Current Critical Care Considerations:

Implications for Practicing Emergency Physicians

5 May 2016

Our Panel

- Dave Barounis, MD
  - Advocate Christ Medical Center
- Nick Mohr, MD, MS, FACEP
  - University of Iowa
- Matt Siedsma, MD
  - University of Pittsburgh

Rules of the Game

SEPSIS-III

The new sepsis definition is more useful than the old definition

SEPSIS SMACCDOWN

WEINGART | MYBURGH | MAITLAND | FINFER | MACHADO | MARIK | SINGER

PRO

The New Sepsis Definition IS More Useful than the Old Definition: Top 3 Reasons

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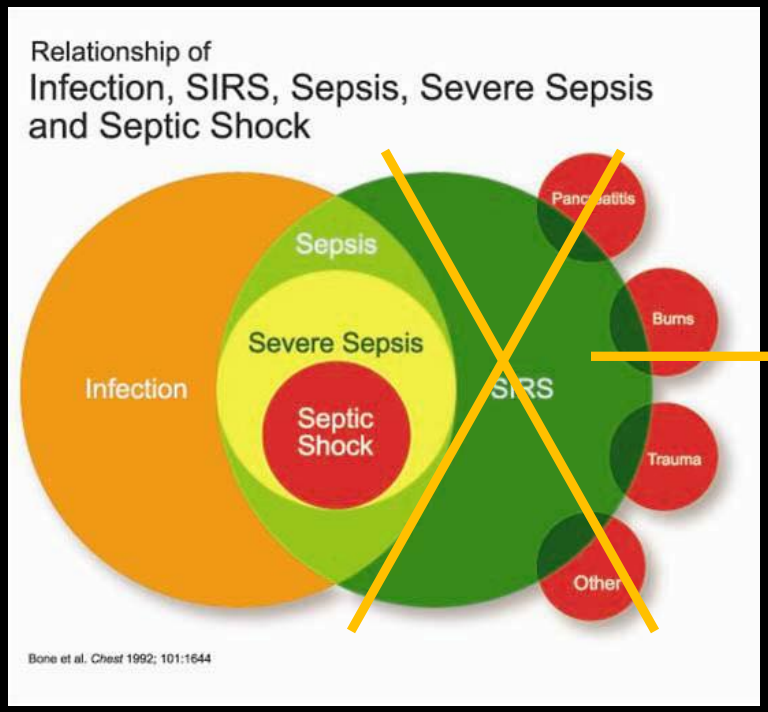
Disclosure of Commercial Relationships

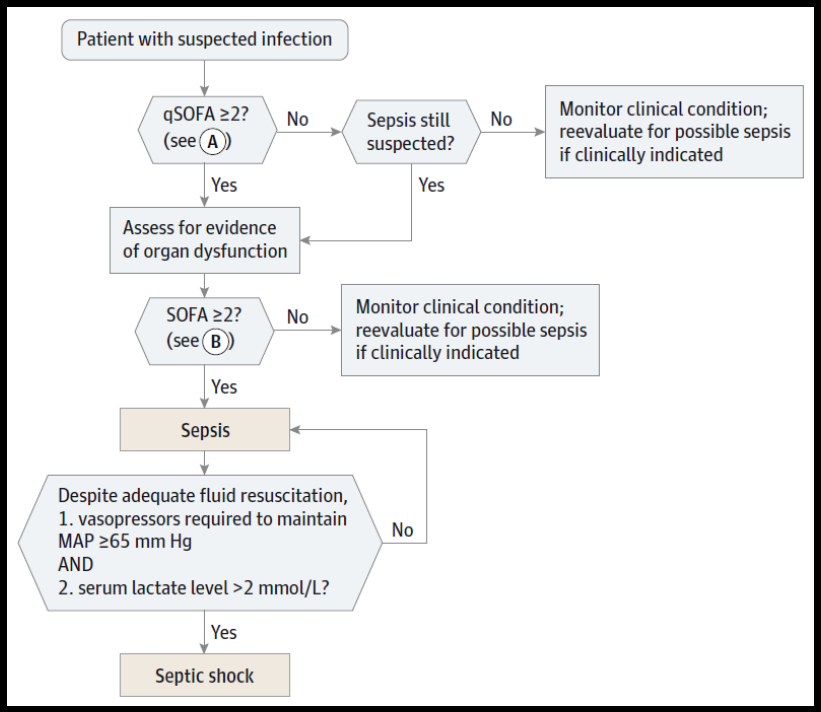
No financial conflicts of interest to disclose

The Death of SIRS

Old Definition



New Definition



Bone RC, et al. Chest 1992;101:1644-55.

Singer M, et al. JAMA 2016;315:801-10.

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Understanding Sepsis

Old Definition

- Sepsis is a disease of inflammation caused by infection
- Organ dysfunction is caused by hypoperfusion
- Organ failure is nebulously defined

New Definition

- Sepsis is a disease of organ dysfunction as a result of dysregulated host response to infection
- Organ failure is clearly defined

Severe Sepsis

#1. We forgot how nebulous the old definition is.

sepsis via four arbitrary criteria. Instead, the clinician goes to the bedside, identifies a myriad of symptoms, and regardless of an evident infection declares the patient to "look septic". If no obvious source of infection

sepsis. The use of the word "some" (Table 1) reflects the clinical reality at the bedside rather than an arbitrary list invented for the purpose of clinical trial entry criteria. Should the definition of sepsis reflect reality as seen at the bedside, thereby facilitating a clinical diagnosis, or should the definition enable investigators to develop clear and simple entry criteria for clinical trials? It was

Levy MM, et al. Intensive Care Med 2003;29:530-8.

Severe Sepsis

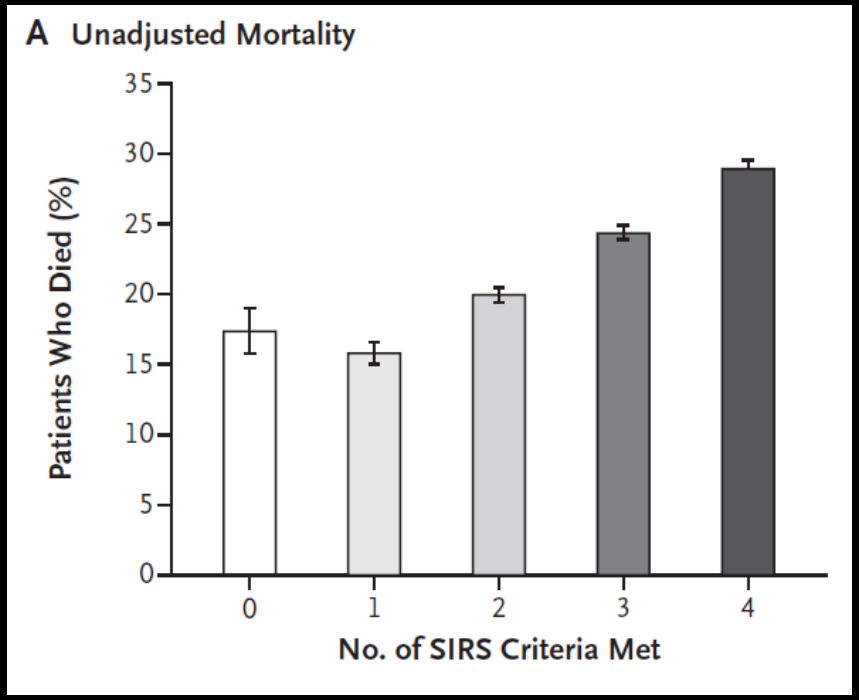
#2. The new definition is much simpler and more objective than the old one.

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Severe Sepsis

#3. SIRS didn't catch all the sick patients, either.



Kaukonen KM, et al. N Engl J Med. 2015;372:1629-1638.

Endorsing Societies

- *Academy of Medical Royal Colleges (UK)*
- *American Association of Critical Care Nurses*
- *American Thoracic Society*
- *Australian–New Zealand Intensive Care Society*
- *Asia Pacific Association of Critical Care Medicine*
- *Brasilian Society of Critical Care*
- *Central American and Caribbean Intensive Therapy Consortium*
- *Chinese Society of Critical Care Medicine*
- *Chinese Society of Critical Care Medicine–China Medical Association*
- *Critical Care Society of South Africa*
- *Emirates Intensive Care Society*
- *European Respiratory Society*
- *European Resuscitation Council*
- *European Society of Clinical Microbiology and Infectious Diseases*
- *European Society of Emergency Medicine*
- *European Society of Intensive Care Medicine*
- *European Society of Paediatric and Neonatal Intensive Care*
- *German Sepsis Society*
- *Indian Society of Critical Care Medicine*
- *International Pan Arabian Critical Care Medicine Society*
- *Japanese Association for Acute Medicine*
- *Japanese Society of Intensive Care Medicine*
- *Pan American/Pan Iberian Congress of*
- *Intensive Care*
- *Red Intensiva*
- *Sociedad Peruana de Medicina Critica*
- *Shock Society*
- *Sociedad Argentina de Terapia Intensiva*
- *Society of Critical Care*
- *Medicine*
- *Surgical Infection Society*
- *World Federation of Pediatric Intensive and Critical Care Societies*
- *World Federation of Critical Care Nurses*
- *World Federation of Societies of Intensive and Critical Care Medicine*

Misconception #1

Myth

- Are we throwing out all that we've learned about early sepsis care?

