ClinicalTrials.gov number, NCT05697770

SODa-BIC
Sodium Bicarbonate for Metabolic Acidosis in the Intensive Care Unit

Sodium Bicarbonate for Metabolic Acidosis in the Intensive Care Unit

The SODa-BIC Trial

Ary Serpa Neto
on behalf of the SODa-BIC investigators

anzic research centre

ANZICS Clinical Trials Group

Australian Government
National Health and Medical Research Council
NHMRC

Disclosures

- **Lecture Fee**
  - Hamilton Medical
- **Consultancy Fee**
  - Aerogen
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  - Monash University

- **Endorsement**
  - Australian and New Zealand Intensive Care Society Clinical Trials Group

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- Rinaldo Bellomo
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**Members of the Writing Committee*

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- **Data Safety Monitoring Committee**
  - John Kellum – Pittsburgh, USA (Chair)
  - Lakhmir Chawla – San Diego, USA
  - Anais Charles-Nelson – Melbourne, Australia

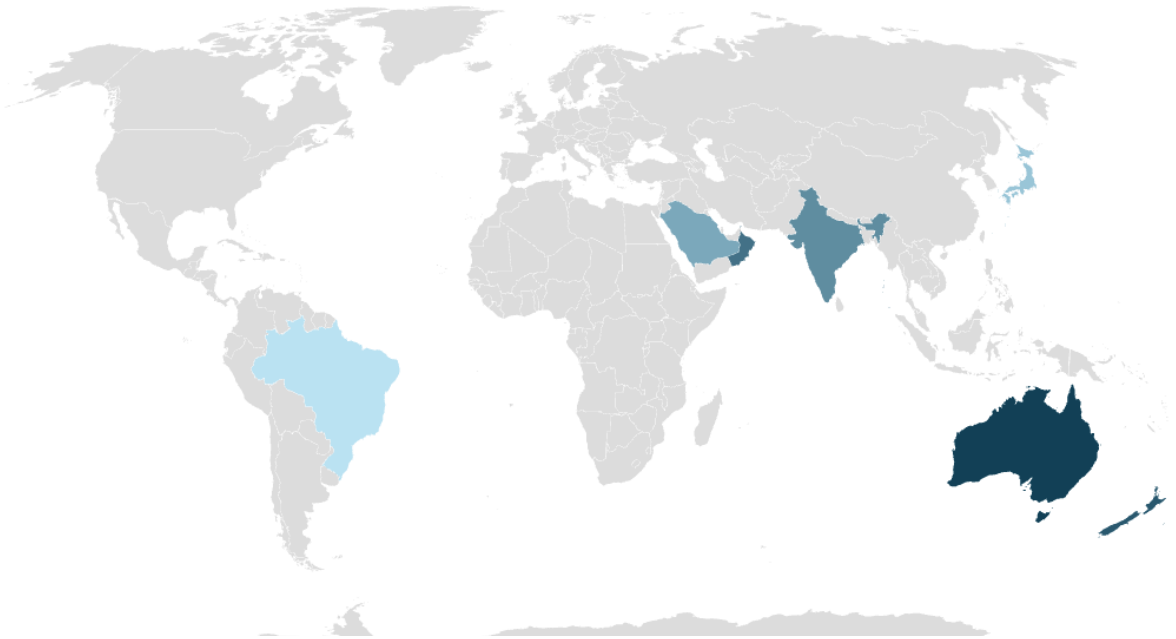
Sites

Australia

- Austin Hospital
- Bendigo Health
- Bunbury Regional Hospital
- Cairns Hospital
- Calvary Mater Newcastle
- Canberra Hospital
- Casey Hospital
- Dandenong Hospital
- Epworth
- Flinders Medical Centre
- Footscray Hospital
- Frankston Hospital
- Gold Coast University Hospital
- Gosford Hospital
- Grampians Health
- Ipswich Hospital
- Lyell McEwin Hospital
- Mater Health
- Monash Medical Centre
- Nepean Hospital
- Orange Health Service
- Peninsula Private Hospital
- Princess Alexandra Hospital
- Queen Elizabeth II Jubilee Hospital
- Royal Adelaide Hospital
- Royal Brisbane and Women's Hospital
- Royal Darwin Hospital
- Royal North Shore Hospital
- Royal Perth Hospital
- Royal Prince Alfred Hospital
- St Vincent's Hospital Melbourne
- St Vincent's Hospital Sydney
- Sunshine Coast University Hospital
- Sunshine Hospital
- Sydney Adventist Hospital
- The Alfred Hospital
- The Queen Elizabeth Hospital
- The Sutherland Hospital
- Townsville University Hospital
- University Hospital Geelong
- Victorian Heart Hospital

New Zealand

- Auckland CVICU
- Auckland DCCM
- Christchurch Hospital
- Dunedin Hospital
- Middlemore Hospital
- Rotorua Hospital
- Waikato Hospital
- Wellington Regional Hospital



Japan

- Jikei University Hospital

India

- Deep Hospital
- Jawaharlal Institute of Postgraduate Medical Education & Research

Oman

- Sultan Qaboos Comprehensive Cancer Care and Research Centre

Saudi Arabia

- King Abdullah International Medical Research Center

Brazil

- Centro de Estudos e de Pesquisas em Terapia Intensiva

Agenda

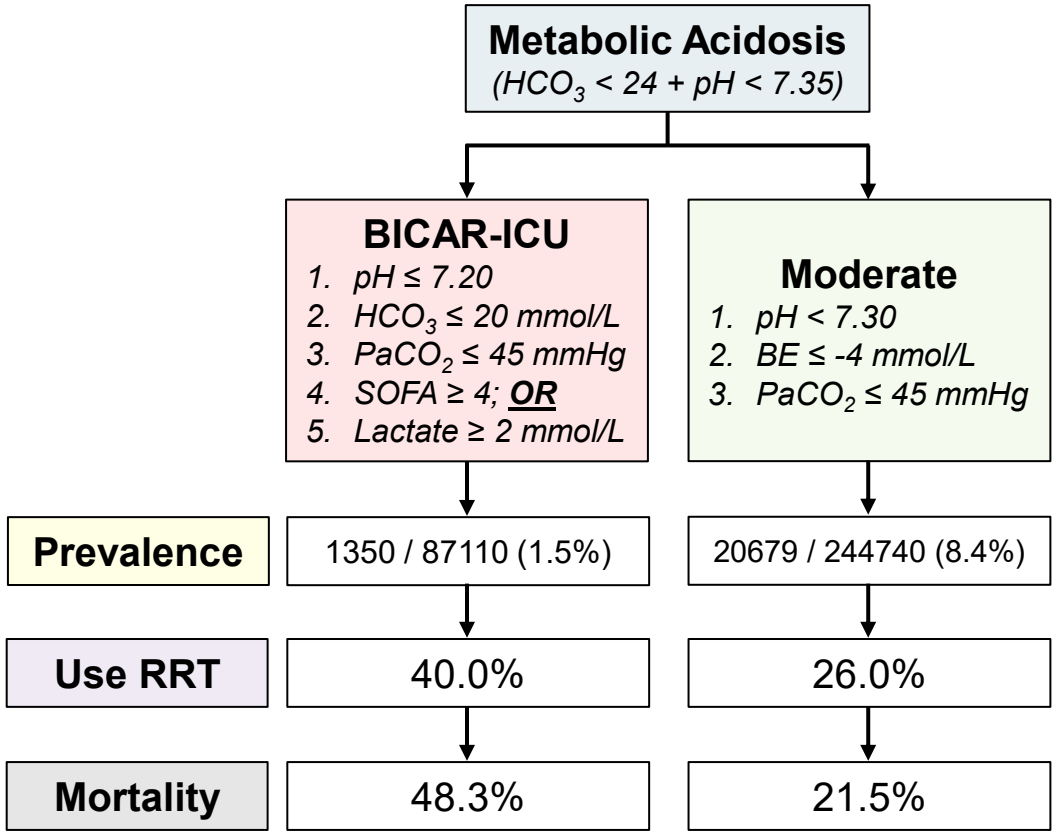
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  - Importance of metabolic acidosis
  - Use of sodium bicarbonate in metabolic acidosis
  - Evidence on the use of sodium bicarbonate in metabolic acidosis
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- **Methods**
  - Patients
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  - Statistical analysis
- **Results**
- **Conclusions**

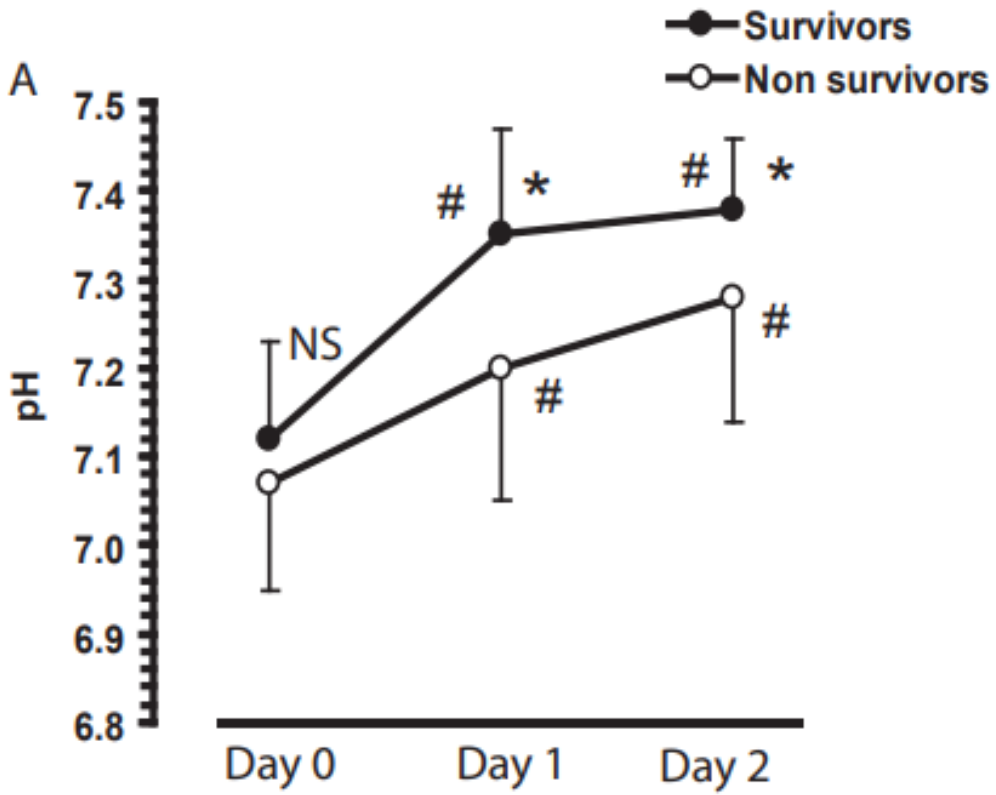
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Importance of Metabolic Acidosis

Early metabolic acidosis in critically ill patients: a binational multicentre study





Although pH upon ICU admission **was not a predictor of outcome**, the **persistence of a low pH** after 24 hours in the ICU was an **independent risk factor for mortality**.

Mochizuki K, *et al*. Crit Care Resusc 2021;23:67-75
Jung B, *et al*. Crit Care 2011;15:R238

Summary

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Sodium Bicarbonate in Metabolic Acidosis

$$HCO_3^- + H^+ \rightarrow H_2CO_3$$

Immediate buffer effect
Bicarbonate (HCO_3^-) buffers excess hydrogen ions (H^+), forming carbonic acid (H_2CO_3), which dissociates into **CO_2 and H_2O**

Volume expansion & hypernatremia
Sodium bicarbonate is usually administered as hypertonic solution → **increases intravascular volume** and serum sodium

Increased CO_2 production
CO_2 diffuses rapidly across cell membranes and into alveoli—**must be eliminated by the lungs**. In ventilated patients, this may increase **ventilation** requirements

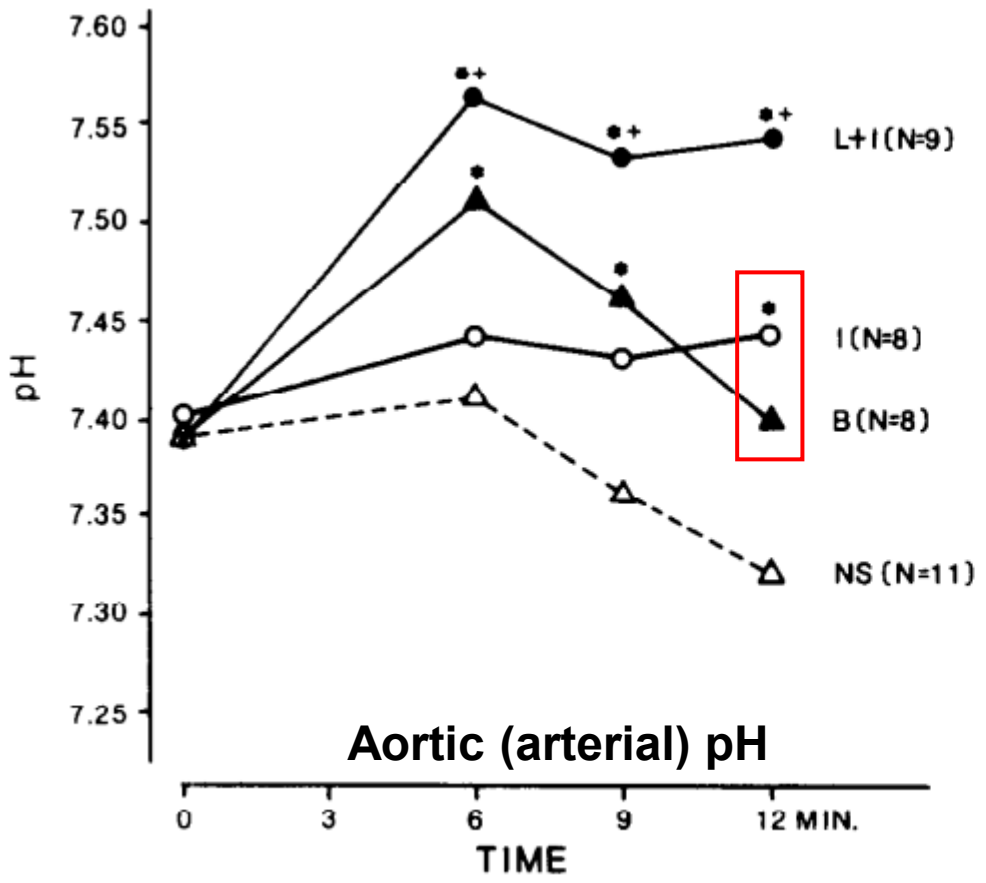
Temporary alkalinization of
Plas pH in ases transient ut **intracellula may fall** due to rapid O_2 entry into cells (so-called "paradoxical intracellular acidosis")

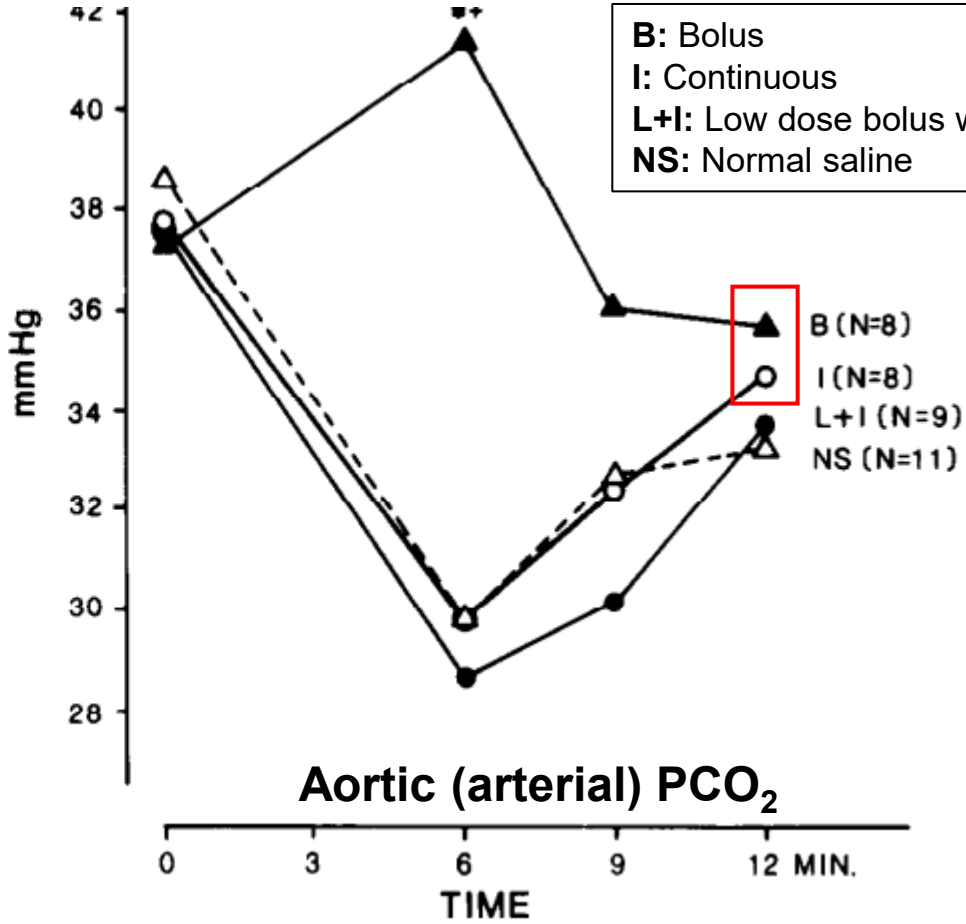
Speed of bicarbonate infusion plays a role

