Brigham and Women's Hospital
Founding Member, Mass General Brigham

Can't Miss Articles in Critical Care Medicine 2021 - 2022

Scott Schissel, MD, PhD

Chief Medical Officer
Brigham and Women's Faulkner Hospital

Assistant Professor of Medicine
Harvard Medical School

Kate Walker, MD, MSc

Attending Physician
Medical Intensive Care Unit

Instructor of Medicine
Harvard Medical School

Division of Pulmonary and Critical Care Medicine
Brigham and Women's Hospital

CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Scott Schissel, MD, PhD

- Columbia University, College of Physicians and Surgeons
- Medicine Residency @Brigham and Women's Hospital
- Pulmonary and Critical Care Fellowship @Harvard Combined Program (BWH, MGH, BIDMC)
- Assistant Professor of Medicine@ HMS

Kate Walker, MD, MSc

- Harvard Medical School
- Medicine Residency @Brigham and Women's Hospital
- Pulmonary and Critical Care Fellowship @Brigham and Women's Hospital
- Instructor of Medicine@ HMS

Disclosures

None

Outline

- Intravenous saline versus balanced salt solutions for resuscitation in critically ill patients
  - Old controversy… new data!
- Intravenous fluid volume strategies in management of sepsis
  - Reaching a limit of “fine tuning”?

Balanced Crystalloid versus Saline in Critically-ill Patients

Balanced Crystalloid versus Saline in Critically-ill Patients

- 72 yo F with HTN, CKD (creatinine 1.3, eGFR 61)
  - + prior h/o AKI after complicated ‘CCY -> renal replacement
- Now with C Diff colitis and transient hypotension
- Admitted to the ICU, labs notable for:
  - Na 135 K 3.9 Cl 98 HCO3 18 BUN 21 Creat 1.9 AG 19, LA 2.9

- Start IVF resuscitation with:
  a. Normal Saline (0.9% sodium chloride)
  b. D5W + 3 amps of sodium bicarbonate
  c. Lactated Ringers solution
  d. 4% albumin in sodium chloride

A Quick Word on Colloids

- Saline versus **Albumin (4%)** Fluid Evaluation (SAFE trial)
  - *N Engl J Med* 2004, **350**: 2247-56
  - 6,997 patients: no difference in 28D mortality, ICU LOS, mechanical ventilation days, organ failure
  - *N Engl J Med* 2007, **357**: 874-84
  - SAFE extension trial, examining *TRAUMATIC BRAIN INJURY* patients
  - 33% mortality with albumin versus 20% with saline
- **Hydroxyethyl starch (6% HES)** versus Saline
  - *N Engl J Med* 2012, **367**: 1901-11
  - 7,000 patients: no difference in 90D mortality; *21% increase in need for renal replacement with HES*

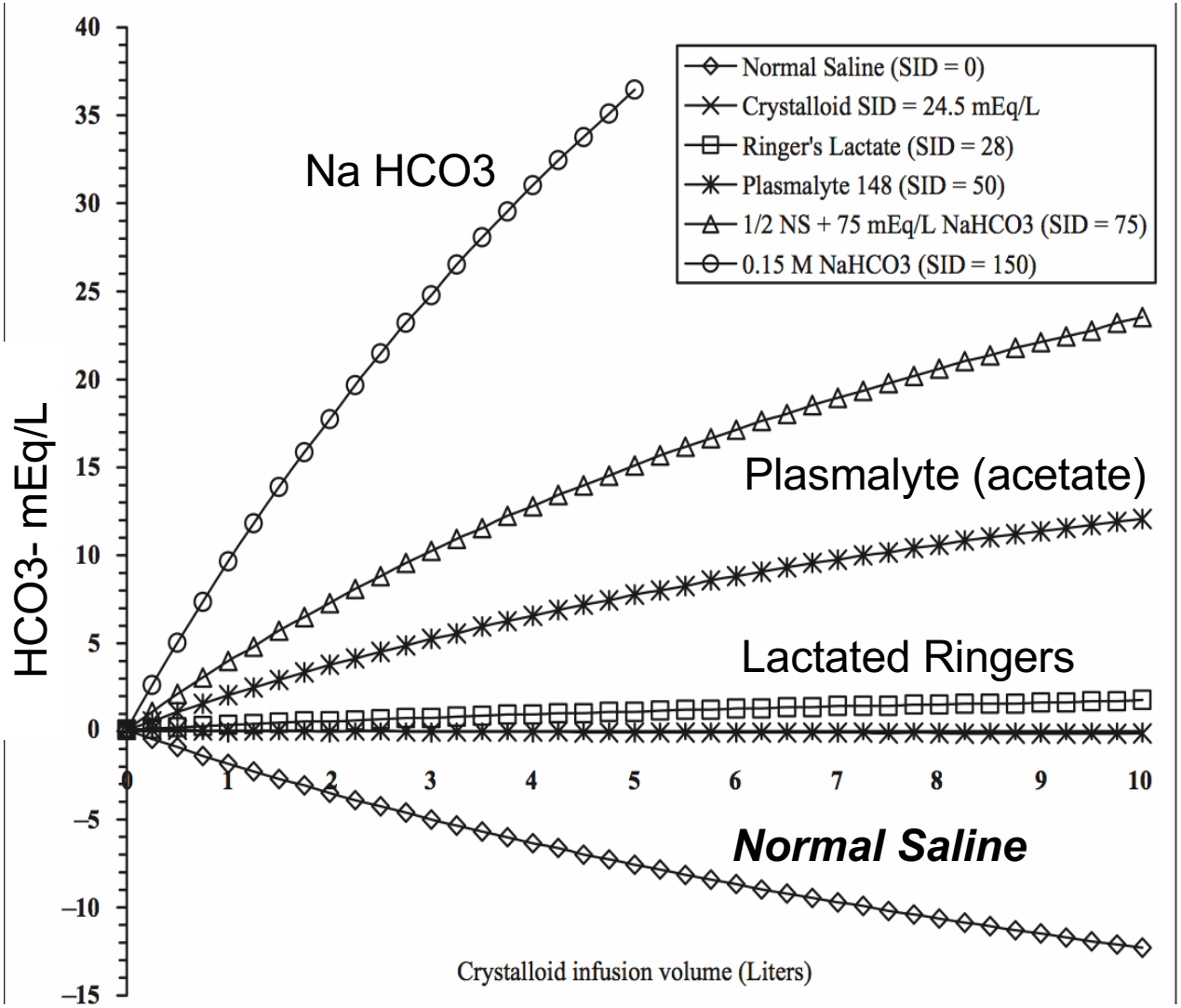
What's wrong with normal saline?

- Large volume resuscitation with 0.9% NaCl can:
  - Cause a hyperchloremic, metabolic acidosis
  - Induce renal arterial vasoconstriction
  - Worsen hypotension and possibly vasoplegia
  - Be associated with ***acute kidney injury***
  - And… increased risk of death
  - *JAMA* 2012. **308**: 1566

- What other IVF options do we have?

- "Balanced" salt solutions (i.e. mimic plasma)

Base / HCO3- Equivalents in Different IVFs



LR / PL-A v Normal Saline in Critically Ill Patients

- SMART trial, *NEJM* 2018, **378**: 829
- 15,802 patients admitted to the ICU
  - Randomized to:
  - NS versus LR (or plasma-Lyte A)

- Major adverse kidney event = new RRT or Cr 2X basline
  - Normal Saline 15.4%
  - LR or Plasma-lyte 14.3% p=0.04

- In hospital mortality
  - Normal Saline 11.1%
  - LR or Plasma-lyte 10.3% p=0.06

- No difference in need for renal replacement therapy or persistent renal dysfunction

Are Balanced Crystalloids Better?

*** *Do balanced crystalloids prevent acute kidney injury?* ***

What's NEW in 2021 - 2022?

Balanced Crystalloid v. Normal Saline in Critical Illness

- New Zealand Intensive Care Society
- *N Engl J Med* 2022, **386**: 815-26

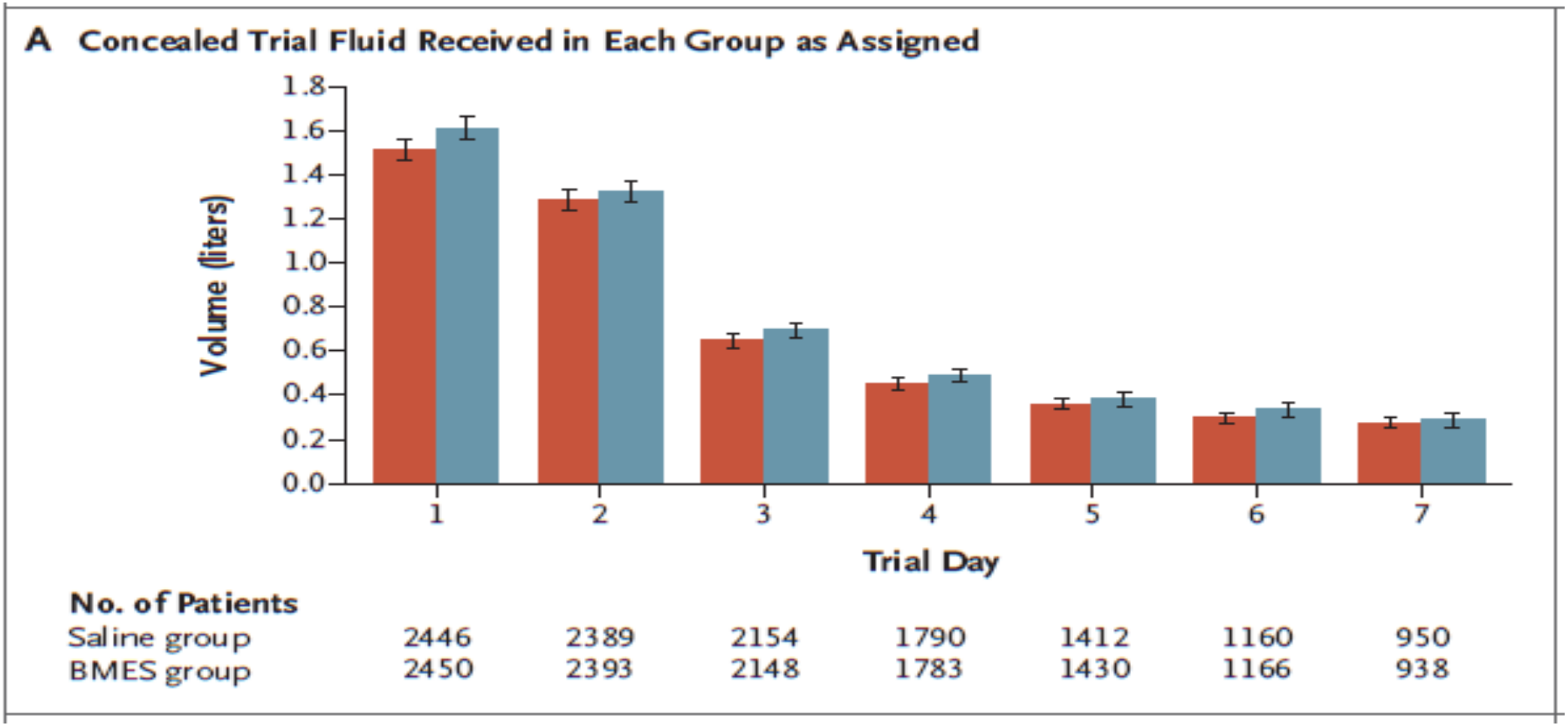
- 5,037 patients across 53 ICUs
  - Randomized to:
  - Normal Saline versus balanced crystalloid (Plasma-Lyte 148)
  - EXCLUDED patients with traumatic brain injury patients or at-risk for cerebral edema

- Outcome at 90 days:
  - Any cause MORTALITY
  - New renal replacement therapy and peak serum creatinine

