5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 16

Traumatic Brain Injury, stroke and subarachnoid haemorrhage – How to Make an Impact in neurocritical care management and research (Level 2)

Hypothermia for TBI, anoxic ischemic encephalopathy and stroke

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Hypothermia for TBI, anoxic ischemic encephalopathy and stroke

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AGENDA

- Therapeutic Hypothermia: mechanisms and methods
- Hypothermia for TBI
- Hypothermia for anoxic encephalopathy
- Hypothermia for stroke

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Disclosures

- Speakers´s honoraria from Zoll Medical
- Coordinator in the EuroHYP-1 trial

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Historical perspective

- Use of hypothermia described by ancient Egyptians, Greeks and Romans
- Hippocrates advised to surround badly wounded patients with ice and snow to reduce blood loss
- Celcus and Galaenus also described treatments with hypothermia

Hippocrates (460-375 BC). De Vetere Medicina.
Celcus AC (1ST century AD). De Medicina.
Galaenus C. (129-199 AD) Opera Omnia (Medicorum Graecorum Opera).
Swan H Surgery 1973;73:736-758.

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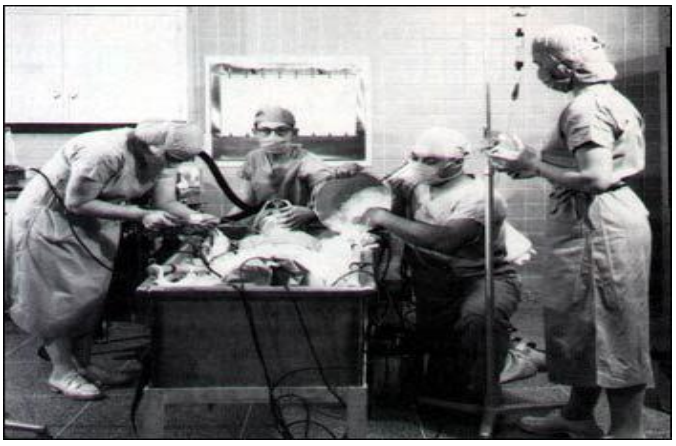
Napoleons Field doctor was a visionary . . .

Dr. Baron Larrey described, that wounded soldiers near the campfire died faster then those, who were not rewarmed.

Larrey IJ. Memoirs of military service and campaigns of the French armies, Vol 2. Baltimore, J Cushing, 1814, pp 156-164.

195 5

Open- eart Surgery - NIH Clinical Center



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Temperature Management

Treatment of fever

Prevention of fever

Therapeutic hypothermia

- Sedated/ ventilated patients
- Awake patients

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Wu & Grotta 2013 Lancet Neurol

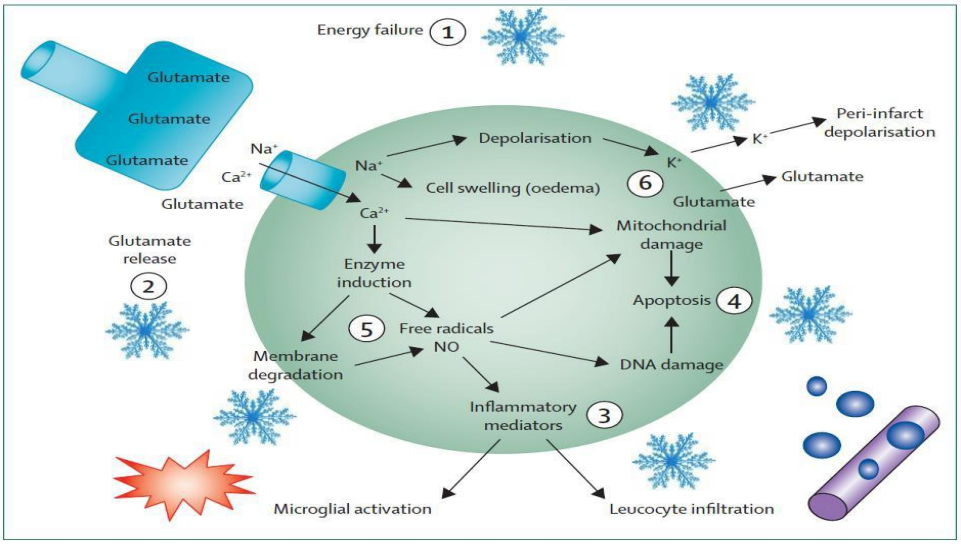


Figure: **Proposed neuroprotective mechanisms of hypothermia**
Therapeutic hypothermia provides neuroprotection after cerebral ischaemic injury by various mechanisms: (1) decreases cerebral metabolism, (2) suppresses glutamate release, (3) reduces neuroinflammatory response, (4) disrupts apoptopic pathways, (5) reduces free radical generation, and (6) minimises oedema formation. NO=nitric oxide. Adapted from Dirnagl and colleagues,[20] by permission of Elsevier.

Systemic cooling

SURFACE COOLING

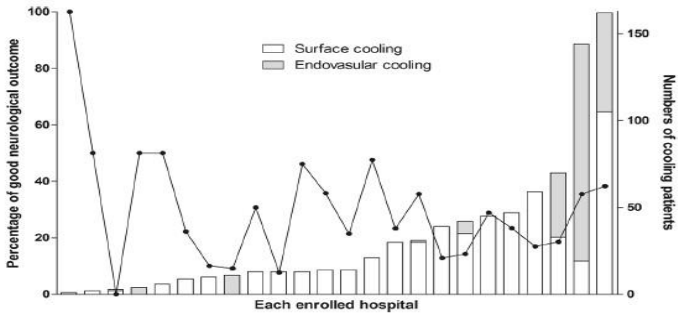
- Heat loss via scan/mucosa
- Non invasive
- Sever counter-regulation/ problematic in adipose patients

ENDOVASCULAR COOLING

- Cooling catheter inserted to central venous system
- Excellent cooling rates
- Risk of thrombosis/ catheter-associated complications

Survace versus endovascular: retrospective data

- Multicenter, retrospective, 24 hospitals in South Korea
- 803 pat. after Cardiac arrest
- 559 (70%) used survace cooling, 244 (30%) endovascular
- Propensity score matching
- Endpoints: Adverse events, Efficacy, Outcome



Oh SH et al., Critical Care, 2015

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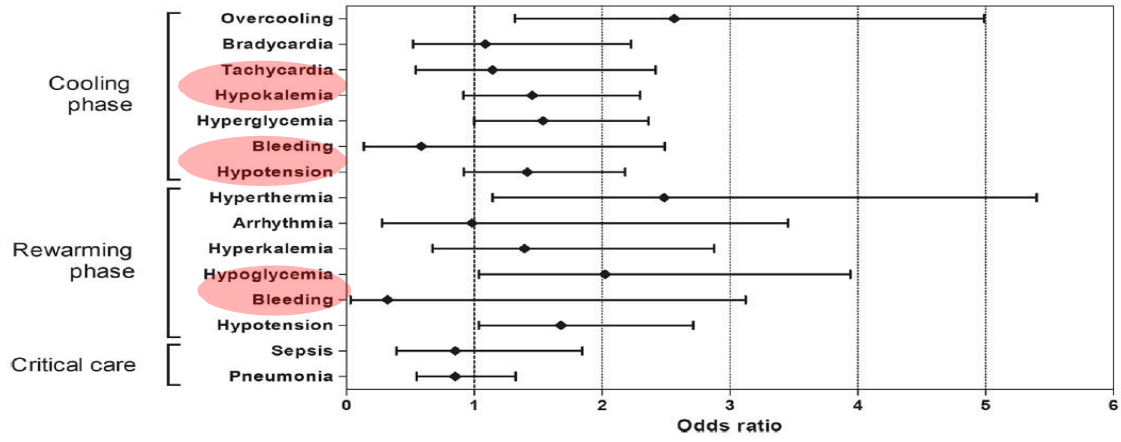
Functional outcome not different.
Risk of hyperglycemia, hyperthermia and hypotension higher with survace cooling



Oh SH et al., Critical Care, 2015

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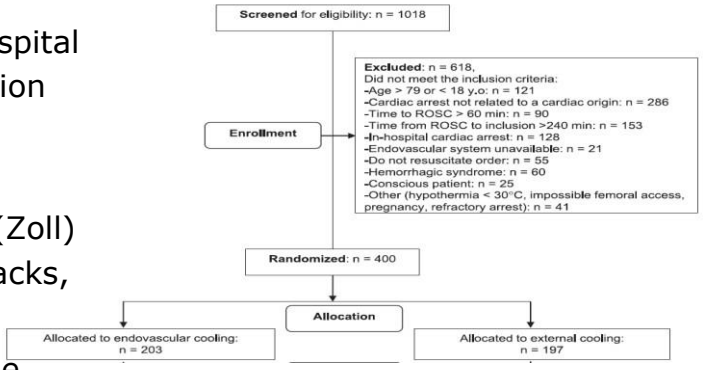
ICERA-Trial

(„Impact of Endovascular Cooling in the Management of Cardiac Arrest")

- 400 patients with out-of-hospital CA, ROSC < 60 Min., Inclusion within 4 hours
- Prospectiv, randomized: endovascular hypothermia (Zoll) versus surface (Fans, Ice Packs, Homemade tent)
- Prim. EP: Favorable outcome, Cerebral Performance Category 1-2 on Tag 28



Deye N. et al., Circulation, 2015

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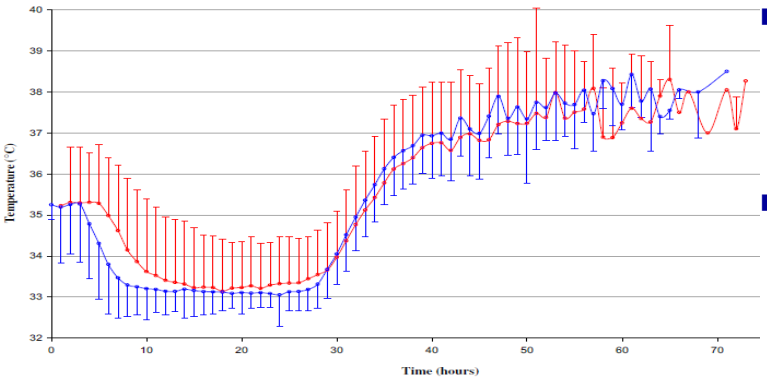
ICERA-Trial: Temperature Control better with endovascular cooling