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Sodium Bicarbonate in Metabolic Acidosis

Effects of Different Dosages and Modes of Sodium Bicarbonate Administration During Cardiopulmonary Resuscitation





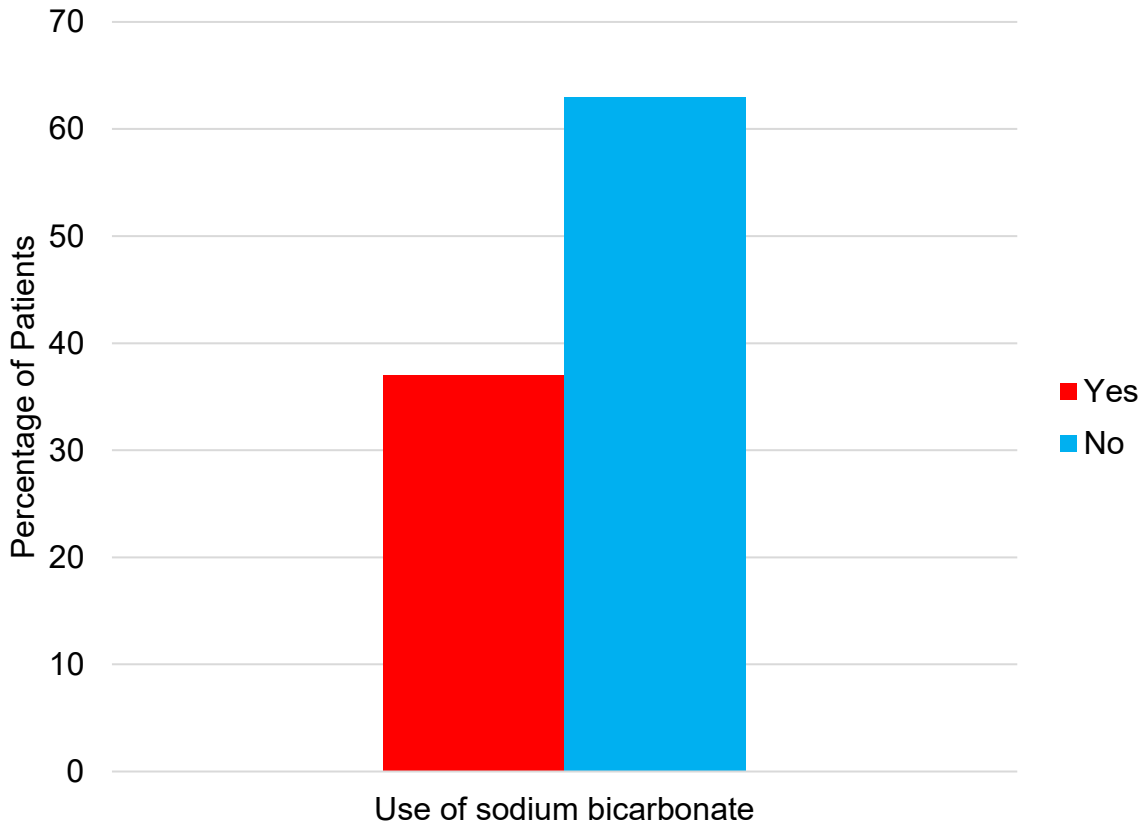
B: Bolus
I: Continuous
L+I: Low dose bolus with continuous
NS: Normal saline

Serpa Neto A

Bleske BE, *et al*. Am J Emerg Med 1992;10:525-32

Sodium Bicarbonate in Metabolic Acidosis

Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy – A prospective, multiple-center study



Proportion of bicarbonate administration varied markedly

- By site: 5% to 55%

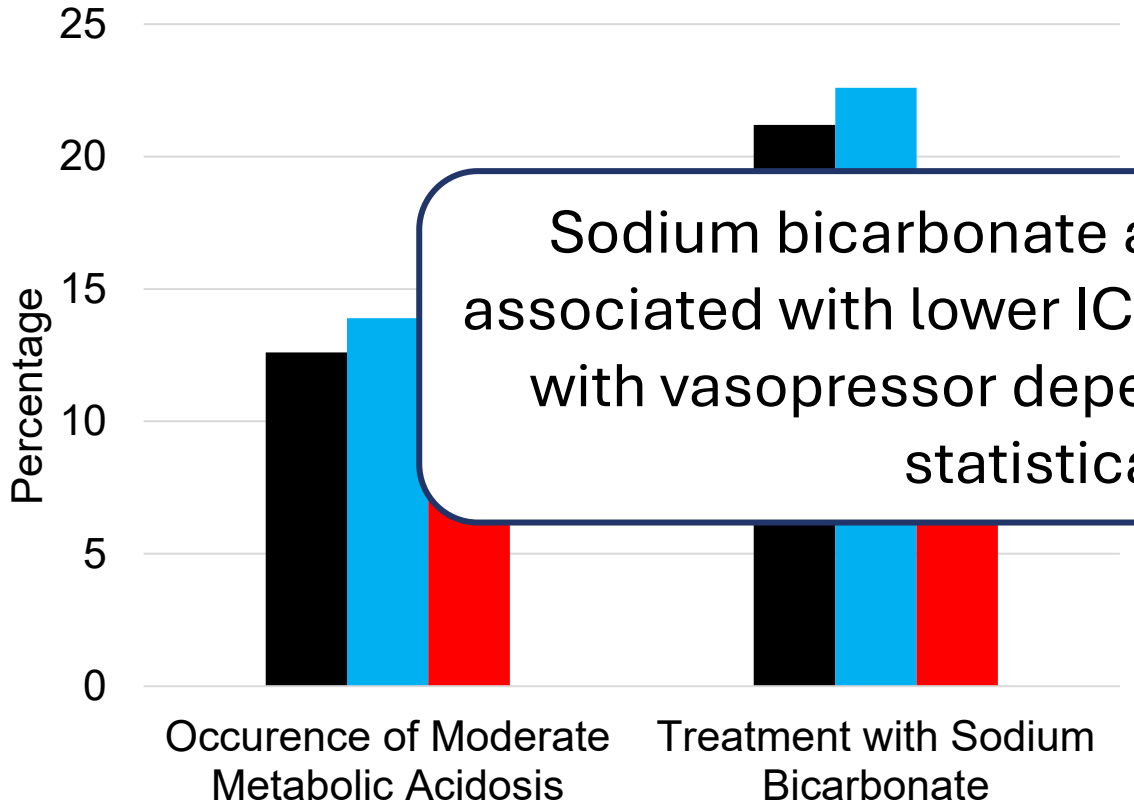
Predictors of sodium bicarbonate administration

- Severity of acidemia (pH level) was not associated with bicarbonate administration
- Strongly related to bicarbonate and base excess levels
- Administration depended mostly on the center delivering treatment rather than on the acidemia mechanism

Jung B, *et al*. Crit Care 2011;15:R238

Sodium Bicarbonate in Metabolic Acidosis

Incidence and management of metabolic acidosis with sodium bicarbonate in the ICU: An international observational study



Proportion of bicarbonate administration varied markedly

- By site: 5.1% to 78.2%
- By country: 10.3% in AUS, 12.5% in JPN and 63.1% in Taiwan

inistration

vs. 42.8%)
.12 µg/kg/min)

Sodium bicarbonate administration was possibly associated with lower ICU mortality in acidotic patients with vasopressor dependency, albeit with a lack of statistical significance.

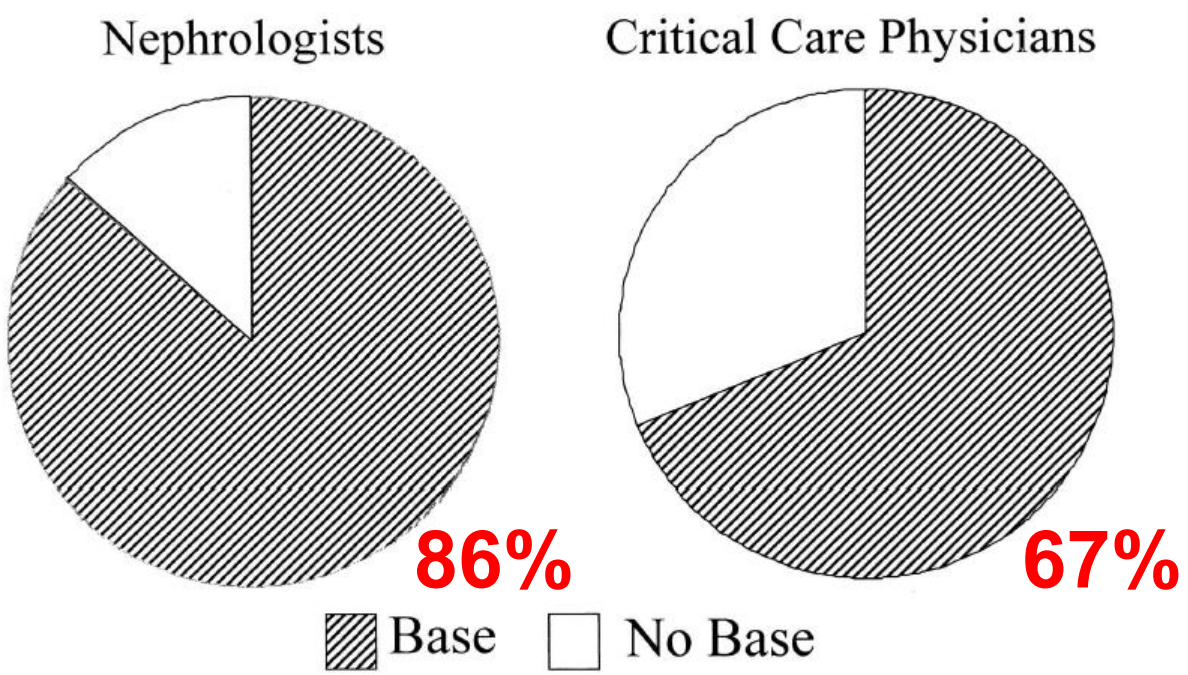
Serpa Neto A

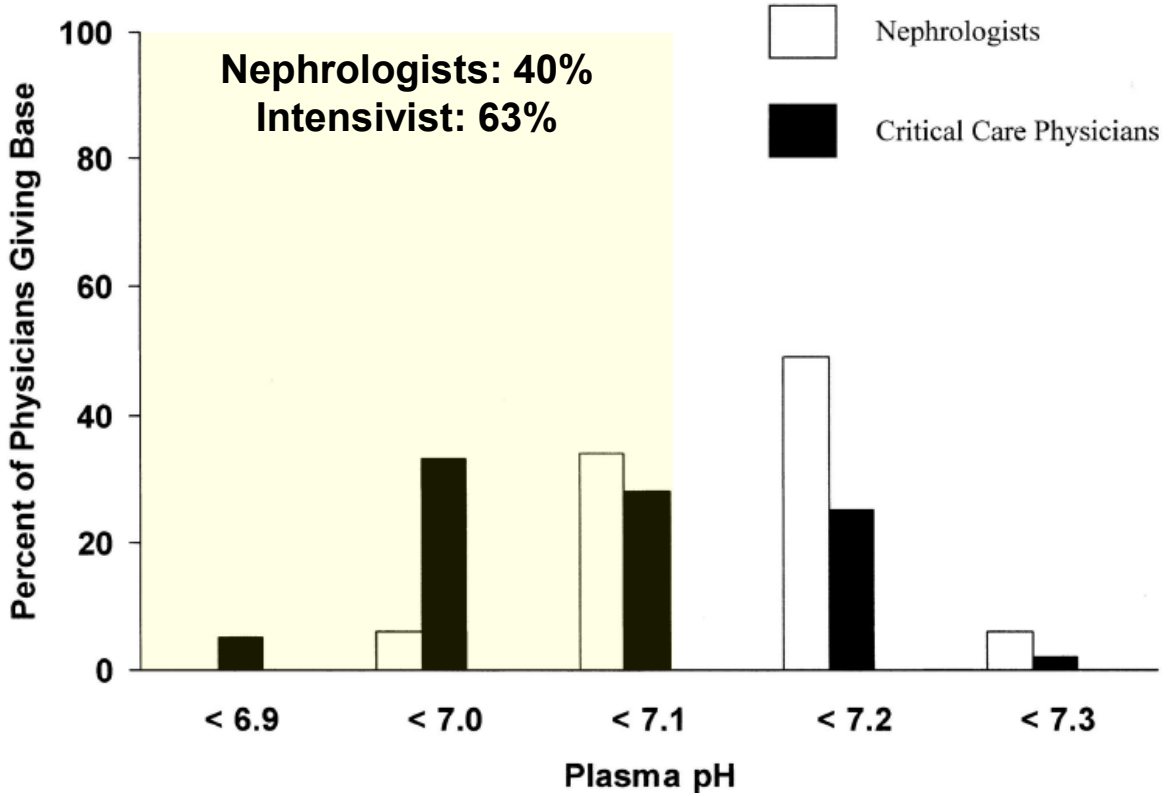
Fujii T, *et al*. Crit Care 2021;25:45

Sodium Bicarbonate in Metabolic Acidosis

Use of base in the treatment of acute severe organic acidosis by nephrologists and critical care physicians: results of an online survey

Lactic Acidosis





Serpa Neto A

Kraut JA, *et al*. Clin Exp Nephrol 2006;10:111-7

Summary

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  - ~20-25% of mortality (similar to sepsis)
- **The sooner the better?**
  - Persistence of acidosis is associated with worse outcomes
- **Use of sodium bicarbonate is heterogeneous**
  - ~20-40% of patients with acidosis
  - Local preferences

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Sodium Bicarbonate Evidence

Sodium bicarbonate therapy for critically ill patients with metabolic acidosis: A scoping and a systematic review

Only TWO RCTs assessed clinical efficacy

Serpa Neto A

Fujii T, *et al*. J Crit Care 2019;51:184-91

Sodium Bicarbonate Evidence

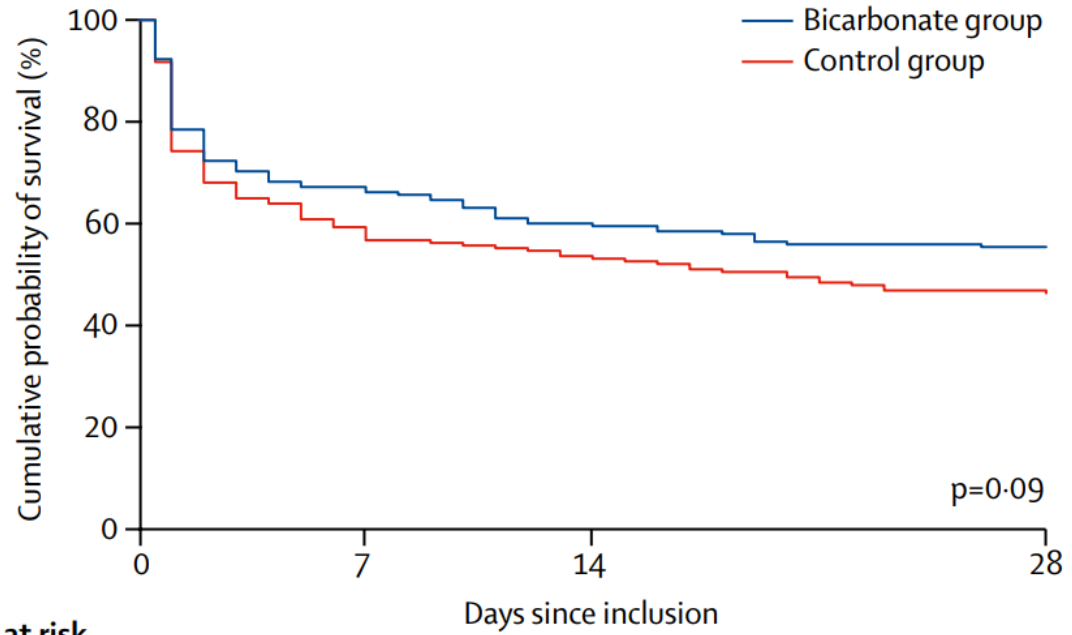
Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial

Design	Multicenter, open-label RCT at 26 ICUs in France
Patients	pH ≤ 7.20, PaCO2 ≤ 45 mmHg, $HCO3^-$ ≤ 20 mmol/L SOFA ≥ 4 or Lac ≥ 2 mmol/L
Intervention	4.2% (0.5mol/L) sodium bicarbonate infusion to maintain the arterial pH ≥ 7.30 during the ICU stay
Control	No sodium bicarbonate
Sample size	400