Balanced Crystalloid v. Normal Saline in Critical Illness

- New Zealand Intensive Care Society
- *N Engl J Med* 2022, **386**: 815-26

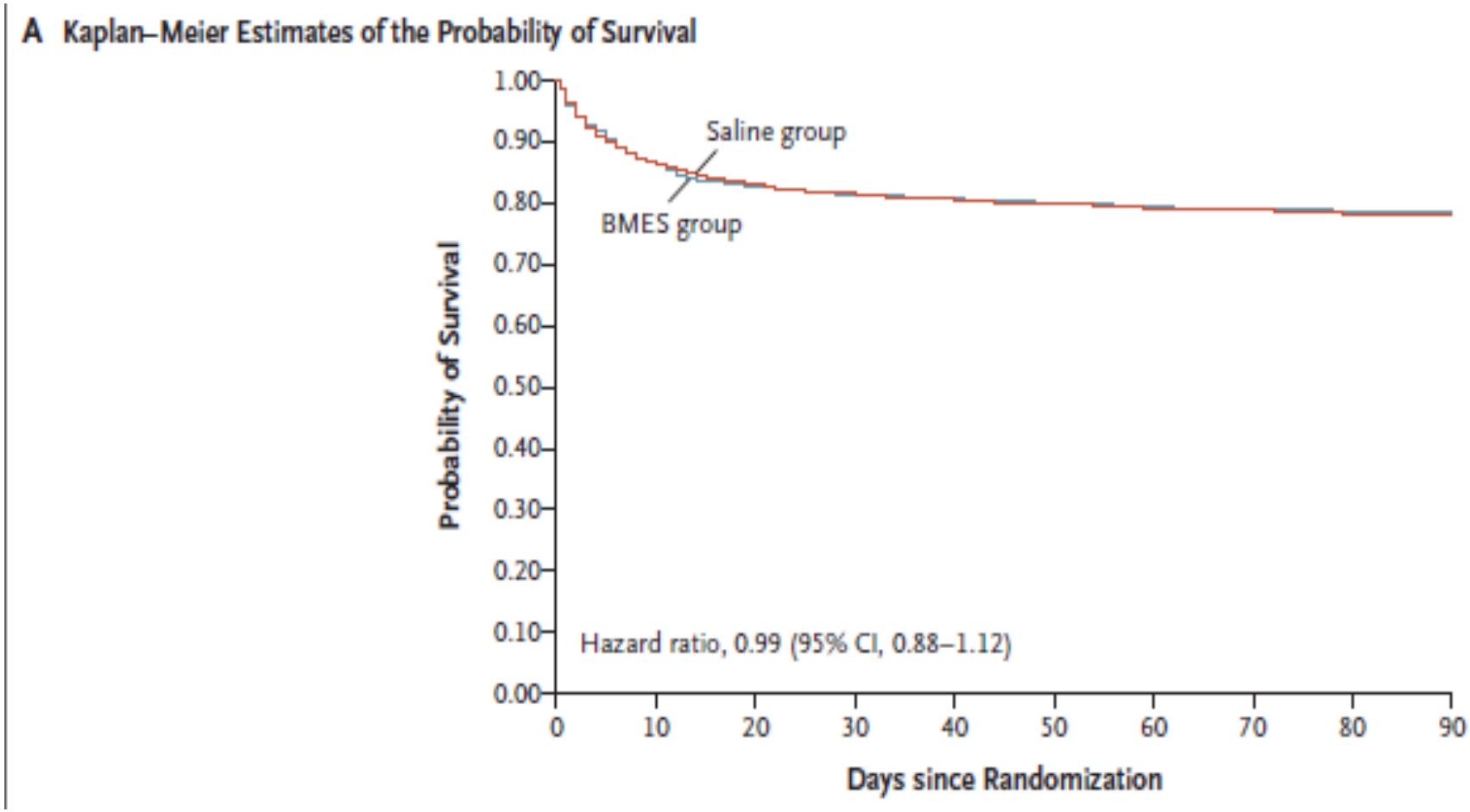
- Total IV Fluids



Balanced Crystalloid v. Normal Saline in Critical Illness

- New Zealand Intensive Care Society
- *N Engl J Med* 2022, **386**: 815-26

- 90 Day Mortality



Balanced Crystalloid v. Normal Saline in Critical Illness

- New Zealand Intensive Care Society
- *N Engl J Med* 2022, **386**: 815-26

- AKI and RENAL REPLACEMENT – no difference!

Table 2. Trial Outcomes.*

Outcome	BMES Group (N=2515)	Saline Group (N=2522)	Odds Ratio (95% CI)	Absolute Difference (95% CI)†
Other binary outcomes				
Receipt of new renal-replacement therapy — no./total no. (%)	306/2403 (12.7)	310/2394 (12.9)	0.98 (0.83 to 1.16)	−0.20 (−2.96 to 2.56)
Receipt of vasoactive drugs — no./total no. (%)	2115/2453 (86.2)	2133/2448 (87.1)	0.92 (0.78 to 1.09)	−0.85 (−4.06 to 2.36)
Continuous outcomes				
Maximum creatinine level in the ICU during days 1 to 7 — mg/dl	1.76±1.44	1.75±1.43		0.01 (−0.04 to 0.06)
Maximum increase in creatinine level in the ICU — mg/dl	0.41±1.06	0.41±1.02		0.01 (−0.05 to 0.06)

Balanced Crystalloid v. Normal Saline in Critical Illness

- New Zealand Intensive Care Society
- *N Engl J Med* 2022, **386**: 815-26

- *Overall, NEGATIVE trial for the use of Balanced Crystalloid in critically ill patients*

Balanced Crystalloid v. Normal Saline in Critical Illness

- BaSICS Trial
  - 75 ICUs in Brazil; 11,052 patients
  - RCT of saline v. balanced crystalloid
- *JAMA* 2021, **326**(9): 818-29

- Primary outcome at 90 days:
  - All-cause MORTALITY
  - Many secondary end-points, including renal failure

Balanced Crystalloid v. Normal Saline in Critical Illness

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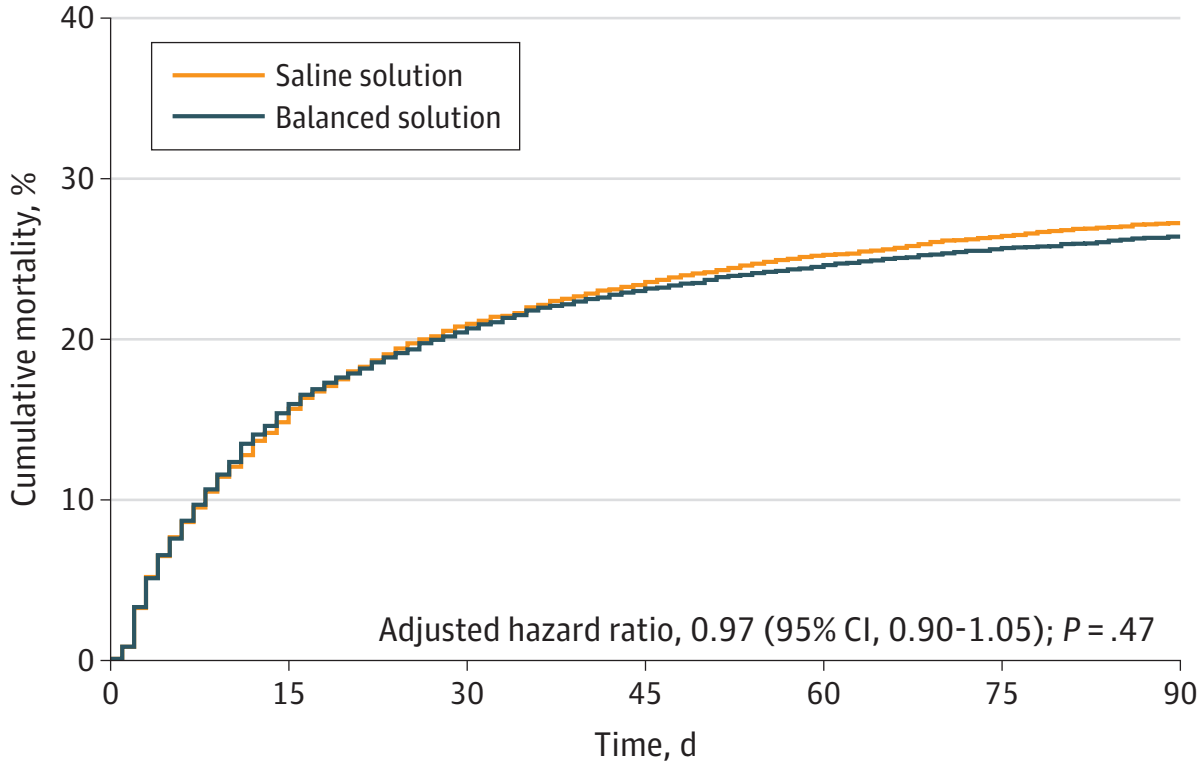
- *JAMA* 2021, **326**(9): 818-29



An Additional, NEW Meta-analysis of Balanced Crystalloids

Balanced Crystalloid v. Normal Saline in Critical Illness

- Hammond, NE *et al* *NEJM Evidence* 2022, **1**(2) [DOI: 10.1056/EVIDoa2100010]

- 13 RCTs of saline versus crystalloid (6 “low-bias” or higher quality)
- 35,884 patients

- Outcome at 90 days:

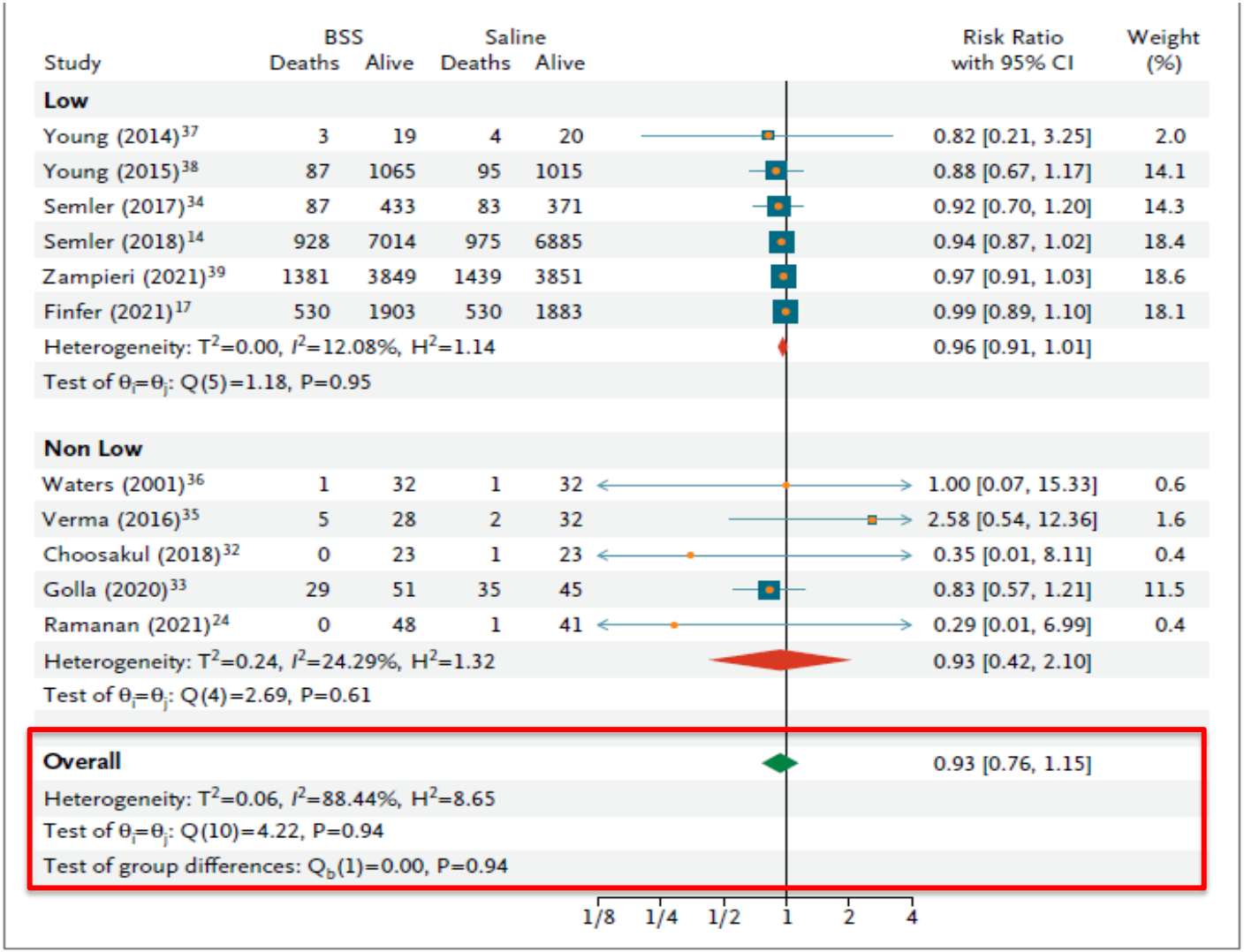
  – Any cause MORTALITY NOT clearly different
    - Statistical method-dependent SMALL effect on mortality (Bayesian v Frequentist)

