Sodium Bicarbonate and Renal Function after Cardiac Surgery

A Prospectively Planned Individual Patient Meta-analysis

Michael Bailey, Ph.D., Shay McGuinness, M.B., Ch.B., F.R.C.A., F.A.N.Z.C.A., Michael Haase, M.D., Anja Haase-Fielitz, Pharm.D., Rachael Parke, Ph.D., R.N., M.H.Sc., Carol L. Hodgson, Ph.D., F.A.C.P. B.App.Sc.(Physio.), Andrew Forbes, Ph.D., Sean M. Bagshaw, M.D., M.Sc., Rinaldo Bellomo, M.B.B.S., M.D.

ABSTRACT

Background: The effect of urinary alkalinization in cardiac surgery patients at risk of acute kidney injury (AKI) is controversial and trial findings conflicting. Accordingly, the authors performed a prospectively planned individual patient data meta-analysis of the double-blind randomized trials in this field.

Methods: The authors studied 877 patients from three double-blind, randomized controlled trials enrolled to receive either 24 h of intravenous infusion of sodium bicarbonate or sodium chloride. The primary outcome measure was a postoperative increase in serum creatinine concentration of greater than 25% or 0.5 mg/dl (> 44 μM/L) within the first five postoperative days. Secondary outcomes included the raw change in serum creatinine, greater than 50% and greater than 100% rises in serum creatinine, developing AKI (Acute Kidney Injury Network criteria), initiation of renal replacement therapy, morbidity, and mortality.

Results: Patients were similar in demographics, comorbidities, and cardiac procedures. Sodium bicarbonate increased plasma bicarbonate ($P < 0.001$) and urine pH ($P < 0.001$). There were no differences in the development of the primary outcome (Bicarbonate 45% [39–51%] *vs.* Saline 42% [36–48%], $P = 0.29$). This result remained unchanged when controlling for study and covariates (odds ratio [OR], 99% confidence interval [CI]: Bicarbonate *vs.* Control, 1.11 [0.77–1.60], $P = 0.45$). There was, however, a significant study-adjusted benefit in elective coronary artery bypass surgery patients in terms of renal replacement therapy (Bicarbonate *vs.* Control, OR: 0.38 [99% CI: 0.25–0.58], $P < 0.0001$) and the development of an Acute Kidney Injury Network grade = 3 (Bicarbonate *vs.* Control, OR: 0.45 [99% CI: 0.43–0.48], $P < 0.0001$).

Conclusions: Urinary alkalinization using sodium bicarbonate infusion is not associated with an overall lower incidence of AKI; however, it reduces severe AKI and need for renal replacement therapy in elective coronary artery bypass patients.
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ACUTE kidney injury (AKI)[1,2] is a common postoperative complication in cardiac surgery patients and is independently related to increased mortality and long-term morbidity.[3] Even minimal serum creatinine increases are independently associated with poorer outcomes[4] and, as over a million cardiac surgery operations are carried out annually, the associated costs are extensive.[5,6]

Multiple mechanisms of cardiac surgery–associated acute kidney injury (CSA-AKI) have been suggested. These include generation of reactive oxygen species, ischemia reperfusion injury, activation of inflammatory pathways, and hemolysis.[7–10] If such mechanisms exist, the process behind it may relate to the ability of bicarbonate to slow the Haber–Weiss reaction that generates free radicals.[11,12] Bicarbonate may also scavenge other reactive species such as peroxynitrite.[13] By inducing urinary alkalinization, it may

What We Already Know about This Topic

- Acute kidney injury is a common postoperative complication in cardiac surgery patients
- Urinary alkalinization in patients at risk of acute kidney injury undergoing cardiac surgery remains an important and controversial issue

What This Article Tells Us That Is New

- The authors have performed a novel, prospectively planned individual patient data meta-analysis of the double-blind randomized trials in this important field
- Urinary alkalinization with sodium bicarbonate infusion is not associated with a significant reduction in the overall risk of acute kidney injury in cardiac surgery patients
- However, urinary alkalinization was associated with significant renal protection in the subgroup of patients undergoing elective coronary artery bypass graft surgery, suggesting that further investigation in these patients is warranted

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reduce kidney injury mediated by free hemoglobin species, the generation of methemoglobin-containing tubular casts, and ferrous ion–catalyzed production of free radicals.[14] These potential benefits are important because no simple, safe, and effective intervention to prevent cardiopulmonary bypass–associated AKI has yet been found in the broad cardiac surgery population.[15–19]

Meta-analysis is a powerful statistical technique designed to contrast and combine results from individual studies providing increased precision of estimates along with greater generalizability of findings. In a critical care setting, however, the heterogeneous nature of critically ill patients and their treatment complicates the use of standard aggregate meta-analysis techniques and can result in misleading conclusions.[20] This problem can be overcome through the use of individual patient data meta-analysis (IPDMA),[21] which uses individual patient data rather than summary data from each of the participating studies. Unlike standard meta-analysis techniques, IPDMA enables interaction effects to be estimated within trials, thus reducing the potential for confounding bias. IPDMA has the additional benefit of enabling time-to-event analysis, covariate adjustment, definitive subgroup analysis, and a more balanced interpretation of results—all of which are difficult if not impossible to achieve using standard meta-analysis techniques. Despite being the acknowledged gold standard for meta-analyses,[22] IPDMAs are infrequently carried out, primarily because of the lack of consistency between studies and the difficulty in obtaining and combining detailed trial data.[23,24] To avoid such hurdles, the Cochrane Collaboration* advocates the use of prospectively planned meta-analysis, which enables outcomes, variables, methods, and data collection to be standardized before study commencement, thus ensuring homogeneity from all participating studies. In recent times, there has been a subsequent push toward using this approach in intensive care medicine.[25]

In 2009, a single-center pilot randomized controlled trial enrolling a broad cohort of cardiac surgical patients reported a statistically significant reduction in the incidence of AKI after the infusion of perioperative sodium bicarbonate.[26] A recent review identified urinary alkalinization as the single most important drug-based intervention with convincing evidence to prevent AKI.[27] To confirm these findings in broader geographic and institutional settings, two additional multicenter randomized clinical trials[28,29] were planned and conducted, facilitating a prospectively planned IPDMA of these three studies.

Materials and Methods

Study Design

This study was a prospectively planned IPDMA of the only three published double-blinded randomized controlled trials using a 24-h regimen of bicarbonate infusion (one single-center, two multicenter in design). It was conducted to assess if the administration of sodium bicarbonate as a continuous infusion commenced before cardiopulmonary bypass would result in less postoperative AKI in patients undergoing cardiac surgery. Each individual trial was conducted at university-affiliated hospitals and was registered with ClinicalTrials.gov (NCT00334191, NCT00672334, and NCT00878956). After an interim analysis by the Data Safety Monitoring Board, a decision was made based on a lack of efficacy and potential harm, to halt one of the multicenter studies with recruitment at 70%. In accordance with this finding, a subsequent interim analysis was also conducted at the second multicentre study, and recruitment was halted for a lack of efficacy with 95% of recruitment complete. The Human Research Ethics Committee of each center approved the study, and all sites obtained written informed consent to participate from each patient before surgery. Patient flow for the combined studies is reported in a CONSORT diagram (fig. 1).