- Time to target temperature of 33°C shorter (7,1 versus 10 h, p<0.001)
- Precision and stability of hypothermia better (Devation>1°C: 1,0 versus 5,5, p<0.0001)

Deye N. et al., Circulation, 2015

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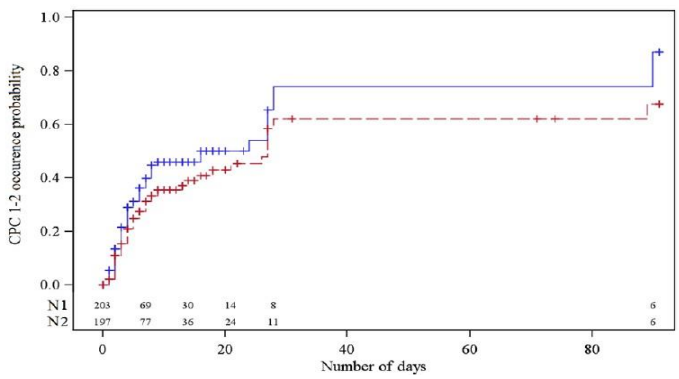
ICERA- Functional outcome unchanged

- Favorable Outcome on day 28: 35% (endovasc.) versus 26% (external), OR 1.41, 95% CI 0.93-2.16, p=0,107)
- After 90 days: Trend in favor of the endovascular tecnique (p=0.052)



Deye N. et al., Circulation, 2015

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ICER -Studie: Side effects

- Catheter-associated bleeding and hematoma: n=25
  Bakt. colonisation and Infektionen n=27
  2 patients with ischemia of the leg
- Accidential hypothermia < 30°C in 3 patients, all in the external cooling group

	Total Reported and Induced Side Effects, n	
	Endovascular (n=57)	External (n=34)
Hypothermia <30°C	0	3
Complication during KTvc insertion	1	0
Minor bleeding, hematoma, or arteriovenous fistula at KTvc insertion sites	25	10
Minor bleeding	16	7
Hematoma	8	2
Arteriovenous fistula	0	0
Unknown	3	1
Bleeding at KTvc insertion sites requiring blood transfusion	2	2
KTvc colonization or infection	27	17
Colonization	22	9
Infection	2	6
KTvc-related bloodstream infection with positive blood culture	1	1
Unknown	3	2
Septic shock related to KTvc	0	0
Thrombophlebitis at KTvc insertion sites	0	1
Lower-limb ischemia	2	0
Burns (skin)	0	1
Death related to therapeutic hypothermia	0	0

Deye N. et al., Circulation, 2015

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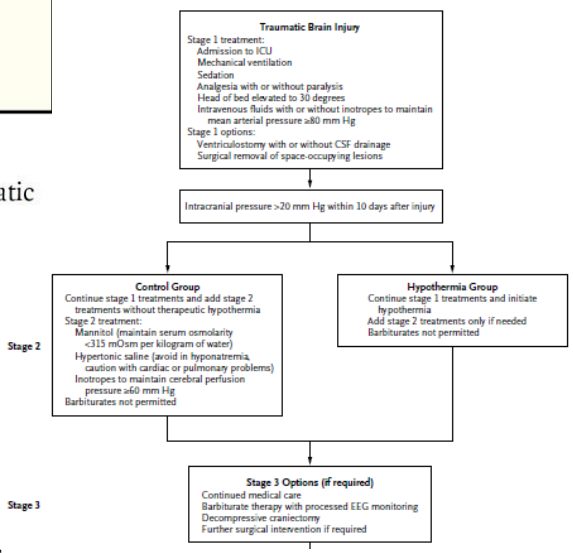
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 17, 2015 VOL. 373 NO. 25

Hypothermia for Intracranial Hypertension after Traumatic Brain Injury

- 387 Pat. with elevated ICP>20 mmHg
- Hypothermie 32°C to 35°C plus Standard Care versus Standard Care
- 47 centers in 18 countries
- Recruitment 09/09-10/14
- Prim. EP: GOS-E Score after 6 months



Andrews P et al., New Engl J Med, 2015

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Eurotherm3235: Methods of cooling

- Induction: Bolus (20-30 ml/kg) of refrigerated sodium chloride i.v.
- Maintainance: usual cooling tecnique of each side. Duration: At least 48 hours
- Rewarming: 0.25°C/ hour, provided that ICP < 20 mmHg

Andrews P et al., New Engl J Med, 2015

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Characteristic	Hypothermia (N=195)	Control (N=192)
Age <45 yr — no. (%)	131 (67.2)	131 (68.2)
Age — yr	37.4±15.4	36.7±14.9
GCS motor score — no. (%)†		
1 or 2	56 (28.7)	51 (26.6)
3–6	139 (71.3)	141 (73.4)
Pupillary response — no. (%)		
Both reacting	144 (73.8)	143 (74.5)
One or neither reacting	51 (26.2)	49 (25.5)
Time from injury — no. (%)		
<12 hr	19 (9.7)	15 (7.8)
≥12 hr	176 (90.3)	177 (92.2)
Intracranial pressure at randomization — mm Hg	25.2±4.8	25.5±6.4
Core temperature at randomization — °C	37.0±0.72	37.1±0.72
Isolated TBI — no. (%)	123 (63.1)	133 (69.3)
Marshall classification — no. (%)‡		
Diffuse axonal injury I–III	72 (36.9)	78 (40.6)
Diffuse axonal injury IV	21 (10.8)	15 (7.8)
Any lesion surgically removed	46 (23.6)	52 (27.1)
High-density or mixed-density lesion	56 (28.7)	47 (24.5)
Mechanism of injury — no. (%)§		
Road-traffic accident, pedestrian	22 (11.3)	31 (16.1)
Road-traffic accident, motor vehicle	68 (35.1)	51 (26.6)
Bicycling accident	7 (3.6)	10 (5.2)
Fall	78 (40.2)	78 (40.6)
Sports injury	1 (0.5)	1 (0.5)
Assault	18 (9.3)	21 (10.9)

- Well balanced
- ¼ with Surgery
- Start of cooling late after injury (>12 hours)

Andrews P et al., New Engl J Med, 2015

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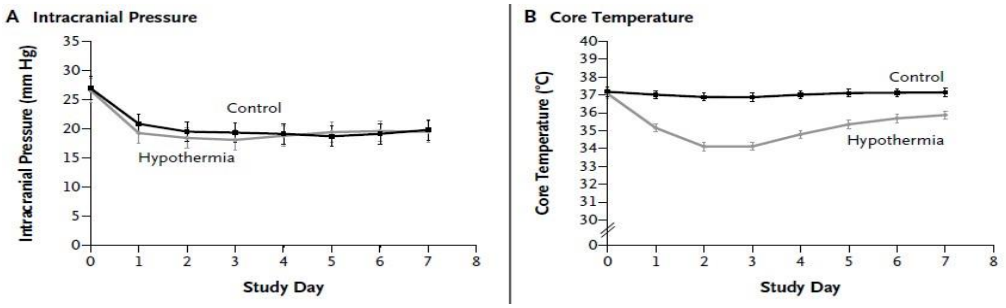
Eurotherm3235 Trial



- Temperature in the intervention group significantly lower
- No better control of ICP with hypothermia compared to standard of care

Andrews P et al., New Engl J Med, 2015

Eurotherm3235 Trial

After 6 month: Evidence of harm with hypothermia

Favorable outcome in 26% (hypothermia) versus 37% (control)

Mortality wi 7)

Worrying results with hypothermia after TBI.
Possible reasons:

- Start of hypothermia to late?
- Induction of hypothermia to slow?
- Rewarming to fast?

Variable		lue
Physiological measu		
Adjusted mean d		5
Adjusted mean d		001
Adjusted mean d		6
Adjusted mean difference in cerebral perfusion pressure on days 1–7 — mm Hg	1.61 (–0.36 to 3.58)	0.11
Primary analysis: adjusted common odds ratio for GOS-E score at 6 mo‡§	1.53 (1.02 to 2.30)¶	0.04
Adjusted odds ratio for unfavorable outcome‡‖	1.69 (1.06 to 2.70)¶	0.03
Unadjusted hazard ratio for death at 6 mo	1.45 (1.01 to 2.10)	0.047

Andrews P et al., New Engl J Med, 2015

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Early Sustained Prophylactic Hypothermia on Neurologic Outcomes Among Patients njury cal Trial

POLAR-RCT

- Early prophylactic hypothermia after sever TBI
- Early enrollment after trauma: pre-hospital or in the ER
- 511 patients in 6 countries
- Recruitment 12/10-11/2017
- Control group: No mothermie 37°C
- Prim. EP: Good outcome/ functional independence (GOS-E 5-8) after 6 Monaten

Cooper D et al., JAMA, 2018

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Effect of Early Sustained Prophylactic Hypothermia on Neurologic Outcomes Among Patients

POLAR-RCT

al

Methods:

- Induction: Exposure, cooling wraps, 2000 ml ice-cooled saline i.v., target 35.0°C
- Maintainance: Surface cooling, 33°C or 35°C (if bleeding concerns), duration 3-7 days;
- Controlled Rewarming at 0,25°C/ hour to 37°C as long as ICP <20 mmHg.
- After rewarming: Normothermia for 7 days using automated surface cooling wraps

Cooper D et al., JAMA, 2018

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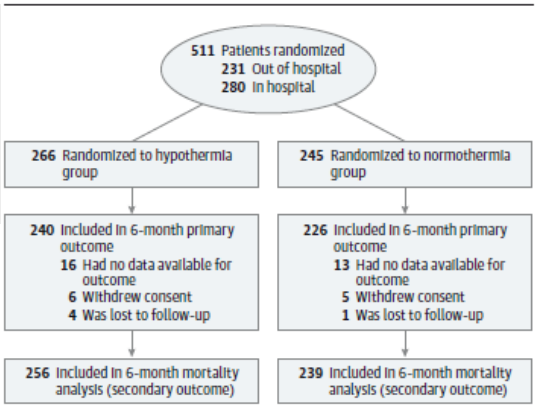
Prophylactic Hypothermia after TBI: POLAR-RCT

