TTM and post-arrest care: clinical trials and recent evidence

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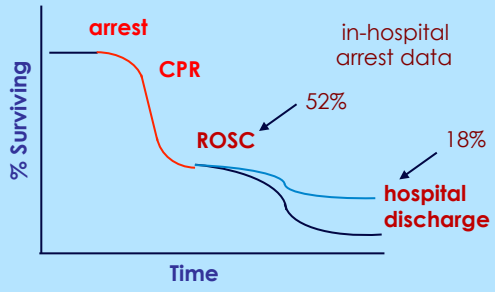
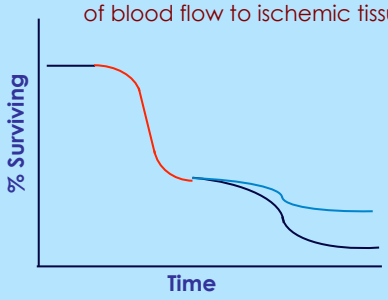
Survival in cardiac arrest

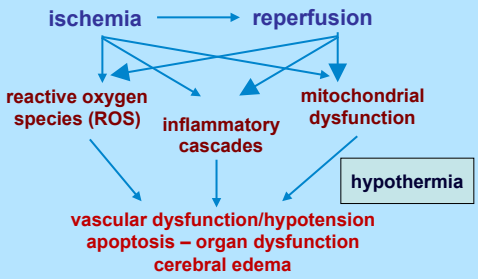


Reperfusion injury

Damage observed after restoration of blood flow to ischemic tissues

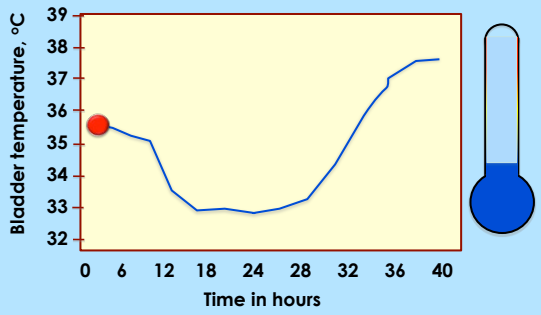


Reperfusion injury pathways



Key RCTs from 2001-2002

Concept of post-arrest TTM



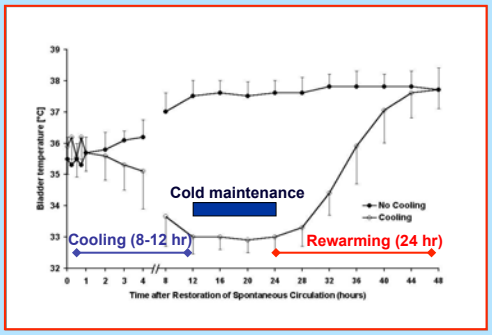
RCT details

	Multicenter?	Main site	pt rhythm	pt location	N
HACA	YES	Austria	VF	OOH	275
Bernard	YES	Australia	VF	OOH	77
Idrissi	NO	Belgium	PEA/asystole	OOH	30

More RCT details

	Age (years)	Female sex (%)	VF (#)	ROSC (min)	Target temp (°C)	Duration (hours)	Method
HACA	59 (51-68)	65 (24)	254 (92%)	22 (16-30)	33	24	Cool air
Bernard	68 (57-75)	25 (32)	77 (100%)	24 (17-32)	33	12	Ice packs
Idrissi	74 (66-79)	13 (39)	0 -	33 (27-37)	34	Up to 4	Helmet

HACA temperature curves



HACA, 2002

RCT outcomes

	Hypothermia (%)	Normothermia (%)	RR (95% CI)	P value
Alive at hospital discharge with favourable neurological recovery				
HACA	72/136 (53%)	50/137 (36%)	1.51 (1.14-1.89)	0.006
Bernard	21/43 (49%)	9/34 (26%)	1.75 (0.99-2.43)	0.052
Idrissi	4/16 (25%)	1/17 (6%)	4.25 (0.70-53.83)	0.16
Alive at 6 months with favourable neurological recovery				
HACA	71/136 (52%)	50/137 (36%)	1.44 (1.11-1.76)	0.009

