

Therapeutic Hypothermia,

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DECLARATION OF INTEREST

- Others (Physician Proctor: Edwards Lifesciences
- EPS Vascular. Speaking honorariums: BBraun
- Biotronik
- Adtra Zeneca)

Disclosure Slide

Speaker's name:

☒ I have the following potential conflicts of interest to report:

- Honorarium, grant,etc :
 - Edwards Lifesciences
 - AztraZeneca
 - Biosensors
 - Biotronik
 - BBraun

Hypothermia

For whom?

- Successfully Resuscitated patients still in coma following cardiac arrest due to cardiac causes and with reasonable chances of a good neurologic outcome

Why & When

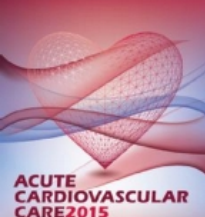
- As soon as possible after hospital arrival to increase survival.

How?

- Targeted temperature managements (TTM) with intravascular or topical cooling devices to target temperature $\leq 36^{\circ}\text{C}$ for 24 hrs.

What is the mechanism by which hypothermia reduces Cell death ???

- Reduction of metabolism
- Reduction of oxygen consumption
- Multifactorial chemical and physical mechanisms
 - Retardation of destructive enzymatic reactions,
 - Suppression of free-radical reactions,
 - Protection of the fluidity of lipoprotein membranes,
 - reduction of the oxygen demand in low flow regions,
 - Reduction of intracellular acidosis,
 - Inhibition of the biosynthesis, release, and uptake of excitatory neurotransmitters.



Hypothermia after Cardiac Arrest Landmark trials

The New England Journal of Medicine

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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.

2002



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CARE 2015

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Vienna, Austria

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Hypothermia Registry

- 986 patients from 34 hospitals
- 975 patients with 6 months follow-up
- 50 % survival rate at 6 months
 - 46% good outcome
- Few vegetative patients (n=4)
- Time from arrest to hypothermia *and* time from arrest to target temperature *were not related to outcome*

Part 9: Post–Cardiac Arrest Care : 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Mary Ann Peberdy, Clifton W. Callaway, Robert W. Neumar, Romergryko G. Geocadin, Janice L. Zimmerman, Michael Donnino, Andrea Gabrielli, Scott M. Silvers, Arno L. Zaritsky, Raina Merchant, Terry L. Vanden Hoek and Steven L. Kronick

Hyp
cardiopulmonary resuscitation (Review)

Arrich J, Holzer M, Herkner H, Müllner M



- ERC
- AHA
- Cochrane
- Multiple national guidelines

European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary

Jerry P. Nolan^{a,*}, Jasmeet Soar^b, David A. Zideman^c, Dominique Biarent^d, Leo L. Bossaert^e, Charles Deakin^f, Rudolph W. Koster^g, Jonathan Wyllie^h, Bernd Böttigerⁱ,
on behalf of the ERC Guidelines Writing Group¹

2010 Guidelines based on

- Randomised clinical trials: 2
- Observational studies: More
- Expert opinions: Even more

Update needed on optimal temperature and Timing of Hypothermia

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.Sc., Janneke Horn, M.D., Ph.D., Jan Hovdenes, M.D., Ph.D., Jesper Kjaergaard, M.D., D.M.Sc., Michael Kuiper, M.D., Ph.D., Tommaso Pellis, M.D., Pascal Stammert, 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.Sc., 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.Sc., Jørund Langørgen, M.D., Gisela Lilja, O.T., Jacob Eifer Møller, M.D., D.M.Sc., 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.Sc., and Hans Friberg, M.D., Ph.D., for the TTM Trial Investigators*

Original Investigation | January 1, 2014

Effect of Prehospital Induction of Mild Hypothermia on Survival and Neurological Status Among Adults With Cardiac Arrest A Randomized Clinical Trial

Francis Kim, MD¹; Graham Nichol, MD, MPH¹; Charles Maynard, PhD²; Al Hallstrom, PhD³; Peter J. Kudenchuk, MD⁴; Thomas Rea, MD, MPH⁵; Michael K. Copass, MD⁶; David Carlborn, MD⁷; Steven Deem, MD⁸; W. T. Longstreth Jr, MD^{4*}; Michele Olsufka, RN¹; Leonard A. Cobb, MD¹

[+]
Author Affiliations

JAMA. 2014;311(1):45-52. doi:10.1001/jama.2013.282173.