Patient Population

Patient eligibility was consistent across the three trials. Patients were eligible for inclusion if they were scheduled for elective or urgent cardiac surgery utilizing cardiopulmonary bypass and were identified preoperatively to be at increased risk for CSA-AKI.

This high-risk group was identified using previously published criteria shown to accurately predict patients deemed at risk of developing AKI.[30] Whilst this scoring system developed by the Cleveland Clinic group was originally designed to predict a tiered level of risk associated with AKI requiring dialysis, like Burns *et al.*[16] we have simplified and customized this scoring process to enable identification of patients with an increased risk in a nondialysis AKI setting, thus facilitating recruitment of an increased number of cardiac surgery patients. Details of inclusion and exclusion criteria are shown in table 1.

Randomization

At each study center, the hospital pharmacy clinical trials coordinator or unblinded site research coordinator used a Microsoft Excel–based (Microsoft Corp., Redmond, WA) random number generator to create the randomization list using a permuted block strategy with varying blocks sizes. The active study treatment or saline was prepared either in infusion bags contained in shrink-wrapped black plastic bags or 500-ml glass bottles. Both treatments were identical in appearance, ensuring allocation concealment to patients, anesthesiologists, cardiac surgeons, intensive care specialists, bedside nurses, and investigators. Treatment allocation was only revealed after the study had been completed, the database locked, and statistical analysis completed.

Intervention

Study intervention was similar in all trials, although there were some minor differences in the total dose of bicarbonate

* Available at: www.cochrane.org. Accessed August 11, 2014.

given and the total volume of fluid used as diluent. Patients from the pilot study received a loading dose of 0.5 mM/kg body weight (=bolus) over 1 h immediately after the induction of anesthesia followed by continuous intravenous infusion of 0.15 mM kg^{-1} h^{-1} over 23 h (24-h total = 4.0 mM/kg). Each patient from the subsequent multicenter studies received a dose of 0.5 mM/kg body weight (=bolus) over 1 h immediately after the induction of anesthesia followed by continuous intravenous infusion of 0.2 mM kg^{-1} h^{-1} over 23 h. Bolus and continuous infusion achieved a total dose of 5.1 mM/kg over 24 h, which resulted in a 25% greater dosing regimen than that used in the first study. For the multicenter studies, both bicarbonate and saline were administered as hypertonic (1 mM/ml) solutions giving a total dose per patient of 5.1 mM/kg. For these two studies, a regime that administered the bicarbonate or saline in a total volume of 1,250 ml was used.

Apart from the addition of the infusion of study drug, there were no changes to normal clinical practice. Anesthetic techniques, including preoperative medications, were at the discretion of the attending anesthetist. Surgical approach and cardiopulmonary bypass were conducted according to the standard technique of each institution. Postoperative care, including hemodynamic, fluid, and analgesic management, was at the discretion of the intensivists and nursing staff at each institution.

Outcome Measures and Subgroups

The primary outcome measure was the number of patients who developed postoperative AKI. This was defined *a priori* as an increase in plasma creatinine concentration of greater than 25% or 44 μM/l from baseline to its peak value at any time within the first 5 days after cardiopulmonary bypass and was identical in all three studies. This end point had been used for previous studies of CSA-AKI.[16,18]

Renal secondary outcomes included the change in serum creatinine from induction to the 5-day maximum, number of patients who received renal replacement therapy (RRT) during their hospital stay, and number of patients who had an increase in serum creatinine of greater than 50% and greater than 100%. In addition, the number of patients who developed acute kidney dysfunction according to the Acute Kidney Injury Network classifications (AKIN ≥ 1, AKIN stage 1, AKIN stage 2, and AKIN stage 3)[31] was also used. Secondary clinical outcomes included the duration of mechanical ventilation, length of intensive care unit and hospital stay, and hospital and 90-day mortality.

Two clinically relevant subgroups were considered:

- Preoperative chronic kidney disease (as defined by baseline creatinine of more than 130 μM/l)
- Low-risk *versus* high-risk surgery defined by elective coronary artery bypass surgery (CABG) *versus* all other

Statistical Analysis

With a total of 877 randomized patients, this meta-analysis had a 90% power to detect an absolute reduction in the incidence of AKI (as defined by a postoperative increase in serum creatinine concentration of greater than 25% or 0.5 mg/dl (>44 μM/l) within the first five postoperative days) of 13% (50% *vs.* 37%) or a relative risk reduction of 26% with a two-sided *P* value of 0.01.

Data were analyzed according to the intention-to-treat principle. All variables were assessed for normality and log-transformed if appropriate. Baseline comparisons were performed using chi-square tests for equal proportion and reported as percentages (n). Continuously normally

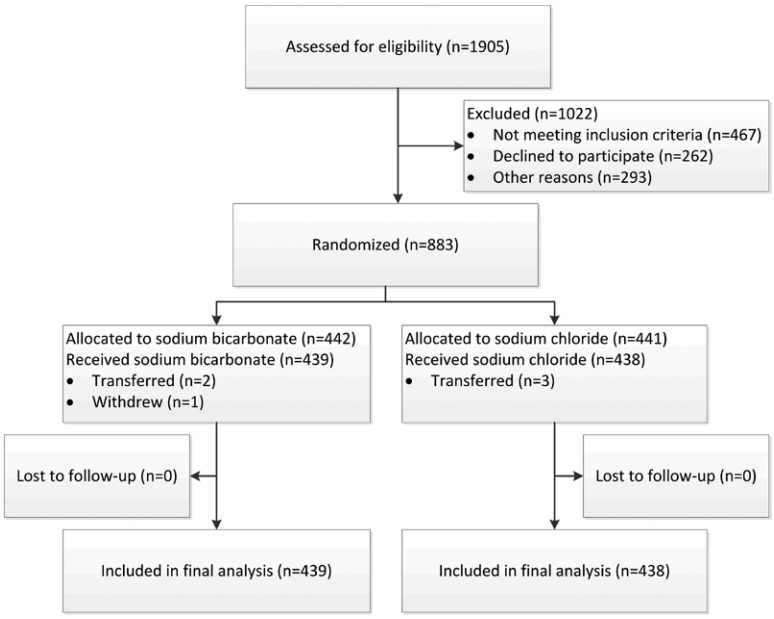

Fig. 1. CONSORT diagram, 883 randomized, 877 analyzed (6 patients transferred or withdrew).