Jaber S, *et al*. Lancet 2018;392:31-40

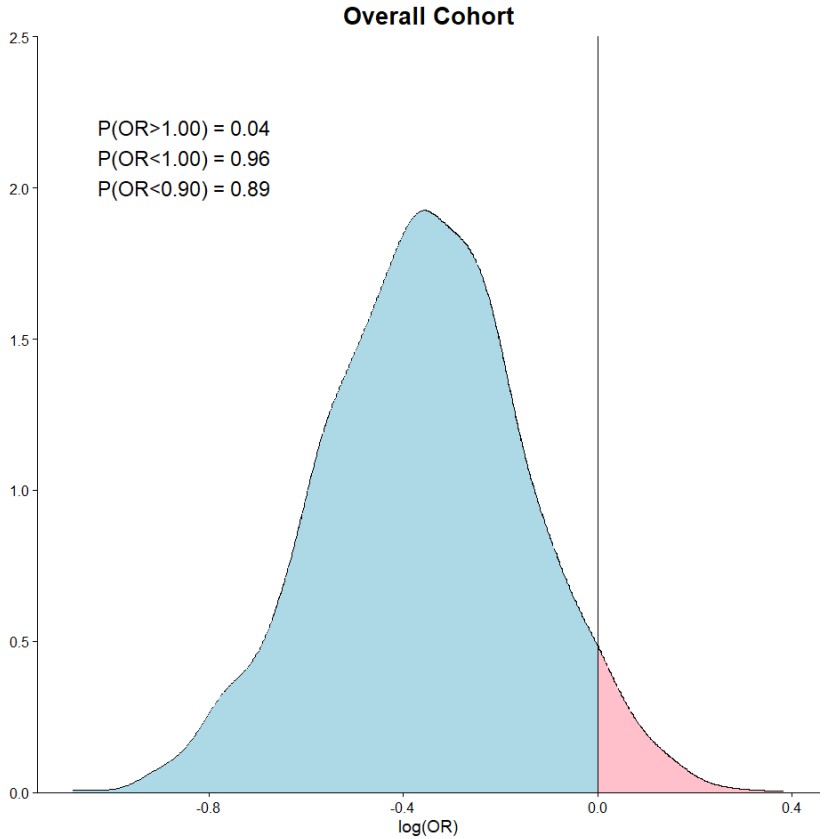
Sodium Bicarbonate Evidence

Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial



Number at risk

Control group	194	115	103	89
Bicarbonate group	195	131	117	108

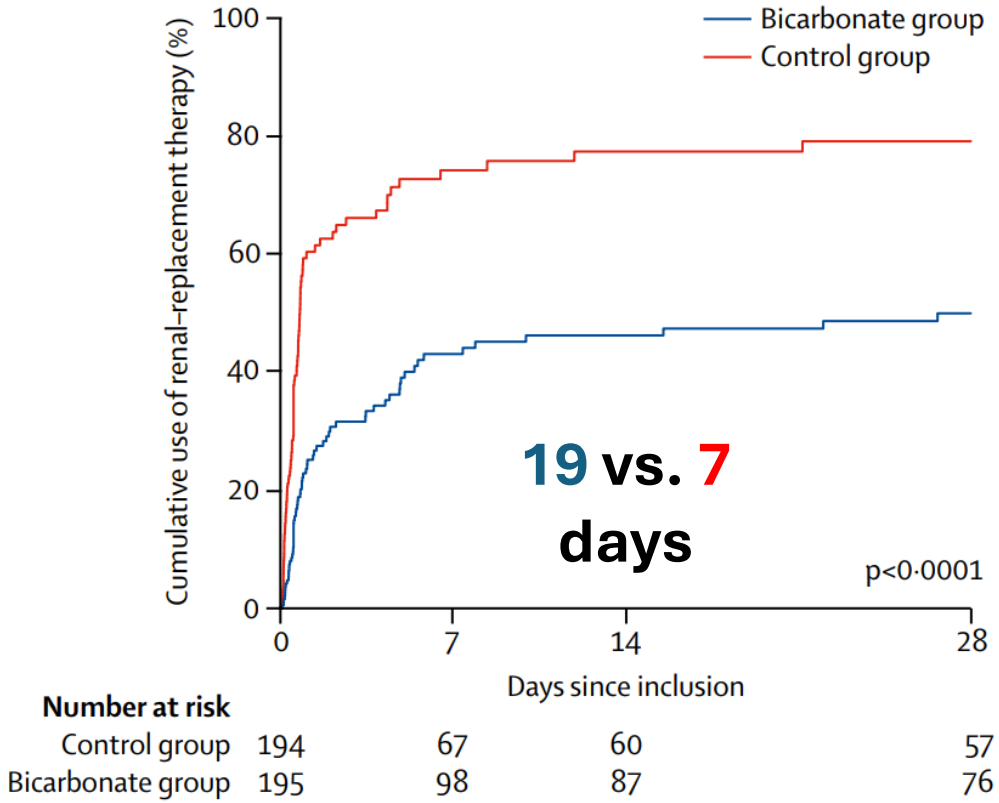


Serpa Neto A

Jaber S, *et al*. Lancet 2018;392:31-40

Sodium Bicarbonate Evidence

Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial



Standardised indication of renal replacement therapy

24 hours	at least 2 of the following criteria • Urine output < 0.3 ml/kg/24h • pH < 7.20 despite resuscitation • K > 6.5 mmol/l

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Jaber S, *et al*. Lancet 2018;392:31-40

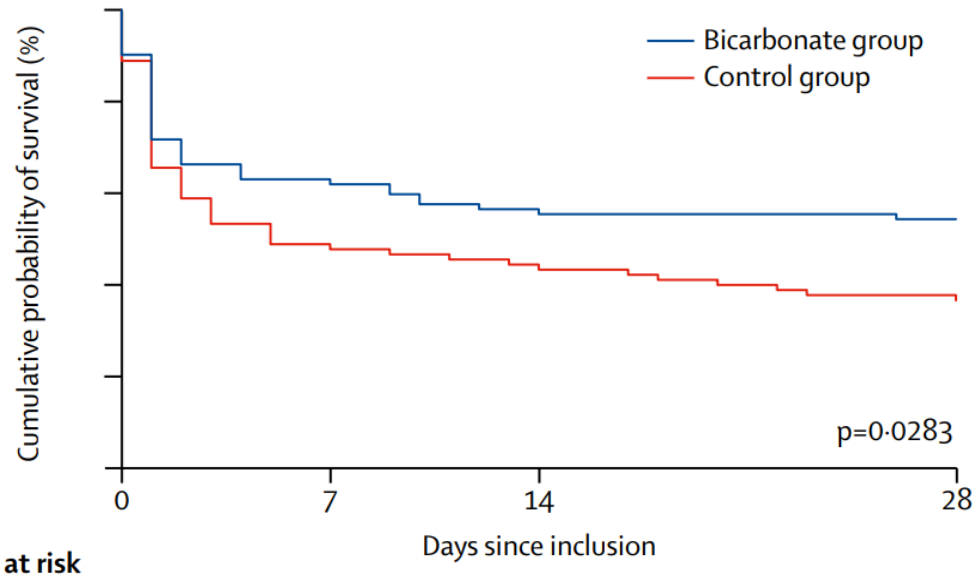
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  - Local preferences
- **Sodium bicarbonate potentially improves outcomes**

Sodium Bicarbonate Evidence

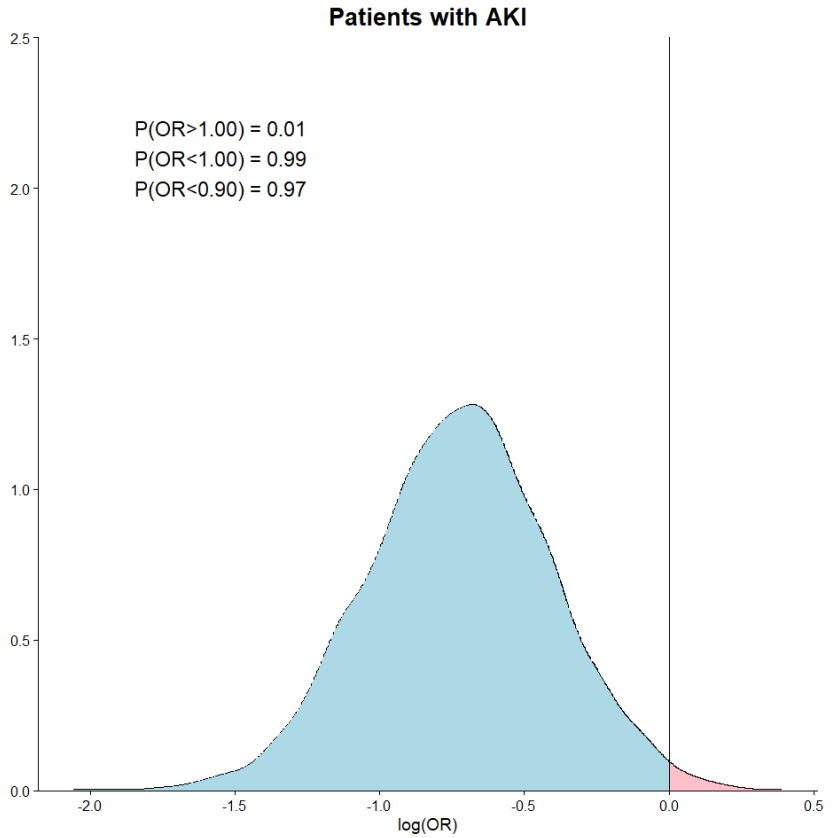
Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial

Patients with AKI Stage 2 or 3



Number at risk

Control group	90	44	40	33
Bicarbonate group	92	58	52	50

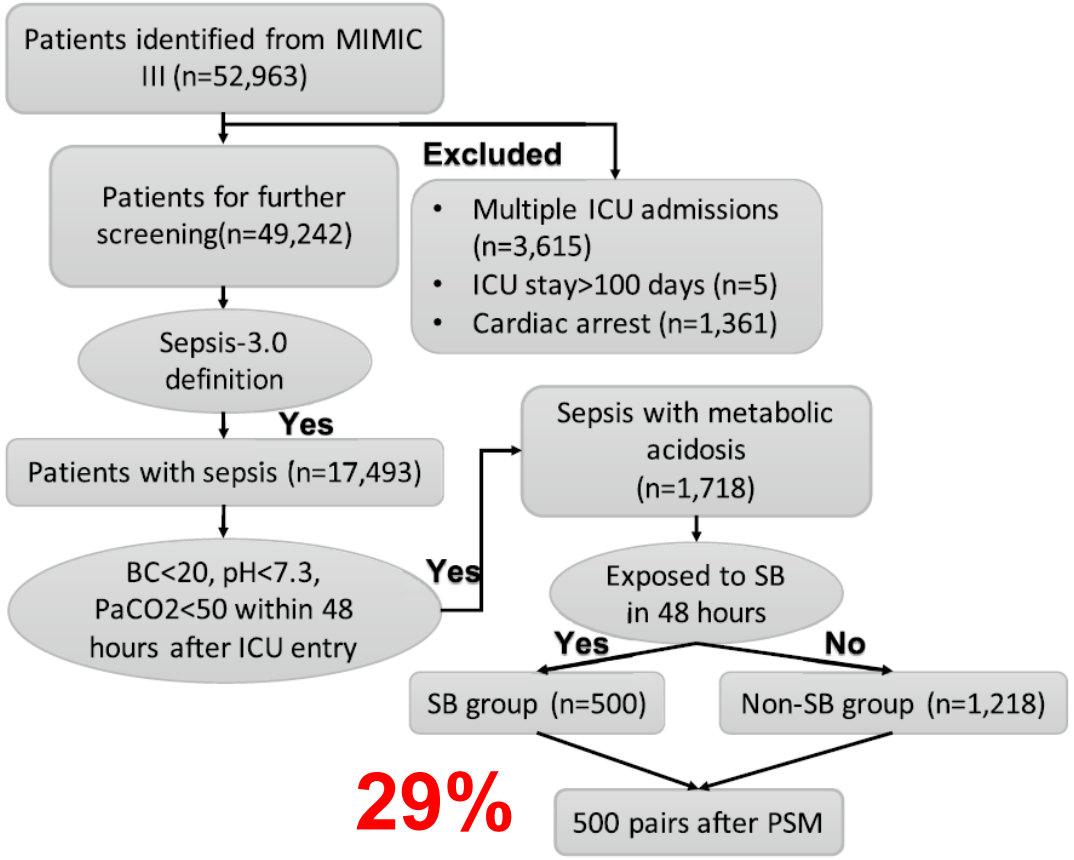


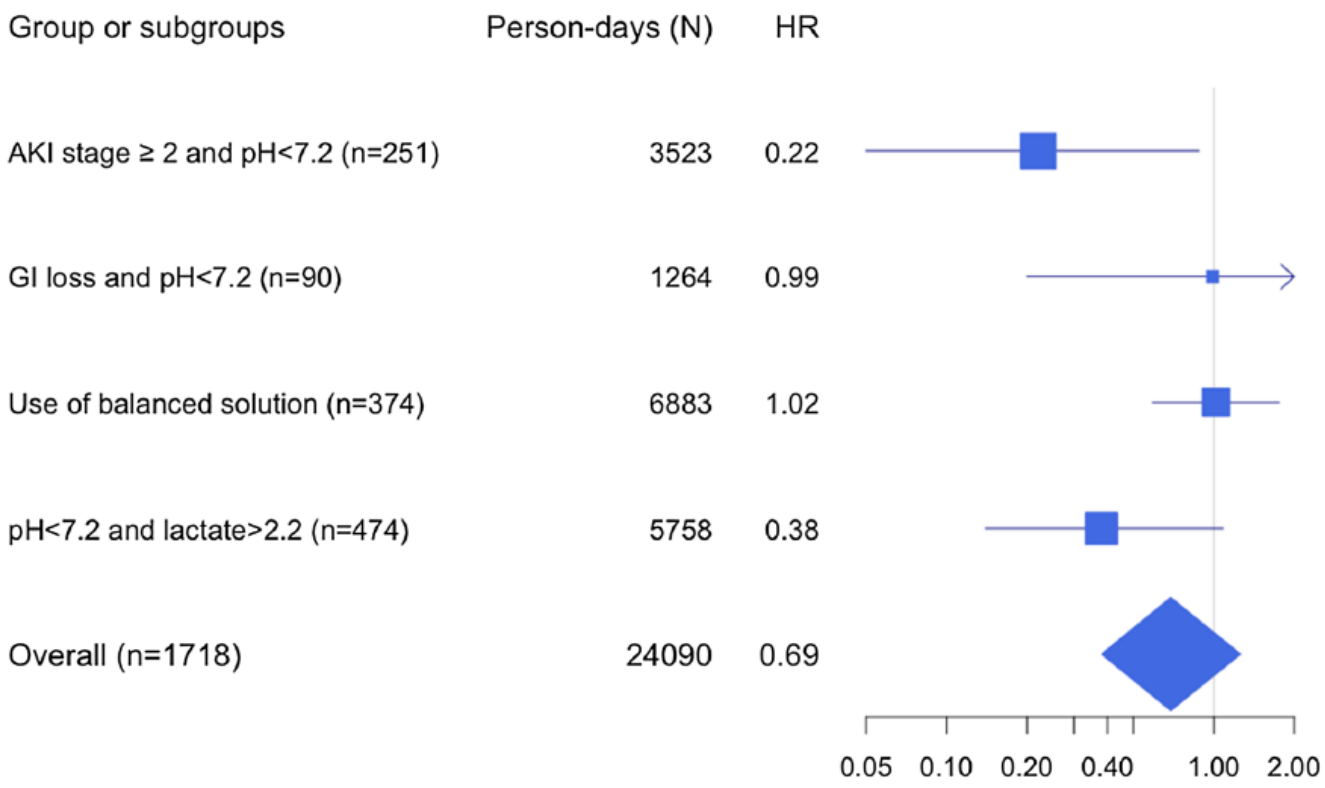
Serpa Neto A

Jaber S, *et al*. Lancet 2018;392:31-40

Sodium Bicarbonate in Metabolic Acidosis

Effectiveness of sodium bicarbonate infusion on mortality in septic patients with metabolic acidosis





Zhang Z, *et al*. Intensive Care Med 2018;44:1888-95

Sodium Bicarbonate Evidence

Sodium bicarbonate administration for metabolic acidosis in the intensive care unit: a target trial emulation

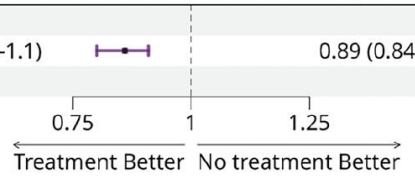
Primary Outcome - Mortality

Model	Estimated Mortality (%) No bicarbonate	Bicarbonate	RD (95% CI)	RR (95% CI)	E-value
Primary model	13.0%	11.1%	-1.9 (-2.7 to -1.3)	0.86 (0.80 to 0.91)	1.61
n=6157					
AKI	16.5%	13.9%	-2.5 (-4.0 to -0.8)	0.85 (0.76 to 0.95)	1.63
n=1982					
Vaso-active support	26.5%	23.8%	-2.8 (-4.5 to -0.7)	0.90 (0.83 to 0.97)	1.46
n=1656					
pH < 7.2	21.3%	18.3%	-3.0 (-5.1 to -1.0)	0.86 (0.76 to 0.96)	1.60
n=1353					
pH ≥ 7.2*	6.5%	5.2%	-1.3 (-2.1 to -0.5)	0.80 (0.70 to 0.93)	1.81
n=2851					
REM: ICU	21.5%	19.4%	-2.1 (-4.9 to 0.6)	0.90 (0.78 to 1.02)	1.46
n=3370					
REM: 30-day	26.4%	23.4%	-3.0 (-5.9 to -0.1)	0.89 (0.78 to 0.99)	1.50
n=3370					



Secondary Outcome - Renal Replacement Therapy

Model	Estimated RRT use (%) No bicarbonate	Bicarbonate	RD (95% CI)	RR (95% CI)	E-value
Primary model	23.1%	20.7%	-2.5 (-3.9 to -1.1)	0.89 (0.84 to 0.95)	1.50
n=6157					



Blank S, *et al*. Intensive Care Med 2025;51:1078-86

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- **Sodium bicarbonate potentially improves outcomes**
- **Equipoise is less likely in severe cases with AKI**

Sodium Bicarbonate Evidence

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2026

Strength of Recommendation
- Strong Recommendation For
- Conditional Recommendation For
- Conditional Recommendation Against
- Strong Recommendation Against

Certainty of Evidence
- ⊕◯◯◯ Very Low
- ⊕⊕◯◯ Low
- ⊕⊕⊕◯ Moderate
- ⊕⊕⊕⊕ High

Type of Recommendation
- Carry Over
- New, Revised, or Revisited but Unchanged Statements

95	⊕⊕◯◯	For adults with septic shock and hypoperfusion-induced lactic acidemia, we **suggest against** using sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements.
96	⊕◯◯◯	For adults with septic shock, severe metabolic acidemia (pH ≤7.2), and acute kidney injury (AKIN score 2 or 3), we **suggest** using sodium bicarbonate therapy.