	No./Total (%)	
	Hypothermia (n = 260)	Normothermia (n = 240)
Men	207 (79.6)	194 (80.8)
Women	53 (20.4)	46 (19.2)
Age, mean (SD), y	35.0 (13.5)	34.1 (13.4)
GCS score, median (IQR)		
Overall score[a]	6 (4-7)	6 (4-7)
Motor score	3 (1-4)	3 (2-5)
One or both pupils reacting[b]	220 (84.6)	202 (84.2)
Cause of injury		
Motor vehicle	84 (32.3)	89 (37.1)
Motorcycle	29 (11.2)	18 (7.5)
Bicycle	20 (7.7)	20 (8.3)
Pedestrian	28 (10.8)	37 (15.4)
Hit by object	24 (9.2)	16 (6.7)
Fall/jump	60 (23.1)	54 (22.5)
Other	15 (5.8)	6 (2.5)
Time from injury to randomization, median (IQR), h	1.8 (1.0-2.7)	2.0 (1.1-2.8)



Cooper D et al., JAMA, 2018

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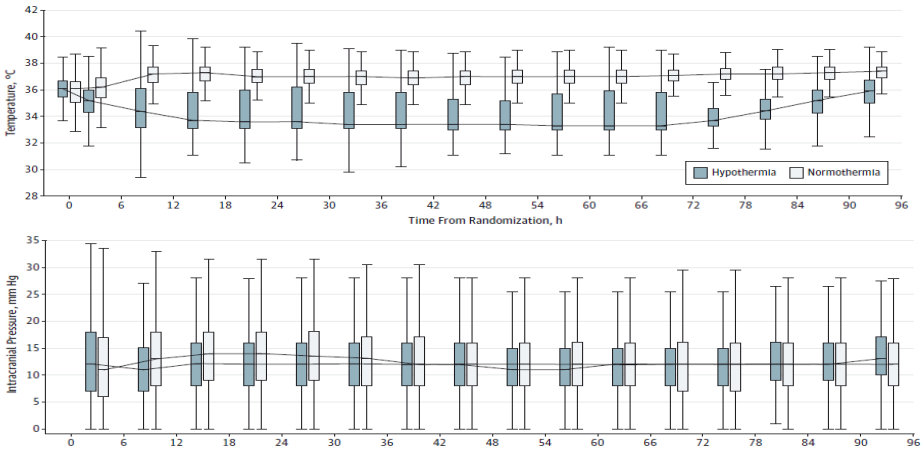
POLAR-RCT: ICP unchanged despite sufficient temperature control



Cooper D et al., JAMA, 2018

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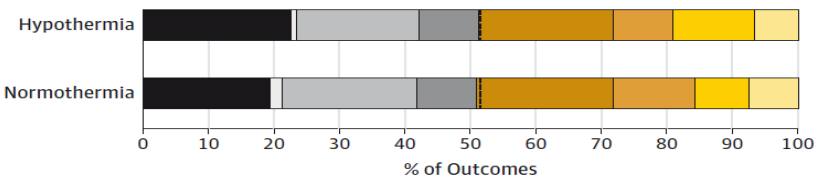
POLAR-RCT: Functional outcome unchanged



Glasgow Outcome Scale scores
1 Death
2 Vegetative state
3 Lower end of severe disability
4 Upper end of severe disability

Favorable outcome
5 Lower end of moderate disability
6 Upper end of moderate disability
7 Lower end of good recovery
8 Upper end of good recovery

	No./Total No. (%)		Absolute Difference (95% CI)	Relative Risk (95% CI)	*P* Value
	Hypothermia	Normothermia			
Primary Outcome					
Favorable outcome (GOS-E score 5-8)	117/240 (48.8)	111/226 (49.1)	−0.4 (−9.4 to 8.7)	0.99 (0.82-1.19)	.94

Cooper D et al., JAMA, 2018

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POLAR-RCT: Risk of pneumonia and bleeding equal

	No./Total No. (%)		Absolute Difference (95% CI)	Relative Risk (95% CI)	*P* Value
	Hypothermia	Normothermia			
Death at 6 mo	54/256 (21.1)	44/239 (18.4)	2.7 (−4.3 to 9.7)	1.15 (0.80-1.64)	.45
Infections					
Pneumonia	143/260 (55.0)	123/240 (51.3)	3.8 (−5.0 to 12.5)	1.07 (0.91-1.27)	.40
Bacteremia	19/260 (7.3)	12/240 (5.0)	2.3 (−1.9 to 6.5)	1.46 (0.72-2.95)	.29
Other infection	36/260 (13.8)	38/240 (15.8)	−2.0 (−8.2 to 4.3)	0.87 (0.57-1.33)	.53
Bleeding					
New or increased intracranial bleeding	47/260 (18.1)	37/240 (15.4)	2.7 (−3.9 to 9.2)	1.23 (0.43-3.5)	.70
New significant extracranial bleeding	8/260 (3.1)	6/240 (2.5)	0.6 (−2.3 to 3.5)	1.17 (0.79-1.74)	.43

Cooper D et al., JAMA, 2018

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Summary: No benefit with Hypothermia after severe TBI

- Did not control ICP better than standard of care
- Did not improve outcome, even if started prophylactically ultra-early
- Might be harmful, if used secondarily after ICP has increase

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ESTABLISHED IN 1812 DECEMBER 17, 2015 VOL. 373 NO. 25

Hypothermia for Intracranial Hypertension after Traumatic Brain Injury

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Early Sustained Prophylactic Hypothermia on Neurologic Outcomes Among Patients With Severe Traumatic Brain Injury
The POLAR Randomized Clinical Trial

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Cochrane Database of Systematic Reviews

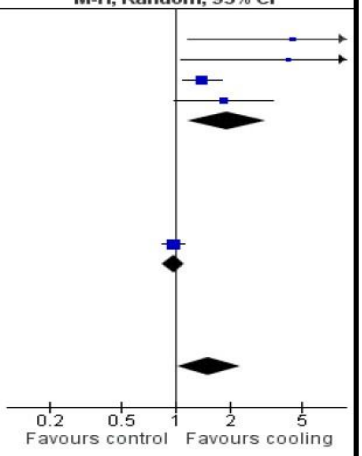
...othermia for neuroprotection in adults after ...diopulmonary resuscitation (Review)

Arrich ... Herkner H

Cochrane Database Systemic Rev, 2016

Cochrane Library

Study or Subgroup	cooling to 33°C Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Conventional cooling vs no cooling						
Mori 2000	18	36	2	18	7.3%	4.50 [1.17, 17.30]
Hachimi-Idrissi 2001	8	16	2	17	6.9%	4.25 [1.06, 17.08]
HACA 2002	75	136	54	137	31.7%	1.40 [1.08, 1.81]
Bernard 2002	21	43	9	34	19.1%	1.84 [0.97, 3.49]
Subtotal (95% CI)		**231**		**206**	**65.1%**	**1.94 [1.18, 3.21]**
Total events	122		67			
Heterogeneity: Tau² = 0.12; Chi² = 5.70, df = 3 (P = 0.13); I² = 47%						
Test for overall effect: Z = 2.60 (P = 0.009)						
1.2.2 Conventional cooling vs 36° temperature management						
Nielsen 2013	218	469	222	464	34.9%	0.97 [0.85, 1.11]
Subtotal (95% CI)		**469**		**464**	**34.9%**	**0.97 [0.85, 1.11]**
Total events	218		222			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.68)						
Total (95% CI)		**700**		**670**	**100.0%**	**1.53 [1.02, 2.29]**
Total events	340		289			
Heterogeneity: Tau² = 0.12; Chi² = 17.28, df = 4 (P = 0.002); I² = 77%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Chi² = 6.84, df = 1 (P = 0.009), I² = 85.4%						



Cochrane Database Systemic Rev, 2016, Feb 15

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The TTM-Trial

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.,

- Prospective, randomized, 36 centers, Europe and Australia
- N=950, comatous survivors of CA (>20 minutes)
- Excluded: unwitnessed CA, prim. Asystolia
- Methods: Surface cooling (76%) or endovascular cooling (24%)
- Duration: 36 hours (incl. Rewarming)
- Target: **33°C versus 36°C**
- EP primary: Mortality after 180 days
  Secondary: functional outcome (mRS 4-6; CPC 3-5)

Nielsen N et al., N Eng J Med, 2013

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TTM Trial - Results

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

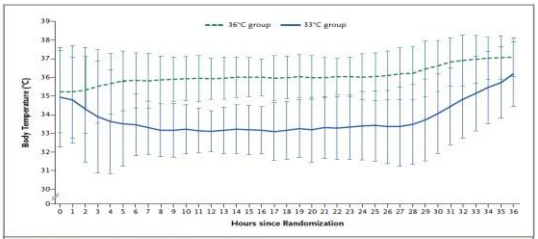

Figure 1. Body Temperature during the Intervention Period.
Shown are body-temperature curves in the 33°C and 36°C groups for the 860 patients in whom a bladder temperature was recorded. In the remaining 79 patients, the temperature was recorded with an intravascular or esophageal probe, with a similar temperature profile (data not shown). Rewarming was commenced at 28 hours after randomization. The temperature curves display the means, and the I bars indicate ±2 SD (95% of the observations are within the error bars).