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria: Cardiac surgery patients in whom the use of cardiopulmonary bypass is planned and having one or more of the following risk factors for postoperative acute kidney injury
• Age above 70 yr
• Preoperative plasma creatinine concentration > 120 μm/l
• New York Heart Association class III/IV or left ventricular ejection fraction < 35%
• Valvular surgery or concomitant valvular and coronary artery bypass graft surgery
• Redo cardiac surgery
• Insulin-dependent diabetes mellitus
Exclusion criteria
• End-stage renal disease (plasma creatinine concentration > 300 μM/l
• Emergency cardiac surgery
• Planned off-pump cardiac surgery
• Known blood-borne infectious disease
• Chronic inflammatory disease on immunosuppression
• Chronic dose corticosteroid therapy (>10 mg/d prednisone or equivalent)
• Enrolled in conflicting research study
• Age < 18 yr

distributed variables were compared using Student *t*-tests and reported as mean (standard deviation) while nonnormally distributed data were compared using Wilcoxon rank sum tests and reported as medians (interquartile range). Binomial outcomes were analyzed using logistic regression and reported as odds ratios with 99% confidence intervals (CIs) whilst the change in creatinine was analyzed using linear modeling and reported as differences (99% CI). Continuous secondary outcomes measuring duration (intensive care and hospital lengths of stay and duration of ventilation) were found to be well approximated by log-normal distributions so were log-transformed and analyzed using linear modeling with results reported as ratios of geometric means (99% CI). Survival analysis was performed using Cox-proportional hazards regression and reported as hazard ratios (99% CI). Combined overall survival was reported using a Kaplan–Meier curve with a corresponding log-rank test. Patient survival was censored at 90 days or at hospital discharge if further follow-up data were not available. As this was a prospectively planned IPDMA of three functionally identical studies and the goal was to compute a common effect size, in accordance with Borenstein[32] overall treatment effects were determined using one-stage multivariate analysis with each individual study treated as fixed effects. Heterogeneity across studies and sites was determined by fitting interactions between treatment and study and treatment and sites. To determine if the relationship between treatment and outcome differed significantly between subgroups, interactions were fitted between treatment and subgroup. To further ensure that observed effects could not be attributed to specific hospitals within each study or from baseline imbalances, additional covariate adjusted sensitivity analysis was performed accounting for attending hospital

Table 2. Baseline and Demographic Characteristics of Combined Study Patients

Characteristics	Sodium Bicarbonate	Sodium Chloride
	(N = 439)	(n = 438)
Demographic data		
• Age (yr)	66.9 (12.9)	66.8 (12.9)
• Male gender	69% (304)	67% (294)
• Weight	81.8 (16.4)	80.9 (18.6)
• Body mass index	28.2 (5.1)	27.9 (5.5)
Inclusion criteria		
• Age above 70	52% (228)	54% (235)
• Valve surgery	74% (323)	75% (330)
• Ejection fraction < 35%	12% (52)	10% (44)
• Plasma creatinine > 120 μM/l	15% (66)	12% (53)
• Previous cardiac surgery	18% (78)	16% (71)
• Insulin dependent diabetes	7% (30)	4% (17)
Comorbidities		
• Noninsulin-dependent diabetes	13% (55)	15% (66)
• Chronic obstructive pulmonary disease	13% (59)	13% (55)
• Acute myocardial infarction in previous 6 months	14% (61)	10% (45)
• Peripheral vascular disease	14% (60)	9% (38)
• Atrial fibrillation	25% (108)	24% (105)
Medications		
• Current β-blockers	55% (243)	53% (233)
• Current calcium channel blocker	24% (105)	25% (109)
• Current ace inhibitors	53% (233)	50% (221)
• Current statins	57% (249)	53% (230)
Baseline renal function		
• Creatinine at induction (μM/l)	89.7 (27.8)	87.4 (25.3)
• Urea at induction (mM/l)	6.7 (5.2–11.0)	6.8 (5.1–10.6)

and all potentially imbalanced baseline variables with $P < 0.2$ (peripheral vascular disease, insulin dependent diabetes, and acute myocardial infarction). Given the large number of outcomes considered, to reduce the chance of type I error and increase robustness of the analysis, a two-sided P value of 0.01 was used to indicate statistical significance with meta-analysis results reported using forest plots (99% CI). All analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Between June 2006 and June 2011, the three trials enrolled a total of 883 patients at five hospitals in New Zealand, Australia, Germany, Canada, and Ireland. A total of six patients were transferred or withdrawn (fig. 1), leaving 877 patients included in the final analysis, with 439 patients randomized to the intervention arm and receiving intravenous sodium bicarbonate and 438 patients receiving saline. Patient and operative characteristics are shown in table 2. While there were no statistically significant differences ($P < 0.01$) between the two groups at baseline, there were, however, some minor

Table 3. Changes in Plasma Biochemical Variables and Urine pH

Biochemical Variables	Sodium Bicarbonate (N = 439)	Sodium Chloride (n = 438)	*P* Value
Bicarbonate at induction (mM/l)	25 (23.6–26)	25 (23.9–26)	0.99
Bicarbonate at 6 h	26 (24.6–27.9)	23.4 (22–24.7)	<0.0001
Bicarbonate at 24 h	29.2 (27.6–31.5)	23.4 (22–25)	<0.0001
Base excess at induction	0.45 (–0.7 to 1.8)	0.8 (–0.5 to 1.8)	0.38
Base excess at 6 h	2 (0.2–3.4)	–1.3 (–2.9 to 0)	<0.0001
Base excess at 24 h	6 (4.5–7.6)	0.6 (–0.9 to 2)	<0.0001
Sodium at induction (mM/l)	139 (137–140)	138 (137–140)	0.39
Sodium at 6 h	140 (138–142)	140 (138–142)	0.24
Sodium at 24 h	142 (139–144)	142 (140–145)	0.23
Chloride at induction (mM/l)	106 (104–107)	106 (104–108)	0.66
Chloride at 6 h	107 (105–109)	110 (108–112)	<0.0001
Chloride at 24 h	109 (106–111)	114 (112–116)	<0.0001
Potassium at induction (mM/l)	3.9 (3.7–4.1)	3.9 (3.7–4.2)	0.88
Potassium at 6 h	4.1 (3.8–4.4)	4.3 (3.9–4.5)	<0.0001
Potassium at 24 h	4.2 (3.9–4.5)	4.4 (4.1–4.7)	<0.0001
Calcium at induction (mM/l)	1.2 (1.17–1.24)	1.19 (1.16–1.24)	0.13
Calcium at 6 h	1.16 (1.07–1.27)	1.18 (1.09–1.27)	0.31
Calcium at 24 h	1.12 (1.06–1.18)	1.16 (1.1–1.23)	<0.0001
Urine pH at induction (mM/l)	6 (5–6.5)	6 (5–6.5)	0.3
Urine pH at 6 h	6.5 (6–7)	6 (5–6)	<0.0001
Urine pH at 24 h	7.5 (6.5–8)	6 (5–6)	<0.0001
pH at Induction (mM/l)	7.41 (7.38–7.43)	7.41 (7.38–7.44)	0.15
pH at 6 h	7.43 (7.38–7.46)	7.38 (7.34–7.42)	<0.0001
pH at 24 h	7.44 (7.41–7.47)	7.38 (7.35–7.41)	<0.0001

imbalances ($P < 0.2$) that could potentially confound results. Bicarbonate patients were more likely to have peripheral vascular disease (14% *vs.* 9%, $P = 0.02$), insulin-dependent diabetes (7% *vs.* 4%, $P = 0.05$), and acute myocardial infarction in the previous 6 months (14% *vs.* 10%, $P = 0.10$).