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TTM Study

NEJM 2013

Kim et al.

JAMA 2014

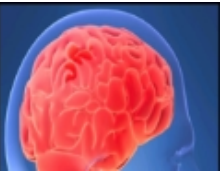


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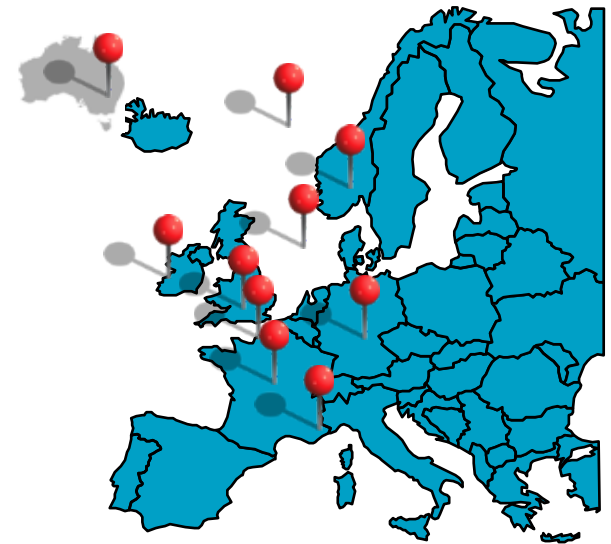
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TTM-trial 2010-2013

Targeted Temperature Management



- 950 patients randomized
- 36 hospitals
- 10 countries
- Europe and Australia



Funded by:

Swedish Heart Lung Foundation

AFA-insurance Foundation, Sweden

Swedish Research Council

Governmental and Regional funding within the Swedish National Health System

TrygFoundation, Denmark

Zoega, Krapperup, Thure Carlsson, Trolle-Wachtmeister foundations, Sweden



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Main Objectives TTM study

- To assess the benefits and harms of a targeted temperature management at 33°C versus 36°C in a prospective randomized trial
- Avoiding fever in post-cardiac arrest patients in both groups

