Targeted Temperature Management: Operationalizing the New Guidelines

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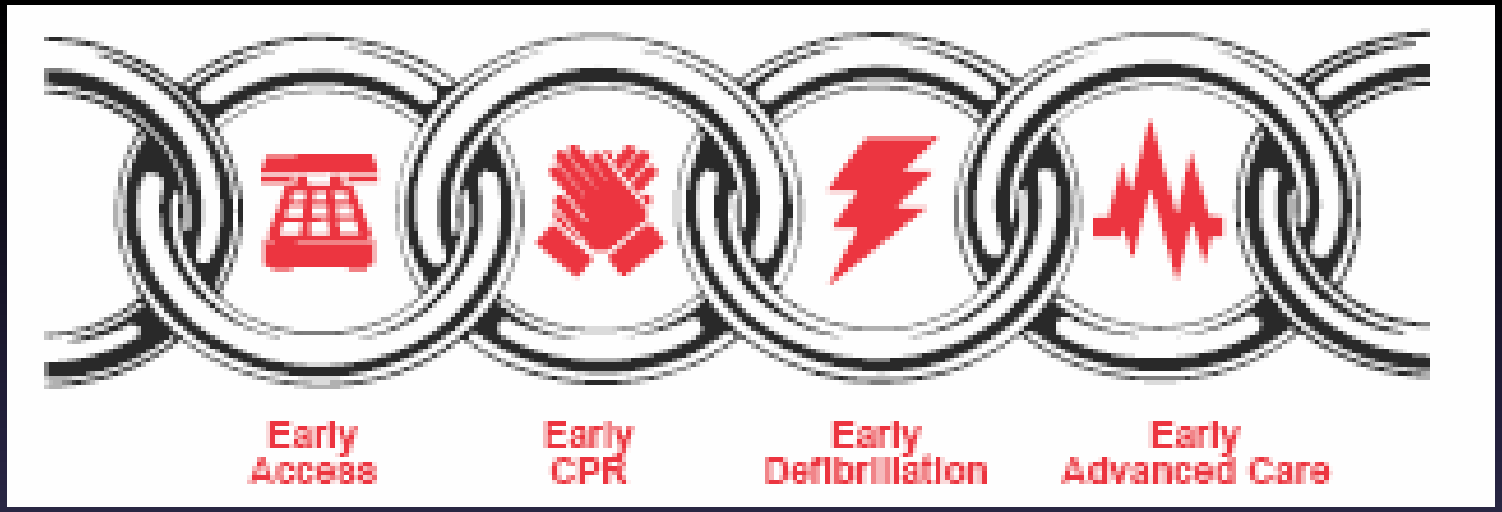
Disclosures

- Speaker fees: None
- Research Grants: NIH, AHA, Kaneka
- American Heart Association
  - Advanced Life Support Chapter Collaborator, 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

Outline

- Briefly review the evidence for therapeutic hypothermia
- Discuss the 2013 TTM Trial + new ILCOR/AHA guidelines
- Explore how practice may be changing
- Share a practical approach for TTM in the current era
- Discuss patient scenarios

The Chain of Survival



The *5th Link* in the Chain of Survival

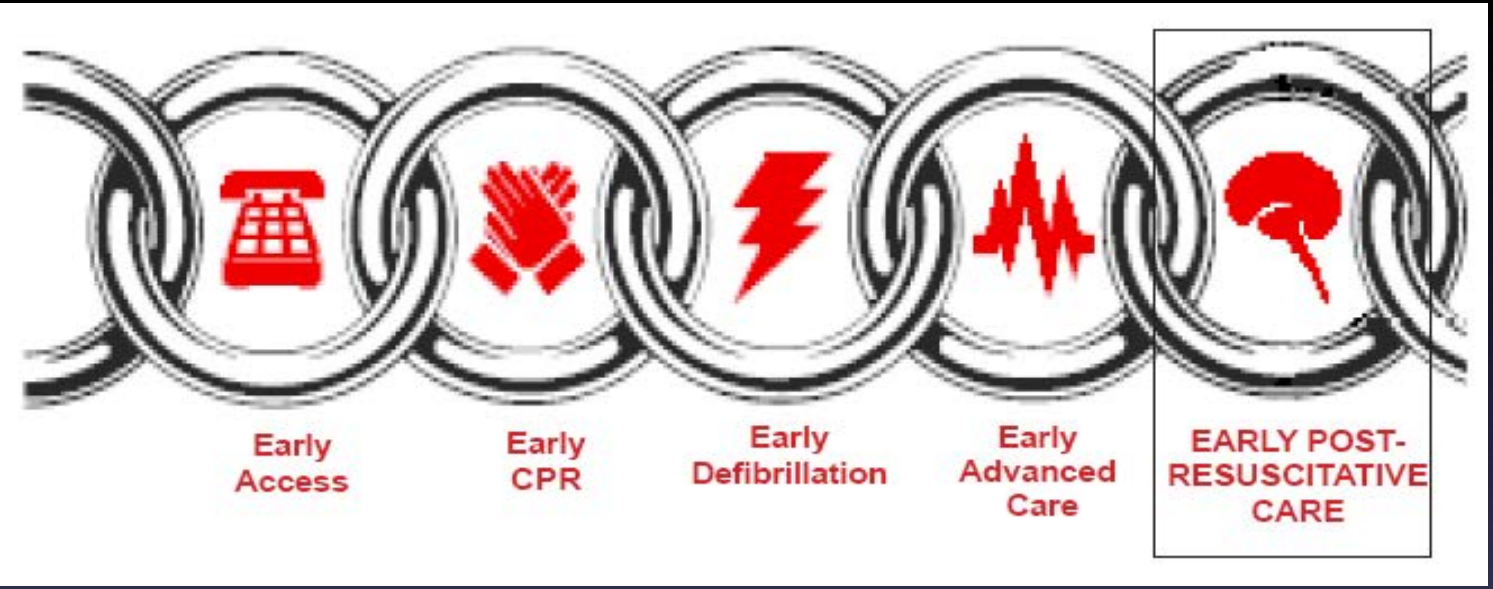
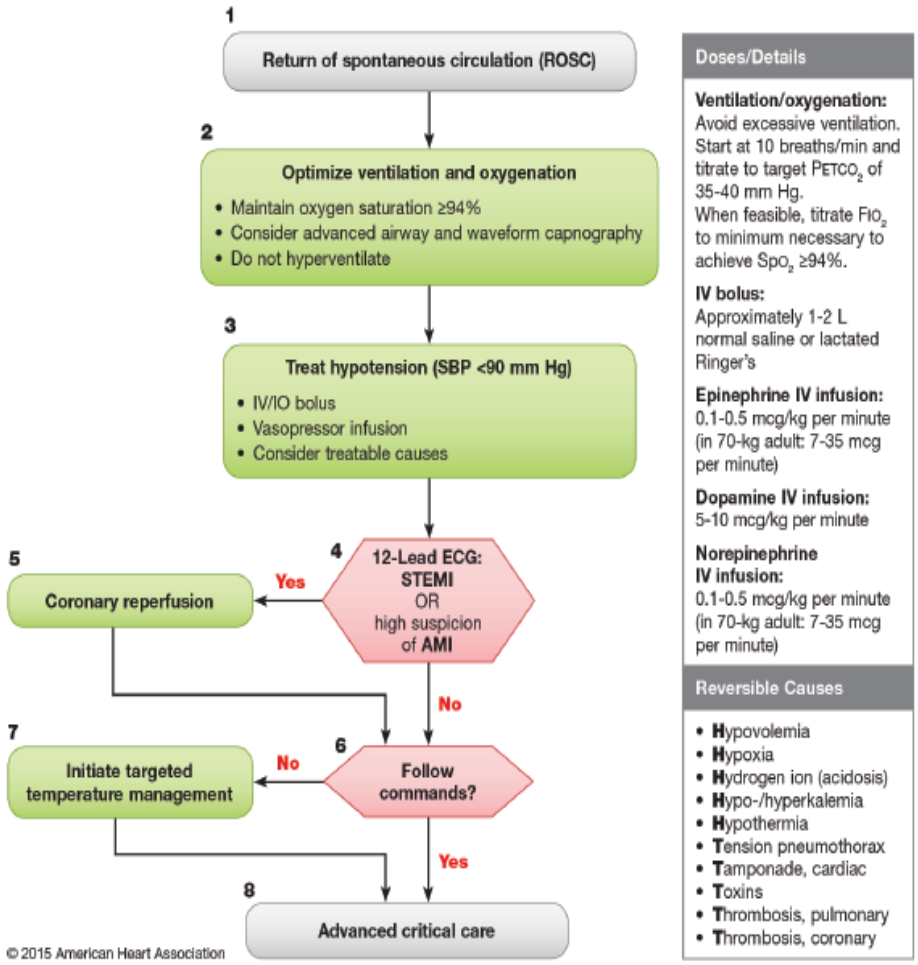