Reality

- The new definition doesn't say anything about sepsis care
- Stay tuned for 2016

Misconception #2

Myth

- qSOFA has not been validated
- We are going to start missing a bunch of patients

Reality

- qSOFA is not necessary for the diagnosis of sepsis

Conclusions

- It's hard to define a syndrome without a gold standard test
  - Sepsis-3 is better than Sepsis-2
- The new definition is simpler and easier to use than the old definition
- This is a definition: it shouldn't change how you practice

The New Sepsis Definition IS More Useful than the Old Definition: Top 3 Reasons

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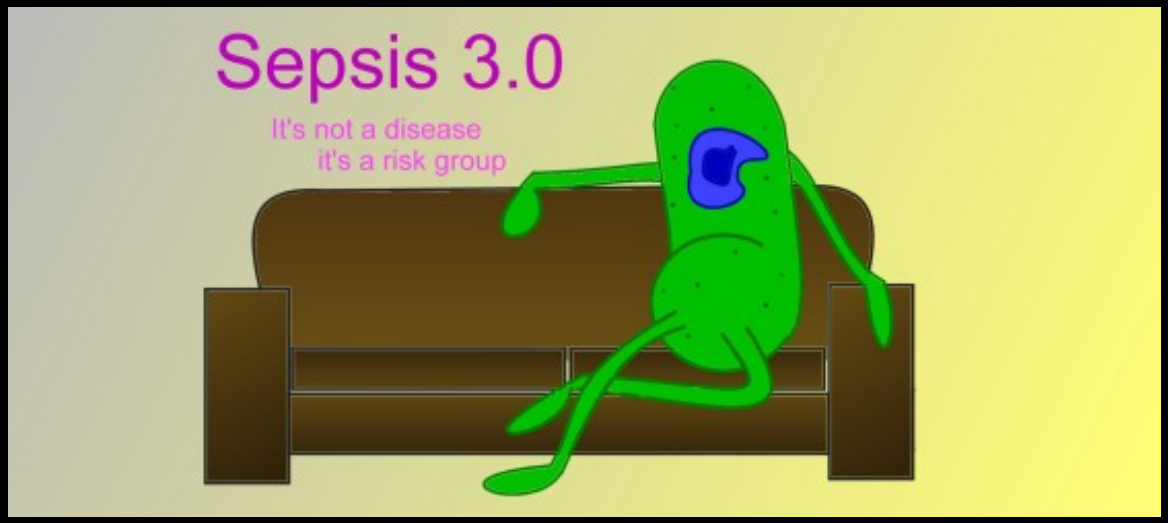

CON

Sepsis 3.0: The Bad and the Ugly

David Barounis
Emergency Medicine & Critical Care
Advocate Christ Medical Center

Why do we need new definitions

-We spend a lot of time defining syndromes (ARDS, Sepsis, AKI)

-We spend more time redefining them

-The science is incomplete

Why do we need new definitions

-We spend a lot of time defining syndromes (ARDS, Sepsis, AKI)

-We spend more time and money redefining them

-The science is incomplete

Why do we need new definitions

-We spend a lot of time defining syndromes (ARDS, Sepsis, AKI)

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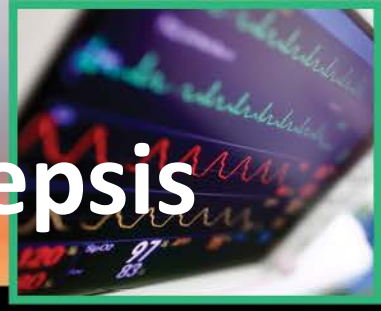
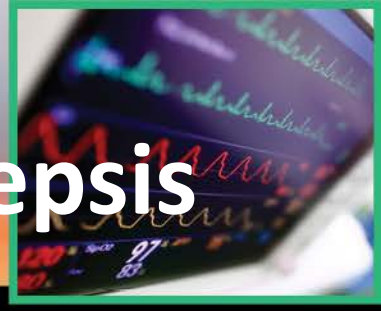
No simple criteria to identify sepsis



No simple criteria to identify sepsis



Life-threatening organ dysfunction caused by dysregulated host response to infection

What isn’t qSOFA

- NOT A SEPSIS SCREENING TOOL
- IS a mortality predictor

What isn't QSOFA

- Requires clinical judgment to suspect infection

How does QSOFA perform?

- Outside of the ICU:

- Sensitivity for mortality 55%
- Specificity for mortality 84%

BUT…When do you suspect infection?

When do you suspect infection?

1. Fever?

When do you suspect infection?

1. Fever?
2. WBC?

When do you suspect infection?

1. Fever?
2. WBC?
3. RR?

When do you suspect infection?

1. Fever?
2. WBC?
3. RR?
4. Tachycardia?

When do you suspect infection?

1. Fever?
2. WBC?
3. RR?
4. Tachycardia?

SIRS???

Clinical Judgement

Does qSOFA add anything to your judgment?

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Were you missing sepsis in patients with hypotension and altered mental status?

Did you inappropriately risk stratify patients who were tachypneic and hypotensive to the floor?

Clinical Judgement

Does qSOFA add anything to your judgement?

Were you missing sepsis in patients with hypotension and altered mental status?

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qSOFA Bottom Line

- qSOFA is sexy for headlines

qSOFA Bottom Line

- qSOFA is sexy for headlines

- But…. at this time is unlikely to change your clinical management.

Thanks!

Therapeutic Hypothermia

What's the right temp?

32 degrees?

PRO

Therapeutic Hypothermia: You still can't beat a cool 32C

Matthew Siedsma, MD
Department of Critical Care Medicine
University of Pittsburgh

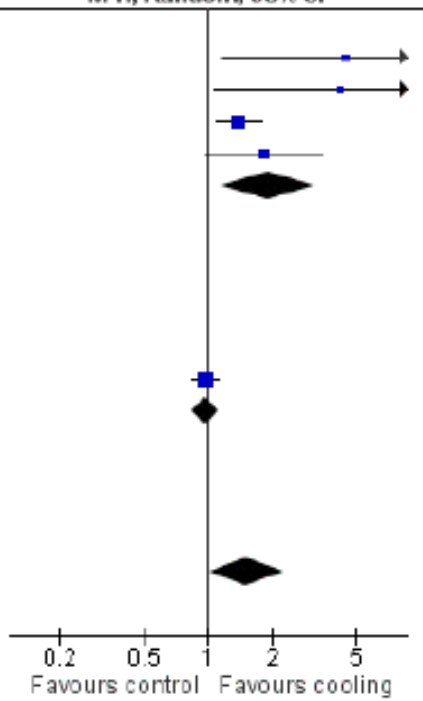
Bernard & HACA 2002 NEJM

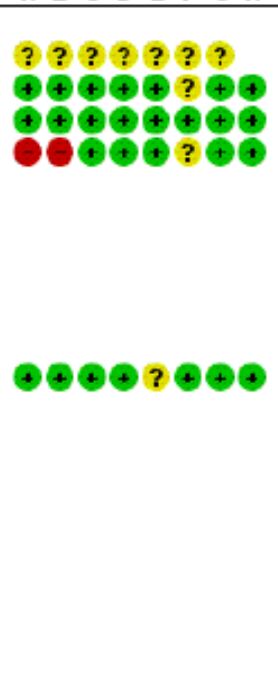
- Landmark and practice changing
- Focused on OHCA, VF/VT
- Intervention: temp management
  - 32 – 34C within 4 hours for 12-24 hours
  - Control group had no temp management at all
- Outcomes
  - Death or severe disability vs poor neuro function
  - Both ARR 23-24% with NNT of 4

That was a long time ago…

Figure 5. Forest plot of comparison: 1 Neurological outcome: therapeutic hypothermia versus no hypothermia, outcome: 1.2 Conventional cooling.

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%						





You keep talking about VF/VT

- What about non shockable rhythms??
- Austria, Testori, et al. Resus 2011
  - Retrospective, witness OHCA asystole / PEA
  - Tx was 32 – 34C, outcomes at 6 months
  - Good neuro: OR 1.84; mortality OR 0.56
- Lopez, et al
  - All 10 of 36 with asystole died prior to 6 months
- Cochrane Review
  - Insufficient evidence to evaluate asystole, IHCA

Implementation of Cooling

- Bernard / HACA closer to real world than TTM
- TTM tightly controlled efficacy study
- Higher rates cerebral hyperthermia at 36C
- No increase in adverse events at 33C
- 36C still requires shivering suppression
- Protocol more important than specific temp

Unanswered questions

- There are many
- Who benefits from which temperature?
  - Dose response curves
  - Treat VT/VF different than asystole / PEA?
- Right duration of cooling?
- Pre hospital & intra-arrest cooling?
- Optimal rate and time of re-warming?

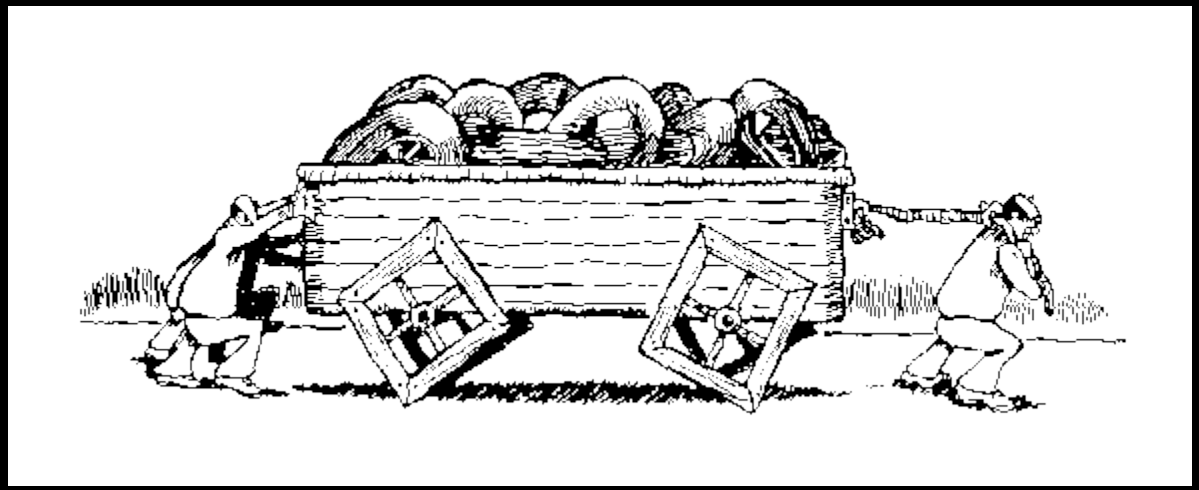
Bottom Line

- ILCOR ALS 2015 Guidelines
  - Recommend: 32 – 36C for OHCA VF/VT ROSC
  - Suggest: 32 – 36C for IHCA, PEA/asystole
- Protocols are greater than sum of parts
- Don’t generalize studies to wrong population
- We still have much to learn

BRINDLEY

Resuscitation: What's the Point

CON



“That’s cool…”

Hypothermia After Cardiac Arrest: In Search of the Right Temperature

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Disclosure of Commercial Relationships

