



Sodium bicarbonate for severe metabolic acidaemia

Severe metabolic acidaemia (blood pH ≤ 7.20) is associated with impaired haemodynamics and increased mortality in critically ill patients.¹ Administration of sodium bicarbonate can increase blood pH, but its ability to improve haemodynamics and reduce mortality remains unproven.²⁻⁶ Sodium bicarbonate has been shown to increase blood pH levels but did not increase cardiac output compared with saline when examined at 30 min or 60 min after infusion,^{3,6} and did not reduce mortality in studies involving cohorts of 34–150 individuals with severe acidaemia.^{2,4,5,7}

To further examine the effect of sodium bicarbonate administration on morbidity and mortality, Samir Jaber and colleagues⁸ report in *The Lancet* the results of a multicentre, open-label, randomised controlled trial, in which they randomly assigned 389 patients from the intensive care unit (ICU) with blood pH levels of 7.20 or less to treatment with 4.2% sodium bicarbonate (ie, the bicarbonate group) to increase and maintain blood pH to 7.30 or more, or no bicarbonate infusion (ie, the control group). The primary outcome was a composite of death by day 28 and the presence of at least one organ failure at day 7. No difference in the primary outcome was observed between the bicarbonate group and control group (66% vs 71%; $p=0.24$). However, in a prespecified stratum of patients with Acute Kidney Injury Network (AKIN) scores of 2–3 ($n=182$), the primary outcome occurred less frequently in the bicarbonate group than in the control group (70% vs 82%; $p=0.0462$). Moreover, the need for renal-replacement therapy during the ICU stay was lower in the bicarbonate group than in the control group for both the overall population (35% vs 52%; $p<0.0001$) and the prespecified AKIN stratum (51% vs 73%; $p=0.0020$).

The main strengths of Jaber and colleagues' study⁸ are the large cohort of patients randomly assigned to receive sodium bicarbonate or no sodium bicarbonate therapy, and that the outcomes of patients with advanced acute kidney injury were analysed separately. Reflecting the challenges of such clinical trials in the critically ill, 24% of the patients in the control group received sodium bicarbonate infusion after randomisation (patients were excluded from the intention-to-treat analysis) and 52% of patients in the control group were dialysed and, therefore, received sodium bicarbonate

treatment. Moreover, on the basis of the inclusion criteria, a substantial number of enrolled participants must have had mixed acidaemia rather than metabolic acidaemia. Finally, although there is no consensus, we would have opted for a target blood pH of more than 7.20. Setting a target blood pH of 7.30 or more increases the risk of excessive pH level correction (16% of patients in the bicarbonate group had at least one blood pH >7.45 after enrolment) with a number of potential adverse effects, including increased lactic acid production, hypocalcaemia (seen in 25% of patients receiving sodium bicarbonate treatment), and hypertonicity, thereby contributing to decreased cardiac contractility and increased arrhythmogenicity.^{3,9}

The fact that sodium bicarbonate infusion did not affect the primary outcome in the overall population of this trial is consistent with the results of previous studies.^{2,4,5,7} This absence of benefit has been largely attributed to two adverse effects of bicarbonate infusion: a pH-dependent decrease in the concentration of ionised calcium,³ and intracellular acidification due to tissue accumulation of carbon dioxide.¹⁰ In this regard, the use of central venous blood gases to assess tissue acid-base status could have identified the frequency and magnitude of intracellular acidification, likely to be common because large amounts of sodium bicarbonate were infused in patients with severe circulatory compromise.¹¹ The importance of the prevention of hypocalcaemia and tissue accumulation of carbon dioxide following sodium bicarbonate infusion is emphasised by the fact that their prevention in an experimental rat model of acute lactic acidosis resulted in improved cardiac contractility and vascular responsiveness to catecholamines.¹²

The lower incidence of the primary outcome in patients with advanced acute kidney injury receiving sodium bicarbonate treatment is intriguing, and it requires further study. The reduced need for renal-replacement therapy during the ICU stay in the bicarbonate group of the trial most likely reflects less severe hyperkalaemia or acidaemia. Nonetheless, renal-replacement therapy has great appeal, as it is likely to allow for better control of serum osmolality, ionised calcium, and extracellular volume—factors that are likely to affect the response to sodium bicarbonate.



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The treatment of severe metabolic acidaemia in critically ill patients remains a challenging problem. Further assessment of the potential roles of sodium bicarbonate, other bases, and dialysis is needed, primarily evaluated with randomised controlled studies, such as the one reported here. Also, the effect of inhibition of an activated NHE1 (sodium/hydrogen exchanger 1)¹ and catecholamine-induced stimulation of Na⁺-K⁺-ATPase¹ as well as aerobic glycolysis, which have all been shown to improve haemodynamics and clinical outcome in experimental studies, deserves exploration.

*Jeffrey A Kraut, Nicolaos E Madias

Medical and Research Services and Division of Nephrology, VA Greater Los Angeles Healthcare System, UCLA Membrane Biology Laboratory, David Geffen School of Medicine at UCLA, Los Angeles, CA 90073, USA (JAK); Department of Medicine, Division of Nephrology, St Elizabeth's Medical Center, Boston, MA, USA (NEM); and Department of Medicine, Tufts University School of Medicine, Boston, MA, USA (NEM)
 jkraut@ucla.edu

JAK and NEM contributed equally to this Comment. JAK has a pending patent for improving the treatment of acute metabolic acidosis. NEM declares no competing interests.

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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

Samir Jaber, Catherine Paugam, Emmanuel Futier, Jean-Yves Lefrant, Sigismond Lasocki, Thomas Lescot, Julien Pottecher, Alexandre Demoule, Martine Ferrandière, Karim Asehnoune, Jean Dellamonica, Lionel Velly, Paër-Sélim Abback, Audrey de Jong, Vincent Brunot, Fouad Belafia, Antoine Roquilly, Gérald Chanques, Laurent Muller, Jean-Michel Constantin, Helena Bertet, Kada Klouche, Nicolas Molinari, Boris Jung, for the BICAR-ICU Study Group*

Summary

Background Acute acidaemia is frequently observed during critical illness. Sodium bicarbonate infusion for the treatment of severe metabolic acidaemia is a possible treatment option but remains controversial, as no studies to date have examined its effect on clinical outcomes. Therefore, we aimed to evaluate whether sodium bicarbonate infusion would improve these outcomes in critically ill patients.

Methods We did a multicentre, open-label, randomised controlled, phase 3 trial. Local investigators screened eligible patients from 26 intensive care units (ICUs) in France. We included adult patients (aged ≥ 18 years) who were admitted within 48 h to the ICU with severe acidaemia (pH ≤ 7.20 , PaCO₂ ≤ 45 mm Hg, and sodium bicarbonate concentration ≤ 20 mmol/L) and with a total Sequential Organ Failure Assessment score of 4 or more or an arterial lactate concentration of 2 mmol/L or more. We randomly assigned patients (1:1), by stratified randomisation with minimisation via a restricted web platform, to receive either no sodium bicarbonate (control group) or 4.2% of intravenous sodium bicarbonate infusion (bicarbonate group) to maintain the arterial pH above 7.30. Our protocol recommended that the volume of each infusion should be within the range of 125–250 mL in 30 min, with a maximum of 1000 mL within 24 h after inclusion. Randomisation criteria were stratified among three prespecified strata: age, sepsis status, and the Acute Kidney Injury Network (AKIN) score. The primary outcome was a composite of death from any cause by day 28 and the presence of at least one organ failure at day 7. All analyses were done on data from the intention-to-treat population, which included all patients who underwent randomisation. This study is registered with ClinicalTrials.gov, number NCT02476253.

Findings Between May 5, 2015, and May 7, 2017, we enrolled 389 patients into the intention-to-treat analysis in the overall population (194 in the control group and 195 in the bicarbonate group). The primary outcome occurred in 138 (71%) of 194 patients in the control group and 128 (66%) of 195 in the bicarbonate group (absolute difference estimate -5.5% , 95% CI -15.2 to 4.2 ; $p=0.24$). The Kaplan-Meier method estimate of the probability of survival at day 28 between the control group and bicarbonate group was not significant (46% [95% CI 40–54] vs 55% [49–63]; $p=0.09$). In the prespecified AKIN stratum of patients with a score of 2 or 3, the Kaplan-Meier method estimate of survival by day 28 between the control group and bicarbonate group was significant (63% [95% CI 52–72] vs 46% [35–55]; $p=0.0283$). Metabolic alkalosis, hypernatraemia, and hypocalcaemia were observed more frequently in the bicarbonate group than in the control group, with no life-threatening complications reported.

Interpretation In patients with severe metabolic acidaemia, sodium bicarbonate had no effect on the primary composite outcome. However, sodium bicarbonate decreased the primary composite outcome and day 28 mortality in the a-priori defined stratum of patients with acute kidney injury.