AHA guidelines

Comatose out-of-hospital VF:
Class IIa recommendation

2010: *Changed to Class I*

In-hospital arrest, other rhythms:
Class IIb recommendation

2010: *Still Class IIb*

Example of "real world" study

From evidence to clinical practice: Effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest* **2006**

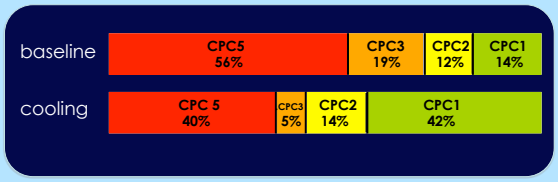
Mauro Oddo, MD; Marie-Denise Schaller, MD; François Feihl, MD; Vincent Ribordy, MD; Lucas Liaudet, MD

Oddo M et al, 2006

Retrospective study at one hospital in Switzerland
Cooling intervention with historical controls
Survivors of out-of-hospital arrest (n=109)
Cooling initially via ice bags, then cooling mattress
Target temperature 33°C, maintained for 24 hrs
All post-arrest ST elevations received cardiac cath

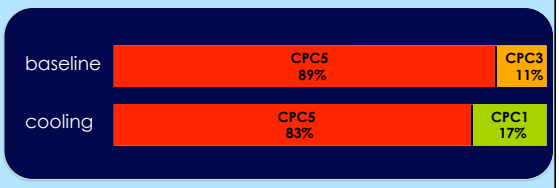
Outcomes for VF patients

Outcome at discharge for out-of-hospital VF arrest



Outcome for asystole patients

Outcome at discharge for out-of-hospital asystole arrest



TTM for nonshockable rhythms

Therapeutic hypothermia after cardiac arrest in clinical practice: Review and compilation of recent experiences **2009**

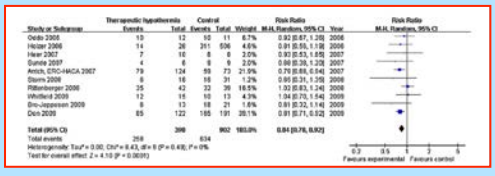
Emily Sagalyn, MD; Roger A. Band, MD; David F. Gaieski, MD; Benjamin S. Abella, MD, MPhil

Author	n HC	n TH	Survival: Historical Control n (%)*	Survival: Therapeutic Hypothermia n (%)	OR	95% CI
Arrich et al (17)	123	462	39 (32)	267 (58)	2.9	1.9–4.6
Belliard et al (21)	36	32	13 (36)	18 (56)	2.3	0.8–6.8
Busch et al (14)	34	27	11 (32)	16 (59)	3.0	0.9–9.9
Oddo et al (13)	54	55	20 (37)	28 (51)	1.8	0.8–3.8
Schefold et al (30)	31	31	21 (70)	21 (70)	1.0	.3–2.9
Sunde et al (18)	58	61	18 (31)	34 (56)	2.8	1.2–6.4
Combined ORs					2.5	1.8–3.3

Hypothermia clinical benefit is robust (consistent across Numerous studies)

TTM for nonshockable rhythms

Meta-analysis of hypothermia for non-shockable Rhythms (non-VF/VT)



Kim Y et al, 2012

Nielsen registry study

(a) Adverse events: all 34 centres and (b) adverse events: 22 reporting centers.

	n = 986
(a)	
Bradycardia <40 beats/min	127 (13)
Tachycardia >130 beats/min	57 (6)
Atrial fibrillation	88 (9)
VT	89 (9)
VF	71 (7)
Any combination of arrhythmia	325 (33)
Pneumonia	407(41)
Sepsis	35 (4)
Other infection	41 (4)
Bleeding requiring transfusion	44 (4)
Intracerebral bleeding	2 (0.2)
Seizures	233 (24)

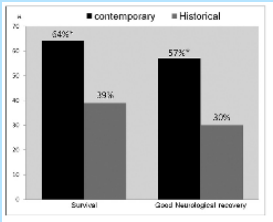
Nielsen et al, 2009

Bradycardia (13%)
Significant bleed (4%)

