

Brain Cooling: Missing the Therapeutic Window

Strategies to Overcome Hurdles in Clinical Practices

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BLK MAX SS HOSPITAL & MAX SS DWARKA DELHI

Objective

Brain
Selection



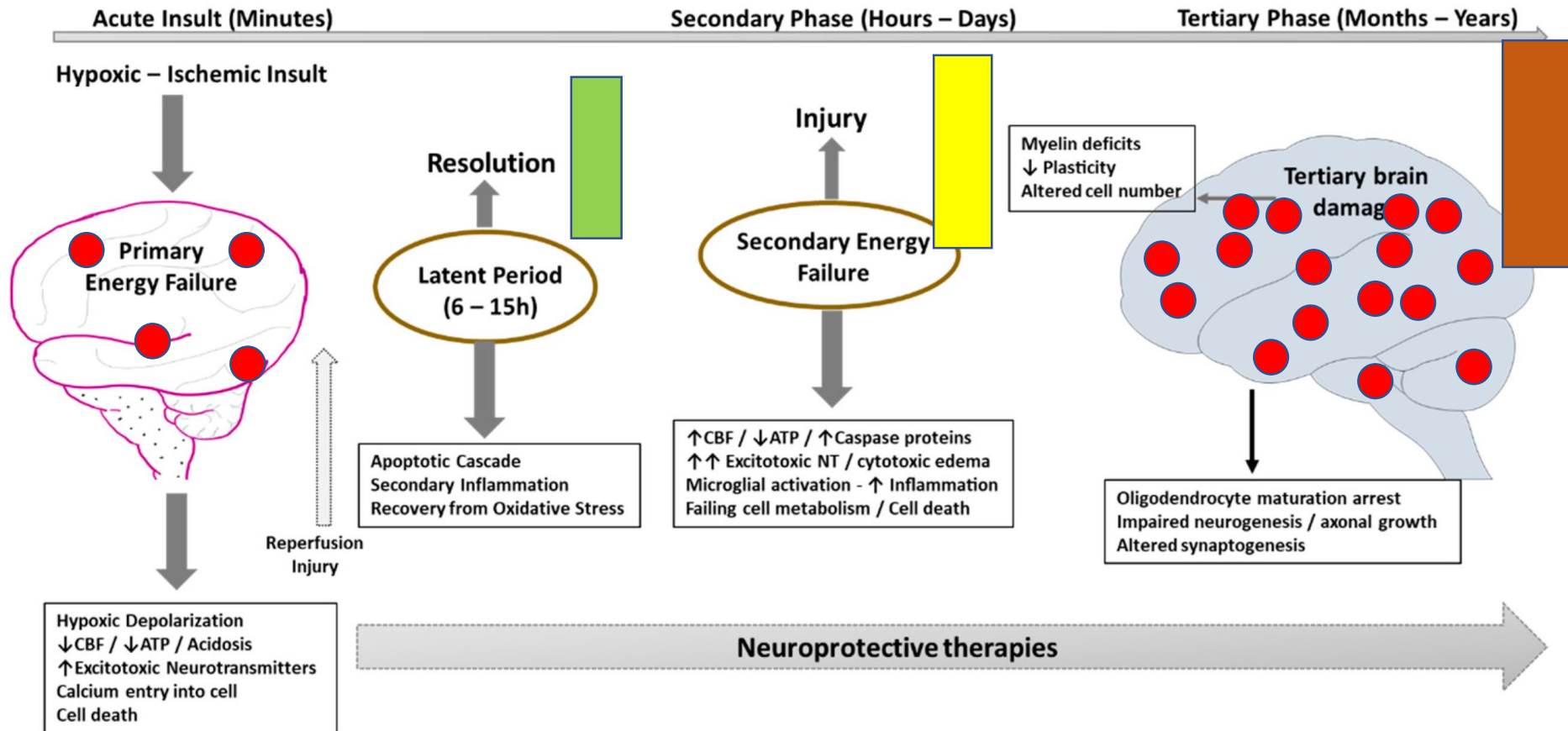
Selecting Right Candidate

HIE Prevalence

Incidence	HIC	LMIC
Incidence	1.5/1000	2.3– 26.3/1000
Death & Disability	44% → 29 % 2005 -2017	50 % +

40% to 55% of HIE treated with TH will still suffer substantial neurologic disability in the future or will die.