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Introduction

Acute acidaemia is frequently observed during critical illness, with a reported incidence varying from 14% to 42%.^{1–5} Persistent acidaemia has been associated with poor prognosis,^{1–3,6} with a mortality rate as high as 57% when the pH stays below 7.20.⁵ Along with case-specific treatment, improvement of tissue perfusion and supportive measures such as mechanical ventilation and renal-replacement therapy are the cornerstones of

severe metabolic acidaemia management in critically ill patients.^{2,3,7} Because an acidotic cellular environment can cause cellular dysfunction, intravenous sodium bicarbonate administration to increase the pH might also be beneficial. In a survey done in North America, more than two-thirds of the programme directors in nephrology or intensive care units (ICUs) declared that they used sodium bicarbonate for the treatment of acidaemia with hyperlactataemia.⁸

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*The BICAR-ICU study investigators are listed in the appendix

Saint Eloi ICU (Prof S Jaber MD, A de Jong MD, F Belafia MD, Prof G Chanques MD) and Département de Médecine Intensive et Réanimation (V Brunot MD, Prof K Klouche MD, Prof B Jung MD), Montpellier University Hospital, PhyMedExp, INSERM, CNRS, Montpellier, France; AP-HP, Département Anesthésie et Réanimation, Hôpital Beaujon, Hôpitaux Universitaires Paris Nord Val de Seine, Paris, France (Prof C Paugam MD, P-S Abback MD); CHU de Clermont-Ferrand, Department of Perioperative Medicine, GReD, UMR/CNRS6293, University Clermont Auvergne, INSERM U1103, Clermont-Ferrand, France (Prof E Futier MD, Prof J-M Constantin MD); CHU de Nîmes, Département Anesthésie et Réanimation, University of Montpellier-Nîmes, Nîmes, France (Prof J-Y Lefrant MD, L Muller MD); CHU d'Angers, Réanimation Chirurgicale, Angers, France (Prof S Lasocki MD); AP-HP, Département Anesthésie et Réanimation, Hôpital Saint Antoine, Paris, France (Prof T Lescot MD); Hôpitaux Universitaires de Strasbourg, Service d'Anesthésie-Réanimation Chirurgicale-Université de Strasbourg, Fédération de Médecine Translotionnelle de Strasbourg, Strasbourg, France

(Prof J Pottecher MD); Service de Pneumologie, Sorbonne Université, INSERM, UMR51158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France (Prof A Demoule MD); AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie et Réanimation Médicale du Département R35, Paris, France (Prof A Demoule); CHU de Tours, Réanimation Chirurgicale, Tours, France (M Ferrandière MD); CHU de Nantes, Département Anesthésie et Réanimation Chirurgicale, Nantes, France (Prof K Asehounne MD, A Roquilly MD); CHU de Nice, Département de Réanimation Médicale, INSERM-C3M-Université Côte d'Azur, Nice, France (Prof J Dellamona MD); Aix-Marseille Université, AP-HM, Département Anesthésie et Réanimation Chirurgicale, Groupe Hospitalier Timone, UMR 7289, CNRS, Marseille, France (Prof L Velly MD); and CHU de Montpellier, Department of Statistics, Montpellier University, Montpellier, France (Prof N Molinari PhD, H Bertet MSc)

Correspondence to: Prof Samir Jaber, Saint Eloi ICU, Montpellier University Hospital, PhyMedExp, INSERM, CNRS, Montpellier 34295, France s-jaber@chu-montpellier.fr

See Online for appendix

Research in context

Evidence before this study

We searched PubMed from Jan 1, 1990, to Feb 1, 2018, using the search terms “sodium bicarbonate” or “metabolic acidemia”. Studies were included if they evaluated sodium bicarbonate infusion as an intervention to treat severe metabolic acidemia. Our review indicates that sodium bicarbonate infusion to increase the arterial pH in this condition has been sparsely evaluated. Animal studies, single centre crossover studies with physiological parameters as a main outcome, and reviews from experts have recommended against its use. Surveys and observational studies have, however, reported that more than half of the critical care physicians or nephrologists would consider sodium bicarbonate infusion for a patient with severe metabolic acidemia whatever its cause. Finally, the 2017 Surviving Sepsis Campaign stated that “the effect of sodium bicarbonate administration on hemodynamics and vasopressor requirements at lower pH (than 7–15 as well as the effect on clinical outcomes at any pH level, is unknown” and that “no studies have examined the effect of bicarbonate administration on outcomes”.

Added value of this study

This is the first large randomised clinical trial comparing two groups of no sodium bicarbonate infusion (control group) with sodium bicarbonate infusion (bicarbonate group) in 400 critically ill patients with severe metabolic acidemia (pH ≤ 7.20) from 26 Intensive Care Units. In this trial, we report

that in the overall population sodium bicarbonate infusion was not associated with an improvement in the primary outcome (ie, composite criteria of organ failure at day 7 and any cause of death at day 28). In the a-priori defined clinical stratum of patients with acute kidney injury (with Acute Kidney Injury Network scores of 2 or 3 at enrolment), the primary outcome occurred less frequently in the bicarbonate group than in the control group. Additionally, the number of days alive and free from renal-replacement therapy was higher in the bicarbonate group than in the control group both in the overall study population and in the a-priori defined stratum of patients with acute kidney injury. No other organ support parameters were different among treatment groups.

Implications of all the available evidence

The findings of the BICAR-ICU trial suggest that sodium bicarbonate infusion is associated with an improved outcome and a reduced rate of mortality from enrolment to day 28 in critically ill patients with severe metabolic acidemia (pH ≤ 7.20) and acute kidney injury. Sodium bicarbonate infusion was also associated with more days alive and free from renal-replacement therapy. However, in the overall non-selected patients, sodium bicarbonate infusion was not associated with a clinical outcome. Further studies should be done to investigate whether sodium bicarbonate infusion might improve survival in a larger dataset and in selected patients with severe metabolic acidemia and acute kidney injury.

Despite the frequency of its use in ICUs across the world, the effect of sodium bicarbonate infusion for the treatment of metabolic acidemia remains **controversial**.⁹ Small physiological studies,^{10,11} along with retrospective or observational studies,^{12,13} have not shown clear conclusions. The reluctance to use sodium bicarbonate for the treatment of severe metabolic acidemia might be related to the **absence of cardiovascular effects in two physiological studies^{10,11} and potential side-effects, principally intracellular acidification** due to the accumulation of carbon dioxide and the risk of **hypocalcaemia**.^{3,10,14} However, sodium bicarbonate could compensate for the deleterious effects of acidotic cells on cardiovascular and oxygen delivery, and might delay or avoid unnecessary early renal-replacement therapy.

The 2016 update of the Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic Shock¹⁵ suggested that the effect of sodium bicarbonate administration on haemodynamics and vasopressor requirements at lower pH as well as its effect on clinical outcomes at any pH level is unknown, and no studies have examined the effect of sodium bicarbonate administration on clinical outcomes. The **absence of high-level evidence leaves ICU clinicians uncertain** whether sodium bicarbonate infusion is beneficial, ineffective, or indeed harmful to patients with severe

metabolic acidemia. Given such uncertainties, we aimed to evaluate whether sodium bicarbonate infusion would improve clinical outcome in critically ill patients with severe metabolic acidemia. Specifically, we hypothesised that early sodium bicarbonate infusion compared with no infusion would result in fewer deaths from any cause by 28 days and lower incidence of at least one organ failure at 7 days in adult ICU patients with severe metabolic acidemia.

Methods

Study design and patients

We did a multicentre, open-label, randomised controlled, phase 3 trial. Local investigators screened eligible patients from 26 ICUs in France. The study protocol and statistical analysis plan was approved for all centres by a central ethics committee (Comité de Protection des Personnes Sud-Est IV, Montpellier, France; EudraCT, number 2014-000245-73) in accordance with both French law and the Declaration of Helsinki.

We included adult patients (aged ≥ 18 years) who were admitted within 48 h to the ICU with **severe acidemia (pH ≤ 7.20 , PaCO₂ ≤ 45 mm Hg, and sodium bicarbonate concentration ≤ 20 mmol/L)³ and with a total Sequential Organ Failure Assessment (SOFA) score of 4 or more or an arterial lactate concentration of 2 mmol/L or more.**

We excluded patients who met the following main exclusion criteria: respiratory acidosis, proven digestive or urinary tract loss of sodium bicarbonate (volume loss ≥ 1500 mL per day), stage IV chronic kidney disease,¹⁶ ketoacidosis, and sodium bicarbonate infusion (including renal-replacement therapy) within 24 h before screening. The appendix provides the full exclusion criteria.

We obtained written informed consent from the patient or a relative upon study inclusion. However, considering the severity of the illness, the fact that most of these patients would be unable to consent (sedation or potential delirium)^{17–19} and that their proxies might not be contactable at the time of inclusion, a deferred consent process for emergency situations was enabled. When deferred consent was used, written permission to pursue the research was obtained from the patient or proxy as soon as possible. If this consent was not obtained, the patient's data were not used and they were withdrawn from the trial.

Randomisation and masking

We randomly assigned eligible patients within 48 h of ICU admission in a one-to-one ratio to receive either no sodium bicarbonate infusion (control group) or sodium bicarbonate infusion (bicarbonate group). We randomly assigned patients by stratified randomisation with minimisation using a computer-generated allocation sequence accessible from each centre through a secured-dedicated website with stratification according to study site and three prespecified factors: age with a cutoff of 65 years, presence or absence of suspected sepsis,^{20,21} and presence or absence of Acute Kidney Injury Network (AKIN) score of 2 or 3. Because sodium bicarbonate infusion influences arterial pH levels and because routine arterial blood gases must be done in critically ill patients, masking of the physicians and nurses was not feasible.