  – No difference in renal replacement therapy or AKI

  Increased risk of DEATH in traumatic brain injury patients with balanced crystalloid (RR 1.26)

Balanced Crystalloid v. Normal Saline in Critical Illness

- Hammond, NE *et al* *NEJM Evidence* 2022, **1**(2) [DOI: 10.1056/EVIDoa2100010]

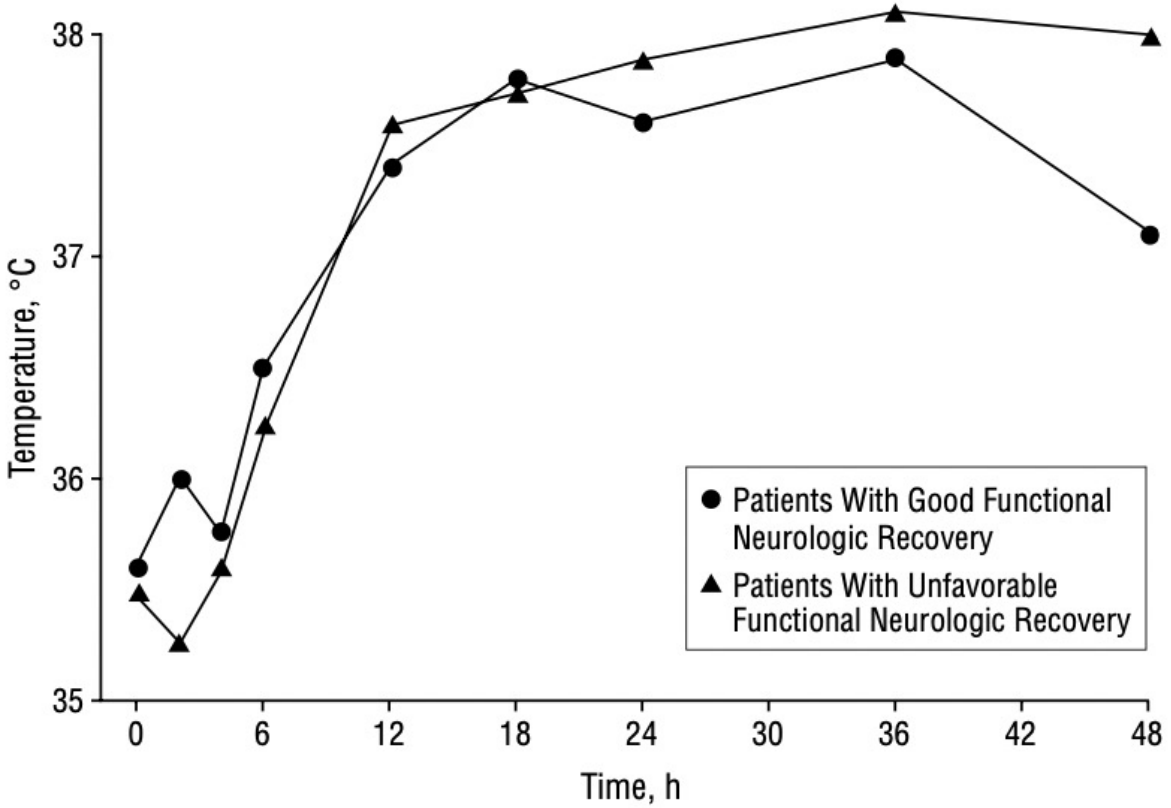


Effect of Balanced Crystalloids Compared with Saline on 90-Day Mortality in Critically Ill Patients by Risk of Bias.

Temperature Management after Return of Spontaneous Circulation

Snow Sculpture of Hippocrates
by Greek-American artists Melissa Vadakara and Marios Tzavellas. February 2021, New York City

Temperature Management after Return of Spontaneous Circulation



Each degree Celsius higher than 37°C showed an increased association with the risk of severe disability, coma, or a persistent vegetative state (CPC 3-4), with an odds ratio of 2.26.

Zeiner A, Holzer M, Sterz F, Schörkhuber W, Eisenburger P, Havel C, Kliegel A, Laggner AN. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med. 2001 Sep 10;161(16):2007-12.

Temperature Management after Return of Spontaneous Circulation

- 45 yo M with HTN who had witnessed arrest at home
  - Bystander CPR by pt's wife, followed by EMS
  - shockable rhythm
  - ROSC obtained after ~10 minutes
- Intubated by EMS for GCS 6
- Admitted to the ICU for post-ROSC care
- Manage temperature with:
  a. Cooling pads for target temp 31-32° C
  b. Cooling pads for target temp 33-34° C
  c. Cooling pads for target temp 35-36° C
  d. Cooling pads for target temp ≤ 38° C

Temperature Management after Return of Spontaneous Circulation: 2012

	32°C, No./Total No. (%)	34°C, No./Total No. (%)	*P*
Primary end point			
All patients	8/18 (44.4)	2/18 (11.1)	0.12
Initial rhythm asystole	0/5 (0)	0/5 (0)	0.24
Initial rhythm VF/VT	8/13 (61.5)	2/13 (15.4)	0.029
Death at 6 mo			
All patients	10/18 (55.6)	16/18 (88.9)	0.03
Initial rhythm asystole	5/5 (100)	5/5 (100)	
Initial rhythm VF/VT	5/13 (38.5)	11/13 (84.6)	
Best neurological status in 6 mo (all)*			0.08
CPC 1–2	9/18 (50)	4/18 (22.2)	
CPC 3–5	9/18 (50)	14/18 (77.8)	
Best neurological outcome in 6 mo (asystole)*			0.2
CPC 1–2	0/5 (0)	1/5 (20.0)	
CPC 3–5	5/5 (100)	4/5 (80.0)	
Best neurological outcome in 6 mo (VF/VT)*			0.02
CPC 1–2	9/13 (69.2)	3/13 (23.1)	
CPC 3–5	4/13 (30.8)	10/13 (76.9)	

Lopez-de-Sa, et al.
Hypothermia in comatose survivors from out-of-hospital cardiac arrest: pilot trial comparing 2 levels of target temperature.
Circulation. 2012 Dec 11;126(24):2826-33.

Temperature Management after Return of Spontaneous Circulation

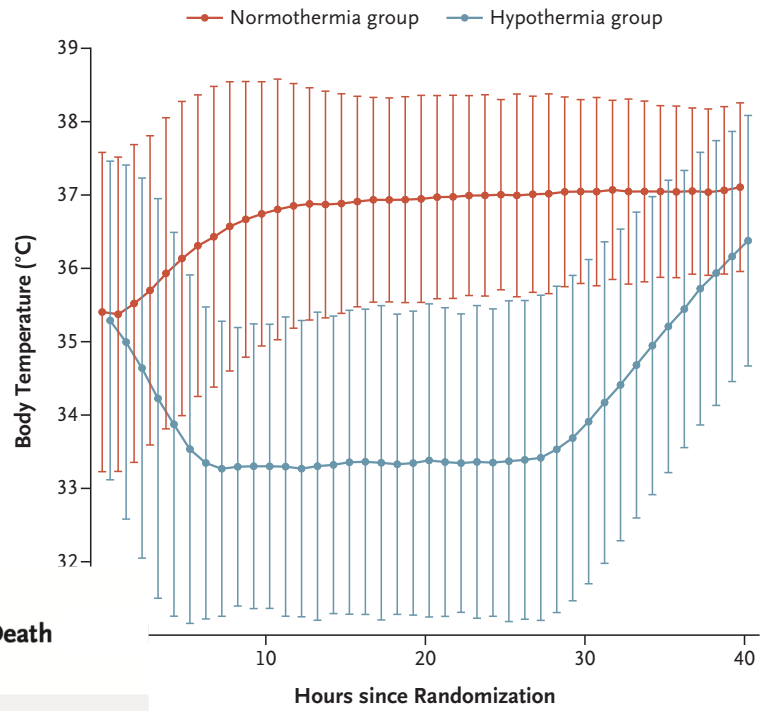
- TTM2 Trial Investigators (International)
- *N Engl J Med* 2021, **384**: 2283-94

- 1,850 patients
  - Adults with coma after out-of-hospital cardiac arrest of unknown or presumed cardiac etiology
  - Randomized to:
    - Targeted hypothermia at 33° C
    - Normothermia at ≥37.8° C

- Outcome at 6 months:
  1. Any cause MORTALITY
  2. Functional outcome by Rankin scale

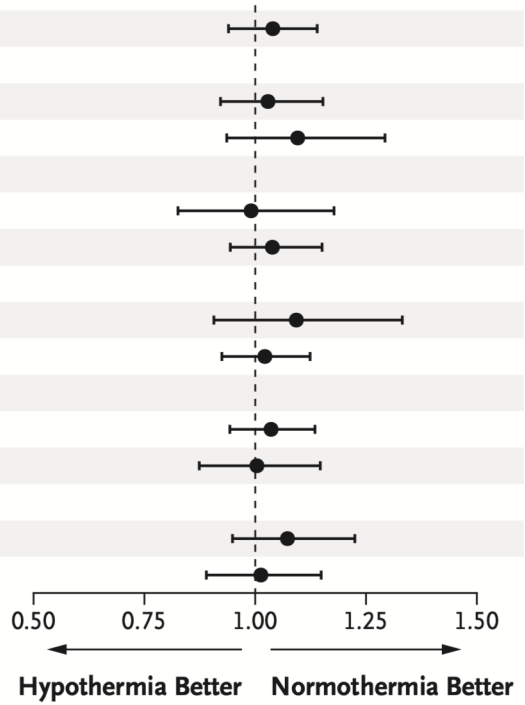
Temperature Management after ROSC

- TTM2 Trial Investigators
- *N Engl J Med* 2021, **384**: 2283-94



A **Death at 6 Months**

Subgroup	Hypothermia	Normothermia
	no. of patients	
All patients	925	925
Sex		
Male	738	729
Female	187	196
Age		
<65 yr	421	457
≥65 yr	504	468
Time to ROSC from cardiac arrest		
<25 min	419	416
≥25 min	506	509
Initial rhythm		
Nonshockable	259	231
Shockable	666	694
Shock on admission		
Not present	665	651
Present	260	274



The Rankin Score

symptoms but able to work

unable to work but able to live independently

dependent but able to ambulate

unable to ambulate without assistance and/or unable to perform bodily self-care

needing continuous care

Saver et al. Standardized Nomenclature for Modified Rankin Scale Global Disability Outcomes: Consensus Recommendations From Stroke Therapy Academic Industry Roundtable XI. *Stroke* 52(9): 3054-3062

