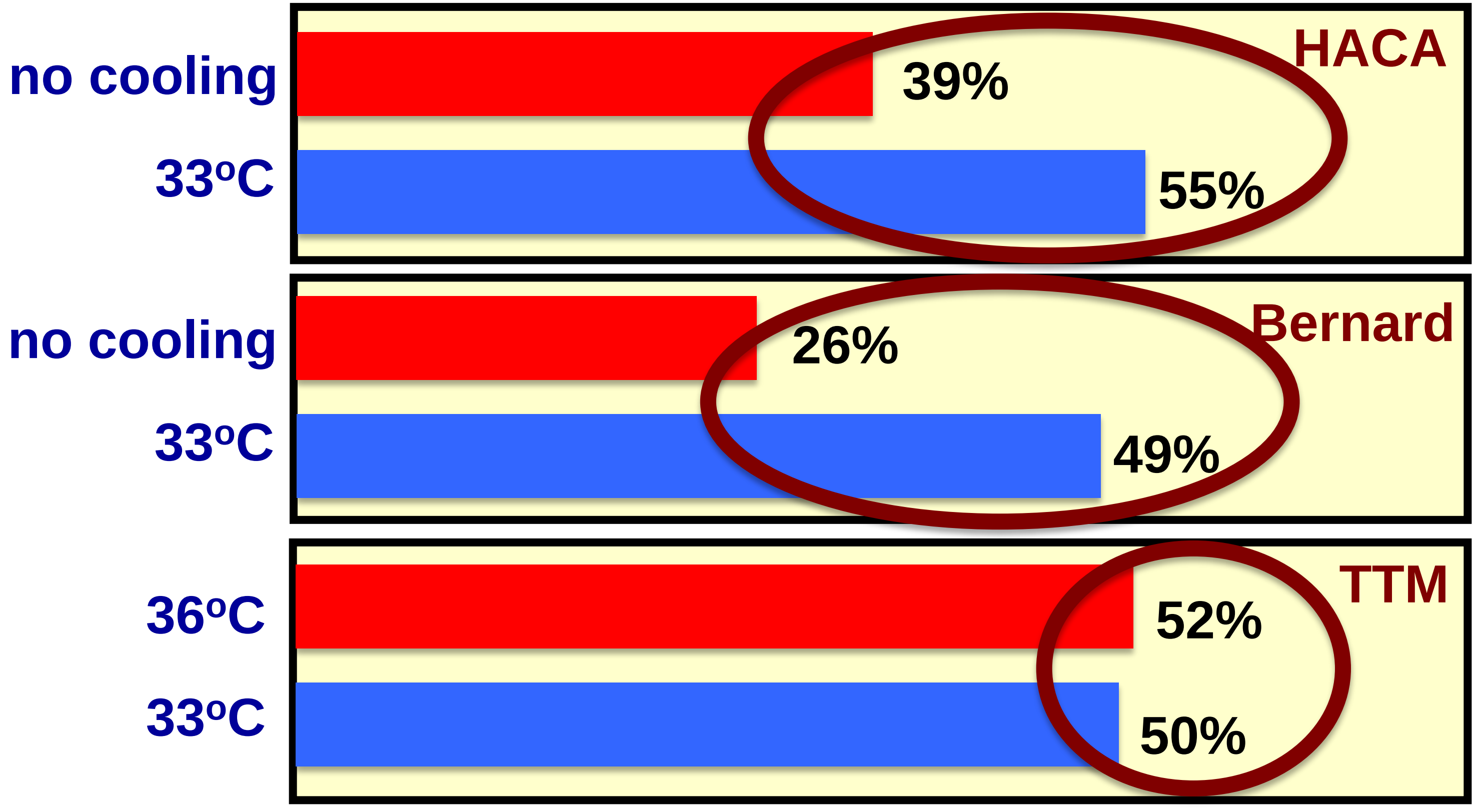
Hospitals adopting a 36° C TT need to be aware that this should not be easy to achieve, requiring adequate sedation + NMB to avoid fever.

OPTIMIZING TTM/TH PROTOCOL

CA PATIENT'S SELECTION

	Target		Achieved	
HACA 2002 N=275	32-34	Normal	33	37.8
Bernard 2002 N=77	33	37	33	37.4
Nielsen 2013 N=939	33	36	33	36

Conclusions from the post-arrest trials: control arm



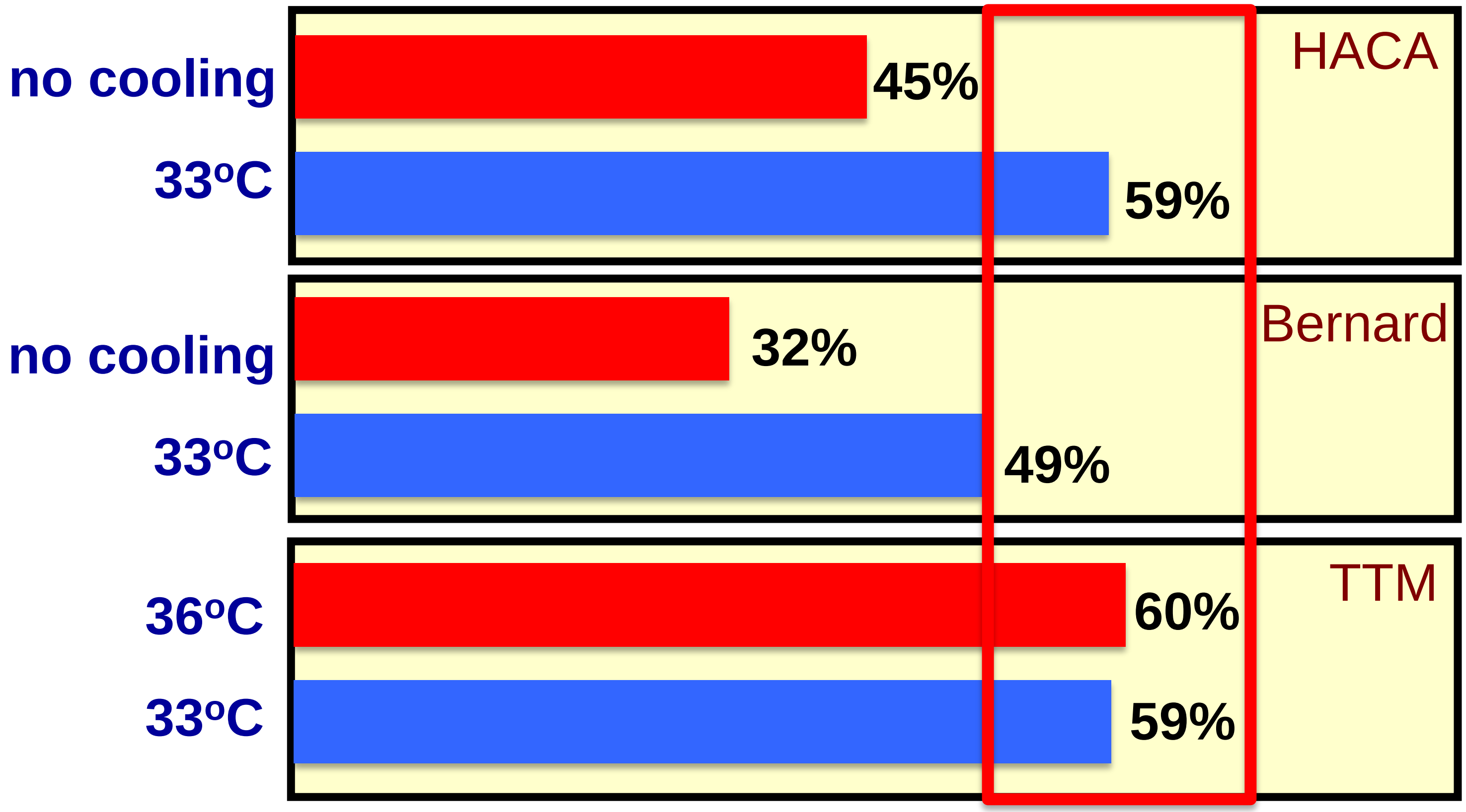
Control differs:

uncontrolled

vs. controlled

Modified from
Abella BS,
AHA Dallas 2013

Conclusions from the post-arrest trials



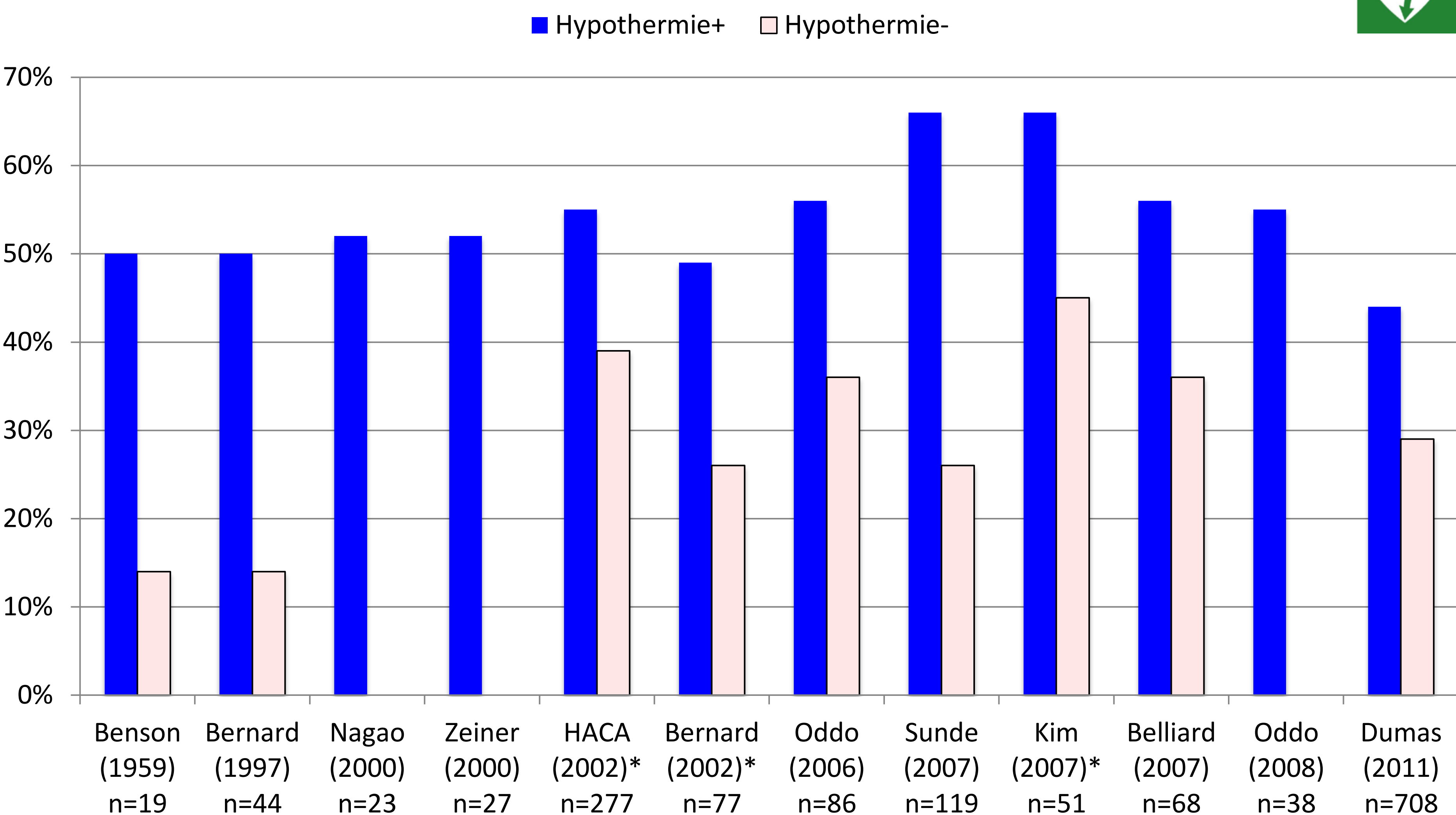
Shockable rhythms (>95% HACA and Bernard 80% TTM)

Still the control arm!

And the rhythm (etiology?)

Modified from
Abella BS,
AHA Dallas 2013

Hypothermia & shockable rhythm



Adapted from Behringer et al. And Polderman K, Lancet 2008

Resuscitation 83 (2012) 188–196

Contents lists available at ScienceDirect

Resuscitation

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

ELSEVIER

Meta-analysis non-VF

Resuscitation 2012

Clinical paper

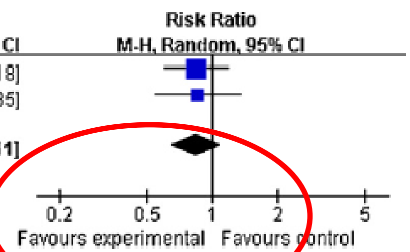
Does therapeutic hypothermia benefit adult cardiac arrest patients presenting with non-shockable initial rhythms?: A systematic review and meta-analysis of randomized and non-randomized studies☆

Young-Min Kim[a], Hyeon-Woo Yim[b,c], Seung-Hee Jeong[c], Mary Lou Klem[d], Clifton W. Callaway[e,*]

Study or Subgroup	Therapeutic hypothermia Events	Therapeutic hypothermia Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hachimi-Idrissi 2005	12	16	15	17	65.4%	0.85 [0.61, 1.18]
Laurent 2005	5	6	5	5	34.6%	0.86 [0.54, 1.35]
Total (95% CI)		22		22	100.0%	**0.85 [0.65, 1.11]**
Total events	17		20			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%

Test for overall effect: Z = 1.17 (P = 0.24)



TH is associated with reduced in-hospital mortality for adults resuscitated from non-shockable CA

Neurological outcome

Study or Subgroup	Therapeutic hypothermia Events	Therapeutic hypothermia Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Holzer 2006	20	28	378	506	11.3%	0.96 [0.75, 1.22]	2006
Oddo 2006	10	12	11	11	3.4%	0.84 [0.63, 1.13]	2006
Sunde 2007	5	6	9	9	2.2%	0.83 [0.55, 1.25]	2007
Arrich, ERC-HACA 2007	89	124	59	73	21.2%	0.89 [0.76, 1.04]	2007
Rittenberger 2008	38	42	35	39	10.4%	1.01 [0.87, 1.16]	2008
Storm 2008	9	18	24	31	5.0%	0.65 [0.39, 1.06]	2008
Don 2009	108	122	174	191	38.7%	0.97 [0.90, 1.05]	2009
Whitfield 2009	12	15	9	13	2.8%	1.16 [0.74, 1.80]	2009
Derwall 2009	9	13	10	15	2.7%	1.04 [0.62, 1.73]	2009
Gaieski 2009	6	9	8	9	2.3%	0.75 [0.45, 1.26]	2009
Total (95% CI)		389		897	100.0%	**0.93 [0.88, 1.00]**	
Total events	306		717				

Heterogeneity: Chi² = 7.18, df = 9 (P = 0.62); I² = 0%

Test for overall effect: Z = 2.10 (P = 0.04)

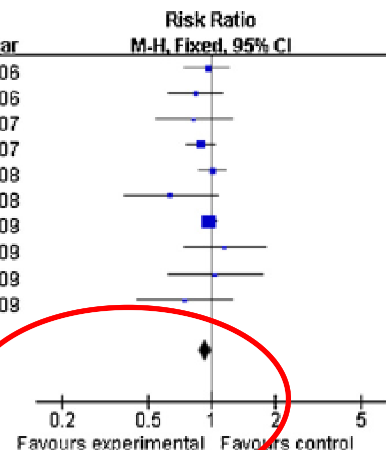
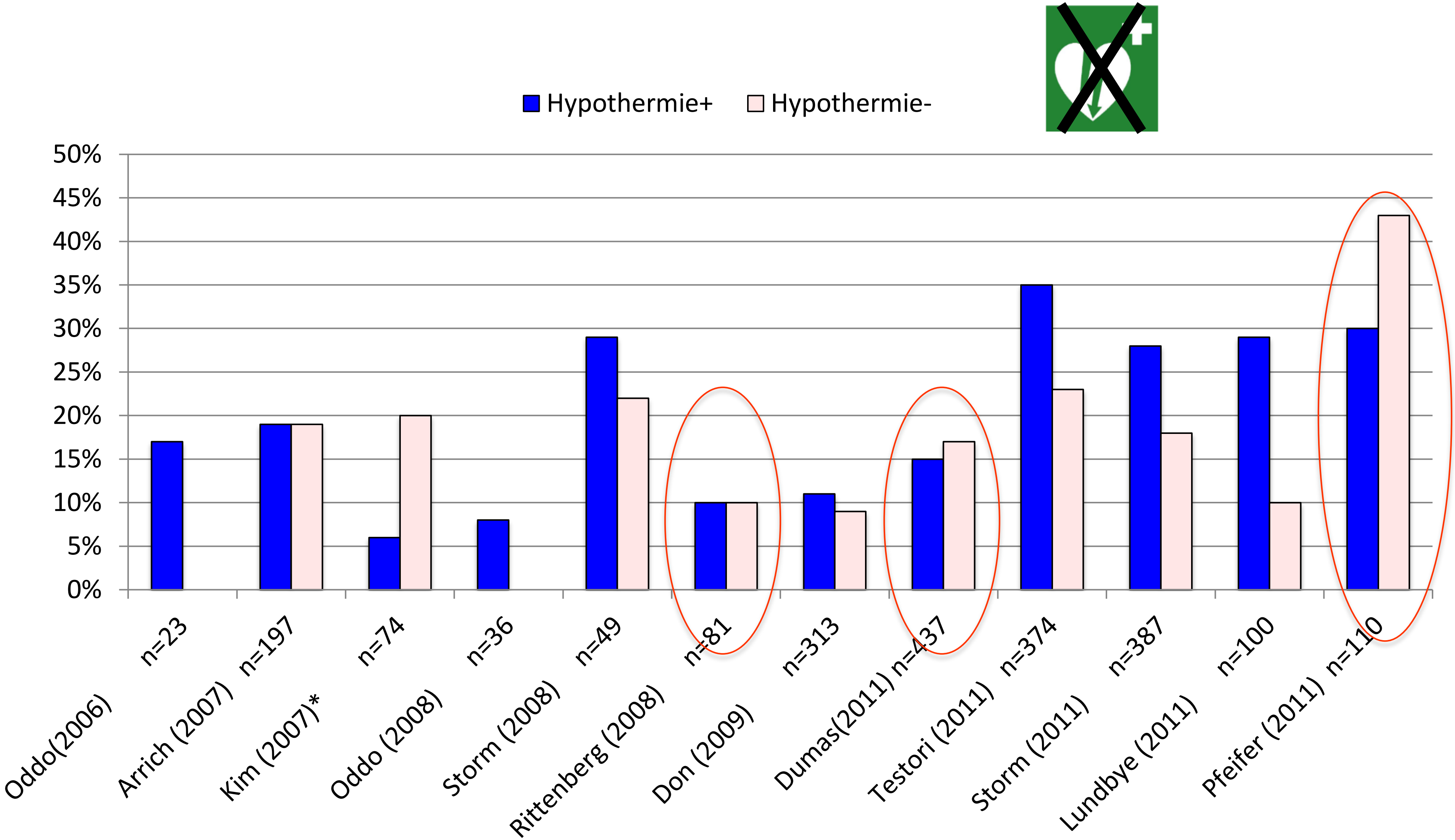


Fig. 4. The effect of therapeutic hypothermia on neurological outcome in non-randomized studies.

However, most of the studies had substantial risks of bias and quality of evidence was very low.

Hypothermia & non-shockable rhythm



Meta-analyses: BioMedResIntern 16 (Song+, nonRCT), Crit Care 15 (Zhang-)…

Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study

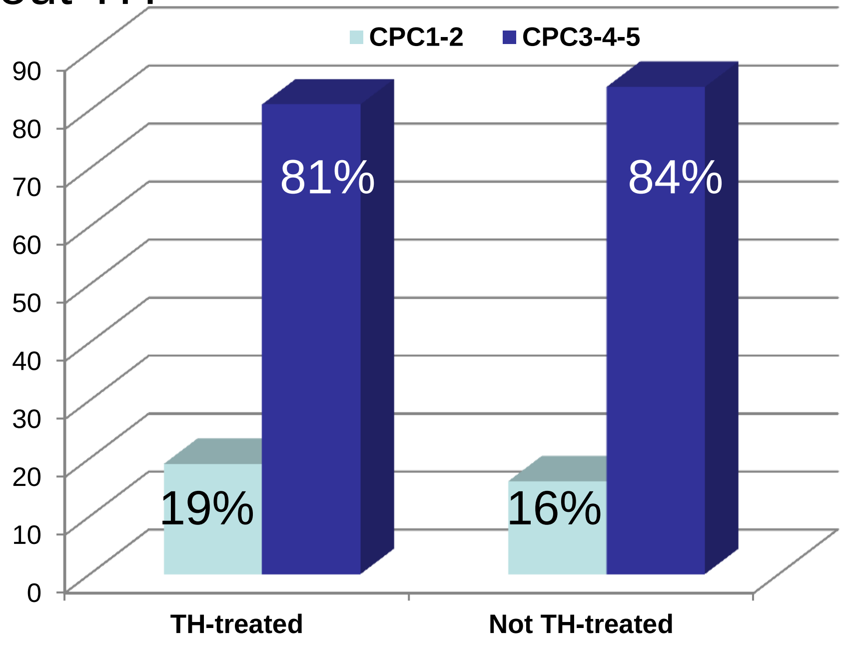
ICM 2013. Vaahersalo J, et al.

281 shockable CA (TH 86%)
223 non-shockable CA with TH = 70 (31%): prolonged time to ROSC, more cardiac etiology, more pneumonia, mechanical ventilation and lengh of stay

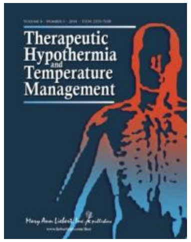
64% survivors at ICU discharge (with or without TH)
At hospital discharge, 37% if TH vs 32% without TH
TH-treated 1y survival: 27%
Not-TH 1y survival: 19%

NS

Non significant (p=0.56)
even after adjustment for propensity score



Comparative Effectiveness of Therapeutic Hypothermia After Out-of-Hospital Cardiac Arrest: Insight from a Large Data Registry
Mader TJ, Nathanson BH, Soares WE, Coute RA, McNally BF.



Ther Hypothermia Temp Manag. 2014

Retrospective study of OHCA adults in the CARES registry
6369 pts: shockable= 2992 (47%) ; nonshockable= 3377 (53%).
Unadjusted neurological status at hospital discharge with and without TH were similar (*p*=0.3). After multivariate adjustments, **TH had no association with good neurological status at hospital discharge or TH was actually associated with worse neurological outcome, particularly in nonshockable patients**

NS ? Harmful !?

Association Between Therapeutic Hypothermia and Survival After In-Hospital Cardiac Arrest

JAMA 2016

Paul S. Chan, MD; Robert A. Berg, MD; Yuanyuan Tang, PhD; Lesley H. Curtis, PhD; John A. Spertus, MD, MPH; for the American Heart Association's Get With the Guidelines–Resuscitation Investigators

26183 CA (1524 TH treated vs 3714 not treated after propensity score),
TH was associated with lower IH survival for non shockable and for shockable rhythm, and lower rate of favorable neurological survival for the global cohort (both rhythm)

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

ILCOR. 2015

- 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).