PATHOPHYSIOLOGY OF HIE



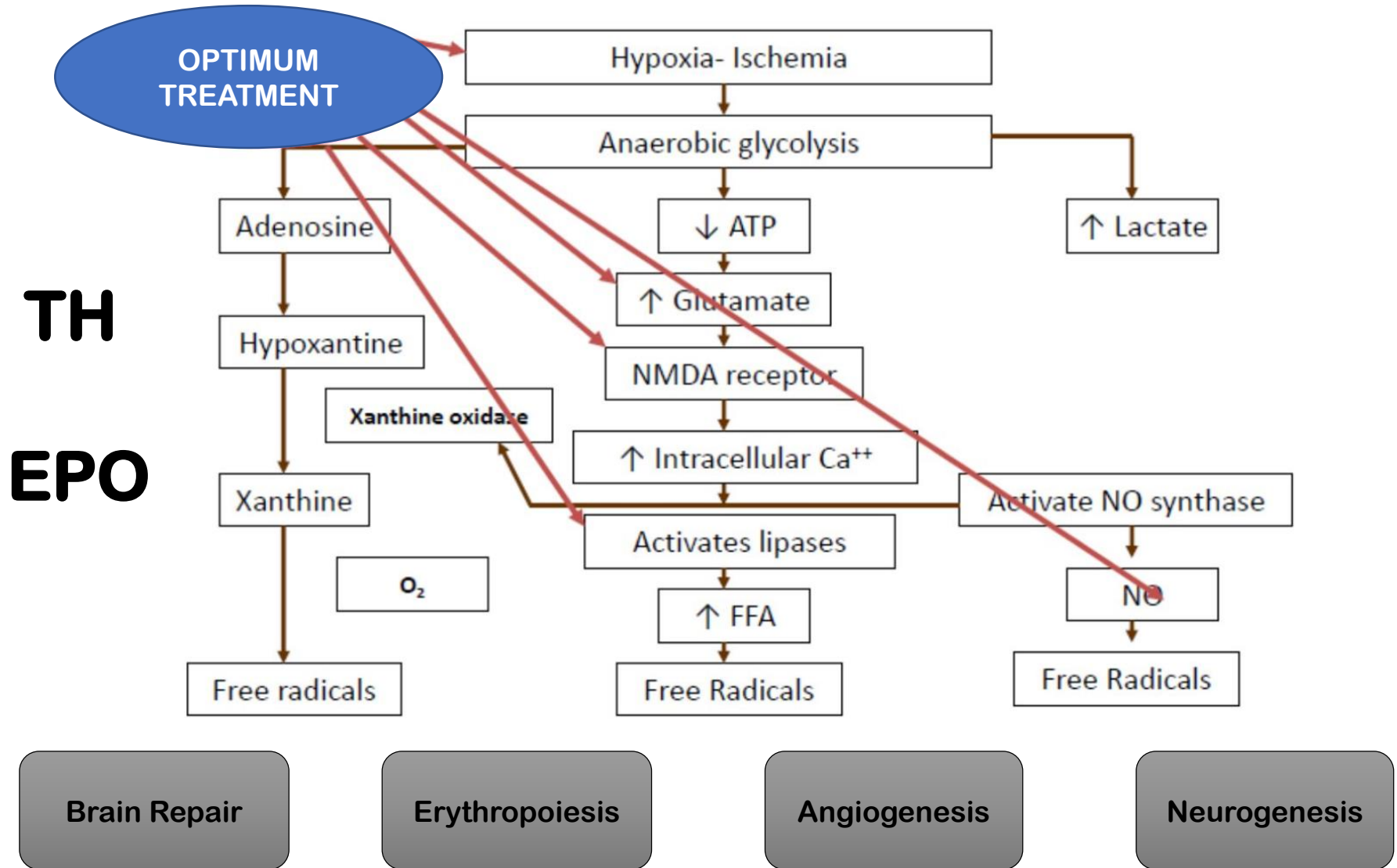
SEVERITY
TREATMENT

TIMING
Before
Delivery

GA

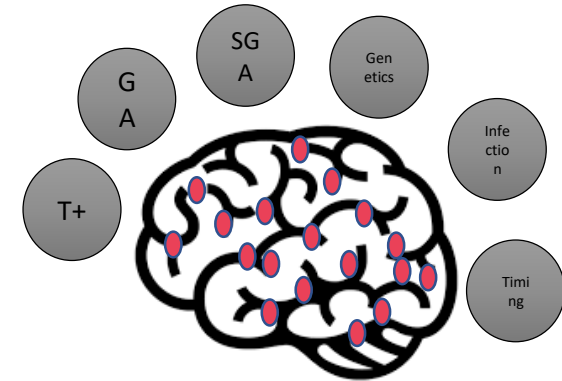
Death/Disability
50%

MECHANISM OF PROTECTION



Selecting Right Candidate

Brain Selection



Temp

33.5°C

Normal

38 °C

Brain Injury

+/-

Normal

++++








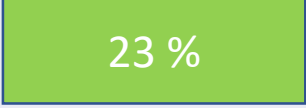
Time

0






6 hours

24 hours

TH in HIC

	Death & Disability 18 month –aOR	
2005 Cool Cap Study	0.61 (95% CI 0.34-1.09, P= 0.1)	
2005 NICHD Study	0.72 (95% CI 0.54-0.95, P=0.01)	
2009 TOBY Study	0.86 (95% CI, 0.68-1.07, P=.17)	
2010 neo.nEURO	0.21 (95% CI 0.09-0.54, P=.001)	
2010 China Study	0.47 (95% CI 0.26-0.84, P=0.01)	
2011 ICE Study	0.77 (95% CI 0.62-0.98, P=0.03)	

TH in HIC-Robust Studies

	Death/Disability 18 month aOR (95% CI)		CP at 18-24 moths aOR (95% CI)	
2005 Cool Cap Study	0.61 (0.34-1.09, $P=0.1$)		0.75 (0.48-1.16)	
2005 NICHD Study	0.72 (0.54-0.95, $P=0.01$)		0.68 (0.38-1.22)	
2009 TOBY Study	0.86 (0.68-1.07, $P=.17$)		0.67 (0.47-0.96)	
2010 neo.nEURO	0.21 (0.09-0.54, $P=.001$)		0.15 (0.04-0.60)	
2011 ICE Study	0.77 (0.62-0.98, $P=0.03$)		0.92 (0.54 -1.59)	

TH in HIC-Robust Studies

	NICHD Study 2005	Optimizing Cooling Strategy 2017
Death or Disability	44 %	29 %
Severe HIE	72 %	62 %
Mortality	24 %	9 %
Cerebral Palsy	19 %	19 %

**Does neuroprotection
persist to childhood in HIC**

6- 7 year outcome of Cool Cap Trial

Guliet et al Peds Research 2012

- 46 % surviving children were assessed with WeeFIM
- Disability status at 18 month was strongly a/w WeeFIM ratings

6- 7 year outcome of NICHD Trial

Shankaran JAMA 2014

- Primary Outcome: Death or IQ < 70
- RR 0.76 (0.58,0.99) / aRR 0.78 (0.61,1.01)

TOBY, Primary Outcome IQ >85

Azzopardi 2014

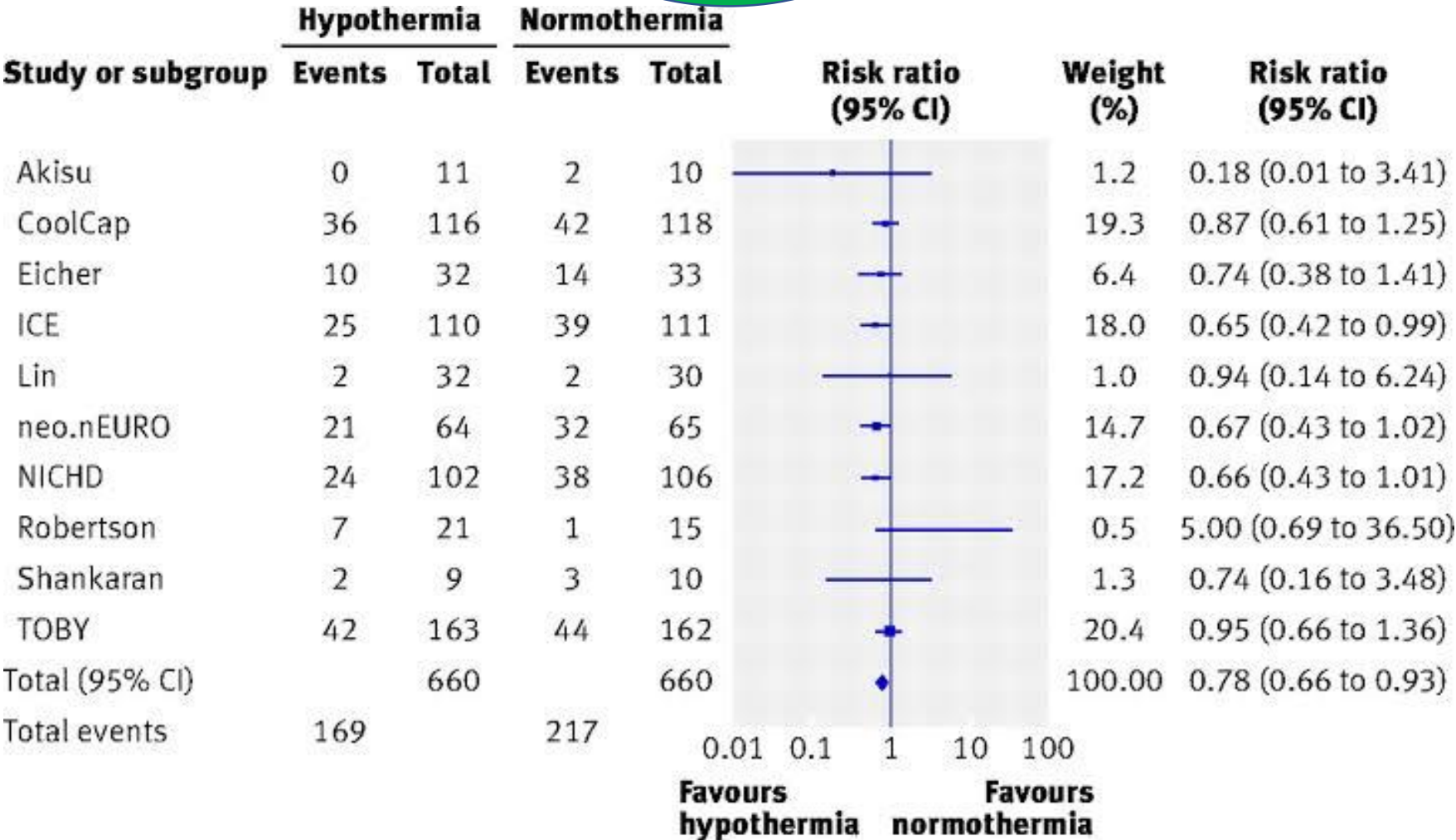
- Primary Outcome: Death or IQ >85
- RR 1.31 (1.01,1.71)

