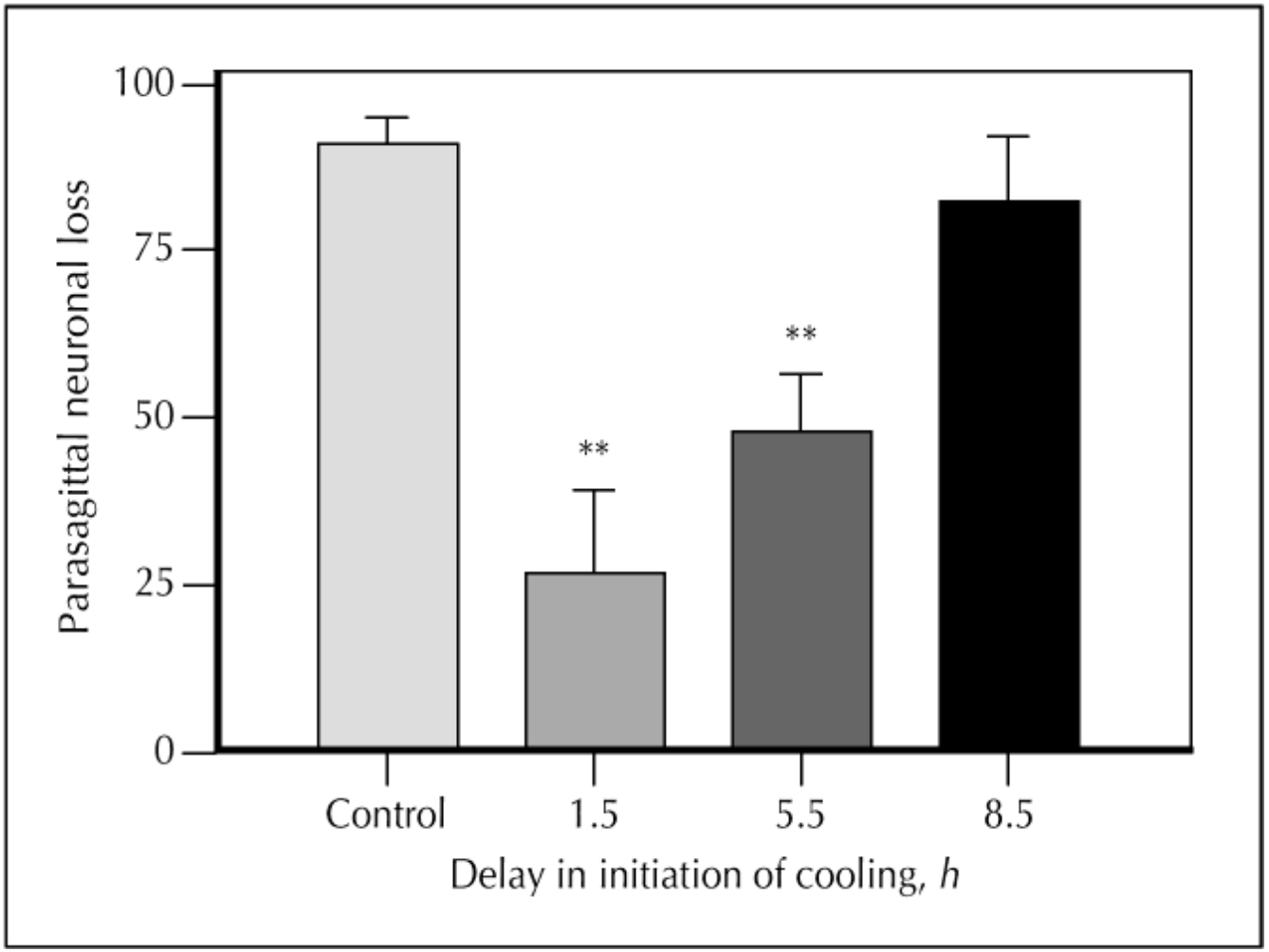
Have we gone cold on cooling after cardiac arrest?