Nicolas Deye
Jasmin Arrich
Alain Cariou

ICM 2013

To cool or not to cool non-shockable cardiac arrest patients: it is time for randomized controlled trials

Hétérogénéité des non choquables?!

Table 1 Pros and cons of TH in patients with non-shockable OHCA

Reason	TH strategy (target 32–34 °C)	Normothermia strategy
Pathophysiological arguments: protective effects in asphyxic animal CA models (in terms of histological and neurobehavioural scores, and survival)	+	–
Beneficial effects on survival and neurological function obtained in neonatal hypoxic-ischaemic encephalopathy (mimicking asphyxia)	+	–
Available RCTs[a]	?	?
Available meta-analyses[a]	?	–
Available non-randomized studies (registries, observational, matched studies…)[a]	+	?
Impact of different targeted temperature management (35–36 °C…)[a]	?	?
No other available treatment to date[a]	+	?
Could prevent neurological damage (increase in likelihood of favourable outcome, CPC 1-2)[a]	+	–
Could save life (decrease in likelihood of unfavourable outcome, CPC 5)[a]	+	?
Severity of the underlying disease (poor prognosis altering the possible impact of the treatment)[a]	+	?

Fever (not hyperthermia) is not always associated with poor prognosis
Control of fever is not always correlated with better prognosis in ICU

	ICU Population	Fever definition	Main findings on fever
Circiumaru	General, n=100	Fever ≥38.4°C	No impact
Barie	Postoperative, n=2419	Fever ≥38.2°C	No impact
Laupland	General, n=10,962	Normal 36°C-38.2°C Low fever≥38.3°C High fever≥39.5°C	No impact
Kiekkas	General, n=239	Fever ≥38.3°C	Maximal body temperature associated with higher mortality
Selladurai	Sepsis, n=106	Fever >38°C	Fever associated with higher mortality
Egi	Sepsis, n=606 No sepis, n=819	Normal 36.5-37.4°C Fever ranges +1°C	Body temperature 37.5-38.4°C associated with lower mortality Body temperature ≥ 39.5°C associated with higher mortality
Netzer	ALI, n=450	Fever≥38°C High Fever>39°4	Fever associated with prolonged mechanical ventilation

Role of inflammatory response, defense against virus-bacteria… and thermomodulation (hypothalamic set-point modification for microbiological control)

Better heat shock response? Role of heat/cold shock proteins?

Critical Care

Egi et al. 2012

CRITICAL CARE

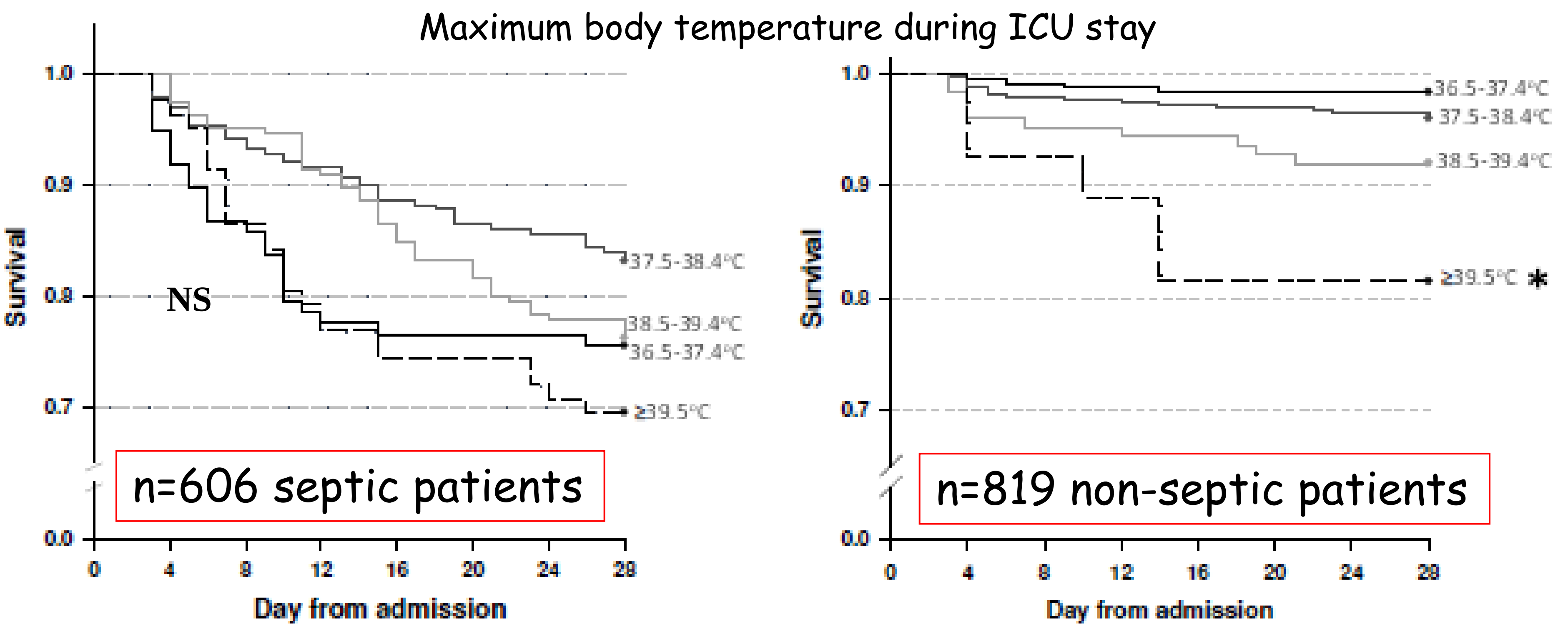
Sepsis?

Fever and Antipyretic in Critically ill patients Evaluation (FACE) Study Group

Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study

In septic patients (temp. > than non-septic), fever = not associated with mortality (antipyretics independently associated with mortality)

In non-septic patients, fever >39.5° C = independently associated with death (no association between antipyretics and mortality)



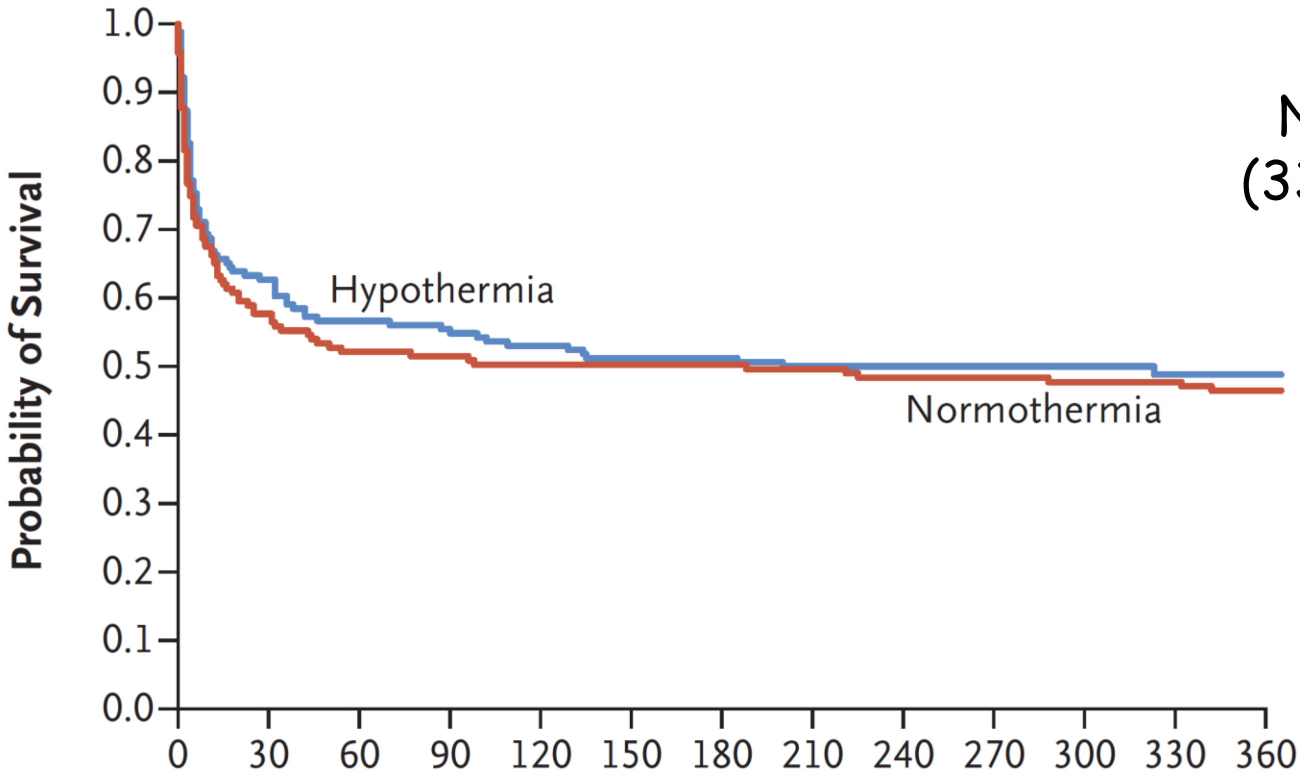
Enfant?

ORIGINAL ARTICLE

Moler et al.
NEJM 2017

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children

Alive with VABS-II score ≥70 at 1 yr	48/133 (36)	48/124 (39)	−2.6 (−14.5 to 9.2)	0.92 (0.67 to 1.27)	0.63†
Alive at 1 yr	81/166 (49)	74/161 (46)	2.8 (−8.0 to 13.7)	1.07 (0.85 to 1.34)	0.56†



N=166 vs 163
(33° vs 36.8°)
P=0.45

All-cause mortality at 28 days — no. (%)	59 (37)	66 (41)	0.40

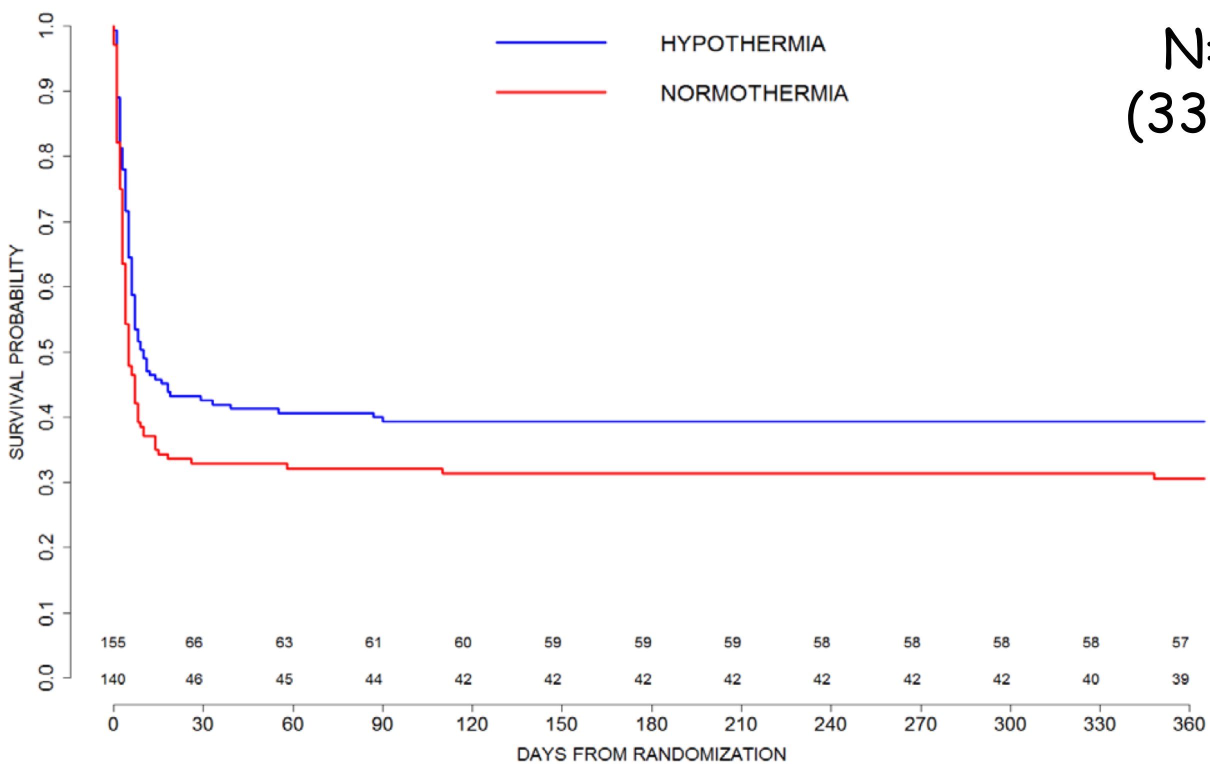
Enfant?

ORIGINAL ARTICLE

Moler et al.
NEJM 2015

Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children

Alive with VABS-II score ≥70 at 1 yr	27/138 (20)	15/122 (12)	7.3 (−1.5 to 16.1)	1.54 (0.86 to 2.76)	0.14†
Alive at 1 yr	57/151 (38)	39/136 (29)	9.1 (−1.8 to 19.9)	1.29 (0.93 to 1.79)	0.13†



N=155 vs 140
(33° vs 36.8°)
P=0.04

All-cause mortality 28 days — no./total no. (%)	87/153 (57)	93/139 (67)	0.08

Cooling for newborns with hypoxic ischaemic encephalopathy (Review)

2013

THE COCHRANE COLLABORATION®

Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG

11 RCTs included / 1505 neonates at term or end of pre-term with moderate to severe encephalopathy and per-partum asphyxia

- **↓ death or major neurological sequellaes at 18 months**

RR 0.75 [IC 95% 0.68-0.83], NNT 7 [95%CI 5-10], 8 studies (1344 children)

- **↓ death** RR 0.75 [95%CI 0.64-0.88], NNT 11 [95%CI 6-50], 11 studies

- **↓ neurological sequellaes in survivors**

RR 0.77 [95%CI 0.63-0.94], NNT 8 [95%CI 5-14], 8 studies (917 children)

TH in neonates with hypoxic ischaemic encephalopathy: concordant RCTs

Neurological impairment: seizures, clinical or EEG encephalopathy, low Apgar score, acidosis, O_2 desaturation (perinatal asphyxia), bradycardia and/or CPR

Pilot study 05 Pedia Neurol

Cool Cap 05

NICHD trial (Toby, NEJM 05)

Toby NEJM, 2009

Zhou 2010; nEURO study 2010 Azzopardi NEJM, ICE study 2012

Concordant meta-analyses (Edwards 06-10, Jacobs CD 07-09, Shah 07, Schulkze 07), etc

Induced hypothermia after cardiac arrest improves cardiogenic shock*

CCM 2012

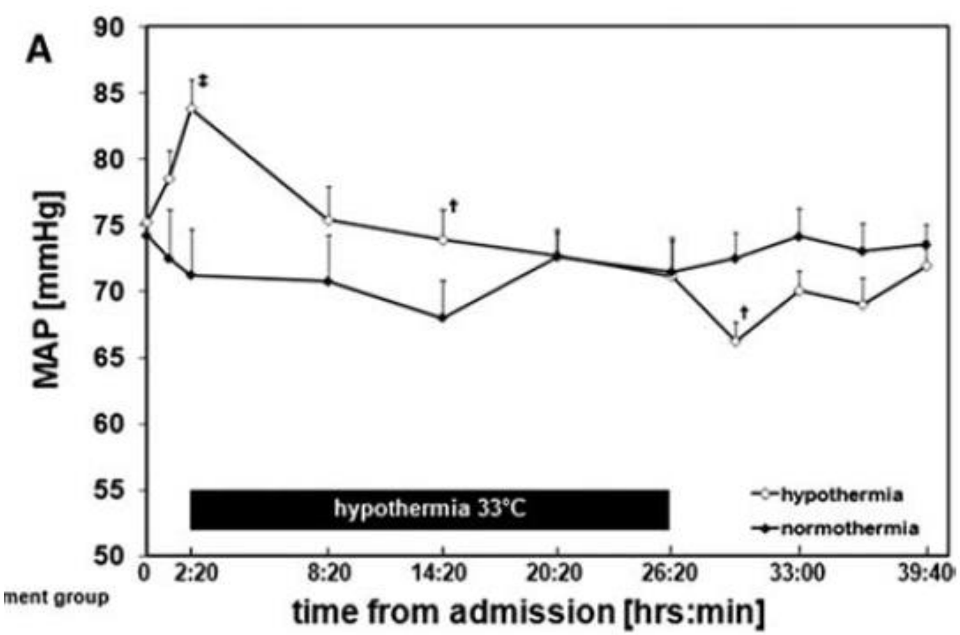
Shock

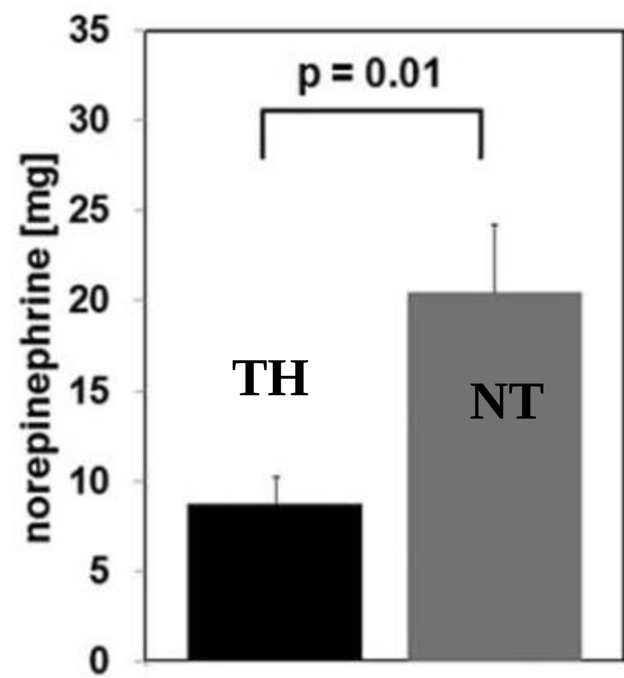
Mild therapeutic hypothermia in cardiogenic shock syndrome*

Carsten Zobel, MD; Christoph Adler, MS; Anna Kranz, MS; Catherine Seck, MD; Roman Pfister, MD; Martin Hellmich, MD; Matthias Kochanek, MD; Hannes Reuter, MD

Matched patients with (n=20, LVEF 42%) or without TH

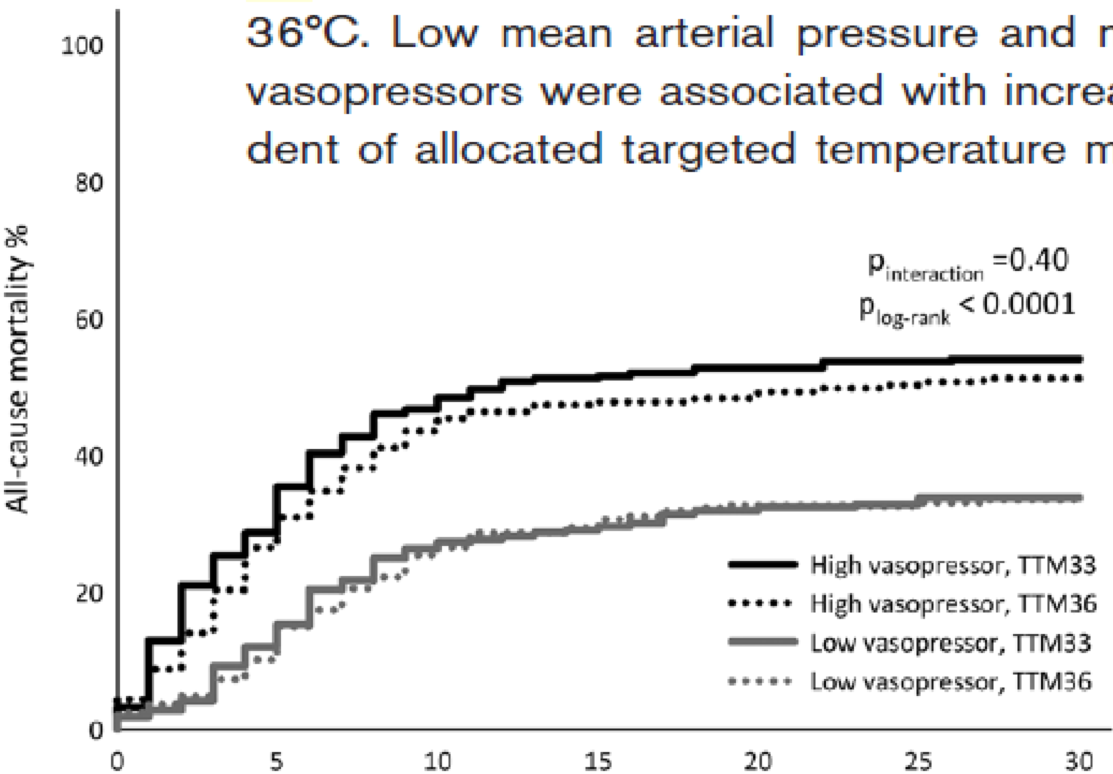
Sparing in catecholamines (SVR ↑, CO preserved if fluids)





Hemodynamics and Vasopressor Support During Targeted Temperature Management at 33°C Versus 36°C After Out-of-Hospital Cardiac Arrest: A Post Hoc Study of the Target Temperature Management Trial

Conclusions: Targeted temperature management at 33°C was associated with hemodynamic alterations with decreased heart rate, elevated levels of lactate, and need for increased vasopressor support compared with targeted temperature management at 36°C. Low mean arterial pressure and need for high doses of vasopressors were associated with increased mortality independent of allocated targeted temperature management. (*Crit Care*