Safety

	NICHD (n=102)	TOBY (n=163)	Cool Gel (JIPMER) n=62	PCM (CMC) n=45
Low platelet		58%	13%	26%
DIC	18%	41%	6.5%	66%
PPHN	25%	10%		10%
Arrythmia	2%	5%	1.6%	6.6%
Sepsis	5%	12%	11%	9%
Hypotension	42%	77%	8%	13%

Level III NICU – Cardiac/IBP Monitoring. -- Blood bank – Imaging – ND assessment

**NNT: 7
(5,10)**



**TH remains the most
evidence-based therapy
for HIE**

AAP/NNF 2021

If they fulfil all of the following criteria

CLINICAL CONSIDERATION	THRESHOLD FOR COOLING
Perinatal insult	Convincing story of ischemic injury during delivery (subjective)
Gestational age at birth	>35 weeks
Age at time of cooling	<6 hours after birth
Apgar scores	<5 at 10 minutes after birth
Resuscitation efforts	Required at >10 minutes after birth
Cord blood samples (or blood gas samples obtained within 60 minutes of age)	pH <7.00, base deficit >16
Neurologic examination	Moderate to severe encephalopathy, as defined by Sarnat staging
Seizures	Presence of seizures (of note, this is not required for cooling but would prompt the initiation if seen at <6 hours of age)

Cooling Checklist

- **Equipment setup**
- **Treatment Initiation**
- **Maintenance Phase**
 - **Rewarming Phase (0.5°C/h- avoid rapid)**

Target Range- 32.5°C- 34.5°C with the Goal of 33.5°C

Equipment Choice

- Olympic Cool Cap
- Criticool with Curve Wrap
- Cincinnati SubZero blanket with gell roll
- Phase Contrast
- ICE Gel Pack
- Flower Pot (John Hopkins)
- Water filled Gloves
- Tecotherm HELIX mattress

Miracradle/PCM- 4

Gelpack/Water bottle- 8

Tecotherm/Blanketroll - 6

Servo Vs. Non Servo

Meta analysis - Low tech methods

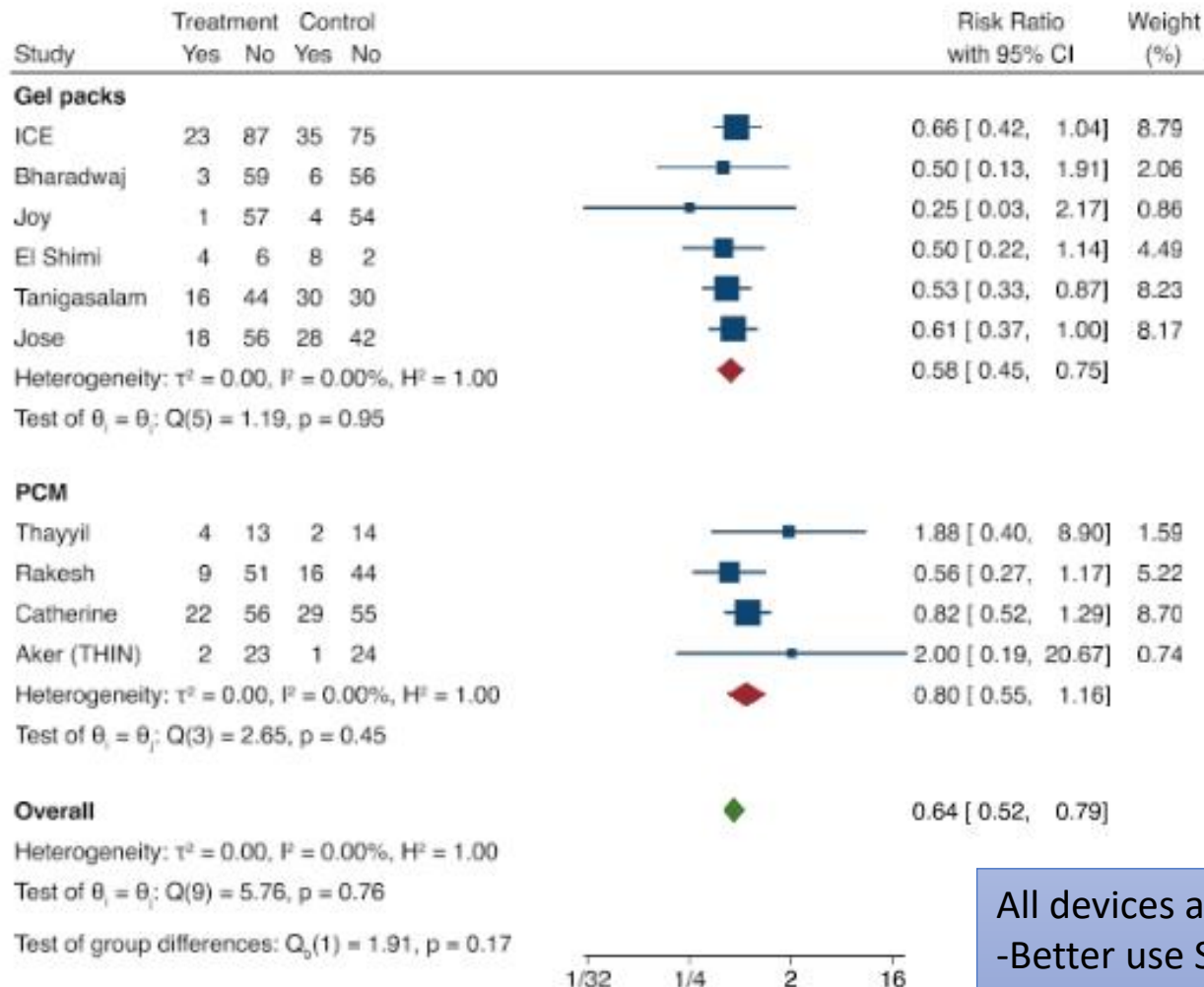
3 trials involving 467 infants

Death before discharge - RR- 0.60 (0.39-0.92)

Reduction in neurological morbidity- RR 0.46 (0.33-0.63)

Decrease in mortality or severe morbidity at 24 months RR 0.77(0.62-0.98)

Forest plot of studies using PCM or gel packs (death before discharge)



Random-effects REML model
Sorted by: year_pub

All devices are good
- Better use Servo controlled
- Non- Servo controlled
(Close temp monitoring/ Nursing 1:1)

TH remains the most evidence-based therapy for HIE, but it is not without clinical controversy.