Temperature Management after ROSC

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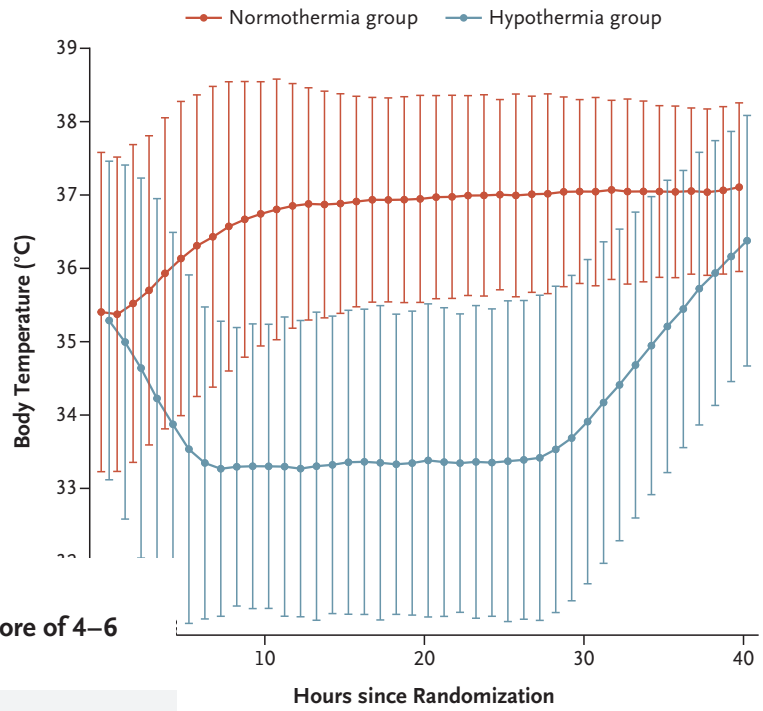
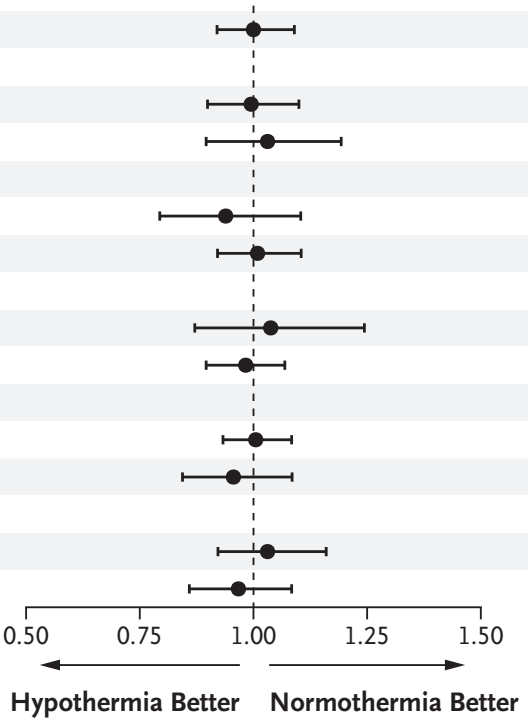


B **Modified Rankin Scale Score of 4–6 at 6 Months**

Subgroup	Hypothermia	Normothermia
	no. of patients	
All patients	881	866
Sex		
Male	701	679
Female	180	187
Age		
<65 yr	391	429
≥65 yr	490	437
Time to ROSC from cardiac arrest		
<25 min	395	389
≥25 min	486	477
Initial rhythm		
Nonshockable	252	218
Shockable	629	648
Shock on admission		
Not present	629	606
Present	252	260



Temperature Management after Return of Spontaneous Circulation

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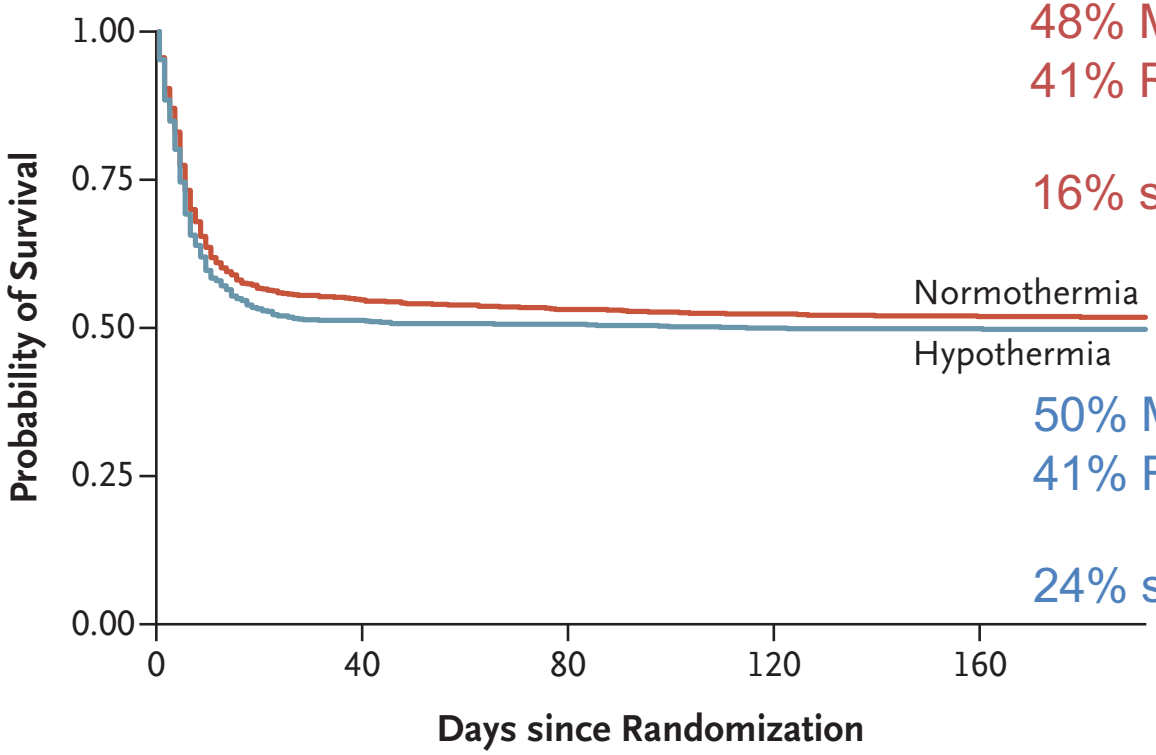

48% Mortality
41% Rankin score ≤2

16% significant arrythmia

50% Mortality
41% Rankin score ≤2

24% significant arrythmia

No. at Risk

Normothermia	925	506	491	484	480
Hypothermia	925	474	468	462	461

Temperature Management after Return of Spontaneous Circulation

- CAPTIAL CHILL Trial (Ottowa, Canada)
- *JAMA*. 2021;326(15):1494-1503

- 367 patients
  - Single center study
  - Adults with coma (GCS ≤8) after out-of-hospital cardiac arrest
  - Randomized to:
    - Targeted hypothermia at 31° C
    - Normothermia at 34° C
  - DOUBLE-BLINDED
  - Withdrawal of care at the discretion of the multidisciplinary team

- Outcome at ~ 6 months:
  1. Any cause MORTALITY –or– poor functional outcome by DRS
  2. 19 secondary outcomes

Temperature Management after Return of Spontaneous Circulation

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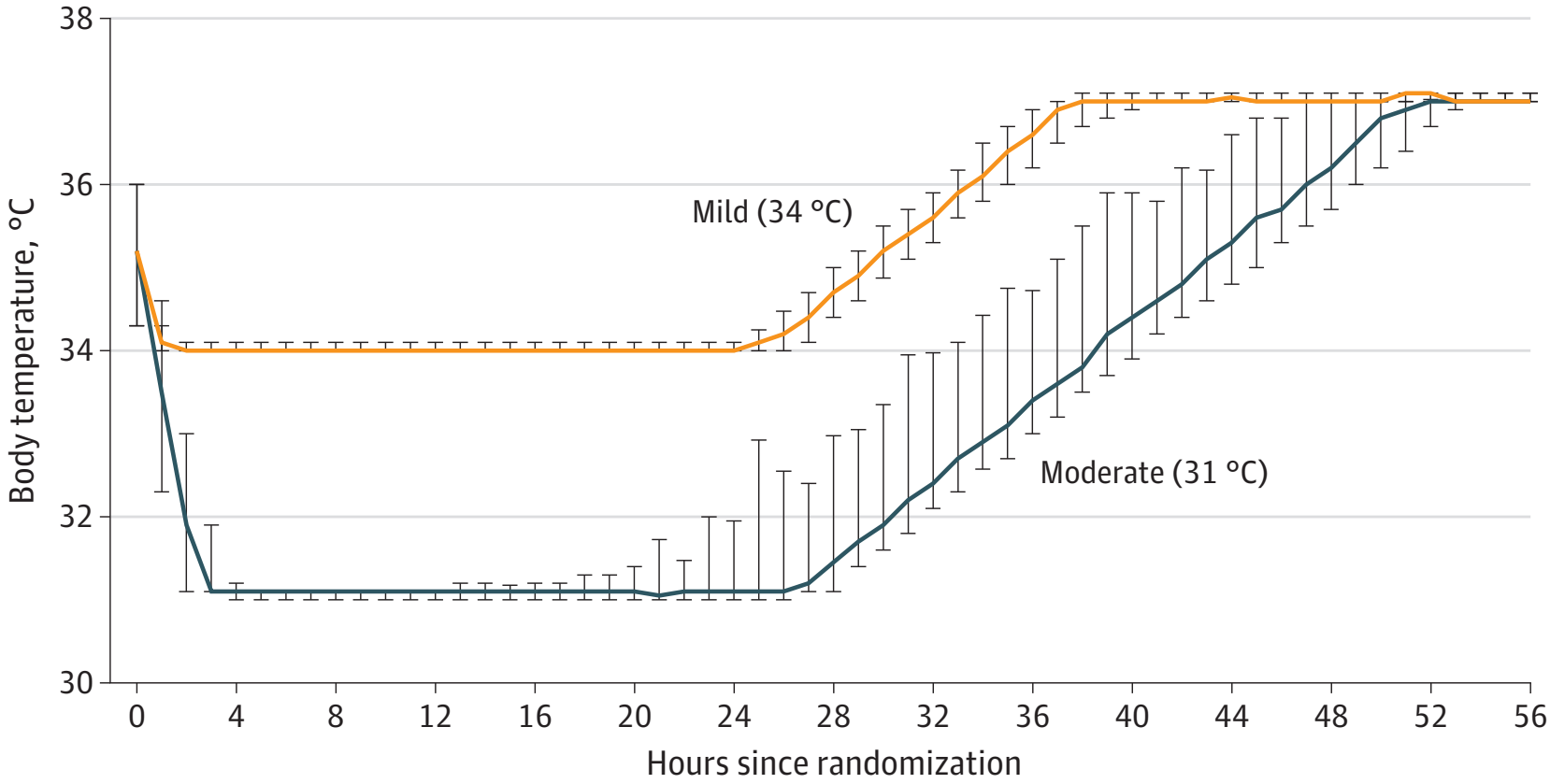