N=950

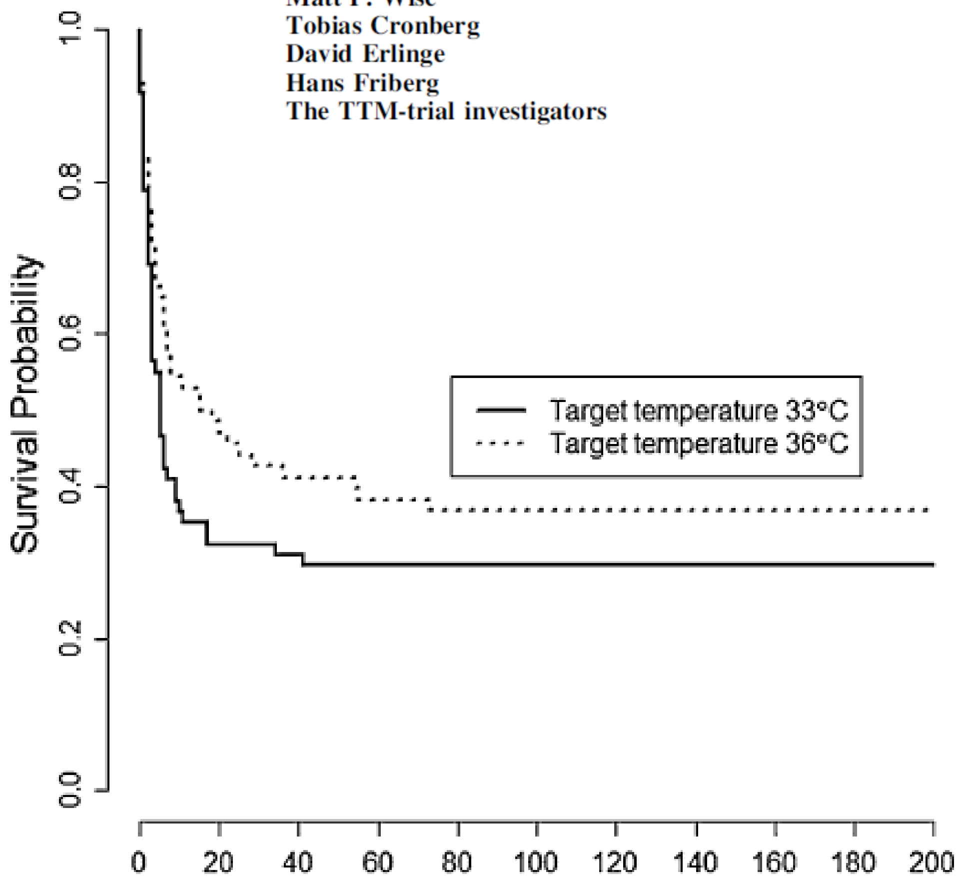
Bro-Jeppesen et al.
CCM 2014

Shock

Martin Annborn
John Bro-Jeppesen
Niklas Nielsen
Susann Ullén
Jesper Kjaergaard
Christian Hassager
Michael Wanscher
Jan Hovdenes
Tommaso Pellis
Paolo Pelosi
Matt P. Wise
Tobias Cronberg
David Erlinge
Hans Friberg
The TTM-trial investigators

The association of targeted temperature management at 33 and 36 °C with outcome in patients with moderate shock on admission after out-of-hospital cardiac arrest: a post hoc analysis of the Target Temperature Management trial

ICM 2014



Mortality D180; p=0.17

Mortality ICU; p=0.06

After adjustment: p=0.03

TTM in PCAS on admission (n=139)

Kilgannon et al. Early arterial hypotension is common in PCAS and associated with increased mortality. **Resuscitation 2008**

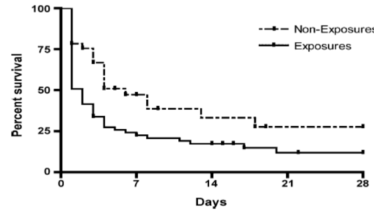


Figure 2 Kaplan–Meier survival curves (truncated at 28 dav

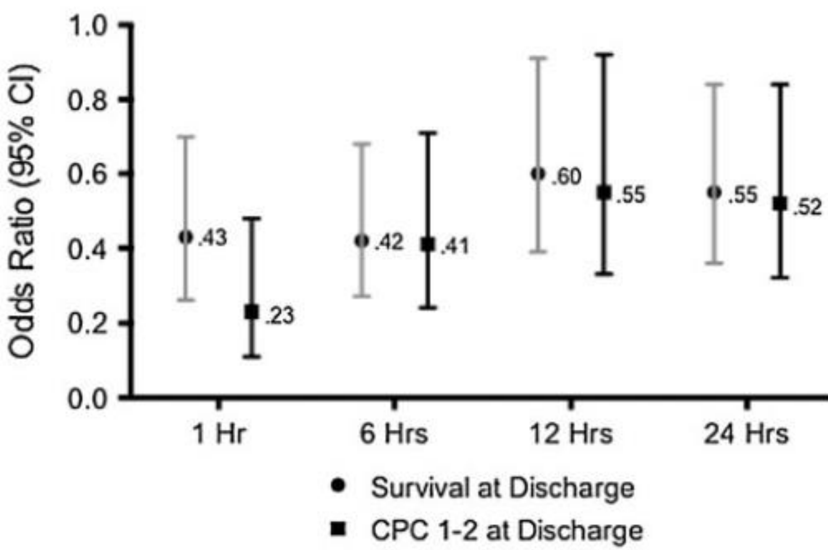
IH mortality ↑ if exposures (n=66) vs not exposed (n=36). More re-CA. Independantly associated with IH death if early exposure

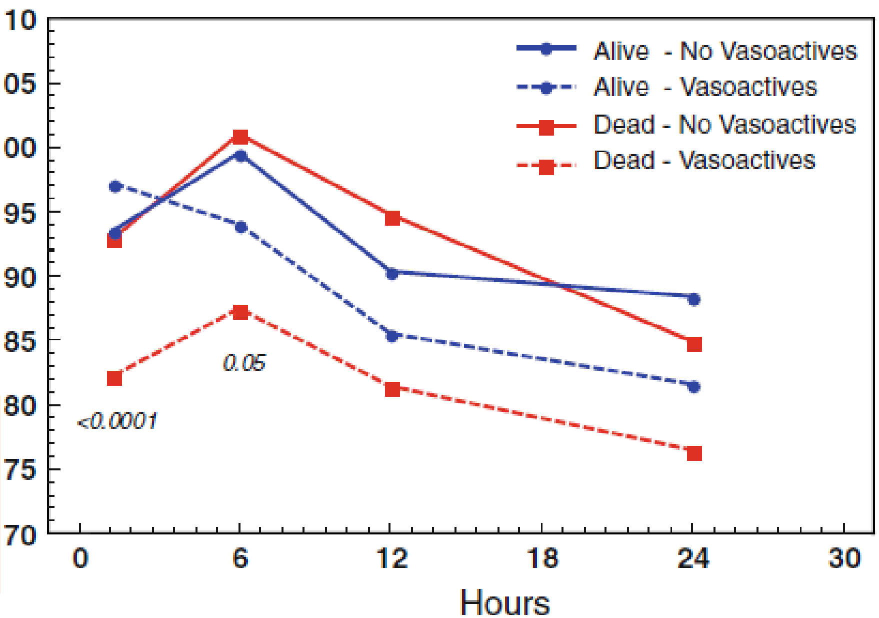
ICM 2013

Marie E. Beylin
Sarah M. Perman
Benjamin S. Abella
Marion Leary
Frances S. Shofer
Anne V. Grossestreuer
David F. Gaieski

Higher mean arterial pressure with or without vasoactive agents is associated with increased survival and better neurological outcomes in comatose survivors of cardiac arrest

(n=168)





From 2010 to 2015

Hemodynamic Optimization

- In adult patients with ROSC after (OH / IH) CA, does **early hemodynamic optimization**, as opposed to standard care, improve outcome (survival)?
- **Post-CA myocardial dysfunction causes hemodynamic instability.**

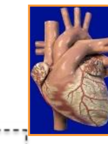
Treatment Recommendation

- Despite limited clinical data, the known pathophysiology of post-CA syndrome provides a rationale for titrating hemodynamics to optimize organ perfusion.
- **Perform early echocardiography, fluid and inotropic support guided by clinical and biological parameters, target pressure for diuresis = 1 ml/kg/h and normal lactate (care if hypertension)**

Knowledge Gaps ADAPT TTM ?

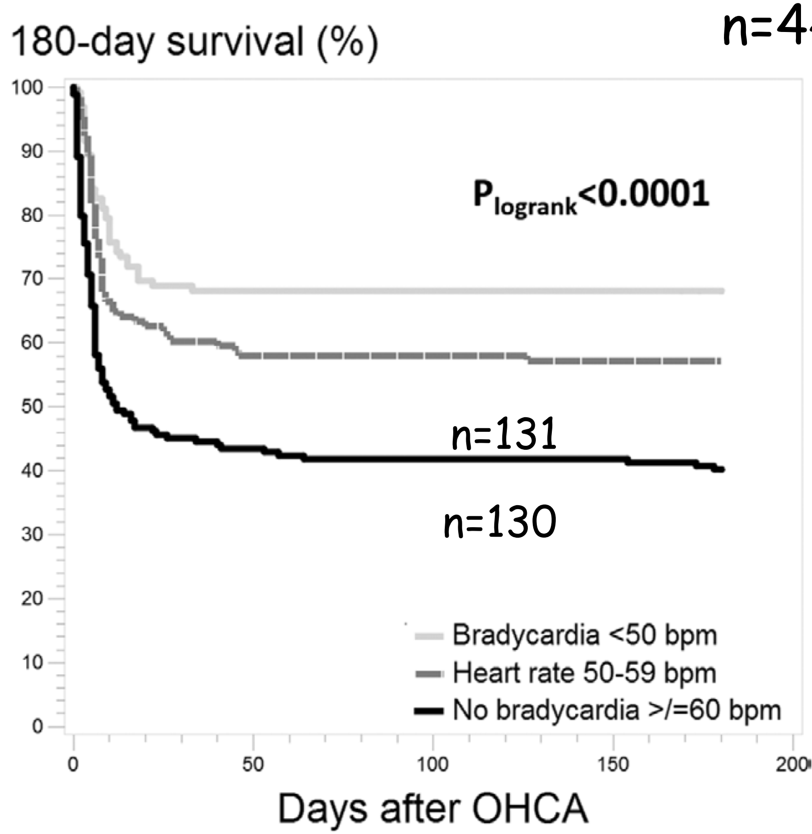
- Clinical research is needed to define the optimal targets for hemodynamic optimization and the best strategies to achieve these targets (fluids, vasopressors, inotropes, circulatory support, etc).

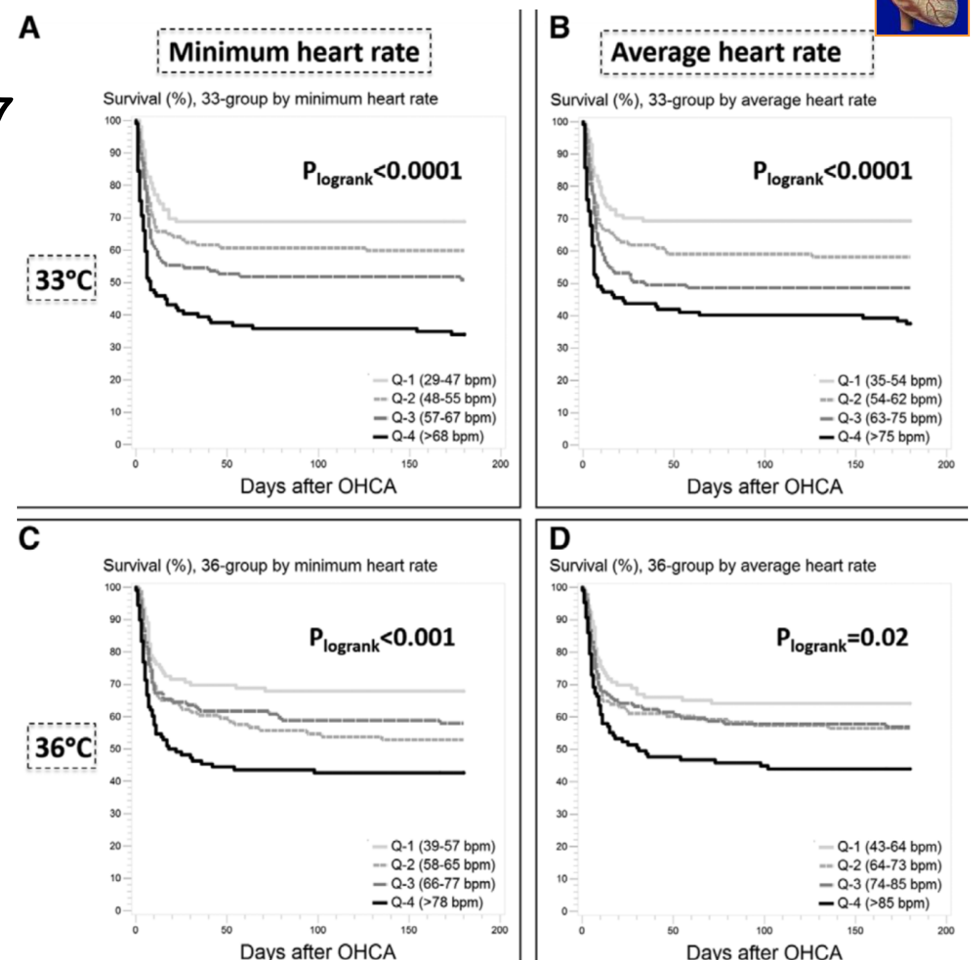
Bradycardia During Targeted Temperature Management: An Early Marker of Lower Mortality and Favorable Neurologic Outcome in Comatose Out-of-Hospital Cardiac Arrest Patients*



Thomsen et al. CCM. 2016

n=447





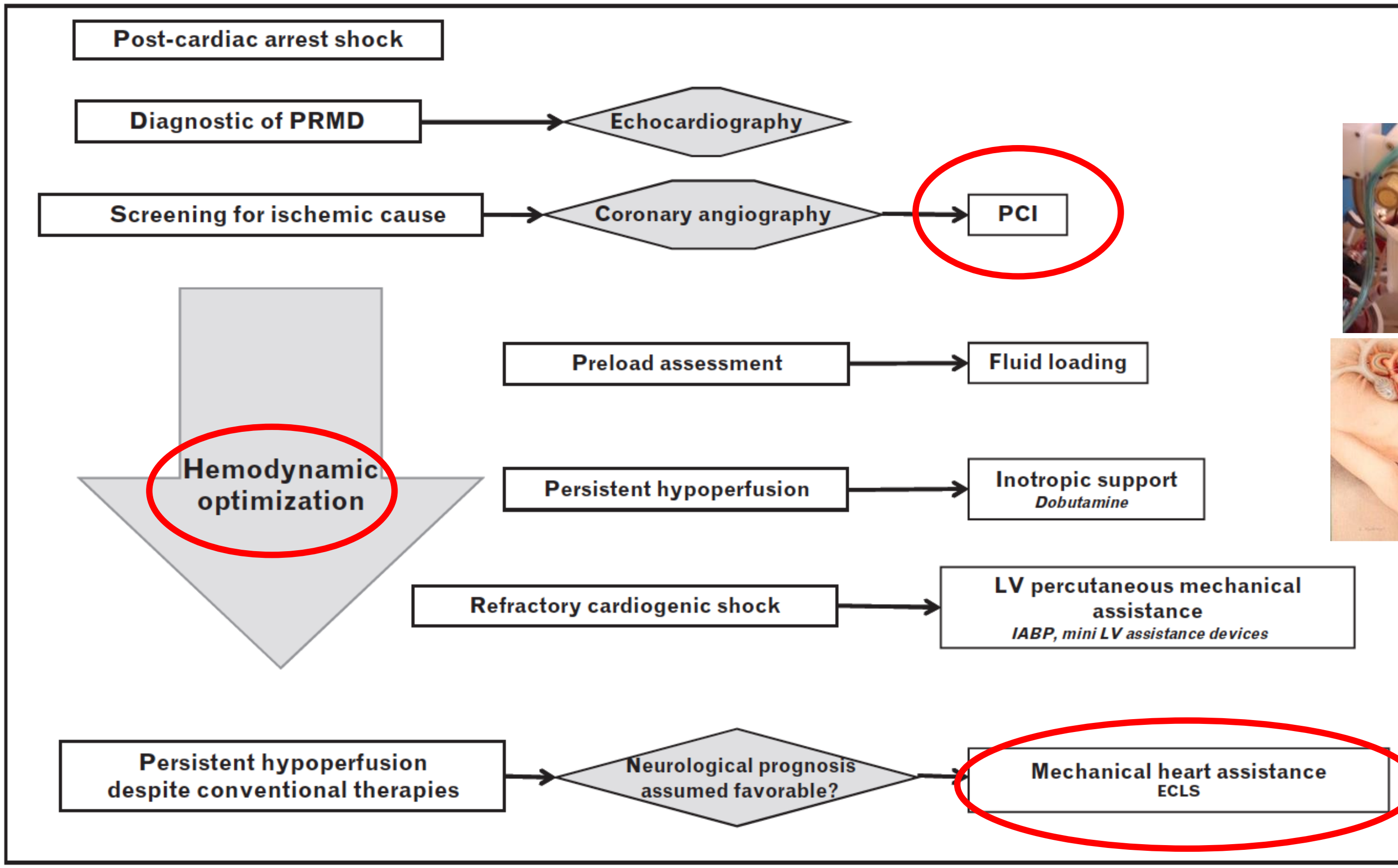
Adjusted OR (CI 95%): 0.38 (0.21-0.68), p<0.01

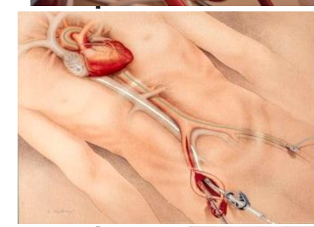
n=430

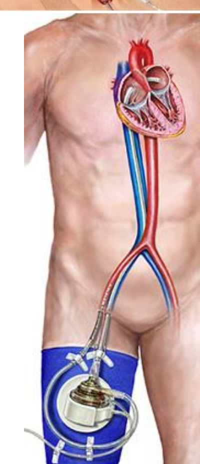
Possible ttt of PCAS patients (CS complicating AMI…)

Algorithm proposed for the detection and management of postresuscitation myocardial dysfunction (PRMD)

Bougouin W, Cariou A. Curr Opin Crit Care 2013







De Chambrun et al ICM 16, Bougouin et al Resu 16

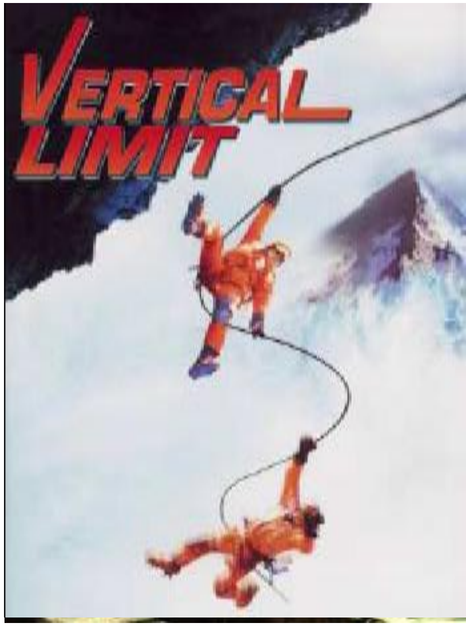
Global hypothermia for neuroprotection after cardiac arrest

ORIGINAL ARTICLE

Acute Cardiac Care. 2006; 8: 25–30

Practical protocol for treatment of patients

FRITZ STERZ, WILHELM BEHRINGER & MICHAEL HOLZER

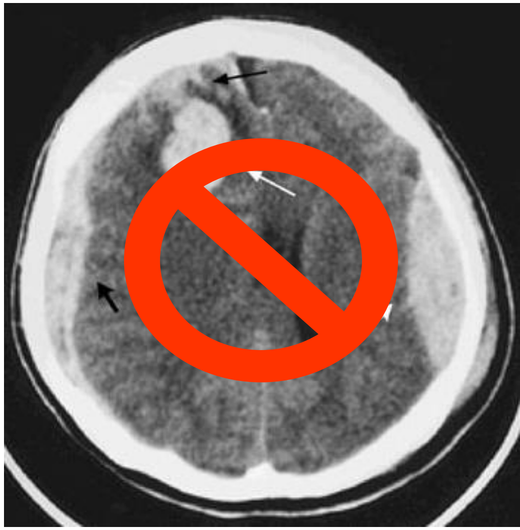


WHO TO CONTROL TEMPERATURE?

All patients after CA
not obeying to verbal command after ROSC

WHO NOT TO TREAT WITH 33-TTM (TH)?

TBI / intracranial hemorrhage,
uncontrolled hemorrhagic shock,
major uncontrolled bleeding (DIC?)
Initial temperature < 30°C, terminal disease, futility (?)



WHEN TO ADAPT TTM?

Uncontrolled sepsis?
Uncontrolled shock ??? (but not bradycardia!)
Infants? pregnancy?

CA etiology

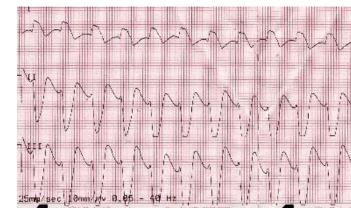
2015

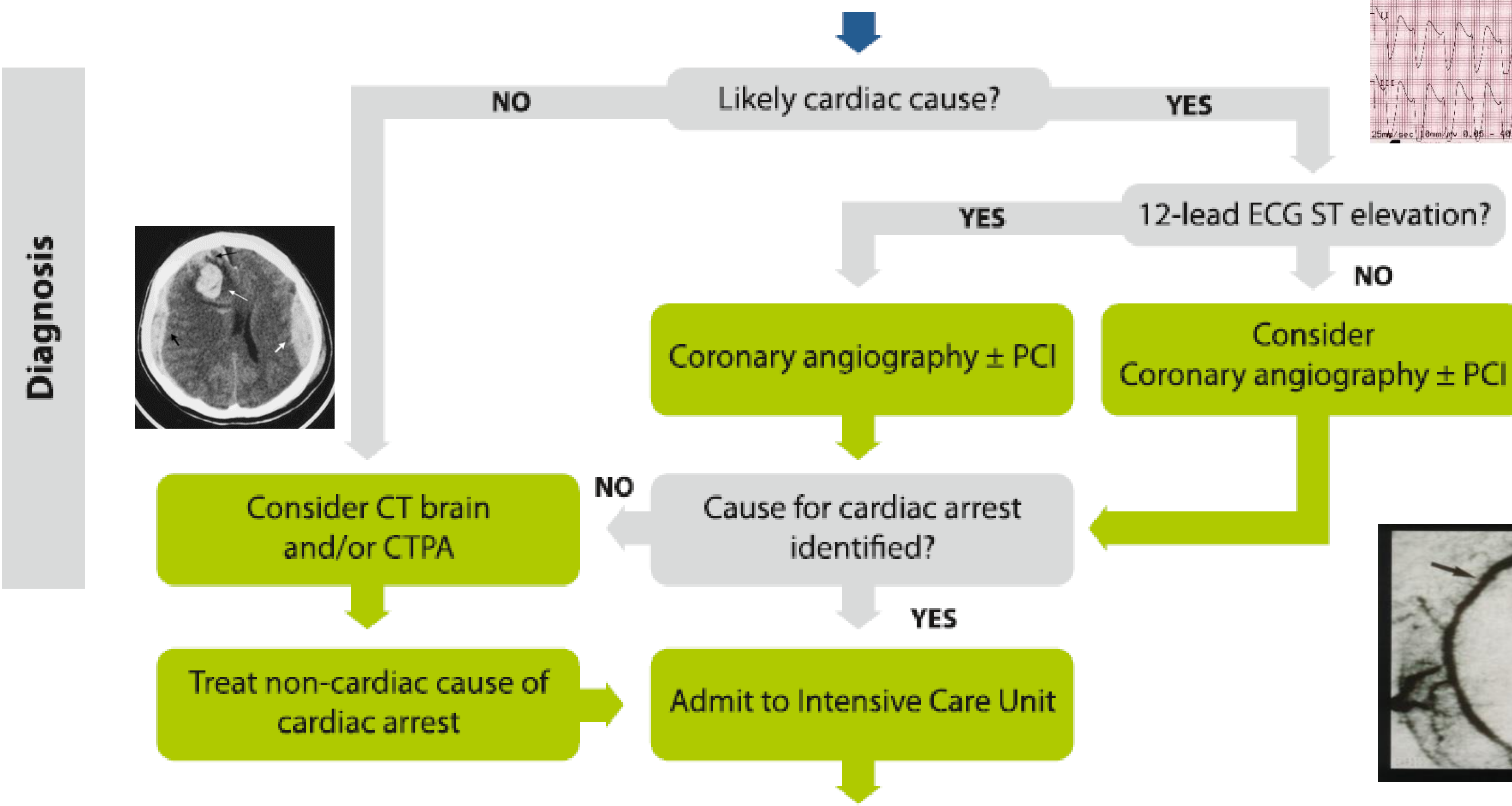
European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015 Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015☆