Figure 1: Adult Immediate Post–Cardiac Arrest Care Algorithm - 2015 Update



American Heart Association. Web-based Integrated Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care – Part 8: Post-Cardiac Arrest Care. ECCguidelines.heart.org.

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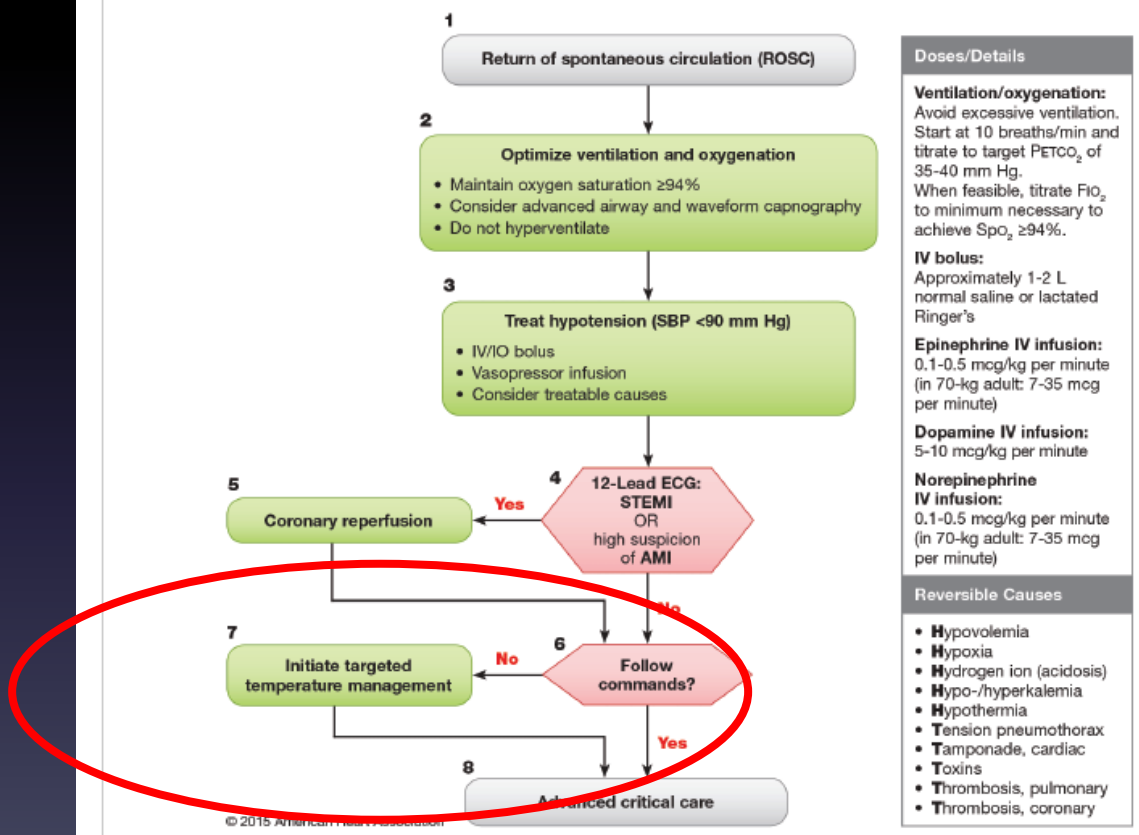

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Temperature Management After Cardiac Arrest

An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation

Michael W. Donnino, MD; Lars W. Andersen, MD; Katherine M. Berg, MD; Joshua C. Reynolds, MD, MS; Jerry P. Nolan, FRCA, FRCP, FFICM, FCEM (Hon); Peter T. Morley, MBBS, FRACP, FANZCA, FCICM, FERC; Eddy Lang, MD; Michael N. Cocchi, MD; Theodoros Xanthos, MD, Pg Dip (Ed), MSc, PhD, FHEA, FAcadMEd; Clifton W. Callaway, MD, PhD*; Jasmeet Soar, FRCA, FFICM, FRCP*; and the ILCOR ALS Task Force

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- We suggest that, if targeted temperature management is used, duration should be at least 24 hours as in the 2 largest previous RCTs.