- 1. What about deeper & longer cooling**
- 2. “When should we start cooling—as early as the delivery room?” (1st 3 hours)**
- 3. “Given the efficacy of TH for moderate to severe HIE when started within 6 hours of birth, can we expand the therapy to infants with mild HIE?”**
- 4. Can we start in Preterm**
- 5. Outcome in HIC vs LMIC**

Can greater neuroprotection be achieved with Deeper & Longer cooling

Rationale

- **Animal Model- Deeper nuclei (BGT) temp higher in severe HIE & brain temp were lower at the end of TH compared**

Moderate HIE

TH in HIC- Deep & Long

	72 hrs	120 hrs	aRR (95 % CI)	33.5°C	32°C	aRR
Primary Outcome	32 %	32%	NS	32%	31 %	NS
Death	13 %	19 %	1.39 (1.02,1.89)	14 %	19%	NS
Moderate/ severe Disability	22 %	15.5	NS	21 %	16 %	NS
Cerebral Palsy	18 %	13 %	NS	16 %	16 %	NS

Arrhythmia/iNO/ECMO/PPHN/LOS

Early Hypothermia – Before 3 hours

- Infants cooled within 3 hours of birth appear to have better neurodevelopmental outcomes compared with infants whose cooling commences between 3 hours and 6 hours
 - No difference in complications
 - PDI was significantly higher in the early cooling group
 - MDI, CP (no Difference)

Can we Cool between 6 -24 hours

	Cooled (n-78)	Non-cooled (n-79)	a RR
Death/Disability	24.4 %	27.9 %	0.86 (0.58-1.29)

Only some benefits

Marginally Better

Other Outcomes

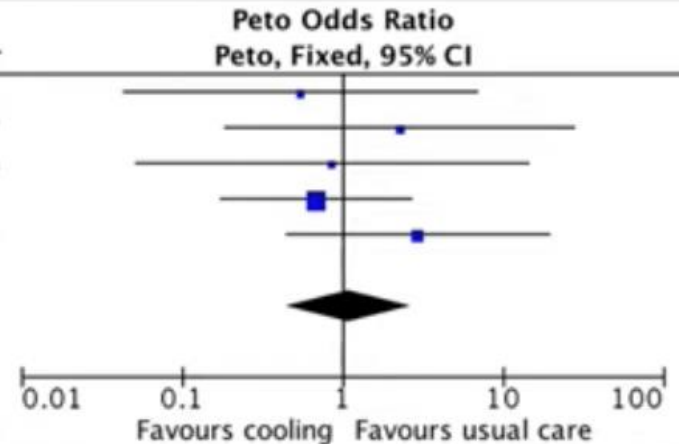
	Cooled (n=69)		Non-cooled (n=70)		<i>p</i> value
	n	X±sd or %	n	X±sd, or %	
Bayley III scores					
Cognitive	68	91.5±16.3	70	86.6±16.6	.08
Language	66	85.9±19.7	69	85.8±21.4	.96
Motor	67	89.2±17.9	70	86.2±21.0	.36
CP: Moderate	3	4	4	6	1.0
Severe	5	7	4	6	
Blindness	2	3	3	4	1.0
Hearing impaired	3	4	4	6	1.0
Seizures + meds	7	10	2	3	.20

Can we start in MILD HIE

Therapeutic hypothermia for mild neonatal encephalopathy: a systematic review and meta-analysis

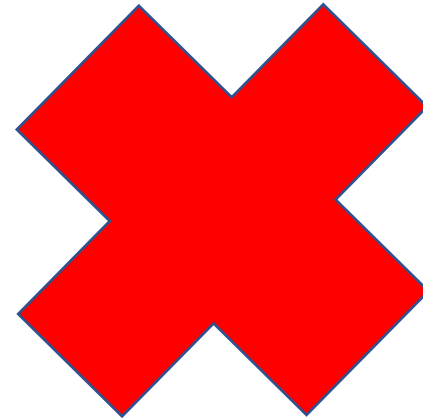
Ujwal Kariholu,^{1,2} Paolo Montaldo,¹ Theodora Markati,^{1,2} Peter J Lally,¹ Russell Pryce,^{1,3} Justinas Teiserskas,² Natasha Liow,² Vânia Oliveira,¹ Aung Soe,³ Seetha Shankaran,⁴ Sudhin Thayyil¹

Study or Subgroup	Cooling		Usual care		Weight	Peto Odds Ratio		Year
	Events	Total	Events	Total		Peto, Fixed, 95% CI		
Battin 2001 (SHC)	1	5	2	6	12.3%	0.54 [0.04, 6.89]	2001	
Wyatt 2007 (SHC)	2	6	1	6	12.7%	2.26 [0.19, 27.57]	2007	
Zhou 2010 (SHC)	1	21	1	18	10.0%	0.85 [0.05, 14.27]	2010	
Jacobs 2011 (WBC)	4	16	8	24	42.7%	0.68 [0.17, 2.65]	2011	
Lally 2013 (WBC)	4	9	2	10	22.3%	2.92 [0.44, 19.25]	2013	
Total (95% CI)		57		64	100.0%	1.09 [0.45, 2.66]		
Total events	12		14					
Heterogeneity: Chi ² = 2.16, df = 4 (P = 0.71); I ² = 0%								
Test for overall effect: Z = 0.19 (P = 0.85)								



Short term outcomes

- Length of stay
- Need for gavage feeding
- DIC
- Liver Dysfunction
- Cardiac Dysfunction
- Abnormal Imaging (Injury more in watershed area)



USA/UK/European – still using however, they have not published any long term 5 year data

Concerns

- Not standard of care- AAP/NNF
- Difficult selection of Mild HIE- ? Who are actually at highest risk
- Need more robust trial before we should consider this in LMIC

People are trying EPO in MILD HIE

TH in LMIC

In **HIC**, therapeutic hypothermia significantly reduces the combined outcome of mortality or major neurodevelopmental disability by 18 months of age **(NNT: 7; 95 % CI: 5 to 10).**

(Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013, CD003311.)

However, the benefit of therapeutic hypothermia in **LMIC** remains unconvincing with different studies and systematic reviews reporting conflicting results.

(Thayyil S, Pant S, Montaldo P, et al. Hypothermia for moderate or severe neonatal encephalopathy in low-income and middle-income countries (HELIX): a randomised controlled trial in India, Sri Lanka, and Bangladesh. Lancet Global Health. 2021;9: e1273–e1285.)