Sufficient temperature control
Prim. EP unchanged between 33°C und 36°C

Nielsen N et al., N Eng J Med, 2013

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TTM Trial: Discussion

High rate of "bystander witnessed cardiac arrest" (90%)

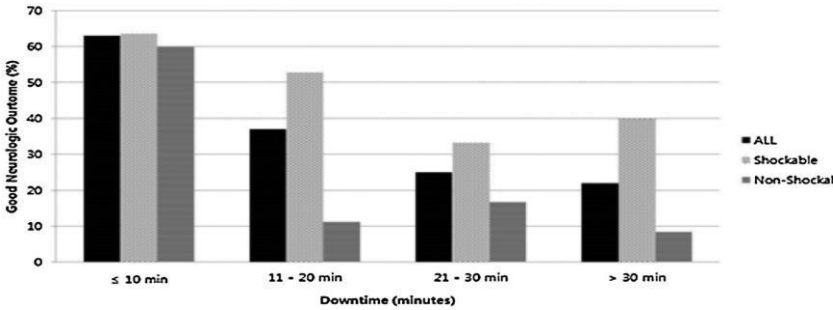
- -> short down time
- -> very early Start of ALS
- -> early ROSC
- -> mainly shockable rhythms
- -> low rate of sever hypoxic injury

Nielsen N et al., N Eng J Med., 2013

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

32



Downtime (minutes)	0 - 10 (n=24)	11 - 20 (n=27)	21 - 30 (n=12)	> 30 (n=23)	p-value
Good CPC(≤2)	15(62.5)	10(37.0)	3(25.0)	5(21.7)	0.02
Non-shockable rhythm (n=42)	8(61.5)	1(10.0)	1(16.7)	1(7.7)	0.01
Shockable rhythm (n=44)	7(63.6)	9(52.9)	2(33.3)	4(40.0)	0.58

CPC, cerebral category score, reported as median with interquartile range.

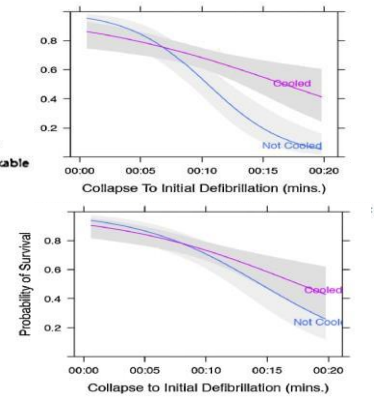


Fig. 3. Effect of time to initial diffbrillation and targeted temperature management on survival to hospital discharge.

TH effective especially among patients with Downtime > 10 Minuten

W.Y. Kim et al., Resuscitation, 2014
Drennan IR et al., Resuscitation, 2014

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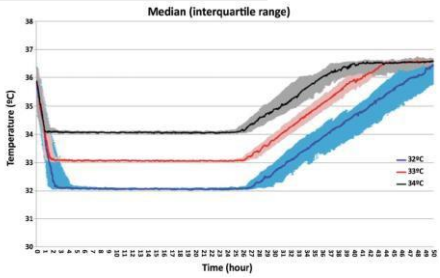
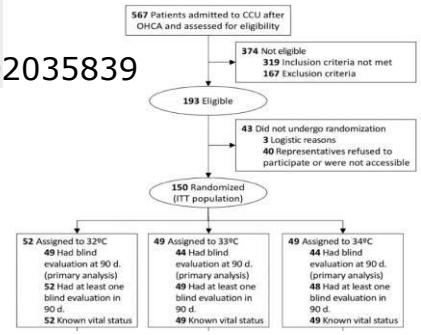
Seeking the optimal target temperature: FROST-I trial

- 150 Pat., OHCA, shockable rhythms
- Prospectiv-randomised, multicenter, 24 h hypothermia at 32° versus 33°C versus 34°C, endovascular cooling
- Prim. EP: mRS≤3 after 90 d
- 16 centers in Spain und Germany, NCT02035839



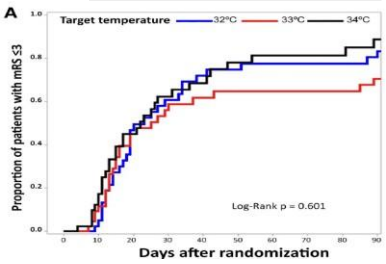


Lopez-de-Sa E. et al., Intensive Care Med, 2018

Universitätsklinikum Erlangen

FROST-I trial

- Outcome unchanged with lower target tempertures
- Limitation: Bystander-CA not equally distributed (14% within 32° versus 35% within 33° versus 29% within 34°)
- Multivariate Cox Proportional Hazard Model identifys 2 predictors for good outcome: Early Defibrillation und male gender



	Sample size	HR	95% CI	*p* value
mRS ≤ 3	149			
32 vs 34 °C		0.82	(0.50–1.36)	0.412
33 vs 34 °C		0.63	(0.38–1.03)	0.056
ROSC > 20 min		0.86	(0.58–1.29)	0.456
Age > 65 years		0.77	(0.47–1.21)	0.229
Male gender		1.85	(1.10–3.30)	0.04
Bystander defibrillation (AED)		1.66	(1.03–2.60)	0.024

Lopez-de-Sa E. et al., Intensive Care Med, 2018

Universitätsklinikum Erlangen

Review article

Therapeutic hypothermia after cardiac arrest: A systematic review/meta-analysis exploring the impact of expanded criteria and targeted temperature☆

Aldo L. Schenone[a,*], Aaron Cohen[a], Gabriel Patarroyo[b], Logan Harper[a], XiaoFeng Wang[c], Mehdi H. Shishehbor[d], Venu Menon[d], Abhijit Duggal[e]

- Metaanalysis, liberal Inclusion criteria for the initiation of TH:
- Initial Rhythm: non-shockable included
- Downtime, bystander, witnessed arrest: unknown included
- **Persisting shock**: included
- Prim. EP: Mortality and Outcome (CPC1-2) at discharge

Schenone A. et al, Resuscitation, 2016

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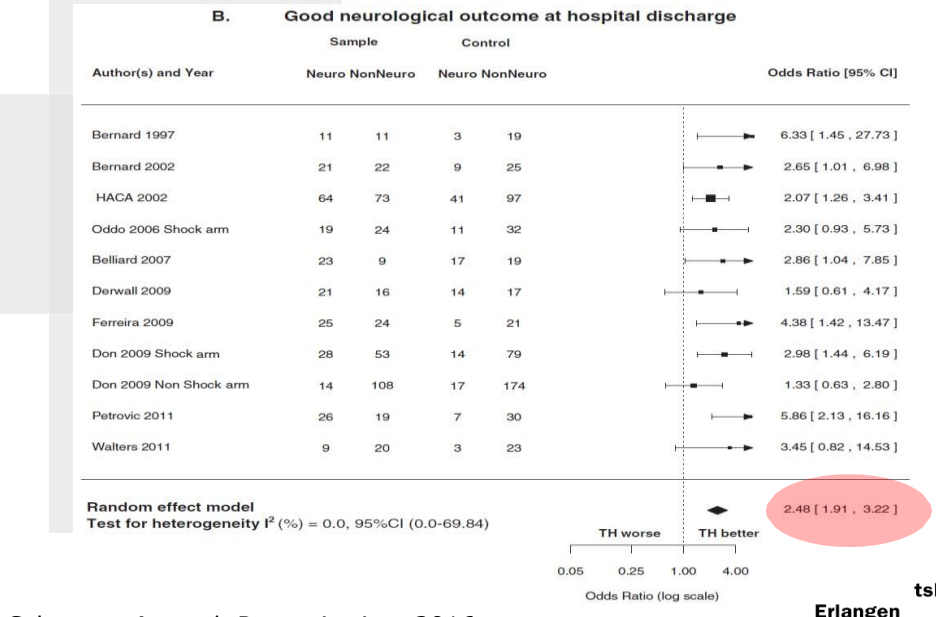


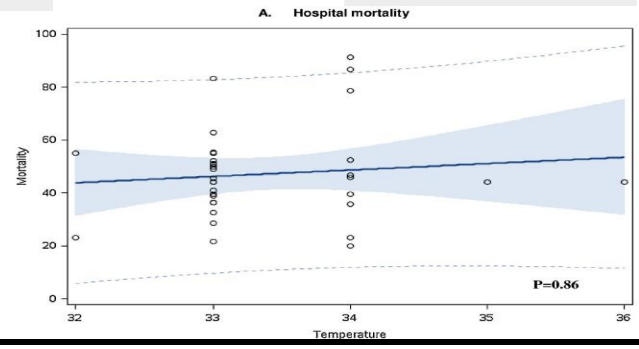
Schenone A. et al, Resuscitation, 2016

tsklinikum Erlangen

Difference between different target temperatures not significant

Achieve

	32 °C (N – 2)	33 °C (N – 20)	34 °C (N – 10)	35 °C (N – 1)	36 °C (N – 1)	Total (N – 34)
atients	35	2610	1258	32	466	4373
ge (y)	60	60	61	54	64	60
)	77	75	63	81	79	73
ole rhythm (%)	57	72	63	100	81	70
me (min)	26	26.2	26.9	20	25	26.1
cause (%)	77	74	79	81	100	78
ty						
	2	20	10	1	1	34
(SD)	39.0 (22.6)	45.9 (13.3)[a]	52.0 (25.4) [a]	44.0 (.)	44.0 (.)	47.2 (17.5)
an	39.0	44.8	46.2	44.0	44.0	44.8
3	23.0, 55.0	37.7, 51.7	35.7, 78.7	44.0, 44.0	44.0, 44.0	36.4, 52.5
	(23.0–55.0)	(21.6–83.3)	(19.9–91.4)	(44.0–44.0)	(44.0–44.0)	(19.9–91.4)



Schenone A. et al, Resuscitation, 2016

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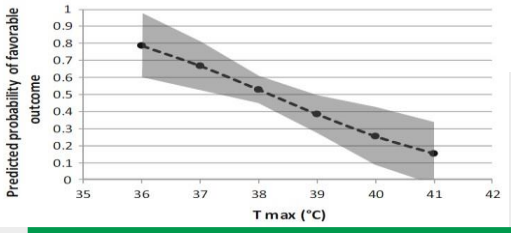
Delayed Fever and Neurological Outcome after Cardiac Arrest: A Retrospective Clinical Study

Edoardo Picetti[1] · Marta Velia Antonini[1] · Yerma Bartolini[2] · Antonino DeAngelis[3] · Laura Delaj[2] · Irene Florindo[4] · Fabio Villani[3] · Maria Luisa Caspani[1]

