European Heart Journal (2012) **33**, 2071–2079
doi:10.1093/eurheartj/ehr501

CLINICAL RESEARCH
Interventional cardiology

Sodium chloride vs. sodium bicarbonate for the prevention of contrast medium-induced nephropathy: a randomized controlled trial

Theresia Klima[1†], Andreas Christ[2†], Ivana Marana[3], Stefan Kalbermatter[4], Heiko Uthoff[2], Emanuel Burri[5], Sabine Hartwiger[2], Christian Schindler[6], Tobias Breidthardt[1], Giancarlo Marenzi[3], and Christian Mueller[7*]

[1]Department of Nephrology, University Hospital Basel, Basel, Switzerland; [2]Department of Internal Medicine, University Hospital Basel, Basel, Switzerland; [3]Centro Cardiologico Monzino, Milan University, Milan, Italy; [4]Department of Nephrology, Kantonsspital Liestal, Liestal, Switzerland; [5]Department of Gastroenterology, University Hospital Basel, Basel, Switzerland; [6]Swiss Tropical and Public Health Institute, University Hospital Basel, Basel, Switzerland; and [7]Department of Cardiology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland

Received 15 July 2011; revised 19 September 2011; accepted 19 December 2011; online publish-ahead-of-print 19 January 2012

Aims The most effective regimen for the prevention of contrast-induced nephropathy (CIN) remains uncertain. Our purpose was to compare two regimens of sodium bicarbonate with 24 h sodium chloride 0.9% infusion in the prevention of CIN.

Methods and results We performed a prospective, randomized trial between March 2005 and December 2009, including 258 consecutive patients with renal insufficiency undergoing intravascular contrast procedures. Patients were randomized to receive intravenous volume supplementation with either (A) sodium chloride 0.9% 1 mL/kg/h for at least 12 h prior and after the procedure or (B) sodium bicarbonate (166 mEq/L) 3 mL/kg for 1 h before and 1 mL/kg/h for 6 h after the procedure or (C) sodium bicarbonate (166 mEq/L) 3 mL/kg over 20 min before the procedure plus sodium bicarbonate orally (500 mg per 10 kg). The primary endpoint was the change in estimated glomerular filtration rate (eGFR) within 48 h after contrast. Secondary endpoints included the development of CIN. The maximum change in eGFR was significantly greater in Group B compared with Group A {mean difference −3.9 [95% confidence interval (CI), −6.8 to −1] mL/min/1.73 m^2, $P = 0.009$} and similar between Groups C and B [mean difference 1.3 (95% CI, −1.7–4.3) mL/min/1.73 m^2, $P = 0.39$]. The incidence of CIN was significantly lower in Group A (1%) vs. Group B (9%, $P = 0.02$) and similar between Groups B and C (10%, $P = 0.9$).

Conclusion Volume supplementation with 24 h sodium chloride 0.9% is superior to sodium bicarbonate for the prevention of CIN. A short-term regimen with sodium bicarbonate is non-inferior to a 7 h regimen.
ClinicalTrials.gov Identifier: NCT00130598

Keywords Contrast-induced nephropathy • Prevention • Sodium bicarbonate • Sodium chloride

Introduction

Acute deterioration in renal function caused by radiographic contrast agents is generally mild and transient but can result in lasting renal dysfunction and the need for renal replacement therapy. Contrast-induced nephropathy (CIN) is a leading cause of new-onset renal failure in hospitalized patients, with the highest risk observed in patients with pre-existing impaired renal function.[1,2] It is associated with significantly increased in-hospital and long-term morbidity and mortality, acceleration of chronic renal disease, and increased costs of medical care.[3]

Since there is no specific therapy of CIN and the disease is iatrogenic, prevention is of paramount importance. The

† These authors contributed equally and should be considered first authors.

* Corresponding author. Tel: +41 61 2652525, Fax: +41 61 2655353, Email: chmueller@uhbs.ch

pathophysiology of CIN is poorly understood but may include acute vasoconstriction resulting in renal hypoperfusion, hypoxia-induced oxidative stress, and free radicals generated within the acid environment of the renal medulla.[4,5] Varieties of approaches have been suggested for the prevention of CIN with target on these pathomechanisms.[6–11] Twenty-four hour volume supplementation with sodium chloride 0.9% is uniformly accepted and used in clinical practice for prevention and can be considered a cornerstone in the prevention of CIN.[12,13]

Recently, studies have begun to evaluate whether volume supplementation with sodium bicarbonate may be superior to volume supplementation with sodium chloride 0.9%. Based on the hypothesis that alkalinizing renal tubular fluid with bicarbonate may reduce renal injury, Merten *et al.*[14] presented a 7 h sodium bicarbonate regimen that appeared to be superior to a 7 h sodium chloride 0.9% regimen. The strategy of 24 h volume supplementation with sodium chloride 0.9%, supporting the hypothesis that the extent of volume supplementation *per se* is the most effective mechanism, has never been directly compared with the strategy of alkalinization.