TTM and the cath lab

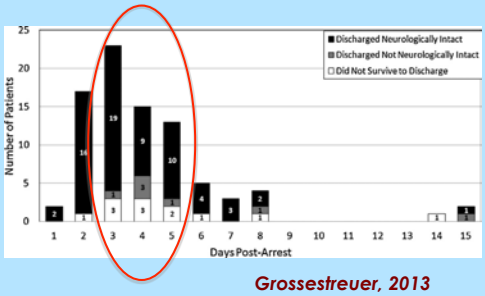
Usefulness of Cooling and Coronary Catheterization to Improve Survival in Out-of-Hospital Cardiac Arrest *2011*

Dion Stub, MBBS[a,b,*], Christopher Hengel, MBBS[a], William Chan, MBBS[a,b], Damon Jackson, MBBS[a], Karen Sanders, RN, GradDipEd[a], Anthony M. Dart, BA, BM, BCh, DPhil[a,b], Andrew Hilton, MBBS[c], Vincent Pellegrino, MBBS[c], James A. Shaw, MBBS, PhD[a,b], Stephen J. Duffy, MBBS, PhD[a], Stephen Bernard, MBBS, MD[c], and David M. Kaye, MBBS, PhD[a,b]



Less than 40% of patients had STEMI; yet huge survival benefits when OHCA patients cathed

Post-arrest awakening



Grossestreuer, 2013

Comparing TTM devices

Table 2 Outcome of the MIH-treated patients (78) presented number (percentage) representing survival, neurological function and cooling-associated complications

	AS (n = 39)	CG (n = 39)	p value
Survival and neurological function according to the Glasgow-Pittsburgh Cerebral Performance Categories			
Survived hospitalization, n (%)	21 (53.8)	24 (61.5)	0.65
CPC 1/2, n (%)	14 (35.9)	14 (35.9)	0.99
Complication of cooling			
Bleeding complication, n (%)	7 (17.9)	17 (43.6)	0.03
Major bleeding, n (%)	4 (10.3)	14 (35.9)	0.01
Minor bleeding, n (%)	2 (5.1)	3 (7.7)	0.99
Bacteria found in blood cultures, n (%)	17 (43.6)	21 (53.8)	0.50
Sepsis, n (%)	2 (5.1)	6 (15.4)	0.26
Death due to sepsis, n (%)	1 (2.6)	1 (2.6)	1.00
Pneumonia, n (%)	24 (61.5)	28 (71.8)	0.47
Antibiotic treatment, n (%)	28 (71.8)	33 (84.6)	0.16
Therapy necessitating arrhythmia, n (%)	13 (33.3)	12 (30.8)	0.99
Renal failure, n (%)	21 (55.3)	22 (56.4)	0.99

AS ArcticSun® non-invasive surface cooling, *CG* invasive Coolgard® cooling, *CPC* ½ good neurological outcome

No study has shown significant outcome or adverse event differences between devices

Pittl, 2013

Prehospital cooling?

Induction of Therapeutic Hypothermia by Paramedics After Resuscitation From Out-of-Hospital Ventricular Fibrillation Cardiac Arrest
A Randomized Controlled Trial *2010*

Stephen A. Bernard, MD; Karen Smith, BSc, PhD; Peter Cameron, MD; Kevin Masci; David M. Taylor, MD; D. James Cooper, MD; Anne-Maree Kelly, MD; William Silvester, MB, BS; for the Rapid Infusion of Cold Hartmanns (RICH) Investigators*

Table 3. Outcomes at Hospital Discharge

	Paramedic Cooling (n=118)	Hospital Cooling (n=116)	P*
Favorable outcome, n (%; 95% CI)	56 (47.5; 38.2–56.9)	61 (52.6; 43.1–61.9)	0.433
Discharge to home, n (%; 95% CI)	24 (20.3; 13.5–28.7)	34 (29.3; 21.2–38.5)	....
Discharge to rehabilitation, n (%; 95% CI)	32 (27.1; 19.3–36.1)	27 (23.3; 15.9–32.0)	....
Discharge to nursing home awake, n	0	0	....
Discharge to nursing home comatose, n (%; 95% CI)	0	1 (0.9; 0.02–4.7)	....
Dead, n (%; 95% CI)	62 (52.5; 43.1–61.8)	54 (46.6; 27.2–56.0)	....