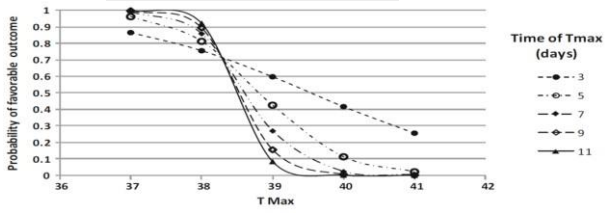
	Study population (n = 132)	Missing
Male, n (%)	92 (69.7)	0
Age (years), median (IQR)	68 (58–75)	0
Intra-hospital CA, n (%)	48 (36.4)	0
First rhythm, n (%)		0
VF	66 (50.0)	
PEA	26 (19.7)	
Asystolia	40 (30.3)	
SAPS II, median (IQR)	65 (55–75)	0
Fever during ICU stay, n patients (%)	105 (79.6)	0
Time of ROSC (minutes), median (IQR)	10 (10–20)	54
Cause of the CA, n (%)		0
Arrhythmias	28 (21.2)	
Coronaropathy	71 (53.8)	
Other	33 (25.0)	
TH, n (%)	80 (61.1)	1
LOS (days) in ICU, median (IQR)	7.5 (5–12)	0
CPC 1–2 at 6 months post-CA, n (%)	63 (47.7 %)	0
Death at ICU discharge, n (%)	37 (28.0)	0

Picetti E. et al., Neurocrit Care, 2016



	Coefficients	Odds ratio	OR 95 % CI	P
Sex	0.223	1.25	0.48–3.22	0.645
Age	−0.061	0.94	0.90–0.98	0.003
ΔTmax	−1.168	0.31	0.15–0.63	0.001
SAPS	−0.034	0.97	0.94–0.99	0.025
Rhythm (as a whole)				0.003
VF[a]	1.804	6.07	2.16–17.01	0.001
PEA[a]	1.096	2.99	0.89–10.08	0.077
Pupils (as a whole)				0.067
Non-isochoric[b]	0.690	1.99	0.65–6.14	0.230

TTM may not end on day2
Temperature in the following days is of importance.



Rise of body temperature by 1°C:
-> Odds ratio for good outcome drops by 31%

Picetti E. et al., Neurocrit Care, 2016

ORIGINAL ARTICLE

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children

- Children (Age:48 hours-18 years) with in-hospital CA at 37 children hospitals
- Temperature management within 6 hours: Hypothermia (33°C) versus normothermia (36,8°C)
- Duration: 48 hours, controlled rewarming over 16 hours followed by normothermia until a total of 120 hours of TTM
- Survace cooling

Moler FW et. Al., NEJM, 2017

Characteristic	Hypothermia Group (N=166)	Normothermia Group (N=163)
Initial cardiac rhythm — no. (%)		
Asystole	14 (8)	10 (6)
Bradycardia	95 (57)	94 (58)
Pulseless electrical activity	33 (20)	36 (22)
Ventricular fibrillation or tachycardia	17 (10)	17 (10)
Unknown	7 (4)	6 (4)
Cardiac arrest occurred at a trial hospital — no. (%)	155 (93)	152 (93)
Time from cardiac arrest to CPR in 314 patients — min		
Median	0	0
Interquartile range	0–0	0–0
Duration of CPR in 321 patients — min		
Median	23.0	22.0
Interquartile range	7.0–42.0	7.0–51.0
No. of doses of epinephrine administered in 328 patients		
Median	4.0	5.0
Interquartile range	2.0–9.0	2.0–8.0
ECMO used after cardiac arrest and before randomization — no. (%)	87 (52)	95 (58)
ECMO used at the time of treatment initiation — no. (%)	85 (51)	95 (58)

Moler FW et. Al., NEJM, 2017

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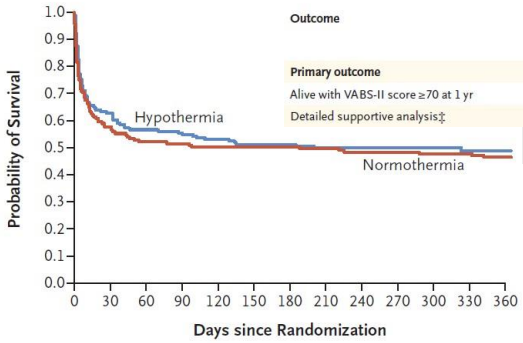
ORIGINAL ARTICLE

THAPCA-Trial

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children



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§

No. at Risk													
Hypothermia	166	104	94	92	88	85	85	83	83	83	83	81	81
Normothermia	163	94	84	82	80	80	80	79	77	77	76	76	74

Moler FW et. Al., NEJM, 2017

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ORIGINAL ARTICLE

THAPCA-Trial

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children

Secondary outcomes		
Alive		
Chang		
De		
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)

No benefit with hypothermia among children with IHCA

Moler FW et. Al., NEJM, 2017

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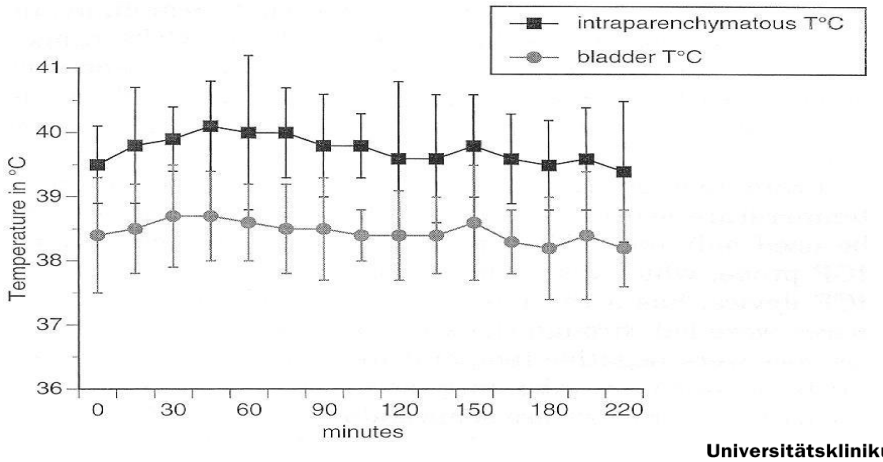
Cerebral temperature and body core temperature



Schwab et al, Neurology, 1997

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Concordance of Brain and Core Temperature in Comatose Patients After Cardiac Arrest

ct characteristics	N = *11*
years	47 ± 10
sex	6 (55%)
of-hospital cardiac arrest	11 (100%)
l rhythm (%)	
/VF	2 (18)
A	3 (27)
ystole	5 (46)
known	1 (9)
Pittsburgh cardiac arrest category (%)	
I	0 (0)
II	1 (9)
III	0 (0)
IV	10 (91)
Core temperature monitoring site (%)	
Rectal	4 (36)
Esophageal	7 (64)
Cooling device	
CoolGard 3000©	9 (73%)
Artic Sun©	2 (27%)
Arrival to brain monitoring interval, hours	7 ± 3
Survival to hospital discharge	1 (9%)

PEA, pulseless electrical activity; VT/VF, ventricular tachycardia/ventricular fibrillation.

Coppler et al., THTM, 2016

Inclusion criteria

- Invasive Neuromonitoring within 12 h after ROSC
- Borehole trepanation
- Monitoring of ICP, T, tO2 frontal subcortical
- TTM: 33°C for 24 h

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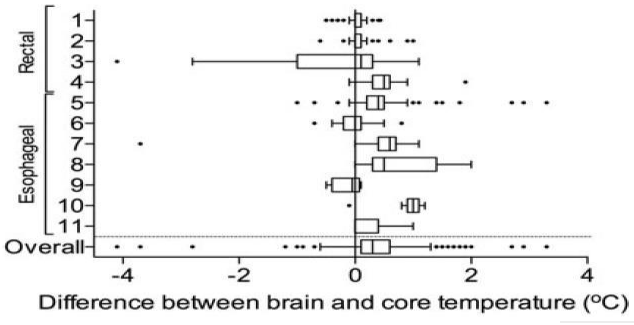

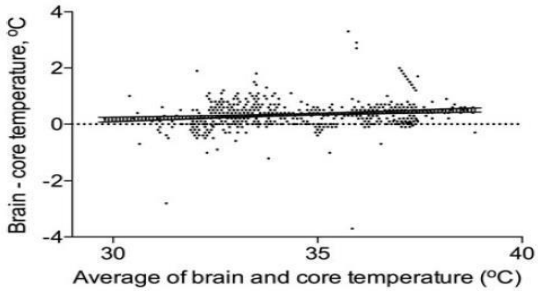

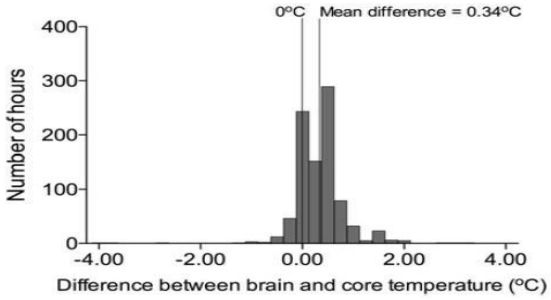

Mean difference in temperature: 0,34°C (95%CI 0,31-0,37°C)

Coppler et al., THTM, 2016

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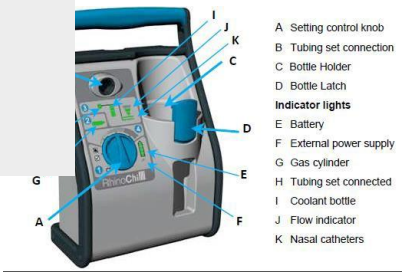

- Mixture of air/oxygen and a liquid coolant (perfluorohexane) via nasal catheter
- The coolant evaporates and absorbes heat from the surrounding tissue
- Cools the nasal cavity to 2°C
- Systemic and local cooling effects

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JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Trans-Nasal Evaporative Intra-arrest Cooling on Functional Neurologic Outcome in Out-of-Hospital Cardiac Arrest