Hypothermia for Moderate or Severe Neonatal Encephalopathy in LMIC:HELIX

Thayyil et al Lancet Global Health 2021

Design	Open label phase III RCT with masked outcome assessments
Inclusion	408 term babies with moderate or severe encephalopathy from 7 tertiary neonatal units in South Asia
Control group	Intensive care with avoidance of hyperthermia (core temperature of 36.5 C)
Intervention group	Whole body cooling (33.5 C) x 72 hours using Tecotherm Neo
Primary outcome	Death or moderate or severe disability at 18 to 22 months



Journey of HELIX Trial

2009
2011-13

FEASIBILITY STUDY

Mortality: 54% vs 29%

**TH – Standard Clinical Practice
(Grade A)**

2021

**4 times Interim
Analysis**

**TH – Mortality showing high
Still trial continued**

**THE LANCET
Global Health**

**Controversy
Expected**

**DSMC so much convinced
about Robust methodology**

Helix Trial

	Hypothermia (N=202)	Usual Care (N= 206)
Birth weight	2844+450	2939+455
GA	38.9+1.3	39+1.3
Outborn (%)	140 (70 %)	145 (70%)
Cord pH	6.94+0.25	6.97+2.01
Intubation at birth	89 (45%)	89 (44%)
Moderate Encephalopathy	161 (80%)	167 (81%)
Severe Encephalopathy	41 (20%)	39 (19%)
Seizure	149 (74 %)	150(73%)

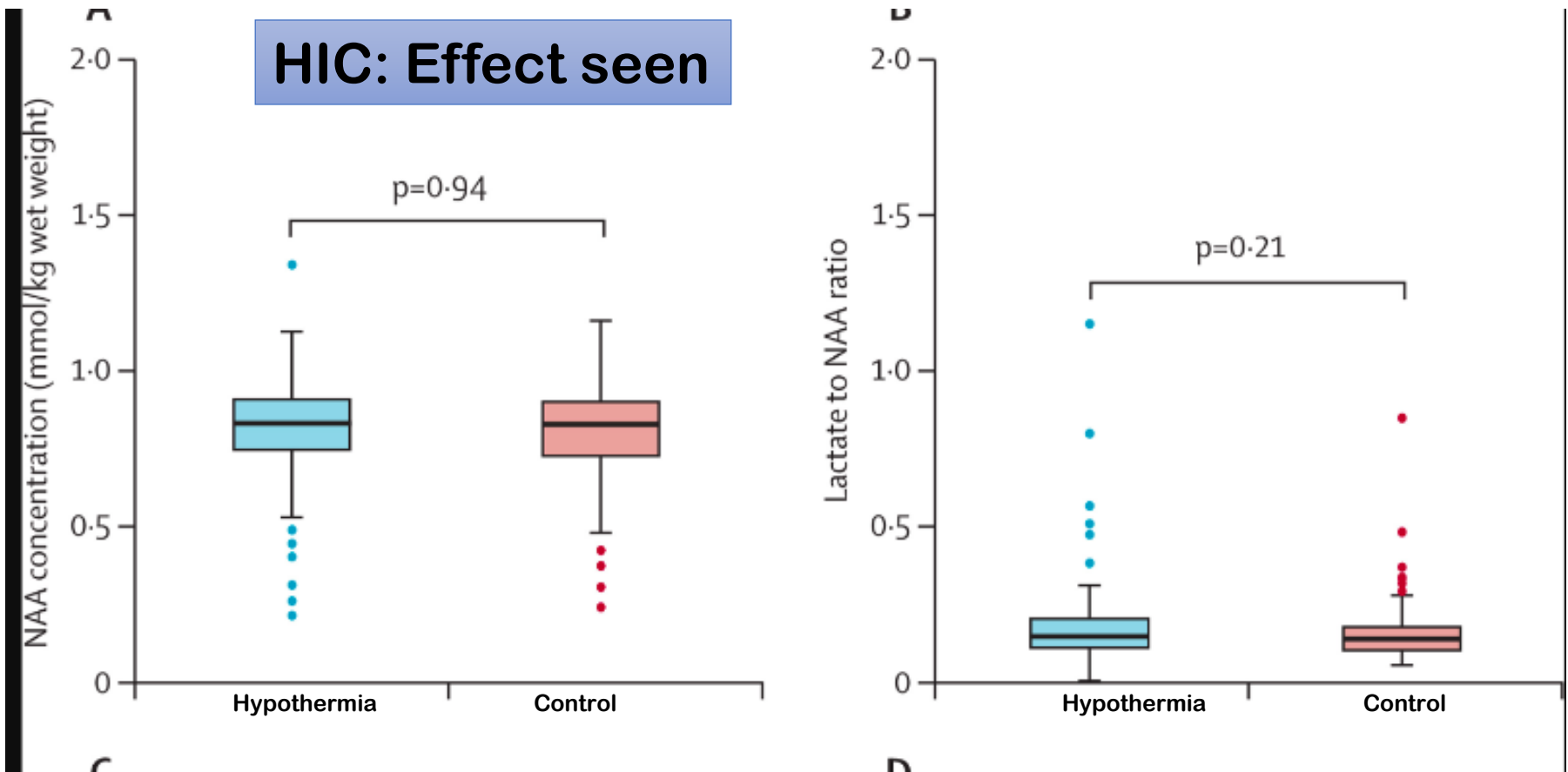
Helix Trial

	Hypothermia (N=202)	Usual Care (N= 206)	P value
Gastric Bleeding	31 %	17 %	0.001
Persistent Hypotension	22 %	12 %	0.007
Pulmonary Hemorrhage	21 %	14 %	0.05
Prolonged Blood Coagulation	39 %	25 %	0.003
Severe Thrombocytopenia	16 %	7 %	0.0056
Culture + EOS	6 %	5 %	0.6
Death Before Discharge	72 (36 %)	49 (24 %)	0.009

Helix Trial

	Hypothermia (N=202)	Usual Care (N= 206)	P value
Death or Moderate or severe Disability	98 (50 %)	94 (47%)	NS
Death Untill 18 months	84 (42 %)	63 (31 %)	0.02
Severe Disabilty among Survivors	13 %	21 %	NS
Microcephaly	30 %	27 %	NS
Survival without neurodisability	42 %	35 %	NS
Persistent Sz Disorder	3%	7 %	NS
Blindness	4 %	7%	NS
Hearing Impairment	3 %	4 %	NS

MRS (Thalamic NAA & Lac/NAA)



TH should not be offered as treatment for neonatal encephalopathy in LMIC, even when tertiary neonatal intensive care facilities are available.