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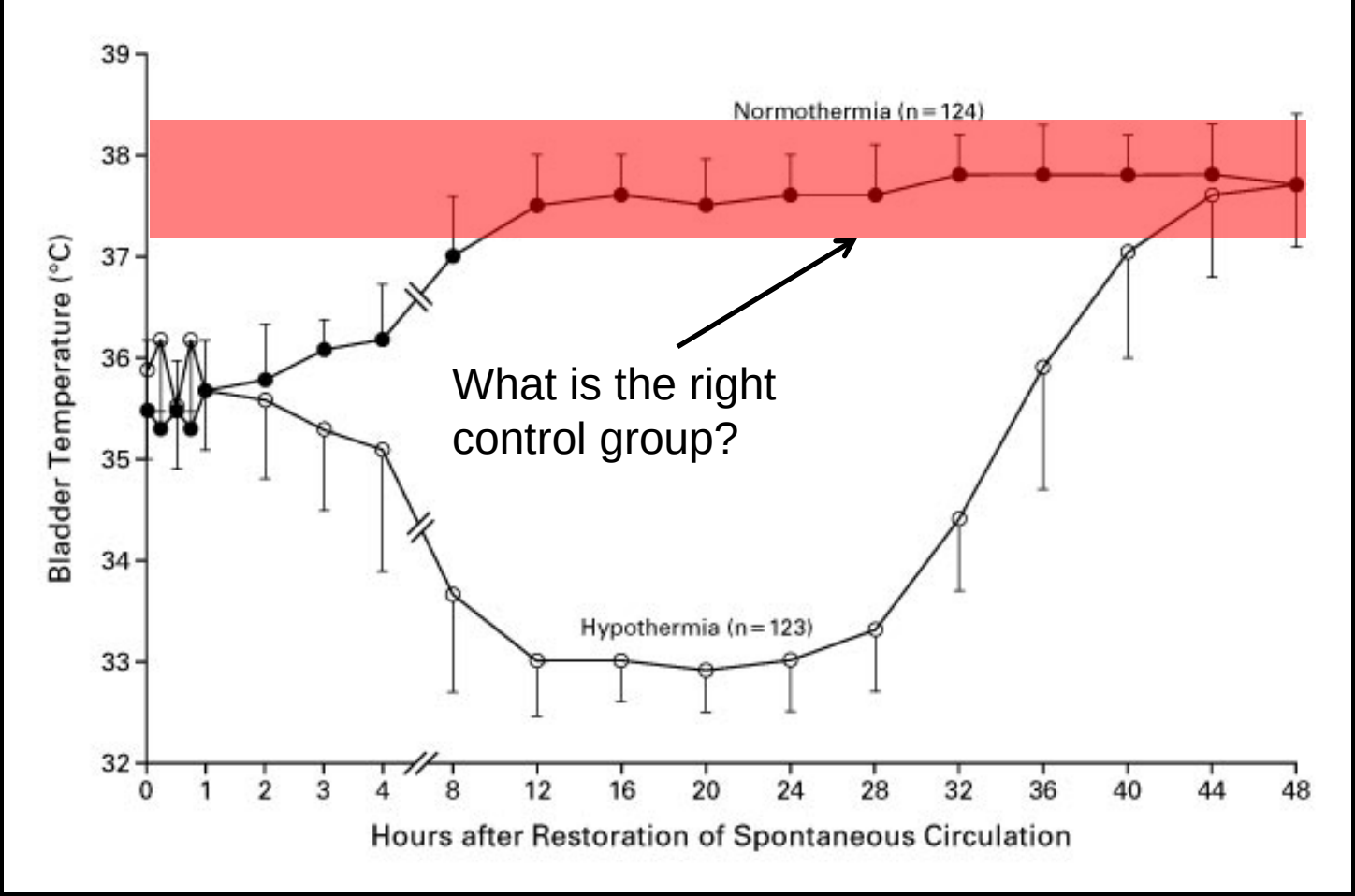
MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*



The Hypothermia after Cardiac Arrest Study Group. NEJM 2002;346:549-556

ORIGINAL ARTICLE

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

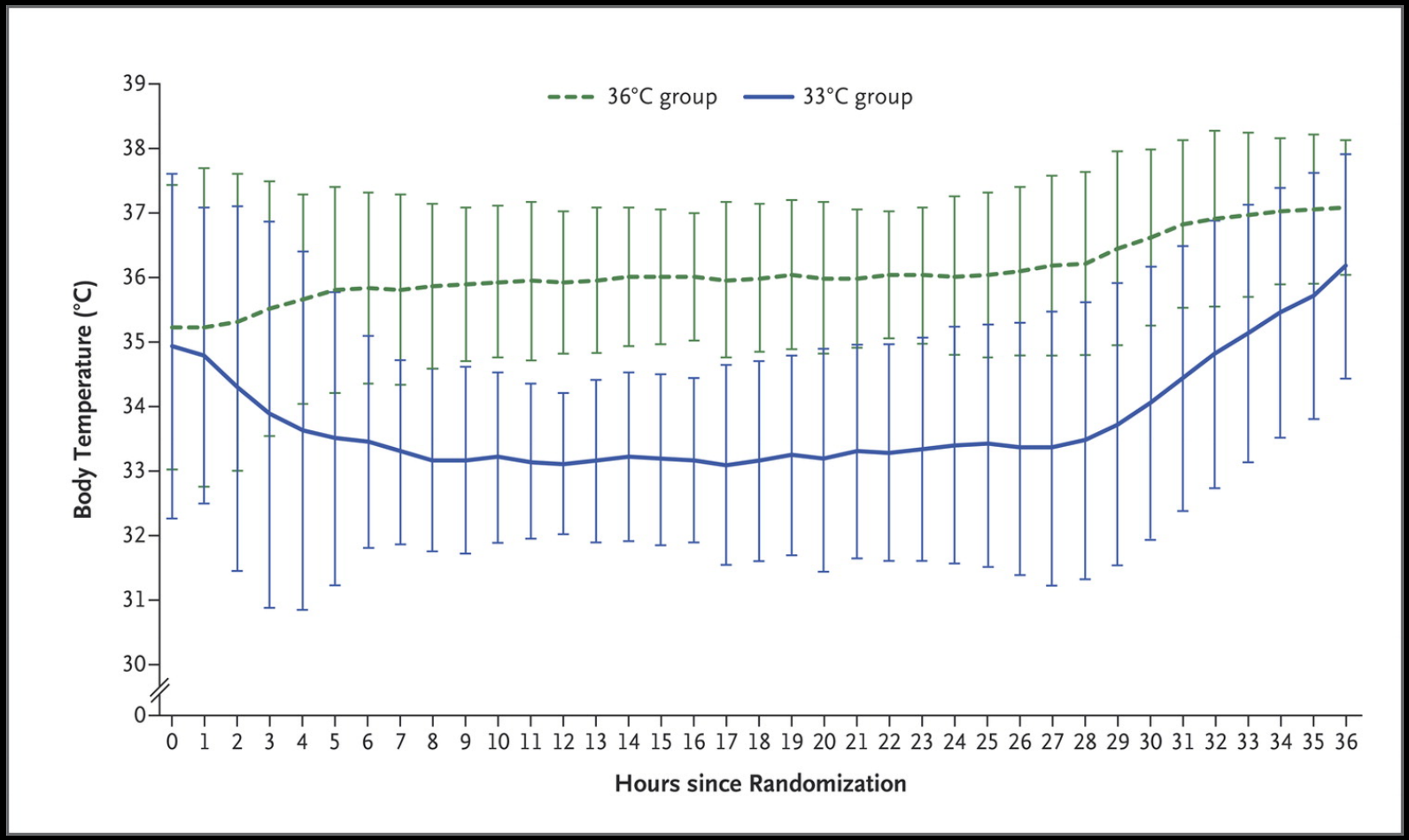
Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D., David Erlinge, M.D., Ph.D., Yvan Gasche, M.D., Christian Hassager, M.D., D.M.Sci., Janneke Horn, M.D., Ph.D., Jan Hovdenes, M.D., Ph.D., Jesper Kjaergaard, M.D., D.M.Sci., Michael Kuiper, M.D., Ph.D., Tommaso Pellis, M.D., Pascal Stammet, M.D., Michael Wanscher, M.D., Ph.D., Matt P. Wise, M.D., D.Phil., Anders Åneman, M.D., Ph.D., Nawaf Al-Subaie, M.D., Søren Boesgaard, M.D., D.M.Sci., John Bro-Jeppesen, M.D., Iole Brunetti, M.D., Jan Frederik Bugge, M.D., Ph.D., Christopher D. Hingston, M.D., Nicole P. Juffermans, M.D., Ph.D., Matty Koopmans, R.N., M.Sc., Lars Køber, M.D., D.M.Sci., Jørund Langørgen, M.D., Gisela Lilja, O.T., Jacob Eifer Møller, M.D., D.M.Sci., Malin Rundgren, M.D., Ph.D., Christian Rylander, M.D., Ph.D., Ondrej Smid, M.D., Christophe Werer, M.D., Per Winkel, M.D., D.M.Sci., and Hans Friberg, M.D., Ph.D., for the TTM Trial Investigators*

ABSTRACT

BACKGROUND

Nielsen N, et al. New Engl J Med 2013;369:2197-206

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



T < 37.5C for 72 hours

Nielsen N, et al. New Engl J Med 2013;369:2197-206

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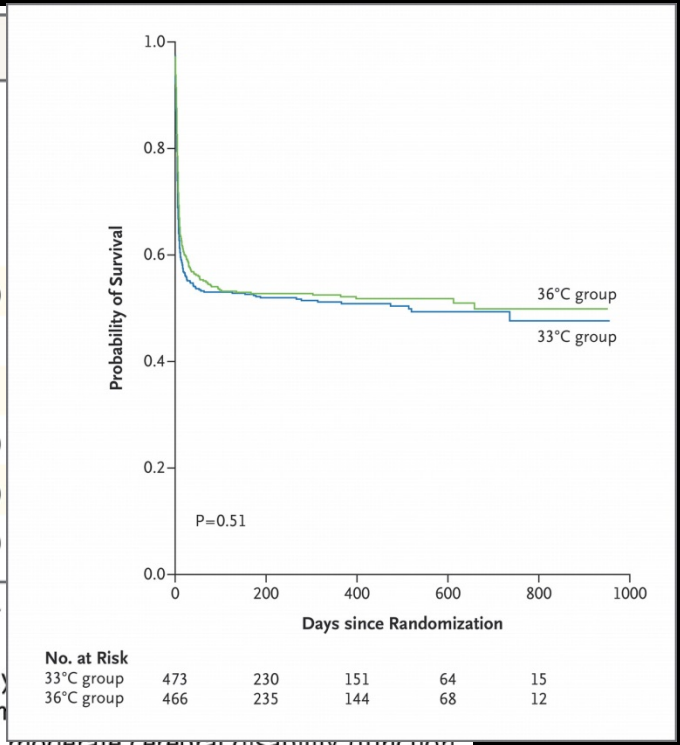
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Table 2. Outcomes.