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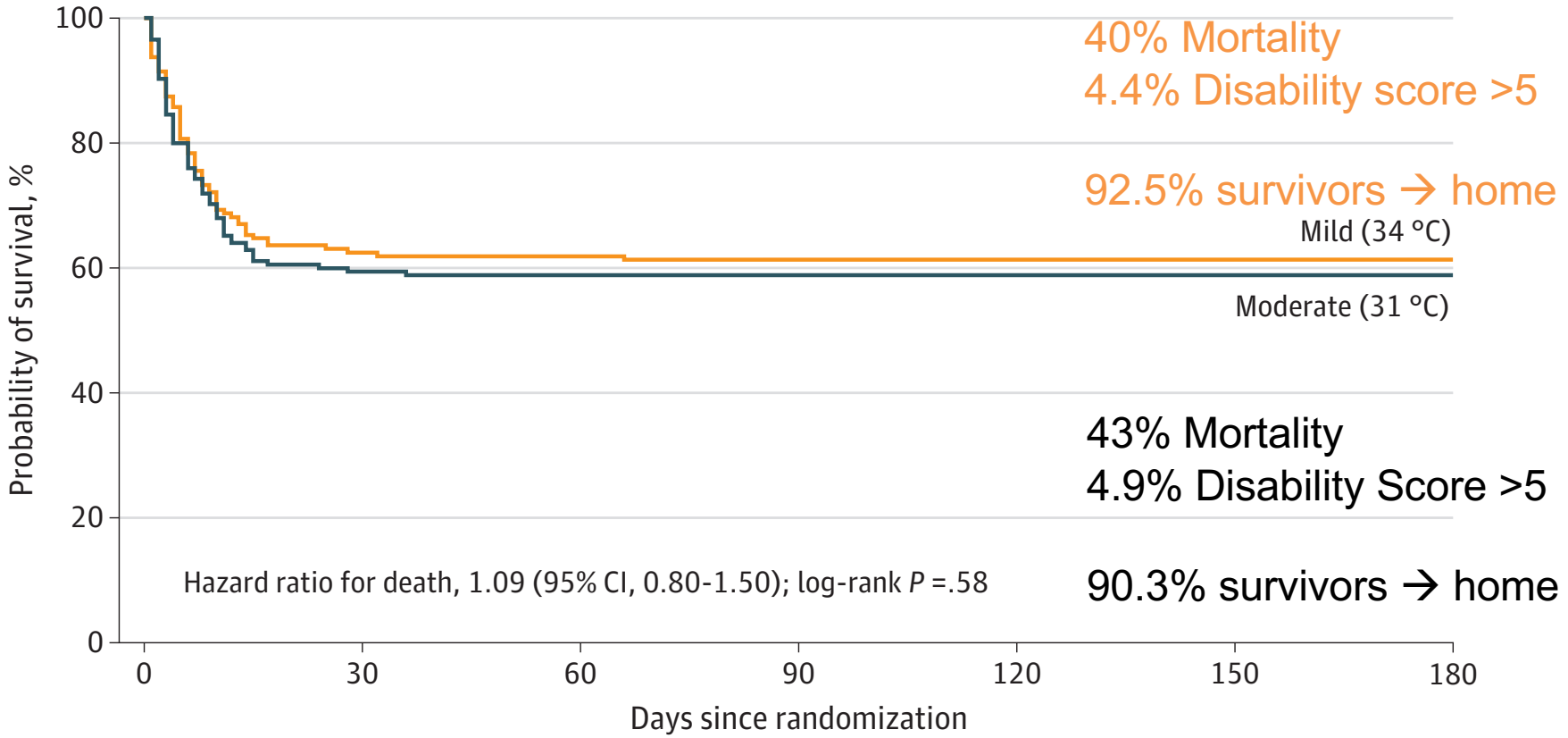

The Disability Rating Scale

DRS Total Score	Disability Category Description
1	Mild disability
2-3	Partial disability
4-6	Moderate
7-11	Moderately severe
12-16	Severe
≥ 22	Vegetative state

Outcomes	Moderate hypothermia (31 °C) (n = 184)	Mild hypothermia (34 °C) (n = 183)	Difference, % (95% CI)	Relative risk (95% CI)	*P* value
Primary outcome					
Death or poor neurologic outcome (DRS score >5) at 180 d[b]	89 (48.4)	83 (45.4)	3.0 (−7.2 to 13.2)	1.07 (0.86-1.33)	.56
Secondary outcomes					
Death during initial hospitalization	80 (43.5)	74 (40.4)	3.0 (−7.1 to 13.1)	1.08 (0.85-1.37)	.56
Death at 30 d	79 (42.9)	73 (39.9)	3.0 (−7.0 to 13.1)	1.08 (0.84-1.37)	.55
Death at 180 d	80 (43.5)	75 (41.0)	2.5 (−7.6 to 12.6)	1.06 (0.83-1.35)	.63
Stroke during initial hospitalization	8 (4.4)	3 (1.6)	2.7 (−0.8 to 6.2)	2.65 (0.71-9.84)	.22
Stroke at 180 d	8 (4.4)	3 (1.6)	2.7 (−0.8 to 6.2)	2.65 (0.71-9.84)	.22
Stent thrombosis	2 (1.1)	4 (2.2)	−1.1 (−3.7 to 1.5)	0.50 (0.09-2.68)	.45
Seizures	23 (12.5)	13 (7.1)	5.4 (−0.7 to 11.5)	1.76 (0.92-3.37)	.08
Kidney replacement therapy	17 (9.2)	17 (9.3)	0.1 (−6.0 to 5.9)	0.99 (0.52-1.89)	.99
Pneumonia	124 (67.4)	116 (63.4)	4.0 (−5.7 to 13.7)	1.06 (0.92-1.23)	.42
Cardiogenic shock	71 (38.6)	61 (33.3)	5.3 (−4.6 to 15.1)	1.16 (0.88-1.52)	.29
Need for anti-arrhythmic therapy[c]	56 (30.4)	66 (36.1)	−5.6 (−15.3 to 4.0)	0.84 (0.63-1.13)	.25
Recurrent cardiac arrest requiring CPR	20 (10.9)	17 (9.3)	1.6 (−4.6 to 7.7)	1.17 (0.63-2.16)	.62
TIMI non-CABG major bleeding within 7 d[d]	43 (23.4)	36 (19.7)	3.7 (−4.7 to 12.1)	1.19 (0.80-1.76)	.39
Blood transfusion	36 (19.6)	41 (22.4)	−2.8 (−11.2 to 5.5)	0.87 (0.59-1.30)	.50
Survivors discharged to home from hospital[e]	93/103 (90.3)	99/107 (92.5)	2.2 (−9.8 to 5.4)	0.98 (0.90-1.06)	.56
Peak creatine kinase, mean (SD), IU/L[f]	3400 (4039)	2882 (3679)	518 (−277 to 1312)		.20
LVEF at 3 d, mean (SD), %	41.6 (13.8)	41.8 (15.1)	−0.2 (−3.3 to 2.9)		.89
LVEF at 3 mo, mean (SD), %[g]	46.2 (12.1)	50.7 (13.3)	−4.5 (−11.0 to 2.0)		.17
Length of stay in unit, median, (IQR), d	10 (7-15)	7 (6-12)	1.4 (−1.2 to 4.1)[h]		.004
Length of hospital stay, median (IQR), d[i]	22 (16-30)	20 (13-36)	−0.4 (−5.1 to 4.3)[h]		.27
Adverse events					
Deep vein thrombosis	21 (11.4)	20 (10.9)	0.5 (−6.0 to 6.9)	1.04 (0.59-1.86)	.88
Inferior vena cava thrombus	7 (3.8)	14 (7.7)	−3.9 (−8.6 to 0.9)	0.50 (0.21-1.20)	.11

IV Fluid Resuscitation *Volume* in Sepsis

Sepsis patients receive how much volume from:

IVF RESUSCITATION? 4 - 6 L / 5 days

TOTAL FLUIDS (IV meds, enteral, etc)? 10 – 15 L / 7 days

Lower versus Higher IV Fluid Volumes in Sepsis

- 2011, early observations: Vasopressin in Septic Shock Trial (VASST) patient analysis

- *Crit Care Med* 2011, **39**: 259-65
- 778 septic patients
  - Retrospective analysis of net fluid balance and 28D mortality
  - Analysis corrected for age and APACHE II score

Table 1. Fluid intake, urine output, and net fluid balance at 12 hrs and cumulative day 4 balance

	Quartile 1 (Dry)	Quartile 2	Quartile 3	Quartile 4 (Wet)
12 hrs				
Intake, mL	2900 (2050–3900)	4520 (3700–5450)	6110 (5330–7360)	10,100 (8430–12,100)
Output, mL	2200 (1100–3920)	1590 (960–2560)	1180 (600–2070)	1260 (600–2400)
Balance, mL	710 (−132–1480)	2880 (2510–3300)	4900 (4290–5530)	8150 (7110–10,100)
Day 4				
Intake, mL	16,100 (12,800–19700)	18,500 (15,700–22,500)	22,800 (19,700–26,700)	30,600 (26,200–36,000)
Output, mL	14,600 (11,500–20100)	11,000 (8210–14,500)	9960 (6940–12,900)	8350 (5100–12,300)
Balance, mL	1560 (−723–3210)	8120 (6210–9090)	13,000 (11,800–14,700)	20,500 (17,700–24,500)
	0.71L and 1.5L	2.8L and 8.1L	4.9L and 13L	8.1L and 20L

Lower versus Higher IV Fluid Volumes in Sepsis

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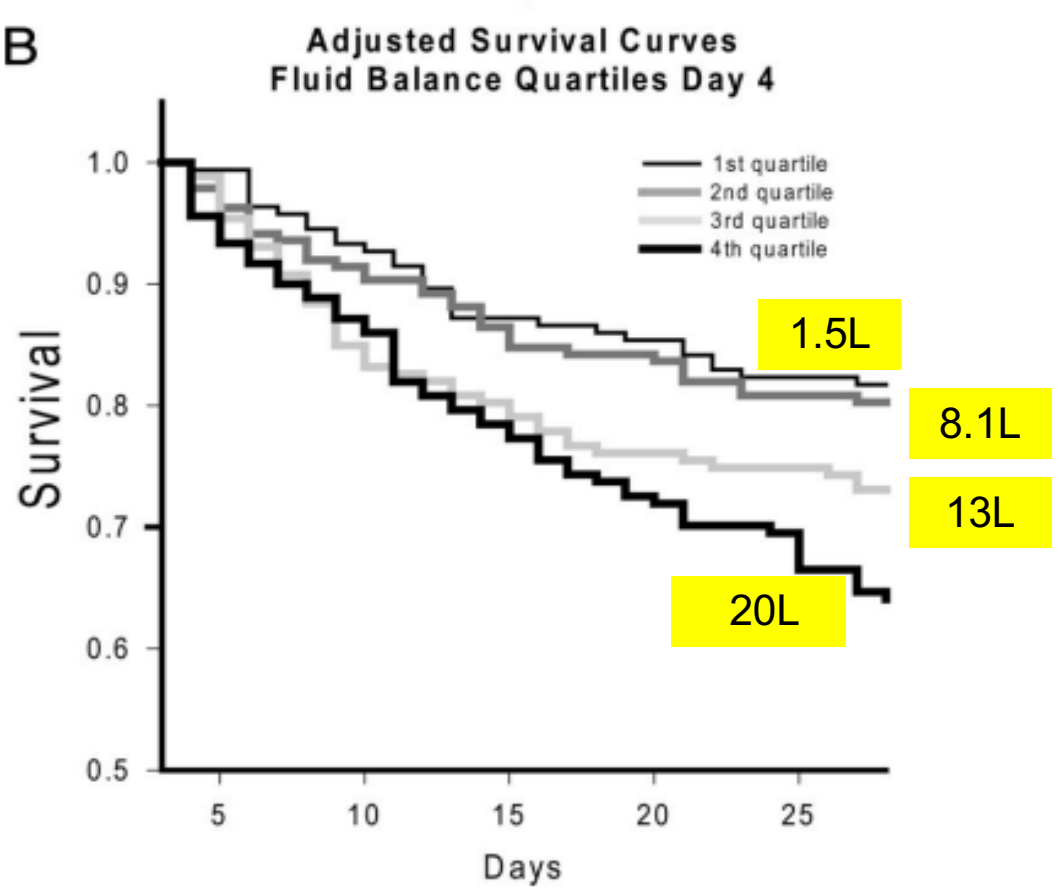

Lower versus Higher IV Fluid Volumes in Sepsis

- 2016, Conservative v Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC): feasibility trial
- *Intensive Care Med* 2016, **42**: 1695-1705
- 151 septic patients
  - After initial resuscitation (30 ml/Kg IVF) and with persistent shock, patients enrolled to conservative fluid management v usual care
  - IVF boluses of 250 – 500cc were only permitted in the conservative arm if there were ongoing markers of hypo-perfusion
    - *Lactate >4 mmol/L; MAP < 50 mmHg; Mottling above the knees; oliguria (UOP < 0.1 ml/Kg)*