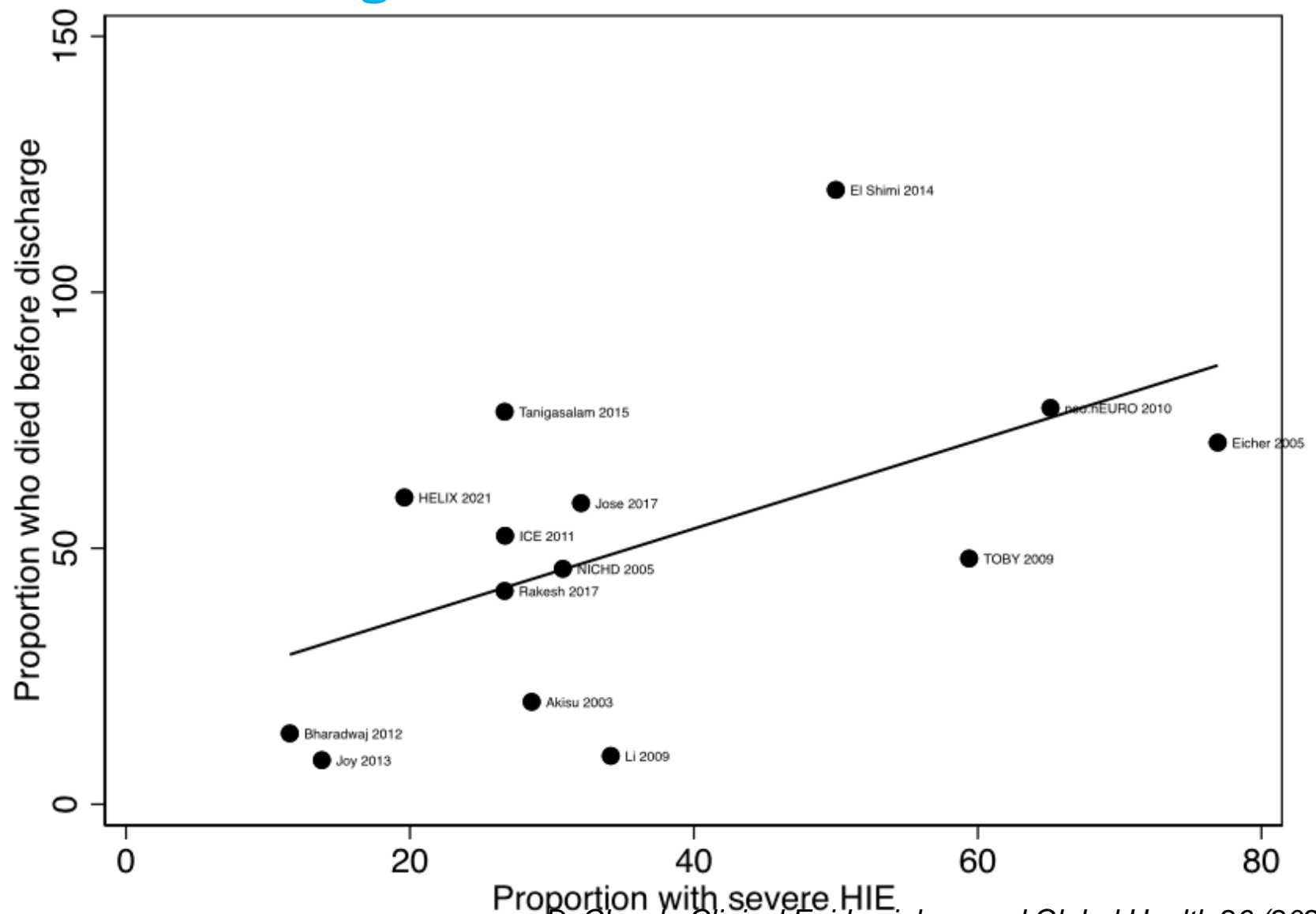
Helix vs. HIC Trials

	HELIX	HIC
Birth weight	2891	> 3300 g
Outborn (%)	70 %	45 to 64 %
Perinatal Sentinel Events	11 %	43 to 74 %
Emergency CS	20 %	48 to 73 %
Hyperthermia in Control group	5 %	14 -38 %
MRI Brain	WMI > BGT	BGT
Fetal Monitoring	Not assesed	Universal
Seizure	74 %	33 to 61 %

NNF Position statement 2021

	Death Before Discharge RR (95 % CI)
Admission temp < 36 *C	1.58 (1.18,2.12) More death
Cord pH not reported	0.96 (0.67, 1.37) No benefit in survival
Outborn neonates	0.74 (0.53, 1,02) No benefit in survival or more death

Severity of HIE & Death



Position Statement
and Guidelines For Use of
Therapeutic Hypothermia
to treat Neonatal Hypoxic
Ischemic Encephalopathy In
India

October 2021



Mandatory

- 24*7 Neonatologist
- Good quality NICU-II/IV
- Intensive Monitoring
- Bedside USG/EEG/MRI
- Multidisciplinary team
- Follow up @18 months

It is recommended that TH should be offered to neonates with HIE with gestational ***age > 36 weeks, <6 hrs of age of life and with admission temperature 36-37.4°C***, IF they fulfil all of the following criteria:

During preparation for cooling if the neonate's encephalopathy **has improved (becomes mild or normal)**, therapeutic hypothermia may be deferred and neonate observed closely.

TH in LMIC-Studies

Color coded: Risk of Bias- **Red**...**Amber**...**Green**

	Death/Disability 18 month
2021 HELIX	1.06 (0.87,1.30)
2010 Zhou	0.63 (0.44,0.91)
	0.92 (0.77,1.10)

Metanalysis

Mortality at hospital discharge

2021 HELIX	1.36 (1.05,1.77)
9 studies (2003-2019)	0.73 (0.51,1.03)
6 studies (2012-2020) Same center	0.60 (0.45,0.80)

Hypothermia for Other Conditions

- Major ICH
- Postnatal Collapse
- Congenital Heart Disease
- Surgical conditions

No evidence of
safety & efficacy

Hypothermia For Preterm HIE

- AAP/NNF- 35 weeks or more
- TOBY registry reports cooling of infants who are < 36 weeks- No long term data
- VON registry – No outcome data for < 36 weeks GA

Single Centre (2017-2015) 33-35 weeks	Death Disability	DIC	Seizure	Hypotension	Persistent Acidosis
N=30	4 (8 lost)	50%	43 %	40 %	37 %