FPOPP

Delay-dependent protection with hypothermia



Gunn et al 1997, 1998, 1999

Neonates

High consistency between trials

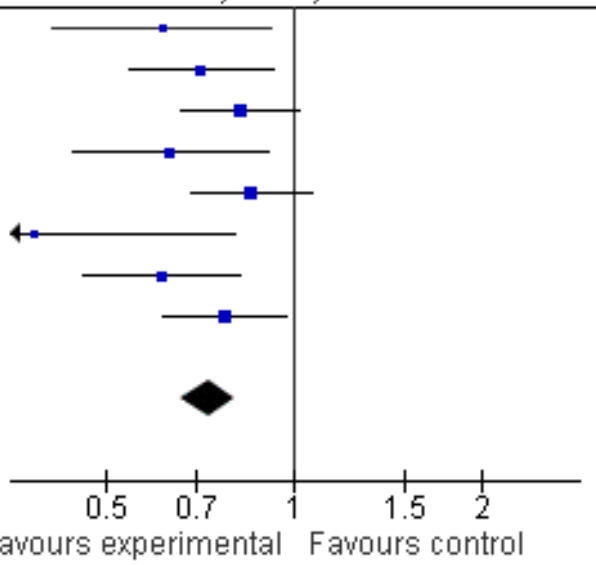
- Period of hypothermia: 48 to 72 hours
- Target temperature 34.5°C for head cooling, 33.5°C for WBC
- Outcome assessment: death or moderate-severe disability

Death or disability at 12 or 18m

Study or Subgroup	Hypothermia Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Eicher 2005	14	27	21	25	5.1%	0.62 [0.41, 0.92]	2005
NICHD 2005	45	102	64	103	15.0%	0.71 [0.54, 0.93]	2005
CoolCap	59	108	73	110	17.0%	0.82 [0.66, 1.02]	2005
Fudan 2005	31	100	46	94	11.1%	0.63 [0.44, 0.91]	2005
TOBY	74	163	86	162	20.3%	0.86 [0.68, 1.07]	2009
Zhengzhou 2009	7	38	21	44	4.6%	0.39 [0.18, 0.81]	2009
Neo.nEURO	27	53	48	58	10.8%	0.62 [0.46, 0.82]	2010
ICE	55	107	67	101	16.2%	0.77 [0.62, 0.98]	2011
Total (95% CI)		**698**		**697**	**100.0%**	**0.73 [0.66, 0.81]**	
Total events	312		426				

Heterogeneity: Chi² = 8.89, df = 7 (P = 0.26); I² = 21%

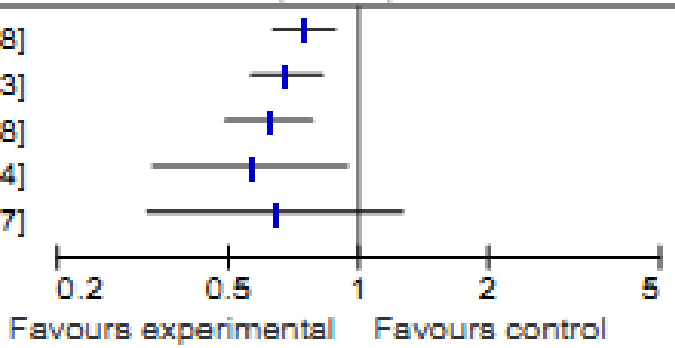
Test for overall effect: Z = 6.12 (P < 0.00001)



- NNT 6 (5, 9)
- Absolute risk reduction: 0.16

Components of outcome are concordant

Study or Subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Risk Ratio M-H, Fixed, 95% CI
Death	171	652	229	652	0.75 [0.63, 0.88]
Major disability	126	478	159	411	0.68 [0.56, 0.83]
Cerebral palsy	92	475	127	406	0.62 [0.49, 0.78]
Blindness	22	391	33	329	0.56 [0.33, 0.94]
Deafness	14	379	18	312	0.64 [0.32, 1.27]