2015 AHA guidelines:

We recommend that comatose adult patients with ROSC after cardiac arrest have TTM between 32-36° Celsius.

(Class I recommendation)

Callaway et al. *Circulation* 2015

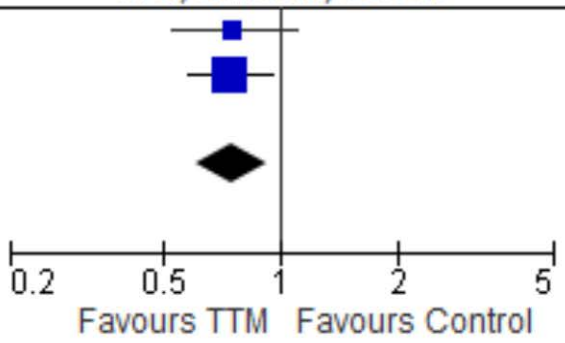
Circulation 2015; 132:2448-2456.

Mortality

Study or Subgroup	TTM Events	TTM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bernard, 2002	22	43	23	34	31.2%	0.76 [0.52, 1.10]
HACA, 2002	56	137	76	138	68.8%	0.74 [0.58, 0.95]
Total (95% CI)		**180**		**172**	**100.0%**	**0.75 [0.61, 0.92]**
Total events	78		99			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%

Test for overall effect: Z = 2.75 (P = 0.006)

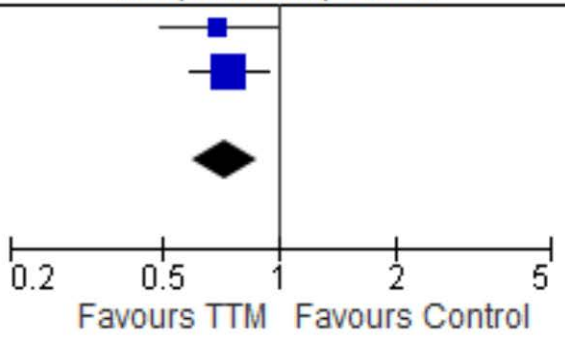


Neurologic

Study or Subgroup	TTM Events	TTM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bernard, 2002	22	43	25	34	29.6%	0.70 [0.49, 0.99]
HACA, 2002	61	136	83	137	70.4%	0.74 [0.59, 0.93]
Total (95% CI)		**179**		**171**	**100.0%**	**0.73 [0.60, 0.88]**
Total events	83		108			

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%

Test for overall effect: Z = 3.24 (P = 0.001)



Circulation 2015; 132:2448-2456.

HACA + Bernard study limitations

- Large numbers of patients excluded
- Unclear attention to temperature management in the control arm
- Non-blinded assessors of outcomes
- No report of longer term neurologic outcomes or granular neurologic outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D., David Erlinge, M.D., Ph.D., Yvan Gasche, M.D., Christian Hassager, M.D., D.M.Sci., Janneke Horn, M.D., Ph.D., Jan Hovdenes, M.D., Ph.D., Jesper Kjaergaard, M.D., D.M.Sci., Michael Kuiper, M.D., Ph.D., Tommaso Pellis, M.D., Pascal Stammet, M.D., Michael Wanscher, M.D., Ph.D., Matt P. Wise, M.D., D.Phil., Anders Åneman, M.D., Ph.D., Nawaf Al-Subaie, M.D., Søren Boesgaard, M.D., D.M.Sci., John Bro-Jeppesen, M.D., Iole Brunetti, M.D., Jan Frederik Bugge, M.D., Ph.D., Christopher D. Hingston, M.D., Nicole P. Juffermans, M.D., Ph.D., Matty Koopmans, R.N., M.Sc., Lars Køber, M.D., D.M.Sci., Jørund Langørgen, M.D., Gisela Lilja, O.T., Jacob Eifer Møller, M.D., D.M.Sci., Malin Rundgren, M.D., Ph.D., Christian Rylander, M.D., Ph.D., Ondrej Smid, M.D., Christophe Werer, M.D., Per Winkel, M.D., D.M.Sci., and Hans Friberg, M.D., Ph.D., for the TTM Trial Investigators*

Table 1. Characteristics of the Modified Intention-to-Treat Population before Randomization.*

Characteristic	33°C Group (N = 473)	36°C Group (N = 466)
Demographic characteristics		
Age — yr	64±12	64±13
Male sex — no. (%)	393 (83)	368 (79)
Medical history — no. (%)		
Chronic heart failure	32 (7)	29 (6)
Previous AMI	107 (23)	86 (18)
Ischemic heart disease	145 (31)	115 (25)
Previous cardiac arrhythmia	87 (18)	79 (17)
Arterial hypertension	193 (41)	181 (39)
Previous TIA or stroke	35 (7)	38 (8)
Diabetes mellitus	61 (13)	80 (17)
Asthma or COPD	48 (10)	49 (11)
Previous percutaneous coronary intervention	58 (12)	50 (11)
Previous coronary-artery bypass grafting	47 (10)	42 (9)
Characteristics of the cardiac arrest		
Location of cardiac arrest — no. (%) †		
Place of residence	245 (52)	255 (55)
Public place	197 (42)	188 (40)
Other	31 (7)	22 (5)
Bystander witnessed cardiac arrest — no. (%)	420 (89)	418 (90)
Bystander performed CPR — no. (%)	344 (73)	339 (73)
First monitored rhythm — no. (%) †		
Shockable rhythm	375 (79)	377 (81)
Ventricular fibrillation	349 (74)	356 (77)
Nonperfusing ventricular tachycardia	12 (3)	12 (3)
Unknown rhythm but responsive to shock	5 (1)	5 (1)
Perfusing rhythm after bystander-initiated defibrillation	9 (2)	4 (1)
Asystole	59 (12)	54 (12)
Pulseless electrical activity	37 (8)	28 (6)
Unknown first rhythm, not responsive to shock or not shocked	2 (<0.5)	6 (1)
Time from cardiac arrest to event — min‡:		
Start of basic life support		
Median	1	1
Interquartile range	0–2	0–2
Start of advanced life support		
Median	10	9
Interquartile range	6–13	5–13
Return of spontaneous circulation		
Median	25	25
Interquartile range	18–40	16–40