Procedures

In the intervention group, 4.2% sodium bicarbonate was intravenously infused with the aim of achieving an arterial pH of 7.30 or more during the 28-day ICU admission or ICU discharge because preliminary results suggested that arterial pH in survivors approximated 7.30 by day 1 although persistent severe acidaemia was observed in non-survivors.⁵ Our protocol recommended that the volume of each sodium bicarbonate infusion should be within the range of 125–250 mL in 30 min, with a maximum of 1000 mL within 24 h after inclusion, and that measurement of arterial blood gas should be done 1–4 h after the end of each infusion (appendix p 17). Hypertonic 4.2% sodium bicarbonate was chosen according to the scarce literature available,^{10,11,22} the current practice when sodium bicarbonate is used as reported by Jung and colleagues,⁵ and the objective of titrating a pH target of 7.30 or more.

In both groups, indications for renal-replacement therapy were standardised. Upon admission, urgent

renal-replacement therapy was strongly recommended in the event of kallaemia that was more than 6.5 mmol/L with electrocardiogram signs or cardiogenic pulmonary oedema with no urine output, or both. At 24 h after inclusion, renal-replacement therapy was recommended when two of three criteria were present: urine output less than 0.3 mL/kg per h for at least 24 h, arterial pH less than 7.20 despite resuscitation, and kallaemia more than 6.5 mmol/L. Each study site chose the method of renal-replacement therapy according to the local guidelines, which provided additional base because the dialysis included sodium bicarbonate as a buffer.²³ In both groups, initiation of invasive mechanical ventilation was indicated if patients had one major or two minor predefined clinical events (appendix).²⁴

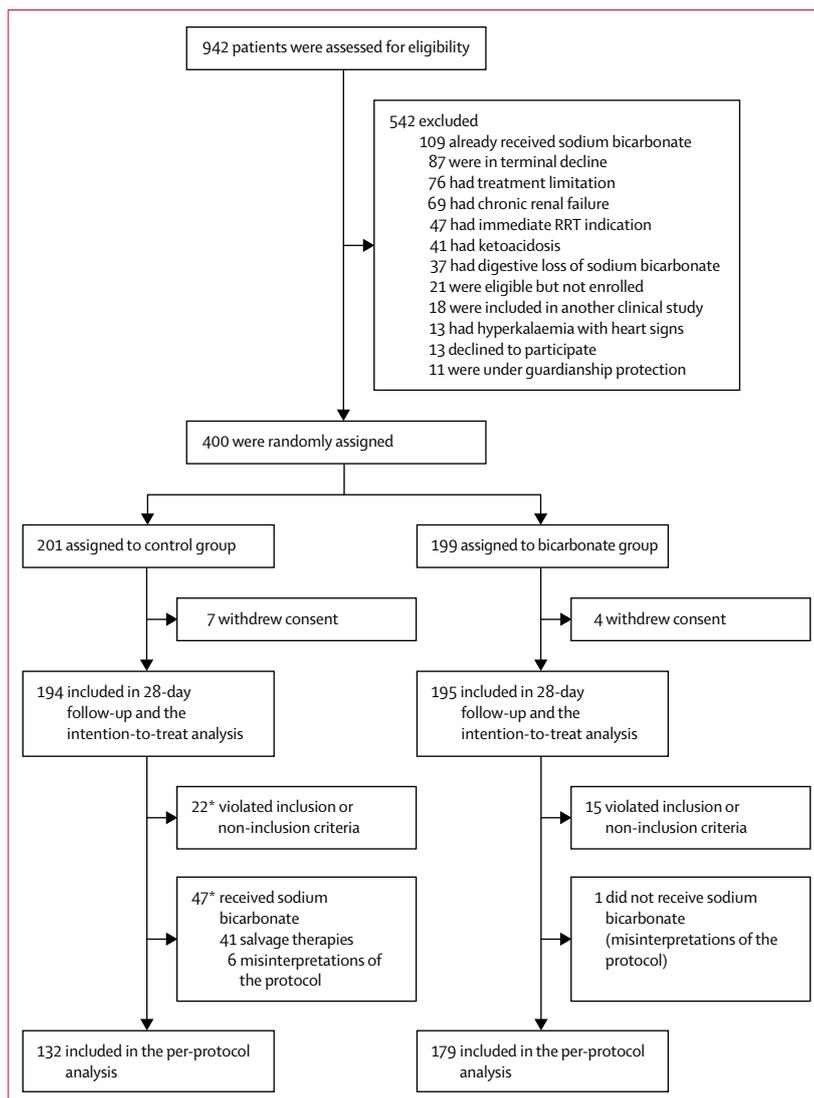


Figure 1: Trial profile

RRT=renal-replacement therapy. *Seven patients both violated inclusion or non-inclusion criteria and received sodium bicarbonate.

Demographic characteristics, including Simplified Acute Physiology Score II and McCabe class, were collected at enrolment. Electrolytes were collected for the study's purposes using each site's local laboratory facility at enrolment, 12 h, 24 h, 48 h, and day 7.

Outcomes

The primary outcome measure was a composite of death from any cause by 28 days after randomisation and the presence of at least one organ failure at 7 days after randomisation. A-priori secondary outcome measures were the use, duration, and number of days alive free of life-support interventions (such as renal-replacement therapy, mechanical ventilation, and vasopressors); the SOFA score at enrolment and at 1 day, 2 days, and 7 days after enrolment; the total fluid intake between enrolment and day 2; the adverse events of electrolytes that occurred during the ICU stay (plasma pH >7.45, kallaemia >5 mmol/L or <3.2 mmol/L; natraemia >145 mmol/L, and ionised calcaemia <0.9 mmol/L); the occurrence of ICU-acquired infections; and the length of stay in the ICU.

Statistical analysis

This trial was planned with an interim analysis after the observation of the primary outcome of 200 patients (appendix). On the basis of a previous study,⁵ we calculated that a total of 376 patients would be needed for an 80% statistical power to show an absolute between-group difference of 15% in the primary outcome at a two-sided α level of 0.03 (0.02 for the interim analysis and 0.03 for the final analysis), assuming that the administration of sodium bicarbonate would be associated with a decrease from 45% to 30% in the primary endpoint. Assuming less than 8% non-analysable patients (loss to follow-up or consent withdrawal), we planned to randomly assign 400 patients.

All analyses were done on data from the intention-to-treat population, which included all patients who underwent randomisation. In the per-protocol analysis, we excluded patients with protocol violations (appendix). We made no imputation for missing values. Baseline characteristics in each study group were analysed as frequencies and percentages for categorical variables and as means and SDs or medians and IQRs for continuous variables, as appropriate. We used an unadjusted χ^2 test for the primary outcome analysis and its two components (ie, death from any cause by 28 days and the presence of at least one organ failure at 7 days). We did a multiple logistic regression for the primary outcome. The survival time was described by means of Kaplan-Meier method and compared with a log-rank test. A Cox proportional-hazards model was used to calculate hazard ratios (HRs) for death. For this analysis, data from all patients were censored at the time of death or at day 28. Logistic and Cox regression models were adjusted on relevant baseline covariates. Covariates were defined as binary variables and continuous variables dichotomised according to their median tested in the model, and were selected in a backward selection procedure if $p < 0.15$ in the univariate analysis and then presented as adjusted odds ratios (ORs) or HRs with 95% CIs (appendix pp 28–34). An adjusted χ^2 test was done to compare day 28 mortality proportion in each group. For multiple comparisons in each prespecified stratum, a

	Control group (n=194)	Bicarbonate group (n=195)
Age		
Median age (years)	65 (55–75)	66 (55–75)
≥65	100 (52%)	104 (53%)
<65	94 (48%)	104 (47%)
Sex		
Men	123 (63%)	115 (59%)
Women	71 (37%)	80 (41%)
Body-mass index (kg/m ²)	27 (23–30)	26 (23–29)
Simplified Acute Physiology Score II*	60 (48–73)	59 (49–73)
Pre-existing conditions†		
Alcohol abuse	46 (24%)	38 (19%)
Current smoker	61 (31%)	53 (27%)
Diabetes mellitus	43 (22%)	54 (28%)
Chronic hypertension	90 (46%)	88 (45%)
Ischaemic heart disease	28 (14%)	31 (16%)
Chronic heart failure	7 (4%)	8 (4%)
Chronic kidney disease	15 (8%)	14 (7%)
Severe liver insufficiency	17 (9%)	11 (6%)
Cirrhosis	29 (15%)	23 (12%)
Chronic respiratory insufficiency	8 (4%)	9 (5%)
Chronic obstructive pulmonary disease	29 (15%)	18 (9%)
Immunocompromised‡	36 (19%)	30 (15%)
McCabe class§		
0	83 (53%)	94 (56%)
1	62 (39%)	50 (30%)
2	13 (8%)	24 (14%)
Sepsis	115 (59%)	123 (63%)
AKIN status¶		
AKIN 0–1	104 (54%)	103 (53%)
AKIN 2–3	90 (46%)	92 (47%)
Source of admission		
Medical	112 (58%)	110 (56%)
Surgical	82 (42%)	85 (44%)
Main condition associated with acidaemia at enrolment		
Cardiac arrest	18 (9%)	18 (9%)
Septic shock	98 (51%)	107 (55%)
Haemorrhagic shock	40 (21%)	45 (23%)
Others	38 (20%)	25 (13%)
SOFA score at enrolment		
Cardiovascular	4 (4–4)	4 (4–4)
Respiratory	2 (1–3)	2 (1–3)
Neurologic	1 (0–4)	0 (0–3)
Renal	2 (1–3)	2 (0–2)
Hepatic	0 (0–2)	1 (0–2)
Haematological	0 (0–1)	0 (0–2)
Total	10 (7–13)	10 (7–13)

(Table 1 continues on next page)

Holm-Bonferroni method was done to compute an adjusted p value. A mixed regression model was used to model repeated measures (appendix pp 18–21). Interactions between variables and time were tested. We also did all the analyses described above among prespecified strata of the randomisation. Tests for all outcomes were two-sided.