95. For adults with septic shock and hypoperfusion-induced lactic acidemia, we "suggest against" using sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements. (conditional recommendation, low certainty of evidence) — Carryover

96. For adults with septic shock, severe metabolic acidemia (pH ≤7.2), and acute kidney injury (AKIN score 2 or 3), we "suggest" using sodium bicarbonate therapy. (conditional recommendation, very low certainty of evidence) — Carryover

Serpa Neto A

Prescott HC, *et al*. Crit Care Med 2026;54:725-812

Sodium Bicarbonate Evidence

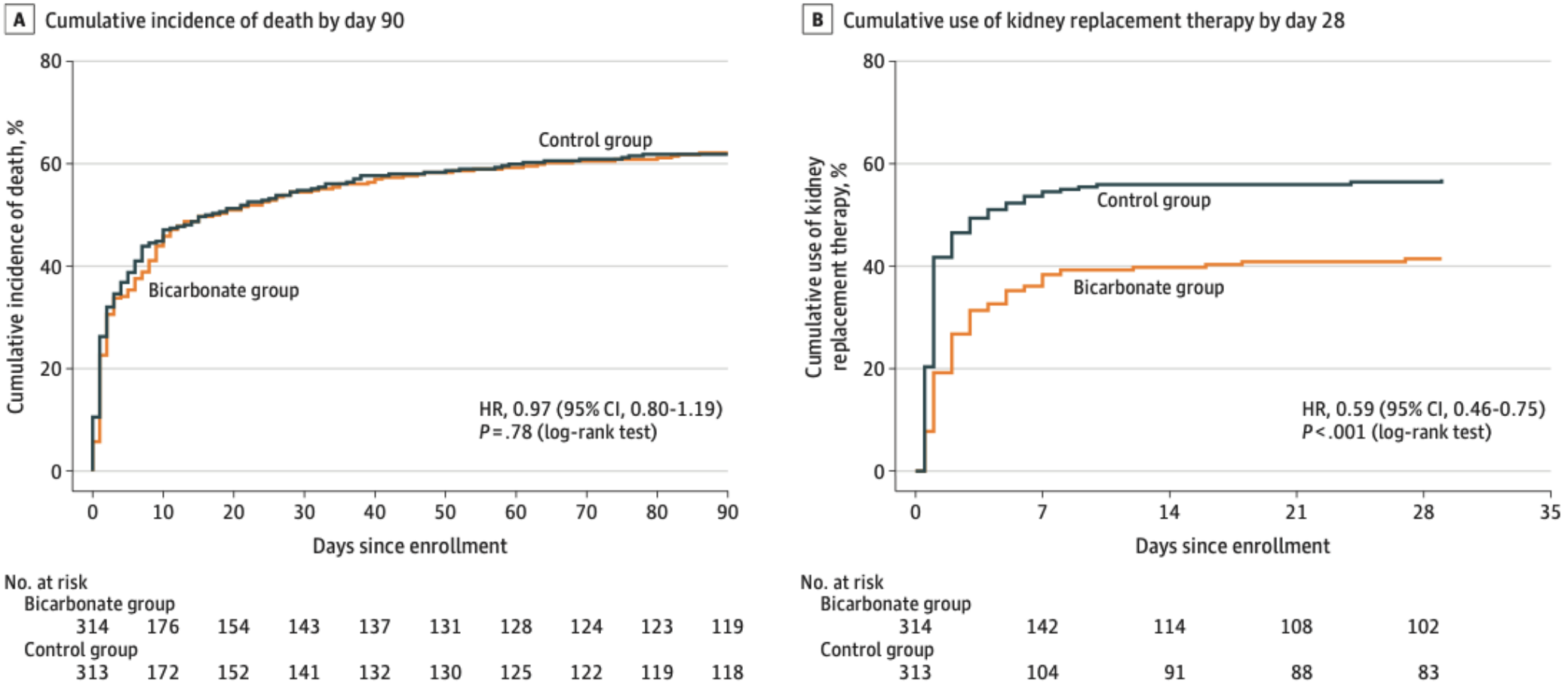
Sodium Bicarbonate for Severe Metabolic Acidemia and Acute Kidney Injury
The BICARICU-2 Randomized Clinical Trial

Design	Multicenter, open-label RCT at 43 ICUs in France
Patients	pH ≤ 7.20, $PaCO_2$ ≤ 45 mmHg, HCO_3^- ≤ 20 mmol/L SOFA ≥ 4 or Lactate ≥ 2 mmol/L Stage 2 or 3 KDIGO AKI
Intervention	4.2% (0.5mol/L) sodium bicarbonate infusion to maintain the arterial pH ≥ 7.30 during the ICU stay
Control	No sodium bicarbonate
Sample size	627

Jung B, *et al*. JAMA 2025;334:2000-10

Sodium Bicarbonate Evidence

Sodium Bicarbonate for Severe Metabolic Acidemia and Acute Kidney Injury
The BICARICU-2 Randomized Clinical Trial



Serpa Neto A

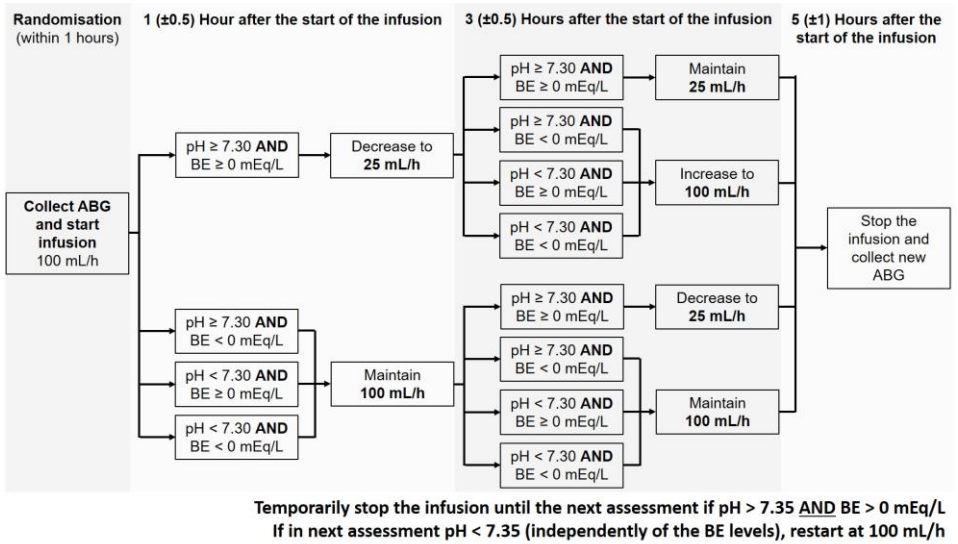
Jung B, *et al*. JAMA 2025;334:2000-10

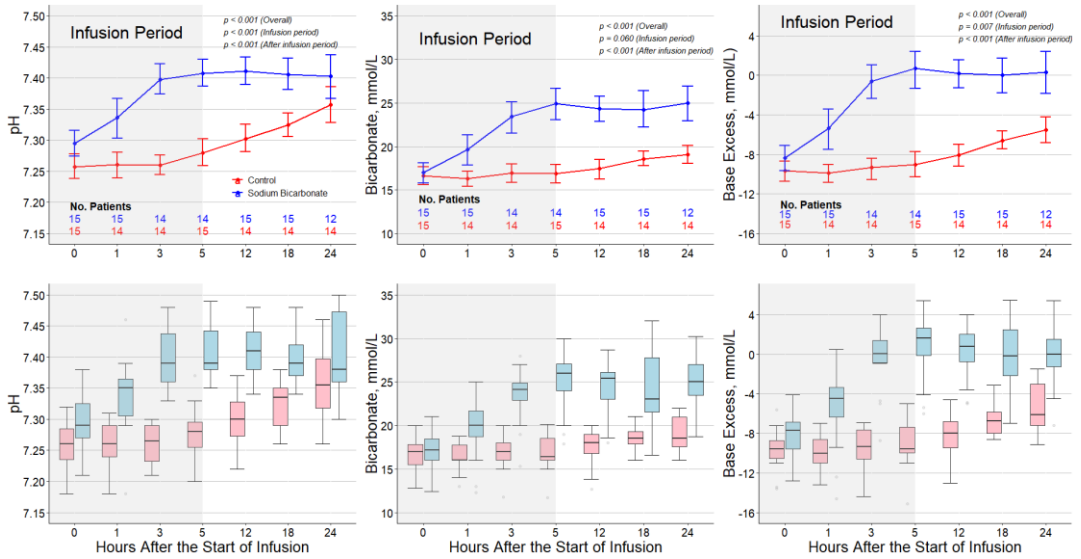
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Sodium Bicarbonate Evidence

Sodium Bicarbonate for Metabolic Acidosis in the ICU: Results of a Pilot Randomized Double-Blind Clinical Trial





	Sodium Bicarbonate (*n* = 15)	Control (*n* = 15)	*p* value
Hours between randomization and start of infusion	0.7 (0.6 - 0.9)	0.6 (0.4 - 0.7)	0.206
Duration of infusion, hours	5.0 (5.0 - 5.2)	5.0 (5.0 - 5.1)	0.357
Volume infused, mL	425 (323 - 500)	500 (500 - 500)	0.008
Total sodium bicarbonate concentration, mmol	255 (194 – 300)	0 (0 – 0)	< 0.001
Change of study drug infusion – no. (%)	8 (53.3)	4 (26.7)	0.264
Use of open sodium bicarbonate – no. (%)	0 (0.0)	1 (6.7)	0.999

	Sodium Bicarbonate (*n* = 15)	Control (*n* = 15)	Effect Estimate (95% CI)	*p* value
Hours until BE correction (BE ≥ 0 mmol/L)	5.2 (4.0 - 23.7)	50.9 (43.0 - 62.9)	MD, -45.86 (-63.11 to -28.61)	< 0.001
Hours until pH correction (pH ≥ 7.30)	1.2 (0.7 - 2.3)	11.3 (4.7 - 18.0)	MD, -10.69 (-19.16 to -2.22)	0.020
Recurrence of acidosis at day 7 – no. (%)	3 (20.0)	15 (100.0)	---	< 0.001[a]
Days with recurrence	0 (0 – 0)	2 (1 – 2)	MD, -2.00 (-2.55 to -1.45)	< 0.001
Mean HCO_3 levels in the first 24 hours, mmol/L	23.7 (22.3 – 25.9)	17.2 (16.5 – 18.9)	MD, 6.50 (4.18 to 8.82)	< 0.001

Abbreviations: CI is confidence interval; MD is median difference; BE is base excess; HCO_3 is bicarbonate

[a] Fisher exact test

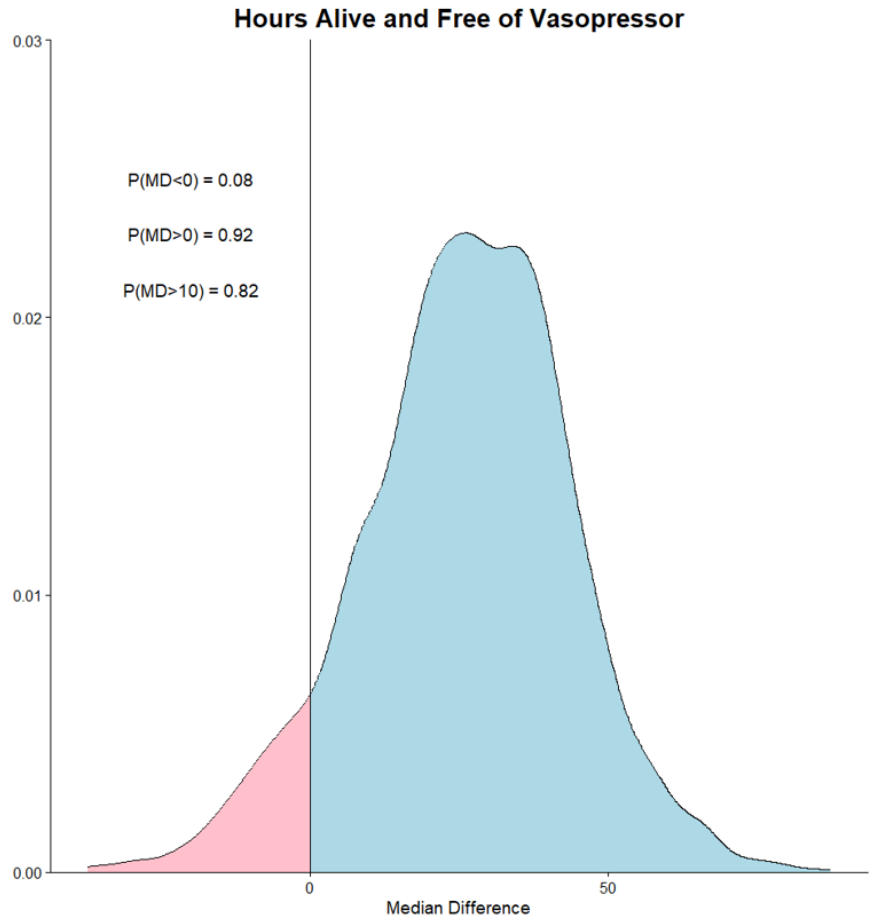
Serpa Neto A

Serpa Neto A, *et al*. Crit Care Med 2023;51:e221-33

Sodium Bicarbonate Evidence

Sodium Bicarbonate for Metabolic Acidosis in the ICU: Results of a Pilot Randomized Double-Blind Clinical Trial