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EQUALLY MATCHED GROUPS

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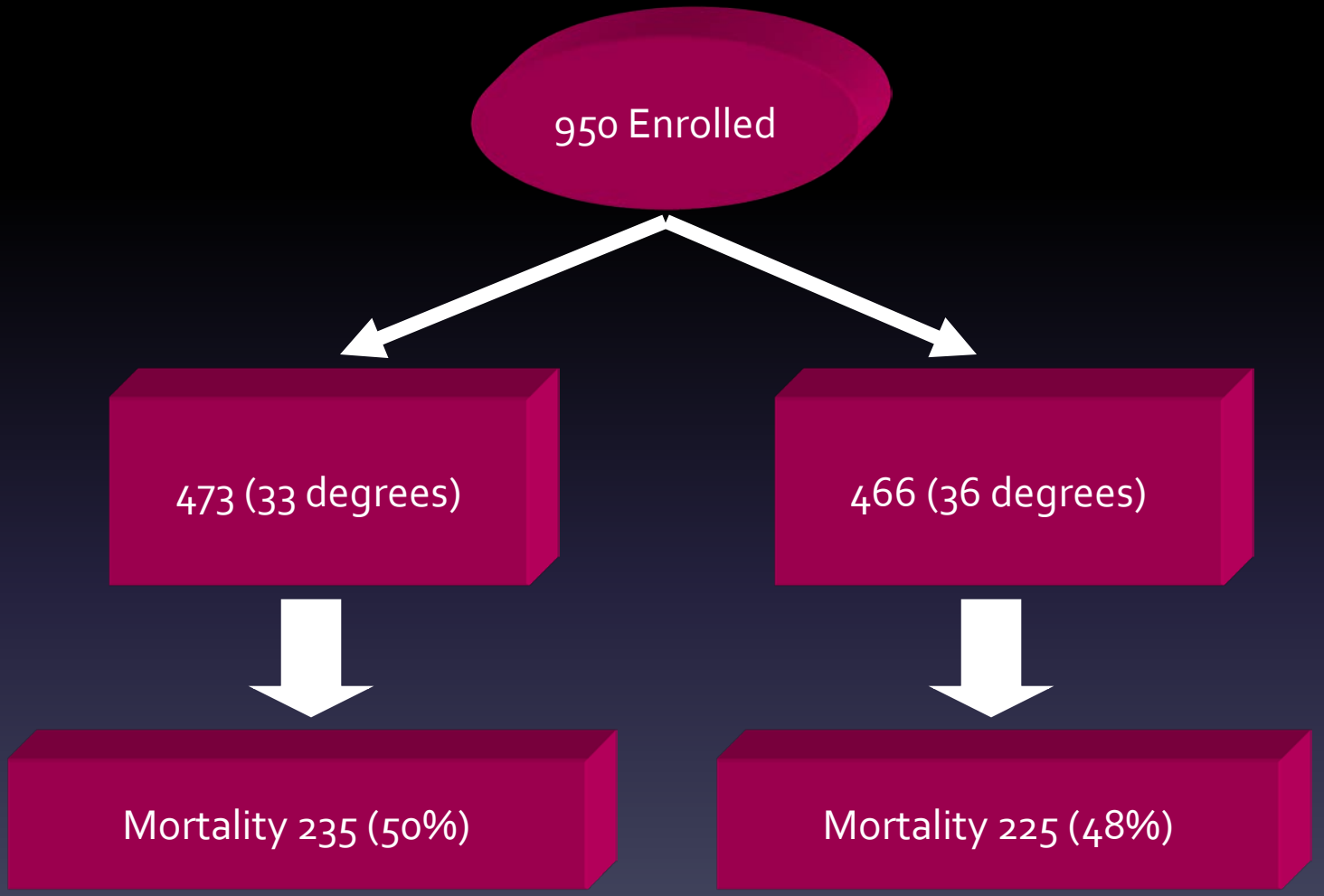
EQUALLY MATCHED GROUPS

Median Time BLS: 1 min [0-2] 1 min [0-2]

33 degrees vs 36 degrees

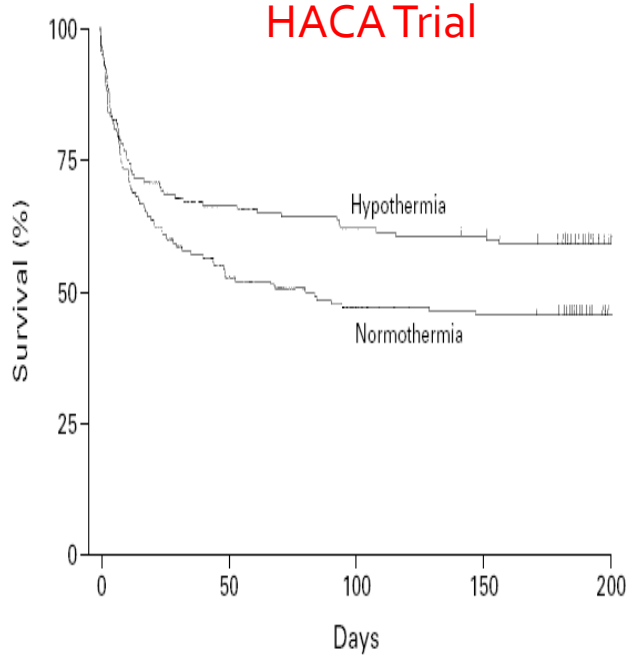


p = 0.51

Nielsen et. al Targeted Temperature Management at 33 versus 36 degrees after cardiac arrest. New England Journal of Medicine (2013)