In addition, it is unknown whether the administration of a similar amount of sodium bicarbonate as a short-term (e.g. 20 min) regimen including intravenous and oral sodium bicarbonate may be as effective as the 7 h intravenous approach.[15] For obvious logistic reasons, the short-term regimen would be highly attractive in clinical practice including outpatient procedures.

Methods

Study design

In this multicentre (three centres), randomized, open-label, controlled trial, we compared three different prevention procedures of CIN.

Study patients

All patients admitted with renal dysfunction {actual serum creatinine level above the upper limit of normal of the serum creatinine (>93 μmol/L for women and >117 μmol/L for men) or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 [eGFR calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation[16]]} scheduled to undergo an intra-arterial or intravenous radiographic contrast procedure on the next day were screened.

This study was conducted according to the principles of the revised Declaration of Helsinki and good clinical practice guidelines and was approved by the local Ethics Committees. All patients gave written informed consent before study entry.

Renal insufficiency was defined as a decrease in GFR and since the GFR has to be reduced by 50% before a rise in serum creatinine occurs, an elevated serum creatinine level was used as the cut-off point for the definition for renal dysfunction.[17]

Exclusion criteria were age <18 years, pre-existing dialysis, allergy to radiographic contrast, pregnancy, severe heart failure (NYHA functional class III and IV), *N*-acetylcysteine ≤24 h before contrast, and clinical condition requiring continuous fluid therapy, e.g. severe sepsis. Gold standard diagnosis of heart failure was built on the basis of all available medical records pertaining to the individual patient, on history, clinical presentation, and standard investigations, including natriuretic peptides and echocardiography (according to the current guidelines for heart failure of the European society of cardiology).[18]

Laboratory measures

Serum creatinine was measured with the enzymatic method in two centres (Centre 1: COBAS INTEGRA®, Roche Diagnostics GmbH, at 37°C, calibrated to IDMS standard; Centre 2: Wako Chemicals GmbH, at 37°C, calibrated to NIST-Standard SRM914a) and with the Jaffe method in the third centre [Olympus AU640®, at 37°C, modified Jaffe method (kinetic alkaline picrate)]. Cystatin C of all patients of the three centres was measured in a core laboratory in the University Hospital of Basel (nephelometry, Dako; IMMAGE® 800, Beckman Coulter).

Procedures

Patients were randomized to one of the three regimens of volume supplementation described below. Randomization with stratification for intra-arterial and intravenous radiographic contrast procedures and for each participating institution was performed by using sealed envelopes, 1:1:1 to each group.[19] The analysis was performed according to the intent-to-treat principle.

(A) 24 h sodium chloride 0.9%

The infusion of 0.9% sodium chloride was administered at a continuous rate of 1 mL/kg/h,[20] beginning from 8 p.m. on the day before the procedure and for at least 12 h after the procedure.

(B) 7 h sodium bicarbonate

The initial intravenous bolus was 3 mL/kg/h of 166 mEq/L sodium bicarbonate for 1 h immediately before radiocontrast injection. Following this, patients received the same fluid at a rate of 1 mL/kg/h during the contrast exposure and for 6 h after the procedure.[14]

(C) Short-term sodium bicarbonate

Patients received sodium bicarbonate 166 mEq/L as a bolus (3 mL/kg; maximally 300 mL) administered over 20 min immediately before contrast. Additionally, patients received oral sodium bicarbonate using Nephrotrans®, (Salmon, Basel, Switzerland; 500 mg $NaHCO_3$/capsule: 1 capsule/10 kg) with 1–2 dL of non-sparkling mineral water (San Pellegrino®) at the start of the infusion.[15] After contrast, patients received additional 500 mL of non-sparkling mineral water that had to be consumed within 6 h.

Additional oral fluid intake was encouraged in all groups. Additional infusions were strongly discouraged and initiated only if clinically indicated for other reasons. The rate of the study infusion was reduced in patients who developed signs or symptoms of pulmonary congestion. The administration of dopamine, mannitol, fenoldopam, *N*-acetylcysteine (as it might reduce serum creatinine by interference with the metabolism of creatinine), and theophylline during the study period was strongly discouraged.[11] The baseline serum creatinine and cystatin C levels were measured from peripheral blood samples obtained on the day preceding the contrast exposure. Post-contrast serum creatinine and cystatin C levels were measured at 7 a.m. in the morning of Days 1 and 2 after the contrast procedure in all patients.[8,10,21]

Endpoints

This trial was primarily designed to evaluate whether a regimen of a 24 h infusion of sodium chloride 0.9% is superior to an infusion of 7 h sodium bicarbonate at preventing contrast nephropathy (superiority analysis). In addition, we evaluated whether a short-term regimen with sodium bicarbonate is non-inferior to sodium bicarbonate during 7 h.