Children

- No difference in mortality in 2 cohort studies

  Fink, PCCM, 2010; Doherty, Circulation, 2009

- HypCAP, Hutchison – Toronto, Auckland, GOS
  - Phase 2 pilot RCT

	Hypothermia (N=19)	**Normothermia (N=19)**	**P-value**
PCPC 4-6 (6 months)	13 (68)	10 (53)	0.60
Mortality (28 days)	12 (63)	8 (42)	0.19

ORIGINAL ARTICLE

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

Frank W. Moler, M.D., Faye S. Silverstein, M.D., Richard Holubkov, Ph.D.,

- 48hr - 18yr, chest compressions >2 min
- Motor score < 5
- Undergo randomisation within 6hrs
- Blocked by centre and age (<2, 2-12, >12)
- TTM for 120hr in both groups
  - 33°C (32-34°C) for 48hr, rewarmed over 16hr to 36.8°C to 120hr
  - 36.8°C (36-37.5°C) for 120hr

NEJM, April 2015, p1898

ORIGINAL ARTICLE

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

Frank W. Moler, M.D., Faye S. Silverstein, M.D., Richard Holubkov, Ph.D.,

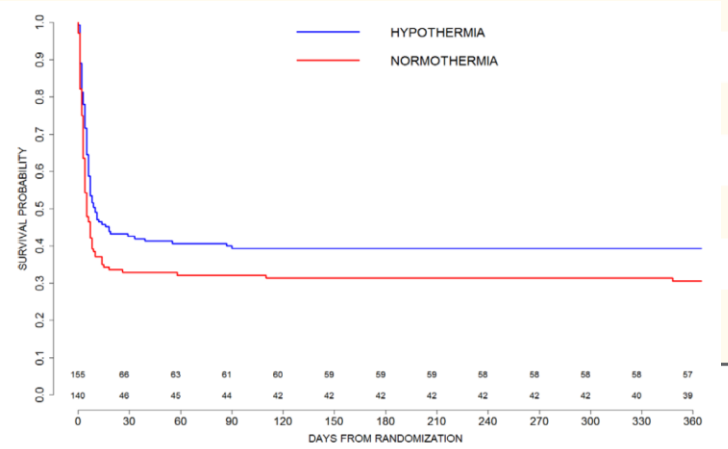
- Primary outcome – good neurobehavioural score
  - VABS-II > 70
- Secondary outcomes
  - Survival @ 12 months
  - Change in neurobehavioural score from baseline
- Sample size
  - Primary outcome rate 15-35%
  - Absolute effect size 15-20%
  - 276 patients for 85% power to detect 20% effect
- Screened 1355 children, enrolled 295

THAPCA

- Bystander witnessed 39%
  - CPR performed 66%
- Pre-existing condition 49%
- Cause
  - 72% respiratory
  - VT/VF 8%
- CPR
  - Median duration 25min (37% >30min)
  - Still required on arrival in ED 67%
  - Median doses adrenaline 3

Table 2. Primary and Secondary Outcomes.*

Outcome	Hypothermia Group	Normothermia Group	Risk Difference	Relative Likelihood (95% CI)	P Value
	no./total no. (%)		*percentage points (95% CI)*		
Primary outcome					
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†
Detailed supportive analysis					0.14‡
Death	87/138 (63)	88/122 (72)			
Disability					
Profound§	16/138 (12)	11/122 (9)			
Moderate-to-severe¶	8/138 (6)	8/122 (7)			
Good functional status‖	27/138 (20)	15/122 (12)			
Secondary outcomes					
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†
1-yr change in VABS-II score from baseline					0.13**
Death	94/151 (62)	97/134 (72)			
Lowest possible VABS-II score	6/151 (4)	1/134 (1)			
Decrease in VABS-II score					
>30 points	19/151 (13)	15/134 (11)			
16–30 points	11/151 (7)	4/134 (3)			
≤15 points or improved	21/151 (14)	17/134 (13)			



THAPCA

- No difference in primary or secondary outcome

- Issues
  - Power – too small
    - Outcome rate 15-35%, absolute effect size 15-20%
    - If outcome rate 12% and effect size 8%, need ≈ 900 patients
  - Time to be cold – too late
    - Median time to start cooling 5.9hr, reach goal 2.6hr
  - Heterogeneity of injury