Survival Curve Differences

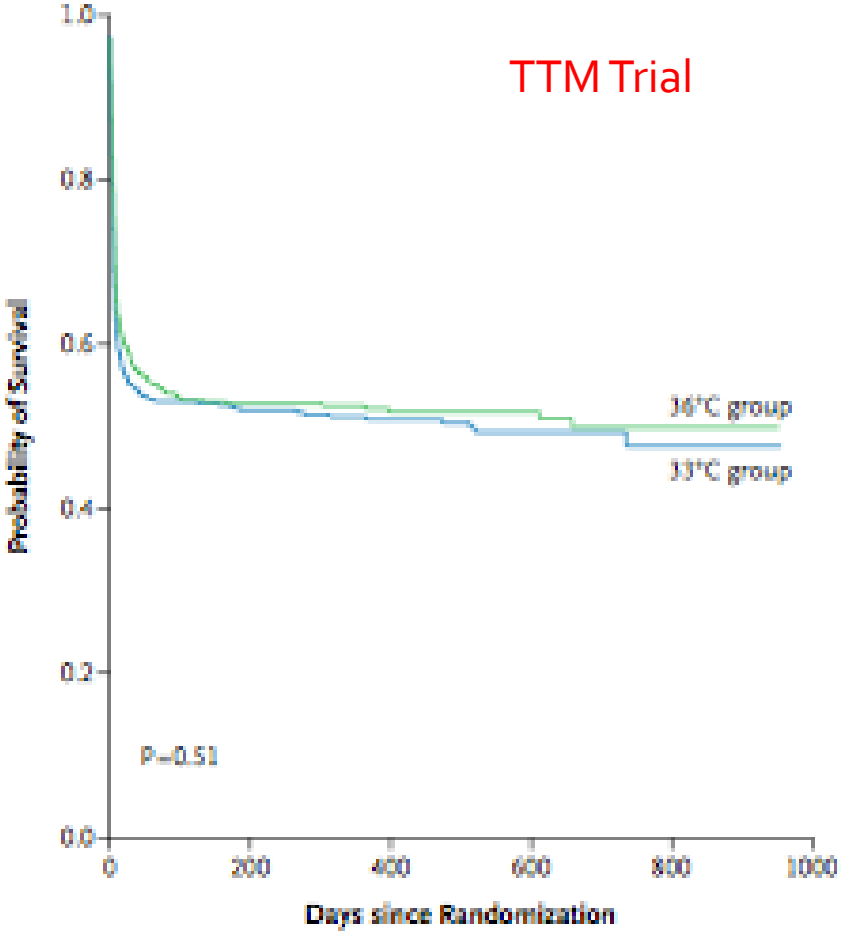
HACA Trial



No. at Risk					
Hypothermia	137	92	86	83	11
Normothermia	138	74	66	64	9

Figure 2. Cumulative Survival in the Normothermia and Hypothermia Groups. Censored data are indicated by tick marks.

TTM Trial



Temperature Differences

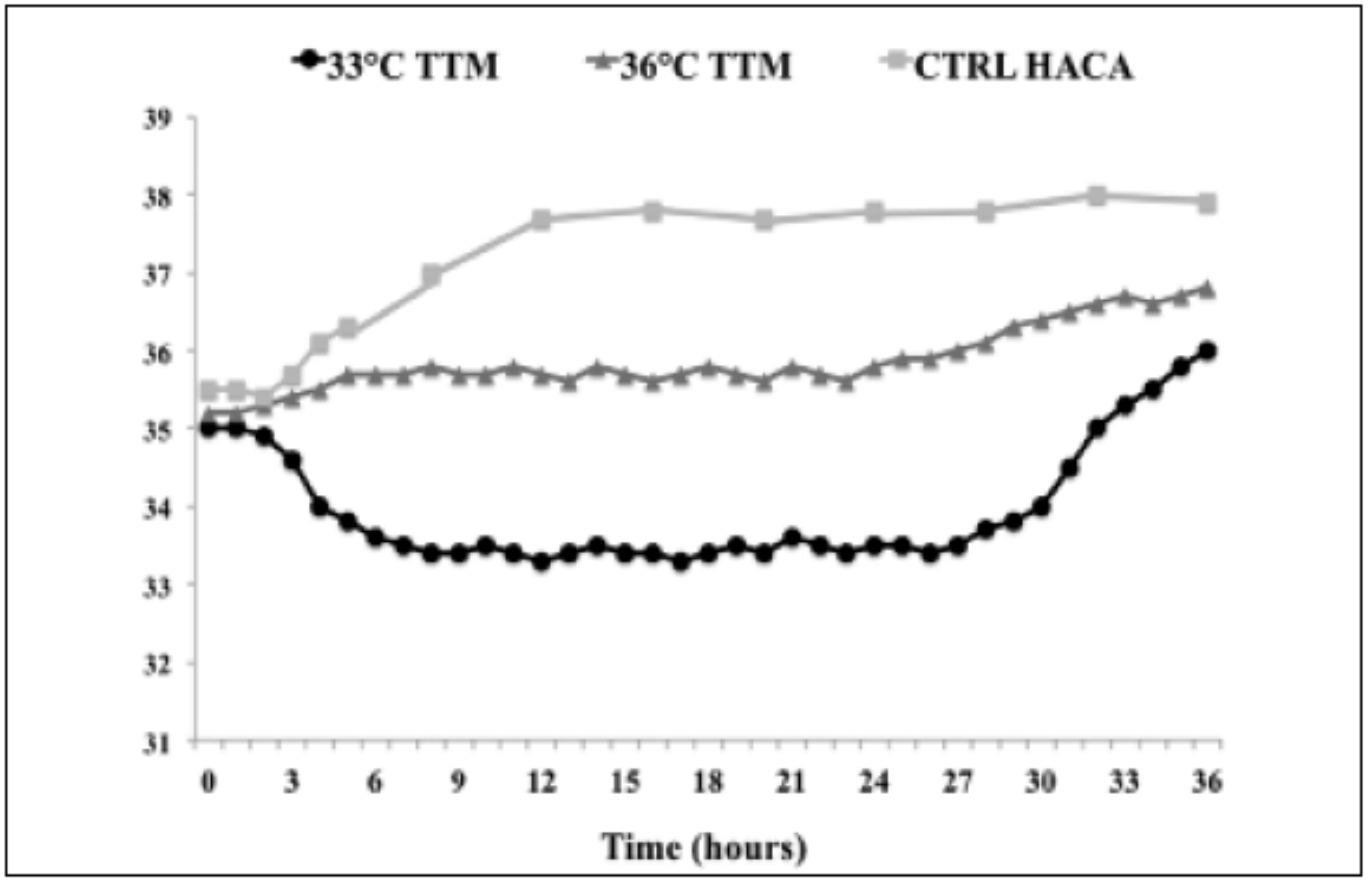


Figure 1.—Median temperature over the first 36 hours after arrest in the Targeted Temperature Management (TTM) study (33 °C and 36 °C) and the control group of the Hypothermia After Cardiac Arrest (HACA) Study. Data are adapted from the two studies.[7, 15]