Primary endpoint

The maximum change in eGFR within 48 h was calculated with the highest creatinine level and using the abbreviated MDRD study equation.[16]

Secondary endpoints

Development of CIN was defined as an increase of ≥25% or an increase of ≥44 μmol/L in the baseline serum creatinine concentration within 48 h.[8,10,21] Further endpoints included post-contrast change in serum cystatin C within 48 h, in-hospital morbidity and mortality, 90-day mortality, renal replacement therapy, and time to hospital discharge.

All endpoints were assessed by physicians not involved in patient care using all medical records pertaining to the patient. Follow-up data were obtained by review of medical records and by contacting patients at specified intervals by telephone interview performed by two trained researchers. Primary care physicians were contacted in the case of uncertainties regarding health status.

Statistical analysis

The trial was designed to enrol a total of 258 patients. The power calculation was based on a hypothesized standard deviation of 20 mL/min/1.73 m^2 for individual reductions in the eGFR, a two-tailed *t*-test, and an α level of 0.05.[14,22] This study had a 90% power to detect a difference in the change of the GFR of 10 mL/min/1.73 m^2 between the 24 h sodium chloride group and the group with 7 h sodium bicarbonate (superiority analysis). In addition, this study had a 90% power for the non-inferiority analysis with an α level of 0.025 and a non-inferiority threshold of 10 mL/min/1.73 m^2 for the difference in the means of maximum change in glomerular filtration rate between treatment arms C and B (non-inferiority analysis). Thus, non-inferiority of Treatment C compared with Treatment B could be concluded if the two-sided 95% confidence interval (CI) of the difference in these means was larger than −10 mL/min/1.73 m^2. Our study was sufficiently powered to test each of the two main hypotheses separately at an α level of 0.05, but not to maintain an overall α level of 0.05.

Continuous data are summarized by their mean (standard deviation) or by their median (inter-quartile range) as appropriate. Categorical data are presented as absolute values (percentages). Comparisons between groups were performed using the *t*-test, ANOVA, Mann–Whitney *U*-test, Fisher's exact test, or Kruskal–Wallis test as appropriate. Statistical analyses were performed with SPSS software (version 16.0).

Results

Between March 2005 and December 2009, we screened consecutive hospitalized patients with renal insufficiency scheduled to undergo intra-arterial or intravenous contrast procedures within the next 24 h. Of 471 patients screened, a total of 273 patients were randomized to receive one of the three prevention regimens (*Figure 1*). Fifteen patients were excluded because they either did not receive contrast medium or withdrew their consent after randomization. This left 258 patients for final analysis.