Lower versus Higher IV Fluid Volumes in Sepsis

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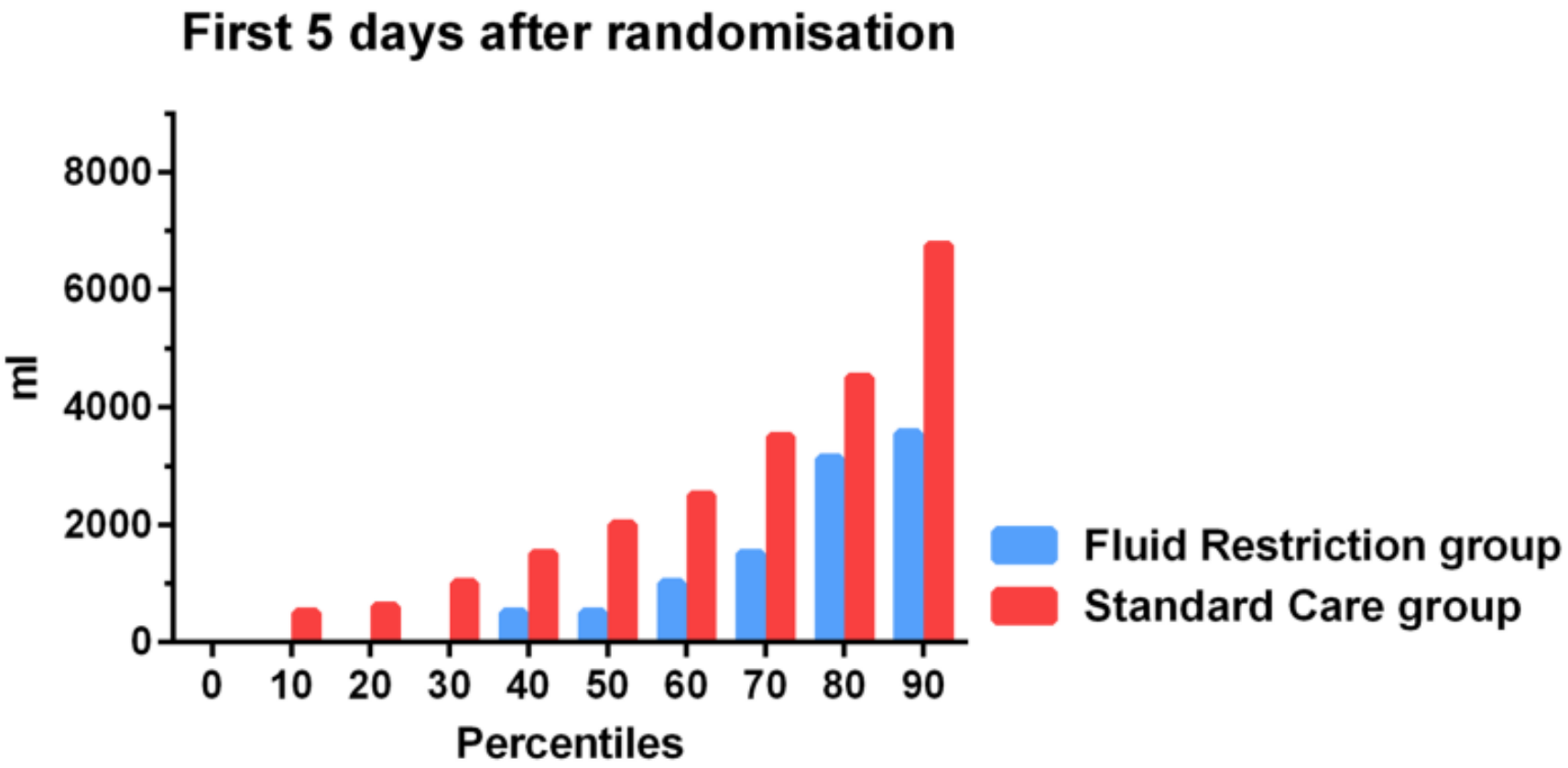
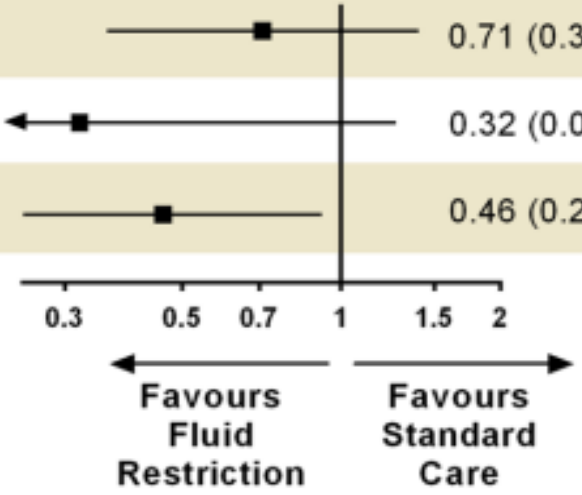


Lower versus Higher IV Fluid Volumes in Sepsis

- 2016, Conservative v Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC): feasibility trial
- *Intensive Care Med* 2016, **42**: 1695-1705

a **Odds ratios of exploratory outcomes**

	Fluid Restriction	Standard Care	Odds ratio (95% CI)	P value
	No. of events / No. at risk			
Death by day 90	25/75 (33%)	31/76 (41%)	0.71 (0.36-1.40)	0.32
Ischemic events in the ICU	3/75 (4%)	9/76 (12%)	0.32 (0.08-1.27)	0.11
Worsening of AKI	27/73 (37%)	39/72 (54%)	0.46 (0.23-0.92)	0.03



Restriction of IV Fluids in Septic Shock: 2022

- Conservative v Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC): full RCT 2022
- *N Engl J Med* 2022, **386**: 2459-70
- 1554 septic patients; 31 ICUs in Europe
  - After initial resuscitation (30 ml/Kg IVF) and with persistent shock, patients enrolled to conservative fluid management v usual care

Restriction of IV Fluids in Septic Shock: 2022

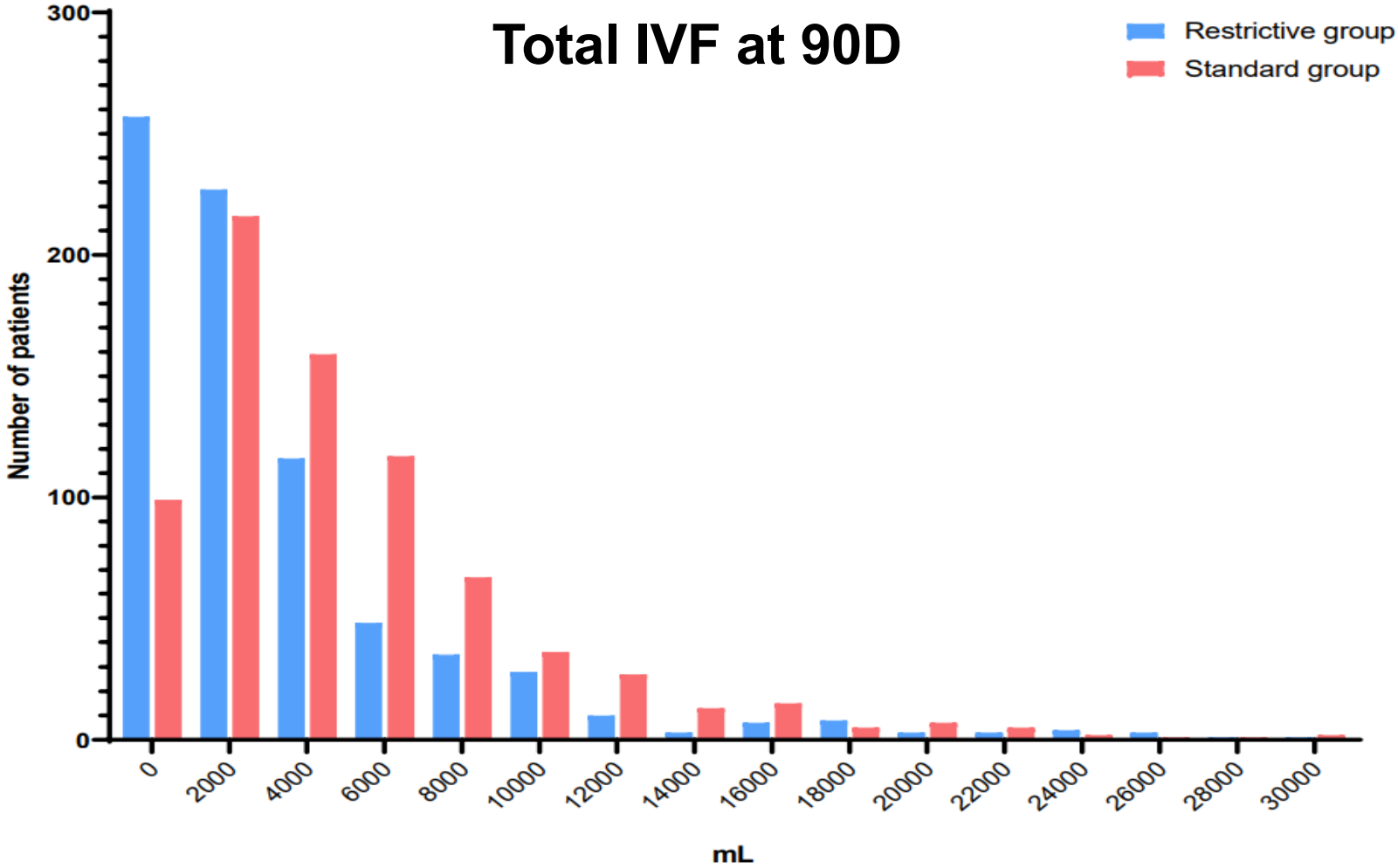
- Conservative v Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC): full RCT 2022

- Patients in the conservative arm could receive an IVF bolus of 250 – 500cc with one of the following:

- ***Severe hypoperfusion or severe circulatory impairment defined by either:***
  - Lactate > 4 mmol/l
  - Mean arterial blood pressure < 50 mmHg
  - Mottling beyond the kneecap
  - Urinary output less 0.1ml/kg bodyweight/h
- ***Overt fluid losses*** (e.g. vomiting, diarrhea, drain losses, bleeding
- ***If the enteral route for water or electrolyte solutions is contraindicated***
- ***Correct dehydration or electrolyte imbalances***
- ***Ensure a total fluid input of 1L / 24 hours***

Restriction of IV Fluids in Septic Shock: 2022

- Conservative v Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC): full RCT 2022
- IV Fluid Volumes



Restriction of IV Fluids in Septic Shock: 2022

Table 2. Cumulative Fluid Volumes and Balances in ICU in the Two Intervention Groups.*

Variable	Restrictive-Fluid Group (N=755)	Standard-Fluid Group (N=776)	Difference (Restrictive vs. Standard)
		milliliters	
Intravenous fluid volume†			
After 1 day‡			
Median (IQR)	500 (0 to 1400)	1,313 (500 to 2500)	−813
Mean	1,024	1,724	−700
After 5 days			
Median (IQR)	1,450 (445 to 3200)	3,077 (1535 to 5300)	−1627
Mean	2,327	3,836	−1509
Total fluid volume§			
After 1 day‡			
Median (IQR)	1,843 (964 to 3150)	2,708 (1403 to 4267)	−865
Mean	2,315	3,070	−755
After 5 days			
Median (IQR)	8,864 (4865 to 13,488)	10,800 (6178 to 15,459)	−1936
Mean	9,630	11,181	−1551

Restriction of IV Fluids in Septic Shock: 2022

Table 2. Cumulative Fluid Volumes and Balances in ICU in the Two Intervention Groups.*

Variable	Restrictive-Fluid Group (N=755)	Standard-Fluid Group (N=776)	Difference (Restrictive vs. Standard)
		milliliters	
Cumulative fluid balance¶			
After 1 day‡			
Median (IQR)	725 (0 to 1837)	1,342 (308 to 2759)	−617
Mean	1,100	1,689	−589
After 5 days			
Median (IQR)	1,676 (−137 to 4117)	2,420 (759 to 4996)	−744
Mean	2,297	3,187	−890