Dell'anna et al. *Minerva Anestesiologica* 2014;80:736-43

Other Differences

- Patients in shock
- Rhythm inclusion differences
- Greater bystander CPR in TTM trial
- Targeted temperature control for **3 days** (no fevers in all patients in both groups in TTM trial)
- Follow-up protocol for neuro-prognostication
- Blinded assessment of outcomes

Temperature Management After Cardiac Arrest

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2015 AHA guidelines:

We recommend that comatose adult patients with ROSC after cardiac arrest have TTM between 32-36° Celsius.

(Class I recommendation)

Callaway et al. *Circulation* 2015

Circulation 2015; 132:2448-2456.

Post-rewarming management

Part 4: Advanced Life Support

2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

Clifton W. Callaway, Co-Chair*; Jasmeet Soar, Co-Chair*; Mayuki Aibiki; Bernd W. Böttiger; Steven C. Brooks; Charles D. Deakin; Michael W. Donnino; Saul Drajer; Walter Kloeck; Peter T. Morley; Laurie J. Morrison; Robert W. Neumar; Tonia C. Nicholson; Jerry P. Nolan; Kazuo Okada; Brian J. O'Neil; Edison F. Paiva; Michael J. Parr; Tzong-Luen Wang; Jonathan Witt; on behalf of the Advanced Life Support Chapter Collaborators

Treatment Recommenda

We suggest prevention a

comatose adults after co

36°C (weak recommenda

2015 AHA guideline:

It may be reasonable to actively prevent fever in comatose patients after TTM.

(Class IIb, very low quality evidence)

Callaway et al. *Circulation* 2015

Circulation 2015 Oct 20;132(16 Suppl 1):S84-145.

How is clinical practice changing?

Leary et al. Variability in postarrest targeted temperature management practice: implications of the 2015 guidelines. *Ther hypo and temp management* (2015): 5.4.

- 10 question survey, convenience sample U.S.
- Dec 2014 to May 2015 (before release of 2015 guidelines)
- 219 health care providers from 112 institutions
- Goal temp:
    - 33C (65%) 36 (8%) either (25%) unknown (2%)
- Study conclusion: Across US hospitals, and within institutions, target temperature varies widely

How is clinical practice changing?

Deye et al. Changes in cardiac arrest patients' temperature management after the 2013 TTM trial: results from an international survey. *Annals Intensive Care* (2106) 6:4.

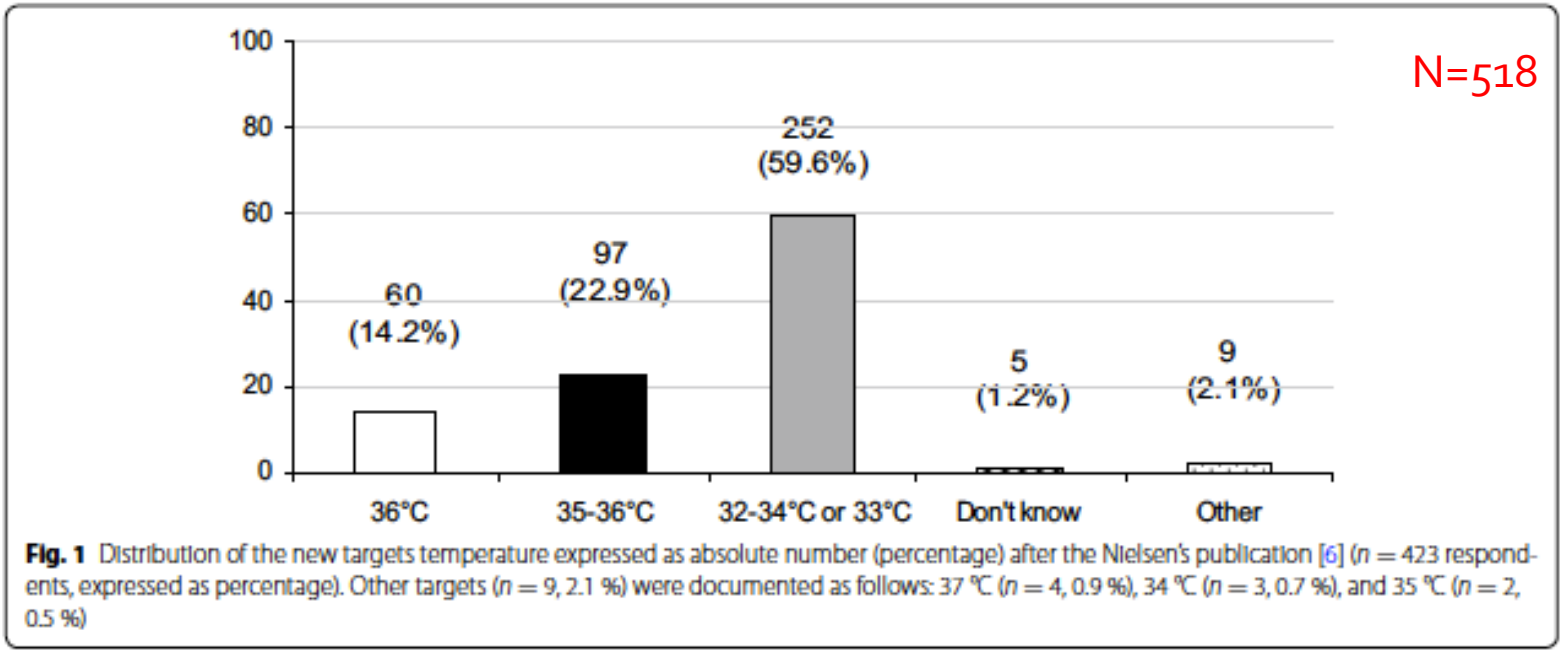

Fig. 1 Distribution of the new targets temperature expressed as absolute number (percentage) after the Nielsen's publication [6] ($n = 423$ respondents, expressed as percentage). Other targets ($n = 9$, 2.1 %) were documented as follows: 37 °C ($n = 4$, 0.9 %), 34 °C ($n = 3$, 0.7 %), and 35 °C ($n = 2$, 0.5 %)

How is clinical practice changing?