Outcome	33°C Group	36°C Group
	no./total no. (%)	
Primary outcome: deaths at end of trial	235/473 (50)	225/466 (48)
Secondary outcomes		
Neurologic function at follow-up†		
CPC of 3–5	251/469 (54)	242/464 (52)
Modified Rankin scale score of 4–6	245/469 (52)	239/464 (52)
Deaths at 180 days	226/473 (48)	220/466 (47)

* The hazard ratio is shown for the primary outcome, and risk ratios are shown for
confidence interval.
† The neurologic follow-up was specified in the protocol to be performed at 180 da
was in some cases several weeks longer for logistic reasons. The Cerebral Perforn
from 1 to 5, with 1 representing good cerebral performance or minor disability, 2 moderate cerebral disability (function
is sufficient for independent activities of daily life), 3 severe cerebral disability, 4 coma or vegetative state, and 5 brain
death. Scores on the modified Rankin scale range from 0 to 6, with 0 representing no symptoms, 1 no clinically signifi-
cant disability despite some symptoms, 2 slight disability (patient is able to look after own affairs without assistance),
3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient
is unable to attend to own bodily needs), 5 severe disability (patient is bedridden), and 6 death.



Nielsen N, et al. New Engl J Med 2013;369:2197-206

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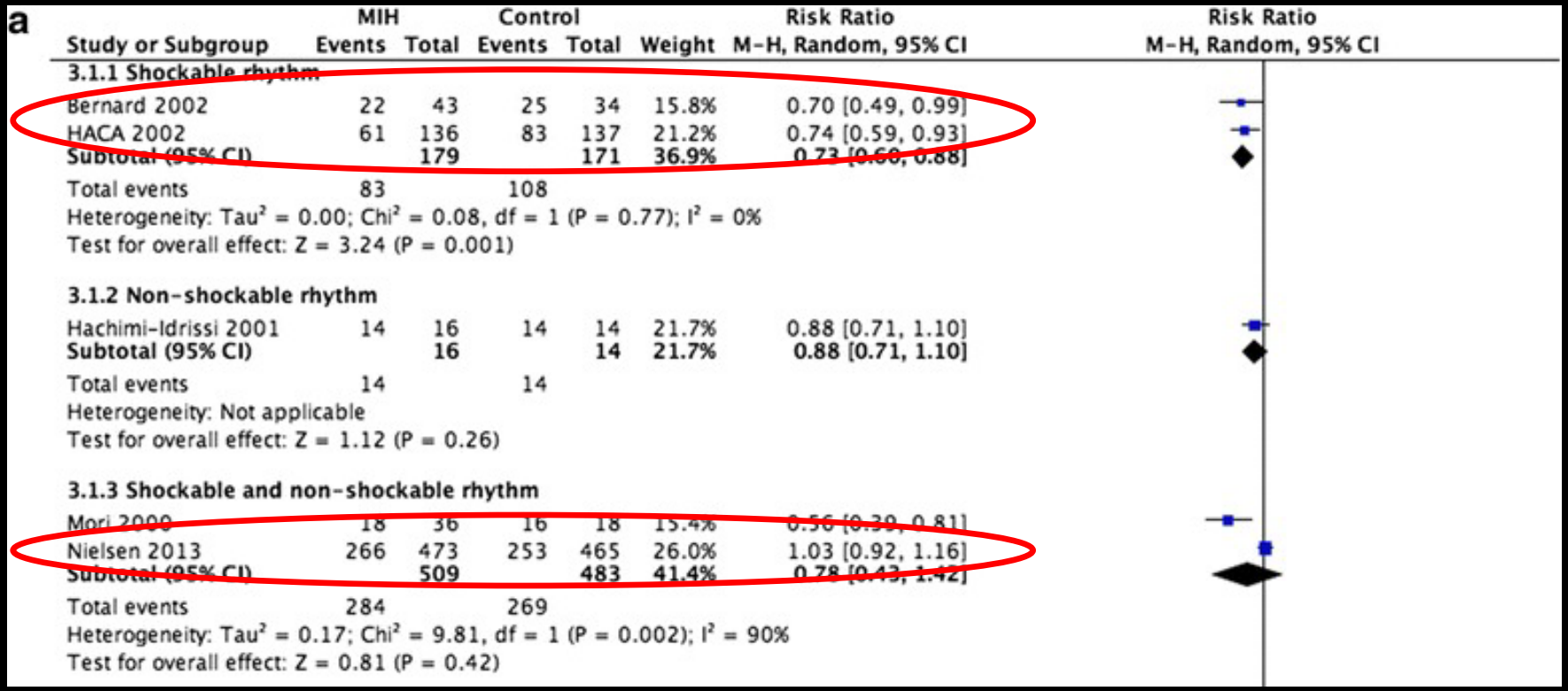
Targeted Temperature Management
at 33°C versus 36°C after Cardiac Arrest

Maybe we just didn't have enough power?



a

Study or Subgroup	MIH Events	MIH Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Shockable rhythm						
Bernard 2002	22	43	25	34	15.8%	0.70 [0.49, 0.99]
HACA 2002	61	136	83	137	21.2%	0.74 [0.59, 0.93]
Subtotal (95% CI)		**179**		**171**	**36.9%**	**0.73 [0.60, 0.88]**
Total events	83		108			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.08$, df = 1 (P = 0.77); $I^2 = 0\%$						
Test for overall effect: Z = 3.24 (P = 0.001)						
3.1.2 Non-shockable rhythm						
Hachimi-Idrissi 2001	14	16	14	14	21.7%	0.88 [0.71, 1.10]
Subtotal (95% CI)		**16**		**14**	**21.7%**	**0.88 [0.71, 1.10]**
Total events	14		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
3.1.3 Shockable and non-shockable rhythm						
Mori 2000	18	36	16	18	15.4%	0.56 [0.39, 0.81]
Nielsen 2013	266	473	253	465	26.0%	1.03 [0.92, 1.16]
Subtotal (95% CI)		**509**		**483**	**41.4%**	**0.78 [0.43, 1.42]**
Total events	284		269			
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 9.81$, df = 1 (P = 0.002); $I^2 = 90\%$						
Test for overall effect: Z = 0.81 (P = 0.42)						

Risk Ratio M-H, Random, 95% CI

Zhang XW, et al. Crit Care 2015;19:417.

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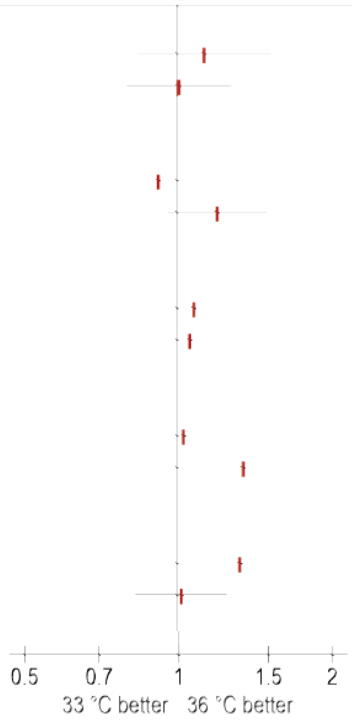
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Maybe it's because the patients were less selected

Subgroup	Target 33 °C No. of events/Total	Target 36 °C no. of patients	Hazard Ratio 95% CI	Test of interaction
Age				P = 0.52
Less than or equal to 65 years	91/238	85/250	1.13 [0.84, 1.53]	
More than 65 years	144/235	140/216	1.01 [0.80, 1.28]	
Time from cardiac arrest to ROSC				P = 0.20
Less than or equal to 25 min	79/243	86/241	0.92 [0.68, 1.24]	
More than 25 min	156/230	138/224	1.20 [0.96, 1.50]	
Initial rhythm				P = 0.92
Non-shockable	82/98	74/88	1.08 [0.79, 1.48]	
Shockable	153/375	150/377	1.06 [0.84, 1.34]	
Shock at admission				P = 0.17
Not present	183/402	180/398	1.03 [0.83, 1.28]	
Present	52/70	44/67	1.35 [0.90, 2.03]	
Site category				P = 0.19
Two largest sites	50/110	40/108	1.33 [0.87, 2.03]	
Sites except two largest	185/363	185/358	1.02 [0.83, 1.25]	