Biochemical Outcomes

While there were no significant differences in biochemical variables between groups at baseline, at both 6 and 24 h, there were significant treatment-induced biochemical differences between groups ($P < 0.0001$) with the bicarbonate group having higher levels of plasma bicarbonate, base excess, plasma, and urine pH and lower levels of chloride, potassium, and calcium (table 3).

Renal and Duration of Stay Outcomes

The primary outcome (creatinine rise > 25% or > 44 μM/l over 5 days) occurred in 199 patients in the bicarbonate group and 183 patients in the control group. There were no significant differences in the proportion of patients developing the primary outcome (Bicarbonate 45% [99% CI: 39–51%] *vs.* Control 42% [99% CI: 36–48%], $P = 0.29$, table 4). This result remained unchanged when adjusting for study as a fixed effect (Bicarbonate *vs.* Control, odds ratio [OR]: 1.15 [99% CI: 0.81–1.64], $P = 0.29$) or controlling for covariates (Bicarbonate *vs.* Control, OR: 1.11 [99% CI: 0.77–1.60], $P = 0.45$, fig. 2). There was no overall difference between groups when considering the need for RRT. There was, however, a highly significant reduction in risk for bicarbonate patients who received elective CABG (lower risk patients) (Bicarbonate *vs.* Control, OR: 0.38 [99% CI: 0.25–0.58], $P < 0.0001$, fig. 3). Similarly, when considering a far more severe measure of AKI severity such as the risk of developing AKIN grade = 3, despite there being no overall difference between groups, within the subgroup of patients who received elective CABG surgery, there was a significant reduction in risk for bicarbonate patients (Bicarbonate *vs.* Control, OR: 0.45 [99% CI: 0.43–0.48], $P < 0.0001$, fig. 4). These results were further reflected by statistically significant heterogeneity ($P < 0.01$) between CABG and non-CABG patients for both outcomes with this heterogeneity potentially driven by a significant difference in the cardiopulmonary bypass times (CABG only 2.1 ± 0.9 h *vs.* non-CABG 2.4 ± 1.2 h, $P < 0.001$). There were no significant differences in the change in serum creatinine between groups.

When considering other renal outcomes, there was no difference between groups in the risk of developing an AKIN grade = 2 (OR: 0.65 [0.31–1.39], $P = 0.15$) or an AKIN grade ≥ 1 (OR: 1.03 [0.72–1.47], $P = 0.82$, fig. 3). There were no differences in intensive care or hospital length of stay or duration of mechanical ventilation (fig. 5).

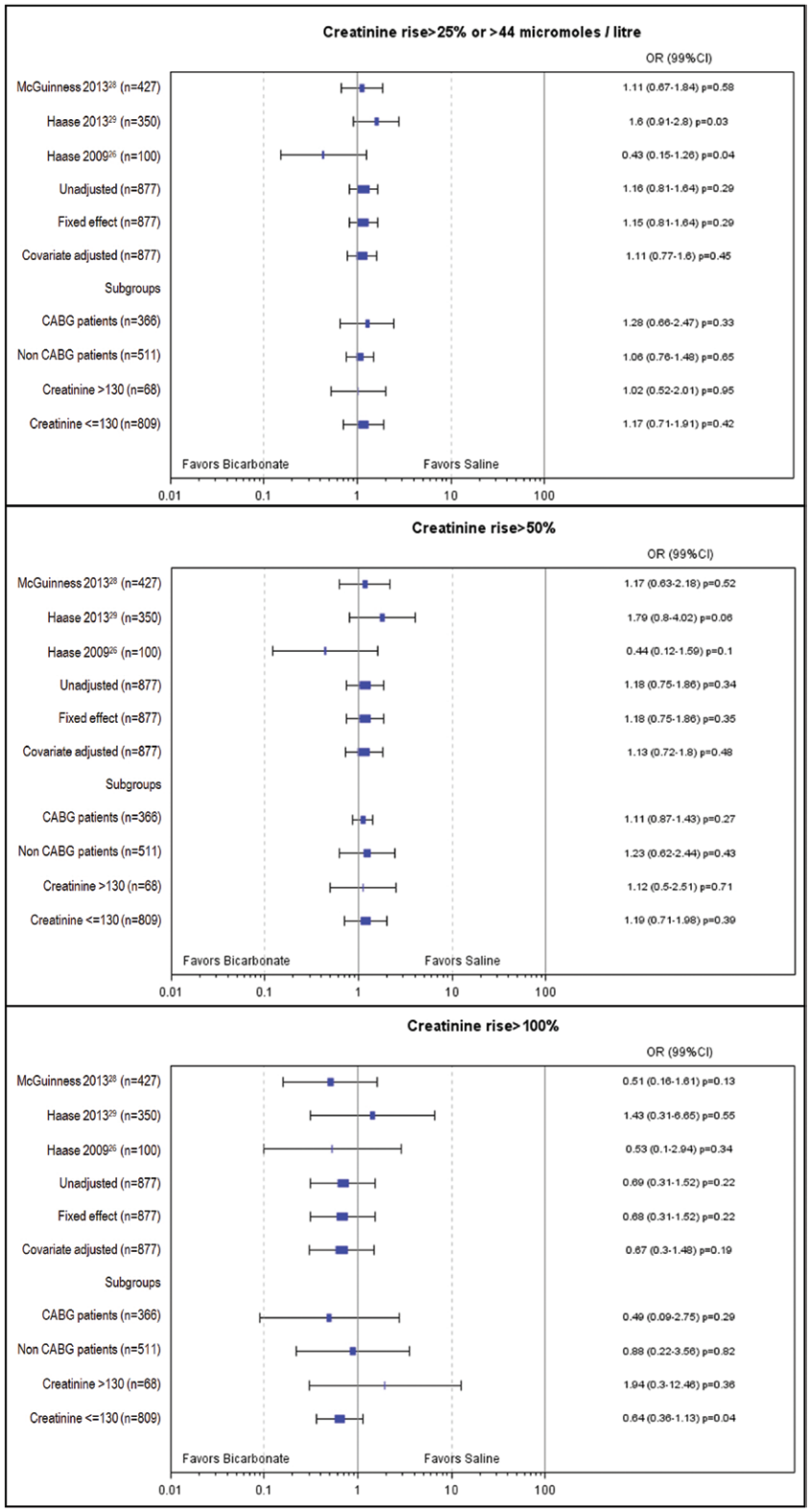

Fig. 2. Forest plots of creatinine rise > 25% or > 44 μM/l (primary outcome), creatinine rise > 50%, and creatinine rise > 100%. Each plot reports odds ratios (ORs) with 99% confidence intervals (CIs) for individual studies (McGuiness 2013,[28] Haase 2013,[29] and Haase 2009[26]), combined unadjusted results, combined results with each study treated as a fixed effect, combined results covariate adjusted for attending hospital and baseline imbalances, subgroup analysis stratified by coronary artery bypass graft (CABG), and subgroup analysis stratified by baseline creatinine.