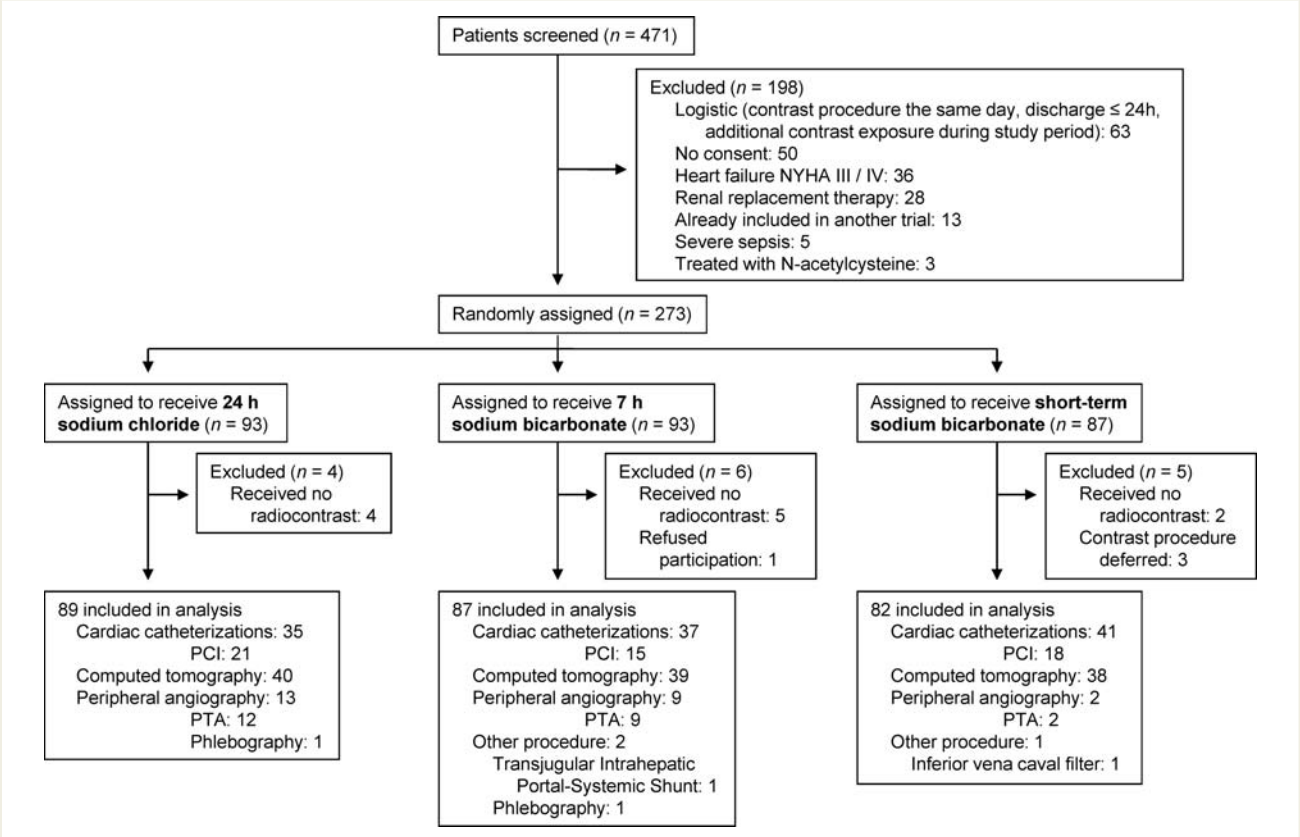

Figure 1 Study flow diagram.

Table I Baseline characteristics

Characteristic	All patients (*n* = 258)	Standard 24 h sodium chloride (Group A) (*n* = 89)	7 h sodium bicarbonate (Group B) (*n* = 87)	Short-term sodium bicarbonate (Group C) (*n* = 82)
Age, median (IQR), years	77 (69–81)	75 (70–82)	78 (70–82)	75 (65–81)
Male	166 (64)	55 (62)	57 (66)	54 (66)
BMI, mean (SD)	26.6 (5.3)	27.1 (5.8)	26.2 (5)	26.4 (5)
Renal function				
Serum creatinine, median (IQR), μmol/L	137 (113–158)	141 (112–158)	141 (115–164)	128 (114–157)
eGFR, mean (SD)	43.6 (11.6)	43.0 (11.8)	43.1 (10.7)	44.8 (12.2)
Serum Cystatin C, median (IQR), mg/L	1.75 (1.47–2.1)	1.7 (1.49–2.09)	1.79 (1.51–2.16)	1.7 (1.42–2.05)
Protein/creatinine ratio (IQR), mg/mmol[a]	16 (9–35)	14 (7–35)	17 (10–42)	17 (10–29)
Albumin/creatinine ratio (IQR), mg/mmol[a]	3 (1–11)	2 (1–9)	4 (2–18)	3 (1–12)
Vital signs				
Blood pressure, median (IQR), mmHg				
Systolic	130 (120–147)	130 (120–145)	133 (120–150)	130 (115–147)
Diastolic	70 (60–80)	70 (60–80)	70 (60–80)	70 (60–80)
Heart rate, median (IQR), b.p.m.	70 (64–80)	70 (64–81)	70 (64–78)	69 (60–82)
History				
Hypertension	213 (83)	72 (81)	78 (90)	63 (77)
Diabetes mellitus	96 (37)	30 (34)	34 (39)	32 (39)
Current smoker	40 (16)	13 (15)	13 (15)	14 (18)
Previous smoker	113 (45)	37 (43)	40 (46)	36 (46)
Dyslipidaemia	151 (59)	55 (63)	50 (58)	46 (56)
Coronary artery disease	150 (58)	54 (61)	53 (61)	43 (52)
Heart failure				
No history of heart failure	144 (56)	47 (53)	53 (61)	44 (54)
History of heart failure, NYHA class I	34 (13)	15 (17)	10 (12)	9 (11)
History of heart failure, NYHA class II	80 (31)	27 (30)	24 (28)	29 (35)
Causes of renal dysfunction				
Diabetic nephropathy[b]	16 (6)	8 (9)	6 (7)	2 (2)
Vascular nephropathy[b]	124 (48)	41 (46)	44 (51)	39 (48)
Combined diabetic and hypertensive nephropathy[b]	60 (23)	20 (23)	18 (21)	22 (27)
Other causes[c]	38 (15)	12 (14)	14 (16)	12 (15)
Unknown	20 (8)	8 (9)	5 (6)	7 (9)
Medication				
Angiotensin-converting enzyme inhibitors	112 (44)	39 (44)	39 (45)	34 (42)
Angiotensin receptor blockers	72 (28)	22 (25)	25 (29)	25 (31)
Diuretics	180 (70)	70 (80)	55 (63)	55 (67)
Metformin	18 (7)	8 (9)	3 (4)	7 (9)
Systemic glucocorticosteroids	31 (12)	10 (11)	12 (14)	9 (11)
Aspirin	143 (56)	50 (57)	44 (51)	49 (60)
NSAIDs	8 (3)	2 (2)	3 (3)	3 (4)
Radiocontrast procedures[d]				
Cardiac catheterizations	59 (23)	14 (16)	22 (25)	23 (28)
PCI	54 (21)	21 (24)	15 (17)	18 (22)
Computed tomography	117 (45)	40 (45)	39 (45)	38 (46)
Peripheral angiography	24 (9)	13 (15)	9 (10)	2 (2)
PTA	23 (9)	12 (14)	9 (10)	2 (2)