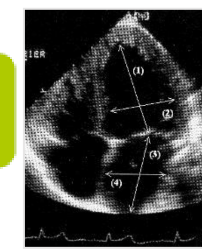
Jerry P. Nolan[a,b,*], Jasmeet Soar[c], Alain Cariou[d], Tobias Cronberg[e], Véronique R.M. Moulaert[f], Charles D. Deakin[g], Bernd W. Bottiger[h], Hans Friberg[i], Kjetil Sunde[j], Claudio Sandroni[k]

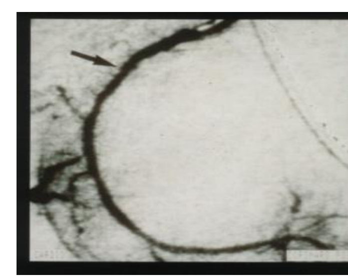
EUROPEAN RESUSCITATION COUNCIL

Summary of changes since 2010 guidelines









OPTIMIZING TTM/TH PROTOCOL

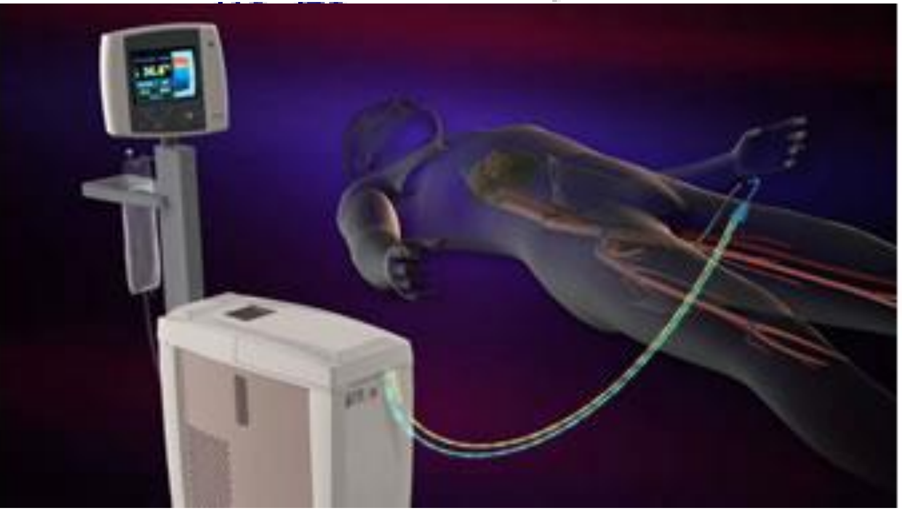
TEMPERATURE MONITORING

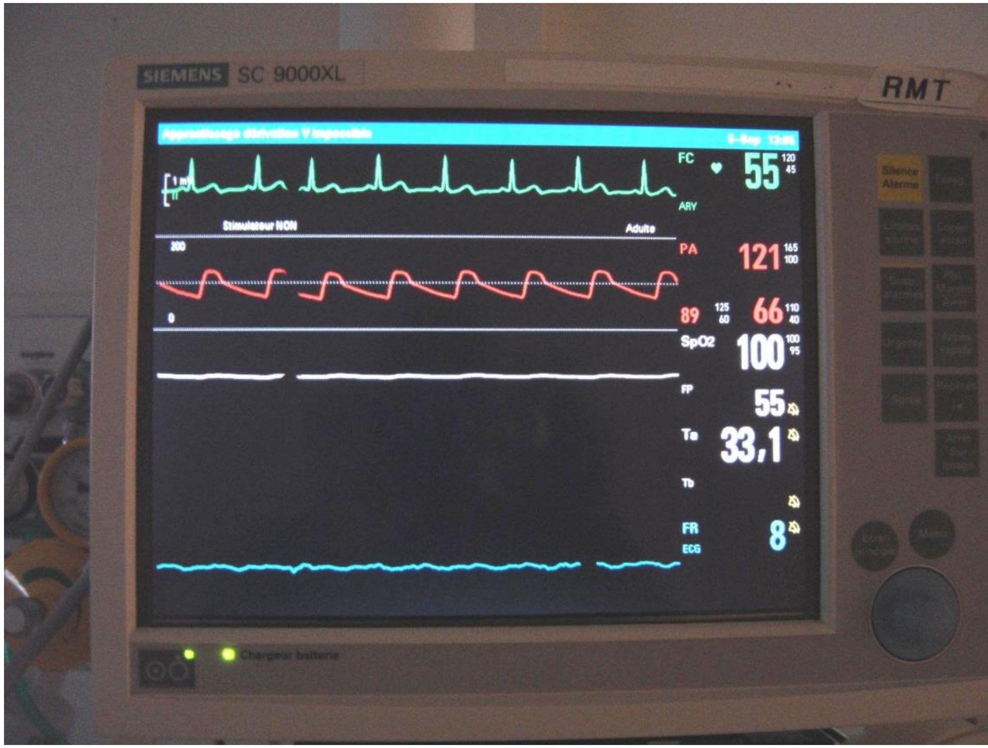
European Resuscitation Council

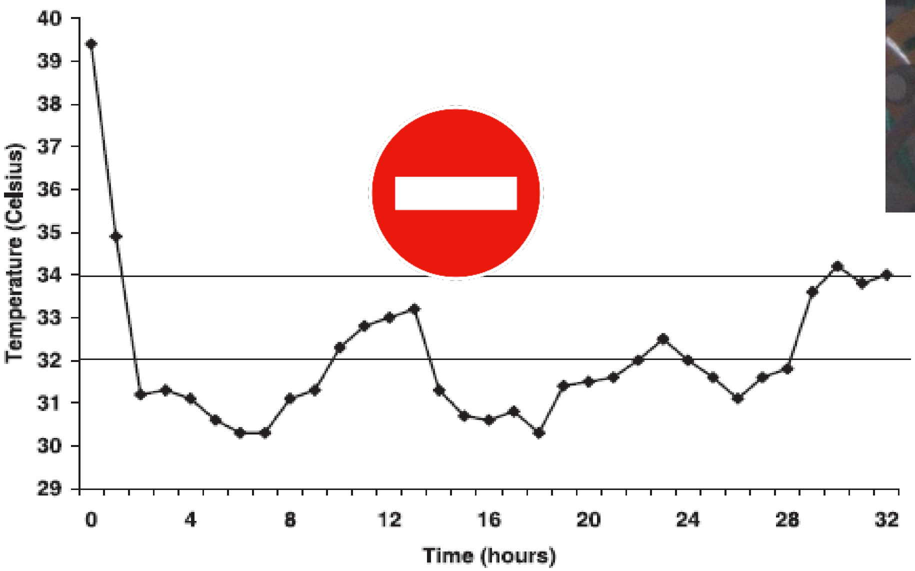
CCT

EUROPEAN RESUSCITATION COUNCIL

Studies documenting improved outcome with therapeutic hypothermia after cardiac arrest used continuous temperature monitoring (LOE 1[468]; LOE

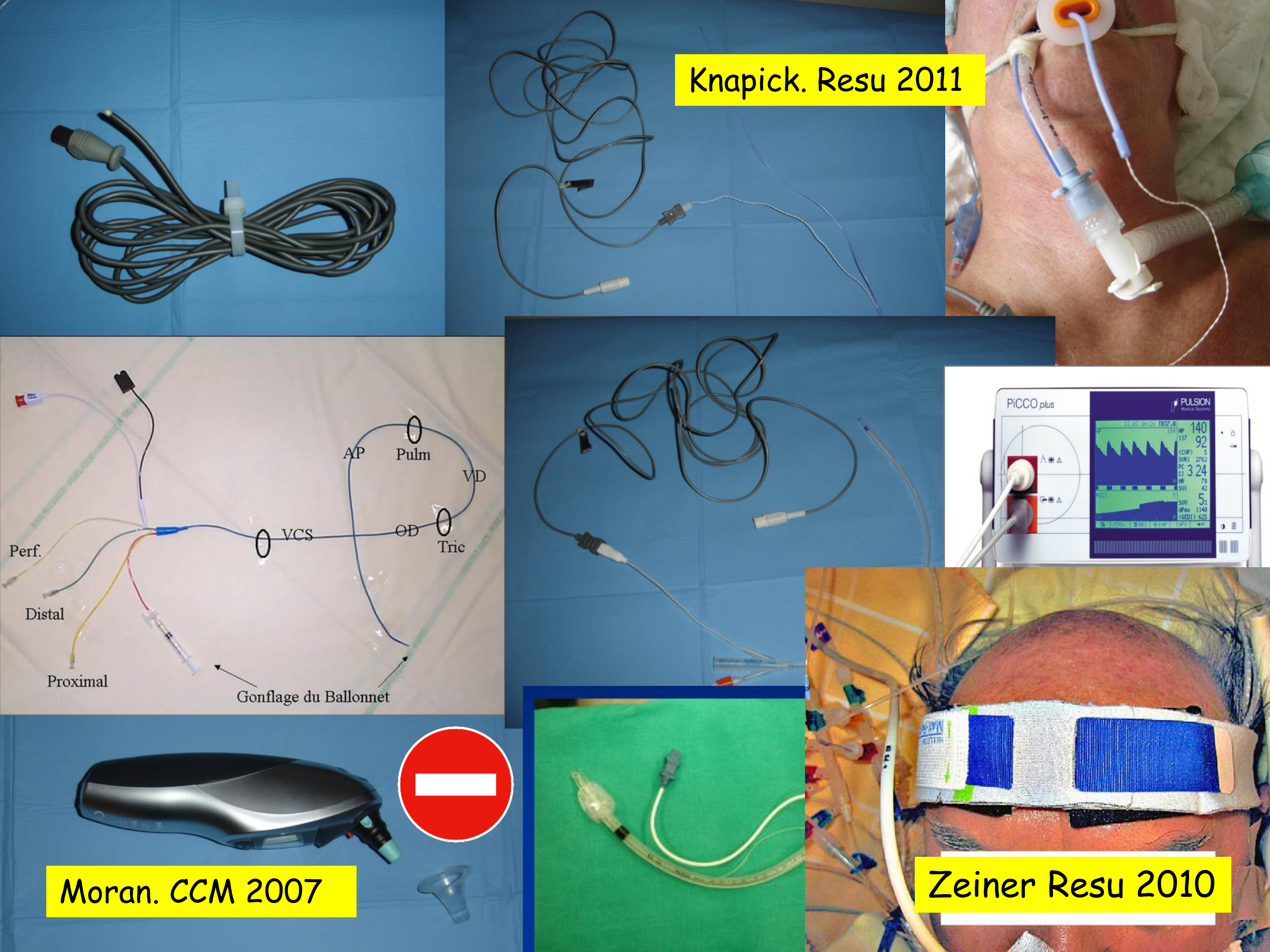






Avoid overcooling and overheating!

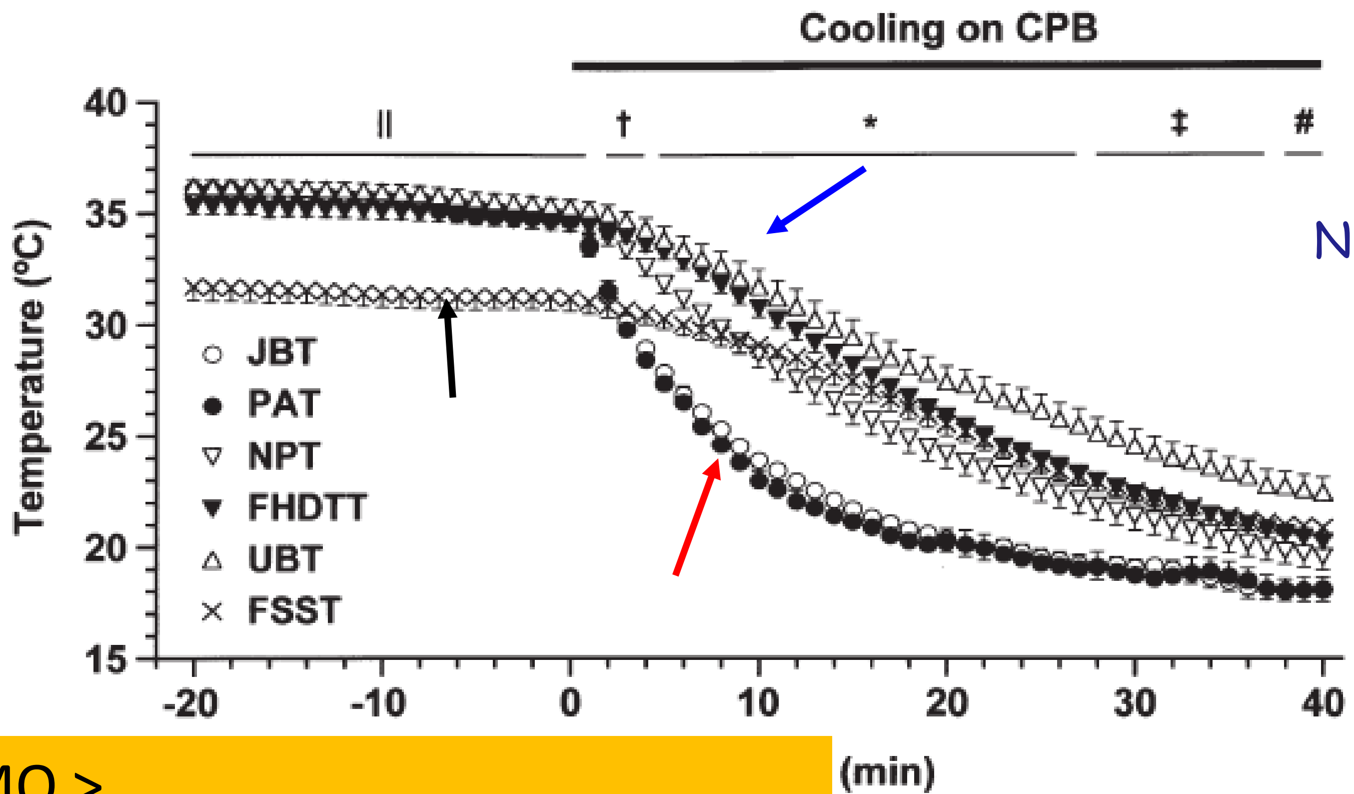
2/3 patients = overcooling (Merchant CCM 2006)


Knapick. Resu 2011
AP
Pulm
VD
VCS
OD
Tric
Perf.
Distal
Proximal
Gonflage du Ballonnet
PiCCO plus
PULSION
Moran. CCM 2007
Zeiner Resu 2010

ECMO ≅ jugular bulb > esophagus ≅ nasophar. > bladder ≅ rectal

Akata et al.
J Thorac Cardiovasc Surg. 2007

Nussmeier.
Anesth Analg 2006



N=20

Reliability mesure t°

ECMO >

Jugular bulb (>) pulmonary artery

Naso-pharyngeal >

Bladder; Rectal >>> Tympanic

Cutaneous (unreliable)

Niven et al.
A review.
Ann Med Int 2015

TTM IN ICU (EXCEPT NEONATES)

French TTM recommendations 2016
Société de Réanimation de Langue Française
Société Française d'Anesthésie et de Réanimation

In collaboration with 5 French Medical Societies: Intensive care, Anesthesiology Resuscitation Council, Emergency Medicine, Neuro Intensive care, Neurovascular, Pediatric Society

Clinical fields: CA, TBI, stroke, status epilepticus, shock

Recommendations are ranked by evidence (grade) and level of consensus reached among the experts (strong to weak)

Practical implementation and monitoring of TTM (question 6)

R 6.3. In patients treated by TTM, core body temperature measurement should probably be preferentially used

(Grade 2+) Strong agreement

Alain Cariou, JF Payen et al. AIC 2017

OPTIMIZING TTM/TH PROTOCOL

SIDE EFFECTS / MONITORING

ACSOS

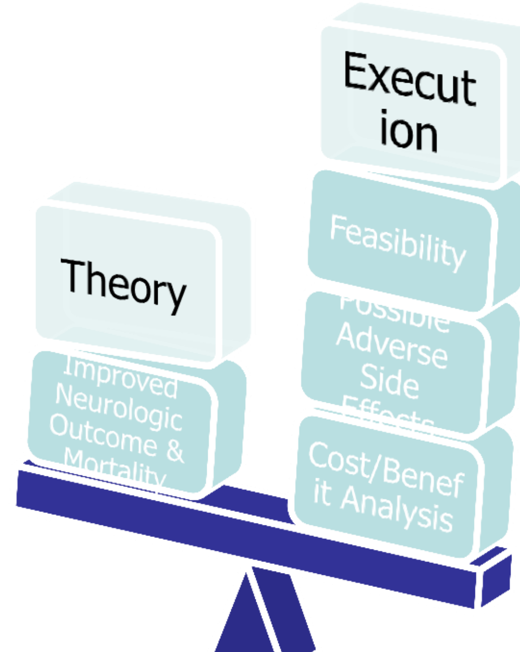
Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation (Review)

THE COCHRANE COLLABORATION®

CD 2010-2016

Arrich J, Holzer M, Herkner H, Müllner M

No significant difference in reported adverse events between TH and control



Rapport risque/bénéfice?

Safety profile and outcome of mild therapeutic hypothermia in patients following cardiac arrest: systematic review and meta-analysis

Guoguang Xiao,[1] Qin Guo,[1] Min Shu,[1] Xiaoping Xie,[2] Jianjun Deng,[1] Yu Zhu,[1] Chaomin Wan[1,3]

EMJ 2012 *(n=63 studies)*

Most of adverse events potentially associated with TH (sepsis, bleeding…) were NS between HT and NT

(except hypoK+; pneumonia: $p=0.06$; arrhythmia: $p=0.05$)

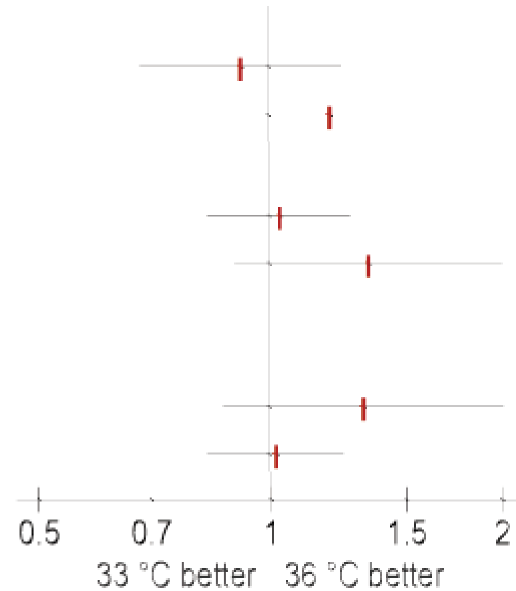
The NEW ENGLAND JOURNAL of MEDICINE

Nielsen Niklas
NEJM 2013

ORIGINAL ARTICLE

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

Time from cardiac arrest to ROSC				P = 0.20
Less than or equal to 25 min	79/243	86/241	0.92 [0.68, 1.24]	
More than 25 min	156/230	138/224	1.20 [0.96, 1.50]	
Shock at admission				P = 0.17
Not present	183/402	180/398	1.03 [0.83, 1.28]	
Present	52/70	44/67	1.35 [0.90, 2.03]	
Site category				P = 0.19
Two largest sites	50/110	40/108	1.33 [0.87, 2.03]	
Sites except two largest	185/363	185/358	1.02 [0.83, 1.25]	



	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

Main side-effects of TTM 30-36°C

Risks

- **shivering**, rhabdomyolysis, **vasoconstriction**
- **cardiovascular** → ischemia, C_I ↓, **brady-arrythmias**
- **respiratory** → **pCO_2 ↓, pO_2 ↓**, pH ↑, congestion
- **coagulation** → coagulopathy, hemorrhage, platelets, WBC (neutro) ↓
- **infectious** → sepsis, pneumonia, immunosuppression
- **renal: hyperdiuresis** → **hypovolemia**
- **electrolytes** → **↓ K, Ph, Mg, Ca**
- **metabolic…** → **Hyperglycemia**; ileus; ↑ **cortisol**, epi+nor, ASAT, amylase; **acidosis** (lactate, fatty acid, ketone)
- **pharmacokinetic**

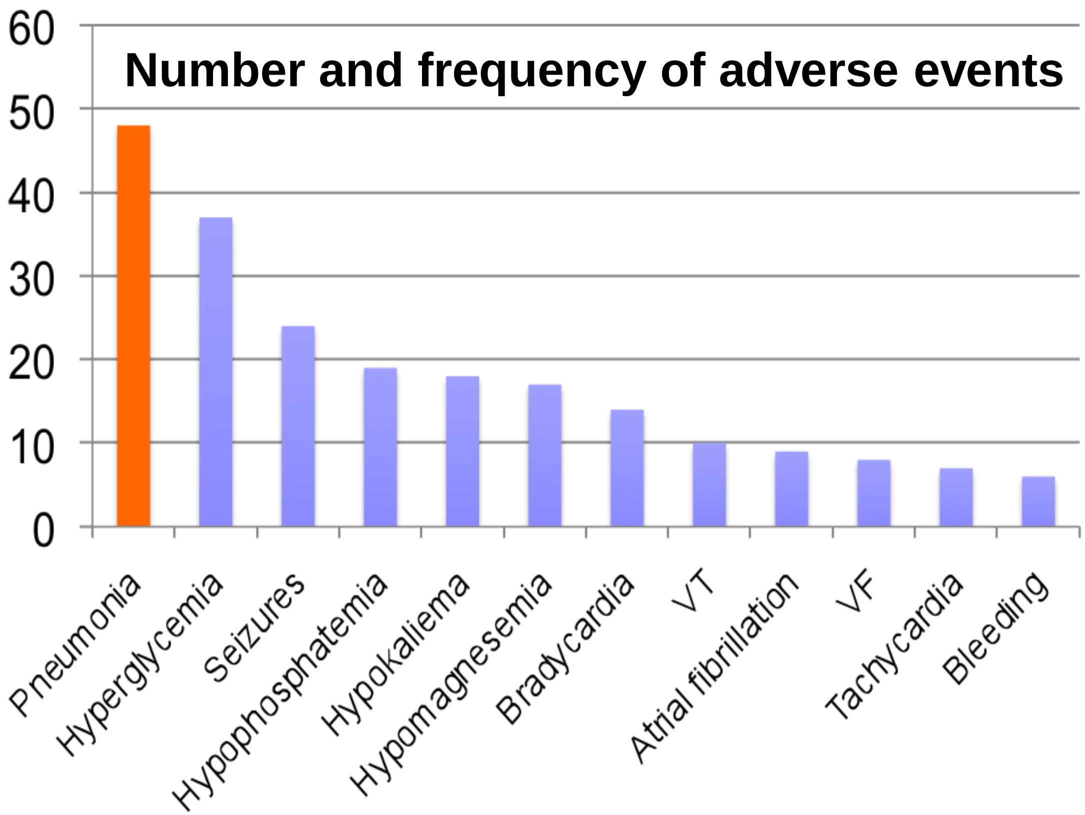
Polderman K. CCM. 2009

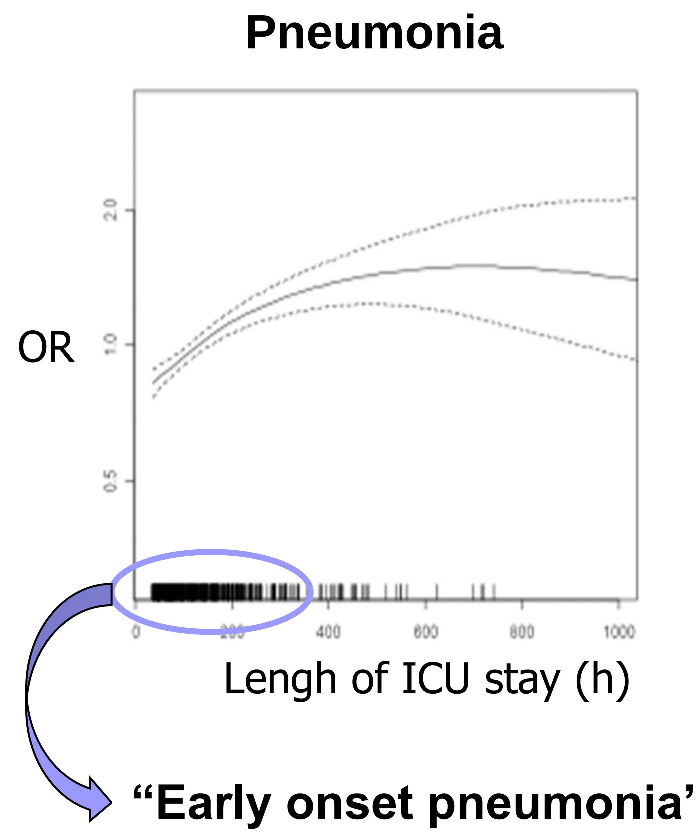
Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia*

Niklas Nielsen, MD, PhD; Kjetil Sunde, MD, PhD; Jan Hovdenes, MD, PhD; Richard R. Riker, MD; Sten Rubertsson, MD, PhD; Pascal Stammet, MD; Fredrik Nilsson, PhD; Hans Friberg, MD, PhD; the Hypothermia Network

Crit Care Med 2011 Vol. 39, No. 1

(n=765 patients with full AE data collection, 22 centers)





Adverse events were common after OHCA.