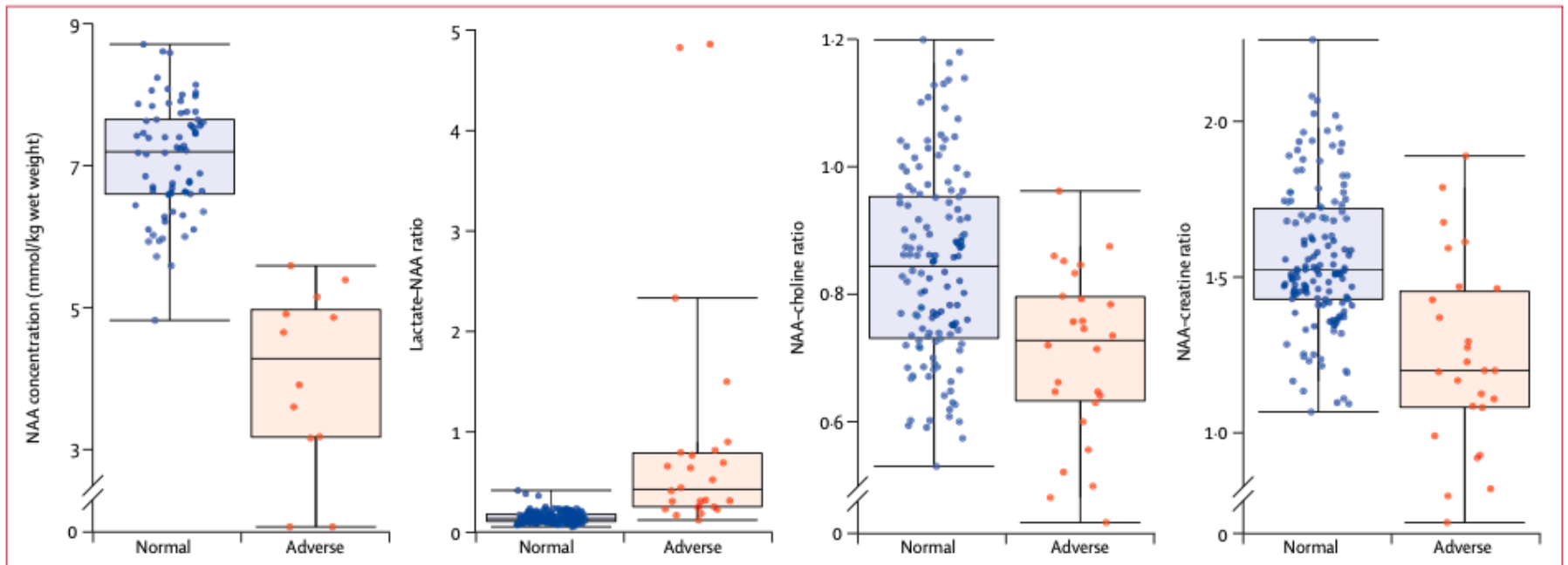
Which Investigations

correlates well with long term

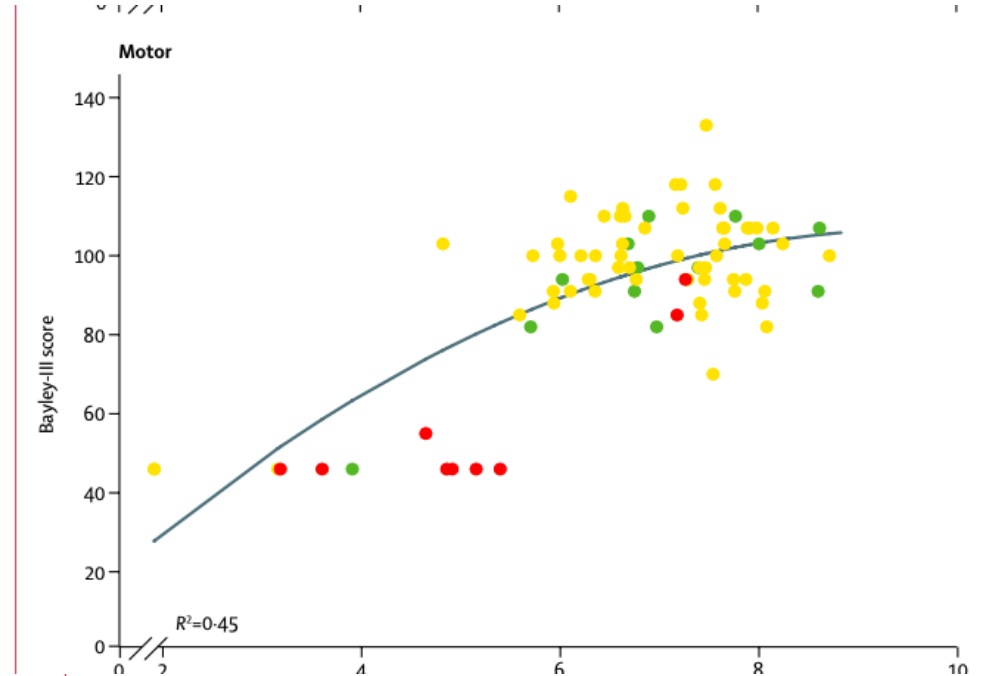
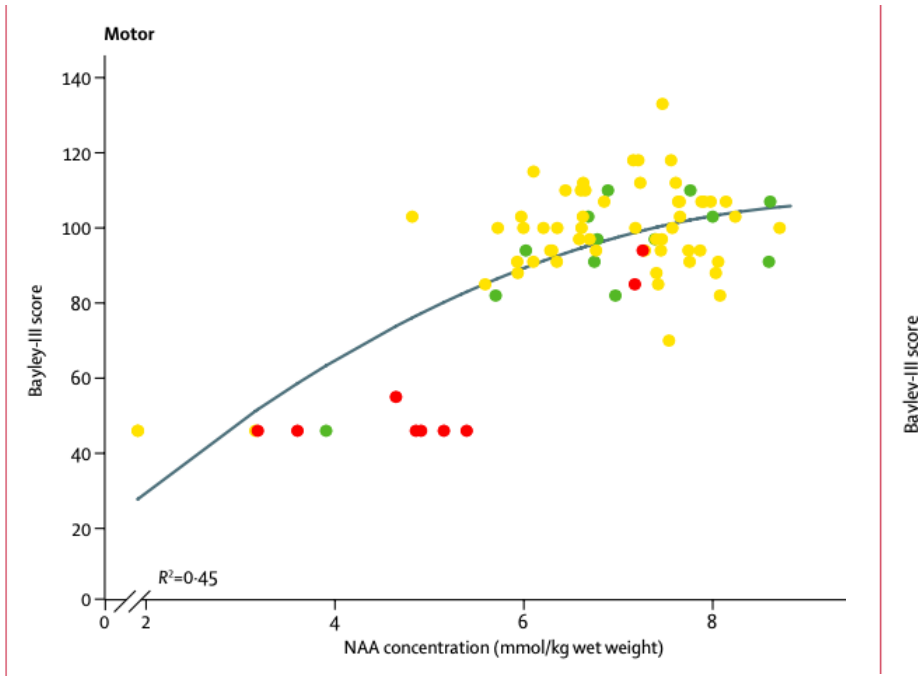
outcome

MARBLE Study

- Magnetic resonance spectroscopy assessment of brain injury after moderate hypothermia in neonatal encephalopathy



NAA Level & Severity of HIE



Correlation with Bayley Score at 2 years of age

Best Prognostic Marker

	SS (%)	SP (%)	Post TH effect
Discharge Neurological Exam	26	95	Yes
a EEG	45	92	Yes
MRI Brain (Day 5)			MRI Brain better with IQ > 70
• Cortex	48	81	
• BGT	71	88	
• PLIC	71	90	
Diffusion MRI	75	98	
MRS			HIC- Yes LMIC- No
• NAA/Cr	65	89	
• Lac/NAA	89	91	
• NAA	100	97	

**HEAL Trial: MRI Brain prediction for Mild to Moderate HIE
Similar to Normal neonates. Only Global/severe injury predicts death/NDI**

MRI Brain after day 8- Pseudo normalization

Hypothermia Plus

Therapeutic Agent Adjunct therapy with TH	Stage on the pipeline of development
NOBLE GASES Xenon Argon	Clinical Trials completed Preclinical studies completed
Melatonin	New formulation Pre-clinical studies Regulatory bodies
Erythropoietin	Phase 1 study Phase Study starting in US
Allopurinol (ALBINO Study) MgSO ₄	Horizon 2020 study. 14 European Centers 2016-2020 Mag-COOL Study Feasibility
N- Acetyl Cysteine Cannabinoids	

HEAL TRIAL

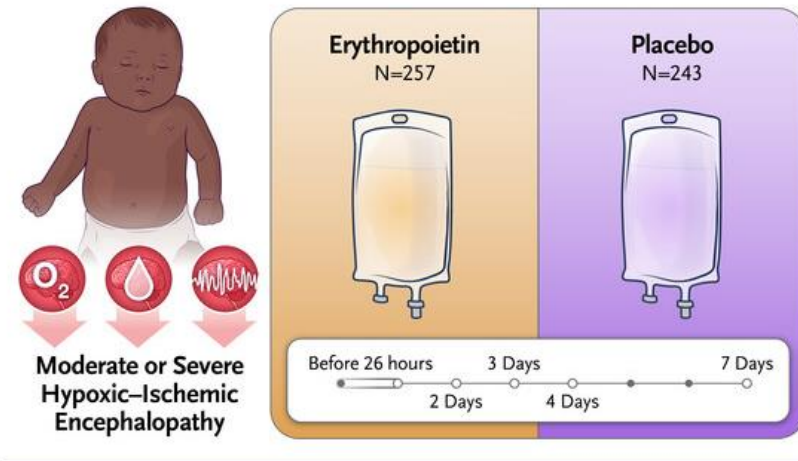
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Trial of Erythropoietin for Hypoxic–Ischemic Encephalopathy in Newborns