The PRINCESS Randomized Clinical Trial

- Investigator-initiate d trial, 7 European countries, Recruitment 2010-2018
- Bystander witnessed CA, Inclusion by the ALS-team after airway management
- Intervention group: Intra-arrest evaporative transnasal cooling, open lable
- Both groups: Hypothermia at 33°C for 24 hours

Nordberg P et al., JAMA 2019

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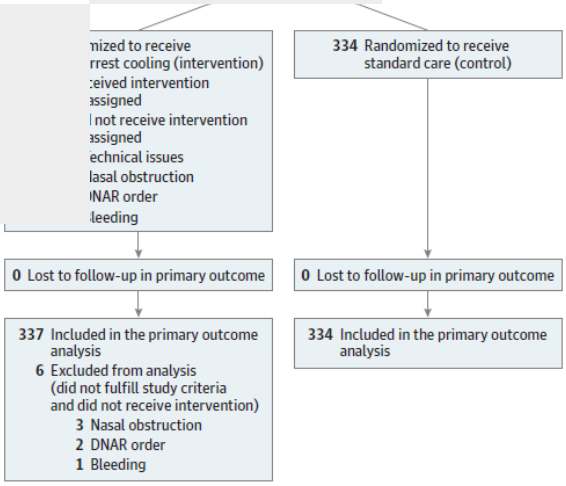

Characteristic	Intervention (n = 337)	Control (n = 334)
Demographic Characteristics		
Age, median (IQR), y	64 (55-72) (n = 328)	66 (56-72) (n = 329)
Men, No./total (%)	253/336 (75.3)	252/333 (75.7)
Women, No./total (%)	83/336 (24.7)	81/333 (24.3)
Height, median (IQR), cm	177 (170-180) (n = 306)	177 (170-180) (n = 307)
Weight, median (IQR), kg	85 (74-95) (n = 307)	85 (75-95) (n = 304)
Resuscitation Characteristics, No./Total (%)		
Location outside home	123/300 (41.0)	108/306 (35.3)
Presumed cardiac cause	260/308 (84.4)	267/311 (85.9)
Shockable rhythm[a]	138/336 (41.1)	135/334 (40.4)
Bystander CPR	208/321 (64.8)	194/325 (59.7)
CPR by first responder	186/306 (60.8)	205/312 (65.7)
Airway, No./total (%)		
Intubation	259/328 (79.0)	248/322 (77.0)
Laryngeal mask	63/328 (19.2)	71/322 (22.0)
Laryngeal tube	6/328 (1.8)	3/322 (0.9)

Nordberg P et al., JAMA 2019

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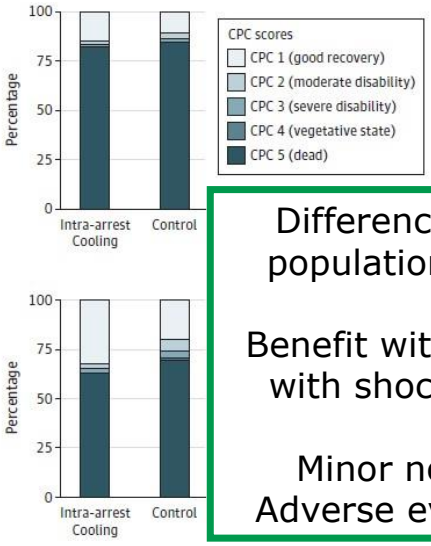
A All patients

CPC Score	No. (%) Intra-arrest Cooling	Control	Difference, % (95% CI)
CPC 1	50 (14.8)	35 (10.5)	4.4 (-0.7 to 9.4)
CPC 2	6 (1.8)	10 (3.0)	-1.2 (-3.5 to 1.1)
CPC 3	3 (0.9)	6 (1.8)	-0.9 (-2.6 to 0.8)
CPC 4	1 (0.3)	1 (0.3)	0.0 (-0.8 to 0.8)
CPC 5	277 (82.2)	282 (84.4)	-2.2 (-7.9 to 3.4)

B Patients with shockable rhythm

CPC Score	No. (%) Intra-arrest Cooling	Control	Difference, % (95% CI)
CPC 1	45 (32.6)	27 (20.0)	12.6 (2.3 to 22.9)
CPC 2	3 (2.2)	8 (5.9)	-3.8 (-8.4 to 0.9)
CPC 3	3 (2.2)	5 (3.7)	-1.5 (-5.5 to 2.5)
CPC 4	0 (0.0)	1 (0.7)	-0.7 (-2.2 to 0.7)
CPC 5	87 (63.0)	94 (69.6)	-6.6 (-17.8 to 4.6)



Differences in the whole population not significant.

Benefit with TH for patients with shockable rhythms?

Minor nose bleed 13%
Adverse event rate similar.

Nordberg P et al., JAMA 2019

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Target temperatures were reached earlier with the intervention.
-> not only local cooling, but relevant effect on the core body tempoerature

Sustained ROSC and admitted to hospital, No./total (%)					
All patients	149/337 (44.2)	142/334 (42.5)	1.7 (−5.8 to 9.2)	1.04 (0.87 to 1.22)	.66
Patients with shockable rhythm	83/138 (60.1)	78/135 (57.8)	2.4 (−9.3 to 14.0)	1.02 (0.82 to 1.21)	.69
Patients with nonshockable rhythm	65/198 (32.8)	64/199 (32.2)	0.7 (−8.5 to 9.9)	1.03 (0.76 to 1.34)	.89
Time to core body temperature <34°C, median (IQR), min					
All patients	105 (80 to 183)	182 (132 to 312)	−70 (−100 to −44)	0.59 (0.49 to 0.71)	<.001
Patients with shockable rhythm	110 (80 to 192)	236 (158 to 415)	−102 (−169 to −60)	0.52 (0.39 to 0.65)	<.001
Patients with nonshockable rhythm	99 (82 to 166)	152 (125 to 202)	−50 (−86 to −16)	0.66 (0.50 to 0.87)	.004

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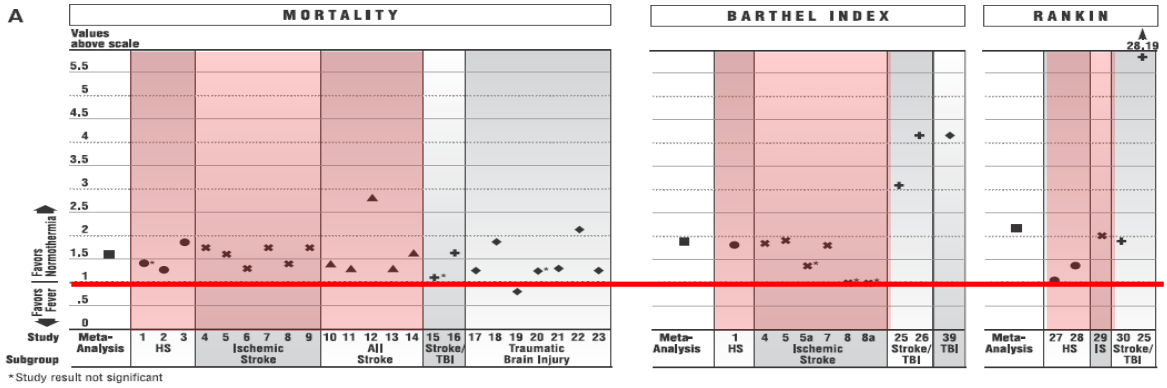
Greer 2008, Stroke

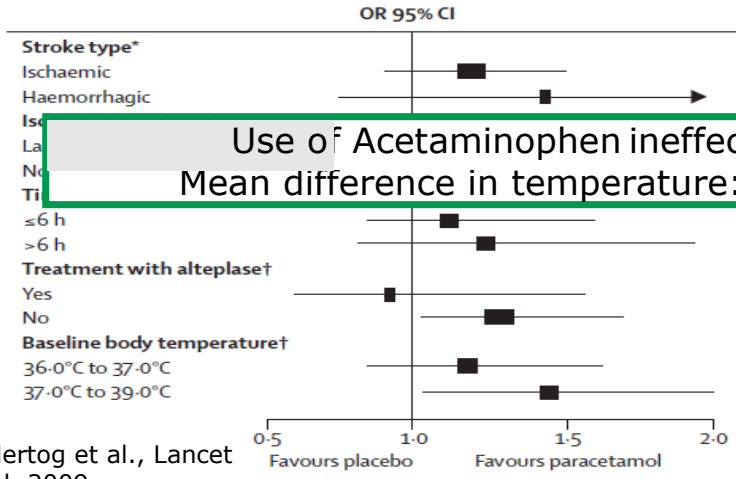
Fever after stroke is detrimental



Meta-analysis 39 trials, n=14.431

The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial

Heleen M den Hertog, H Bart van der Worp, H Maarten A van Gemert, Ale Algra, L Jaap Kappelle, Jan van Gijn, Peter J Koudstaal, Diederik W J Dippel; on behalf of the PAIS investigators



Use of Acetaminophen ineffective:
Mean difference in temperature: -0,26°C

den Hertog et al., Lancet Neurol, 2009

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PAIS 2 A double-blind, randomized, placebo-controlled clinical trial of high-dose paracetamol in patients with acute stroke and a body temperature of 36.5 °C or above

PARACETAMOL IN STROKE 2

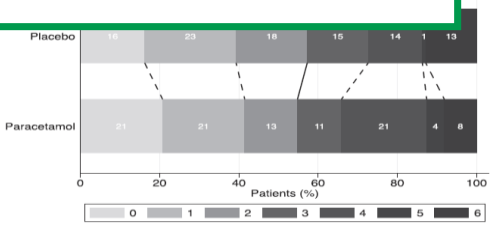
Progress of the trial

PAIS 2 is started in July 2011 and will be finished in January 2016. The graphs indicate the

Premature termination 10/2015 after inclusion of 256 Patients.