ORIGINAL ARTICLE

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children

F.W. Moler, F.S. Silverstein, R. Holubkov, B.S. Slomine, J.R. Christensen,

- Same inclusion/exclusion criteria and treatment protocol
- Sample size 558 patients
  - assumed 35-55% favourable outcome
  - 90% power to detect 15% difference
- Terminated for futility after 329 patients enrolled
- Median age 1yr, 91% pre-existing condition
- Median 6hr from ROSC to target temperature

Moler, NEJM, 2017

ORIGINAL ARTICLE

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children

F.W. Moler, F.S. Silverstein, R. Holubkov, B.S. Slomine, J.R. Christensen,

- Survival with good outcome 36% (TH) vs 39% (norm)
  - RR 0.92 (0.67-1.27)
  - vs 16% for THAPCA-OH

- No differences in any outcome measure or in rates of adverse events

Moler, NEJM, 2017

Table 2. Primary and Secondary Outcomes.*

Outcome	Hypothermia Group	Normothermia Group	Risk Difference	Relative Risk (95% CI)	P Value
	no./total no. (%)		*percentage points (95% CI)*		
Primary outcome					
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†
Detailed supportive analysis‡					0.85§
Death	65/133 (49)	67/124 (54)			
VABS-II score					
<45 or lowest possible	2/133 (2)	0/124			
45–69	18/133 (14)	9/124 (7)			
≥70	48/133 (36)	48/124 (39)			
Secondary outcomes					
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†
Change in VABS-II score from baseline to 1 yr¶					0.70‖
Death	85/164 (52)	87/153 (57)			
Lowest possible VABS-II score	1/164 (1)	0/153			
Decrease in VABS-II score from baseline					
>30 points	12/164 (7)	8/153 (5)			
16–30 points	17/164 (10)	14/153 (9)			
≤15 points or improved	49/164 (30)	44/153 (29)			

ORIGINAL ARTICLE

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children

F.W. Moler, F.S. Silverstein, R. Holubkov, B.S. Slomine, J.R. Christensen,

- Survival with good outcome 36% (TH) vs 39% (norm)
  - RR 0.92 (0.67-1.27)
  - vs 16% for THAPCA-OH
- No differences in any outcome measure or in rates of adverse events
- 65% had cardiac condition, 55% received ECMO
- Less asystole, more bradycardia
- 36% stopped for “neurological” reasons – vs 79% in THAPCA-OH
- Active normothermia
- Too small, too heterogeneous

Moler, NEJM, 2017

Targeted Temperature Management After Pediatric Cardiac Arrest Due To Drowning: Outcomes and Complications*

Frank W. Moler, MD, MS, FCCM[1]; Jamie S. Hutchison, MD, FRCPC[2]; Vinay M. Nadkarni, MD, MS[3]; Faye S. Silverstein, MD[1]; Kathleen L. Meert, MD, FCCM[4]; Richard Holubkov, PhD[5]; Kent Page, MStat[5]; Beth S. Slomine, PhD[6]; James R. Christensen, MD[6]; J. Michael Dean, MD, MBA, FCCM[5]; for the Therapeutic Hypothermia After Pediatric Cardiac Arrest Out-of-Hospital Trial Investigators

PCCM, August 2016

- Drowning
  - typically 1/3 of OHCA
  - Outcome generally better than other respiratory
- 74 children
- Survival with VABS-II > 70
  - TH 29%, N 17%
- Proportion within 15pts of baseline
  - TH 23%, N 20%
- No good outcomes if
  - CPR>30min
  - >4 doses adrenaline

Prognostic Factors Out of Hospital

- Good
  - Cardiac
  - VT/VF
  - Shorter CPR, less adrenaline
  - Witnessed
  - 1-5 years old

- Bad
  - ALTE/SUDI
  - Weekend
  - >30min chest compressions
  - Non-drowning respiratory cause