Continued

Table I *Continued*

Characteristic	All patients ($n = 258$)	Standard 24 h sodium chloride (Group A) ($n = 89$)	7 h sodium bicarbonate (Group B) ($n = 87$)	Short-term sodium bicarbonate (Group C) ($n = 82$)
Other procedures	4 (2)	1 (1)	2 (2)	1 (1)
Contrast volume, median (IQR), mL	100 (80–158)	100 (80–163)	100 (80–143)	100 (80–170)
Contrast product: iso-osmolar[e]	29 (11)	8 (9)	11 (13)	10 (12)

To convert serum creatinine to mg/dL, divide by 88.4. Values are presented as *n* (%), unless otherwise indicated. Percentages may not equal 100 due to rounding. NYHA heart failure class I and II indicate no symptoms and no limitation in ordinary physical activity and mild symptoms and slight limitation during ordinary activity, respectively. BMI, body mass index, calculated as weight in kilograms divided by height in square metres; eGFR, estimated glomerular filtration rate mL/min/1.73 m^2; IQR, inter-quartile range; NSAIDs, non-steroidal anti-inflammatory drugs; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty.
[a]Available in 113 patients.
[b]Patients with diabetic and/or hypertensive nephropathy could also have other nephropathy.
[c]Including vasculitis/glomerulonephritis, obstructive uropathy, interstitial nephritis, congenital nephropathy, functional single kidney, and drug toxicity.
[d]One patient in Group A had angiography without PTA (0.4%).
[e]All other patients received low-osmolar contrast medium, one patient received both.

Twenty-four hour sodium chloride infusion was administered in 89 patients (Group A), 87 patients received sodium bicarbonate for 7 h (Group B), and 82 patients received the short-term regimen of sodium bicarbonate (Group C). The baseline characteristics were well matched among the groups (*Table 1*). The mean age of the study population was 77 years and 64% were males. The mean eGFR at baseline was 43.6 ± 11.6 mL/min/1.73 m^2. In the majority of the patients, the cause of kidney dysfunction was vascular nephropathy (48%) followed by the combination of vascular and diabetic nephropathy (23%). All patients received a non-ionic contrast agent, the vast majority (88%) a low-osmolar contrast agent. Eleven per cent (missing data in two patients) received an iso-osmolar contrast agent. Six different products of contrast medium were used: iopromide (590–770 mOsm/kg), iomeprol (521–618 mOsm/kg), iopentol (810 mOsm/kg), iohexol (640–844 mOsm/kg), iobitridol (695–915 mOsm/kg), and the iso-osmolar iodixanol (290 mOsm/kg). Cardiac catheterization (23%), percutaneous coronary intervention (21%) and computed tomography (45%) were the main contrast procedures. Peripheral angiography was conducted in 9% and percutaneous transluminal angioplasty in 9% of the patients. Contrast volume was similar among groups.

Safety

No patient experienced a serious adverse event related to the infusion (death, intensive care unit admission). Also, no patient required intravenous diuretics or nitrates due to pulmonary congestion. Infusion rate was maintained constant in 97% of the patients, and it was reduced in 7 patients in Group A and in 1 patient in Group C who developed symptoms of pulmonary congestion. The uneven distribution of these cases across groups can hardly be explained by chance alone ($P = 0.005$ for differences among groups and $P = 0.008$ for Group A vs. Group B). Additional volume was initiated in two patients due to other clinical indications (one in Group B and one in Group C).

Efficacy

Group A vs. Group B

The primary and secondary endpoints are displayed in *Table 2*. The maximum change in eGFR within 48 h was significantly greater in Group B when compared with Group A [mean difference −3.9 (95% CI, −6.8 to −1) mL/min/1.73 m^2, $P = 0.009$]. Similarly, the maximum change in serum cystatin C was significantly greater in Group B when compared with Group A [mean difference 0.15 (95% CI, 0.04–0.27) mg/L, $P = 0.01$; *Figure 2A*]. The incidence of CIN, defined as a maximum increase in serum creatinine of ≥25% from baseline, was significantly lower in Group A ($n = 1$, 1%) vs. Group B ($n = 8$, 9%, $P = 0.02$; *Table 2* and *Figure 3*].