Clinical paper

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

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

[a] Department of Epidemiology and Preventive Medicine, Monash University, Australia

- Retrospective cohort consecutive VF-OHCA
- Australia January 2013 to August 2015
- 76 cases (24 before [33C] and 52 after TTM change [36C x 24h then 37C x 12h then <37.5 until 72h])

Bray et al. Changing target temperature from 33C to 36C in the ICU management of OHCA: a before and after study. *Resuscitation* (2017): 113: 39-43.

Table 1
Comparison of demographics, arrest characteristics of OHCA patients admitted to ICU for the 33 °C and 36 °C TTM periods.

	33 °C N = 24	36 °C N = 52	p-Value
Age (years), mean (SD)	59 (18)	57 (15)	0.62
Males, n (%)	20 (83)	47 (90)	0.45
Independent, n (%)	24 (100)	52 (100)	–
Arrest at home, n (%)	4 (16)	17 (32)	0.18
Unwitnessed, n (%)	3 (12)	5 (10)	0.70
Bystander witnessed, n (%)	19 (79)	47 (90)	0.45
EMS witnessed, n (%)	2 (8)	0 (0)	0.10
Bystander CPR[a], n (%)	18 (86)	48 (92)	0.54
Bystander AED, n (%)	2 (8)	7 (14)	0.71
Duration of arrest (min), median (IQR)	20 (14–30)	22 (15–45)	0.93
STEMI, n (%)	7 (29)	15 (33)	0.99

EMS: emergency medical services; CPR: cardiopulmonary resuscitation; STEMI: ST-elevation myocardial infarction.

[a] Proportion of non-EMS witnessed.

Bray et al. Changing target temperature from 33C to 36C in the ICU management of OHCA: a before and after study. *Resuscitation* (2017): 113: 39-43.

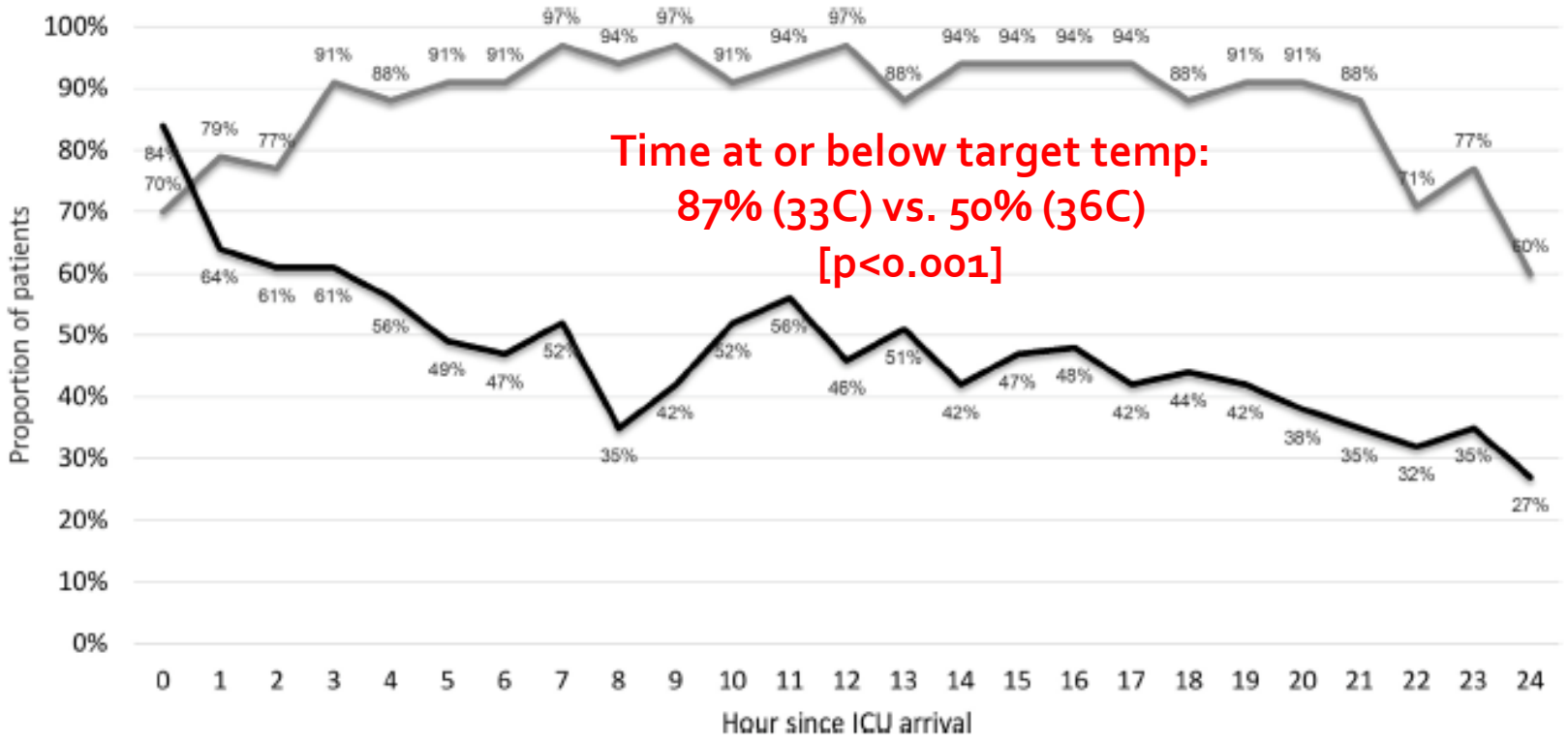

Fig. 1. The proportion of patients at target temperature for each hour of the first day of intensive care stay by the 33 °C (grey line) and 36 °C (black line) TTM periods.

Bray et al. Changing target temperature from 33C to 36C in the ICU management of OHCA: a before and after study. *Resuscitation* (2017): 113: 39-43.