Meert; PCCM, December 2016
Meert; Resuscitation, 2018

Neurobehavioral and Cognitive Outcomes

- Broadly normal baseline function

- In hospital
  - 59% broadly normal
  - 16% lowest possible score
  - >6yr only 4% lack functional communication

- Out of hospital
  - 36% broadly normal
  - 43% lowest possible score
  - >6yr 51% lack functional communication

Slomine; Resuscitation, 2018
Slomine; Pediatrics, 2016

Cooling in Children

- The only RCT in children does not support moderate hypothermia

- Paediatric HIE after cardiac arrest is typically
  - Very severe
  - Cooling achieved late

ORIGINAL ARTICLE

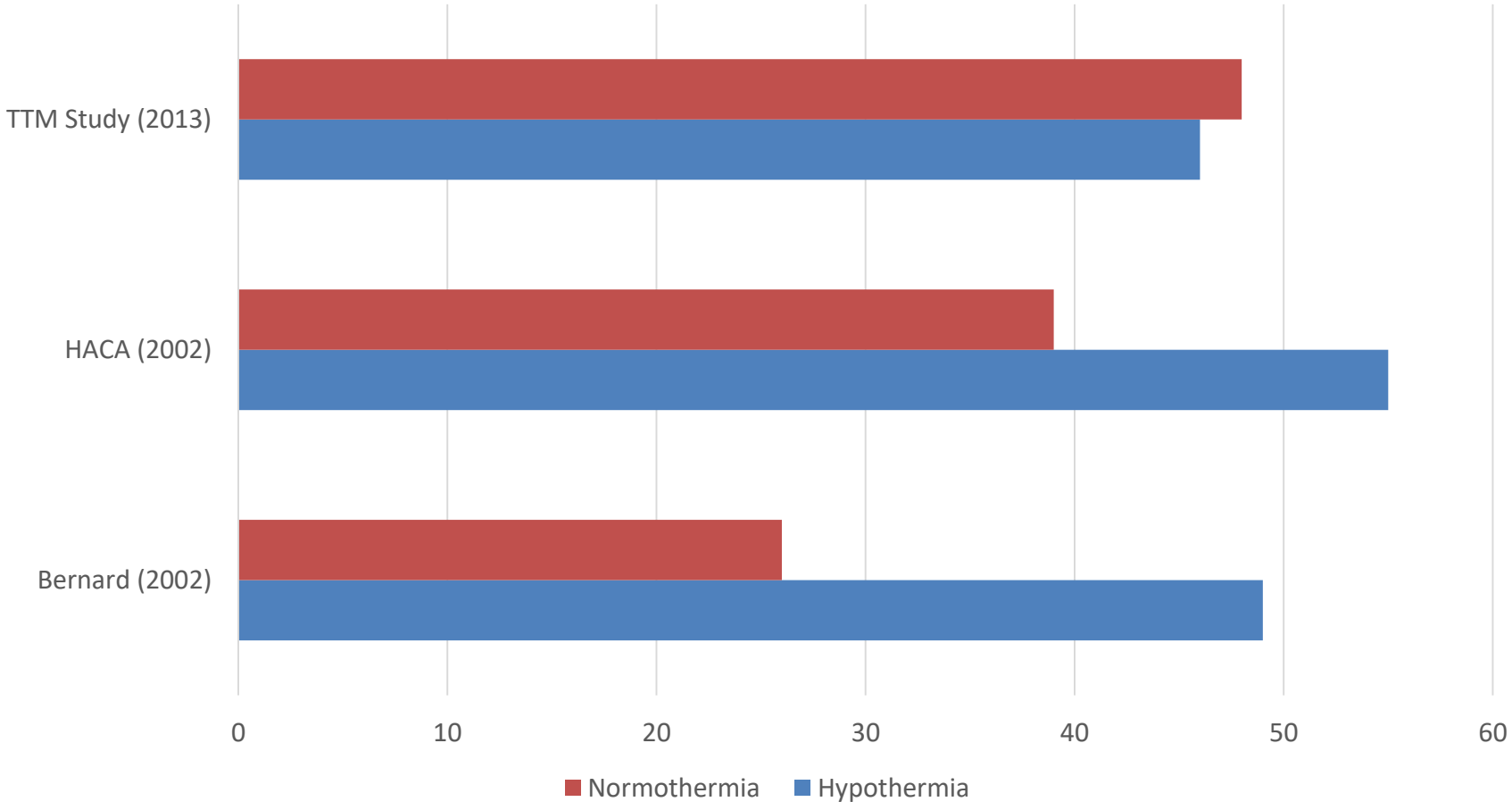
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D.,