Rittenberger JC, et al. New Engl J Med 2013;369:2262-3

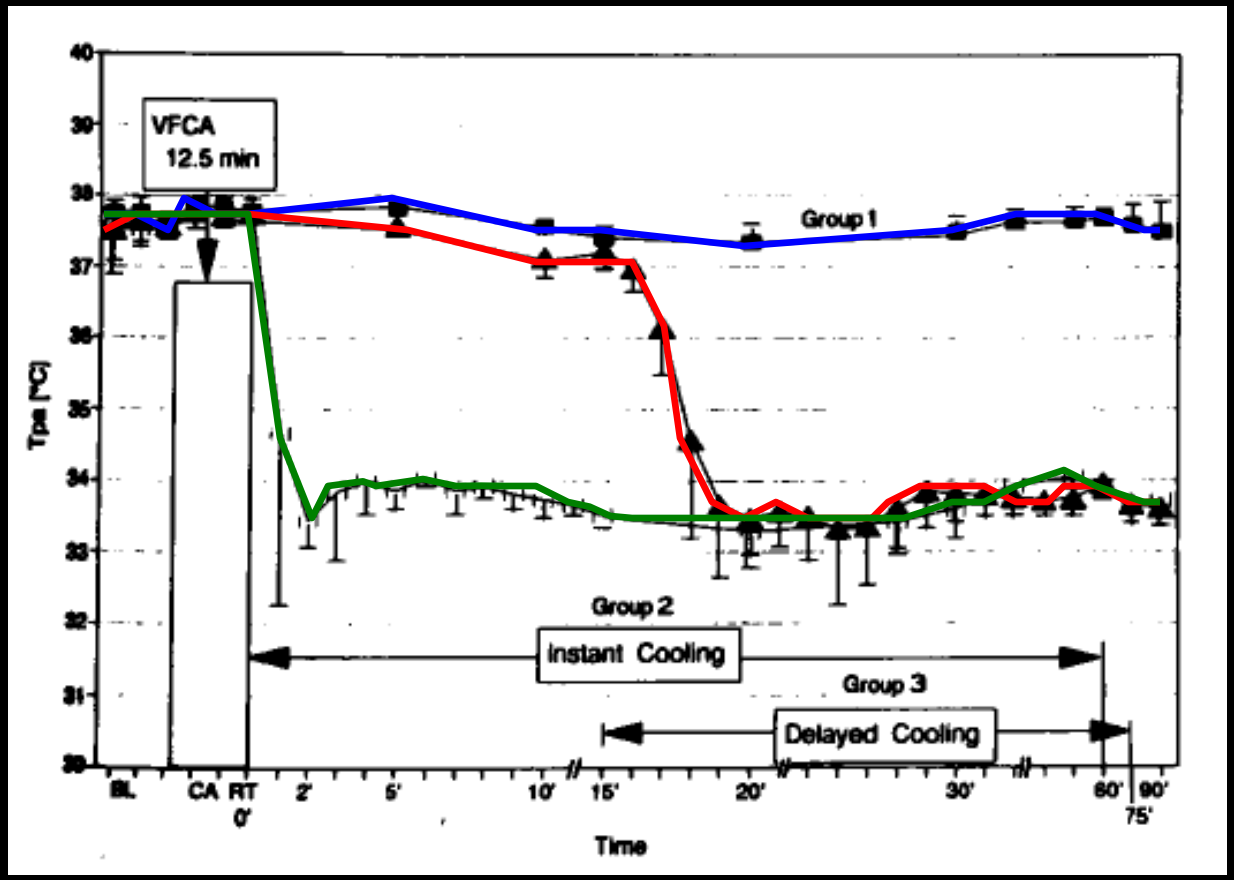
Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: A prospective, randomized study

KAZUTOSHI KUBOYAMA, MD; PETER SAFAR, MD; ANN RADOVSKY, DVM, PHD; SAMUEL A. TISHERMAN, MD; S. WILLIAM STEZOSKI; HENRY ALEXANDER

Maintained at 37.5°C

Cooled at ROSC

Cooled 15 min after ROSC



n = 22 dogs

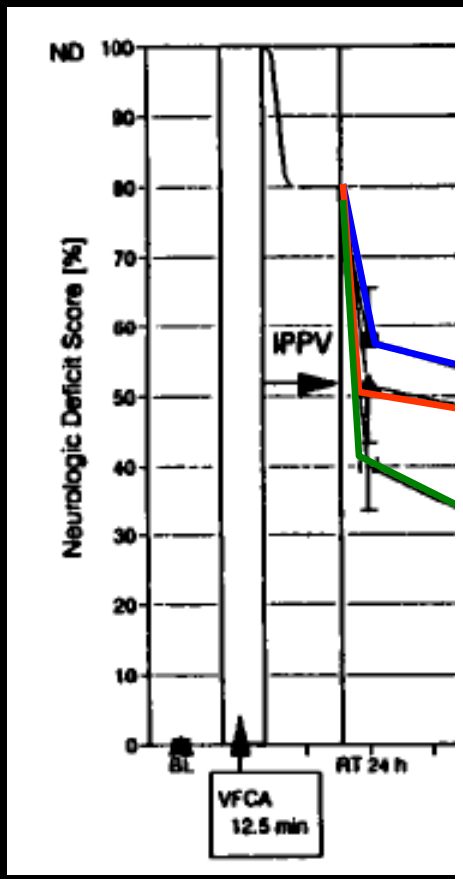
Kuboyama, K. et al. Crit Care 1993;21:1348-58

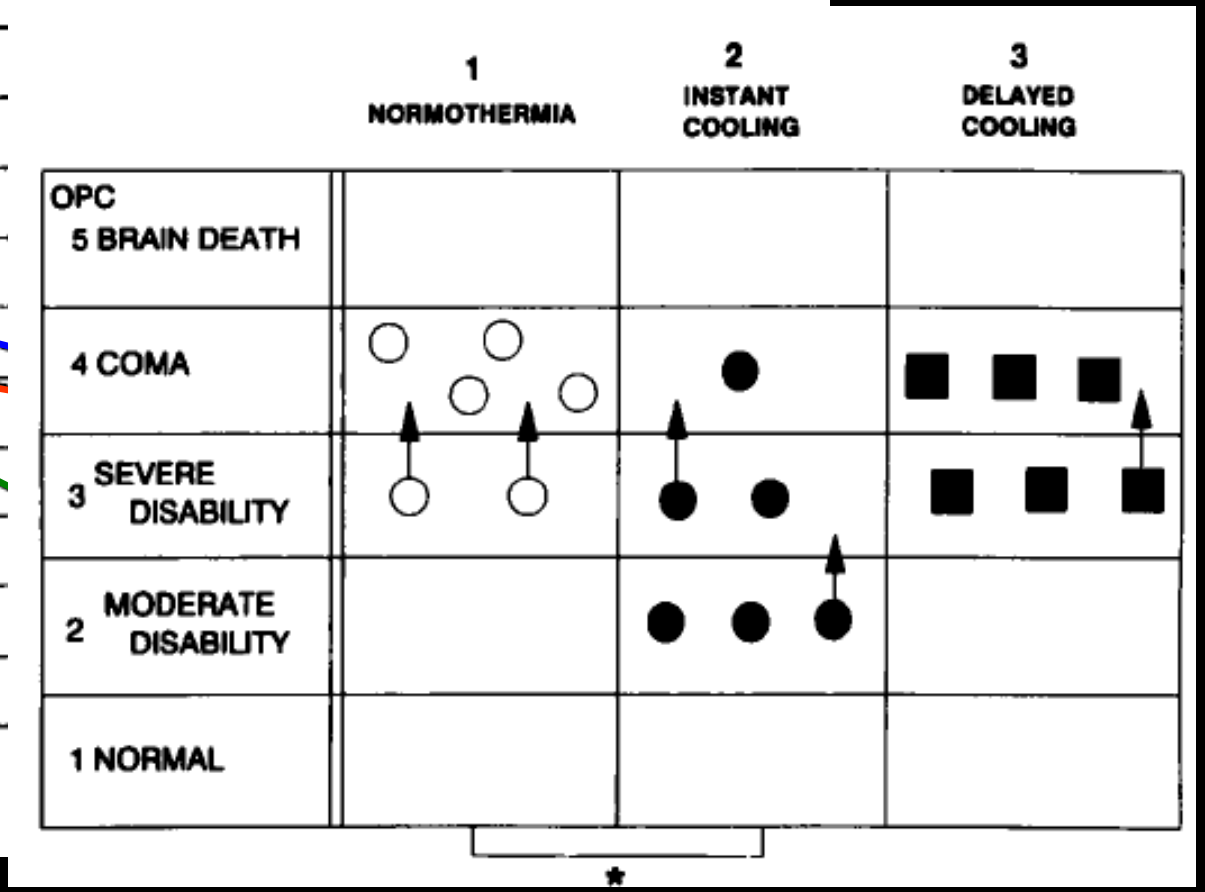
Maybe the mechanism is wrong

Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: A prospective, randomized study

KAZUTOSHI KUBOYAMA, MD; PETER SAFAR, MD; ANN RADOVSKY, DVM, PHD; SAMUEL A. TISHERMAN, MD; S. WILLIAM STEZOSKI; HENRY ALEXANDER

Maintained at 37.5°C
Cooled at ROSC
Cooled 15 min after ROSC





n = 22 dogs

Kuboyama, K. et al. Crit Care 1993;21:1348-58

THE UNIVERSITY OF IOWA

Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: A prospective, randomized study

KAZUTOSHI KUBOYAMA, MD; PETER SAFAR, MD; ANN RADOVSKY, DVM, PHD; SAMUEL A. TISHERMAN, MD; S. WILLIAM STEZOSKI; HENRY ALEXANDER

We conclude that after normothermic cardiac arrest, mild resuscitative cerebral hypothermia induced by cardiopulmonary bypass immediately with reperfusion, improves cerebral functional and morphologic outcome. Induction of cooling, even with cardiopulmonary bypass, with a 15-min delay after reperfusion, does not improve functional outcome, although it might have a beneficial effect on brain tissue damage. We recom-

Kuboyama, K. et al. Crit Care 1993;21:1348-58

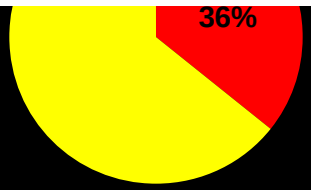
Clinical paper

Prevalence and effect of fever on outcome following resuscitation from cardiac arrest☆

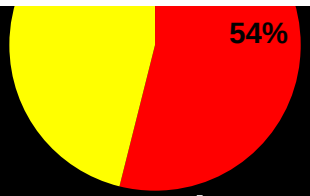
Maybe it's the fever

	Odds ratio	95% CI
Fever in 48 h	0.47	0.20, 1.10
VF/VT	2.28	0.95, 5.47
Category II	2.43	0.67, 8.87
Category III	2.01	0.57, 7.17
Category IV	0.40	0.10, 1.56

Hosmer–Lemeshow value 0.97.



Hypothermia



No Hypothermia

n = 618 from 2005 - 2010

Gebhardt K, et al. Resuscitation 2013;84:1062-7

Conclusions

- In a large well-done RCT, there was no difference in ANY outcome with 33C vs 36C
- There was no benefit in any subgroup
- Fever control is probably really important

Hypothermia After Cardiac Arrest: In Search of the Right Temperature

Nicholas Mohr, MD, MS
Assistant Professor
Department of Emergency Medicine
Division of Critical Care, Department of Anesthesia
University of Iowa Carver College of Medicine
nicholas-mohr@uiowa.edu

Management of massive hemorrhage in trauma

What's the evidence?