Group B vs. Group C

The maximum change in eGFR within 48 h was similar in Groups B and C [mean difference 1.3 (95% CI, −1.7–4.3] mL/min/1.73 m^2, $P = 0.39$). Similarly, the maximum change in serum cystatin C was similar in Groups B and C [mean difference −0.02 (95% CI, −0.12–0.08) mg/L, $P = 0.65$; *Figure 2A*]. The incidence of CIN was similar in Groups B and C ($n = 8$, 10%, $P = 0.9$; *Table 2* and *Figure 3*).

The mean eGFR before and after the contrast procedure in each group is shown in *Figure 2B*. The effect modification of medications interfering with the creatinine was tested in a multivariable regression analysis with dummy variables for the consumption of medications and with interaction terms between these variables and group membership. These interaction variables were far from reaching statistical significance, and when eliminating them from the model, the group differences were very similar to the ones obtained without adjustment for medication intake.

Increases in serum pH and increases in bicarbonate concentration were significantly higher in patients who received a prevention regimen containing sodium bicarbonate compared with sodium chloride (*Table 2*).

Table 2 Post-procedural outcomes—comparison between groups

Characteristic	All patients (n = 258)	Standard 24 h sodium chloride (Group A) (n = 89)	7 h sodium bicarbonate (Group B) (n = 87)	Short-term sodium bicarbonate (Group C) (n = 82)	P-value A vs. B	A vs. C	B vs. C
Changes in renal function							
Creatinine max. change, median (IQR), μmol/L	−3 (−15–10)	−7 (−19–5)	3 (−12–20)	−2 (−13–9)	0.001	0.04	0.24
Creatinine max. change, median (IQR), %	−2 (−12–8)	−6 (−14–3)	2 (−10–13)	−1.5 (−10–8)	0.001	0.04	0.22
eGFR max. change, mean (SD)	1.8 (9.9)	4.0 (9.6)	0.1 (9.9)	1.4 (9.8)	0.009	0.08	0.39
Cystatin C max. change, median (IQR), mg/L	0 (−0.13–0.14)	−0.06 (−0.26–0.08)	0.04 (−0.08–0.22)	0.01 (−0.07–0.17)	<0.001	0.002	0.29
Cystatin C max. change, median (IQR), %	0 (−7.5–8.7)	−4.5 (−12.9–4.1)	2.2 (−4.3–12.8)	0.5 (−4.8–10.6)	<0.001	0.003	0.33
Changes in electrolytes and blood gases (from pre-contrast to 1-day post-contrast)							
pH, mean (SD)	0.02 (0.05)	−0.01 (0.04)	0.03 (0.06)	0.02 (0.04)	<0.001	<0.001	0.09
Bicarbonate, mean (SD), mmol/L	0.8 (3.1)	−1.6 (2.3)	2.2 (2.7)	1.9 (2.7)	<0.001	<0.001	0.49
Incidence of contrast induced nephropathy							
Creatinine max. increase ≥44 μmol/L	14 (5)	1 (1)	7 (8)	6 (7)	0.03	0.06	1.0
Creatinine max. increase ≥25%	17 (7)	1 (1)	8 (9)	8 (10)	0.02	0.02	1.0

Comparison of means of changes in eGFR and maximum change in cystatin C after contrast procedure

Comparison	Difference in means (95% confidence interval)	P-value[a]
Mean max. change eGFR: Group B–Group A	−3.9 (−6.8 to −1)	0.009[b]
Mean max. change eGFR: Group C–Group B	1.3 (−1.7–4.3)	0.39[c]
Mean max. change cystatin C, mg/L: Group B–Group A	0.15 (0.04–0.27)	0.01
Mean max. change cystatin C, mg/L: Group C–Group B	−0.02 (−0.12–0.08)	0.65

Values are presented as n (%), unless otherwise specified. eGFR, estimated glomerular filtration rate, mL/min/1.73 m^2; IQR, inter-quartile range. To convert serum creatinine to mg/dL, divide by 88.4.

[a]All P-values refer to the deviation of observed group differences from 0.

[b]Based on this finding, we conclude superiority of A over B, since all values of the 95% confidence interval of the difference in means are <0.

[c]Based on this finding, we conclude non-inferiority of C compared with B, since all values of the 95% confidence interval of the difference in means are larger than the assumed non-inferiority threshold of −10 mL/min/1.73 m^2.