NEJM, 2013

- 939 patients
  - More than twice the size of the original trials combined
  - Superb methodology and performance
  - Protocol for withdrawal of life-sustaining therapies
  - Approximately 50% “good” outcome

Outcome	33°C Group	36°C Group	Hazard Ratio or Risk Ratio (95% CI)*	P Value
	no./total no. (%)			
Primary outcome: deaths at end of trial	235/473 (50)	225/466 (48)	1.06 (0.89–1.28)	0.51
Secondary outcomes				
Neurologic function at follow-up†				
CPC of 3–5	251/469 (54)	242/464 (52)	1.02 (0.88–1.16)	0.78
Modified Rankin scale score of 4–6	245/469 (52)	239/464 (52)	1.01 (0.89–1.14)	0.87
Deaths at 180 days	226/473 (48)	220/466 (47)	1.01 (0.87–1.15)	0.92


TTM Study (2013)
HACA (2002)
Bernard (2002)
0
10
20
30
40
50
60
Normothermia
Hypothermia

TTM trial did NOT show

1. that hypothermia does not work
2. that fever control is what matters

It showed that if TTM is used, patients will have similar outcomes whether higher or lower target temperature is used

Is it duration?

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

Table 3. Primary and Secondary Outcomes After Targeted Temperature Management

	48-Hour Group (n = 175)	24-Hour Group (n = 176)	Difference, % (95% CI)	Relative Risk or Ratio of Geometric Means (95% CI)	*P* Value
Primary outcome, No. (%)					
CPC score of 1 or 2 at 6 mo[a]	120 (69)	112 (64)	4.9 (−5 to 14.8)	1.08 (0.93 to 1.25)	.33
Secondary outcomes, No. (%)					
ICU mortality	26 (15)	30 (17)	−2.1 (−9.7 to 5.5)	0.88 (0.54 to 1.42)	.59
Hospital mortality	40 (23)	44 (25)	−2 (−10.9 to 6.9)	0.92 (0.63 to 1.34)	.66
Mortality at 6 mo	48 (27)	60 (34)	−6.5 (−16.1 to 3.1)	0.81 (0.59 to 1.11)	.19

- Cooling started within 2hr and target by 5hr
- To show a 5% absolute improvement in good outcome would require 3000 patients

Is it speed?

- Animal studies suggest window of 4-6 hours
- 6 trials, 2379 patients
- All start cooling pre-hospital
- NO difference in outcome

JAMA | Original Investigation

Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy

A Randomized Clinical Trial

- Smaller effect when delayed 6-12hrs
  - Absolute difference 3.5% less for death/disability
  - 76% probability of any reduction (64% at least 2%)

- Depth and duration
  - no better if colder (32˚C) or longer (120hrs)
  - Possibly worse outcome if both