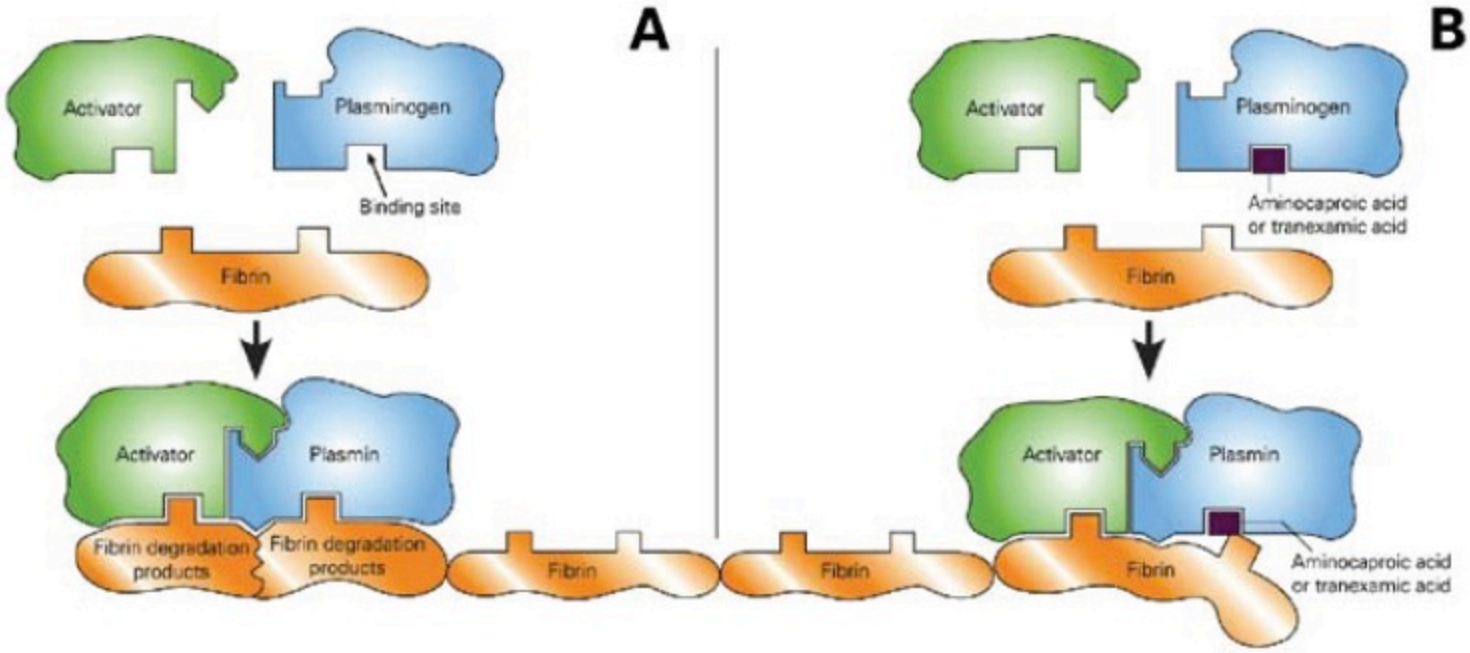
EVIDENCE FOR TXA

Massive hemorrhage control: What the heck is TXA?

Matthew Siedsma, MD
Department of Critical Care Medicine
University of Pittsburgh

No really, what is TXA??

FIGURE 2 Mechanism of activation and inhibition of plasminogen.



A Normal fibrinolysis occurs by binding of plasminogen to fibrin and subsequent activation to plasmin via the interaction with plasminogen activator. Plasmin bound to fibrin results in degradation of fibrin into fibrin degradation products.

B Antifibrinolytic medications such as aminocaproic acid and tranexamic acid bind to the site where plasminogen binds to fibrin, thereby preventing activation of plasminogen on the surface of fibrin. Fibrinolysis is therefore blocked. (Adapted with permission.[48])

gg

CRASH – 2

	Tranexamic acid allocated	Placebo allocated	Risk ratio (99% CI)
Time from injury (h)			
≤1	509/3747 (13·6%)	581/3704 (15·7%)	0·87 (0·75–1·00)
>1–≤3	463/3037 (15·2%)	528/2996 (17·6%)	0·87 (0·75–1·00)
>3	491/3272 (15·0%)	502/3362 (14·9%)	1·00 (0·86–1·17)
χ^2_2=4·411; p=0·11			
Systolic blood pressure (mm Hg)			
≥90	702/6878 (10·2%)	736/6761 (10·9%)	0·94 (0·82–1·07)
76–89	280/1609 (17·5%)	313/1689 (18·5%)	0·94 (0·78–1·14)
≤75	478/1562 (30·6%)	562/1599 (35·1%)	0·87 (0·76–0·99)
χ^2_2=1·345; p=0·51			
GCS			
Severe (3–8)	796/1789 (44·5%)	860/1830 (47·0%)	0·95 (0·86–1·04)
Moderate (9–12)	219/1349 (16·2%)	249/1344 (18·5%)	0·88 (0·70–1·09)
Mild (13–15)	447/6915 (6·5%)	502/6877 (7·3%)	0·88 (0·75–1·04)
χ^2_2=1·387; p=0·50			
Injury type			
Blunt	1134/6788 (16·7%)	1233/6817 (18·1%)	0·92 (0·83–1·02)
Penetrating	329/3272 (10·1%)	380/3250 (11·7%)	0·86 (0·72–1·03)
χ^2_1=0·791; p=0·37			
All patients	**1463/10060 (14·5%)**	**1613/10067 (16·0%)**	**0·91 (0·85–0·97)***
Two-sided p=0·0035			

0·7 0·8 0·9 1·0 1·1 1·2

Tranexamic acid better Tranexamic acid worse

Figure 3: All-cause mortality by subgroups

hrs

But not everyone loves it

- Highly criticized in North America
- Not efficacy trial, poorly randomized
  - Pragmatic / effectiveness trial vs efficacy
  - Consideration of ethical equipoise
- Subjects not generalizable to the West
  - Barely got PRBC transfusion
  - Very difficult to get PRBC in developing countries
- Trend toward more VTE in TXA group

Valle, et al. Acute Care Surg 2014
Napolitano, et al. J Trauma 2013

MATTERs & Other Evidence

- MATTERs
  - Retrospective military study Afghanistan, 2009-10
  - NNT of 7, higher VTE in TXA but higher ISS
- Tactical Combat Casualty Care Guidelines 2011
  - Level A evidence for TXA
  - Protocol use in both US and UK military
- Cochrane Review 2015
  - High quality: TXA reduces risk of death
  - Mod quality: No evidence of VTE risk with TXA

Can I use it in non-trauma?

- Probably
- PPH: WOMAN trial currently enrolling
- TBI with bleed: CRASH-3 also enrolling
- Post-op bleeding?
- GI tract bleeding?
  - 2014 Cochrane review mortality benefit
  - HALT-IT trial enrolling

Chan CC, et al. Eur Arch Oto 2013; Dunn CJ, et al. Drugs 1999;

Bottom Line

- Preponderance of evidence supports TXA
- Evidence even better for sicker patients
- It’s cheap
- It’s on the WHO Essential Medicine List
- Would you rather die or clot?

1+1=1

EVIDENCE FOR 1:1:1 Massive Transfusion Protocol

Transfusion Ratio In Hemorrhagic Shock

David Barounis

Critical Care

Scope of the Problem

- Trauma is the third leading cause of death overall.
- 20-40% of in-hospital deaths occur from massive exsanguination.

Clinical Question

- What is the best ratio of PRBC's, FFP and platelets for trauma patients with hemorrhagic shock?
- Cryo?

Retrospective data

ORIGINAL ARTICLES

Increased Plasma and Platelet to Red Blood Cell Ratios Improves Outcome in 466 Massively Transfused Civilian Trauma Patients

John B. Holcomb, MD, Charles E. Wade, PhD,* Joel E. Michalek, PhD,† Gary B. Chisholm, PhD,† Lee Ann Zarzabal, MS,† Martin A. Schreiber, MD,‡ Ernest A. Gonzalez, MD,§ Gregory J. Pomper, MD,¶ Jeremy G. Perkins, MD,‖ Phillip C. Spinella, MD,** Kari L. Williams, RN,* and Myung S. Park, MD**

467 MT trauma patients transported from the scene to 16 level 1 trauma centers between July 2005 and June 2006. Based on high and low plasma and platelet to RBC ratios, 4 groups were analyzed.

Retrospective data

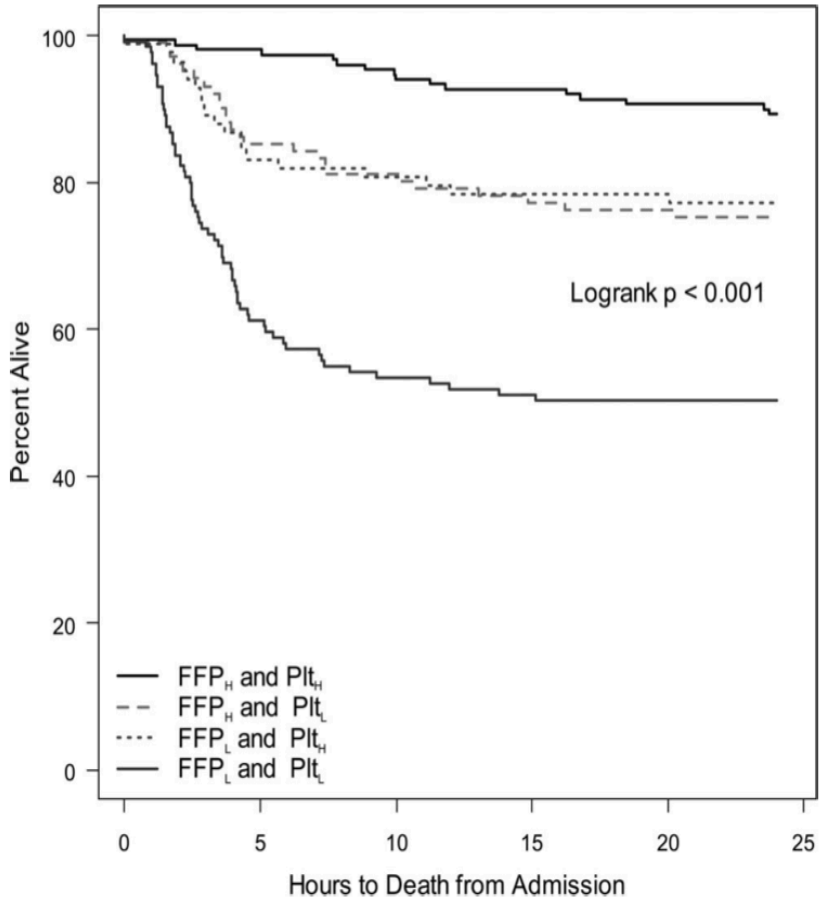


FIGURE 2. Kaplan-Meier survival plot for the first 24 hours after admission for the 4 groups (high plasma (FFP_H) or platelet (Plt_H) to RBC ratio ≥1:2, low plasma (FFP_L) or platelet (Plt_L) to RBC ratio <1:2).