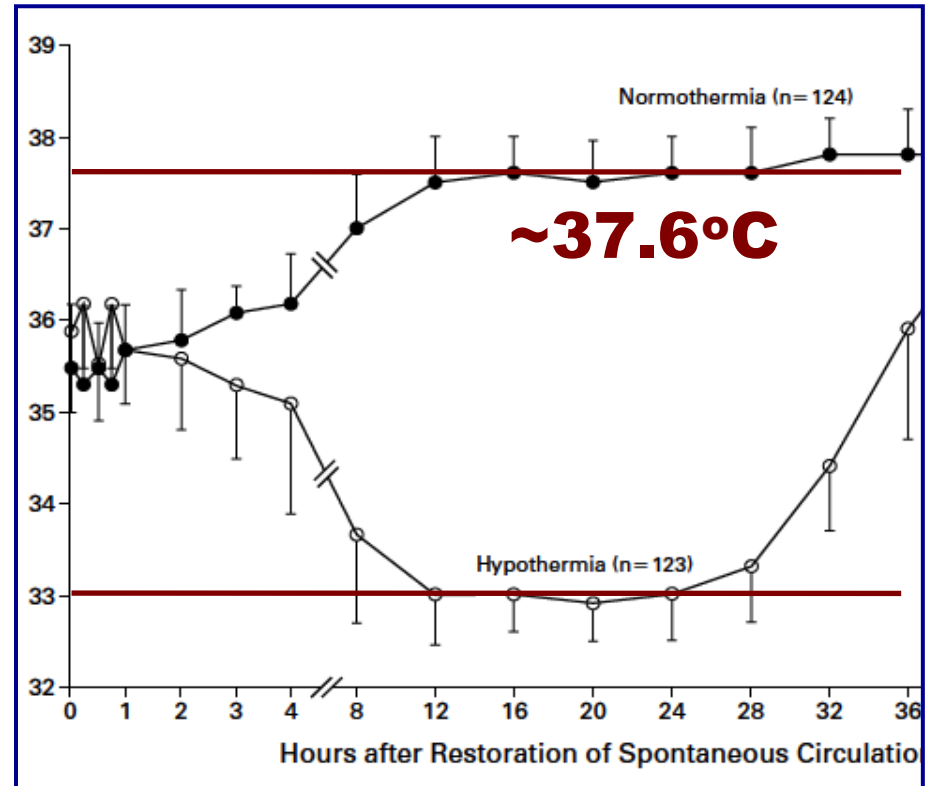
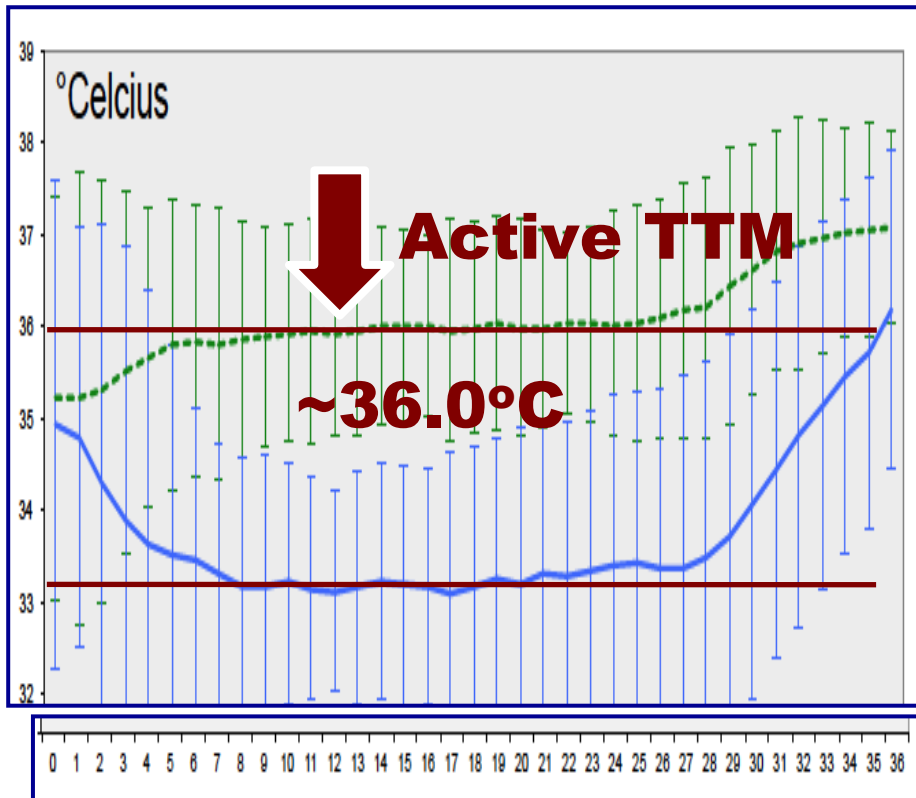
Inclusion Criteria

- Out-of-hospital cardiac arrest
- Adult (18 years and over)
- Presumed cardiac cause
- All initial rhythms
- Unconscious (Glasgow Coma Scale < 8)
- Stable Return of Spontaneous Circulation