JAMA, 2017

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

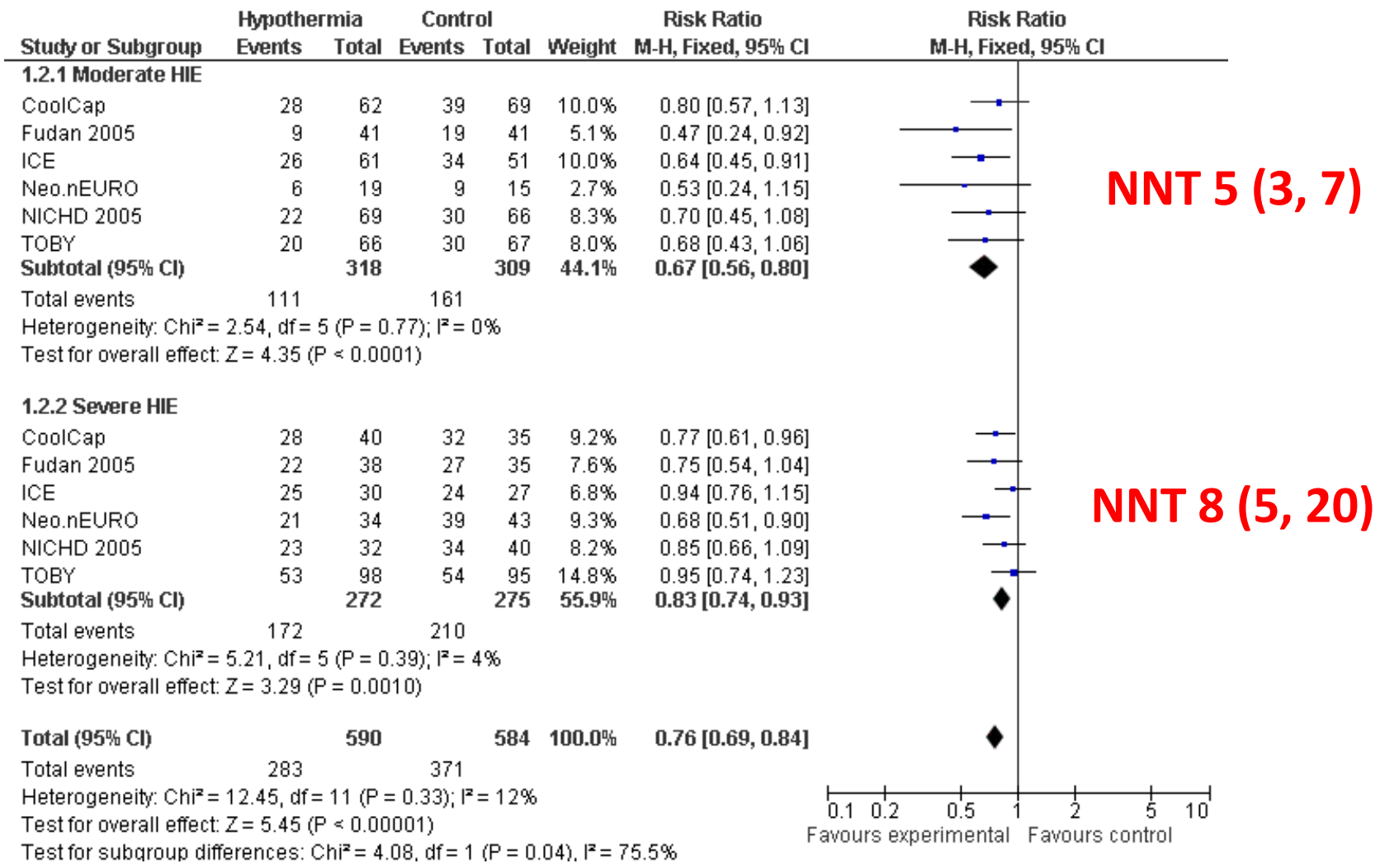
Association Between Therapeutic Hypothermia and Survival After In-Hospital Cardiac Arrest