	Sodium Bicarbonate (*n* = 15)	Control (*n* = 15)	Effect Estimate (95% CI)	*p* value
Hours alive and free of vasopressor at day 7	132.2 (85.6 - 139.1)	97.1 (69.3 - 132.4)	MD, 35.07 (-9.14 to 79.28)	0.131
Mean ± standard deviation	106.7 ± 47.7	94.4 ± 46.9		
7-day mortality	0 (0.0)	0 (0.0)	---	---
Duration of shock, hours	35.8 (28.9 - 82.4)	70.9 (35.6 - 98.7)	MD, -35.07 (-83.42 to 13.29)	0.166
Total duration of vasopressor infusion, hours	25.0 (12.0 - 59.5)	33.0 (15.5 - 61.0)	MD, -8.00 (-44.90 to 28.90)	0.674
Acute kidney injury at day 7[b] – no. (%)	9 (60.0)	12 (80.0)	OR, 0.38 (0.06 to 1.83)	0.239
Stage 1	3 / 9 (33.3)	2 / 12 (16.7)		0.843[a]
Stage 2	2 / 9 (22.2)	3 / 12 (25.0)		
Stage 3	4 / 9 (44.4)	7 / 12 (58.3)		
Renal replacement therapy at day 28 – no. (%)	3 (20.0)	3 (20.0)	OR, 1.00 (0.16 to 6.39)	0.999
Duration of renal replacement therapy, days	2.1 (2.1 - 2.2)	4.0 (3.5 - 4.5)	MD, -1.90 (-4.02 to 0.22)	0.222
Cumulative renal replacement-free days at day 28	12.9 (6.4 – 19.3)	0.0 (0.0 – 0.0)	MD, 12.90 (-12.24 to 38.03)	0.372
Cumulative vasopressor-free days at day 28	27.0 (25.0 – 27.5)	26.2 (12.0 – 27.1)	MD, 0.71 (-6.81 to 8.23)	0.855
Change in SOFA at day 3	1.0 (-4.5 – 2.0)	0.0 (-2.8 – 0.0)	MD, 1.00 (-3.75 to 5.75)	0.683
ICU length of stay, days	5.7 (2.5 - 9.3)	3.9 (3.6 - 8.1)	MD, 1.78 (-2.06 to 5.62)	0.371
Hospital length of stay, days	16.0 (10.0 - 34.0)	12.0 (8.4 - 16.0)	MD, 4.04 (-7.77 to 15.85)	0.508
ICU mortality – no. (%)	1 (6.7)	3 (20.0)	OR, 0.29 (0.01 to 2.57)	0.304
Hospital mortality – no. (%)	1 (6.7)	4 (26.7)	OR, 0.20 (0.01 to 1.57)	0.171
28-day in-hospital mortality – no. (%)	1 (6.7)	4 (26.7)	OR, 0.20 (0.01 to 1.57)	0.171
90-day in-hospital mortality – no. (%)	2 / 14 (14.3)	4 / 15 (26.7)	OR, 0.46 (0.06 to 2.84)	0.417



Serpa Neto A

Serpa Neto A, *et al*. Crit Care Med 2023;51:e221-33

Agenda

- **Rationale**
  - Importance of metabolic acidosis
  - Use of sodium bicarbonate in metabolic acidosis
  - Evidence on the use of sodium bicarbonate in metabolic acidosis
  - SODa-BIC pilot
- **Aim**
- **Methods**
  - Patients
  - Randomisation and interventions
  - Outcomes
  - Statistical analysis
- **Results**
- **Conclusions**

Aim

The aim of the *SODium BICarbonate for Metabolic Acidosis in the ICU* (**SODa-BIC**) trial was to test whether, in adults with metabolic acidosis receiving vasopressor support, use of sodium bicarbonate **reduces major adverse kidney events within 30 days** compared with placebo

Agenda

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SODa-BIC Program

Retrospective study
Prevalence and outcomes of moderate metabolic acidosis

Retrospective study
To assess current clinical practice

Feasibility study
To test the stability of the solution

Feasibility study
To test the feasibility of double blind

Survey study
To help with study design and intervention strategy

Pilot trial
To examine feasibility, treatment separation and effect

SODa-BIC
Sodium Bicarbonate for Metabolic Acidosis in the Intensive Care Unit


ORIGINAL ARTICLES

Early metabolic acidosis in critically ill patients: a binational multicentre study


Critical Care

RESEARCH Open Access

Incidence and management of metabolic acidosis with sodium bicarbonate in the ICU: An international observational study


TECHNICAL NOTES

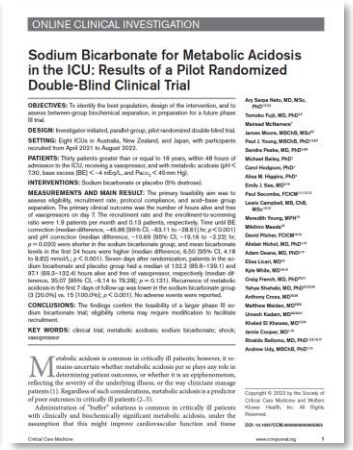
Stability of bicarbonate in normal saline: a technical report


TECHNICAL NOTES

Sodium bicarbonate in 5% dextrose: can clinicians tell the difference?


SURVEYS

Sodium bicarbonate therapy for metabolic acidosis in critically ill patients: a survey of Australian and New Zealand intensive care clinicians


ONLINE CLINICAL INVESTIGATION

Sodium Bicarbonate for Metabolic Acidosis in the ICU: Results of a Pilot Randomized Double-Blind Clinical Trial


Critical Care and Resuscitation

Protocol summary and statistical analysis plan for the sodium bicarbonate for metabolic acidosis in the intensive care unit (SODa-BIC) trial

Serpa Neto A

Methods – Study Design

- International
- Multicentre
- Investigator-initiated
- Double-blind
- Adaptive
- Randomised clinical trial



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Original Article

Protocol summary and statistical analysis plan for the sodium bicarbonate for metabolic acidosis in the intensive care unit (SODa-BIC) trial

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ABSTRACT

Background: Metabolic acidosis is common in critically ill patients and is associated with increased risk of organ dysfunction, need for renal replacement therapy, and death. Despite its frequency and clinical relevance, the optimal treatment approach remains uncertain. Sodium bicarbonate is often used to correct acidosis, but its risk–benefit profile in this setting is unclear.
Objective: To describe the study protocol and statistical analysis plan for the sodium bicarbonate for metabolic acidosis in the intensive care unit (SODa-BIC) trial.
Design, setting and participants: Protocol for an international, multicentre, randomised, double-blind, parallel-group, superiority adaptive clinical trial. Five hundred (n = 500) adults with metabolic acidosis and receiving a continuous infusion of a vasopressor will be randomly assigned to sodium bicarbonate or placebo in a 1:1 ratio. SODa-BIC started recruiting in April 2023. It is anticipated that recruitment will be completed in 2026.
Main outcome measures: The primary outcome will be major adverse kidney events within 30 days (MAKE30). Secondary and tertiary outcomes include 30- and 90-day mortality, receipt of renal replacement therapy, and vasopressor-free and ICU-free days at day 30. All analyses will be conducted on an intention-to-treat basis.
Results and conclusions: SODa-BIC will evaluate whether sodium bicarbonate improves clinically meaningful outcomes in critically ill patients with metabolic acidosis. The trial has the potential to inform international practice guidelines and provide robust evidence to guide the treatment of a common and severe condition in the intensive care unit.

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[s] A list with all investigators is available in the Online Supplement.

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1441-2772/© 2025 Published by Elsevier B.V. on behalf of College of Intensive Care Medicine of Australia and New Zealand. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Serpa Neto A, *et al*. Crit Care Resusc 2025;27:100108

Agenda

- Rationale
  - Importance of metabolic acidosis
  - Use of sodium bicarbonate in metabolic acidosis
  - Evidence on the use of sodium bicarbonate in metabolic acidosis
  - SODa-BIC pilot
- Aim
- **Methods**
  - Patients
  - Randomisation and interventions
  - Outcomes
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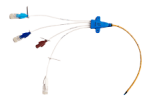
Methods – Inclusion Criteria

All the diagnostic criteria of metabolic acidosis have to be fulfilled within the 2 hours prior to randomisation, and a vasopressor must be continuously infused at the time of randomisation

Adult patients (**≥ 18 years**)



Continuous infusion of a vasopressor to maintain MAP > 65 mmHg (or as determined by the treating clinician)



Dedicated line (central or peripheral) is available (or insertion is planned within the hour after randomisation)



Metabolic acidosis (within the last 2h before randomisation):

- pH < 7.30; and
- BE ≤ -4 mEq/L; and
- $PaCO_2$ ≤ 45 mmHg (non-intubated) OR ≤ 50 mmHg (intubated)

Methods – Exclusion Criteria

1. **Fulfilled all eligibility criteria greater than 48 hours ago**; or
2. Suspected **clinically significant digestive or urinary tract loss of sodium bicarbonate** (e.g., diarrhoea, ileostomy losses, renal tubular acidosis, or drainage of pancreatic or bile duct); or
3. **Diabetic ketoacidosis**; or
4. **Estimated glomerular filtration rate (eGFR) < 30 mL/min due to chronic kidney disease**; or
5. **Currently receiving sodium bicarbonate** at the moment of randomisation (doses of sodium bicarbonate prior to randomisation are allowed); or
6. **Currently receiving RRT (acute or chronic)** or planned to start RRT in the next 3 hours (according to the treating clinical team); or
7. Severe dysnatraemia (serum Na ≥ 155 mEq/L or < 120 mEq/L); or
8. Hypokalaemia (serum K < 2.5 mEq/L); or
9. Pulmonary oedema with PaO2 / FiO2 < 100; or
10. Hypocalcaemia (iCa < 0.8mmol/L); or
11. Patients admitted to the ICU after a **drug overdose or intoxication** (including alcohol intoxication); or
12. Pregnancy or breastfeeding; or
13. Death is deemed to be inevitable as a result of the current acute illness and either the treating clinician, the patient or the substitute decision maker are not committed to full active treatment; or
14. Patients with a life expectancy < 30 days due to a chronic or underlying medical condition; or
15. Considered to be at **high risk of cerebral oedema** by the treating clinician (e.g. traumatic brain injury or acute brain disease); or
16. Clinician believes that being enrolled in intervention or control arm is not in the best interest of the patient; or
17. Previous enrolment in this study.

Agenda

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Methods – Randomisation

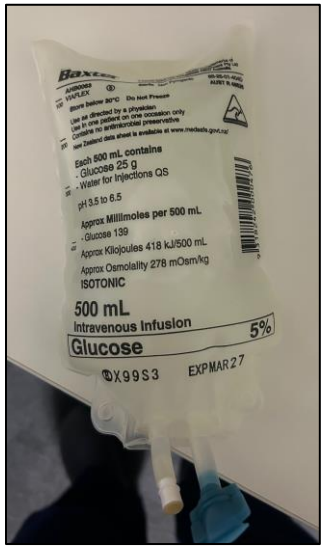
- **Randomisation**
  - Within two hours of the blood gas confirming eligibility
  - Stratified by
    - ✓ Centre
    - ✓ pH level (< 7.25 or ≥ 7.25)
    - ✓ Creatinine level (< 150 or ≥ 150 µmol/L)
  - Permuted blocks of varying size
  - In a 1:1 ratio, patients allocated to sodium bicarbonate or placebo
- **Blinding**
  - Treating clinicians and investigators were blinded

Methods – Intervention

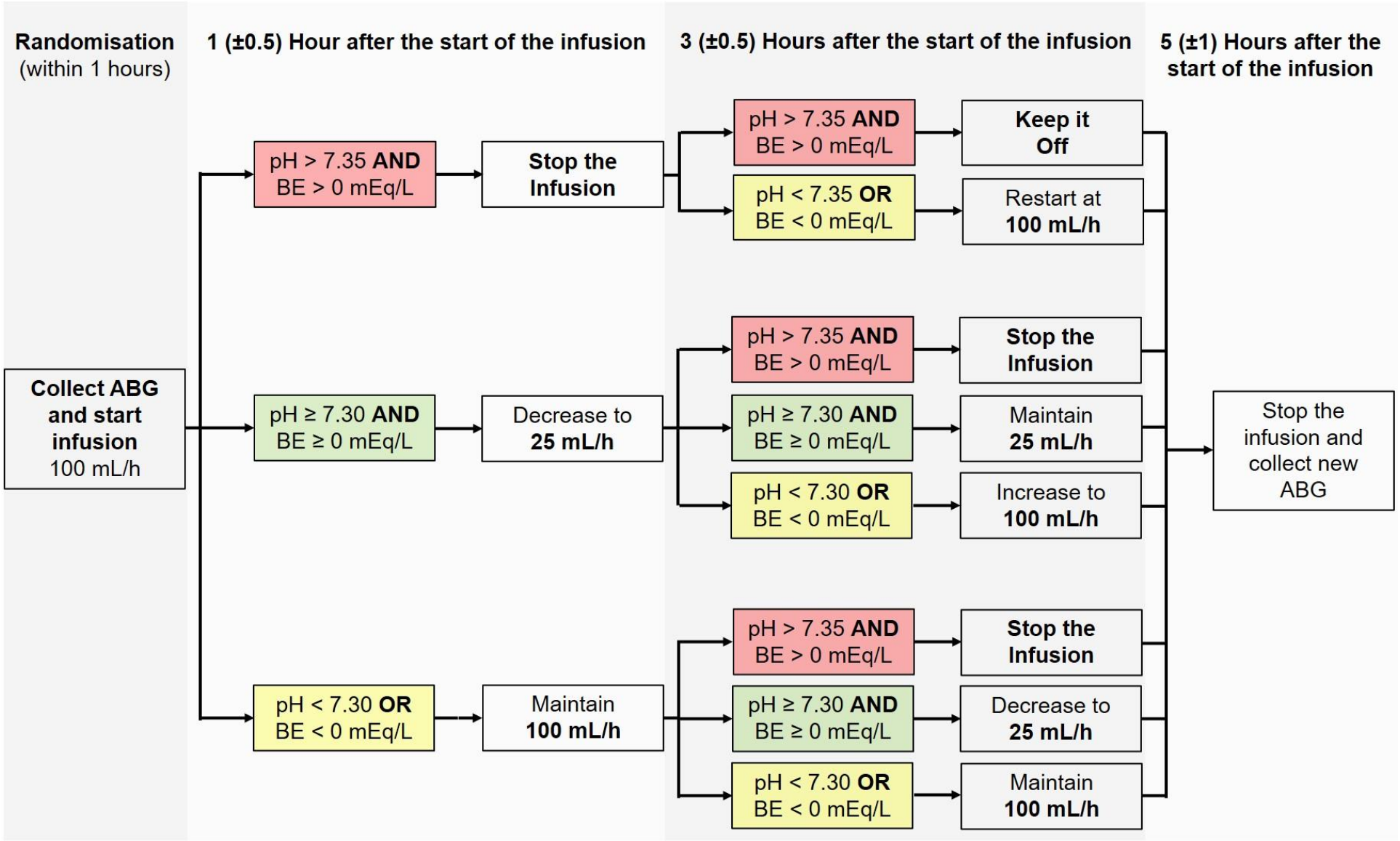
- **Drug preparation**
  - Study drug
    - ✓ **Sodium bicarbonate 8.4%** (1000 mEq/L) diluted in a **5% dextrose** (D5W) solution (500 milliliters bag);
    - ✓ Remove **300 mL of D5W and add 300 mL** of sodium bicarbonate 8.4%;
    - ✓ Final volume: 500 mL;
    - ✓ Final concentration: 600 mEq/L.

  - Placebo
    - ✓ **5% dextrose** (D5W) solution (500 milliliters bag).





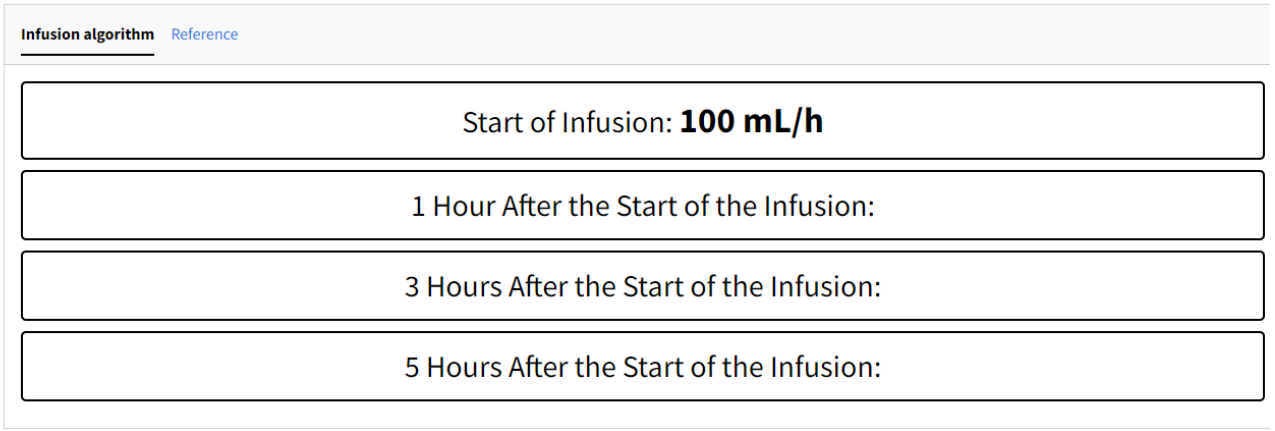
Methods – Intervention



Methods – Intervention

SODa-BIC Infusion Algorithm





https://bit.ly/soda-bic

Methods – Intervention

- **Protocol**
  - Open label bicarbonate allowed but discouraged, suggest if:
    - ✓ pH < 7.10 and $PaCO_2$ < 40 mmHg
    - ✓ Bicarbonate < 8 mmol/L
    - ✓ Base excess < -15 mEq/L
    - ✓ Severe hyperkalaemia (K > 7.0 mmol/L) in the presence of severe acidaemia (pH < 7.10)
  - Infusion should be stopped if:
    - ✓ As per protocol; or
    - ✓ ICU discharge; or
    - ✓ Start of renal replacement therapy; or
    - ✓ Contra-indication(s) to sodium bicarbonate, as:
      - ➢ Development of hypernatraemia (Na > 155 mEq/L);
      - ➢ Hypocalcaemia (iCa < 0.8 mmol/L);
      - ➢ Severe hypokalaemia refractory to potassium replacement (K < 2.5 mEq/L);
      - ➢ Clinically significant fluid overload (e.g., pulmonary oedema);
      - ➢ Any contra-indication according to the treating physician.
    - ✓ Death.