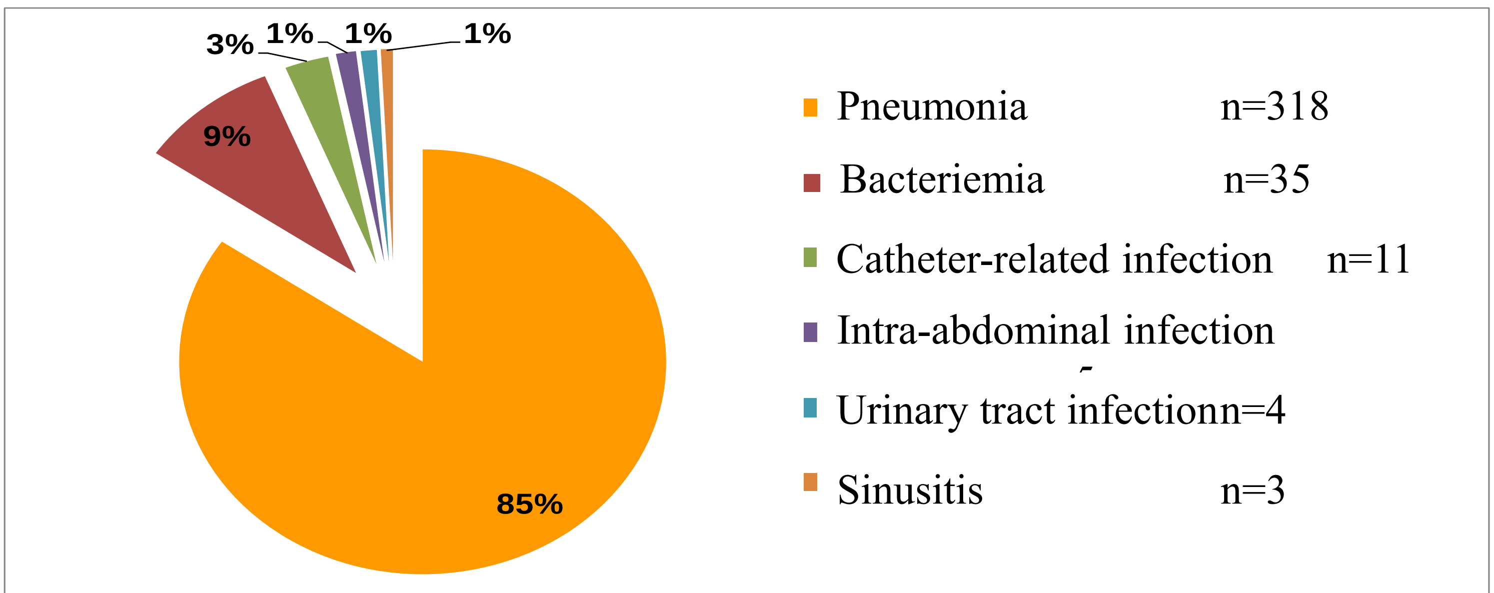
Sustained hyperglycemia & seizures treated with anticonvulsivants were associated with ↑ mortality (multivariate). Bleeding and infection were more common after invasive procedures, but not associated with increased mortality.

Infectious complications in out-of-hospital cardiac arrest patients in the therapeutic hypothermia era*

CCM 2011

Nicolas Mongardon, MD; Sébastien Perbet, MD; Virginie Lemiale, MD; Florence Dumas, MD; Hélène Poupet, MD; Julien Charpentier, MD; Frédéric Péne, MD; Jean-Daniel Chiche, MD; Jean-Paul Mira, MD; Alain Cariou, MD

281/421 patients (67%) developed 373 infections:



New meta-analysis – review: Kavakas et al, J of Infection, 2015

Early-Onset Pneumonia after Cardiac Arrest

Characteristics, Risk Factors and Influence on Prognosis

Sébastien Perbet[1,2], Nicolas Mongardon[1,5], Florence Dumas[3,9], Cédric Bruel[2,8], Virginie Lemiale[1], Bruno Mourvillier[2], Pierre Carli[4,5], Olivier Varenne[5,6]. Jean-Paul Mira[1,5,7]. Michel Wolff[2,8].
and Alain Cariou[1,5,9]

Am J Respir Crit Care Med Vol 184. pp 1048–1054, 2011

n=641 (TH: 500 pts, 78%)
EOP (<D3): 419 (65%)

TH as an independant risk factor for EOP: OR 1.9
↑ MV, ICU stay duration but not VAP

	Odds Ratio	Std. Err.	z	[95% Conf.Interval]	p value
Hypothermia	1.90	0.38	3.20	1.28-2.80	0.001
Male gender	1.15	0.21	0.75	0.80-1.65	0.45
Age (per quartile increase)	0.94	0.08	-0.77	0.79-1.11	0.44
Bystander	1.20	0.35	0.64	0.68-2.11	0.52
Shockable rhythm	1.20	0.22	1.02	0.85-1.71	0.31
Noflow<5 minutes	1.10	0.20	0.56	0.78-1.56	0.58
Lowflow<15 minutes	1.08	0.21	0.39	0.74-1.57	0.70
Epinephrine< 3mg	0.80	0.16	-1.16	0.54-1.17	0.25
Post-resuscitation Shock	1.11	0.20	0.56	0.78-1.56	0.58
SAPS II (per quartile increase)	1.06	0.09	0.63	0.89-1.26	0.53

WE CAN USE ANTIOBIOTICS ! OR PROPHYLAXIS ?

TTM IN ICU (EXCEPT NEONATES)

French TTM recommendations 2016
Société de Réanimation de Langue Française
Société Française d'Anesthésie et de Réanimation

In collaboration with 5 French Medical Societies: Intensive care, Anesthesiology Resuscitation Council, Emergency Medicine, Neuro Intensive care, Neurovascular, Pediatric Society

Clinical fields: CA, TBI, stroke, status epilepticus, shock

Recommendations are ranked by evidence (grade) and level of consensus reached among the experts (strong to weak)

Practical implementation and monitoring of TTM (question 6)

R6.4 – In patients treated by TTM, the occurrence of several complications should be monitored: sepsis, pneumonia, arrythmia, hypokalemia

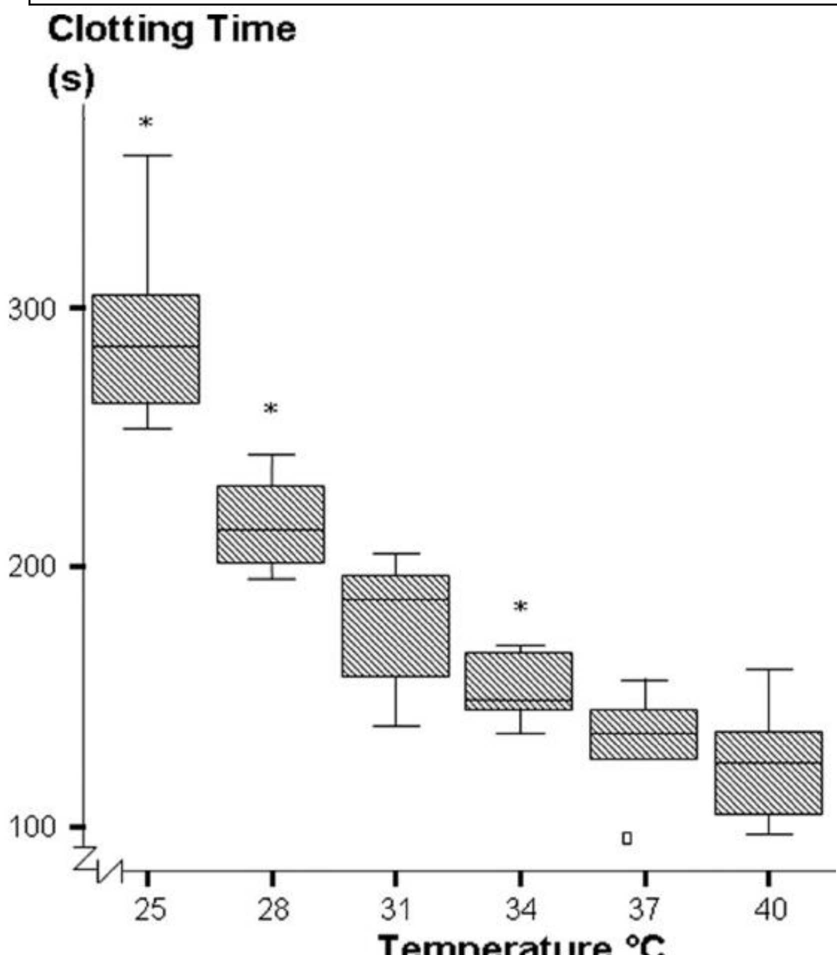
(Grade 2+) Strong agreement

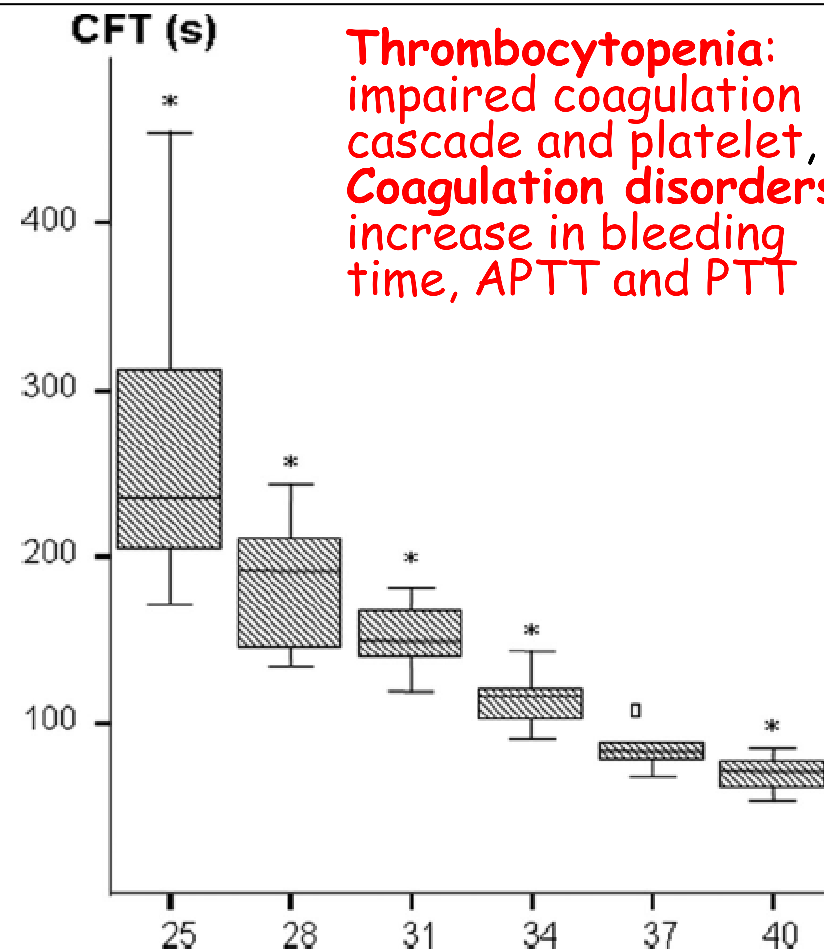
Alain Cariou, JF Payen et al. AIC 2017

A Thromboelastometric Evaluation of the Effects of Hypothermia on the Coagulation System

Malin Rundgren, MD*
Martin Engström, MD, PhD†

(Anesth Analg 2008;107:1465-8)



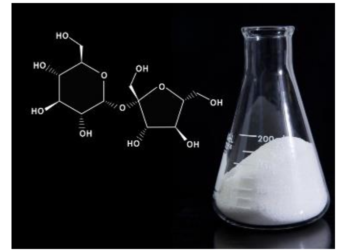


Thrombocytopenia: impaired coagulation cascade and platelet,
Coagulation disorders: increase in bleeding time, APTT and PTT

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

2010-2015



EUROPEAN RESUSCITATION COUNCIL

Blood Glucose Control : Treatment Recommendation

- Strategies to treat hyperglycemia > 180 mg/dL (10 mmol/L) should be considered in adult patients with sustained ROSC after CA.
- Hypoglycemia should be avoided.

Knowledge Gaps

- Adequately powered intervention trials of moderate ranges of glucose control in patients who survive cardiac arrest are required.

Glucose control

There is a strong association between high blood glucose after resuscitation from cardiac arrest and poor neurological outcome.[261,439,440] Based on the available data, following ROSC maintain the blood glucose at $\leq 10\,\text{mmol}\,\text{l}^{-1}$ ($180\,\text{mg}\,\text{dl}^{-1}$) and avoid hypoglycaemia.[441] Do not implement strict glucose control in adult patients with ROSC after cardiac arrest because it increases the risk of hypoglycaemia.

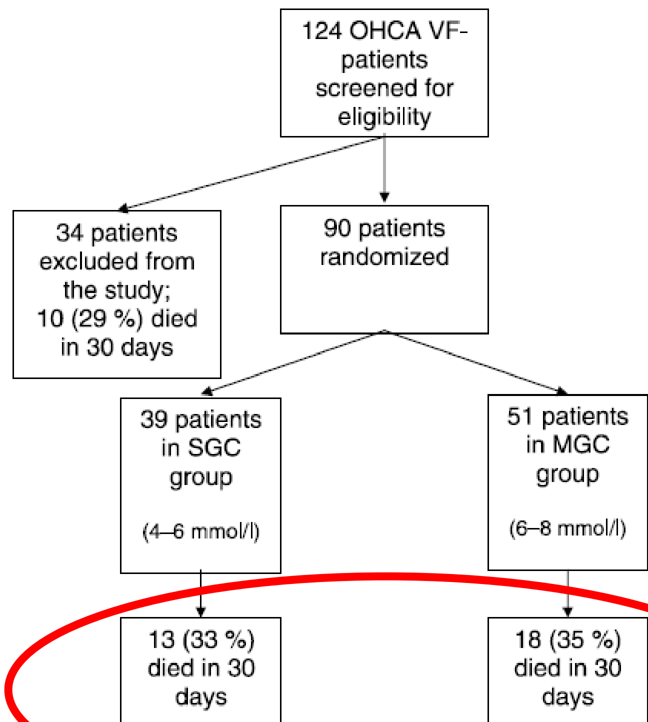
Intensive Care Med (2007) 33:2093–2100
DOI 10.1007/s00134-007-0876-8

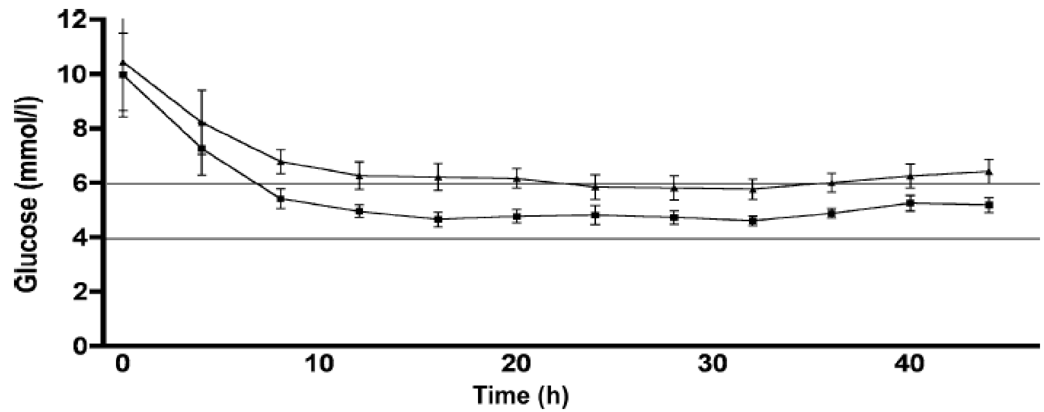
ORIGINAL

ICM 2007

Tuomas Oksanen
Markus B. Skrifvars
Tero Varpula
Anne Kuitunen
Ville Pettilä
Jouni Nurmi
Maaret Castrén

Strict versus moderate glucose control after resuscitation from ventricular fibrillation

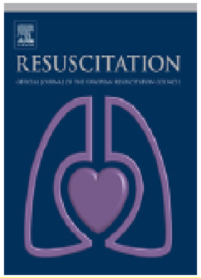




P=0,846

Strict normoglycaemic blood glucose levels in the therapeutic management of patients within 12 h after cardiac arrest might not be necessary

Heidrun Losert[a], Fritz Sterz[a,*], Risto O. Roine[b], Michael Holzer[a],
Patrick Martens[c], Erga Cerchiari[d], Marjaana Tiainen[b], Marcus Müllner[a],
Anton N. Laggner[a], Harald Herkner[a], Martin G. Bischof[e]



Resuscitation 2008

Resuscitation (2008) 76, 214—220

- Retrospective analysis of data obtained from the European RCT about the effect of mild hypothermia after cardiac arrest
- Adjustment (in multivariate analysis) for sex, “no-flow” and “low-flow” ROSC, epinephrine dose administered during CPR, reoccurrence of CA after CPR, hypothermia, history of CHD or MI

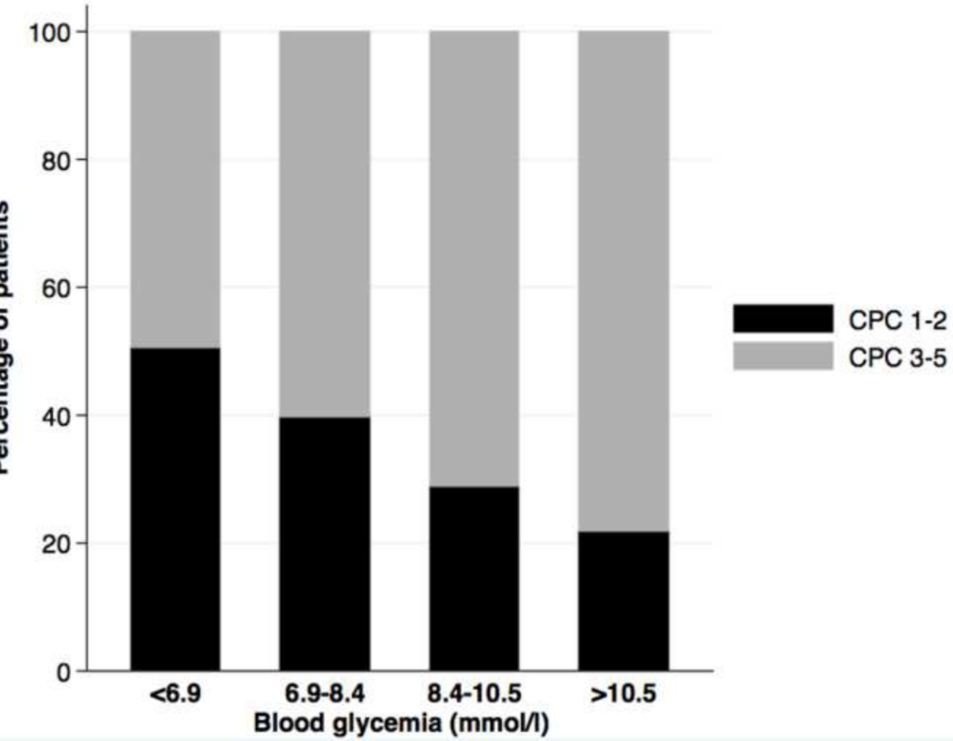
Odds ratio of good neurological recovery after cardiac arrest

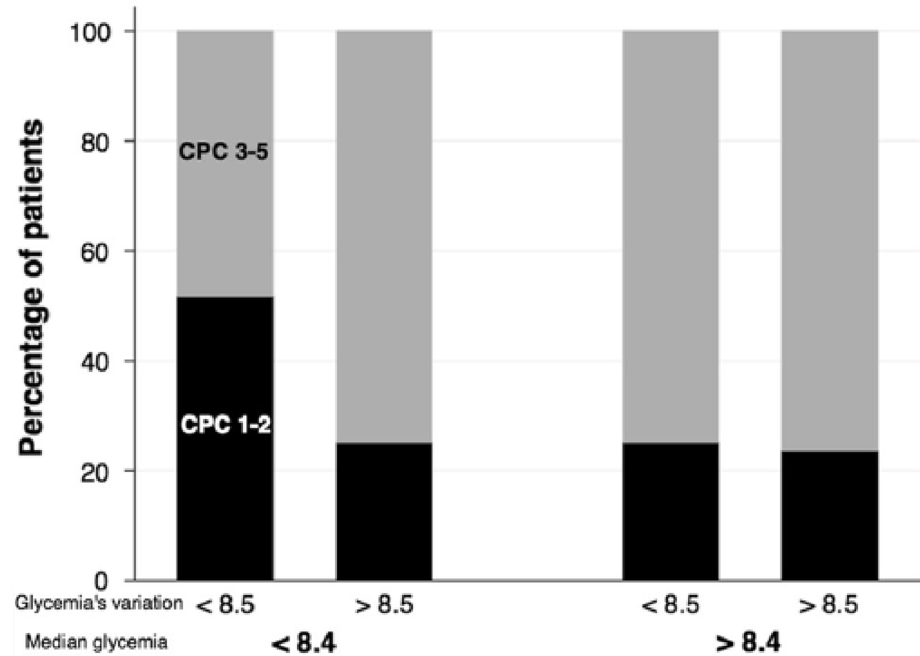
	Group 1 (67-115)	**Group 2 (116-143)**	**Group 3 (144-193)**	**Group 4 (194-464)**
Med [IQR25-75]	100 [94-108]	130 [123-135]	159 [150-175]	255 [207-292]
OR [IC95%]	4.55 (1.28-16.12)	13.02 (3.29-49.9)	1.37 (0.38-5.64)	1 (ref)

Blood glucose level and outcome after cardiac arrest: insights from a large registry in the hypothermia era

ICM 2014

Daviaud F, Dumas F, Demars N, Geri G, Bouglé A, Morichau-Beauchant T, Nguyen YL, Bougouin W, Pène F, Charpentier J, Cariou A





multivariate analysis, an increased median BG level over the first 48 h was found to be an independent predictor of poor issue [OR = 0.43; 95 % CI (0.24–0.78), $p = 0.006$].