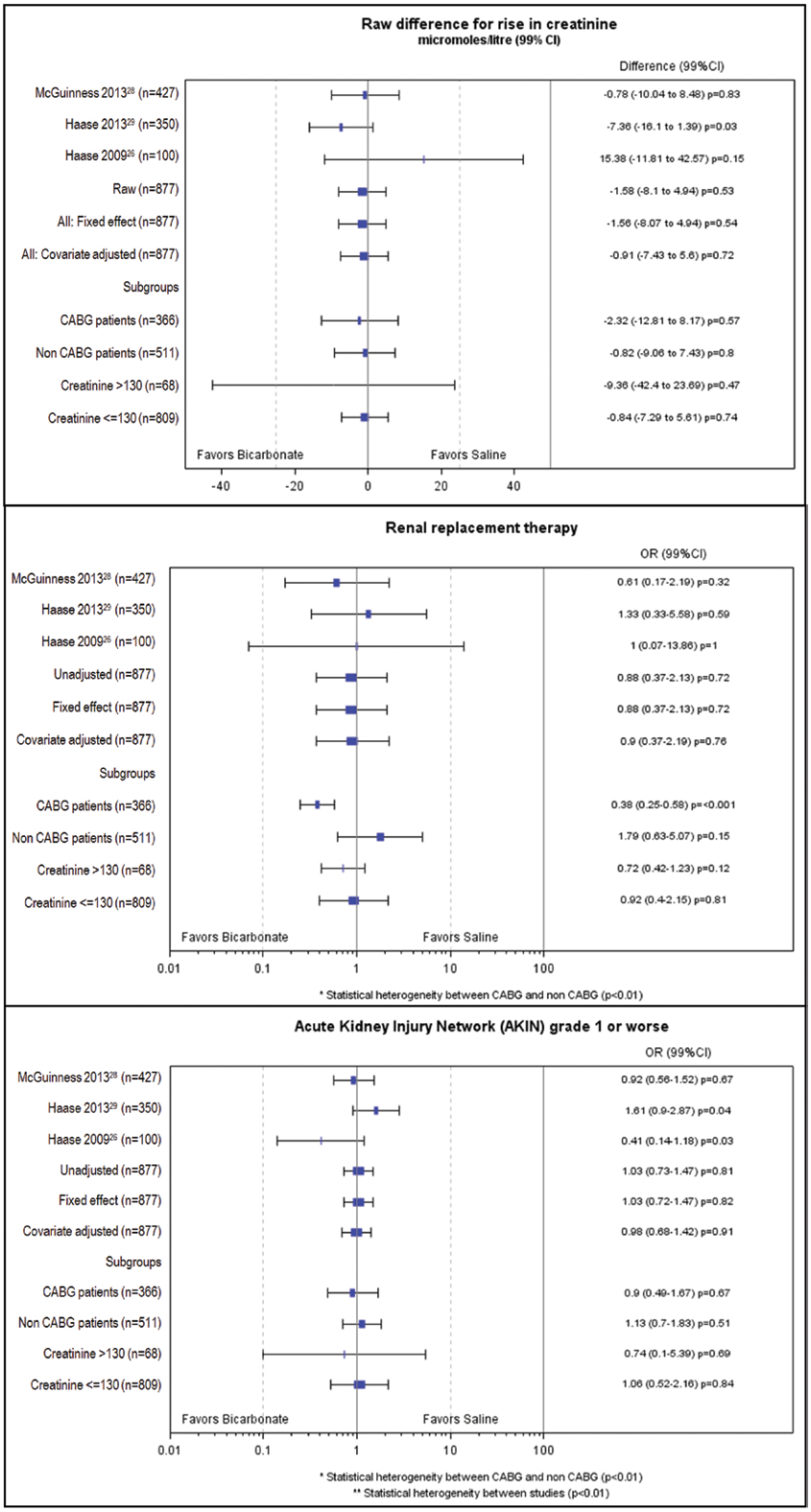

Fig. 3. Forest plots of raw differences with 99% confidence intervals (CIs) for creatinine (μM/l) along with forest plots of odds ratios (99% CI) for renal replacement therapy and an Acute Kidney Injury Network (AKIN) grade ≥ 1. Each plot reports results for individual studies (McGuiness 2013,[28] Haase 2013,[29] and Haase 2009[26]), combined unadjusted results, combined results with each study treated as a fixed effect, combined results covariate adjusted for attending hospital and baseline imbalances, subgroup analysis stratified by coronary artery bypass graft (CABG), and subgroup analysis stratified by baseline creatinine.