Difference compared to previous trials

Nielsen et al

HACA study

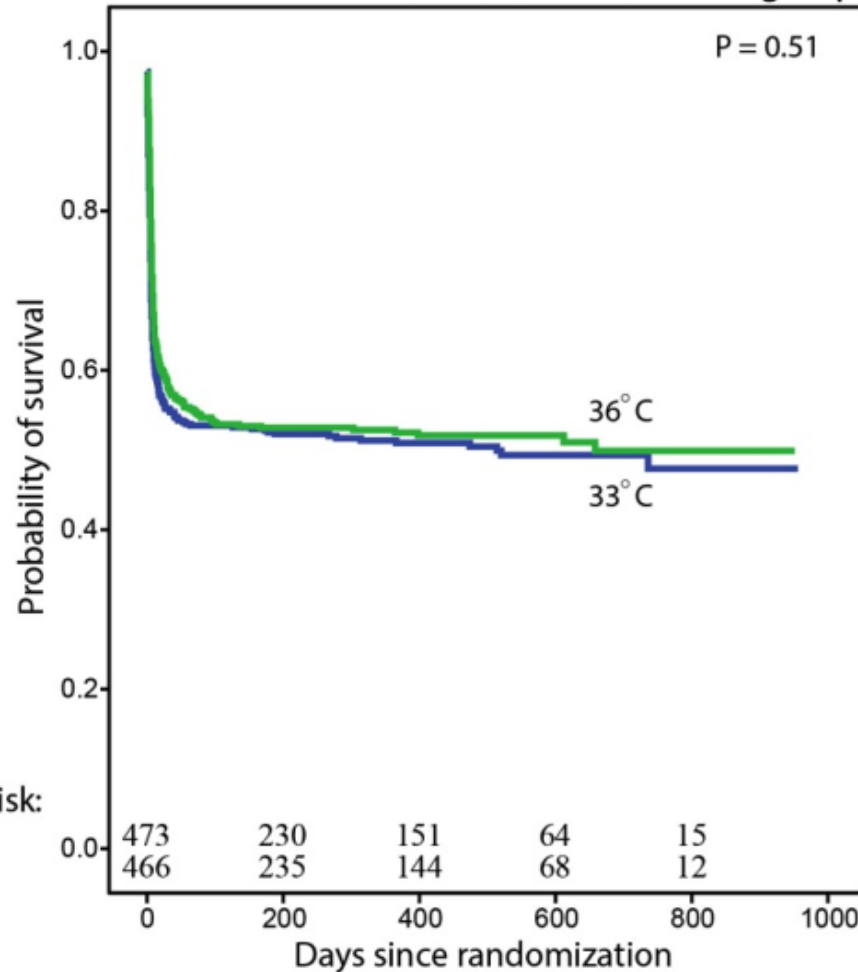


Bernard et al: ~37.3°C

Large difference in maintenance temperatures

Survival

Kaplan-Meier estimates for time to death in TTM-trial intervention groups



No. of patients at risk:
Target 33°C
Target 36°C

No difference in survival

Cerebral Performance Category



Variable	33°C Group	36°C Group
CPC at follow-up†		
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	

No difference in CPC

Seattle & King County Cardiac arrest study

Original Investigation | January 1, 2014

Effect of Prehospital Induction of Mild Hypothermia on Survival and Neurological Status Among Adults With Cardiac Arrest