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

2015

EUROPEAN RESUSCITATION COUNCIL

O2 / CO2: NEW GUIDELINES

cardiac arrest, as soon as arterial blood oxygen saturation can be monitored reliably (by blood gas analysis and/or pulse oximetry), titrate the inspired oxygen concentration to maintain the arterial blood oxygen saturation in the range of 94–98%. Avoid hypoxaemia, which is also harmful – ensure reliable measurement of arterial oxygen saturation before reducing the inspired oxygen concentration.

it is reasonable to adjust ventilation to achieve normocarbia and to monitor this using the end-tidal CO_2 and arterial blood gas values.

Association Between Arterial Hyperoxia Following Resuscitation From Cardiac Arrest and In-Hospital Mortality

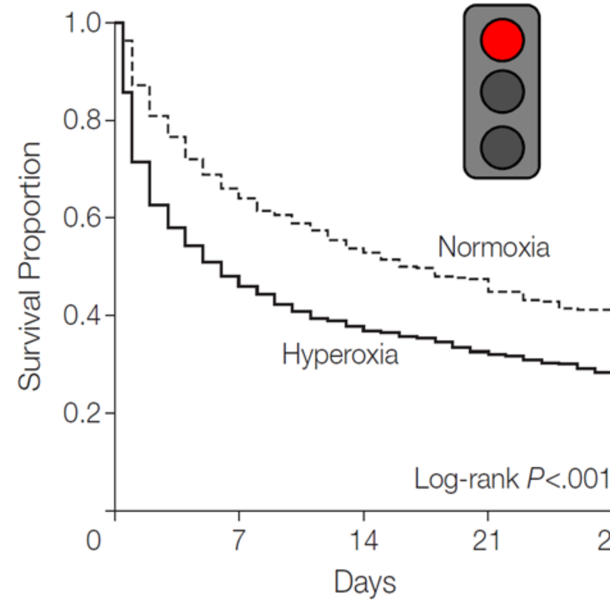
Kilgannon JH et al. The Emergency Medicine Shock Research Network. JAMA. 2010;303:2165-71

Large US database
n=6326 post-CA pts (OHCA 43%)

Exposed to **Hypoxia** **<60mmHg** **n=3999**	*Exposed to* **Normoxia** **60-300mmHg** **n=1171**	*Exposed to* **Hyperoxia** **>300mmHg** **n=1156**
Death 57%	**Death 45%**	**Death 63%**

Independant predictors of in-hospital mortality

Variable	OR (95% CI)	*P* Value
Age decile	1.1 (1.1-1.2)	<.001
Emergency department origin	1.5 (1.3-1.7)	<.001
Nonindependent functional status at admission	1.3 (1.1-1.4)	<.001
Chronic renal failure	1.6 (1.3-1.9)	<.001
Active chemotherapy	2.8 (1.8-4.6)	<.001
High heart rate in ICU[b]	1.9 (1.7-2.1)	<.001
Hypotension at ICU arrival[c]	2.1 (1.9-2.3)	<.001
Hypoxia exposure	1.3 (1.1-1.5)	.009
Hyperoxia exposure	1.8 (1.5-2.2)	<.001



OXYGEN: WHAT'S NEW AFTER ROSC?

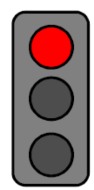
American Journal of Emergency Medicine **2014**

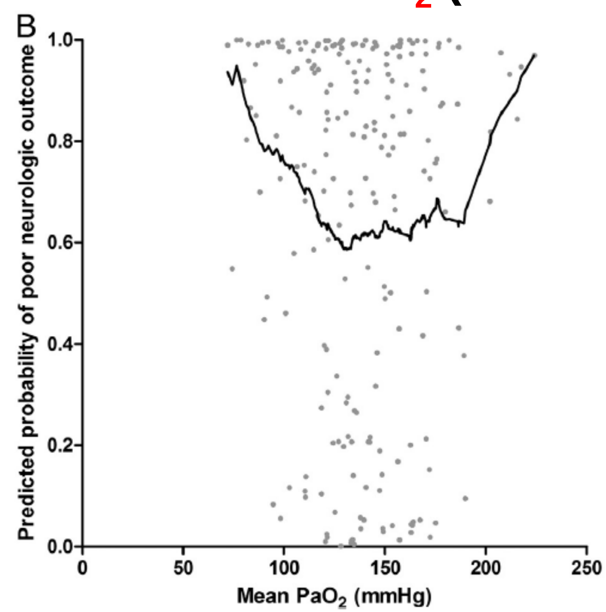
journal homepage: www.elsevier.com/locate/ajem

Association between mean arterial blood gas tension and outcome in cardiac arrest patients treated with therapeutic hypothermia ☆

Byung Kook Lee, MD, PhD [a], Kyung Woon Jeung, MD, PhD [a,*], Hyoung Youn Lee, MD [b], Seung Joon Lee, MD [c], Yong Hun Jung, MD [a], Wang Ki Lee, MD [a], Tag Heo, MD, PhD [a], Yong Il Min, MD, PhD [a]

213 patients > 16 yo with CA (OHCA 83%, 2008-12). TH 100%. Mean PaO_2 (8 ABG) from ROSC to rewarming. Hyperoxia <3%





Multivariate: mean PaO_2 not associated with IH-death

Multivariate: PaO_2 (1st 2nd 3rd quartiles) associated with poor neurologic outcome

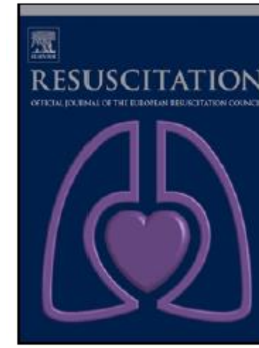
V-shaped relationship between PaO_2 and poor CPC (best ~ 130mmHg)

OXYGEN: WHAT'S NEW AFTER ROSC?

The Effect of Hyperoxia on Survival Following Adult Cardiac Arrest: A Systematic Review and Meta-analysis of Observational Studies

Author: Chih-Hung Wang Wei-Tien Chang Chien-Hua Huang Min-Shan Tsai Ping-Hsun Yu An-Yi Wang Nai-Chuan Chen Wen-Jone Chen

2014



Studies comparing oxygen vs normoxia alone excluded

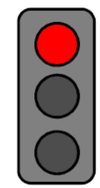
10 studies pooled in meta-analysis (out of 16 assessed for eligibility)

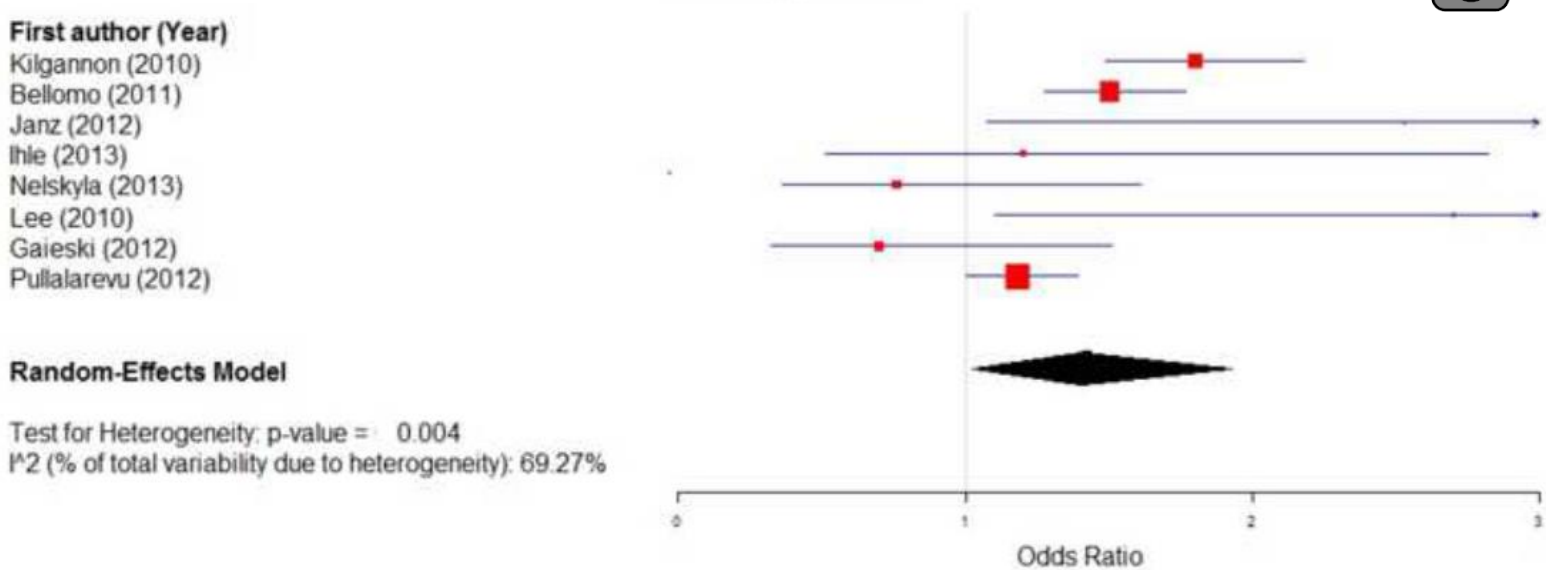
Hyperoxia: PaO_2 > 300 mmHg

Results were inconsistent in subgroups, with significant heterogeneity and limited studies

In hospital mortality

OR 1.40 (1.02-1.93), R^2 0.69





OXYGEN: WHAT'S NEW AFTER ROSC?

The Effect of Hyperoxia on Survival Following Adult Cardiac Arrest: A Systematic Review and Meta-analysis of Observational Studies

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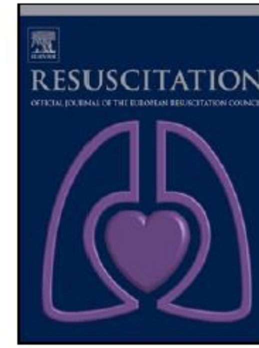

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Studies comparing oxygen vs normoxia alone excluded

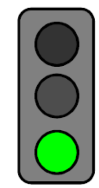
10 studies pooled in meta-analysis (out of 16 assessed for eligibility)

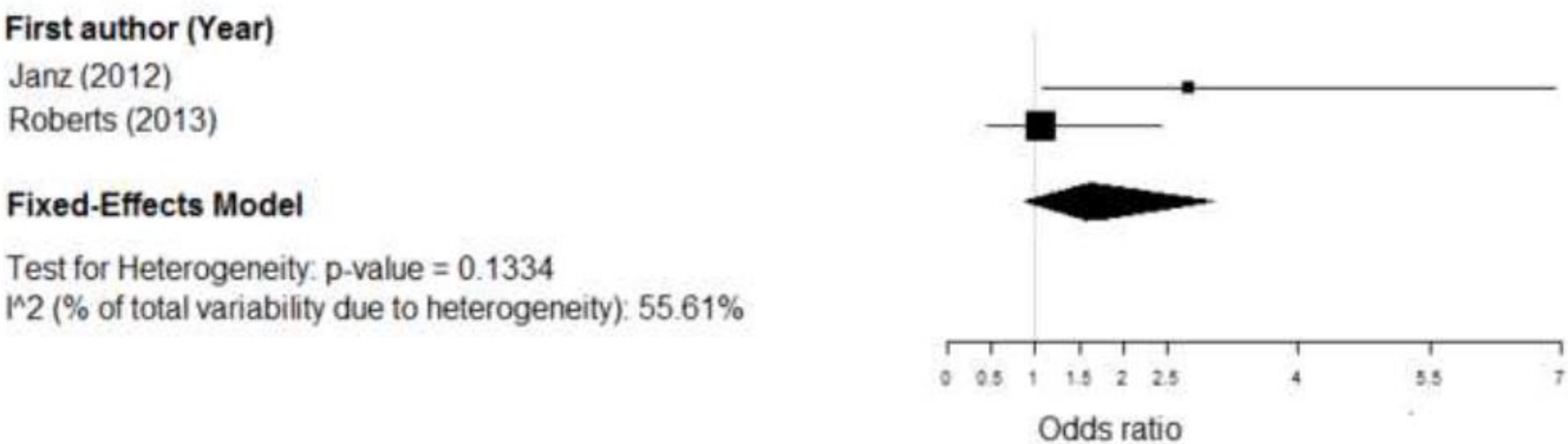
Hyperoxia: $PaO_2 > 300$ mmHg

Results were inconsistent in subgroups, with significant heterogeneity and limited studies

Poor neurologic outcome at hospital discharge

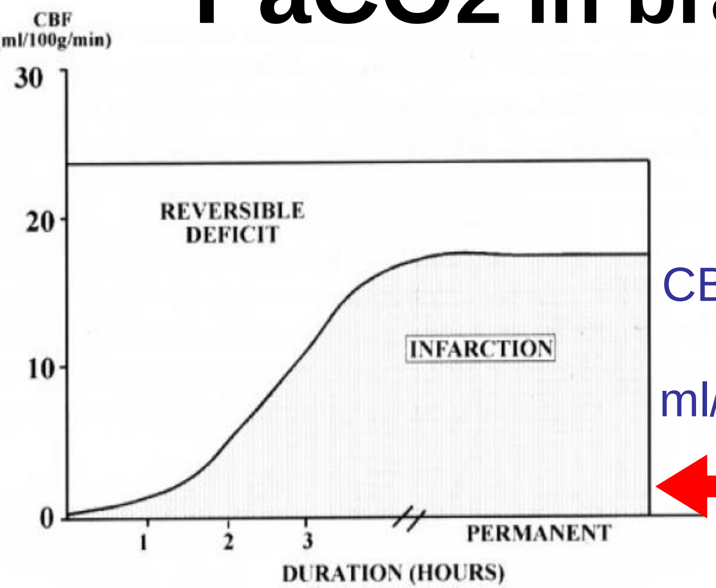
OR 1.62 (0.87-3.02), R^2 0.55





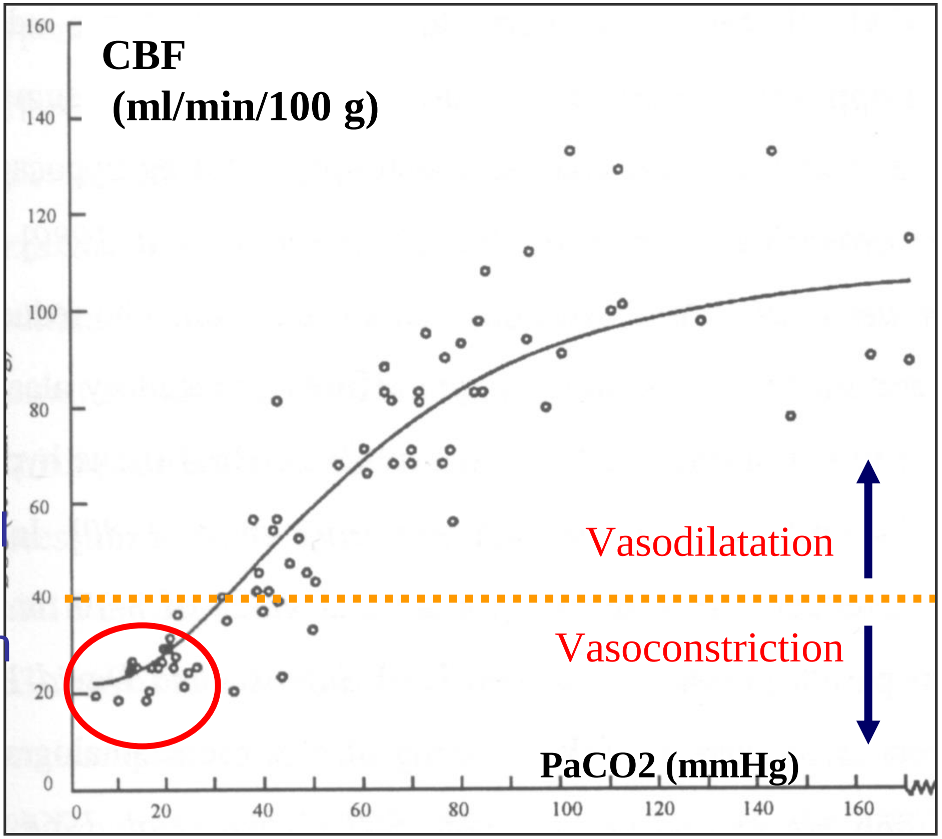
CO2: WHAT'S NEW ?

CBF and PaCO2 in brain



Jones TH, Morawetz RB, Crowell RM, et al. Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg 1981; 54:773–782

CBF normal 40-50 ml/100g/min



Decreasing PaCO2 of 1 mmHg decreasing CBF of 3%

ESTIMATION OF CO_2-INDUCED CHANGES IN CEREBRAL BLOOD FLOW BY TRANSCRANIAL DOPPLER SONOGRAPHY: A VALIDATION STUDY

Weyland J Cardiothorac Vasc Anesth 1994

Association Between Postresuscitation Partial Pressure of Arterial Carbon Dioxide and Neurological Outcome in Patients With Post–Cardiac Arrest Syndrome

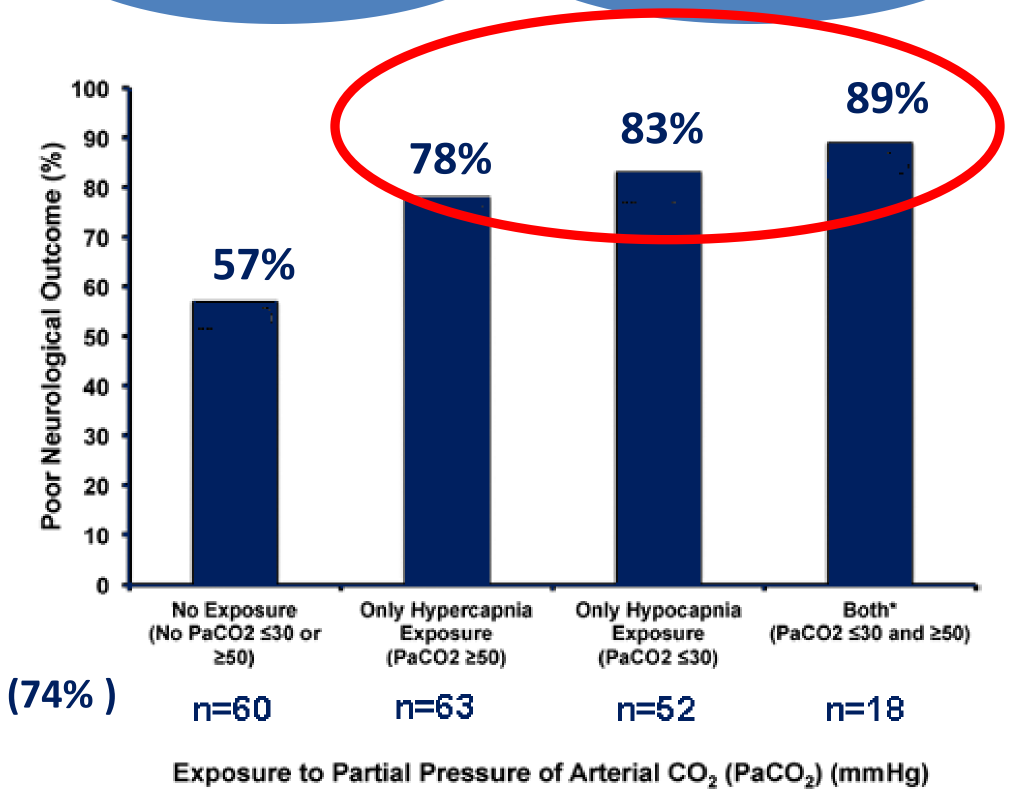
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

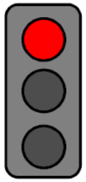
Brian W. Roberts, MD; J. Hope Kilgannon, MD; Michael E. Chansky, MD; Neil Mittal, MD; Jonathan Wooden, MD; Stephen Trzeciak, MD, MPH

2013

Retrospective and single center; 193 nontraumatic comatose OHCA ≥ 18 yo + all ABGs ≤ 24h after ROSC

No exposure 31%	Hypocapnia only 27%	Hypercapnia only 33%	Both 9%
PaCO2 ≥ 50 mmHg	PaCO2 ≤ 30 mmHg	PaCO2 ≥ 50 mmHg	PaCO2 ≤ 30 mmHg





Hypo- & hyper-capnia are common & independently associated with poor neurologic outcome

Contents lists available at ScienceDirect

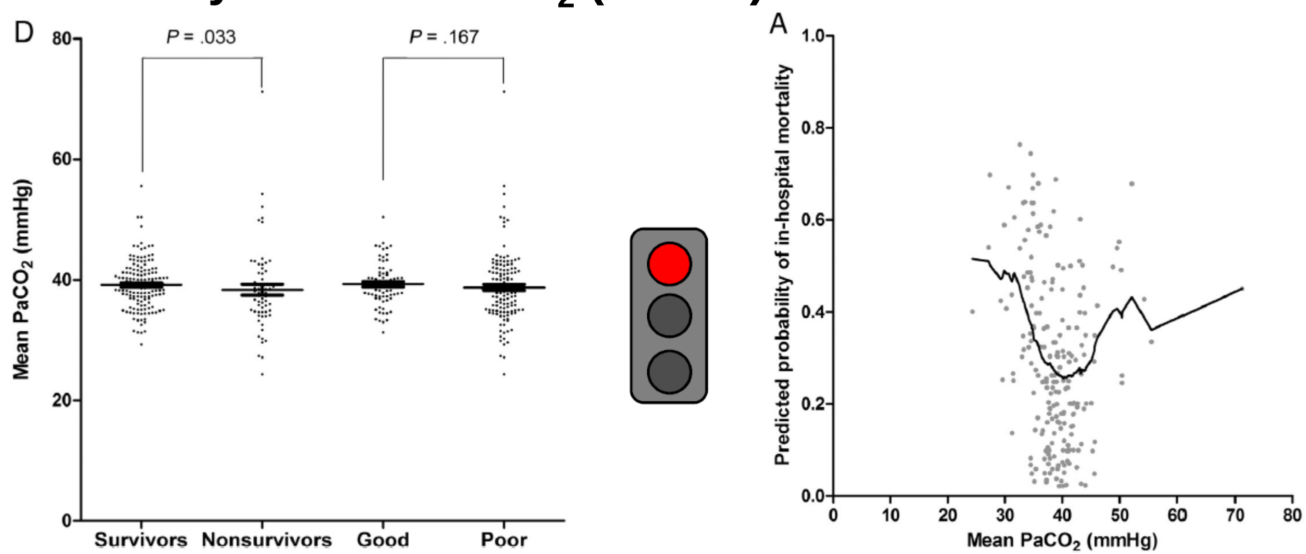
American Journal of Emergency Medicine 2014

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

Association between mean arterial blood gas tension and outcome in cardiac arrest patients treated with therapeutic hypothermia☆

Byung Kook Lee, MD, PhD [a], Kyung Woon Jeung, MD, PhD [a,*], Hyoung Youn Lee, MD [b], Seung Joon Lee, MD [c], Yong Hun Jung, MD [a], Wang Ki Lee, MD [a], Tag Heo, MD, PhD [a], Yong Il Min, MD, PhD [a]

213 CA patients with TH > 16 yo. Mean $PaCO_2$ (8 ABG)



Multivariate: hypocarbia but not hypercarbia independently associated with increased risk of IH-death (OR 2.52, CI95% 1.18-5.37, P=0.016);

U-shaped relationship between $PaCO_2$ and IH mortality (best ~ 35-45mmHg)

Hypocarbia & hypercarbia not associated with increased poor neurologic outcome

Arterial Blood Gas Tensions After Resuscitation From Out-of-Hospital Cardiac Arrest: Associations With Long-Term Neurologic Outcome*

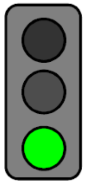
CCM 2014

Jukka Vaahersalo, MD[1]; Stepani Bendel, MD, PhD[2]; Matti Reinikainen, MD, PhD[3]; Jouni Kurola, MD, PhD[4]; Marjaana Tiainen, MD, PhD[5]; Rahul Raj, BM[1]; Ville Pettilä, MD, PhD[1]; Tero Varpula, MD, PhD[1]; Markus B. Skrifvars, MD, PhD, FCICM[1]; for the FINNRESUSCI Study Group

409 OHCA pts with ≥ 1 ABG. TH 71%

8 $PaCO_2$ measurements/patient ≤ 24h.