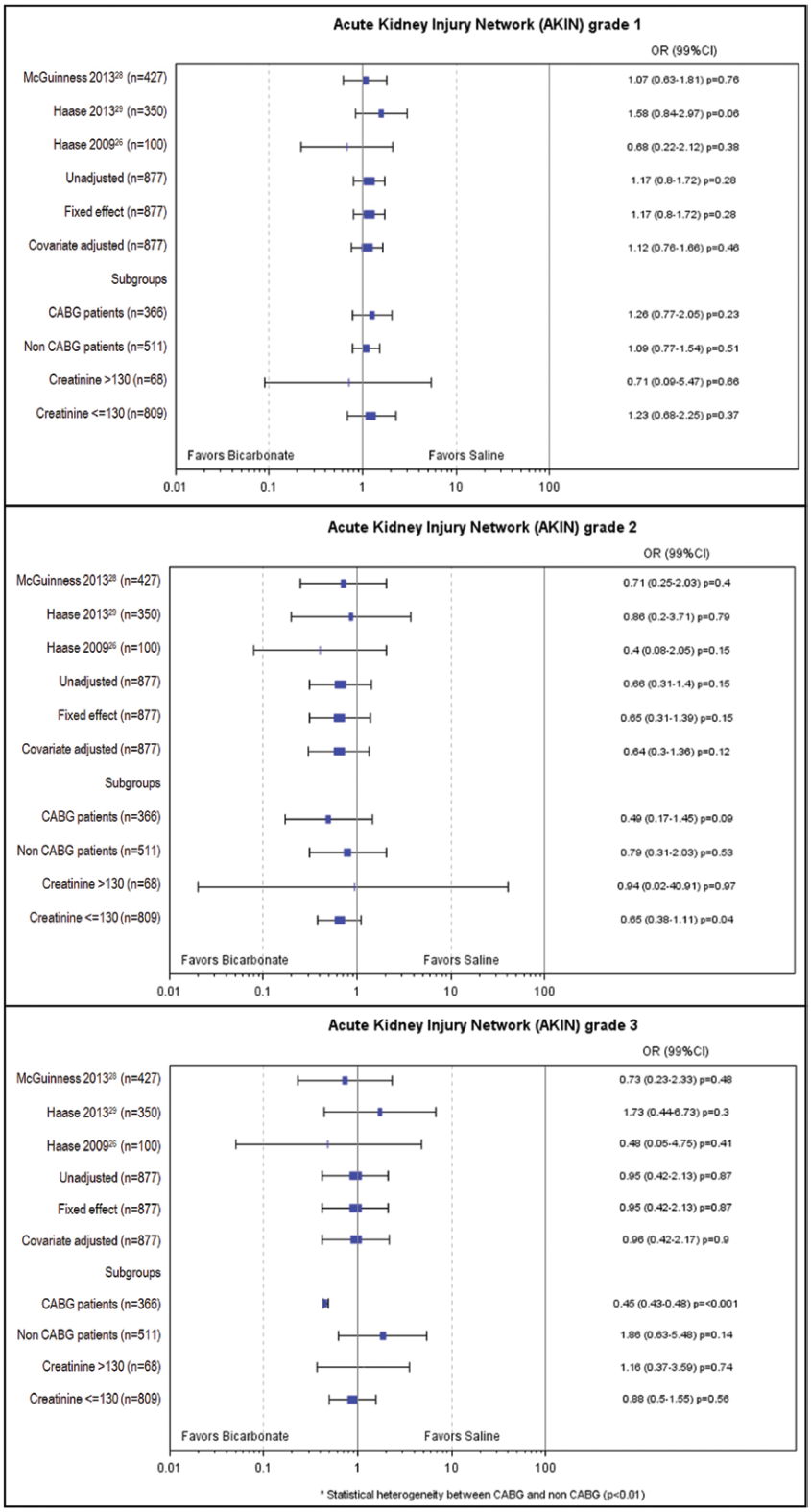

Fig. 4. Forest plots of Acute Kidney Injury Network (AKIN) grades equal to 1, 2, and 3. Each plot reports odds ratios (99% confidence intervals) for individual studies (McGuiness 2013,[28] Haase 2013,[29] and Haase 2009[26]), combined unadjusted results, combined results with each study treated as a fixed effect, combined results covariate adjusted for attending hospital and baseline imbalances, subgroup analysis stratified by coronary artery bypass graft (CABG), and subgroup analysis stratified by baseline creatinine.

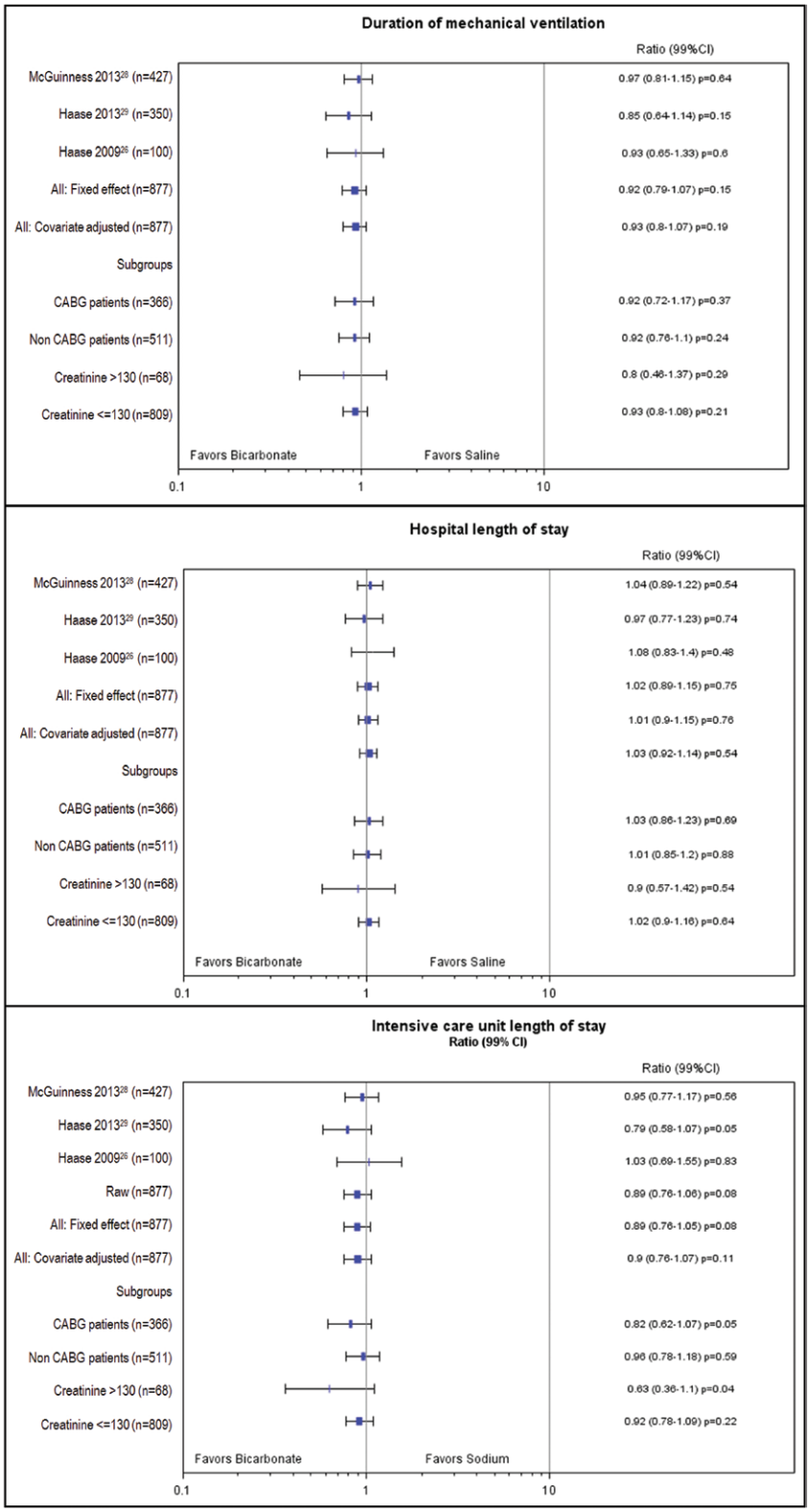

Fig. 5. Forest plots of duration of mechanical ventilation, hospital length of stay, and intensive care unit length of stay. Each plot reports ratios (99% confidence intervals) for individual studies (McGuiness 2013,[28] Haase 2013,[29] and Haase 2009[26]), combined unadjusted results, combined results with each study treated as a fixed effect, combined results covariate adjusted for attending hospital and baseline imbalances, subgroup analysis stratified by coronary artery bypass graft (CABG), and subgroup analysis stratified by baseline creatinine.