We did all analyses with SAS (version 9.2) or R (version 3.2.3). An independent data and safety monitoring committee, who were masked to the group allocation, supervised the conduct of the study and reviewed safety data, with interim analyses done after the inclusion of 100 and 200 patients. This trial is registered with ClinicalTrials.gov, number NCT02476253.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SJ, HB, NM, and BJ had full access to all the data. The corresponding author had final responsibility for the decision to submit for publication.

Results

From May 5, 2015, to May 7, 2017, a total of 942 patients with severe metabolic acidaemia were assessed for trial eligibility (figure 1). Of these patients, 542 were excluded and 400 were randomly assigned to the study groups (201 in the control group and 199 in the bicarbonate group). After secondary exclusion of 11 patients who withdrew consent, a total of 389 patients were included in the intention-to-treat analysis (n=194 in the control group and n=195 in the bicarbonate group). The characteristics of the patients were well balanced between the two groups (table 1; appendix pp 28, 29). At randomisation, sepsis was present in 238 (61%) of 389 patients and acute kidney injury with AKIN scores of 2 or 3 in 182 (47%) patients. Invasive mechanical ventilation was used in 324 (83%) of 389 patients and vasopressors in 310 (80%) patients. Data for the primary outcome were available for all patients.

Overall, 341 (88%) of 389 patients adhered to the planned treatment in their randomisation group. Sodium bicarbonate was infused in 47 (24%) of 194 patients in the control group, starting at a median of 7 h (IQR 3–27) after randomisation, and in 194 (99%) of 195 patients in the bicarbonate group, starting at a median of 0.2 h (0.1–0.4) after randomisation (table 2; appendix p 17). The proportion of patients in whom the targeted pH of 7.30 was reached and maintained for at least 36 h from enrolment to day 2 was 50 (26%) of 194 patients in the control group and 117 (60%) of 195 patients in the bicarbonate group, taking into account patients who died in the first 48 h ($p < 0.0001$; appendix pp 18, 19). Overall, fluid intake from enrolment to day 1 and from day 1 to day 2 was not different between the two groups (table 2; appendix p 30).

Follow-up data were available for all patients for the primary composite outcome (ie, death by day 28 or at least one organ failure at day 7). The primary outcome occurred in 138 (71%) of 194 patients in the control group and

	Control group (n=194)	Bicarbonate group (n=195)
(Continued from previous page)		
Physiological support†		
Invasive mechanical ventilation	160 (82%)	164 (84%)
Vasopressor support	156 (80%)	154 (79%)
Laboratory results		
Arterial pH	7.15 (7.11–7.18)	7.15 (7.09–7.18)
PaO ₂ -to-FiO ₂ ratio (mm Hg)	229 (142–355)	264 (144–403)
PaCO ₂ (mm Hg)	37 (32–42)	38 (33–42)
Serum bicarbonate (mmol/L)	13 (10–15)	13 (10–15)
Serum lactate (mmol/L)	5.3 (3.4–9.0)	6.3 (3.6–9.7)
Serum lactate ≥ 2 mmol/L at enrolment	152 (78%)	168 (86%)
Serum creatinine (mg/dL)	1.76 (1.21–2.48)	1.67 (1.11–2.33)
Blood urea nitrogen (mg/dL)	31 (20–48)	28 (20–45)

Data are median (IQR), mean (SD), or n (%). FiO₂=fractional concentration of oxygen in inspired air. AKIN=Acute Kidney Injury Network. SOFA=Sequential Organ Failure Assessment. *The Simplified Acute Physiology Score II²⁵ is based on 17 variables; score ranges from 0 to 163, with higher scores indicating more severe disease. †Patients could have more than one pre-existing condition or physiological support, respectively. ‡Defined as >1 mg/kg per day prednisone for 30 days or more, HIV infection, biotherapy, or ongoing chemotherapy. §The McCabe score can range from 0 to 3, with higher scores indicating more severe underlying conditions. McCabe scores were available for 158 patients in the control group and for 168 in the bicarbonate group. ¶AKIN²⁶ stages: stage 1 is serum creatinine increase ≥ 0.3 mg/dL (≥ 26.5 μ mol/L), increase to 1.5–2.0-times from baseline, or urine output <0.5 mL/kg per h for 6 h; stage 2 is serum creatinine increase >2.0 – 3.0 -times from baseline or urine output <0.5 mL/kg per h for 12 h; stage 3 is serum creatinine increase >3.0 -times from baseline or serum creatinine ≥ 4.0 mg/dL (≥ 354 μ mol/L) with an acute increase of at least 0.5 mg/dL (44 μ mol/L), the need for renal replacement-therapy, or urine output <0.3 mL/kg per h for 12 h. AKIN zero means no kidney injury. To convert values for creatinine to μ mol/L, multiply by 88.4. To convert values for blood urea nitrogen to mmol/L, multiply by 0.357. ||SOFA²⁷ includes subscores ranging from 0 to 4 for each of six components (cardiovascular, respiratory, neurological, renal, hepatic, and haematological). Aggregated scores range from 0 to 24, with higher scores indicating more severe organ failure. The SOFA scores at days 1 and 2 after enrolment are shown in the appendix (p 24).

Table 1: Baseline characteristics of the intention-to-treat population

128 (66%) of 195 in the bicarbonate group (absolute difference estimate -5.5% , 95% CI -15.2 to 4.2 ; $p=0.24$; table 2) without significant effect of the treatment group (crude OR 0.775, 95% CI 0.505–1.190; $p=0.24$; appendix pp 33, 34). The Kaplan-Meier method estimate of the probability of survival at day 28 between the control group and bicarbonate group was not significant (46% [95% CI 40–54] vs 55% [49–63]; $p=0.09$; figure 2A). After multivariate analysis, sodium bicarbonate treatment was significantly associated with fewer deaths than no sodium bicarbonate treatment at day 28 (crude HR 0.783, 95% CI 0.0589–1.040; $p=0.091$; and adjusted HR 0.727, 95% CI 0.540–0.979; $p=0.0356$; appendix pp 35, 36).

In the a-priori defined stratum of patients enrolled with acute kidney injury with AKIN scores of 2 or 3, the primary outcome occurred in 74 (82%) of 90 patients in the control group and 64 (70%) of 92 patients in the bicarbonate group (absolute difference estimate -12.3% , 95% CI -26.0 to -0.1 ; $p=0.0462$; table 2). The Kaplan-Meier method estimate of survival by day 28 between the control group and bicarbonate group was significant (63% [95% CI 52–72] vs 46% [35–55]; $p=0.0283$; figures 2B, 2C). Univariate and multivariate analysis showed that sodium bicarbonate treatment was significantly associated with better outcome than no sodium bicarbonate treatment at day 28 (primary composite endpoint crude OR 0.494,

95% CI 0.246–0.995; $p=0.0483$; and adjusted OR 0.387, 95% CI 0.163–0.918; $p=0.0312$; and mortality by day 28 crude HR 0.648, 95% CI 0.435–0.966; $p=0.0332$; and adjusted HR 0.592, 95% CI 0.392–0.895, $p=0.0132$; appendix pp 37–40).