Characteristic		All Patients (*n* = 409)	Patients With Good Outcome (*n* = 168)	Patients With Poor Outcome (*n* = 241)	*p*
Proportion of time (%) spent in carbon dioxide range					
Low	< 30 mm Hg	3% (0–59%)	0% (0–82%)	1.001 (0.990–1.012)	0.88
Middle	30–37.5 mm Hg	54% (0–91%)	51% (0–98%)	0.993 (0.985–1.002)	0.12
Intermediate	37.5–45 mm Hg	21% (0–85%)	15% (0–92%)	1.001 (0.992–1.0010)	0.82
High	> 45 mm Hg	0% (0–61%)	0% (0–59%)	1.015 (1.002–1.029)	0.024



Hypercapnia was associated with good 1 year outcome

The mean 24h PaCO2 was independent predictor of good outcome

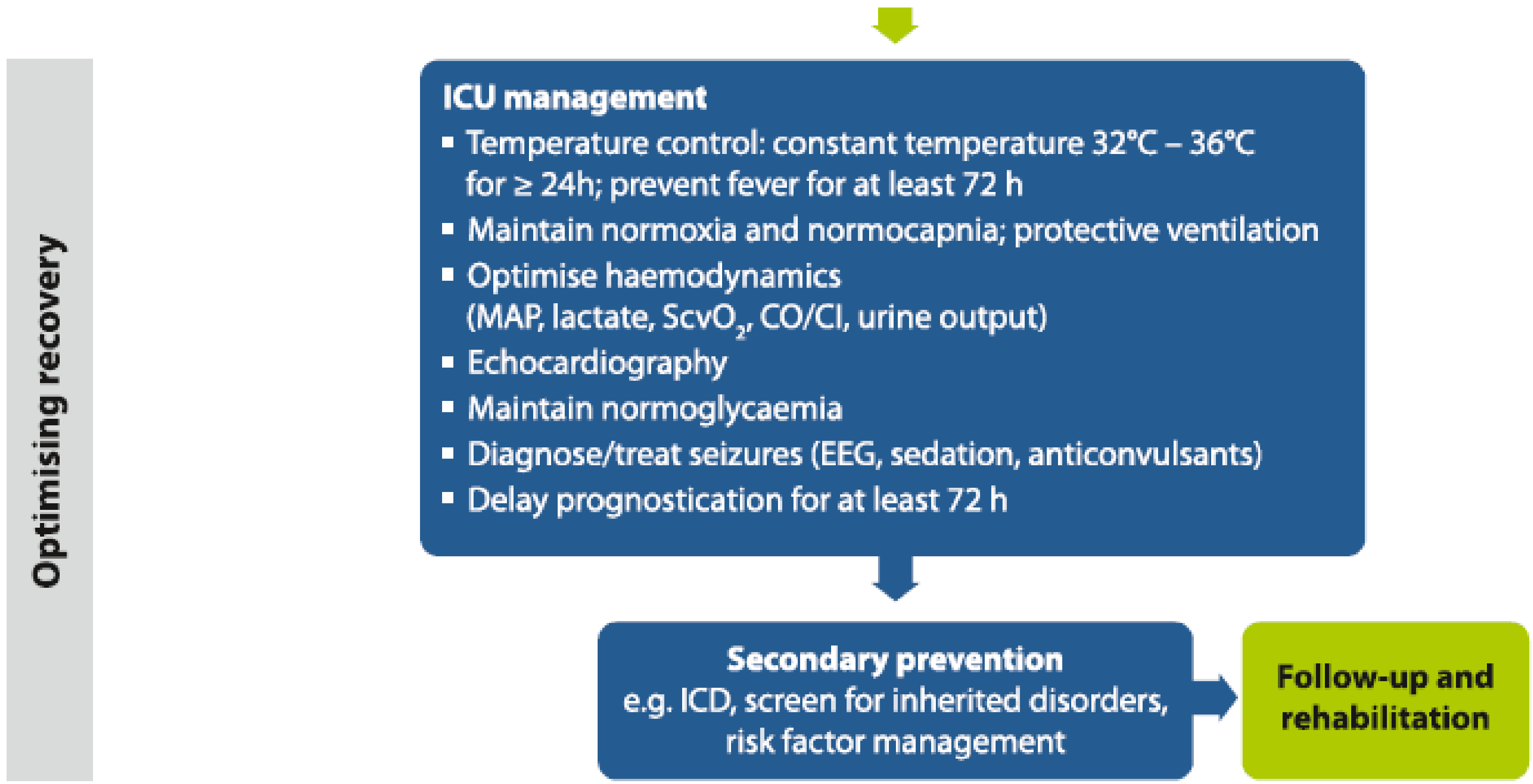
Time spent in PaCO2 > 45 mmHg was independent associated with good outcome

European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015 Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015☆

Jerry P. Nolan[a,b,*], Jasmeet Soar[c], Alain Cariou[d], Tobias Cronberg[e], Véronique R.M. Moulaert[f], Charles D. Deakin[g], Bernd W. Bottiger[h], Hans Friberg[i], Kjetil Sunde[j], Claudio Sandroni[k]

EUROPEAN RESUSCITATION COUNCIL

Summary of changes since 2010 guidelines



Practical protocol for treatment of patients

Sedatives
Analgesics
Neuromuscular blockers

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)

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

Sterz F, Behringer W, Holzer M. 2006. Global hypothermia for neuroprotection. Acute Carddiac Care.
Sunde K. Resuscitation. 2007. Implementation of a standardised protocol for post resuscitation care.
Deye N. Textbook "Acute heart failure syndromes" . 2007. Acute cardiac failure & neuroprotection.
Kupchnick NL. CCM. 2009. Suppl. Implementation of a TH protocol.
Seder DB, Van der Kloot TE. CCM. 2009. Suppl. Methods of cooling. Practical aspects.

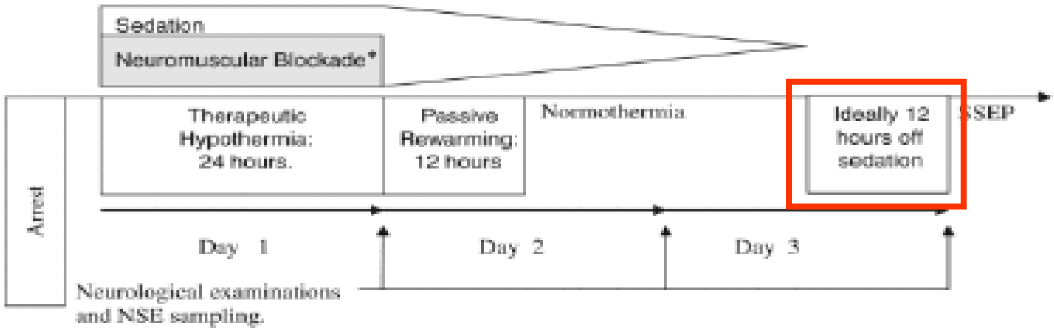
Review of protocol utility during TH (neg. /40) : Freund, Cardiol J, 2017

Sedation Confounds Outcome Prediction in Cardiac Arrest Survivors Treated with Hypothermia

Neurocrit Care 2011

Edgar A. Samaniego, **Michael Mlynash**, **Anna Finley Caulfield**, **Irina Eyngorn**, and **Christine A. C. Wijman**
Stanford University School of Medicine, Stanford University Medical Center, 780 Welch Road, Suite 205, Palo Alto, CA 94304, USA

n=85 (53 poor outcome = 65%; 53 hypothermia = 62% ; 62 sedative H60 = 73%)

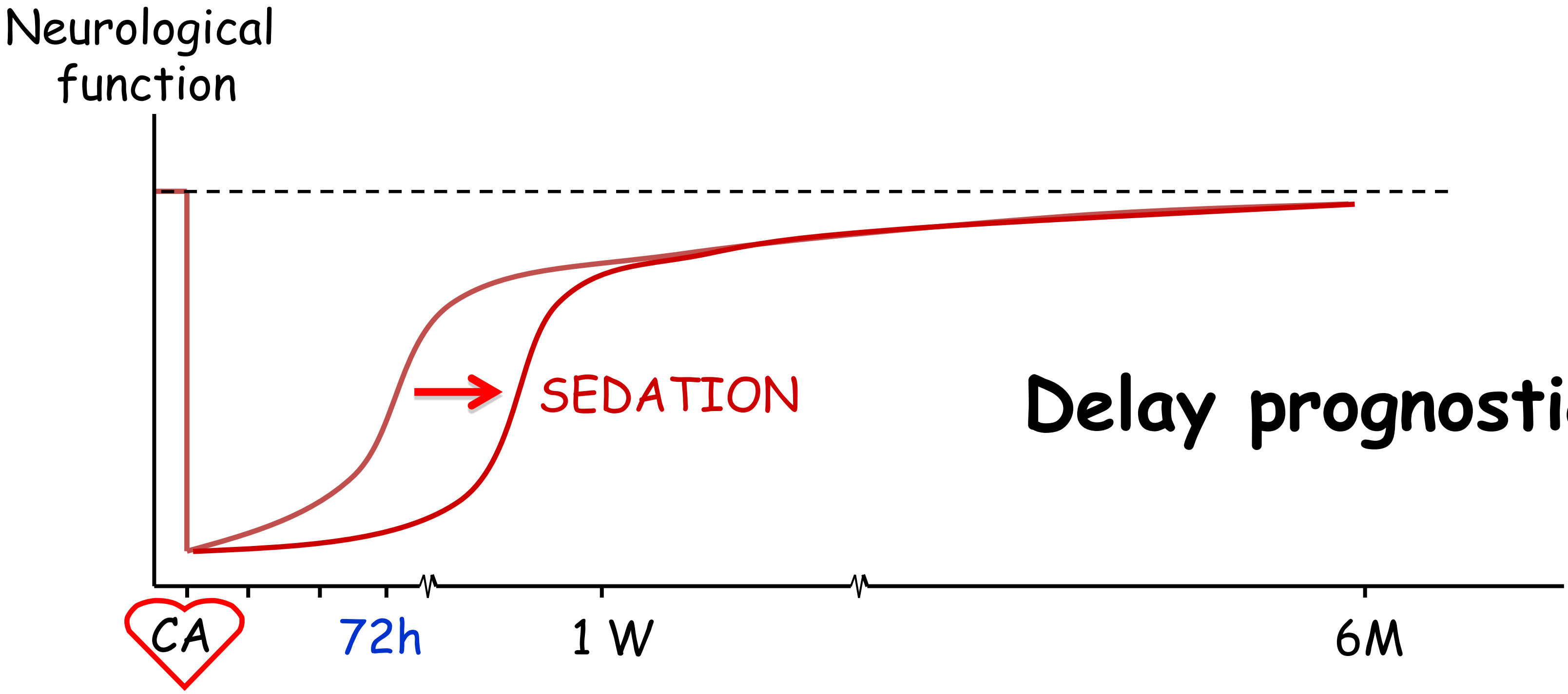


* Neuromuscular blockade was utilized to treat shivering during hypothermia.
SSEP = somatosensory-evoked potentials; NSE = neuron specific enolase.

Patients treated with TH are more likely to receive sedation.
Sedatives are an important prognostication confounder.
Midazolam can prolong conscioussness recovery time & delay extubation
Sedatives in both TH and non-TH patients may confound clinical exam.

Fugate Wijdicks, et al Annals Neurology 2010

Sedation (with their pharmakokinetic) and TH (TTM) will affect recovery ...& prognosis



Delay prognostication!

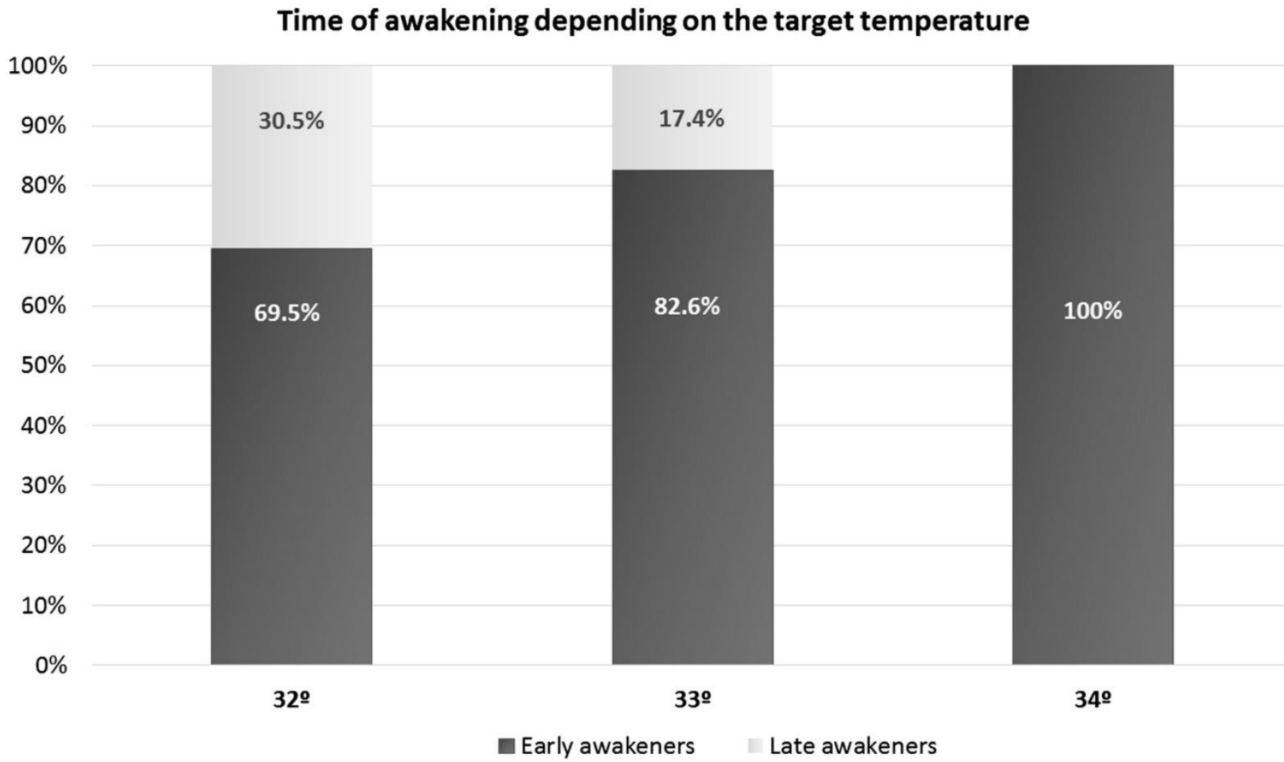
A comparison of therapeutic hypothermia and strict therapeutic normothermia after cardiac arrest

Casamento, et al Resuscitation 2016

In 2 ICUs, a before-after study (2 X 69), no differences in feasibility (proportion of within range temperatures); doses of midazolam, fentanyl, NMB, fever in the first 96H and shivering were lower in 36-TTM compared with TH.

Influence of the temperature on the moment of awakening in patients treated with therapeutic hypothermia after cardiac arrest☆

Ponz et al et al Resuscitation 2017



Delay of 5 days if 33° C ?

Results: We included 163 CA survivors (84.7% male, 60.2 years) who regained consciousness after TTM: target temperature was either 32 °C (36.2%), 33 °C (56.4%) or 34 °C (6.7%). Mean time of awakening was 3.8 days. Thirty-four patients (20.9%) regained neurological responsiveness after 5 days after CA. All of them had been cooled to either 32 °C (18 patients) or 33 °C (16), and no patient cooled to 34 °C awakened after day 5. A lower target temperature was associated with a later awakening ($p < 0.001$). The time to advanced cardiopulmonary resuscitation (CPR) was shorter among the early awakers ($p = 0.04$), but we found no other predictors of an earlier awakening.

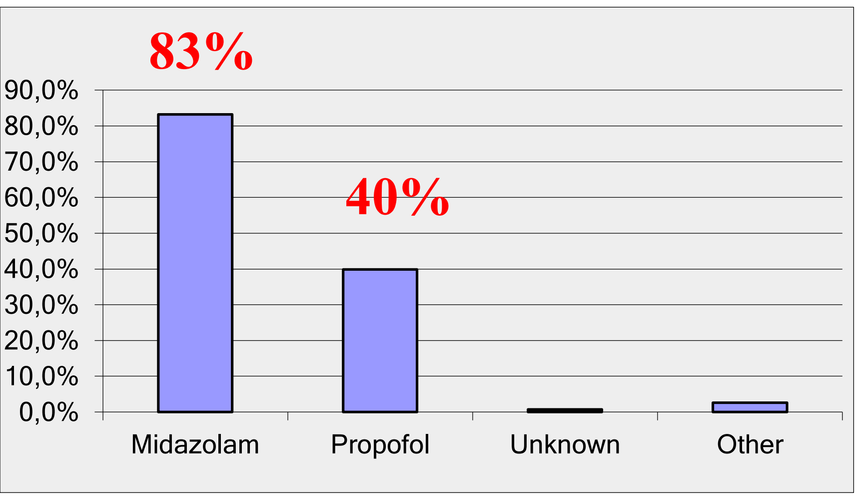
RESEARCH Open Access

Changes in cardiac arrest patients' temperature management after the 2013 "*TTM*" trial: results from an international survey

Nicolas Deye[1*], François Vincent[2], Philippe Michel[3], Stephan Ehrmann[4], Daniel da Silva[5], Michael Piagnerelli[6], Antoine Kimmoun[7], Olfa Hamzaoui[8], Jean-Claude Lacherade[9], Bernard de Jonghe[10], Florence Brouard[3], Corinne Audoin[11], Xavier Monnet[12], Pierre-François Laterre[13] and For the SRLF Trial Group

AIC. 2016

During TTM, do you use sedatives? (n=423)



	Response	N
Always	**85%**	**358**
Frequently	11%	47
Sometimes	4%	16
Never	0,2%	1
Unknown	0,2%	1

Studies with hepatically eliminated (active) drugs suggest ≈ 11 % reduction in clearance per °C change. Hepatic metabolism (CYP450) is decreased if TTM for hepatically metabolized drugs (≈ NMB, sedatives, analgesics, anticonvulsivants…)

Anderson THTM 2016

RESEARCH Open Access

Changes in cardiac arrest patients' temperature management after the 2013 "*TTM*" trial: results from an international survey

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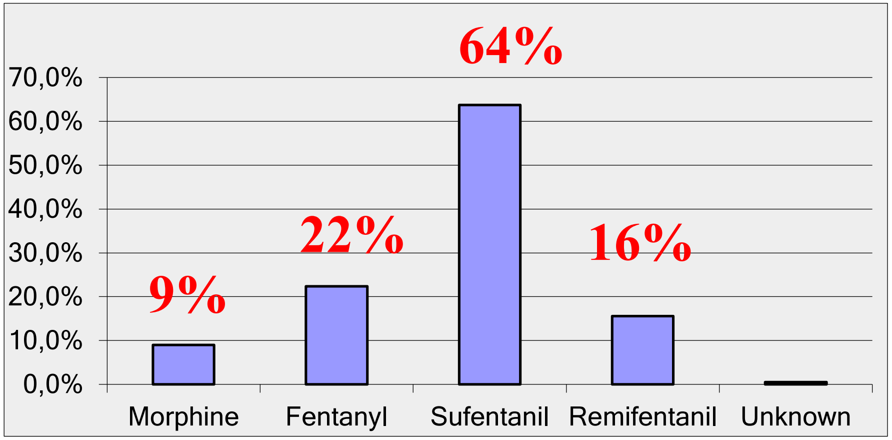
AIC. 2016

During TTM, do you use analgesics?
(n=423)



	Response	N
Always	**79%**	**332**
Frequently	**14%**	**58**
Sometimes	6%	25
Never	1%	6
Unknown	0,5%	2