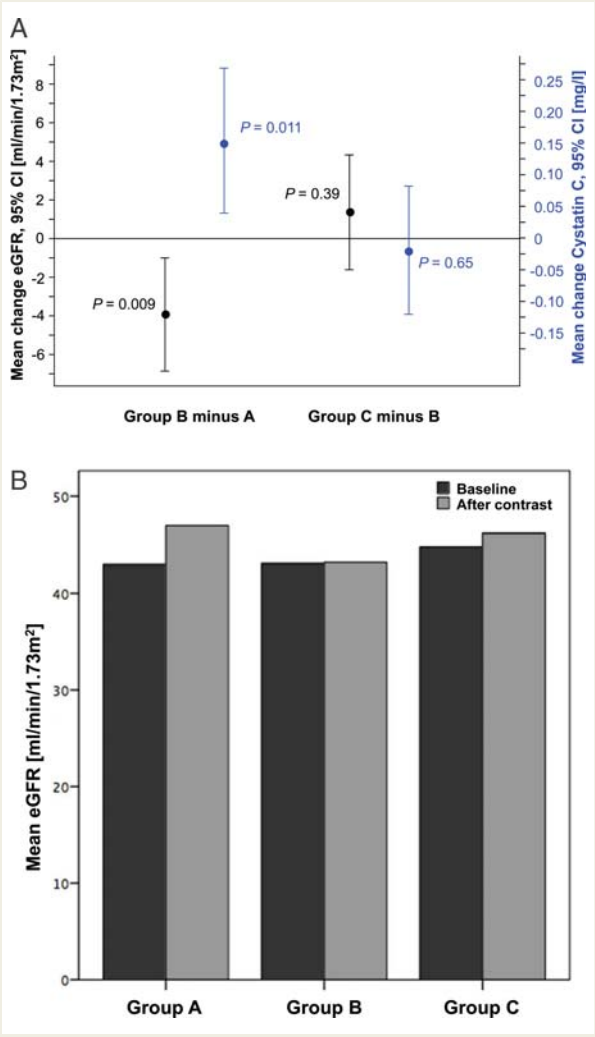

Figure 2 (*A*) Confidence intervals of differences between groups in the means of maximal change in estimated glomerular filtration rate and cystatin C after radiocontrast exposure. (*B*) Means of estimated glomerular filtration rate before and after the radiocontrast procedure in the three groups.

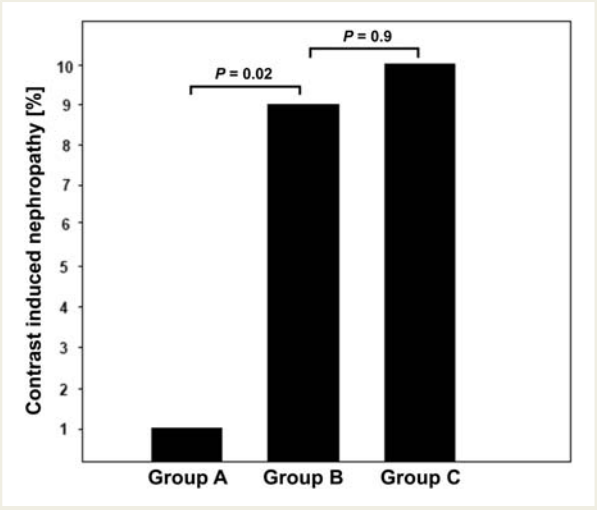

Figure 3 Incidence of contrast induced nephropathy defined as an increase of ≥25% in the baseline serum creatinine concentration within 48 h in the three groups.

Follow-up

In-hospital follow-up was complete in all patients; 90-day follow-up was complete in 254 patients (98%). In-hospital morbidity and mortality, time to hospital discharge, 90-day mortality, and renal replacement therapy at 90 days did not differ significantly between groups (*Table 3*).

Discussion

This study compared three different prevention procedures of CIN in consecutive patients with renal dysfunction: the 24 h sodium chloride 0.9% regimen, a 7 h regimen of sodium bicarbonate, and a novel short-term (20 min) regimen of sodium bicarbonate. We report four major findings: first, 24 h sodium chloride 0.9% regimen is superior to the 7 h sodium bicarbonate regimen. Secondly, a short-term regimen of sodium bicarbonate is non-inferior to 7 h sodium bicarbonate. Thirdly, the safety of all regimens was very high, even in patients with NYHA class I or II heart failure. Fourthly, the incidence of CIN was quite low, documenting the effectiveness of volume supplementation.[4]

These findings have major clinical implications and will help to individualize treatment decisions in the prevention of CIN. If maximal protection is required and it is feasible to initiate the infusion 12 h before contrast, a 24 h sodium chloride 0.9% regimen should be used. In all other patients, short-term sodium bicarbonate may be the regimen of choice as it is very easy to apply, even to outpatient procedures, and seems to have similar efficacy to the 7 h sodium bicarbonate regimen.