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

JAMA, 2016

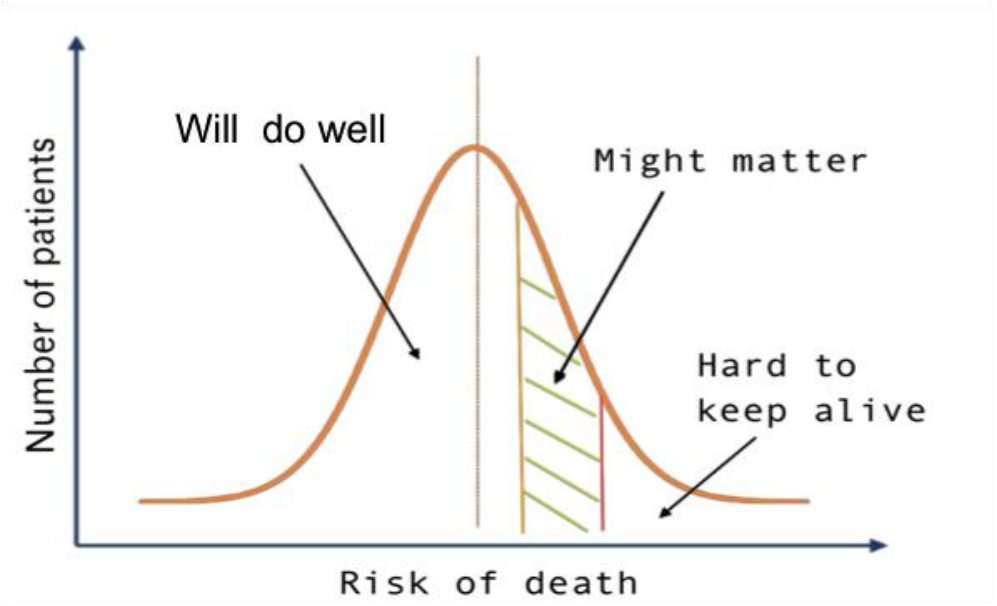
Survival	Patients, No./Total No. (%)		Relative Risk With Hypothermia (95% CI)[a]	Risk Difference With Hypothermia, % (95% CI)[a,b]	*P* Value[c]	*P* Value for Interaction[d]
	Hypothermia	No Hypothermia				
Favorable neurological survival[e]						
All cardiac arrests	246/1443 (17.0)	725/3529 (20.5)	0.79 (0.69 to 0.90)	−4.4 (−6.8 to −2.0)	<.001	
Nonshockable cardiac arrests	137/1054 (13.0)	446/2723 (16.4)	0.78 (0.64 to 0.93)	−3.7 (−6.2 to −1.1)		.88
Shockable cardiac arrests	109/389 (28.0)	279/806 (34.6)	0.79 (0.65 to 0.97)	−7.3 (−13.3 to −1.3)		

Is it severity?



NNT 5 (3, 7)

NNT 8 (5, 20)


Will do well
Might matter
Hard to
keep alive
Number of patients
Risk of death

Fever is bad for the injured brain

- Association not cause
  - In animals active cooling of fever reduces damage
- Adults
  - Fever associated with increased mortality and worse neurological outcome
  - Each degree >37.0°C, OR 2.3 unfav neuro outcome
- Children
  - Temp persistently >38°C in first 24hrs (5.5%), OR 2.7 unfav neuro outcome
- Neonates
  - Each degree >37.0°C, OR 3.6-4 death/disability

Zeiner, Arch Int Med,2001; Bembea, PCCM, 2010; Laptook, Pediatrics, 2008

How well do we control temperature?

- First 24hrs after IHCA in children
  - 43.5% ≥1 temperature >38.0°C
  - 5.5% persistently >38.0°C (OR 2.7 unfav outcome)
  - No difference after 2005 guidelines

Bembea, PCCM, 2010

- Most trials set upper limit 37.5°C in control group
  - CoolKids – 68% exceeded 37.5°C over first 48hrs
  - HiTBIC (<37.0°C) – 40% exceeded 38.0°C over first 72hrs
- Technical challenges of temperature control and cooling blankets

TTM2 will compare 33°C with early treatment of fever (≥ 37.8°C)

Have we gone cool on cooling?

- No evidence in children or adults that moderate hypothermia is better than mild hypothermia
- No evidence that TTM for 48-72hr is better than 24-36hr
- Strong evidence that fever is associated with worse outcome in brain injury. Very weak evidence that fever control improves outcome. TTM2 should answer that

Have we gone cool on cooling?

- Very strong evidence that TTM improves outcome in birth asphyxia.
- Reasons for this difference are not clear but evidence that TTM much less effective in severe injury
- Better tools to rapidly assess severity are required
- Alternative trial designs are required if any further trials are to be done in children
  - E.g. adaptive trial designs, Bayesian analysis