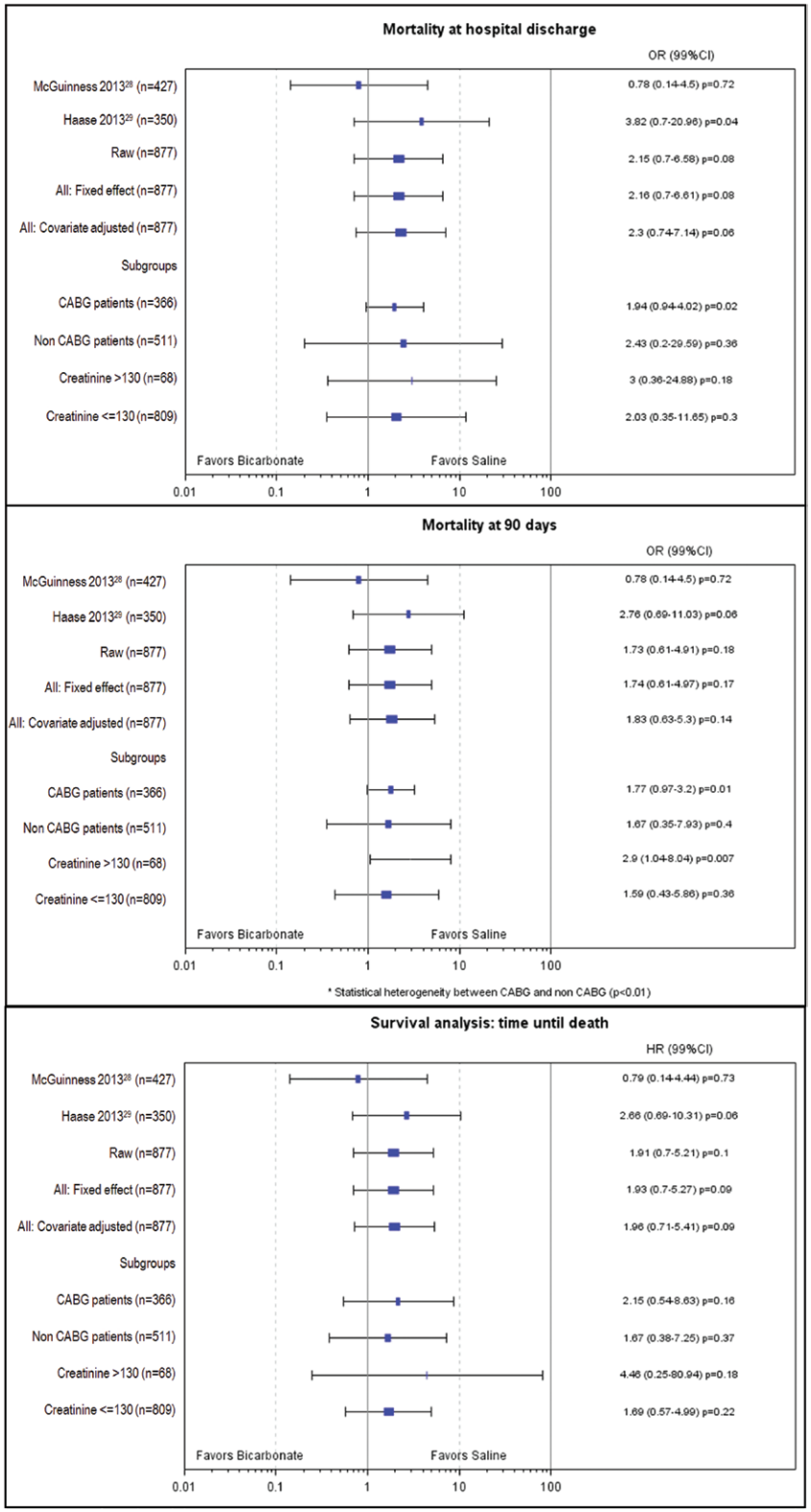

Fig. 6. Forest plots of hospital mortality, 90-day mortality, and survival analysis of time to death. Mortality outcomes are reported as odds ratios (ORs) with 99% confidence intervals (CIs) whilst survival analysis is reported as hazards ratios (HRs) with (99% CI). Results are reported for individual studies (McGuiness 2013[28] and Haase 2013[29]), combined unadjusted results, combined results with each study treated as a fixed effect, combined results covariate adjusted for attending hospital and baseline imbalances, subgroup analysis stratified by coronary artery bypass graft (CABG), and subgroup analysis stratified by baseline creatinine. With only one death per group, results for Haase 2009[26] have not been reported individually.

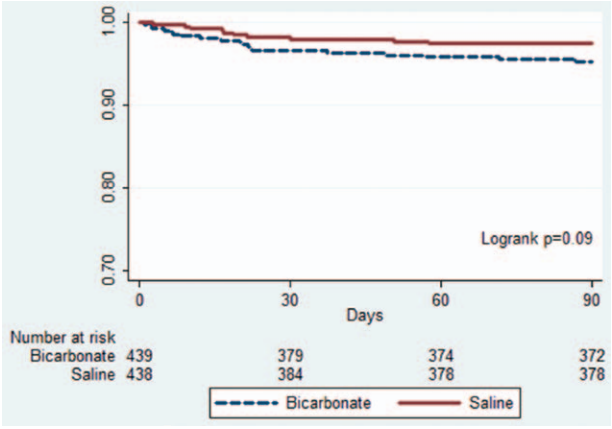

Fig. 7. Kaplan–Meier curve showing time to death for all studies combined.

Mortality

Twenty-five participants died during hospital stay and a further four died between hospital discharge and day 90 with the median time to death being 19 (8–30) days. Nonsurvivors were significantly older (76 [70–79] *vs.* 70 [60–76] yr, $P = 0.004$) spent longer in intensive care (3.4 [1.4–6.2] *vs.* 1.2 [0.9–2.6] days, $P < 0.004$), and were more likely to have developed AKIN grade ≥1 (79% [23/29] *vs.* 40% [335/848], $P < 0.0001$) or AKIN grade 3 (41% [12/29] *vs.* 4% [31/848], $P < 0.0001$). They were also more likely to require postoperative RRT (41% [12/29] *vs.* 3% [24/844], $P < 0.0001$), had longer bypass times (3.6 ± 2.0 *vs.* 2.2 ± 1.0 h, $P < 0.0001$), were ventilated for longer (2.5 [0.9–6.5] *vs.* 0.6 [0.5–0.9] days, $P < 0.0001$), and were more likely to received fresh frozen plasma and packed erythrocytes in the first 48 h (64% [18/29] *vs.* 25% [214/845], $P < 0.0001$) and (79% [23/29] *vs.*46% [390/848], $P = 0.0004$), respectively.