In the per-protocol analysis, the primary outcome occurred in 88 (67%) of 132 patients in the control group and 117 (65%) of 179 in the bicarbonate group ($p=0.81$). 100 (52%) of 194 patients in the control group and 68 (35%) of 195 in the bicarbonate group underwent

	Control group (n=194)	Bicarbonate group (n=195)	Absolute difference estimate (95% CI)	p value
Primary outcome				
Overall population (n=389)				
Composite outcome	138 (71%)	128 (66%)	-5.5 (-15.2 to 4.2)	0.24
Day 28 mortality	104 (54%)	87 (45%)	-9.0 (-19.4 to 1.4)	0.07
At least one organ failure at day 7	134 (69%)	121 (62%)	-2.8 (-15.4 to 9.8)	0.15
Patients with AKIN scores of 2–3* (n=182)				
Composite outcome	74/90 (82%)	64/92 (70%)	-12.3 (-26.0 to -0.1)	0.0462
Day 28 mortality	57/90 (63%)	42/92 (46%)	-17.7 (-33.0 to -2.3)	0.0166
At least one organ failure at day 7	74/90 (82%)	61/92 (66%)	-15.9 (-28.4 to -3.4)	0.0142
Secondary outcomes				
Renal replacement therapy				
Overall population (n=389)				
Use of renal replacement therapy during ICU stay	100 (52%)	68 (35%)	-16.7 (-26.4 to -7.0)	0.0009
Time from enrolment to initiation of renal replacement therapy (h)	7 (3–18)	19 (7–82)	8.8 (3.9 to 15.6)	<0.0001
Renal replacement therapy-free days during ICU stay	8 (0–28)	19 (1–28)	0 (0.0 to 1.0)	0.015
Renal replacement therapy-free days during ICU stay in survivors	28 (25–28)	28 (25–28)	0 (0 to 0)	0.47
Dependence on dialysis at ICU discharge	11/32 (34%)	7/32 (22%)	-12.5 (-34.3 to 9.3)	0.26
Patients with AKIN scores of 2–3* (n=182)				
Use of renal replacement therapy during ICU stay	66/90 (73%)	47/92 (51%)	-22.2 (-36.0 to -8.5)	0.0020
Time from enrolment to initiation of renal replacement therapy (h)	7 (3–17)	20 (8–82)	10.5 (4.0 to 18.5)	<0.0001
Renal replacement therapy-free days during ICU stay	1 (0–22)	10 (1–28)	1.0 (0.0 to 5.0)	0.0040
Renal replacement therapy-free days during ICU stay in survivors	24 (22–28)	28 (19–28)	1.0 (0.0 to 3.0)	0.45
Dependence on dialysis at ICU discharge	10/21 (48%)	5/25 (20%)	-27.6 (-54.1 to -1.1)	0.0465
Other secondary outcomes				
Overall population (n=389)				
Cumulative fluid intake from enrolment to 24 h (mL)	3500 (1500–5250)	3350 (1800–5250)	34.0 (-450 to 500)	0.835
Cumulative sodium bicarbonate volume intake from enrolment to 24 h (mL)	0 (0–0)	500 (250–750)	500 (375 to 500)	<0.0001
Cumulative sodium bicarbonate intake from enrolment to 24 h (mmol)	0 (0–0)	250 (125–375)	250 (187 to 250)	<0.0001
Cumulative fluid intake from 24 h to 48 h (mL)	1050 (0–2000)	1000 (0–2250)	0 (0 to 250)	0.53
Cumulative sodium bicarbonate volume intake from 24 h to 48 h (mL)	0 (0–0)	0 (0–0)	0 (0 to 0)	0.57
Cumulative sodium bicarbonate intake from 24 h to 48 h (mmol)	0 (0–0)	0 (0–0)	0 (0 to 0)	0.57
Duration of invasive mechanical ventilation (days)	3 (2–8)	3 (2–10)	0.0 (0.0 to 1.0)	0.17
Invasive mechanical ventilation-free days	0 (0–24)	4 (0–24)	0 (0 to 0)	0.48
In survivors	24 (17–26)	23 (14–26)	-1.0 (-2.0 to 0.0)	0.13
Duration of vasopressor therapy (days)	2 (1–3)	2 (1–4)	0 (0 to 0)	0.36
Vasopressor-free days	9 (0–26)	19 (0–26)	0.0 (0.0 to 1.0)	0.10
In survivors	26 (24–27)	26 (23–27)	0.0 (-1.0 to 0.0)	0.34
ICU-acquired infections				
Overall	43 (22%)	48 (25%)	2.4 (-6.1 to 10.8)	0.58
Pneumonia	23 (12%)	29 (15%)	3.0 (-3.8 to 9.8)	0.39
Urinary	10 (5%)	3 (2%)	-3.7 (-7.3 to -0.1)	0.0461
Catheter	6 (3%)	8 (4%)	1.0 (-2.8 to 4.7)	0.61
Unexplained bloodstream infection	14 (7%)	13 (7%)	-0.6 (-5.7 to 4.5)	0.81
Length of ICU stay (days)	4 (1–13)	5 (2–16)	1.0 (-2.7 to 0.0)	0.10
ICU-free days	0 (0–18)	0 (0–18)	0.0 (-1.1 to 0.0)	0.77
In survivors	20 (8–24)	16 (1–24)	-1.0 (-4.0 to 0.0)	0.12

(Table 2 continues on next page)

	Control group (n=194)	Bicarbonate group (n=195)	Absolute difference estimate (95% CI)	p value
(Continued from previous page)				
Patients with AKIN scores of 2–3† (n=182)				
Cumulative fluid intake from enrolment to 24 h (mL)	3150 (1450–5250)	3400 (1500–5500)	150 (–560 to 880)	0.67
Cumulative sodium bicarbonate volume intake from enrolment to 24 h (mL)	0 (0–250)	500 (300–1000)	500 (375 to 500)	<0.0001
Cumulative sodium bicarbonate intake from enrolment to 24 h (mmol)	0 (0–125)	250 (150–500)	250 (187–250)	<0.0001
Cumulative fluid intake from 24 h to 48 h (mL)	600 (0–2000)	1000 (0–2200)	0 (0 to 500)	0.29
Cumulative sodium bicarbonate volume intake from 24 h to 48 h (mL)	0 (0–0)	0 (0–0)	0 (0 to 0)	0.99
Cumulative sodium bicarbonate intake from 24 h to 48 h (mmol)	0 (0–0)	0 (0–0)	0 (0–0)	0.99
Duration of invasive mechanical ventilation (days)	3 (2–8)	4 (2–10)	1.0 (0.0 to 2.0)	0.20
Invasive mechanical ventilation-free days	0 (0–18)	2 (0–21)	0 (0 to 0)	0.13
In survivors	22 (18–28)	20 (12–25)	–2 (–5.0 to 1.0)	0.18
Duration of vasopressor therapy (days)	2 (1–3)	2 (1–4)	0.0 (0.0 to 1.0)	0.46
Vasopressor-free days	1 (0–24)	18 (0–26)	1.0 (0 to 4)	0.022
In survivors	25 (24–27)	25 (22–27)	–0.5 (–2 to 1)	0.73
ICU-acquired infections		
Overall	18/90 (20%)	19/92 (21%)	0.9 (–10.9 to 12.6)	0.88
Pneumonia	13/90 (14%)	14/92 (15%)	0.9 (–9.4 to 11.3)	0.86
Urinary	4/90 (4%)	1/92 (1%)	–3.4 (–8.1 to 1.4)	0.21
Catheter	3/90 (3%)	3/92 (3%)	0.0 (–5.3 to 5.2)	1.00
Unexplained bloodstream infection	9/90 (10%)	3/92 (3%)	–6.7 (–13.9 to 0.5)	0.07
Length of ICU stay (days)	4 (1–11)	7 (1–18)	1.0 (0.0 to 4.0)	0.06
ICU-free days	0 (0–13)	0 (0–14)	0 (0 to 0)	0.40
In survivors	17 (12–22)	13 (0–19)	–3.0 (–8.0 to 0.0)	0.10

Data are n (%), n/N (%), or median (IQR). AKIN=Acute Kidney Injury Network. ICU=intensive care unit. *AKIN²⁶ stages: stage 1 is serum creatinine increase ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$), increase to 1.5–2.0-times from baseline, or urine output < 0.5 mL/kg per h for 6 h; stage 2 is serum creatinine increase > 2.0 –3.0-times from baseline or urine output < 0.5 mL/kg per h for 12 h; stage 3 is serum creatinine increase > 3.0 -times from baseline or serum creatinine ≥ 4.0 mg/dL (≥ 354 $\mu\text{mol/L}$) with an acute increase of at least 0.5 mg/dL (44 $\mu\text{mol/L}$), the need for renal replacement-therapy, or urine output < 0.3 mL/kg per h for 12 h. AKIN zero means no kidney injury. To convert values for creatinine to $\mu\text{mol/L}$, multiply by 88.4. To convert values for blood urea nitrogen to mmol/L, multiply by 0.357.

Table 2: Primary and secondary outcomes of the intention-to-treat population

renal-replacement therapy during their ICU stay (absolute difference estimate -16.7 days, 95% CI -26.4 to -7.0 ; $p=0.0009$; figure 3); and when indicated, renal-replacement therapy was started earlier in the control group than in the bicarbonate group (table 2). The number of days alive free from renal-replacement therapy was also significantly lower in the control group than in the bicarbonate group (table 2). Hyperkalaemia and acidaemia were the main reasons for initiation of renal-replacement therapy in the control group (appendix p 41). Sodium bicarbonate treatment was associated with less hyperkalaemia (appendix p 23) and less persistent acidaemia (appendix p 18) than no sodium bicarbonate treatment at day 7. Serum creatinine and serum blood urea nitrogen were the main reasons to start renal-replacement therapy in the bicarbonate group (appendix p 41).

The findings were similar between the overall population and the AKIN 2–3 stratum, with more patients dependent on dialysis at ICU discharge in the control group than in the bicarbonate group (table 2). The number of days free from mechanical ventilation was not different between the two groups for both the overall population and the AKIN 2–3 stratum; and in the AKIN 2–3 stratum, the number of days free from vasopressor was higher in the bicarbonate group than in the control group (table 2).