A Randomized Clinical Trial

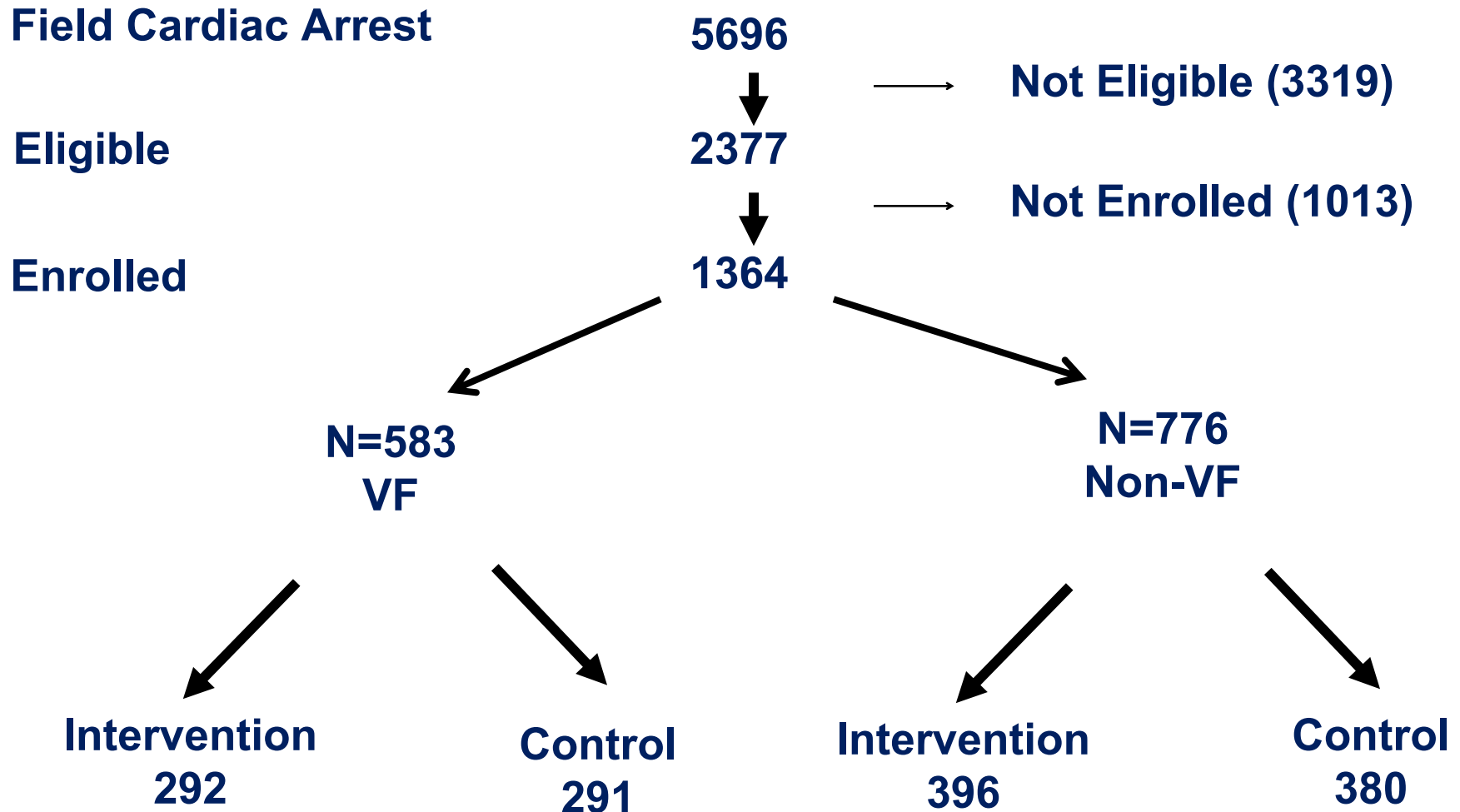
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[\[+\] Author Affiliations](#)

JAMA. 2014;311(1):45-52. doi:10.1001/jama.2013.282173.