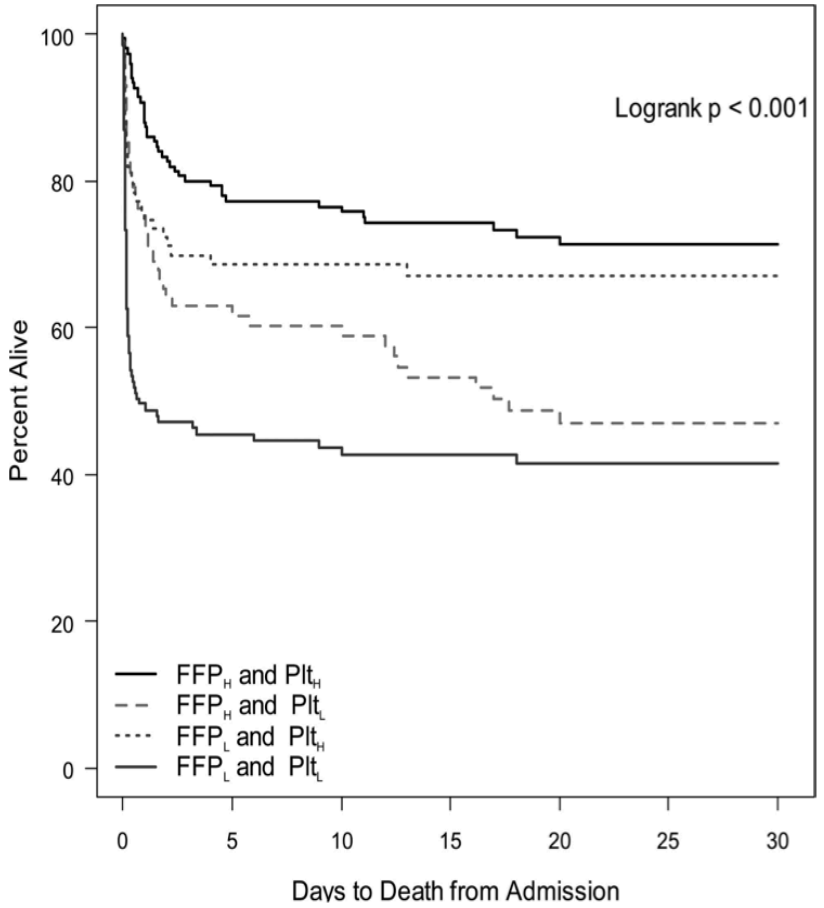


FIGURE 3. Kaplan-Meier survival plot for the first 30 days after admission for the 4 groups (high plasma (FFP_H) or platelet (Plt_H) to RBC ratio ≥1:2, low plasma (FFP_L) or platelet (Plt_L) to RBC ratio <1:2).

Retrospective data

In trauma resuscitation research, reverse causation is whether treatment allowed patients to survive longer or patients received treatment because they survived long enough.

I.E; patients who died waiting for FFP to thaw appear to get lower ratios of FFP to PRBC's.

Prospective Observational

John B. Holcomb, MD[1], Deborah J. del Junco, PhD[1,2], Erin E. Fox, PhD[2], Charles E. Wade, PhD[1], Mitchell J. Cohen, MD[3], Martin A. Schreiber, MD[4], Louis H. Alarcon, MD[5], Yu Bai, MD, PhD[6], Karen J. Brasel, MD, MPH[7], Eileen M. Bulger, MD[8], Bryan A. Cotton, MD, MPH[1], Nena Matijevic, PhD[1], Peter Muskat, MD[9], John G. Myers, MD[10], Herb A. Phelan, MD, MSCS[11], Christopher E. White, MD[12], Jiajie Zhang, PhD[13], and Mohammad H. Rahbar, PhD[2,14] for the PROMMTT Study Group

[1]Center for Translational Injury Research, Division of Acute Care Surgery, Department of Surgery, Medical School, University of Texas Health Science Center at Houston

[2]Biostatistics/Epidemiology/Research Design Core, Center for Clinical and Translational Sciences, University of Texas Health Science Center at Houston

[3]Division of General Surgery, Department of Surgery, School of Medicine, University of California San Francisco

Direct Observational study looking at transfusion ratios in patients receiving at least 3 units of blood products, and outcome at 6 hours, 24 hours and 30 days.

Prospective Observational

A. Time Interval 1: Minute 31 to hour 6 post ED admission[a] (N=876)[b]

	Continuous transfusion ratio variables				*Categorical transfusion ratio variables*					
					Low <1:2		Moderate ≥ 1:2–<1:1		High ≥1:1	
	HR	95% CI		P value	HR	P value	HR	P value	HR	P value
Early initial and time-varying plasma:RBC ratios	0.31	0.16	0.58	<.001	1.00	Ref	0.42	<.001	0.23	<.001
Early initial and time-varying platelet:RBC ratios	0.55	0.31	0.98	.04	1.00	Ref	0.66	0.16	0.37	0.04

In patients transfused moderate (>/= 1:2), to high (>/= 1:1) there was a reduced probability of in-hospital mortality.

*This association was not seen in patients receiving similar transfusion strategies after 6 hours.

Prospective Observational

Conclusions:

This study provided the appropriate data analysis strategies, effect size, sample size and power calculations for the randomized controlled trial:

Pragmatic Randomized Optimal Platelet and Plasma Ratios Trial (PROPPR)

PROPPR Trial

- RCT
- Trauma patients who received at least 1 unit of blood in pre-hospital or within one hour.
- Predicted to need MTP by ABC > 2, or clinician judgment.

PROPPR Trial

- ***Initial containers were as follows:***
- 1:1:1 got PLATELETS first (6-pack) followed by alternating RBC and plasma.
- 1:1:2 got 2 units of RBC first and 1 unit of plasma. Platelets were not transfused until after 9 units of other blood products
- ***Subsequent Containers:***
- Even number – 3 units plasma, 1 dose (6-pack) platelets and 6U RBC with platelets given first then alternating 2 units RBC and 1 unit plasma
- Odd Numbers – 2 units of RBC and 1 unit plasma

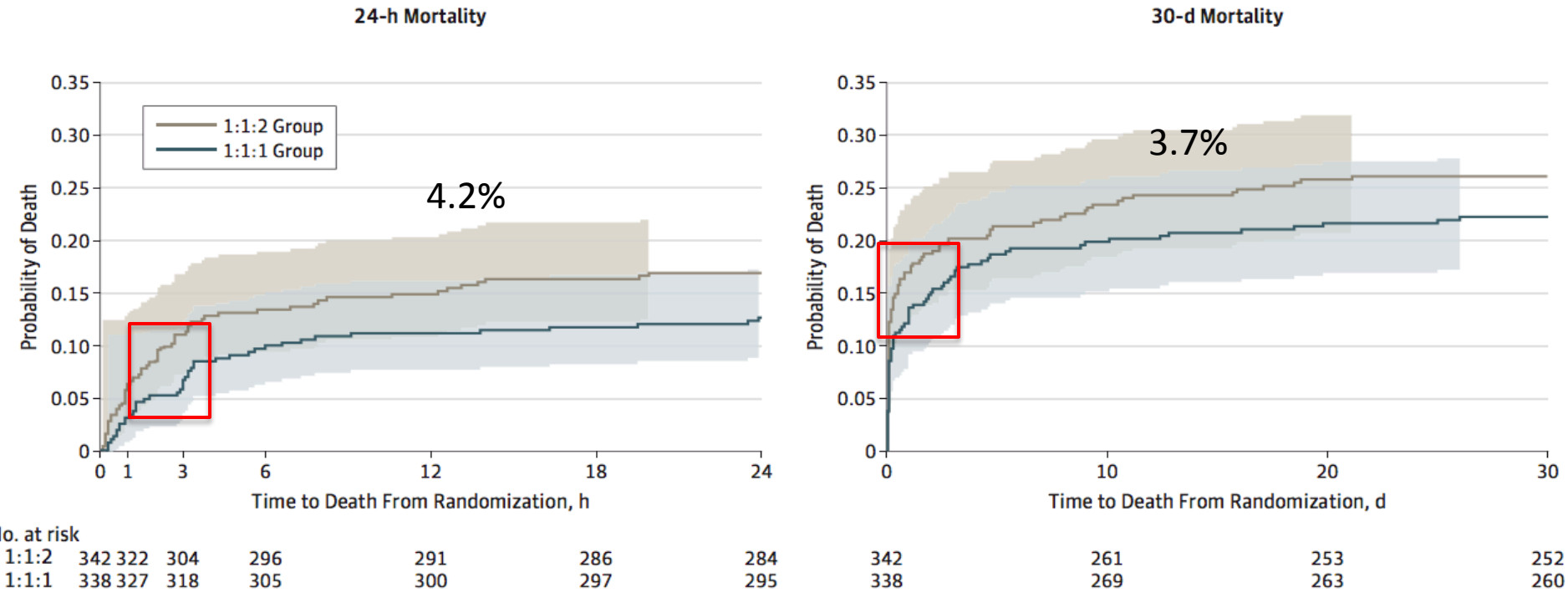
PROPPR Trial

Table 2. Trial Outcomes by Treatment Group

	1:1:1 Group (n = 338)	1:1:2 Group (n = 342)	Difference (95% CI), %	Adjusted RR (95% CI)	*P* Value[a]
24-h Mortality, No. (%)[b]	43 (12.7)	58 (17.0)	−4.2 (−9.6 to 1.1)	0.75 (0.52 to 1.08)	.12
30-d Mortality, No. (%)[b]	75 (22.4)	89 (26.1)	−3.7 (−10.2 to 2.7)	0.86 (0.65 to 1.12)	.26
Achieved hemostasis					
No. (%)	291 (86.1)	267 (78.1)			.006
Anatomic, median (IQR), min[c]	105 (64 to 179)	100 (56 to 181)			.44
Hospital-free days, median (IQR)[c,d]	1 (0 to 17)	0 (0 to 16)			.83
Ventilator-free days[d]					
Total No. of patients	337	340			
Median (IQR)[c]	8 (0 to 16)	7 (0 to 14)			.14
ICU-free days[d]					
Total No. of patients	337	340			
Median (IQR)[c]	5 (0 to 11)	4 (0 to 10)			.10
Incidence of primary surgical procedure	290 (85.8)	284 (83.0)	2.8 (−2.8 to 8.3)		
Disposition at 30 d, No. (%)[e]					
Home	118 (34.9)	105 (30.7)			
Remained hospitalized	82 (24.3)	77 (22.5)			
Other[f]	59 (17.5)	71 (20.8)			.37
Morgue	75 (22.2)	89 (26.0)			
Unknown	4 (1.2)	0			
Glasgow Outcome Scale-Extended score					
Total No. of patients[g]	30	28			
Median (IQR)[c]	4 (3 to 6)	4.5 (3.5 to 7.0)			.11