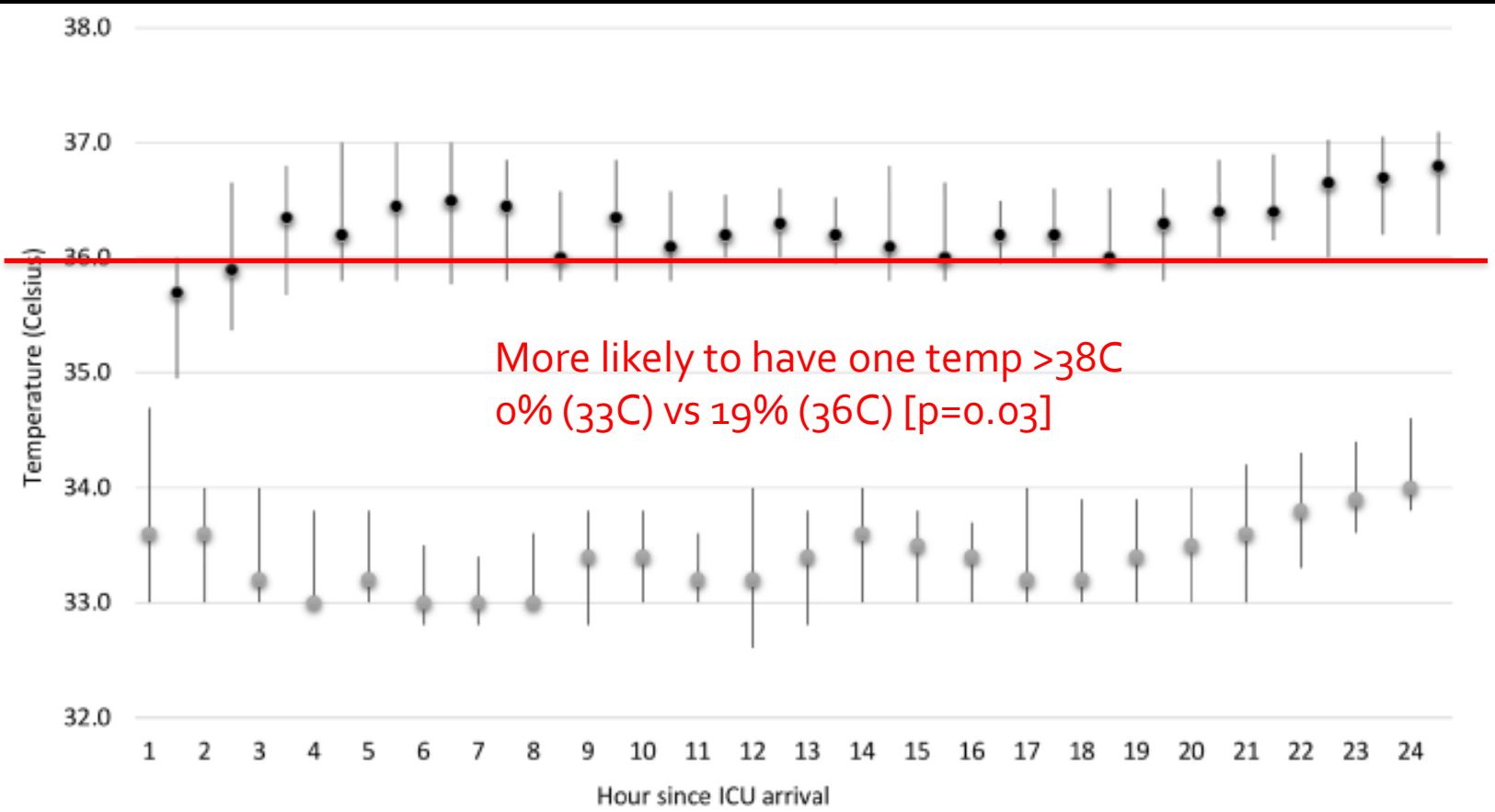

Fig. 2. The hourly median and interquartile range of temperatures over the first 24 h for the 33 °C (grey dots) and 36 °C (black dots) TTM periods.

Bray et al. Changing target temperature from 33C to 36C in the ICU management of OHCA: a before and after study. *Resuscitation* (2017): 113: 39-43.

Clinical paper

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

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

[a] Department of Epidemiology and Preventive Medicine, Monash University, Australia

- Less NMB use + less sedation in 36C patients
- Earlier extubation in 36C (3.7d v 2.4d, p=0.07)
- More patients in 33C period w/ shivering, bleeding and PNA
- Non-significant trend toward
    - decreased survival (71% v 58%, p=0.31)
    - discharged home (82% v 73%, p=0.08)
    - discharged with CPC 1-2 (71% v 56%, p=0.22)
-

Bray et al. Changing target temperature from 33C to 36C in the ICU management of OHCA: a before and after study. *Resuscitation* (2017): 113: 39-43.

Summary of post-TTM trial studies

- There is variability in temperature choice
- We may be overshooting
- Real world application of "36C" may not be the same as the strict Nielsen protocol
- Ultimate effect on outcomes remains to be seen

Case

- 45 year old male collapses in his driveway with VF arrest → 10 minutes of bystander CPR until EMS arrives → defibrillation x 2 with ROSC
- Post-arrest, the patient is comatose with a HR of 110 and blood pressure of 116/70
- Patient arrives to the emergency department and remains comatose/unresponsive to painful stimuli

Case

- Temp: 34.5° C, BP 106/50, HR 106, RR 22, oxygen saturation of 95% on Fio2 of 1.0

- How would you approach the case in terms of TTM?
  - A) Cool to 33C x 24h
  - B) Keep at 34.5C x 24h
  - C) Warm to 36C x 24h
  - D) Allow temp to drift up to 36C then keep there x 24h

Case

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  - A) Cool to 33C x 24h
  - B) Keep at 34.5C x 24h
  - ~~C) Warm to 36C x 24h~~
  - D) Allow temp to drift up to 36C then keep there x 24h

Case

- The patient begins to have blood from the nasogastric tube…you assess that there is a moderate GI bleed
- Would this change your TTM strategy?

Conclusions

1. Provide TTM for patients not following commands after cardiac arrest

2. Pick a target temperature and stick to it
    - Consider a 'cushion' (ie, 35C) to avoid overshooting beyond 36C

3. Don't actively warm patients who are already cooled to within target range*

4. Once rewarmed, avoid fever unless neurologic recovery has been achieved

END