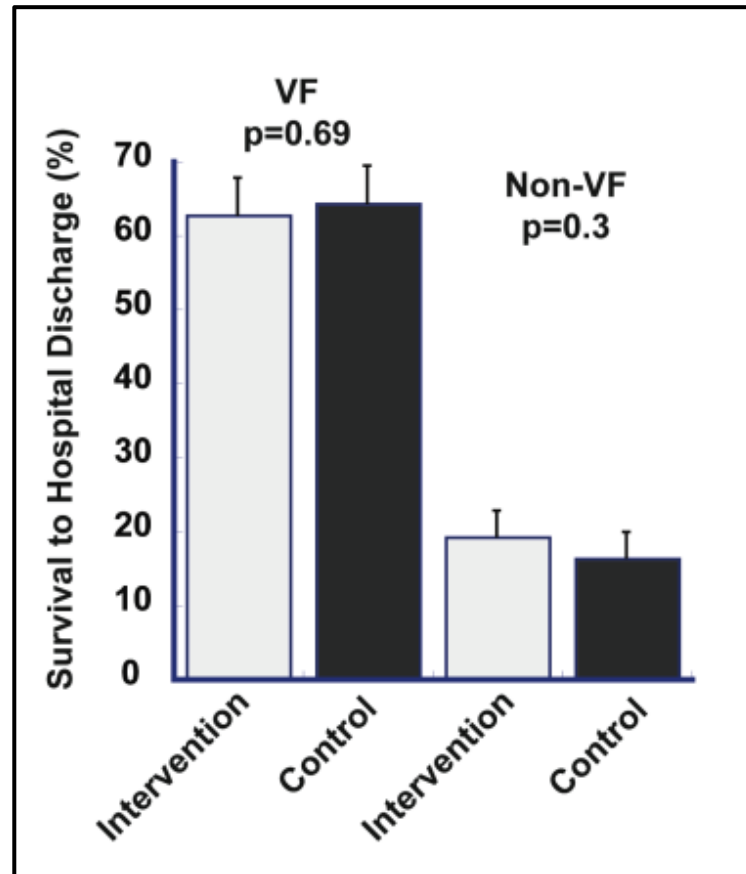
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Trial Flow