Wu YW et al. DOI: 10.1056/NEJMoa2119660

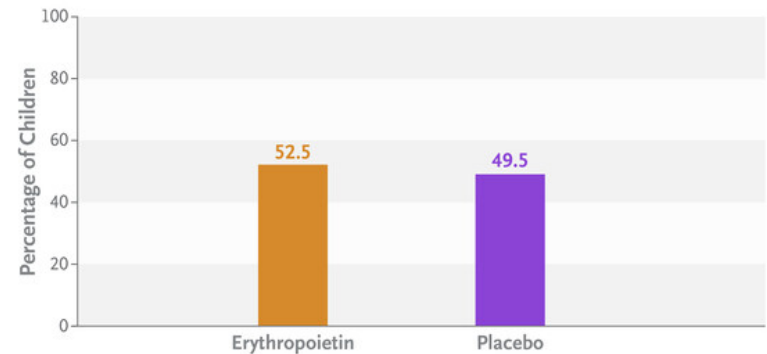
36 weeks Mod/Severe Encephalopathy- 500



**Serious Adverse events: Death/HTN/DIC
Thrombosis/PPPH/ECMO/ICH**

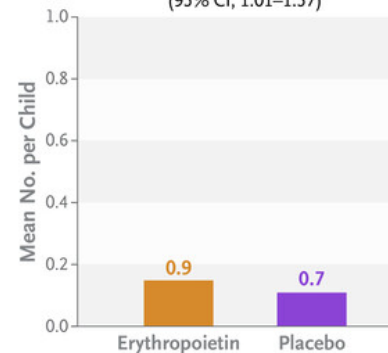
Death or Any Neurodevelopmental Impairment

Relative risk, 1.03 (95% CI, 0.86–1.24; P=0.74)



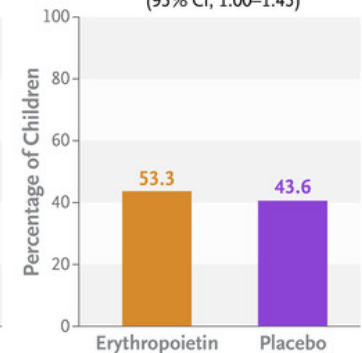
Serious Adverse Events

Relative risk, 1.26
(95% CI, 1.01–1.57)



≥1 Serious Adverse Event

Relative risk, 1.21
(95% CI, 1.00–1.45)





DR
Intubated+CC

NICU

NICU

NICU

10 minute
SPO2- 98 %
IPPV- 30/5/0.8
Cord pH: 7.0/BE-18

45 minute
SPO2- 92 %
A/C- 15/5/0.3
CFT Poor-USG

90 minute
SPO2- 92 %
A/C- 15/5/0.3
Sz/CFM /sedation

120 minute
SPO2- 92 %
A/C- 15/5/0.3
No spont breath

OPTIMIZE

OPTIMIZE

OPTIMIZE

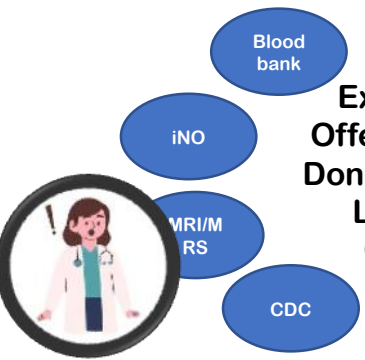
OPTIMIZE

- Temp
- fiO2
- Vent Setting
- Transport

- Nurse: 1:1
- Rectal Temp
- No Hyper/hypothermia
- RBS/Central Line/IBP

- Nurse: 1:1
- Rectal Temp
- IBP/ABX/ASM
- Avoid Sedation

- Nurse: 1:1
- Rectal Temp
- IBP/ABX/ASM
- Detail Examⁿ



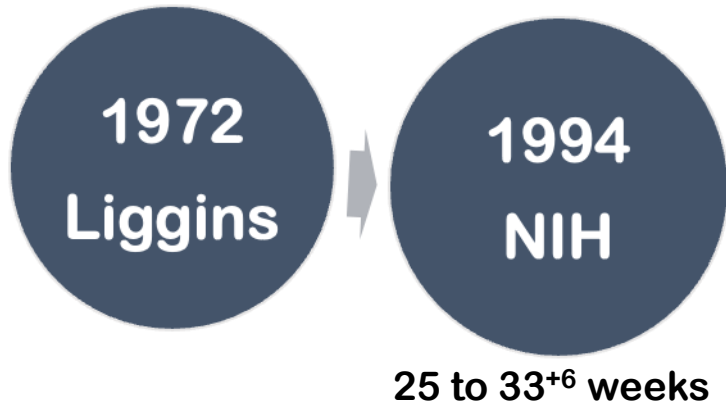
Explain Condition
Offer best possible t/t
Don't give rosy picture
Let them decide
Cool/Continue



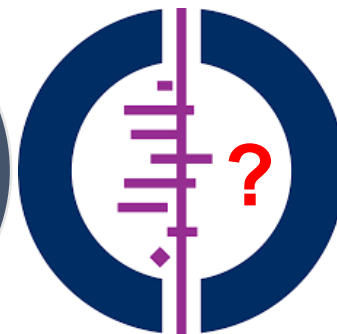
180 minutes
36 weeks/2.9 kg
No Congenital anomaly
Severe Encephalopathy
On Two Inotropes/Sz+

ANS has been one of the most important advances in perinatal care. Grade A

Brain Protection



Brain Injury



? Inclusion
Death/Infection

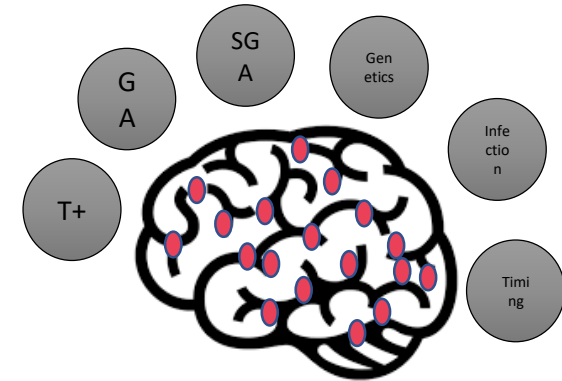
Robust
Methodology

Data Reanalyzed

ANS only if
Delivery imminent in next 7 days

Selecting Right Candidate

Brain Selection



Temp

33°C

Normal

38 °C

Brain Injury

+/-

Normal

++++

3

M/S
Enceph

1

OPTIMIZE

2

Rule Out

Time

0

6 hours

24 hours

Conclusion

- TH at 33.5 *C for 72 hours is safe & effective for moderate to severe HIE > 35 weeks GA
- Subjective & Objective Criteria both important
- Prefer servocontrolled TH machine
- Avoid too deep/ too long/in PT/> 6 hours/ Sedation or any PLUS
- Prognosis important because we can't wait to see outcome till 18 months of age
 - MRI Brain not before 3 days
 - MRS – NAA best