Length of ICU stay did not differ significantly between the treatment groups for the overall population (table 2); length of hospital stay was 12 days (IQR 1–28) in the control group and 15 days (2–28) in the bicarbonate group.

Metabolic alkalosis, hypernatraemia, and hypocalcaemia were observed more frequently in the bicarbonate group than in the control group, with no life-threatening complications reported (appendix p 31). The appendix (pp 31, 32) provides the full details of the metabolic adverse events observed.

Discussion

In this multicentre randomised trial involving critically ill patients with severe metabolic acidaemia ($\text{pH} \leq 7.20$), the **infusion of sodium bicarbonate**, compared with no infusion, to reach and maintain a targeted pH of 7.30 **did not significantly decrease the primary composite outcome of mortality by day 28** or the presence of at least one organ failure at day 7 in the overall population. However, sodium **bicarbonate** infusion **decreased the need for renal-replacement therapy** during the ICU stay. Moreover, in the a-priori stratum of patients with **acute kidney injury at enrolment**, infusion of sodium **bicarbonate** resulted in **fewer deaths** by day 28 than no infusion of sodium bicarbonate.

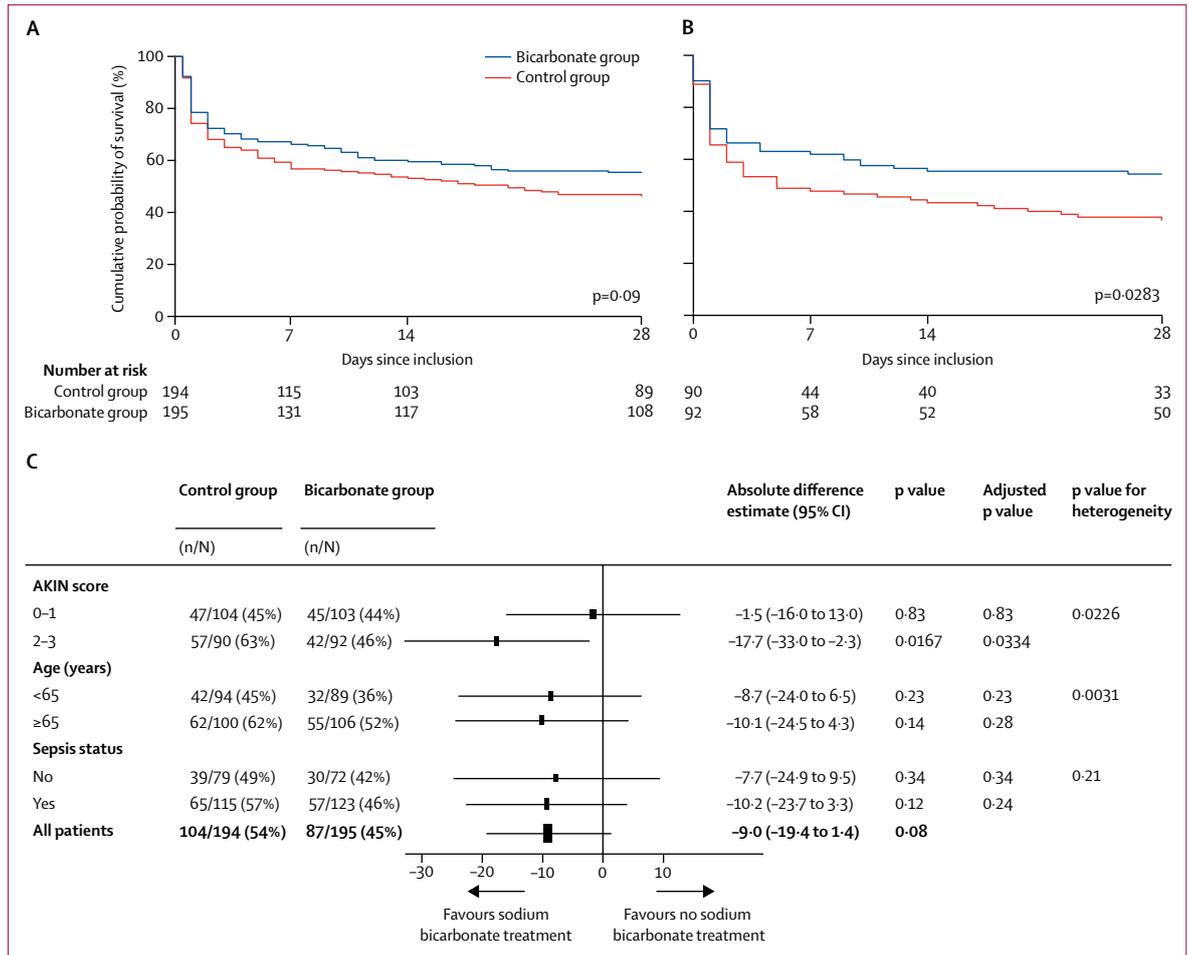


Figure 2: Time to death in the overall population (A) and patients with prespecified acute kidney injury (B), and the 28-day mortality risk difference in the overall population and in the three prespecified strata (C)
 AKIN=Acute Kidney Injury Network. *A χ^2 test was done to compare day 28 mortality proportion in each group. For multiple comparisons in each prespecified stratum, a Holm-Bonferroni method was done to compute an adjusted p value.

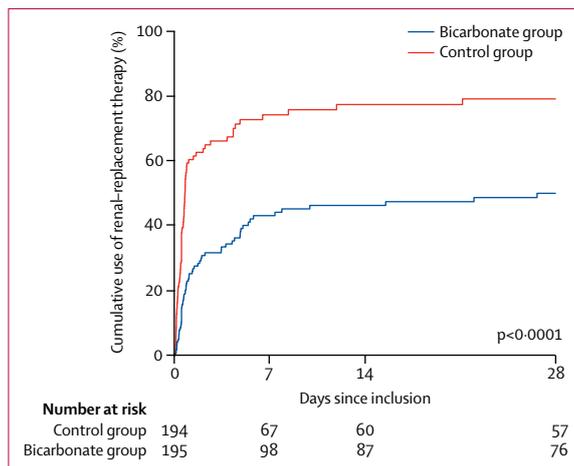


Figure 3: Cumulative use of renal-replacement therapy from enrolment to day 28 in the overall population

The lower mortality in the bicarbonate group among patients with acute kidney injury might have resulted from the combination of more vasopressor-free days and more renal-replacement therapy-free days than for patients in the control group. Sodium bicarbonate infusion in patients with severe metabolic acidaemia and acute kidney injury remains controversial,⁹ and a recent meta-analysis²⁸ from the Cochrane group concluded that there is an inadequate number of randomised clinical trials that have assessed this question. In our trial, almost none of the patients were given sodium bicarbonate in the 24–48 h period, either because of recovery from severe acidaemia or because of death. Although the study was not designed specifically to assess the sodium bicarbonate timing issue, we hypothesise that early sodium bicarbonate infusion is of importance as illustrated by the rapid recovery from severe acidaemia in survivors in our previous observational study,⁵ which evaluated severe acidaemia (pH ≤ 7.20) in the critically ill and its management.

In the AKIKI trial,²⁹ Gaudry and colleagues showed that a delayed renal-replacement therapy strategy was not associated with a significant difference in mortality in critically ill patients with severe acute kidney injury. In our trial, early sodium bicarbonate infusion might have bought time in patients with unstable severe metabolic acidaemia and either avoided or delayed the initiation of the therapy in some patients. Vasopressor-free days were shorter in the control group than in the bicarbonate group of the AKIN 2–3 stratum. Sodium bicarbonate might also have counterbalanced the deleterious consequences of severe acidosis on myocardial contractility, systemic vasodilatation, tissue perfusion, or cellular function³⁴ that might be associated with vasopressor dependency. Although it could be speculated that delayed or absence of renal-replacement therapy in the control group was associated with more cardiovascular instability, recent trials comparing early versus late renal-replacement therapy in critically ill patients do not support this hypothesis.^{29,30} Sodium bicarbonate infusion was associated with metabolic side-effects such as hypernatraemia, hypocalcaemia, and metabolic alkalosis, but none of these episodes were reported as life-threatening in our trial.

There are, however, limitations in our study. No specific control solution was recommended in the control group because there is no fluid without an effect on the acid–base balance. The fluid therapy from enrolment to day 2 was, however, similar in the two groups. Additionally, the physicians caring for the patients in the ICU could not be masked because regular monitoring of arterial blood gases is part of the routine care in patients with severe metabolic acidaemia with a very high risk of mortality. Furthermore, sodium bicarbonate infusion was titrated to reach and maintain a targeted pH of 7·30. However, the endpoints of mortality by day 28 or the presence of at least one organ failure at day 7 were collected and assessed by study members masked to treatment assignment. Another limitation is that the protocol suggested a range of 4·2% sodium bicarbonate volume (125–250 mL per infusion) in the bicarbonate group rather than using a formula to calculate the base deficit and provide a tailored sodium bicarbonate infusion; therefore, we cannot extrapolate whether different ways of administration would have resulted in other outcomes. We also chose not to stratify patients according to the acidaemia mechanism, because the trial was designed to be a pragmatic study. Additionally, the mechanical ventilation settings were not collected. Finally, the causes of acidaemia were heterogeneous, even if septic and haemorrhagic shock were the most common reasons. However, we carefully avoided inclusion of patients with gastrointestinal loss of base or patients with tubular acidosis for whom the indication of sodium bicarbonate infusion is not controversial.