Outcomes: Survival at discharge/neurologic status

Outcomes-Survival

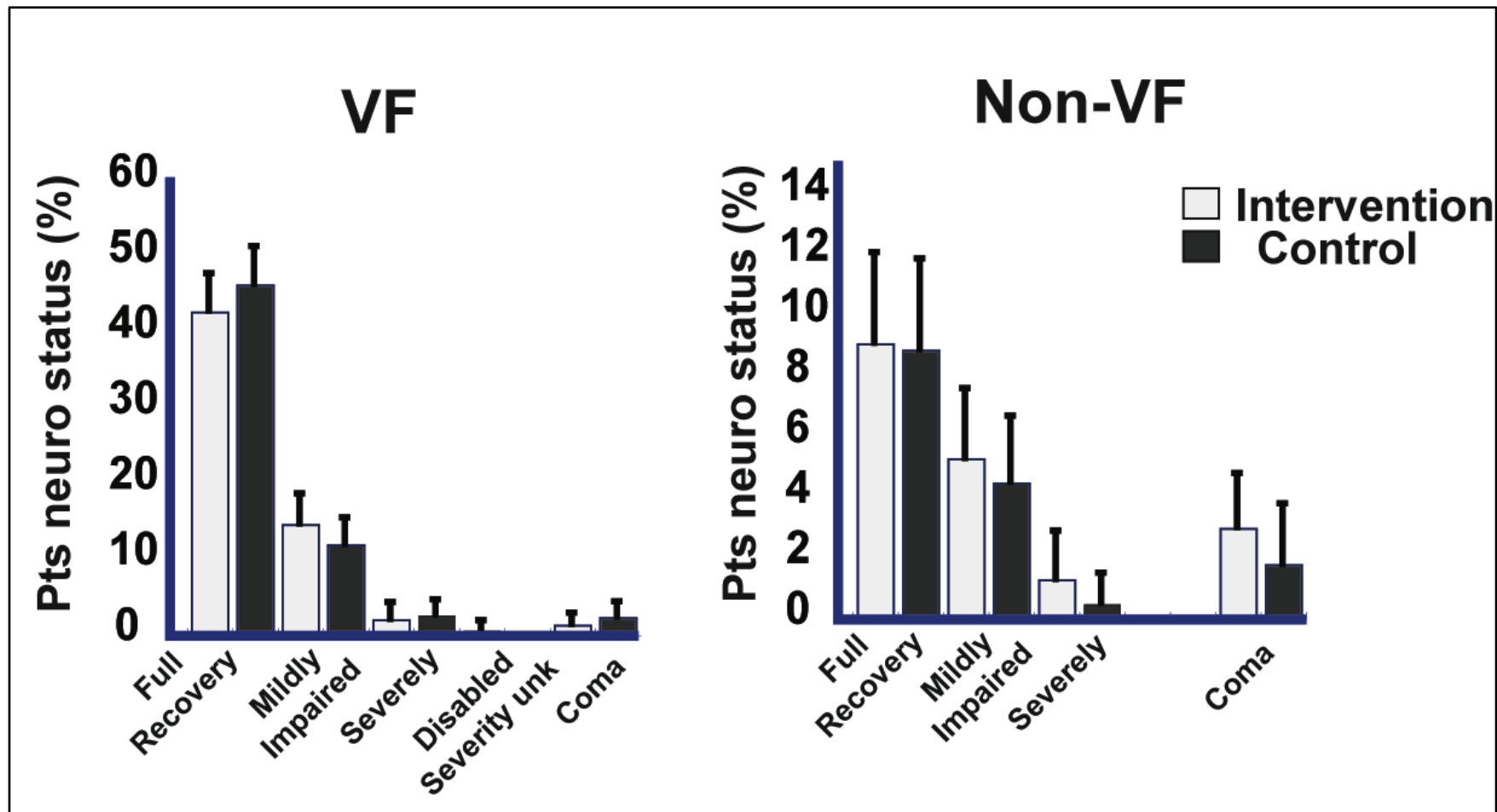


VF
intervention n=292
control n=291

Non-VF
intervention n=396
control n=380

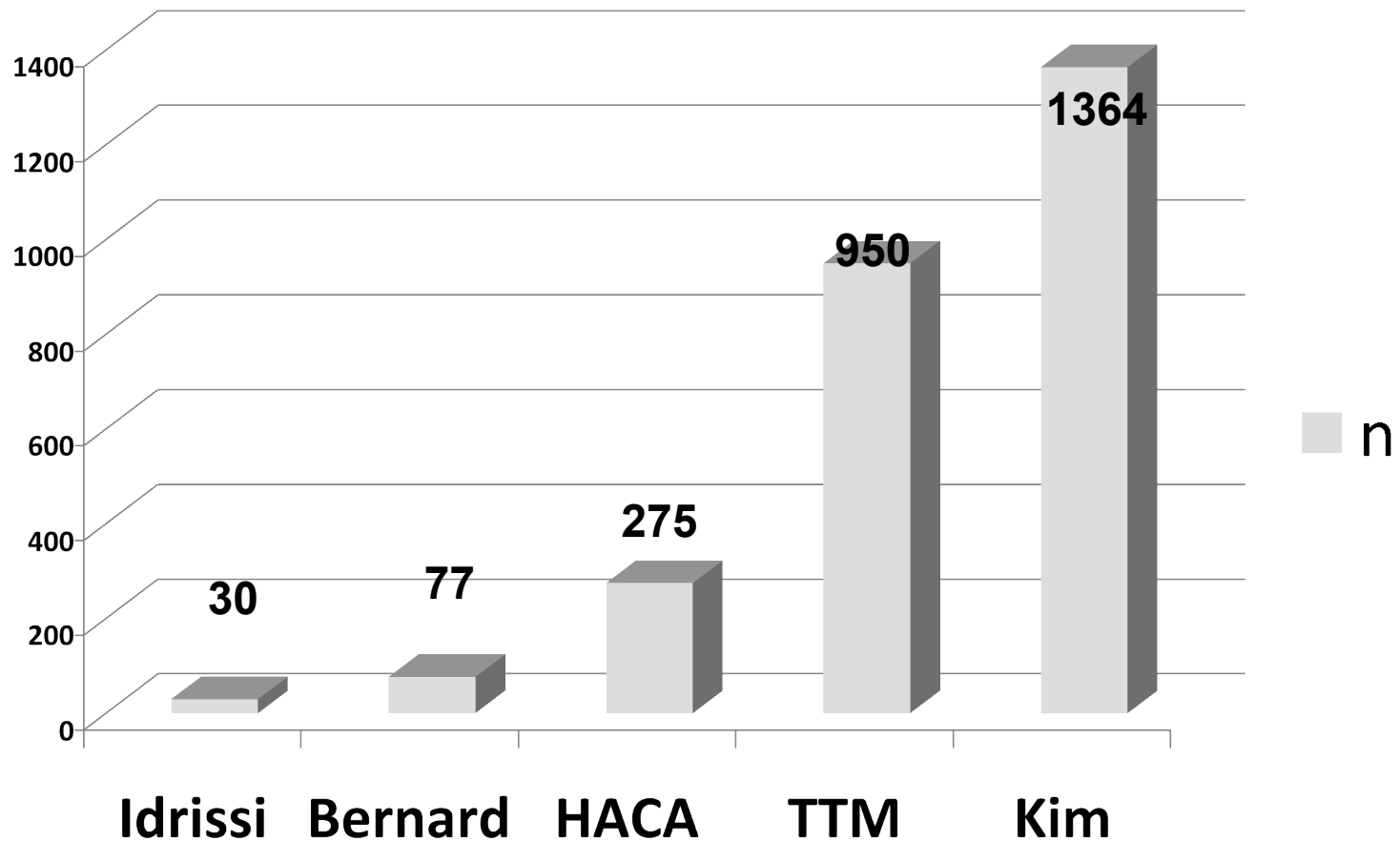
No difference in survival

Outcomes-neurologic status at discharge



No difference in Neurologic Outcome

Landmark Trials



2015 Updated AHA Guidelines

Class I, (LOE B-R)

- Treating comatose adult patients with ROSC after out-of-hospital *VF/VT* cardiac arrest should be cooled to 32°C to 36°C.

Class I, (LOE C-EO)

- Treating comatose adult patients with ROSC after out-of-hospital *with non VF/VT (non shockable)* cardiac arrest or in hospital cardiac arrest should be cooled to 32°C to 36°C.

Class IIa, (LOE C-EO)

- Hypothermia (TTM) post cardiac arrest should be maintained for at least 24 hours after achieving target temperature.

TTM= Targeted Temperature Management

R= based on randomized studies

EO= based on consensus of expert opinions

Callaway et al. Circulation. 2015;132[suppl 1]:S465–S482



2015 Updated AHA Guidelines

Class III: No Benefit, (LOE A)

- ***Recommendation against*** the routine pre hospital administration of cold intravenous fluids in patients with ROSC.

Conclusions: Who to cool

- All “reasonable” Patients with ***VT/VF*** and ***Non-VF/VT*** cardiac arrest both out-of-hospital and in-hospital