While the proportion of deaths was higher in the bicarbonate group (4.3% [19/439] *vs.* 2.3% [10/438], $P = 0.09$), there remained no statistically significant difference after adjustment for study, attending hospital and covariates (OR: 1.83 [99% CI: 0.63–5.30], $P = 0.14$). This result was similar when considering survival analysis of time to death (hazard ratio: 1.96 [99% CI: 0.71–5.41], $P = 0.09$, fig. 6). The pattern of survival between groups can be seen in a Kaplan–Meier survival curve (fig. 7) with the increased number of death in the bicarbonate group most apparent during the first 7 days. However, neither 7-day mortality (Bicarbonate 1.4% [6/429] *vs.* 0.2% [1/438], $P = 0.06$) nor overall survival (log-rank $P = 0.09$) was statistically significant.

The principal cause of death was treatment-resistant cardiogenic shock (Bicarbonate 2.1% [9/439] *vs.* Saline 1.4% [6/438], $P = 0.44$). Other causes of multiple deaths include myocardial infarction (n = 3), multiorgan failure (n = 2), ventricular fibrillation (n = 2), and sepsis (n = 2), all of which had insufficient events to be statistically linked to treatment.

Discussion

Statement of Key Findings

In this IPDMA of three high-quality double-blind randomized controlled clinical trials evaluating the efficacy of sodium bicarbonate infusion to reduce the incidence of CSA-AKI, no overall renal benefit was found. We did, however, find renal benefit in a subgroup of patients receiving low-risk surgery (elective CABG) with patients receiving sodium bicarbonate having a significant reduction in the need for RRT and the development of an AKI (AKIN grade = 3). Of particular interest was the tightness of the CIs around these findings, which may be attributed to the small number of trials considered; however, the finding of heterogeneity between high-risk and low-risk patients for these outcomes clearly suggests that the underlying effect of sodium bicarbonate on AKI differs according to patient risk. This may suggest that, in lower risk patients, the primary mechanism of perioperative AKI is related to cardiopulmonary bypass time, whereas in the higher risk patients, the bypass time becomes secondary to the hemodynamic perturbations that occur before, during, and after.

Despite one of the multicenter studies being halted for potential harm, this IPDMA failed to identify a significant increased risk of death associated with bicarbonate. Cox proportional hazards regression further enables integration of the duration of survival for both survivors and nonsurvivors adjusting for study, attending hospital and potentially imbalanced baseline covariates; however, this analysis also failed to show a significant difference between groups.

Study Strengths and Limitations

IPDMA is the acknowledged gold standard for meta-analyses.[22] The ability to design, capture, and combine patient information from three separate trials conducted across five different countries is unprecedented in intensive care medicine. The use of individual patient data over standard meta-analysis techniques facilitates more informative statistical analysis (such as time to event analysis), enables covariate adjustment, allows avoidance of the ecological fallacy,[33] and further enables definitive comparison of subgroups of interest.

Prospective planning enabled homogeneity between the three studies, including patient population, the intervention used and outcomes captured, and using the same definition of AKI, which has been a significant factor limiting the use of IPDMA for the analysis of studies in this field before. The validity of the findings is further strengthened by the fact that enrollment was completed over a period of 5 yr.

The additional statistical power provided by this technique enabled the study of two clinically important subgroups: those with preexisting renal disease and those undergoing complex surgery. This would not have been possible in any of the individual trials and demonstrates the value of prospective planning and standardization of study data collection whenever possible.

Despite the valuable insights that can be obtained from IPDMA, there are several limitations to the interpretation of data. In particular, both multicentre studies were prematurely

terminated before completion of planned enrollment. As described in Bassler,[34] this has the potential to bias effect estimates, although, as the combined study recruitment of these two trials exceeded 80% of planned enrolment, this bias is unlikely to be large. Additionally, no attempt was made by study investigators to control intraoperative factors, including surgical and anesthetic techniques; however, a large sample size combined with the benefits of randomization into multicentric, double-blinded, and treatment-concealed trials should ensure that confounding from these effects is likely minimized.

Furthermore, the decision to use CABG as a marker of risk for the development of postoperative AKI is limited and may be prone to imbalances in the true baseline risk. While we are hopeful that the principles of blinding and randomization will ensure that the distribution of risk would be similar between groups, we acknowledge that in a truly high-risk population, there may have been differences that we were unable to identify. Similarly, we acknowledge that the decision to use serum creatinine to define preoperative renal insufficiency does have limitations and that the estimated glomerular filtration rate may be better able to define a population at greater risk of AKI. It is further worth noting that, as patient recruitment excluded patients undergoing emergency cardiac surgery, these results are specific to elective cardiac surgery patients and that, as only 61% of eligible patients were randomized, care should be taken when extrapolating results to the larger population.

Relationship to Previous Findings

This study builds on the findings of the three individual trials exploring the relationship between perioperative sodium bicarbonate infusion and AKI. Following the suggestion of benefit in the incidence of AKI in cardiac surgery patients,[26] a further two multicenter randomized controlled trials were conducted with both terminated prematurely by data safety management committee decisions based on lack of benefit[28,29] and potential harm.[29]

The above decisions and early trial findings have been borne out in the IPDMA. Through this technique, we can confirm that there is no statistical evidence to suggest that sodium bicarbonate reduces the overall incidence of kidney injury. However, there is some evidence to suggest a likely beneficial effect on renal function in patients receiving CABG. Finally, at the time of this IPDMA, an additional smaller study where bicarbonate infusion was given for only 6 h was also published[19] showing no benefit.

Implications

This IPDMA provides additional insights beyond those of each study. The observation that there is a reduced incidence of AKI in patients who undergo elective CABG provides a possible explanation for the initially promising findings of the first single-center study[26] and suggests that the hypothesized beneficial effect of bicarbonate on kidney function is likely to exist in low-risk cardiac surgery patients.

Our observations support the value of IPDMA as a statistical technique and argue for greater pretrial harmonization of planned data collection for investigations of similar interventions in different geographical jurisdictions. Finally, the findings of this IPDMA indicate that further clinical use of bicarbonate infusion in unselected cardiac surgery patients may not be justified.

Conclusions

Urinary alkalinization using sodium bicarbonate infusion for cardiac surgery patients does not significantly reduce the overall risk of AKI. However, it provides a degree of renal protection to patients undergoing low-risk surgery. On this basis, we recommend further studies of the use of sodium bicarbonate infusion to reduce CSA-AKI only in lower-risk cardiac surgery patients such as those receiving elective CABG.

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Competing Interests

Dr. Bagshaw has previously received funding by a Canada Research Chair in Critical Care Nephrology and Clinical Investigator Award from Alberta Innovates—Health Solutions (Edmonton, Alberta, Canada). All other authors report no conflicts of interest.

Correspondence

Address correspondence to Dr. Bailey: Australian and New Zealand Intensive Care Research Centre, Monash University, Level 6, 99 Commercial Road, Melbourne 3181, Australia. michael.bailey@monash.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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