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Methods – Outcomes

- **Primary outcome**
  - Major adverse kidney events within 30 days (MAKE30)
    - ✓ In-hospital death by day 30
    - ✓ Receipt of renal replacement therapy within 30 days
    - ✓ Persistent renal dysfunction
    - ✓ All censored at hospital discharge or 30 days, whichever occurs first

Component	Definition	Sensitivity Analysis
In-hospital death by day 30	Any death occurred between randomisation, hospital discharge or day 30 after randomisation, whichever comes first	Any death occurred between randomisation, hospital discharge or day 30 after randomisation, whichever comes first
Receipt of renal replacement therapy	Any receipt of renal replacement therapy between randomisation, hospital discharge or day 30 after randomisation, whichever comes first	Any receipt of renal replacement therapy between randomisation, hospital discharge or day 30 after randomisation, whichever comes first
Persistent renal dysfunction	Final inpatient creatinine value closest to day 30 ≥ 200% of the baseline value	Final inpatient eGFR value closest to day 30 < 75% of estimated baseline value (i.e. a >25% decrease in eGFR)

Methods – Outcomes

- **Secondary outcomes**
  - In-hospital death by day 30
  - Receipt of renal replacement therapy within 30 days
  - Persistent renal dysfunction
  - Renal replacement therapy dependence at day 30
  - ICU mortality
  - In-hospital death by day 90

- **Physiological outcomes**
  - Recurrence of metabolic acidosis in the first seven days after randomization
  - Acute kidney injury in the first seven days after randomization (KDIGO criteria)

Methods – Outcomes

- **Process of care measures**
  - Vasopressor-free days at day 30
  - Renal replacement therapy-free days at day 30
  - ICU-free days at day 30
  - Hospital-free days at day 90

Landmark (30/90) – duration of support (or length of stay)
Non-survivors received 0

Agenda

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Methods – Sample Size Calculation

- **Sample size calculation**
  - Control group MAKE30 of 40%[a]
  - Absolute difference of 14%[b]
  - Power 90% and α 0.05
  - 5% loss to follow-up
  - **N = 500**

- **Sample size re-estimation**
  - Blinded after 100 patients were randomized
  - Using aggregated event rate
  - Capped at 700 patients
  - **Following review, the DSMB did not recommend increasing the sample size**

[a] Conservative estimate based on data from the ANZICS APD

[b] Informed by the BICAR-ICU trial (reductions of 10% in 30-day mortality, 17% in RRT, and 21% in the composite outcome). Given that SODa-BIC included a broader ICU population with less severe acidosis, we conservatively assumed 70% of this treatment effect

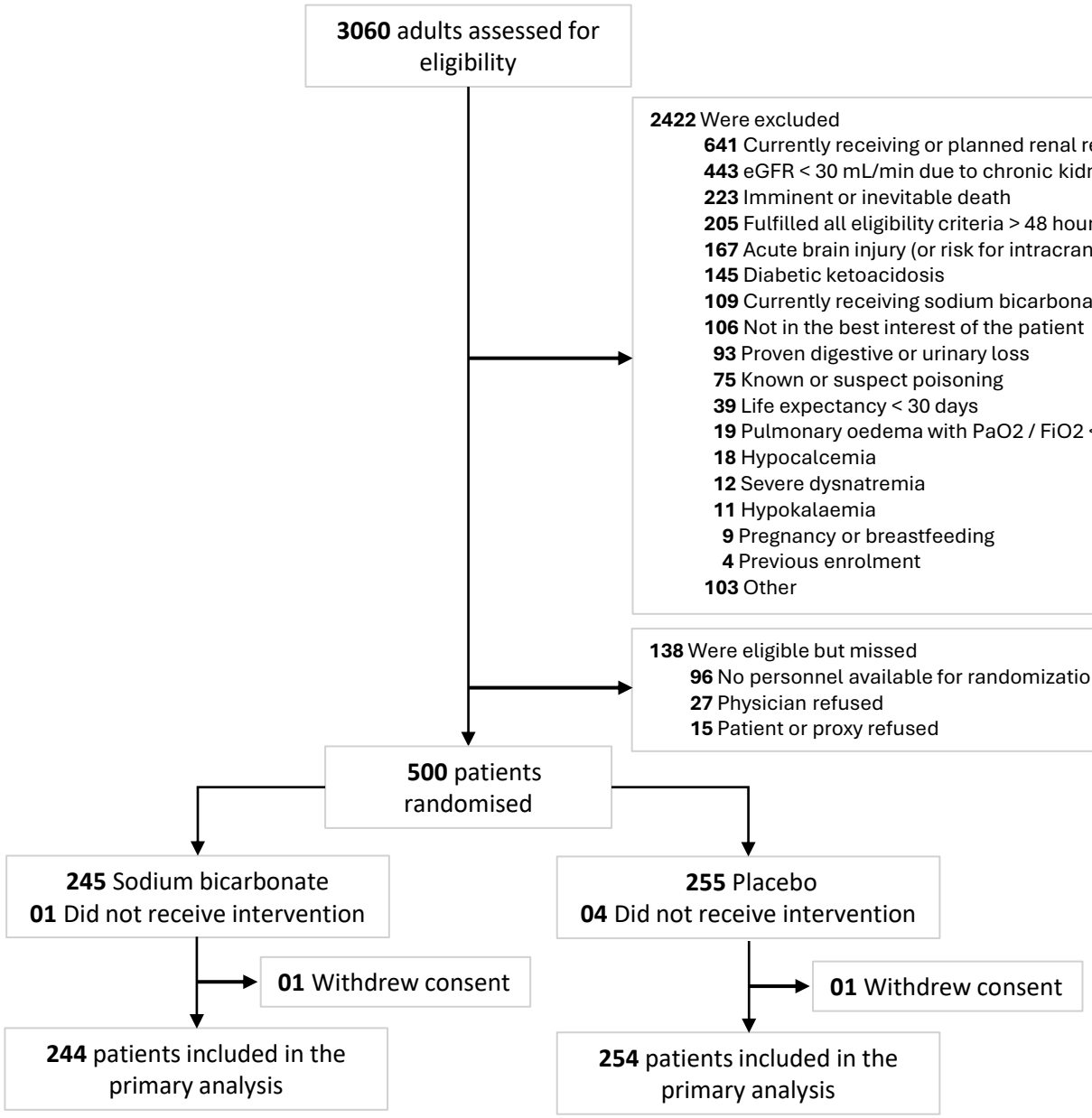
Methods – Statistical Analysis

- **General analysis**
  - Modified intention-to-treat
  - Primary outcome and secondary binary outcomes
    - ✓ Mixed-effect generalized linear model with binomial distribution and identity link
    - ✓ Centre included as random effect and other stratification variables as fixed effects
    - ✓ Absolute difference (95% confidence interval)
  - Continuous outcomes
    - ✓ Mixed-effect median regression models
    - ✓ Absolute difference (95% confidence interval)
  - Survival outcomes
    - ✓ Kaplan-Meier curves and log-rank tests
    - ✓ Cox proportional hazard models
    - ✓ Hazard ration (95% confidence interval)
  - $p < 0.05$ and all analyses performed with R v.4.3.3

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Results – Patients



3060 patients assessed for eligibility from April 2023 through December 2025

500 patients randomised

498 patients included

Results – Patients

	Sodium Bicarbonate (*n* = 244)	Placebo (*n* = 254)
Age – yr	65.0 (51.8 – 74.0)	68.0 (55.2 – 76.0)
Female sex – no. (%)	111 (45.5)	104 (40.9)
Minutes between eligibility and randomisation	39.9 (15.0 – 73.3)	37.8 (12.0 – 70.6)
Type of admission – no (%)		
Medical	119 (48.8)	123 (48.4)
Emergency surgery	64 (26.2)	66 (26.0)
Elective surgery	61 (25.0)	65 (25.6)
APACHE II score on ICU admission	21 (16 – 26)	22 (17 – 27)
SOFA closest to randomisation	7 (6 – 9)	7 (6 – 9)
Blood gas at eligibility		
pH	7.26 (7.22 – 7.28)	7.26 (7.23 – 7.28)
Base excess – mmol/L	-9.2 (-11.5 – -7.0)	-8.8 (-11.0 – -7.0)
Bicarbonate – mmol/L	17.0 (15.0 – 19.2)	18.0 (15.9 – 19.1)

Data are median (quartile 25th – quartile 75th) or N / Total (%)

Results – Patients

	Sodium Bicarbonate (*n* = 244)	Placebo (*n* = 254)
Cause of metabolic acidosis – no. (%)		
Sepsis or septic shock	122 (50.0)	119 (46.9)
Cardiogenic shock	40 (16.4)	56 (22.0)
Hypovolemia / Dehydration	32 (13.1)	20 (7.9)
Cardiac arrest	19 (7.8)	28 (11.0)
Postoperative	9 (3.7)	15 (5.9)
Other	22 (9.0)	16 (6.3)
Pre-randomisation		
Creatinine – µmol/dL	129 (95 – 193)	126 (92 – 189)
Lactate – mmol/L	2.5 (1.4 – 4.5)	2.5 (1.5 – 4.5)
Acute kidney injury – no. (%)	113 / 243 (46.5)	115 / 251 (45.8)
Mechanical ventilation – no. (%)	191 (78.3)	207 (81.5)
Septic shock – no. (%)	95 (38.9)	104 (40.9)
Noradrenaline dose – µg/kg/min	0.14 (0.07 – 0.23)	0.15 (0.07 – 0.23)

Data are median (quartile 25th – quartile 75th) or N / Total (%)

Results – Representativeness

	SODa-BIC Patients (*n* = 434)	All Other ICU Admissions (*n* = 176,090)
Age – yr	63.2 (14.7)	60.4 (17.1)
Male sex – no. (%)	251 (57.8)	103,812 (59.0)
Indigenous – no. (%)	32 (7.4)	13,329 (7.6)
Elective admission – no (%)	96 (22.2)	51,248 (29.4)
APACHE II score on ICU admission	77.2 (25.7)	55.4 (24.8)
SOFA	6.8 (2.7)	4.3 (2.9)
Pathology		
pH	7.26 (0.09)	7.36 (0.09)
Base excess – mmol/L	-8.7 (-11.7 – -5.7)	-2.7 (-5.6 – 0.0)
Bicarbonate – mmol/L	17.4 (3.8)	21.8 (4.6)
Lactate – mmol/L	3.8 (2.2–6.1)	1.8 (1.2–2.7)
Creatinine – µmol/dL	145 (98–215)	78 (60–125)
Mechanical ventilation – no. (%)	334 (87.7)	66,901 (40.8)

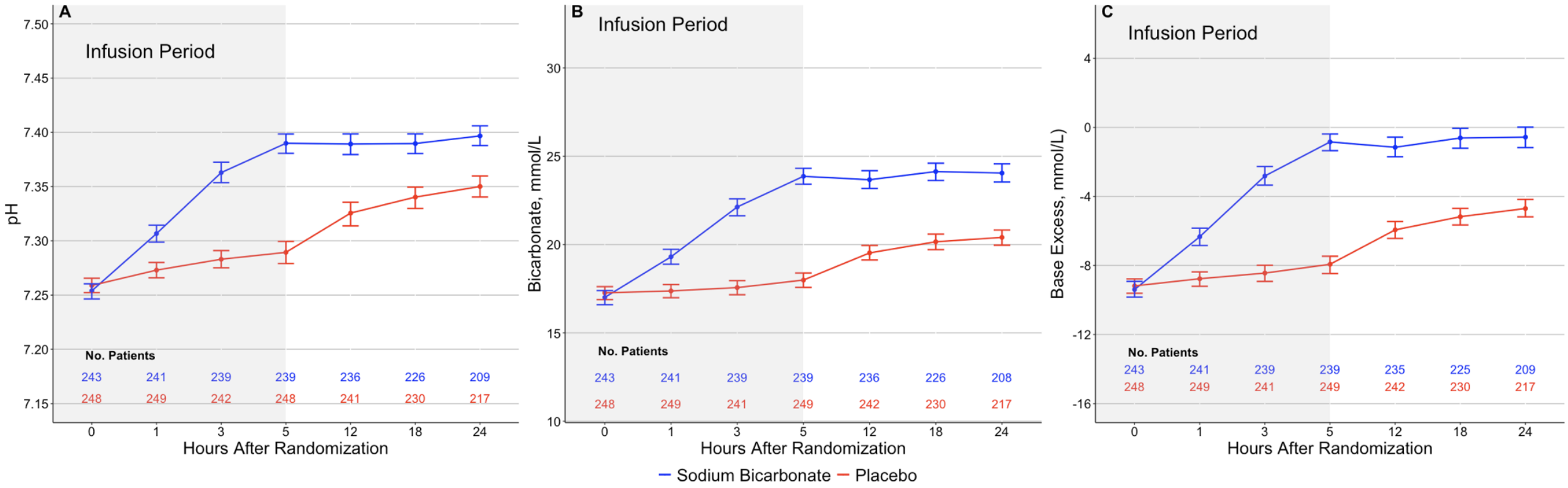
Data are median (standard deviation) or N / Total (%)

Results – Intervention

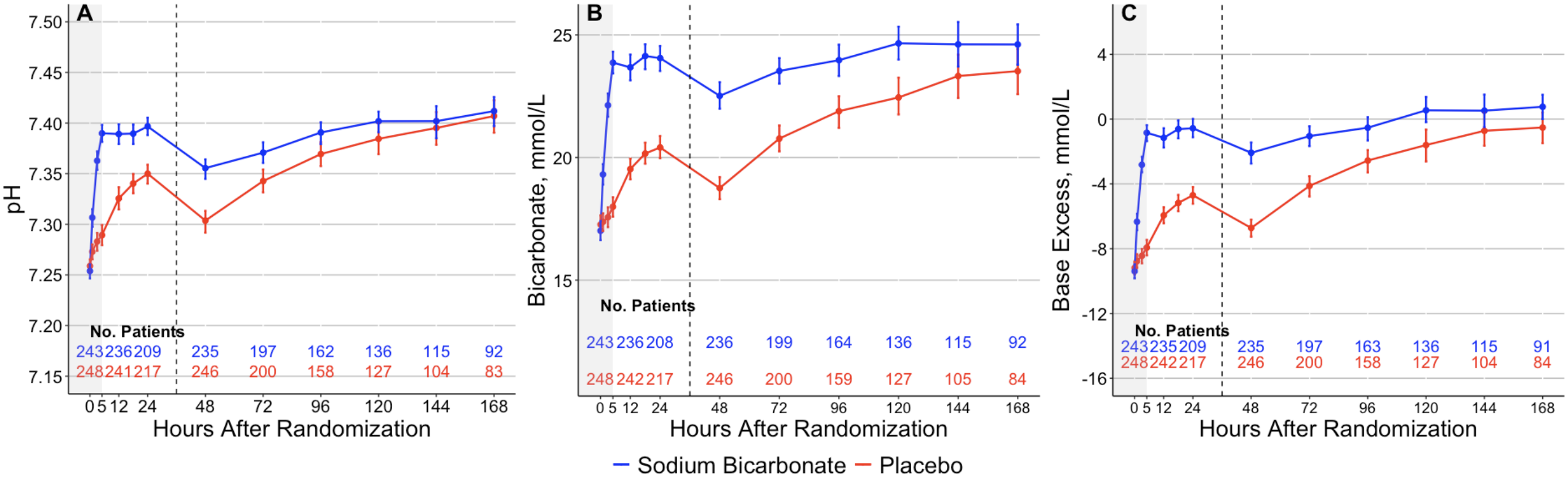
	Sodium Bicarbonate (*n* = 244)	Placebo (*n* = 254)	Absolute Difference (95% CI)
Hours between randomisation and infusion	0.52 (0.39 – 0.72)	0.38 (0.27 – 0.53)	0.14 (0.09 to 0.19)
Duration of infusion – hours	5.0 (4.7 – 5.0)	5.0 (5.0 – 5.0)	-0.0 (-0.0 to 0.0)
Volume infusion – mL	500 (329 – 500)	500 (500 – 500)	-0.0 (-32.0 to 32.0)
Total sodium bicarbonate dose – mmol	300.0 (197.4 – 300.0)	0.0 (0.0 – 0.0)	300.0 (292.4 to 307.6)
Titration of study drug infusion – no. (%)	121 / 243 (49.8)	58 / 250 (23.2)	27.0 (19.5 to 34.5)
Use of open-label sodium bicarbonate – no. (%)	17 / 243 (7.0)	38 / 250 (15.2)	-8.2 (-13.6 to -2.8)