CI indicates confidence interval.
*P calculated by χ^2 test.

Prehospital cooling? (part 2)

Original Investigation

Effect of Prehospital Induction of Mild Hypothermia on Survival and Neurological Status Among Adults With Cardiac Arrest
A Randomized Clinical Trial *2014*

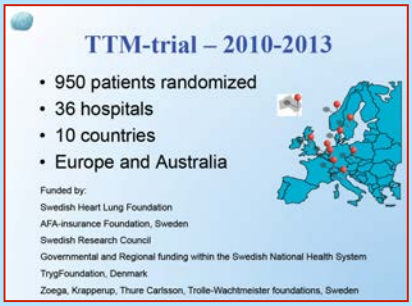
Francis Kim, MD; Graham Nichol, MD, MPH; Charles Maynard, PhD; Al Hallstrom, PhD; Peter J. Kudenchuk, MD; Thomas Rea, MD, MPH; Michael K. Copass, MD; David Carlbom, MD; Steven Deem, MD; W. T. Longstreth Jr, MD; Michele Olsufka, RN; Leonard A. Cobb, MD

Table 2. Status at Time of Discharge

	With Ventricular Fibrillation (n = 583)			Without Ventricular Fibrillation (n = 776)		
	No. (%) [95% CI]			No. (%) [95% CI]		
	Intervention (n = 292)	Control (n = 291)	P Value	Intervention (n = 396)	Control (n = 380)	P Value
Vital status						
Dead	109 (37.3) [32.0-43.0]	104 (35.7) [30.5-41.4]	.69	320 (80.8) [76.6-84.4]	318 (83.7) [79.6-87.1]	.30
Alive	183 (62.7) [57.0-68.0]	187 (64.3) [58.6-69.5]		76 (19.2) [15.6-23.4]	62 (16.3) [12.9-20.4]	
Neurological status at discharge						

The 2013 TTM trial (Nielsen et al)

Details of the TTM trial

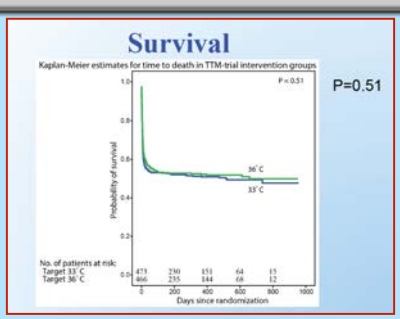


Characteristics of each group

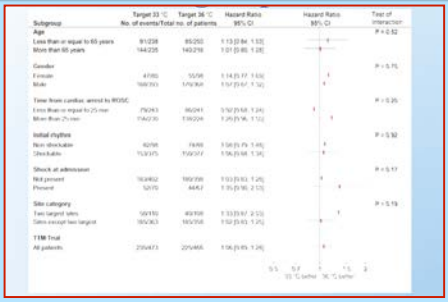
Baseline characteristics

	33°C	36°C
No.	473	466
Age	64+/-12	64+/-13
Male sex	83 %	79 %
Arrest in place of residence	52 %	55 %
Arrest in public place	42 %	40 %
Bystander witnessed	89 %	90 %
Bystander CPR	73 %	73 %
Shockable rhythm	**79 %**	**81 %**
Arrest to ROSC (min)	**25 [18-40]**	**25 [16-40]**
Circulatory shock	15 %	14 %
Lactate mmol/L	6.7±4.5	6.7±4.5
ST-elevation infarction	40 %	42 %
GCS	3 [3-4]	3 [3-4]