Despite these limitations, our trial presents several strengths, including the multicentre study design, the pragmatism of its design, the well balanced

demographic characteristics, and the intention-to-treat analysis, suggesting that its main result might be generalisable to critically ill patients presenting with severe metabolic acidaemia and at least one organ failure.

In conclusion, in patients with severe metabolic acidaemia, sodium bicarbonate treatment had no effect on the primary composite outcome (ie, mortality by day 28 or the presence of at least one organ failure at day 7), but decreased the need for renal-replacement therapy. Additionally, sodium bicarbonate treatment did decrease mortality in the a-priori defined stratum of patients with acute kidney injury. Whether a different protocol of sodium bicarbonate infusion in terms of tonicity or speed of acidaemia correction could influence the outcome remains to be determined and should be evaluated in future trials.

Contributors

SJ, NM, and BJ designed the study and wrote the report. CP, EF, J-YL, SL, TL, JP, AD, MF, KA, JD, LV, P-SA, Adj, VB, FB, AR, GC, LM, J-MC, HB, and KK approved the design of the study, coordinated individual sites, participated in the inclusion of study participants, and collected the data. All authors revised the report and read and approved the final version before submission.

Declaration of interests

SJ reports receiving grants from the French Ministry of Health and Société Française d'Anesthésie Réanimation; and personal fees from Draeger, Hamilton, Maquet, and Fisher Paykel Healthcare, outside the submitted work. EF reports receiving personal fees from Baxter, Fresenius, and Drager; and non-financial support from Fisher Paykel Healthcare, outside the submitted work. SL reports receiving personal fees from Vifor Pharma and Masimo, outside the submitted work. TL reports receiving personal fees from Baxter, Fresenius, and Merck Sharp & Dohme, outside the submitted work. JP reports receiving personal fees from Medtronic, Getinge, Baxter, and LFB; and non-financial support from Pfizer, outside the submitted work. AD reports receiving grants from the French Ministry of Health and Medtronic; personal fees and non-financial support from Philips, Resmed, and Fisher Paykel Healthcare; and personal fees from Hamilton and Baxter, outside the submitted work. KA reports receiving personal fees from Baxter, Fresenius, Medtronic, LFB, and Merck Sharp & Dohme, outside the submitted work. AR reports receiving personal fees from Merck Sharp & Dohme, outside the submitted work. All other authors declare no competing interests.

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Intravenous Sodium Bicarbonate in Treating Patients With Severe Metabolic Acidemia

Jeffrey A. Kraut and Nicolaos E. Madias

Acute metabolic acidemia, defined as a decrease in blood pH originating from a primary reduction in plasma bicarbonate concentration that is accompanied by an appropriate secondary reduction in $Paco_2$ and is present for up to a few days, can impair hemodynamics and increase mortality, particularly when severe (arterial blood pH < 7.20).^{1,2} In addition to supporting the circulation

Commentary on Jaber S, Paugam C, Fulier E, Lefrant JY, Lasocki S, Lescot T. Sodium bicarbonate therapy for treatment of severe metabolic acidemia in the intensive care unit. Lancet. 2018;392(10141):31-40.

and ventilation as needed, addressing the underlying cause is the most effective means of treatment.³ However, administration of base primarily in the form of intravenous sodium bicarbonate to improve blood pH and that of the intracellular and interstitial compartments is also recommended by some experts⁴ and practiced by many, but not all, nephrologists or critical care physicians.⁵ This recommendation is based on evidence that severe acidemia directly impairs cardiac contractility, attenuates the responsiveness of the heart and vessels to catecholamines, decreases hepatic uptake of lactate, and increases mortality.¹ Nonetheless, studies examining the use of sodium bicarbonate in the treatment of acute metabolic acidemia have heretofore revealed little improvement in clinical outcomes (Table 1).⁶⁻¹¹ However, all involved small numbers of patients and only 2 were randomized and controlled,^{7,10} leaving the possibility that any beneficial effects of bicarbonate might have escaped detection. Therefore, the recent study by Jaber et al¹² reported in *The Lancet* is a welcome addition.

What Does This Important Study Show?

The investigators performed a multicenter, open-label, assessor-blinded, randomized, controlled trial. They assigned 389 adult patients admitted within 48 hours to the intensive care unit with arterial blood pH \leq 7.20, $Paco_2 \leq$ 45 mm Hg, plasma bicarbonate level \leq 20 mmol/L, and total Sequential Organ Failure Assessment (SOFA) score \geq 4 or arterial lactate concentration \geq 2 mmol/L to treatment with either 4.2% sodium bicarbonate to increase and maintain arterial blood pH to \geq 7.30 (bicarbonate arm) or no bicarbonate (control arm). The primary outcome was a composite of death by day 28 and at least 1 organ failure at day 7.

The investigators found no difference in the primary outcome between the bicarbonate and control arms (66% vs 71%; $P = 0.24$). By contrast, in a prespecified stratum of 182 patients with Acute Kidney Injury Network (AKIN)

scores of 2 to 3, the primary outcome occurred less frequently in the bicarbonate arm (70% vs 82%; $P < 0.046$). The probability of survival by day 28 was not different between the bicarbonate and control arms for the overall population (55% vs 46%; $P = 0.09$), but it was greater in the bicarbonate arm for the prespecified acute kidney injury (AKI) stratum (63% vs 46%; $P = 0.028$). Furthermore, the need for renal replacement therapy during the intensive care unit stay was lower in the bicarbonate arm for both the overall population (35% vs 52%; $P < 0.001$) and the prespecified AKI stratum (51% vs 73%; $P < 0.002$).

The main strengths of the study include: (1) random assignment of a large number of patients to bicarbonate or no bicarbonate therapy (4-fold more patients than the largest previously published randomized controlled trial), and (2) separate analysis of the impact of bicarbonate therapy on the clinical outcomes of patients who had advanced AKI.

The study has limitations. Because the cause of the acidemia was sepsis or shock and patients with diabetic ketoacidosis, diarrhea, or urinary bicarbonate wasting were excluded, results are most applicable to patients with lactic acidosis. Therefore, besides the mentioned disorders, the findings cannot be extrapolated to other causes of severe metabolic acidemia such as intoxications or non-anion gap acidosis associated with the infusion of chloride-containing solutions.^{13,14}

Twenty-four percent of patients in the control arm received bicarbonate after random assignment as a protocol violation and 52% of patients in the control arm were dialyzed and therefore received some bicarbonate; both these occurrences made it more difficult to demonstrate a treatment effect of sodium bicarbonate. Other than sodium bicarbonate, the type of fluid administered to patients was not standardized across the 26 participating intensive care units, but patients received only normal saline or Ringer's lactate solution and total volume of fluids given was not different between the 2 study arms.

The patients were reported to have metabolic acidemia. However, the vast majority had a higher $Paco_2$ for the prevailing plasma bicarbonate concentration, reflecting mixed metabolic and respiratory acidemia. Finally, setting a treatment target of arterial blood pH \geq 7.30 increased the risk for excessive correction of blood pH; 16% of patients in the bicarbonate arm had at least 1 blood pH value > 7.45 postenrollment. Aggressive administration of sodium bicarbonate might cause derangements that could contribute to decreased cardiac contractility and increased arrhythmogenicity, such as an abrupt increase in pH,

Table 1. Studies Examining the Impact of Sodium Bicarbonate Therapy on Clinical Outcomes in Patients With Acute Acidemia