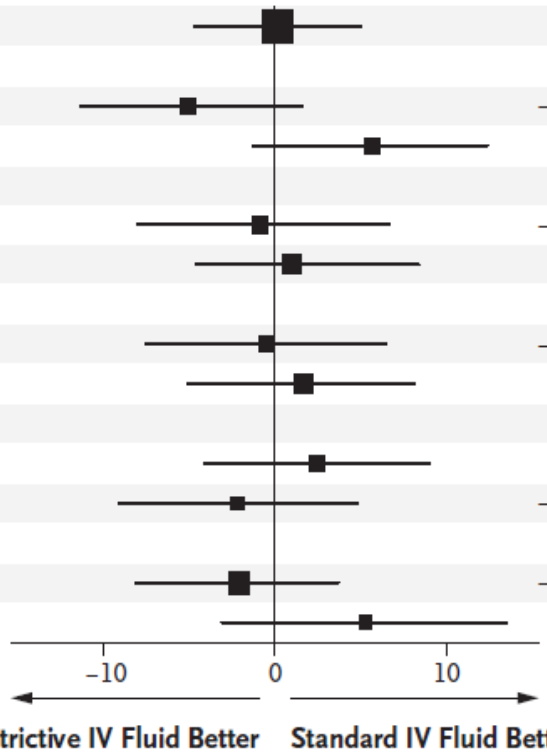
Restriction of IV Fluids in Septic Shock: 2022

- Conservative v Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC): full RCT 2022

- No difference in 90 D mortality
- No difference in AKI, ischemia (limb, intestinal, cardiac)

B Death at 90 Days

Subgroup	Restrictive-Fluid Group *no. of events/no. of patients*	Standard-Fluid Group *no. of events/no. of patients*	Absolute Percentage Point Difference (95% CI)	P Value for Heterogeneity
All patients	323/764	329/781	0.1 (–4.7 to 4.9)	
Respiratory support				0.03
Yes	184/396	196/377	–5.1 (–11.3 to 1.6)	
No	138/385	132/399	5.7 (–1.4 to 12.4)	
Acute kidney injury				0.57
Yes	146/309	169/360	–0.8 (–8.0 to 6.7)	
No	174/439	158/411	2.0 (–4.6 to 8.4)	
Plasma lactate				0.65
>4.0 mmol/liter	164/337	180/366	–0.5 (–7.5 to 6.5)	
≤4.0 mmol/liter	158/416	148/409	1.7 (–5.1 to 8.1)	
Body weight				0.34
≥76 kg	164/401	163/425	2.5 (–4.1 to 9.0)	
<76 kg	158/352	165/350	–2.2 (–9.1 to 4.8)	
IV fluid volume at randomization				0.15
≥30 ml/kg body weight	208/493	230/515	–2.1 (–8.1 to 3.7)	
<30 ml/kg body weight	114/260	98/260	5.3 (–3.1 to 13.5)	



Summary Points

- Balanced electrolyte solutions not clearly superior to normal saline for IVF resuscitation in critically ill patients
  - Unclear role in special clinical circumstances, such as diabetic ketoacidosis

- After return of spontaneous circulation, mortality rates are high and functional outcomes for survivors are high.
  - Target temperature less than 38° C does not change outcomes

- In the context of generally lower IVF volume resuscitation for septic shock, 4 – 6L over 5 days, further IVF volume restriction does not improve mortality

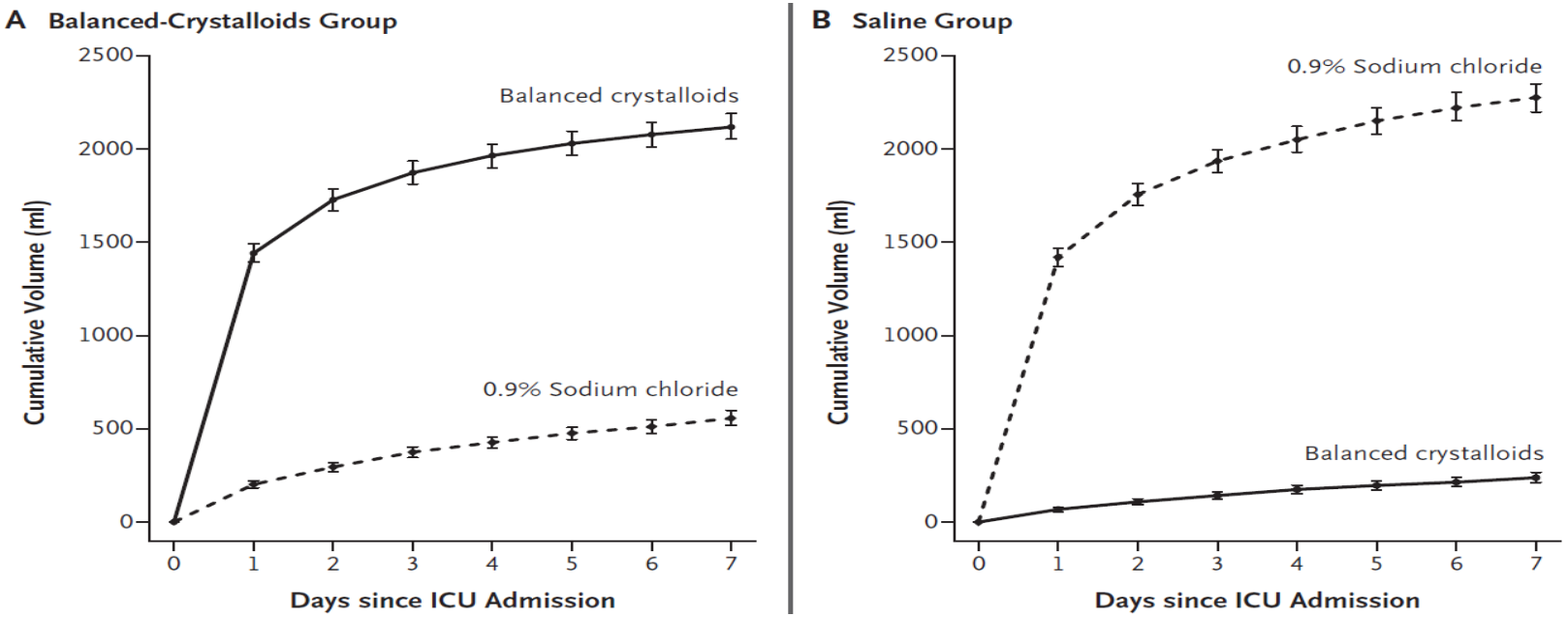
Additional Slides

LR / PL-A v Normal Saline in Critically Ill Patients

- SMART trial, *NEJM* 2018, **378**: 829
- 15,802 patients admitted to the ICU
  - Randomized to:
  - NS versus LR (or plasma-Lyte A)

- Outcome at 30 days (composite):
  - Major Kidney Event = new renal replacement therapy or creatinine 2X baseline
  - Death from any cause

IVF Volume



LR / PL-A v Normal Saline in Critically Ill Patients

- SMART trial, *NEJM* 2018, **378**: 829

- Results…
- ***Major adverse kidney event***
  - ***Normal Saline*** ***15.4%***
  - ***LR or Plasma-lyte*** ***14.3%*** ***p=0.04***

- In hospital mortality
  - Normal Saline 11.1%
  - LR or Plasma-lyte 10.3% p=0.06
- No difference in need for renal replacement therapy or persistent renal dysfunction

Similar results in NON-critically ill patients (accompanying study in NEJM)

*** *Do balanced crystalloids prevent acute kidney injury?* ***

Lactated Ringers and "Plasma-lyte"

- Lactated Ringers (mmol):
  - Na+ 130
  - Cl- 109
  - Lactate (Na+) 28
  - K+ 4
  - Ca++ 1.5
  - Osmolality 273
  - pH 6.9

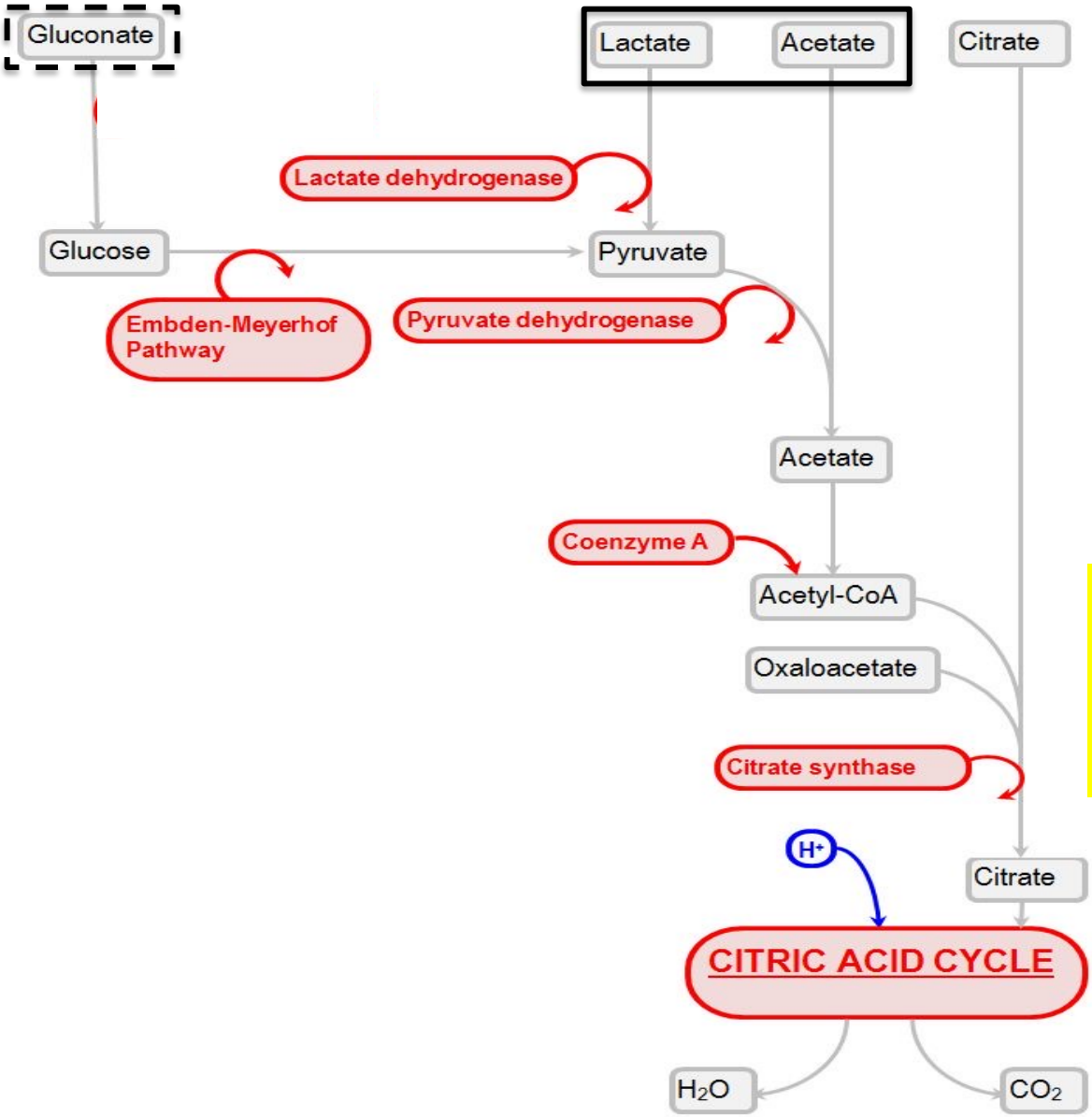
- Plasma-lyte A (mmol):
  - Na+ 140
  - Cl- 98
  - Acetate 27
  - Gluconate 23
  - K+ 5
  - Mg++ 1.5
  - Osmolality 290
  - pH 7.4

Plasma osmolality: ~285 – 300

LR slightly hypotonic: concerns in brain injury / edema

Hyperkalemia a relative contraindication to LR/PL-A

How do Lactate and Acetate -> HCO3- ?