Data are median (quartile 25th – quartile 75th) or N / Total (%)

Results – Intervention

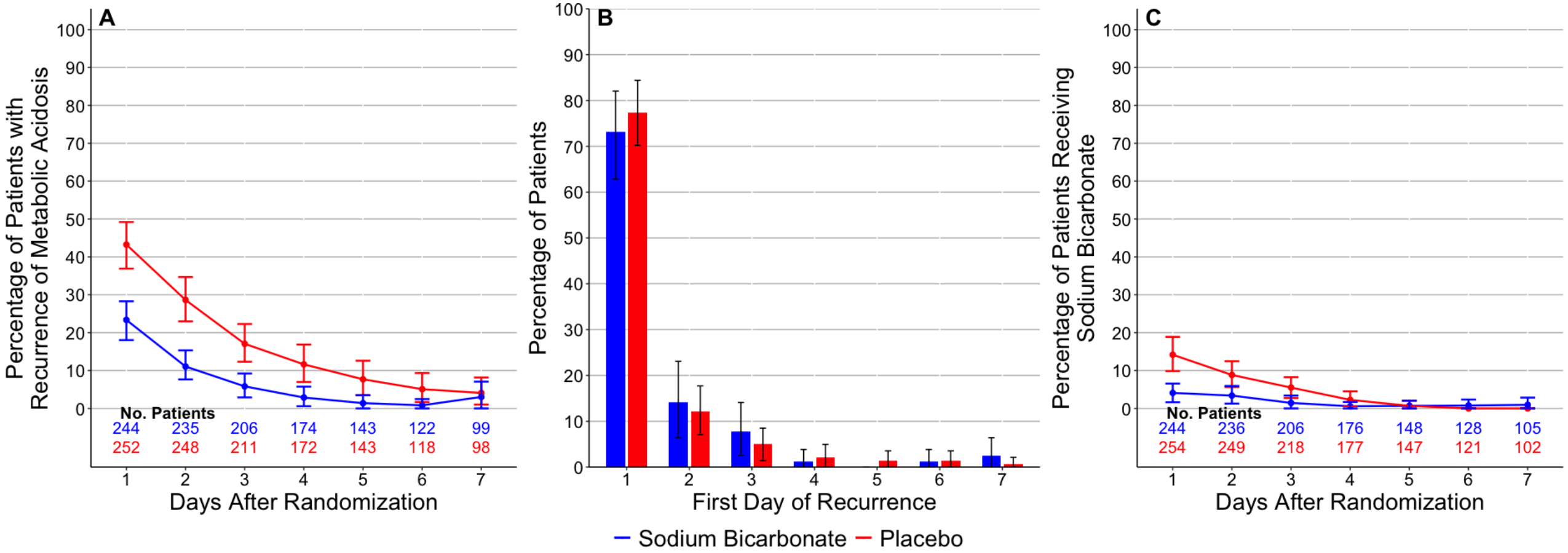


Results – Intervention



Serpa Neto A

Results – Intervention

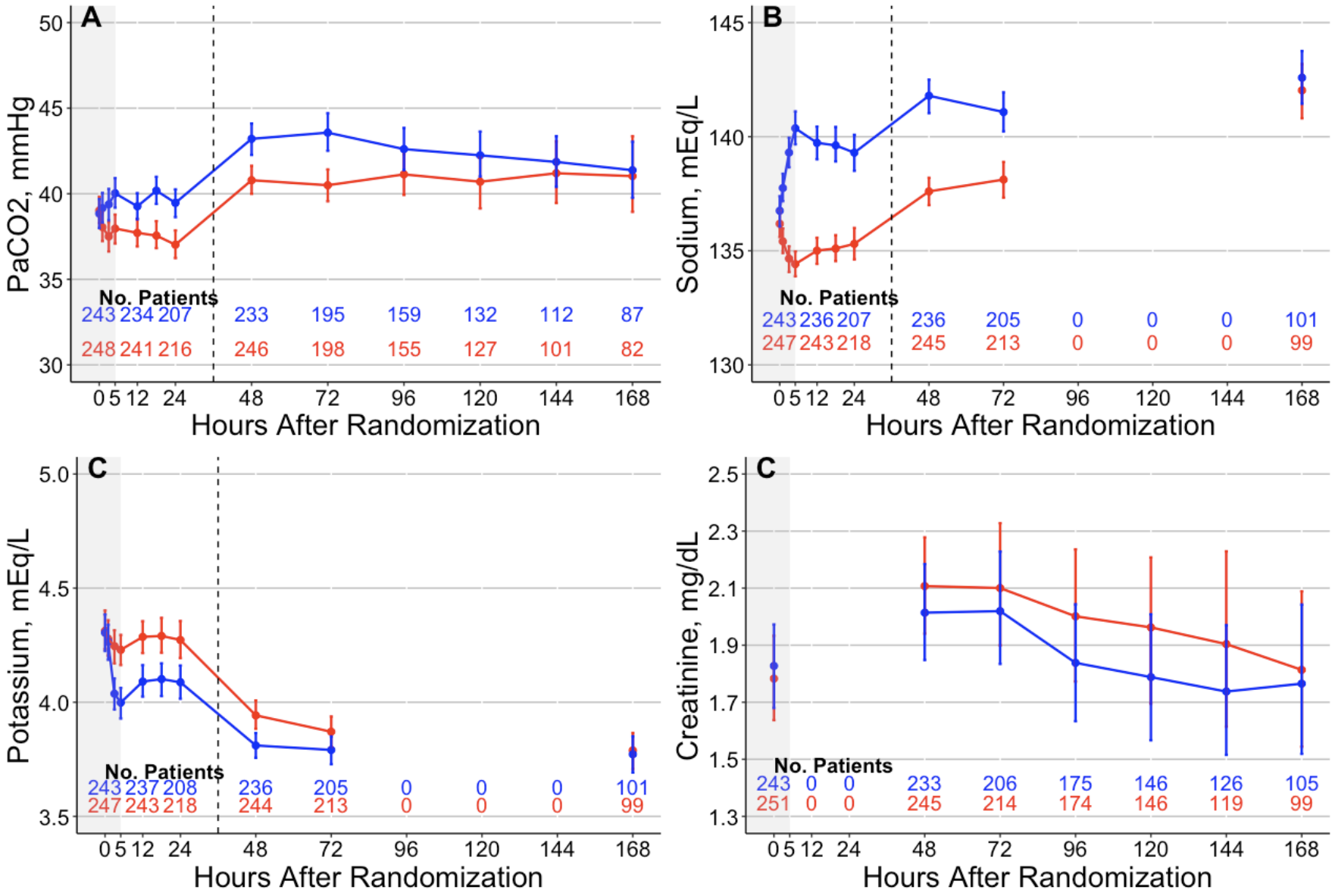


Results – Intervention

	Sodium Bicarbonate (*n* = 244)	Placebo (*n* = 254)
Study drug interrupted earlier – no. (%)	68 / 243 (28.0)	13 / 249 (5.2)
As per protocol	44 / 243 (18.1)	1 / 249 (0.4)
Transferred to other hospital or department	5 / 243 (2.1)	2 / 254 (0.8)
Contra-indication according to treating physician	2 / 243 (0.8)	2 / 249 (0.8)
Problems with intravenous access	1 / 243 (0.4)	2 / 254 (0.8)
Start of renal replacement therapy	0 / 243 (0.0)	3 / 249 (1.2)
Patient died	2 / 243 (0.8)	0 / 249 (0.0)
Severe hypernatremia (Na > 155 mEq/L)	1 / 243 (0.4)	0 / 249 (0.0)
Hypokalemia (K < 2.5 mEq/L refractory to replacement)	0 / 243 (0.0)	0 / 249 (0.0)
Hypocalcemia (iCa < 0.8 mmol/L)	0 / 243 (0.0)	0 / 249 (0.0)
Clinically significant overload	0 / 243 (0.0)	0 / 249 (0.0)
ICU discharge	0 / 243 (0.0)	0 / 249 (0.0)
Other	12 / 243 (4.9)	3 / 249 (1.2)

Data are median (quartile 25th – quartile 75th) or N / Total (%)

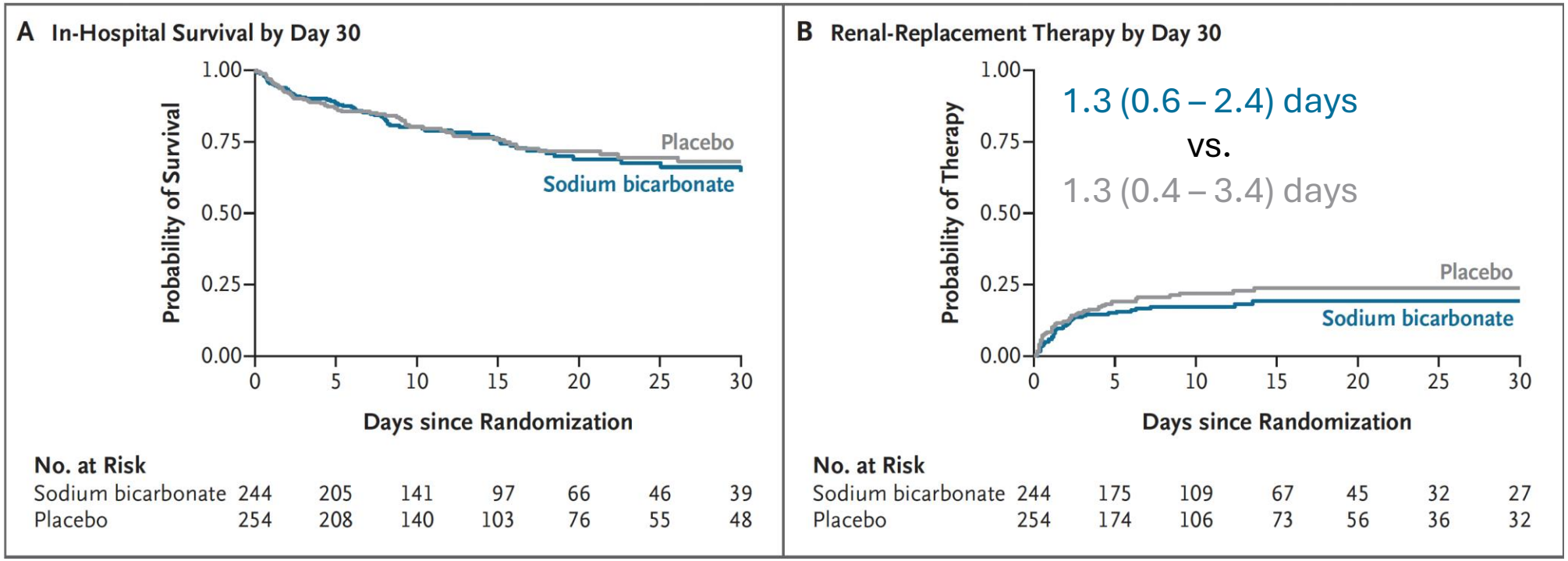
Results – Follow-Up



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Results – Primary Outcome

	Sodium Bicarbonate (*n* = 244)	Placebo (*n* = 254)	Absolute Difference (95% CI)
Major adverse kidney events within 30 days – no. (%)			
In-hospital death by day 30 – no. (%)			
Receipt of renal replacement therapy – no. (%)			
Persistent renal dysfunction – no. (%)			



* *p value = 0.781*
Data are N / Total (%)

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Results – Sensitivity Analysis

	Sodium Bicarbonate (*n* = 244)	Placebo (*n* = 254)	Absolute Difference (95% CI)
Major adverse kidney events within 30 days – no. (%)	98 (40.2)	100 (39.4)	
Original analysis			1.2 (-7.1 to 9.4)
Adjusted analysis†			0.7 (-7.3 to 8.6)
Alternative definition of persistent renal dysfunction‡	113 / 244 (46.3)	115 / 254 (45.3)	1.3 (-7.2 to 9.8)

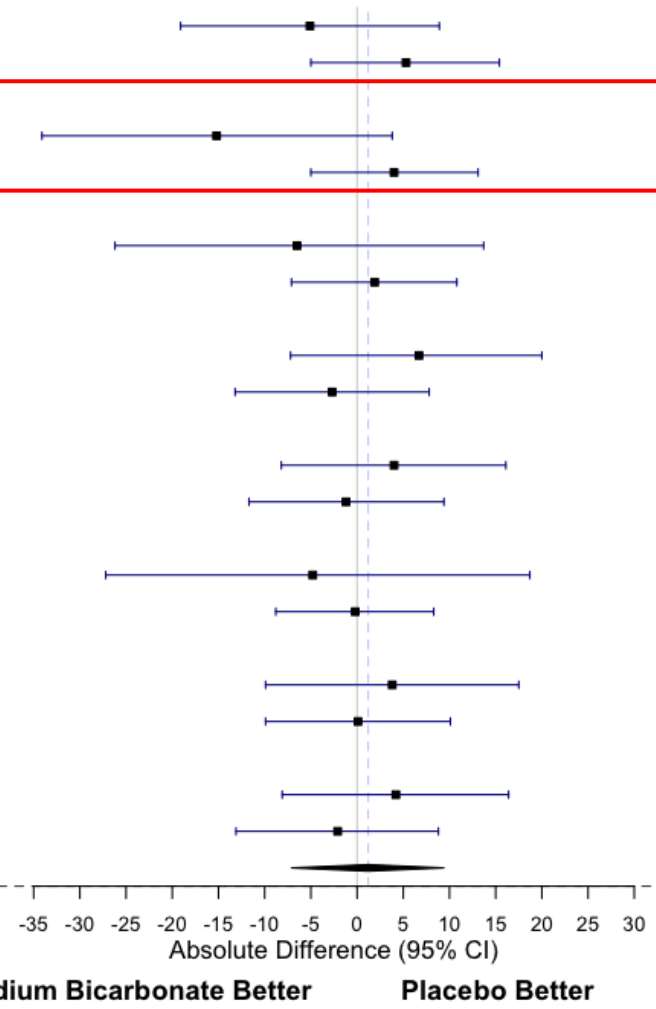
† The analysis was adjusted for age, sex, use of open-label sodium bicarbonate pre-randomisation, APACHE II and SOFA.
‡ Final inpatient estimated glomerular filtration rate (eGFR) value closest to day 30 < 75% of estimated baseline value (i.e. a > 25% decrease in eGFR).