Study	Patient Population	Study Design	Major Outcome Measures	Results	Comments
Stacpoole et al ⁶ (1994)	44 of 126 adult pts with acute lactic acidosis in placebo arm of randomized controlled study of dichloroacetate vs placebo	Some pts in placebo arm given sodium bicarbonate based on clinician's assessment of need for base therapy	Hemodynamics, mortality	No difference in hemodynamics or mortality between pts receiving sodium bicarbonate and those treated conventionally	Not randomized or controlled; treating physicians made decision about need for sodium bicarbonate
Fang et al ⁷ (2008)	94 pts with severe sepsis, lactic acidosis, and hypotension given crystalloid as resuscitation fluid	Prospective randomized multicenter controlled trial; pts received 5 mL/kg of 1 of 3 solutions: 0.9% sodium chloride, 3.5% sodium chloride, or 5% sodium bicarbonate within 15 min of initial treatment; at 100 min all pts received 20 mL/kg of 0.9% sodium chloride; from 120 min on, pts were treated according to guidelines for severe sepsis and septic shock	Cardiac output, BP at 0, 30, 60, 90, 120 min and 8 h after administration of initial solution; mortality at d 28	No difference in absolute cardiac output or BP at all 6 time points; cardiac output increased at 60 min in 5% sodium bicarbonate group compared to 120 min in 0.9% sodium chloride group and 8 h in 3.5% sodium chloride group ($P < 0.05$); no effect of sodium bicarbonate on mortality at d 28	Pts treated with vasopressors, inotropic agents, colloid solutions, or mechanical ventilation during the initial 2 h after admission were excluded
El-Sohl et al ⁸ (2010)	36 consecutive adult pts from single center with septic shock, elevated blood lactate, and blood pH < 7.30 who received sodium bicarbonate to increase blood pH to 7.35-7.40; contemporaneous controls matched for age, site of infection, acid-base parameters, and APACHE scores	Retrospective analysis of pts receiving sodium bicarbonate vs controls	Length of ICU stay, time on mechanical ventilation, reversal of shock, mortality at d 28	Length of ICU stay and time on ventilation were shorter in the sodium bicarbonate group; no difference in percent of pts who had reversal of shock or time until reversal of shock; no difference in mortality between sodium bicarbonate group and controls	Retrospective study; blood lactate was higher in sodium bicarbonate group than controls, 4.9 ± 2.1 vs 3.4 ± 1.7 ($P < 0.02$); sodium bicarbonate group had more hypocalcemia and hypokalemia
Jung et al ⁹ (2011)	155 adult pts with severe acidemia defined as arterial blood pH \leq 7.20 and $Paco_2 <$ 45 mm Hg; 57 pts received sodium bicarbonate	Prospective multicenter observational study; pts received routine solutions or 1.5%-4.5% sodium bicarbonate during first 24 h of admission	Length of ICU stay, mortality	No difference in length of ICU stay or mortality in pts receiving sodium bicarbonate compared with those who received routine solutions	Study not randomized; decision about which fluid to administer made by treating physician; 83% of pts had mixed metabolic and respiratory acidemia; served as template for Jaber et al ¹² study
Chen et al ¹⁰ (2013)	65 pts with hypoperfusion-induced lactic acidosis associated with septic shock	Prospective randomized controlled trial; 35 pts given sodium bicarbonate to first increase blood pH to \geq 7.15 and then additional sodium bicarbonate to increase blood pH to \geq 7.25; 30 controls given sodium bicarbonate to increase blood pH to \geq 7.15	Blood pH, organ dysfunction, days of hospitalization, mortality	Blood pH in pts with target blood pH \geq 7.25 was higher than those with target blood pH of \geq 7.15, 7.29 ± 0.05 vs 7.20 ± 0.05 ; no. of dysfunctional organs was less, 2.68 ± 0.79 vs 3.28 ± 0.80 ; days in hospital were less, 28.3 ± 12.9 days vs 41.9 ± 13.2 ; mortality was lower, 34% vs 60%, (all $P < 0.05$)	Data only from English abstract; full article published in Chinese
Kim et al ¹¹ (2013)	103 pts with lactic acidosis selected of 207 pts with metabolic acidosis; 69 pts received sodium bicarbonate	Retrospective analysis of pts with acute lactic acidosis from single center	SOFA scores, percent of pts receiving sodium bicarbonate, need for intubation or dialysis, mortality	Need for ventilation and dialysis higher in pts receiving sodium bicarbonate; mortality higher in pts receiving sodium bicarbonate, 88% vs 64.7% ($P < 0.007$)	Retrospective study; pts receiving sodium bicarbonate had lower plasma pH and bicarbonate concentration and higher SOFA scores before treatment, therefore more severe disease

Abbreviations: APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; BP, blood pressure; ICU, intensive care unit; pts, patients; SOFA, sequential organ failure assessment.

In the Literature

increased lactic acid production, hypertonicity, and hypocalcemia. Hypocalcemia was observed in 25% of patients receiving bicarbonate.

How Does This Study Compare With Prior Studies?

As noted, prior studies examining the treatment of acidemia with bicarbonate included small numbers of patients, and only 2 studies were randomized and controlled. In the lone positive study, published in the Chinese literature,¹⁰ patients given sodium bicarbonate to increase arterial blood pH to ≥ 7.25 in stages had lower mortality than those given the base to achieve an arterial blood pH ≥ 7.15 (34% vs 60%; $P < 0.05$).

It is presumed that impairment of hemodynamics during severe acidemia is a major factor in increased mortality. However, other than examining the number of days in which vasopressors were necessary to maintain a stable blood pressure (significantly fewer in the bicarbonate arm), this issue was not investigated in the Jaber et al¹² study. The impact of base administration on cardiac function in patients with acidemia has been examined by others. Administration of bicarbonate to patients with lactic acidosis did not improve cardiac output more than an equivalent quantity of normal saline solution when examined either 30¹⁵ or 60¹⁶ minutes postinfusion. In another study, administration of 5% sodium bicarbonate solution caused a more rapid improvement in cardiac output than either hypertonic sodium chloride (3.5%) or isotonic sodium chloride solution (0.9%), although the final cardiac output was similar among the groups⁷ (Table 1).

Carefully performed studies examining the impact of bicarbonate on the outcome of patients with advanced AKI have not been previously reported¹⁷ and therefore the study by Jaber et al¹² is important. The finding that patients with advanced AKI receiving intravenous sodium bicarbonate solution only during the first 24 hours after enrollment had lower mortality is intriguing. The investigators speculated that this was because those patients had more stable blood pressure (shown by more vasopressor-free days) and better recovery of kidney function (shown by less need for renal replacement therapy). Further investigations into potential mechanisms for the benefits of intravenous sodium bicarbonate solution administration in advanced AKI are warranted, particularly because many patients with severe acidemia will have advanced AKI early in their presentation (182/389 [47%] in the Jaber et al study). The lesser need for renal replacement therapy with bicarbonate observed in the advanced AKI stratum, as well as the overall population, is of itself an important benefit, reducing both the cost of therapy and any associated morbidity.

What Are the Implications for Nephrologists?

Although far from definitive, this study supports treating severe metabolic acidemia (largely caused by lactic acidosis) with intravenous sodium bicarbonate solution,

particularly in patients with advanced AKI. However, additional controlled studies will be required to establish the impact of base on the clinical outcomes of severe metabolic acidemia. We would recommend that future studies use a target arterial blood pH of 7.20 to 7.25. Because such trials tend to produce a blood pH higher than the target, setting a goal of ≥ 7.30 , as in the Jaber et al¹² study, is likely to predispose to alkalemia and its attendant consequences. The bicarbonate was administered as a hypertonic 4.2% solution, presumably to limit the quantity of fluid given. Some studies have shown that hypertonicity per se can suppress cardiac function¹⁸ and therefore an isotonic solution might be preferred.⁴ This issue is worth exploring.

The failure of sodium bicarbonate infusion to provide benefit in previous studies has largely been ascribed to retention of the carbon dioxide generated in the process of buffering, as well as a reduction of ionized calcium. The former complication is most likely to occur when large amounts of bicarbonate are administered rapidly, particularly in patients with impaired alveolar ventilation or those with adequate ventilation but having severe circulatory failure. These pathophysiologic settings promote carbon dioxide accumulation in tissues with the potential of aggravating intracellular acidity. Monitoring arterial and central venous blood gases in the course of treatment can identify this adverse effect.¹⁹ The study by Jaber et al¹² did not examine this complication, but we suggest that future studies do so. Both carbon dioxide retention and hypocalcemia (the latter observed in one-fourth of patients administered bicarbonate in the Jaber et al¹² study) have been shown in a rat model of lactic acidosis treated with bicarbonate to contribute to hemodynamic compromise; their avoidance improved cardiac function and the vasopressor response to catecholamines.²⁰ Therefore, future studies should examine whether this approach might improve the response to bicarbonate in humans.

Other buffers, such as THAM (tromethamine) or Carbicarb (sodium bicarbonate and sodium carbonate anhydrous), which are associated with limited or no carbon dioxide generation and improved systemic acid-base parameters and cardiac contractility in experimental models of severe acidemia, might prove useful for the treatment of severe acidemia.^{21,22} Neither agent is presently being manufactured, but re-examination of their potential in the treatment of acute acidemia seems indicated. Development of additional bases with beneficial properties might also prove useful in the treatment of acidemia.²³

Finally, the reduction in intracellular pH during acute acidemia might impair cellular function, not only by compromising the function of critical cellular enzymes and other proteins, but also by accelerating the activity of proteins or pathways that could be deleterious. Studies in animals have indicated that activation of the myocardial sodium/hydrogen exchanger 1 (NHE1) during lactic acidosis contributes to cellular dysfunction and mortality.

Inhibition of this transporter improves cardiac function and reduces mortality.²⁴ Thus, inhibition of the myocardial NHE1 in concert with administration of base could provide an effective treatment strategy and is worthwhile exploring in humans.

Article Information

Authors' Affiliations: Medical and Research Services VHAGLA Healthcare System (JAK); UCLA Membrane Biology Laboratory (JAK); Division of Nephrology VHAGLA Healthcare System (JAK); David Geffen School of Medicine, Los Angeles, CA (JAK); Division of Nephrology, Department of Medicine, St. Elizabeth's Medical Center (NEM); and Department of Medicine, Tufts University School of Medicine, Boston, MA (NEM).

Address for Correspondence: Jeffrey A. Kraut, MD, Division of Nephrology, VHAGLA Healthcare System, 11301 Wilshire Blvd, Los Angeles, CA 90073 (e-mail: jkraut@ucla.edu) or Nicolaos E. Madias, MD, Department of Medicine, St. Elizabeth's Medical Center, 736 Cambridge St, Boston, MA 02135 (e-mail: nicolaos.madias@steward.org).

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