HOME

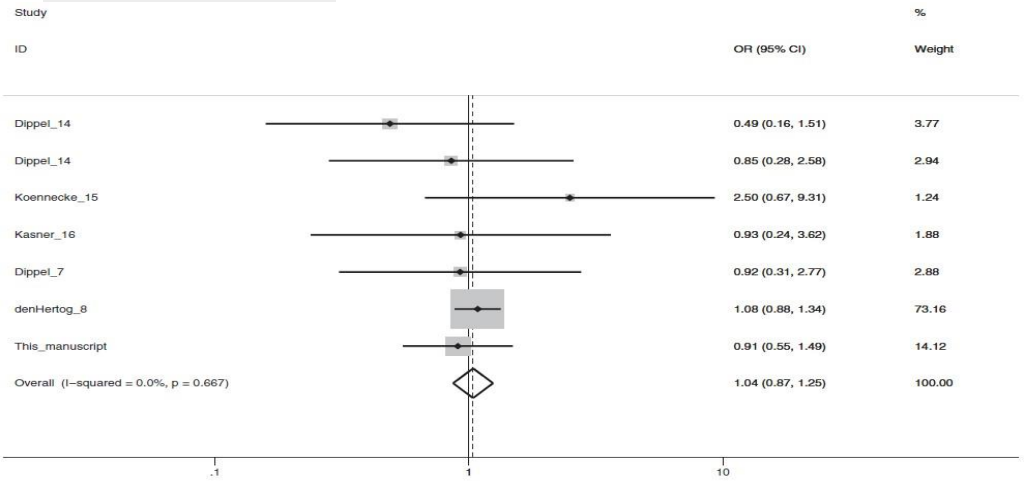
GENERAL INFORMATION
- Introduction
- Rationale
- Study Design
- Protocol
- Participating centers



De Ridder I. et al., Stroke, 2017

Erlangen

Meta-Analysis on antipyretic treatment after stroke: No effect on Outcome



De Ridder I. et al., Stroke, 2017

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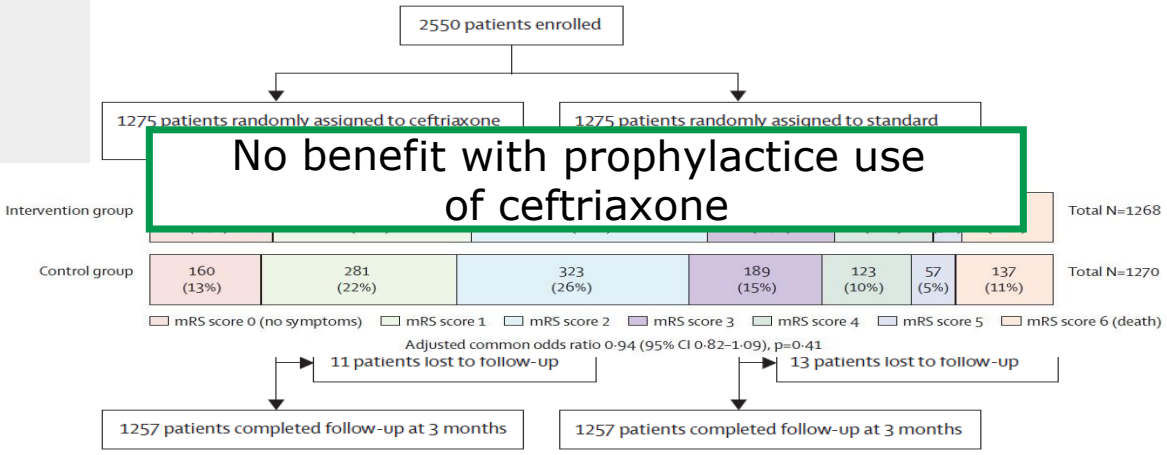
Use of antibiotics: PASS-Study



Westendorp et al., Lancet 2015

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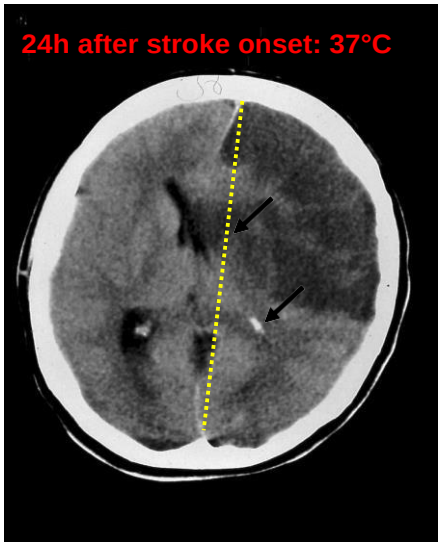
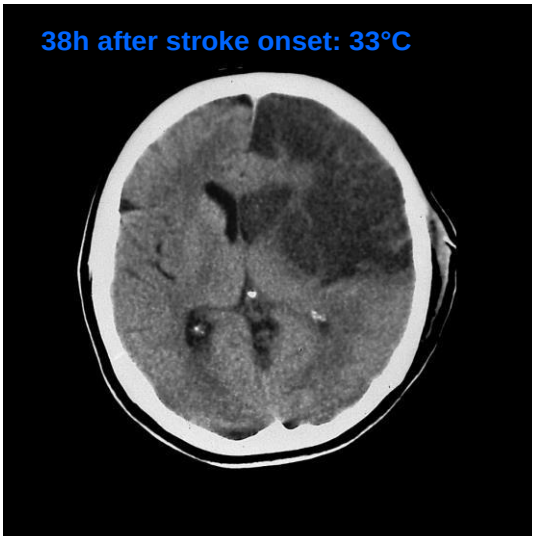
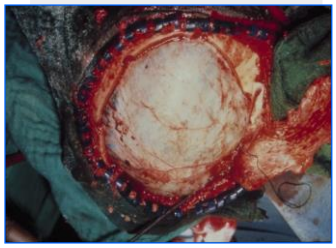
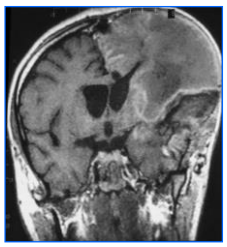
Hypothermia for space-occuping MCA stroke





Author/year	N=	Cooling method	Goal T°C	Time	Duration
Ventilated patients					
Schwab,1998	25	surface	33°C	14±7	2-3 days
Schwab, 2001	50	surface	33°C	22±9	1-3 days
Georgiadis, 2001	6	endovascular	33°C	28±17	2-3 days
Georgiadis, 2002	19	surface (11) endovascular (8)	33°C	24 (18-14)	2-3 days





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JAMA Neurology | Original Investigation

Outcomes of Hypothermia in Addition to Decompressive n Treatment e Cerebral Artery Stroke cal Trial

- RCT in 6 German centers
- Recruitment 08/1 1-09/15
- Patients treated with hemicraniectomy for large MCA stroke
- Hypothermia (33.)°C +/- 1°C for >72 hours) versus standard care
- Prim EP: Mortality rate on day 14

Neugebauer H. et al., JAMA Neurol., 2019

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Depth-SOS – Study Sites

Characteristic	Group, No. (%)	
	Control (n = 24)	Hypothermia (n = 26)
Age, median (range), y	53 (39-60)	51 (33-60)
Male	15 (63)	13 (50)
Preexisting modified Rankin scale score on admission[a]		
0	22 (92)	24 (92)
1	2 (8)	2 (8)
≥2	0	0
Preexisting Barthel Index score on admission, median (range)[b]	100 (100-100)	100 (95-100)
Site of infarction		
Middle cerebral artery only	16 (67)	16 (62)
Middle cerebral artery and anterior cerebral artery	6 (25)	8 (31)
Middle cerebral artery and posterior cerebral artery	2 (8)	2 (8)
Stroke in dominant hemisphere	11 (46)	12 (46)

2 patients assigned to hypothermia did not receive the treatment (Corssover)

Neugebauer H. et al., JAMA Neurol., 2019

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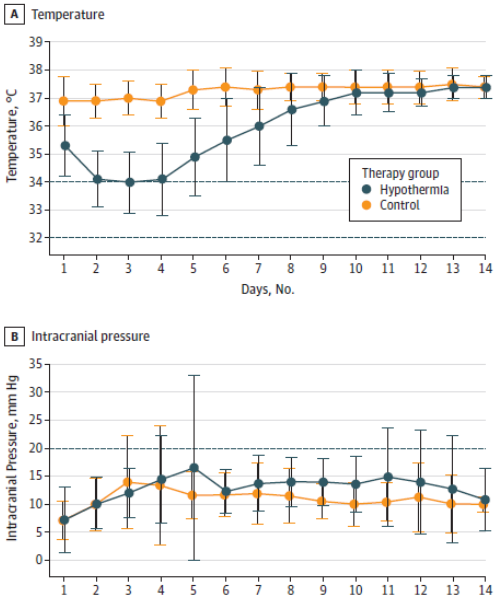

Neugebauer H. et al., JAMA Neurol., 2019

Target temperature was reached and maintained for > 72 h in 88%

Median duration of hypothermia including rewarming: 7 days

Mean intracranial pressure per day not different

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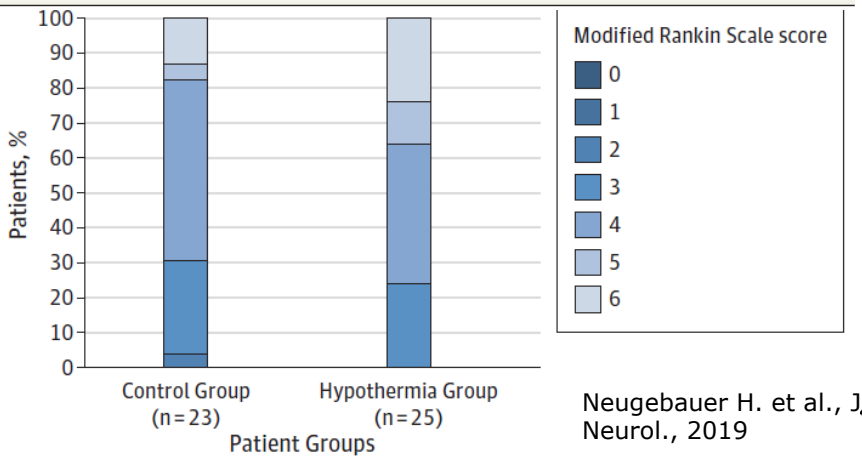
End Point	Participants, No./Total No. (%) Control	Hypothermia	Odds Ratio or Hazard Ratio (95% CI)	*P* Value
At 12 mo				
Death	3/23 (13)	6/25 (24)	1.55 (0.37-6.42)[c]	.54[d]
Patients with SAE	10/23 (43)	20/25 (80)	2.51 (1.16-5.46)[c]	.01[d]



Neugebauer H. et al., JAMA Neurol., 2019

Evidence of harm with hypothermia

Safety measures:
After 14 days: SAEs in 46% (Hypothermia) versus 29 % (SOC)
Associated with Temperature management: 5 of 26 patients (19%).