PROPPR Trial

Figure 2. Kaplan-Meier Failure Curves for Mortality at 24 Hours and 30 Days



The colored areas indicate 95% confidence bands, which were calculated using the Hall-Wellner method. The Hall-Wellner bands extend to the last event (death) in each group. For 24-hour mortality, the Cox proportional hazards regression model, adjusted for site as a random effect, produced a hazard ratio (HR) of 0.72 (95% CI, 0.49-1.07). There were no patients lost to follow-up during the first 24 hours from randomization. For 30-day mortality, the Cox proportional hazards regression model, adjusted for site as a random effect, produced an HR of 0.83 (95% CI, 0.61-1.12). Between 24 hours and 30 days, 4 patients were lost to follow-up and were censored when they withdrew consent or were last known to be alive (3 in the 1:1:1 group and 1 in the 1:1:2 group).

PROPPR Trial

Primary Outcome						
Measure	intervention	Control	adjusted RR	ARR	NNT	p
24 hour mortality	12.7%	17.0%	0.75 (CI 0.52-1.08)	4.2%	24	0.12
30 day mortality	22.40%	26%	0.86 (CI 0.65-1.12)	3.7%	27	0.26
RR = relative risk; CI = confidence interval; ARR = absolute risk reduction; NNT = number needed to treat; p = p-value						

Secondary Outcomes				
Measure	Intervention	Control	Difference (95% CI) %	p
Time to haemostasis, median (min)	105	100	5min	0.44
Any prespecified complication	87.9%	90.6%	-2.8% (-7.6 to 1.9)	
CI = confidence interval; p = p-value				

Post-hoc analysis				
Measure	Intervention	Control	Absolute Difference	p
Achieved haemostasis	86.1%	78.1%	8.0%	0.006
Death by exsanguination within 24 hours	9.2%	14.6%	-5.4% (95% C.I. -10.4 to -0.5)	0.03
Death by exsanguination within 30 days	10.7%	14.7%	-3.9% (95% C.I. -9.1 to 1.2)	

PROPPR Trial

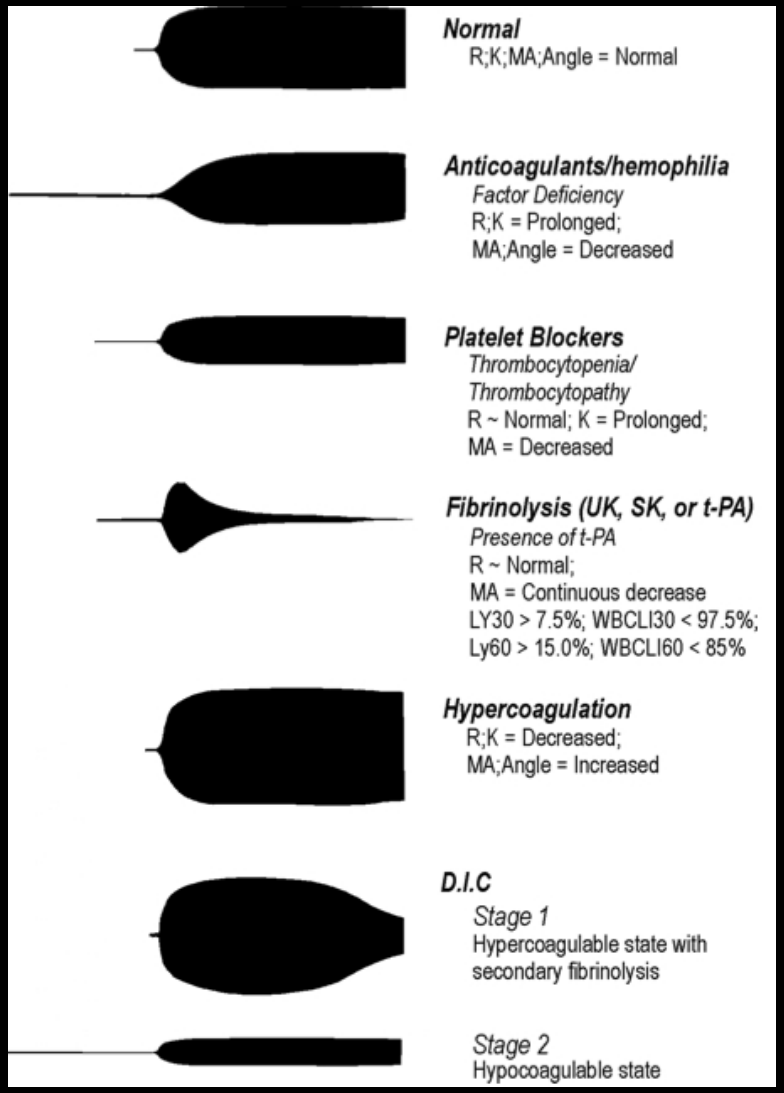
- Unanswered Questions:

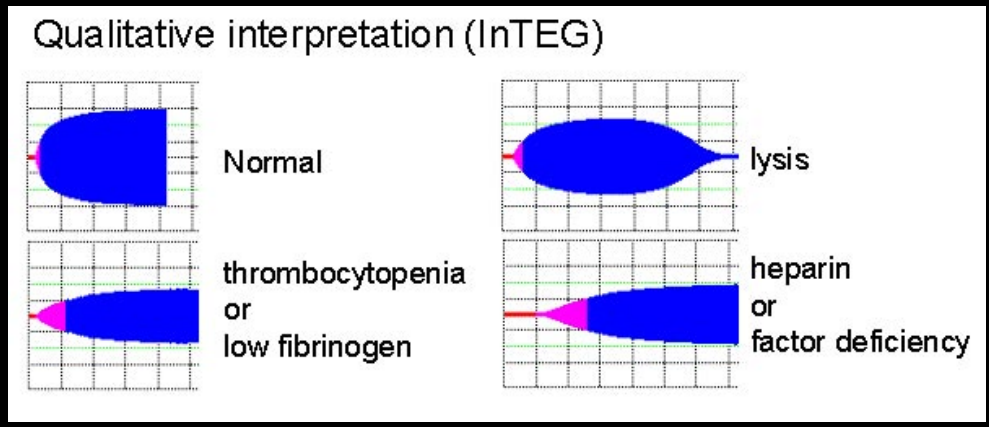
- Why 1:1:2?
- What about Cryo?
- Who should get TXA?
- Can we just use TEG-guided resuscitation?
- What if you can’t get pre-thawed FFP.

BOTTOM LINE

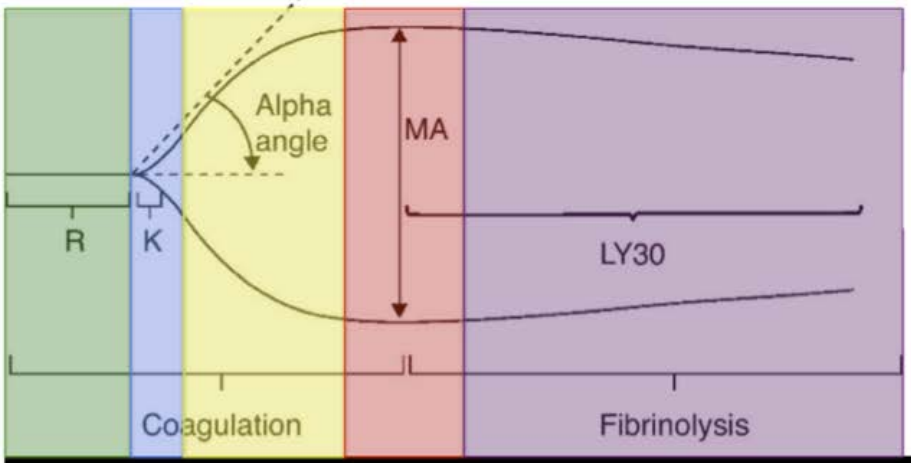
- 1:1:1 might prevent early death from exsanguination.
- But… patients still die from head injury and MOF.
- You need a MTP established to implement this approach.

Thromboelastography





TEG explained



R.E.B.E.L.EM

rebelem.com

Thromboelastogram (TEG)

Components	Definition	Normal Values	Problem with...	Treatment
R Time	Time to start forming clot	5 – 10 minutes	Coagulation Factors	FFP
K Time	Time until clot reaches a fixed strength	1 – 3 minutes	Fibrinogen	Cryoprecipitate
Alpha angle	Speed of fibrin accumulation	53 – 72 degrees	Fibrinogen	Cryoprecipitate
Maximum Amplitude (MA)	Highest vertical amplitude of the TEG	50 – 70 mm	Platelets	Platelets and/or DDAVP
Lysis at 30 Minutes (LY30)	Percentage of amplitude reduction 30 minutes after maximum amplitude	0 – 8%	Excess Fibrinolysis	Tranexemic Acid and/or Aminocaproic Acid

Thank you!