(level I evidence)

- ✓ HACCA criteria: good outcome 49% - 70%
- ✓ All VT/VF: good outcome 45% - 66%
- ✓ Asystole: good outcome 19% - 50%

Conclusions: Why to Cool

- *To reduce Mortality*
- *To Increase Neurologic function*
- *To decrease Myocardial infarct size ?*

Conclusions: How & When to Cool

Following ROSC and arrival in the ER

- Initiate cooling with a topical or intra vascular device.
- Continue to target temperature of 32°-36°C.
- Maintain mild hypothermia (32°-36°C) for at least 24 hrs.
- Liberal use of angiography/PCI in VF patients even without STE-Elevation

Take-home message

Cardiac Arrest

- The optimal target temperature is now 32°-36°C
- Pre hospital cooling has no benefit
- Follow guidelines until more data is available
- Patient selection is important

Remaining questions for post Cardiac arrest patients?

- Hypothermia – *what temperature (<37°C)?*
- Hypothermia – *duration?*
- Rewarming phase – *importance of?*

Conclusions

1. Hypothermia post cardiac arrest is standard of care for All correctly selected patients with ROSC.
2. Cooling should be initiated as soon as possible but can be delayed until arrival in hospital.
3. Target Temperature is now 32°-36°C.
 - Duration is currently 24 hours but needs to be evaluated



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