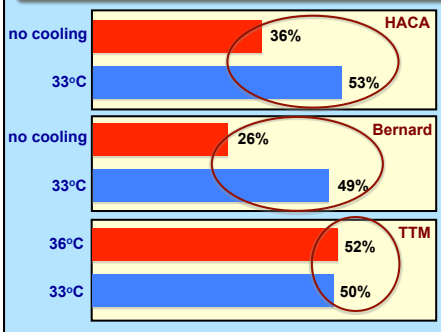
Outcomes in the TTM trial



TTM subgroup analyses



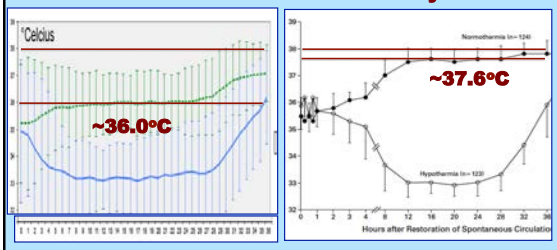
Key question raised by TTM trial



How can this be?

Temperature curve comparison

Nielsen et al **HACA study**



Bernard et al: ~37.3°C

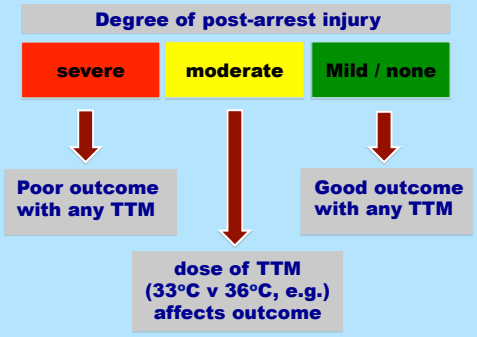
Large difference in maintenance temperatures

2013 TTM trial: key point

2013 TTM trial does not test the same hypothesis as the HACA, Bernard trials

36°C arm in the trial is still active management of temperature

Overview of post-arrest outcomes



Rationale for our approach

Given that:

(1)TTM trial was neutral (no differences in benefit or harms)

(2) Cooling to 33°C is based on extensive laboratory evidence and two RCTs (HACA, 2002; Bernard et al, 2002)

(3) We can't tell who will have significant post-arrest injury based on current technology and clinical factors

(4) the chance to modify neurologic injury is in the acute care of post-arrest patients – and we don't get a second chance

Our consensus approach

Therefore:

it is reasonable to not change current practice based on the TTM trial, but rather continue to treat comatose post-arrest patients with a TTM goal temperature of 33°C.

However, the TTM trial provides evidence that a more flexible approach is possible – for patients intolerant of 33°C (marked bradycardia, increased bleeding, marked QT prolongation, e.g.) or for patients that clinicians feel uncomfortable with treating to 33°C for other clinical factors, it is acceptable to treat with higher TTM temperature goals, up to 36°C.

Other key part of our approach

ALL comatose post-arrest patients should at least receive TTM with a maximum temp goal of 36°C – "normothermia" as defined by lack of any temperature control is not supported by the growing body of literature.

In addition to TTM management in the acute phase (12-24 hours of either 33°C or 36°C TTM), all post arrest patients should receive comprehensive best-practice post arrest care, including aggressive avoidance of fever for up to 48-72 hours following rewarming and avoidance of care withdrawal for at least 72 hours post arrest, as supported in the current AHA guidelines and the TTM trial.

Post-arrest care is multimodal

Requires a critical care "bundle":

- **Therapeutic hypothermia**
- Careful hemodynamic management
- Coronary intervention if STEMI or high probability of coronary cause
- Neurology consultation and assessment

Post-arrest hypothermia: an implementation problem

Many hospitals aren't using the therapy; other hospitals underuse it

Practical training in post-arrest care

Hypothermia and Resuscitation Training (HART) course at Penn

Philadelphia – next course October, 2014

Intensive two day CME course in hypothermia methods, protocols, and applications

Designed for critical care, cardiology or emergency medicine physicians and nurse leaders – i.e., local champions

Offers "hypothermia certification"

Workshop design – small course size – held quarterly

Hands on simulations

Expert faculty proctors

Honoring survivors and rescuers

Interactive learning

Preparing the future of resuscitation

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