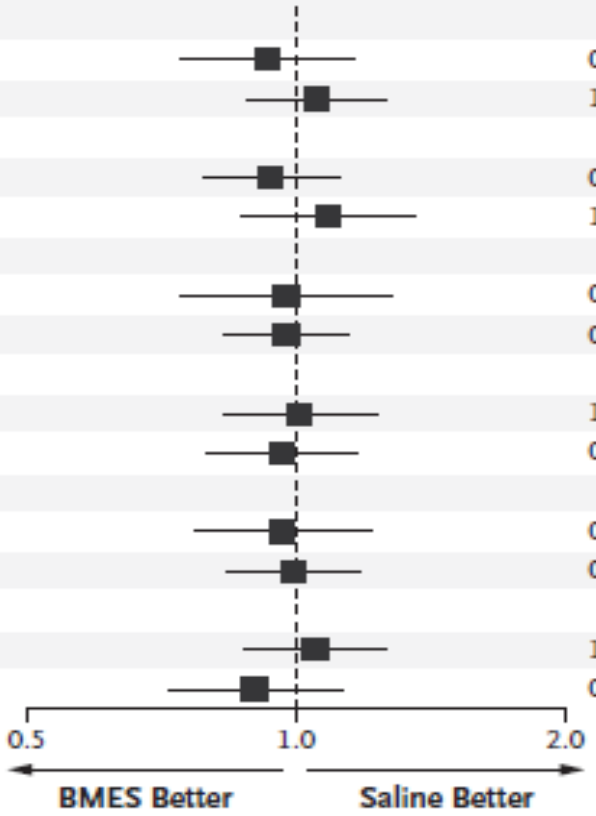
The Citric Acid Cycle consumes H+ 1:1, effectively generating HCO3-

Balanced Crystalloid v. Normal Saline in Critical Illness

- New Zealand Intensive Care Society
- *N Engl J Med* 2022, **386**: 815-26

- 90 Day Mortality

Subgroup	BMES Group	Saline Group	Odds Ratio (95% CI)
	no. of events/total no. (%)		
Age			
<65 yr	184/1250 (14.7)	188/1207 (15.6)	0.93 (0.74–1.16)
≥65 yr	346/1183 (29.2)	342/1206 (28.4)	1.06 (0.88–1.26)
Sex			
Male	328/1531 (21.4)	323/1437 (22.5)	0.94 (0.79–1.12)
Female	202/902 (22.4)	207/976 (21.2)	1.09 (0.87–1.35)
Kidney injury			
Yes	160/468 (34.2)	155/451 (34.4)	0.98 (0.74–1.29)
No	361/1934 (18.7)	370/1931 (19.2)	0.97 (0.83–1.15)
Sepsis			
Yes	276/1068 (25.8)	265/1026 (25.8)	1.01 (0.83–1.23)
No	254/1362 (18.6)	265/1386 (19.1)	0.97 (0.80–1.17)
Admitted from surgery			
Yes	171/1087 (15.7)	179/1109 (16.1)	0.97 (0.77–1.22)
No	359/1344 (26.7)	351/1304 (26.9)	0.99 (0.84–1.18)
APACHE II score			
<25	287/1753 (16.4)	275/1739 (15.8)	1.05 (0.88–1.26)
≥25	243/678 (35.8)	255/673 (37.9)	0.90 (0.72–1.12)

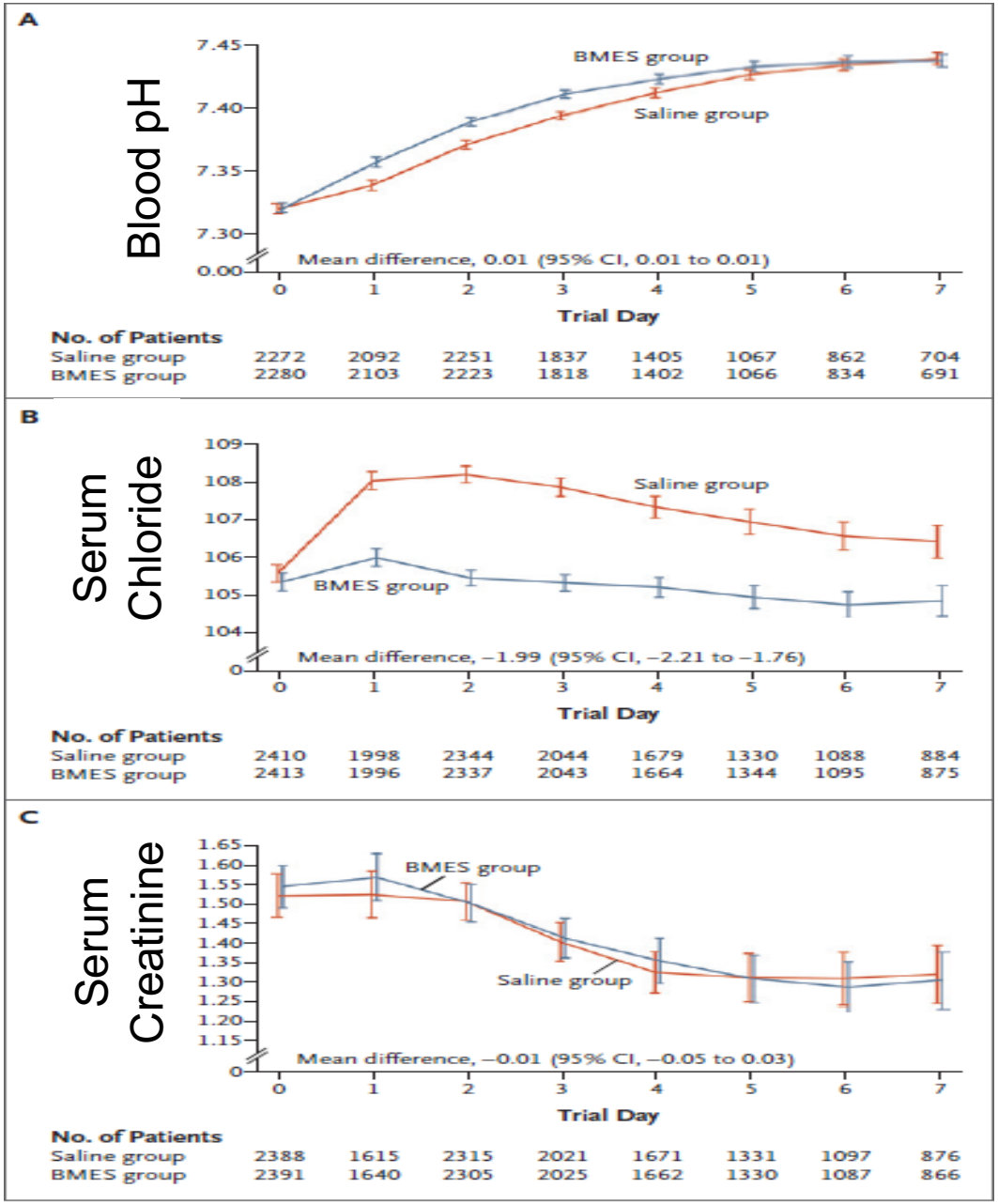


Balanced Crystalloid v. Normal Saline in Critical Illness

- New Zealand Intensive Care Society
- *N Engl J Med* 2022, **386**: 815-26

- Serum Chemistries

- Expected impacts of balanced crystalloids versus saline on blood pH and serum chloride



Temperature Management after Return of Spontaneous Circulation

TTM2 Trial Investigators
N Engl J Med 2021, **384**: 2283-94

Table 1. Baseline Characteristics of the Intention-to-Treat Population.*

Characteristic	Hypothermia (N=930)	Normothermia (N=931)
Demographic characteristics		
Age — yr	64±13	63±14
Male sex — no. (%)	742 (80)	735 (79)
Medical history		
Hypertension — no. (%)	345 (37)	298 (32)
Diabetes — no. (%)	173 (19)	167 (18)
Myocardial infarction — no. (%)	139 (15)	154 (17)
PCI — no. (%)	130 (14)	140 (15)
Coronary-artery bypass grafting — no. (%)	73 (8)	76 (8)
Heart failure — no. (%)	90 (10)	93 (10)
NYHA III or IV heart failure — no./total no. (%)†	20/906 (2)	23/904 (3)
Median Charlson comorbidity index (IQR)‡	3 (2–4)	3 (1–4)
Characteristics of the cardiac arrest — no. (%)		
Location at cardiac arrest		
Place of residence	487 (52)	491 (53)
Public place	338 (36)	320 (34)
Other	105 (11)	120 (13)
Bystander-witnessed cardiac arrest	850 (91)	852 (92)
Bystander-performed CPR	759 (82)	728 (78)
First monitored rhythm — no. (%)		
Shockable rhythm	671 (72)	700 (75)
Ventricular fibrillation	576 (62)	585 (63)
Nonperfusing ventricular tachycardia	31 (3)	29 (3)
ROSC after bystander-initiated defibrillation	24 (3)	41 (4)
Unknown rhythm, shock administered	40 (4)	45 (5)
Nonshockable rhythm	259 (28)	231 (25)
Pulseless electrical activity	117 (13)	113 (12)
Asystole	124 (13)	100 (11)
Unknown rhythm, no shock administered	18 (2)	18 (2)
Median time from cardiac arrest to sustained ROSC (IQR) — min§	25 (16–40)	25 (17–40)
Median time from cardiac arrest to randomization — min (IQR)	136 (103–170)	133 (99–173)
Clinical characteristics on admission		
Tympanic temperature — °C¶	35.3±1.1	35.4±1.1
FOUR motor score‖	0	0
Bilateral corneal reflexes present — no./total no. (%)	168/511 (33)	194/537 (36)
Bilateral pupillary reflexes present — no./total no. (%)	535/761 (70)	529/776 (68)
Arterial pH**	7.2±0.2	7.2±0.2
Arterial lactate level — mmol/liter††	5.9±4.4	5.8±4.2
Shock — no. (%)‡‡	261 (28)	275 (30)
ST-segment elevation myocardial infarction — no./total no. (%)	379/918 (41)	370/921 (40)

Temperature Management after Return of Spontaneous Circulation

Table 2. Outcomes and Adverse Events.

Outcome or Event	Hypothermia (N=930)	Normothermia (N=931)	Relative Risk (95% CI)*	P Value
Primary outcome: death from any cause at 6 mo — no./total no. (%)	465/925 (50)	446/925 (48)	1.04 (0.94–1.14)	0.37
Main secondary outcome — no./total no. (%)				
Score of 4–6 on modified Rankin scale at 6-mo follow-up†	488/881 (55)	479/866 (55)	1.00 (0.92–1.09)	
Poor functional outcome at 6 mo‡	495/918 (54)	493/911 (54)	1.00 (0.91–1.08)	
Score on modified Rankin scale at 6-mo follow-up — no./total no. (%)†				
0	140/881 (16)	148/866 (17)		
1	87/881 (10)	80/866 (9)		
2	132/881 (15)	127/866 (15)		
3	34/881 (4)	32/866 (4)		
4	16/881 (2)	20/866 (2)		
5	7/881 (1)	13/866 (2)		
6	465/881 (53)	446/866 (52)		
Serious adverse events — no./total no. (%)				
Arrhythmia resulting in hemodynamic compromise	222/927 (24)	152/921 (16)	1.45 (1.21–1.75)	<0.001
Bleeding	44/927 (5)	46/922 (5)	0.95 (0.63–1.42)	0.81
Skin complication related to device used for targeted temperature management	10/927 (1)	5/922 (<1)	1.99 (0.71–6.37)	0.21
Pneumonia	330/927 (36)	322/921 (35)	1.02 (0.90–1.15)	0.75
Sepsis	99/926 (11)	83/922 (9)	1.19 (0.90–1.57)	0.23