Data are N / Total (%)

Results – Subgroup Analysis

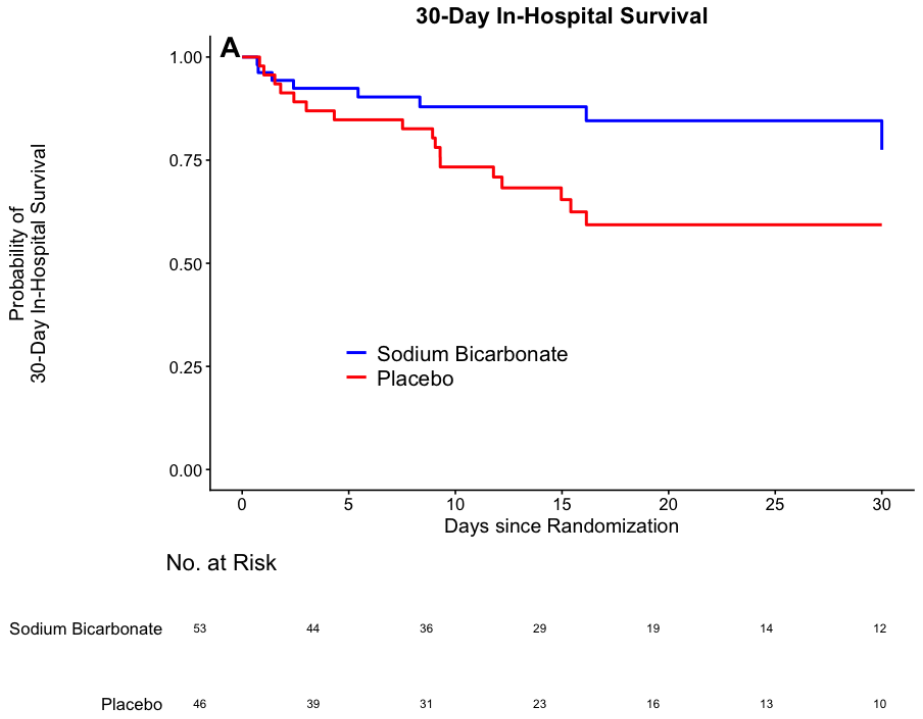
No heterogeneity of treatment effect according to pre-specified subgroups

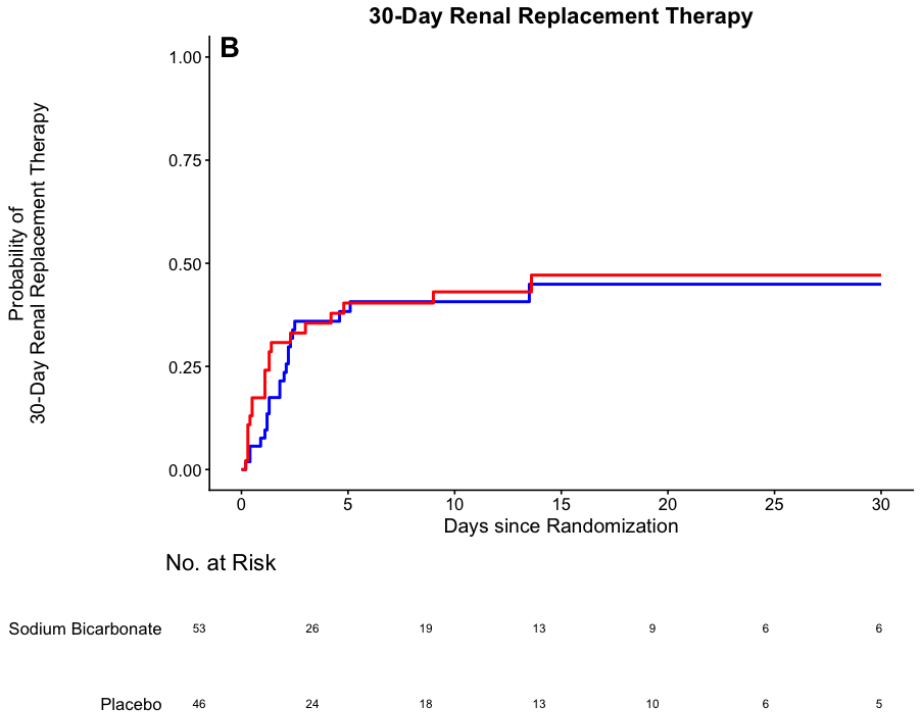
	Sodium Bicarbonate	Placebo	Absolute Difference (95% CI)
pH level			
< 7.25	45 / 93 (48.4%)	53 / 99 (53.5%)	-5.1 (-19.1 to 8.9)
≥ 7.25	53 / 151 (35.1%)	47 / 155 (30.3%)	5.3 (-5.0 to 15.4)
Acute kidney injury			
Stage 2 or 3	30 / 53 (56.6%)	33 / 46 (71.7%)	-15.2 (-34.1 to 3.8)
None or stage 1	68 / 190 (35.8%)	66 / 205 (32.2%)	4.0 (-5.0 to 13.1)
PaCO2 level			
45-50	17 / 41 (41.5%)	15 / 31 (48.4%)	-6.5 (-26.2 to 13.7)
≤ 45	81 / 203 (39.9%)	85 / 223 (38.1%)	1.9 (-7.1 to 10.8)
Type of acidosis			
High anion gap	51 / 105 (48.6%)	44 / 99 (44.4%)	6.7 (-7.2 to 20.0)
Non-anion gap	46 / 138 (33.3%)	54 / 152 (35.5%)	-2.7 (-13.2 to 7.8)
Severity of illness			
High	67 / 119 (56.3%)	66 / 128 (51.6%)	4.0 (-8.2 to 16.1)
Low	31 / 125 (24.8%)	34 / 126 (27.0%)	-1.2 (-11.7 to 9.4)
Received bicarbonate pre-randomisation			
Yes	25 / 35 (71.4%)	17 / 23 (73.9%)	-4.8 (-27.2 to 18.7)
No	73 / 209 (34.9%)	83 / 231 (35.9%)	-0.2 (-8.8 to 8.3)
Septic shock			
Yes	52 / 95 (54.7%)	53 / 104 (51.0%)	3.8 (-9.9 to 17.5)
No	46 / 149 (30.9%)	47 / 150 (31.3%)	0.1 (-9.9 to 10.1)
Type of admission			
Medical	64 / 119 (53.8%)	61 / 123 (49.6%)	4.2 (-8.1 to 16.4)
Surgical	34 / 125 (27.2%)	39 / 131 (29.8%)	-2.1 (-13.1 to 8.8)
Overall	**98 / 244 (40.2%)**	**100 / 254 (39.4%)**	**1.2 (-7.1 to 9.4)**



Results – Stage 2 or 3 AKI Patients

	Sodium Bicarbonate (*n* = 53)	Placebo (*n* = 46)	Absolute Difference (95% CI)
Major adverse kidney events within 30 days – no. (%)	30 (56.6)	33 (71.7)	-15.2 (-34.3 to 4.0)
In-hospital death by day 30 – no. (%)	8 (15.1)	17 (37.0)	-20.8 (-37.6 to -4.0)
Receipt of renal replacement therapy – no. (%)	21 (39.6)	20 (43.5)	-4.2 (-23.7 to 15.3)
Persistent renal dysfunction – no. (%)	14 (26.4)	20 / 45 (44.4)	-17.9 (-36.8 to 1.0)

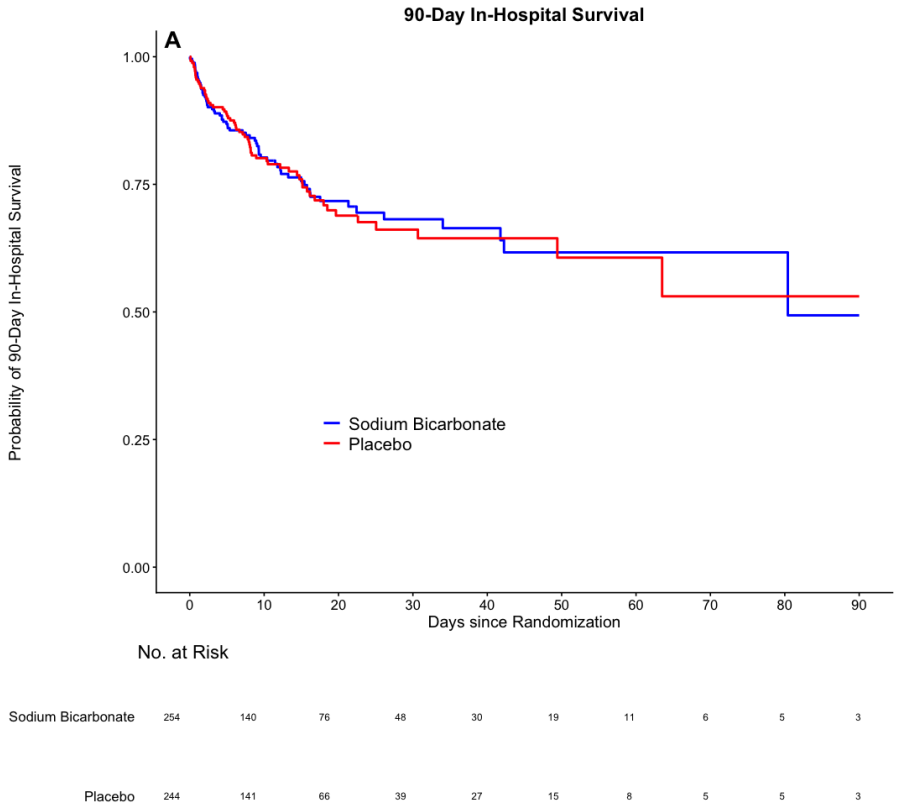




** p value = 0.120*
Data are N / Total (%)

Results – Secondary Outcomes

	Sodium Bicarbonate (*n* = 244)	Placebo (*n* = 254)	Absolute Difference (95% CI)
Renal replacement therapy dependence* – no. (%)	14 (5.7)	23 (9.1)	-3.3 (-7.8 to 1.3)
ICU mortality – no. (%)	49 (20.1)	56 (22.0)	-1.7 (-8.6 to 5.3)
In-hospital death by day 90 – no. (%)	64 (26.2)	65 (25.6)	1.2 (-6.3 to 8.6)



Data are N / Total (%)

Results – Physiological Outcomes

	Sodium Bicarbonate (*n* = 244)	Placebo (*n* = 254)	Absolute Difference (95% CI)
Recurrence of metabolic acidosis – no. (%)	78 (32.0)	141 / 253 (55.7)	-23.3 (-31.4 to -15.1)
Acute kidney injury – no. (%)	156 / 242 (64.5)	162 / 250 (64.8)	-0.0 (-7.7 to 7.6)
Stage 1	64 / 156 (41.0)	58 / 162 (35.8)	
Stage 2	35 / 156 (22.4)	44 / 162 (27.2)	
Stage 3	57 / 156 (36.5)	60 / 162 (37.0)	

Data are N / Total (%)

Results – Process of Care Measures

	Sodium Bicarbonate (*n* = 244)	Placebo (*n* = 254)	Absolute Difference (95% CI)
Vasopressor-free days at day 30	27.2 (0.0 – 28.9)	27.6 (6.1 – 28.9)	-0.5 (-1.3 to 0.4)
Renal replacement therapy-free days at day 30	30.0 (0.0 – 30.0)	30.0 (10.4 – 30.0)	-0.0 (-0.6 to 0.6)
ICU-free days at day 30	23.7 (0.0 – 26.9)	24.0 (0.0 – 27.0)	-0.5 (-2.3 to 1.3)
Hospital-free days at day 90	69.3 (0.0 – 79.8)	69.2 (0.0 – 80.6)	1.1 (-6.4 to 8.6)

Data are median (quartile 25th – quartile 75th)

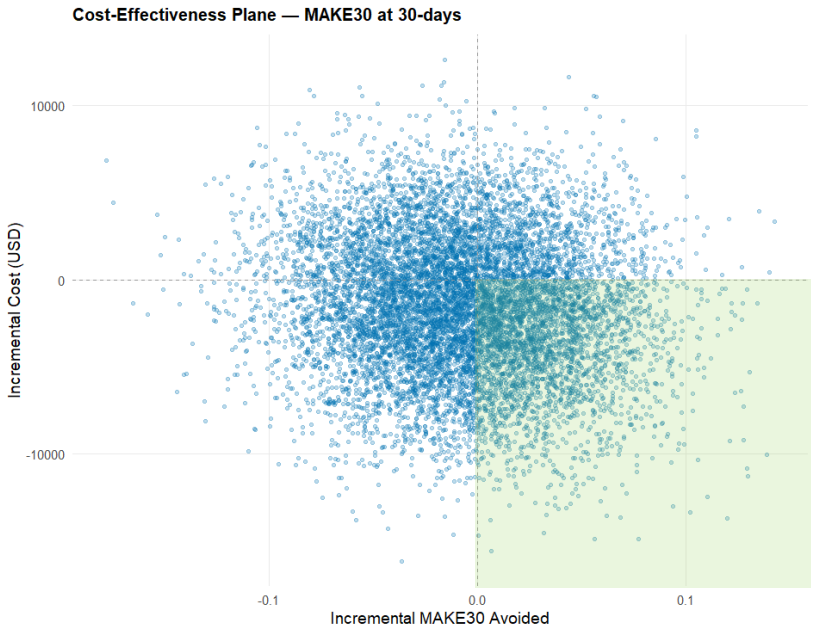
Results – Adverse Events

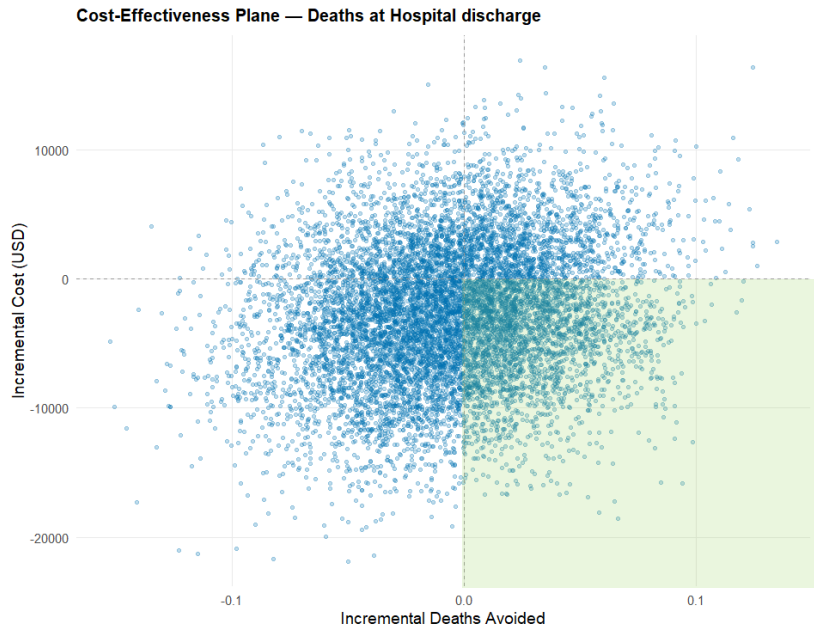
	Sodium Bicarbonate (*n* = 244)	Placebo (*n* = 254)	*p* value
Any adverse event – no. (%)	4 / 244 (1.6)	0 / 254 (0.0)	0.057
Serious adverse event	0 / 244 (0.0)	0 / 254 (0.0)	0.999
During the infusion period – no. (%)			
Hypokalemia (K < 3.0 mmol/L) needing correction	4 / 244 (1.6)	0 / 254 (0.0)	0.057
Dysnatremia (Na > 155 mEq/L)	1 / 244 (0.4)	0 / 254 (0.0)	0.490
Hypocalcemia (iCa < 0.8 mmol/L) needing correction	0 / 244 (0.0)	0 / 254 (0.0)	---
Hypercapnia ($PaCO_2$ > 50 mmHg)	0 / 244 (0.0)	0 / 254 (0.0)	---
Hypervolemia (PaO_2/FiO_2 <100 due to hypervolemia)†	0 / 244 (0.0)	0 / 254 (0.0)	---
Other	0 / 244 (0.0)	0 / 254 (0.0)	0.999

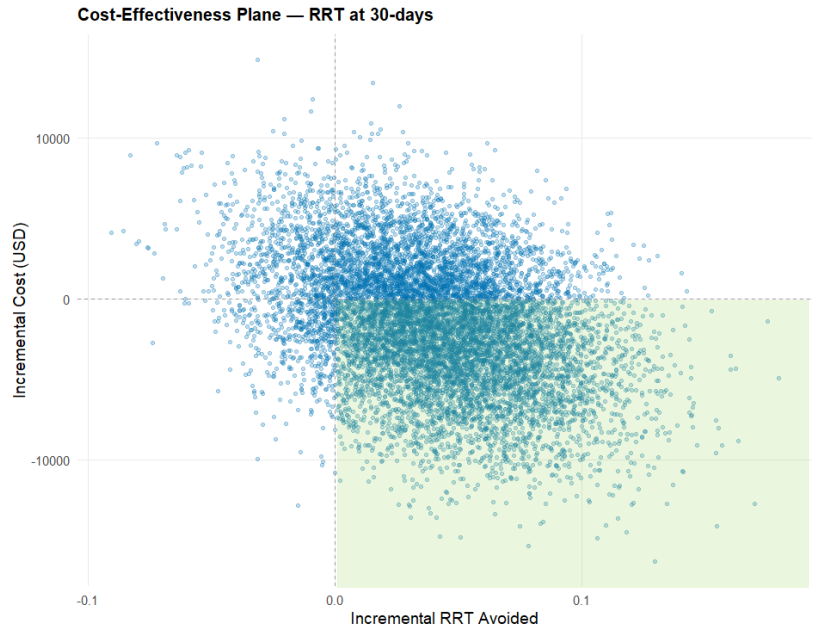
Data are median (quartile 25th – quartile 75th) or N / Total (%)

Results – Health Economic Analysis

	Sodium Bicarbonate (*n* = 244)	Placebo (*n* = 254)	Incremental Cost (95% CI), $	Incremental Outcome (95% CI)	ICER (cost / outcome)
Major adverse kidney events within 30 days	98 (40.2%)	100 (39.4%)	-1,549 (-9,440, 6,098)	-0.01 (-0.09, 0.08)	$207,873
Receipt of renal replacement therapy	41 (16.8%)	53 (20.9%)	-1,472 (-9,458, 6,172)	0.04 (-0.03, 0.11)	Dominant
In-hospital death by day 90	64 (26.2%)	65 (25.6%)	-2,711 (-13,131, 7,726)	-0.01 (-0.09, 0.07)	$462,999







Data are median (quartile 25th – quartile 75th) or N / Total (%)

Agenda

- **Rationale**
  - Importance of metabolic acidosis
  - Use of sodium bicarbonate in metabolic acidosis
  - Evidence on the use of sodium bicarbonate in metabolic acidosis
  - SODa-BIC pilot
- **Aim**
- **Methods**
  - Patients
  - Randomisation and interventions
  - Outcomes
  - Statistical analysis
- **Results**
- **Conclusions**

Conclusion

In critically ill patients with metabolic acidosis and receiving vasopressors to treat hypotension, sodium bicarbonate therapy did not reduce major adverse kidney events within 30 days compared to placebo

Acknowledgements



Acknowledgements



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sodium Bicarbonate for Critically Ill Adults with Metabolic Acidosis and Shock

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ANZICS Clinical Trials Group

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