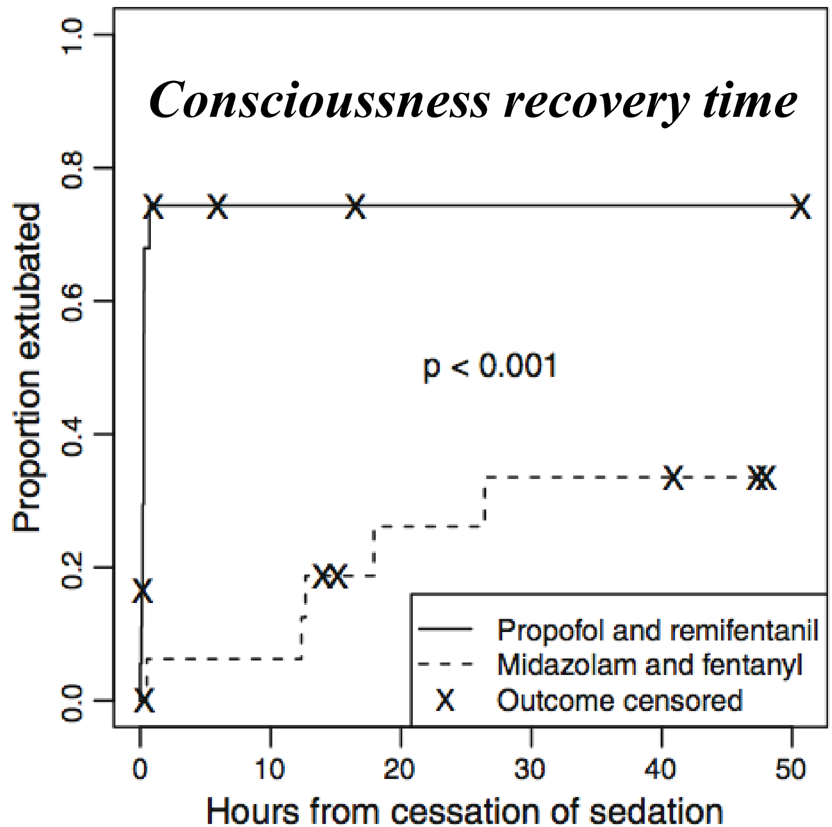
30% reductions in dosage per 5° C for remifentanil

Michelsen Anesth Analg 2001

Thor W. Bjelland
Ola Dale
Kjell Kaisen
Bjørn O. Haugen
Stian Lydersen
Kristian Strand
Pål Klepstad

Propofol and remifentanil versus midazolam and fentanyl for sedation during therapeutic hypothermia after cardiac arrest: a randomised trial

Bjelland ICM 2012



Midazolam can prolong consciousness recovery time & delay extubation

RESEARCH Open Access

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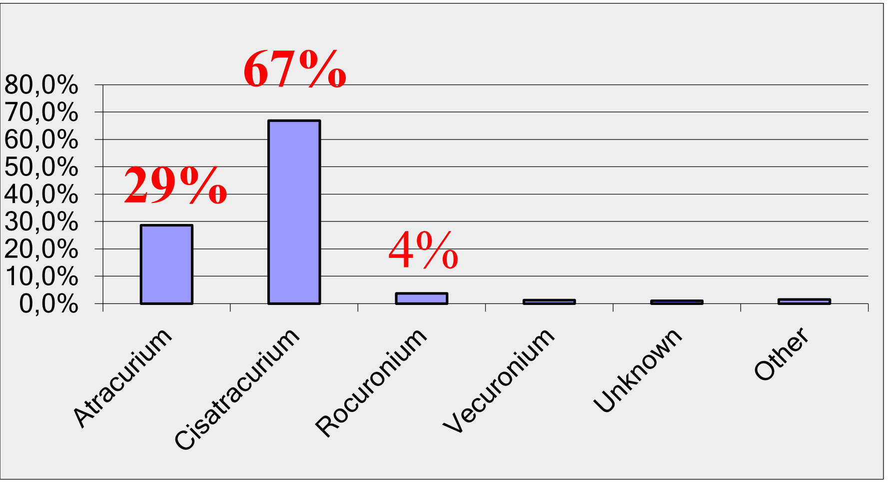
Nicolas Deye[1*], François Vincent[2], Philippe Michel[3], Stephan Ehrmann[4], Daniel da Silva[5], Michael Piagnerelli[6], Antoine Kimmoun[7], Olfa Hamzaoui[8], Jean-Claude Lacherade[9], Bernard de Jonghe[10], Florence Brouard[3], Corinne Audoin[11], Xavier Monnet[12], Pierre-François Laterre[13] and For the SRLF Trial Group

AIC. 2016

During TTM, do you use paralyzers NMB? (n=423)



	Response	N
Always	**48%**	**201**
Frequently	**31%**	**129**
Sometimes	19%	81
Never	3%	11
Unknown	0,2%	1

Shivering monitoring (Bedside Shivering Assessment scale… TOF)

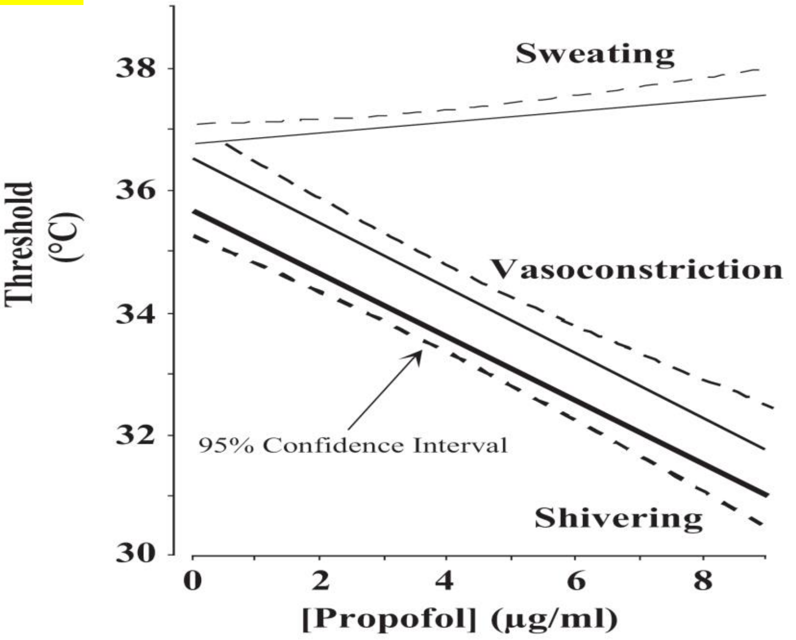
Badjatia, Mayer. CCM 2009

Shivering treatment (Mg, buspirone, meperidine, opioïds, dexmetomidine, propofol… paralyzers)

Impairment of autonomic cold defenses by anesthetics (hypothalamic set point)

Matsukawa T et al. *Anesthesiology* 1995

- Volatile anesthetics ?!
- Propofol
- Opioids
  - Meperidine
- Non opioids
  - Nefopam
  - Clonidine
  - Dexmedetomidine
  - Buspirone
- Drug combinations (without interactions: CYP450) ?!



Prefer IV administration if possible (ileus during TTM)

Use short-acting drugs with short half-life time

Adapt doses and use strict monitoring

Riker et al. Analgesia, sedation and NMB during TTM after CA. 2015

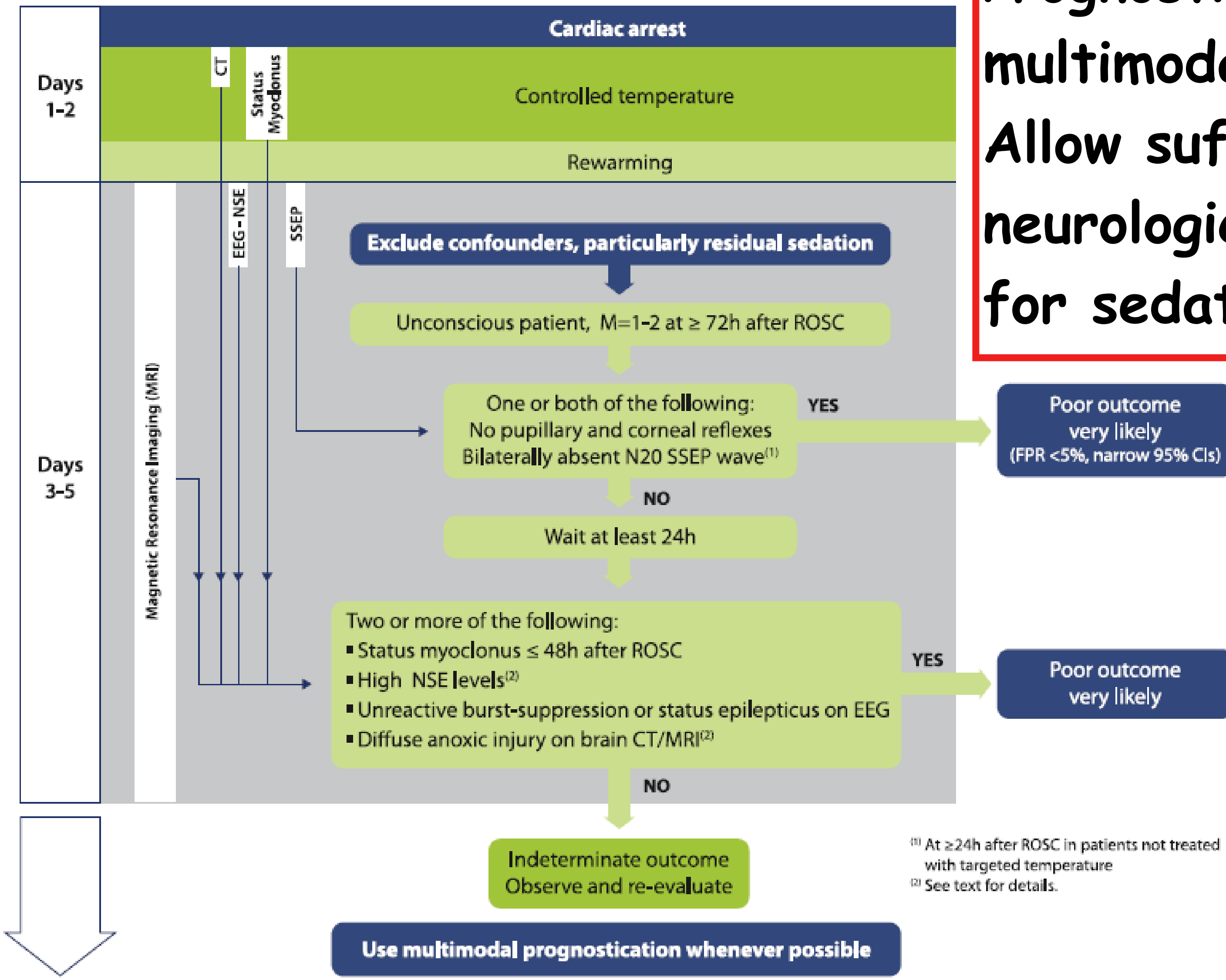
European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015 Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015☆

Jerry P. Nolan[a,b,*], Jasmeet Soar[c], Alain Cariou[d], Tobias Cronberg[e], Véronique R.M. Moulaert[f], Charles D. Deakin[g], Bernd W. Bottiger[h], Hans Friberg[i], Kjetil Sunde[j], Claudio Sandroni[k]

To 2015

EUROPEAN RESUSCITATION COUNCIL

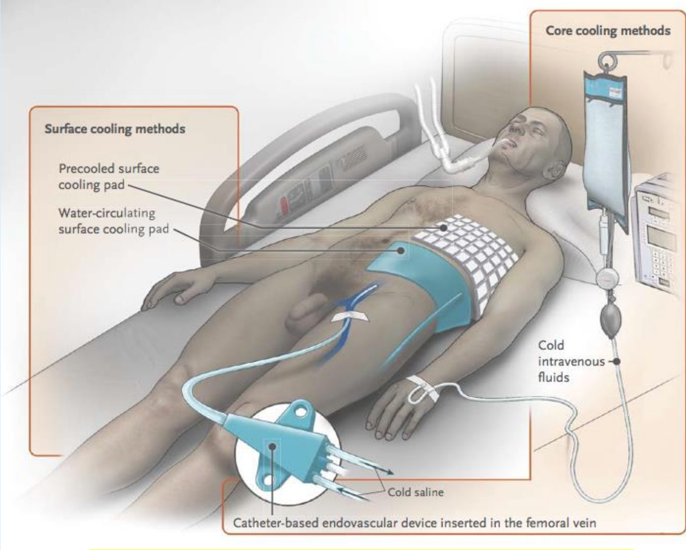
Prognostication with a multimodal strategy ++ Allow sufficient time for neurological recovery & for sedatives' clearance



Clinical data ++
Biomarker
EEG, SEP
Brain CT-scan
(MRI)
(Doppler)

OPTIMIZING TTM/TH PROTOCOL

WHICH METHOD? Advanced vs basic



Holzer NEJM 2010

European Resuscitation Council

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

ILCOR Advisory Statement

Therapeutic Hypothermia After Cardiac Arrest

An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation

External or internal cooling techniques can be used to initiate cooling within minutes to hours

2003

Rapid infusion of ice-cold IV fluid 30 mL/kg or ice packs are feasible, safe, and simple methods for initially lowering core temperature up to 1.5° C. When IV fluids are used to induce hypothermia, additional cooling strategies will be required to maintain hypothermia.

2010

2015

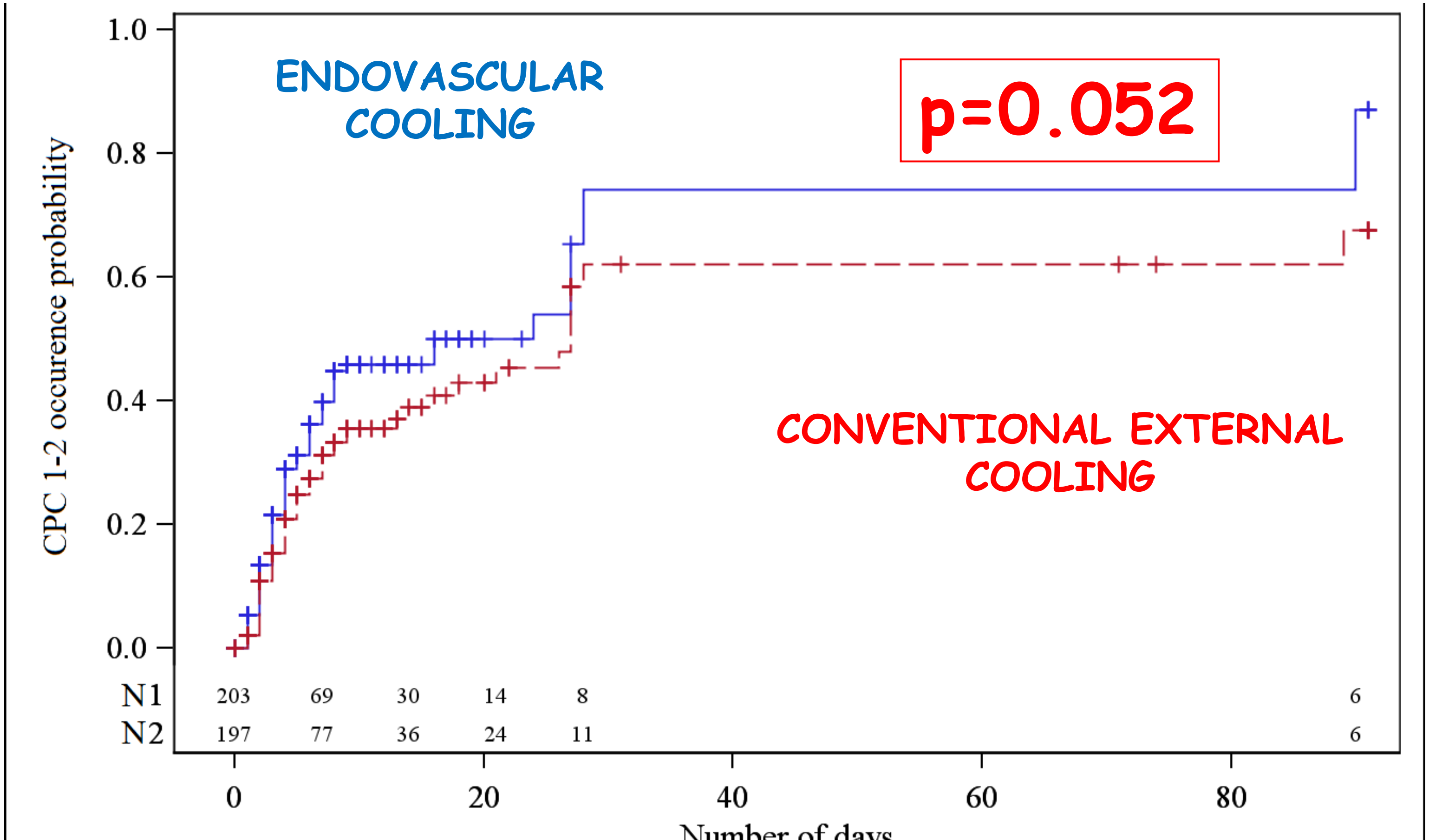
How to control temperature?. As yet, there are no data indicating that any specific cooling technique increases survival when compared with any other cooling technique; however, internal devices enable more precise temperature control compared with external

Endovascular Versus External Targeted Temperature Management for Patients With Out-of-Hospital Cardiac Arrest

A Randomized, Controlled Study

Deye N et al (ICEREA). Circulation 2015

Cumulative survival rate without major sequelae within 90 days



TTM IN ICU (EXCEPT NEONATES)

French TTM recommendations 2016
Société de Réanimation de Langue Française
Société Française d'Anesthésie et de Réanimation

In collaboration with 5 French Medical Societies: Intensive care, Anesthesiology Resuscitation Council, Emergency Medicine, Neuro Intensive care, Neurovascular, Pediatric Society

Clinical fields: CA, TBI, stroke, status epilepticus, shock

Recommendations are ranked by evidence (grade) and level of consensus reached among the experts (strong to weak)

Practical implementation and monitoring of TTM (question 6)

R6.1 - In patients treated by TTM, advanced methods (i.e. with automated feedback) compared to basic methods should be used to optimize TTM

(Grade 1+) Strong agreement

Alain Cariou, JF Payen et al. AIC 2017

OPTIMIZING TTM/TH PROTOCOL

OPTIMIZED START AND DURATION

Circulation
American Heart Association. Learn and Live.

ILCOR 2015

EUROPEAN RESUSCITATION COUNCIL

OPTIMAL DURATION = 24H
for TTM ≤ 36° C
+ Duration of normothermia ≤ 37.5° C = 72H

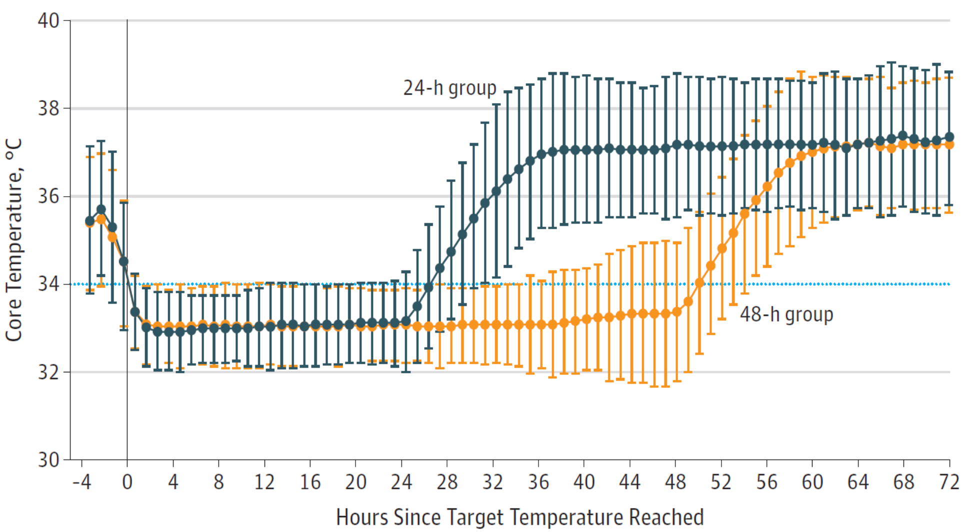
- If targeted temperature management is used, it is suggested that the duration is at least 24 h (as undertaken in the two largest previous RCTs[376,450]) (weak recommendation, very low-quality evidence).

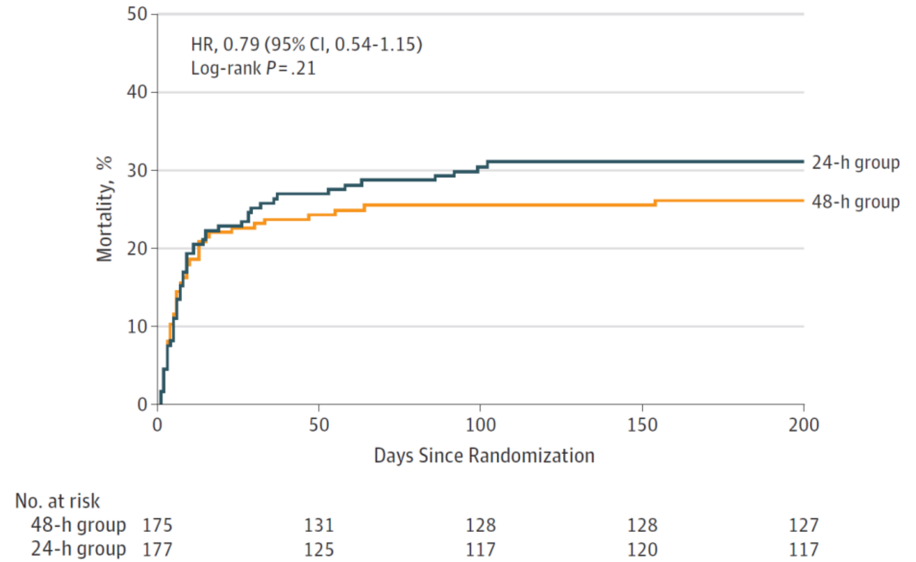
Rebound hyperthermia is associated with worse neurological outcome.[463,464] Thus, rewarming should be achieved slowly: the optimal rate is not known, but the consensus is currently about 0.25–0.5 °C of rewarming per hour.[465]

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

JAMA 2017

Hans Kirkegaard, MD, PhD, DMSci, DEAA, DLS; Eldar Søreide, MD, PhD, FERC; Inge de Haas, MD; Ville Pettilä, MD, PhD, EDIC; Fabio Silvio Taccone, MD, PhD; Urmet Arus, MD; Christian Storm, MD, PhD; Christian Hassager, MD, DMSc; Jørgen Feldbæk Nielsen, MD, DMSci; Christina Ankjær Sørensen, MD; Susanne Ilkjær, MD, PhD; Anni Nørgaard Jeppesen, MD; Anders Morten Grejs, MD, PhD; Christophe Henri Valdemar Duez, MD; Jakob Hjort, MPH; Alf Inge Larsen, MD, PhD, FESC; Valdo Toome, MD; Marjaana Tiainen, MD, PhD; Johanna Hästbacka, MD, PhD; Timo Laitio, MD, PhD; Markus B. Skrifvars, MD, PhD, EDIC, FCICM





N=176 vs 179

	No. (%) of Patients				
	48-Hour Group (n = 175)	24-Hour Group (n = 176)	Difference, % (95% CI)	RR (95% CI)	*P* Value
Primary outcome: CPC score of 1 or 2 at 6 mo	120 (69)	112 (64)	4.9 (−5 to 14.8)	1.08 (0.93 to 1.25)	.33
Secondary outcomes					
Mortality at 6 mo	48 (27)	60 (34)	−6.5 (−16.1 to 3.1)	0.81 (0.59 to 1.11)	.19
Any adverse event	169 (97)	161 (91)	5.6 (0.6 to 10.6)	1.06 (1.01 to 1.12)	.03