After 12 months: 80% (Hypothermia) versus 43% (SOC)

Mortality at day 14:19% (Hypothermnia) verus 13% (SOC)

Neugebauer H. et al., JAMA Neurol., 2019

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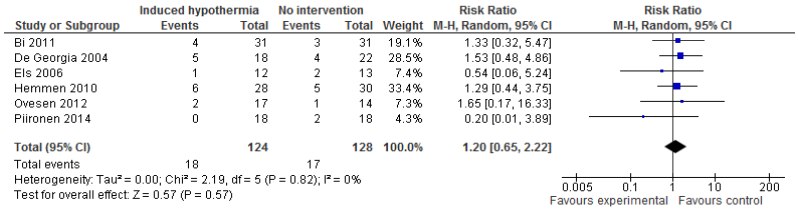
Smaller studies suggested feasibility in awake patients

Functional outcome

2 Large RCTs were initiated:
ICTUS 2/3 (USA) und EuroHYP-1 (Europe)

Mortality



Results of the ICTuS 2 Trial (Intravascular Cooling in the Treatment of Stroke 2)

- ICTUS2/3 program
- Patients with acute iscemic stroke and i.v. Thrombolysis, 3 hours after onset
- Thrombectomy not allowed
- Initially Planned: RCT with 1600 patients
- Hypothermia group: 2 l cooled normal saline i.v., endovascular cooling device for 24 hours
- Target temperature 33°C, controlled rewarming for 12 h
- Antishivering: Meperidine, Buspirone, skin counter warming
- Prim. EP: mRS 0/1 on day 90

Lyden P et al., Stroke, 2016

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ecruitment suspended 12/2014 after inclus ion of 120 patients

	Hypothermia (n=63)	Normothermia (n=57)
	65.5±10.3	67.5±11.1
	54	61
	87.1±19.7	85.0±23.7
s, %	25	30
	81	72
	83±15	80±15
C	36.6±0.46	36.4±0.50
	14.1±4.8	14.5±4.9
min	105±37	114±37

Lyden P et al., Stroke, 2016

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No b enefit with ypothermia

Primary Outcome

nth mRS 0,1:

311 (0.355-1.846)

Hypo

Normo

nth sliding mRS:

372 (0.599-3.189)

- :0 if NIHSS 0-7
- :=1 if NIHSS 8-14
- mRS<=2 if NIHSS > 14

Lyden P et al., Stroke, 2016

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High risk of pneumonia and SAE

Safety

- SAE rates similar, OR 1.3 (0.58-2.92)
  - 35% Normo
  - 41% Hypo
- Mortality not different, OR 1.95 (0.56-7.8)
  - 8.8% Normo
  - 15.9% Hypo
- Pneumonia not different, OR 1.99 (0.63-6.98)
  - 10.5% Normo
  - 19% Hypo

Lyden P et al., Stroke, 2016

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EuroHYP-1

EuroHYP-1

- RCT, n=800
- Therapeutic hypothermia versus Standard Treatment
- Acute Ischemic stroke, awake patients
- NIHSS ≥6
- i.v. tPA and Thrombectomy allowed
- Hypothermia treatment start within 6 hours after onset
- Target: 34-35°C, Duration: 12-24 hours
- Prim EP: Functional outcome day 91

Van der Worp HB et al., ESJ, 2019

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SEVENTH FRAMEWORK PROGRAMME

EuroHYP-1: Methods

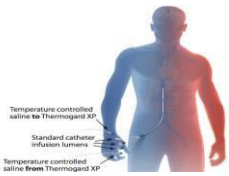

Survace Cooling

- Brain.Pad und Felx.Pad (EMCOOLS)
- Arctic Sun / ArcticGel Pads (Medivance/Bard)
- Criticool / Cool Wrap 3500 (MTRE Advanced Technologies)
- BrainCool System and BrainCool cooling pads (BrainCool)


Endovascular cooling

- Zoll Thermogard/ ICY Katheter (Zoll)





Van der Worp HB et al., ESJ, 2019

Shivering-Prevention protocol

EuroHYP-1

Pharmacological

- i.v. pethidine (max 500 mg/24 h)
- Oral Buspiron (max 30 mg/24 h)
- Ondansetron or Granisetron (prior to pethidine application)

Counterwarming

- Bair hugger
- Gloves, Bandages

Van der Worp HB et al., ESJ, 2019

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Recruitment

- 38 centers in 13 European countries involved
- First patient included in November 2013
- Recruitment suspended on March 2nd 2018 due to slow recruitment and lack of funding
- N=98 patients were included (49 Hypothermia und 49 Control group)

Van der Worp HB et al., ESJ, 2019

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	Intervention $n=49$	Control $n=49$
Age–years mean (*SD*)	69.6 (11.8)	71.1 (12.0)
Male sex – no (%)	28 (57.1)	27 (55.1)
Body weight–kg mean (*SD*)	80 (14.2)	78.9 (13.4)
Height–m mean (*SD*)	170 (10.2)	169 (9.7)
NIHSS score–median (IQR)	11 (7–17)	11 (8–17)
Location of stroke in left hemisphere – no (%)	17 (35)	19 (39)
Pre-stroke mRS score–median (IQR)	0 (0–0)	0 (0–1)
Visible acute ischaemic lesion on CT – no (%)	22 (44.9)	22 (44.9)
Systolic blood pressure–mm Hg	154 (26)	153 (23)
Diastolic blood pressure–mm Hg	84 (18)	85 (14)
Body temperature – °C mean (*SD*)	36.2 (0.49)	36.3 (0.48)
Treatment with i.v. alteplase – no (%)	39 (79.6)	41 (83.7)
Time from stroke onset to randomisation – min	203 (155–244)	220 (164–293)

Van der Worp HB et al., ESJ, 2019

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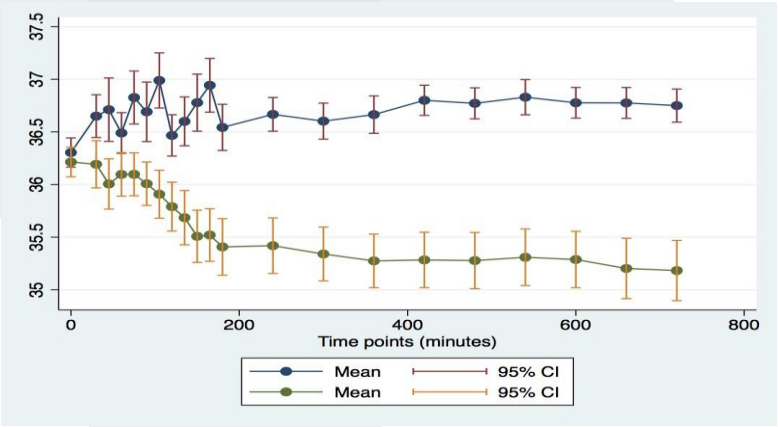
Cours e of body temperature



Only 31% of patients reached the predifined targets of cooling

Van der Worp HB et al., ESJ, 2019

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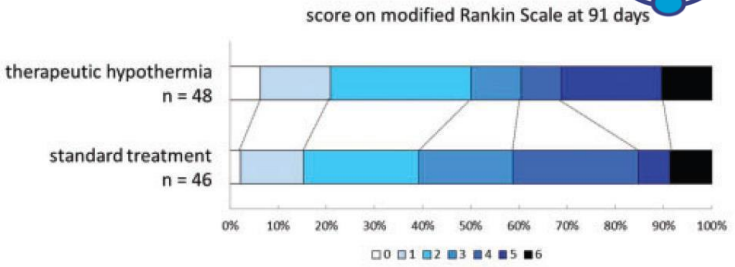
Prim. EP: No benefit

EuroHYP-1



- ITT: OR 1.01; 95% CI, 0.48 to 2.13; p = 0.97
- Per protocol: OR 1.07; 95% CI, 0.35 to 3.32; p = 0.91

Van der Worp HB et al., ESJ, 2019

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Sec. Endpoints: No benefit

Outcome	Intervention $n=48$	Control $n=46$	RR (95% CI)	p
Death – n (%)	5 (10.2)	4 (8.2)	1.25 (0.34–3.81)	0.73
Death or dependency – n (%)	24 (50.0)	28 (60.9)	0.82 (0.50–1.14)	0.29
NIHSS – median (IQR)	3 (1–11)	3 (1–8)	–	0.39
EQ-5D-5L VAS – median (IQR)	70 (50–90)	67 (50–80)	–	0.45
WHODAS 2.0 – median (IQR)	53.5 (5.8–86.5)	38.0 (12.0–74.0)	–	0.11
Infarct volume/mL mean (95% CI) 37.5 (13.0–102.8)	34.3 (10.5–65.5)	–	0.55	

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Adverse events

EuroHYP-1

	othermia 49	Control $n=49$
		2
ema formation	4	1
	9	2
	4	1
e events[a]	11	10

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Conclusion: EuroHYP-1

- Cooling in the majority of patients not feasible: only 31% of patients reached predifined targets of cooling
- No difference for the functional endpoint, patient numbers to small
- Pneumonia remains a problem

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TBI	Eurotherm3235	TH not recommended. Evidence of harm, if initiated > 12 hours after trauma.
	POLAR	
Cardiac Arrest	Bernard	TTM beneficial. Optimal target temperature unknown.
	HACA	
	TTM	
	THAPCA	
	PRINCESS	
Ischemic Stroke	Depth-SOS	TH not recommended. Evidence of harm, if initiated in combination with decompressive hemicraniectomy.
	ICTUS 2/3	
	EuroHYP-1	

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Thank you for your attention.

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