Our findings corroborate and extend previous data. A recent meta-analysis of previous studies concluded that the effectiveness of sodium bicarbonate treatment to prevent CIN in high-risk patients remains uncertain. Earlier reports probably overestimated the magnitude of any benefit, whereas larger, more recent trials have had neutral results.[23] However, early termination of the initial study, publication bias, small differences in the concentration and overall amount of sodium bicarbonate applied, the type of the contrast procedure, and patient selection can only partly explain the discrepant findings.[14,24–31] We hypothesize that the biochemical properties of the contrast agent used might affect the relative effectiveness of 24 h saline and sodium bicarbonate. The vast majority of the patients in our study received non-ionic low-osmolar contrast agents, the most commonly used agent worldwide.[24,27,30–32] For these contrast agents, 24 h saline seems to be the most effective preventive measure. Two recent studies applying iso-osmolar agents showed contrary results.[25,29] Briguori *et al.*[25] used iso-osmolar agents and found the combination of 7 h sodium bicarbonate with high-dose *N*-acetylcysteine to be superior. Maioli *et al.*[29] also used iso-osmolar agents and found similar effectiveness for

Table 3 Clinical outcomes

Characteristic	All patients (n = 258)	Standard 24 h sodium chloride (Group A) (n = 89)	7 h sodium bicarbonate (Group B) (n = 87)	Short-term sodium bicarbonate (Group C) (n = 82)	P-value
In-hospital morbidity (non-fatal myocardial infarction) and mortality	11 (4)	4 (5)	5 (6)	2 (2)	0.56
Dialysis dependency at 3 months	4 (2)	0 (0)	2 (2)	2 (3)	0.34
Length of stay, median (IQR), days	8 (3–16)	8 (3–18)	8 (3–15)	8 (4–16)	0.98
Mortality at 3 months	28 (11)	9 (10)	13 (15)	6 (8)	0.31
Mortality at 12 months	52 (23)	18 (23)	21 (27)	14 (19)	0.55
Hospitalization for cardiac cause at 3 months	40 (16)	15 (16)	18 (21)	9 (12)	0.23
Hospitalization for cardiac cause at 12 months	57 (29)	23 (34)	21 (30)	13 (21)	0.23

Values are presented as n (%), unless otherwise specified. IQR, inter-quartile range.

24 h saline with low-dose *N*-acetylcysteine and 7 h bicarbonate with low-dose *N*-acetylcysteine.

Our findings are in agreement with a recent meta-analysis, suggesting a lack of a clear benefit of bicarbonate in patients undergoing elective procedures compared with emergency procedures.[32] Other possible mechanisms of bicarbonate may play a role, such as buffering of subclinical acidosis-induced vasoconstriction, that is typical of acute settings and that may amplify the vasoconstriction induced by contrast itself.

Our data do not refute the original hypothesis generated by Merten *et al.*,[14] who postulated that alkalization using bicarbonate might provide additional protection.[24–30] We did not use equal volumes in the study arms, but compared sodium bicarbonate with 24 h sodium chloride 0.9% infusion, which is a well-accepted regimen.[20]

This study has some important strengths. First, this is a multicentre study and the population represents a real-life setting of hospitalized patients with renal insufficiency undergoing a contrast procedure. Secondly, the regimens of volume supplementation were compared without the interference of *N*-acetylcysteine, a known confounder of eGFR.[24,25] Thirdly, we included both intra-arterial and intravenous procedures. Many previous studies have exclusively enrolled patients undergoing intra-arterial contrast procedures. Arterio-arterial embolization to the kidneys is an important potential contributor to post-procedural decline in renal function and therefore challenges the evaluation of the prevention of CIN. Furthermore, intravenous administration of contrast agents was postulated to be a risk factor for mortality compared with intra-arterial procedures.[33]

This study has important limitations. First, we used a surrogate marker as primary outcome. The study was not powered to evaluate the impact of regimens of volume supplementation on hard clinical outcomes such as renal replacement therapy and rehospitalization. However, previous data strongly support the concept that post-procedural decrease in eGFR is associated with a higher incidence of clinical events.[3,33] Secondly, our study documented the safety and efficacy of volume supplementation also in patients with NYHA class I and II heart failure; however, we cannot comment on the most effective preventive regimen in patients with NYHA class III and IV heart failure, since such patients were excluded from our study. As heart failure and chronic kidney disease are closely linked and both increasing in prevalence, further research in this area is desperately needed.[34] Thirdly, in this study, true GFR was not measured, but estimated on the basis of the MDRD formula. This estimation has limitations, e.g. in elderly people.[35] However, these limitations should not affect the key findings of our study because of the randomized controlled design. Potential alternative methods include the use of the clearance of the contrast product as a measure of the real GFR.[36] Fourthly, the MDRD formula has been validated on subjects without intravenous infusions. This limitation is inherent to all studies assessing volume supplementation.

In conclusion, volume supplementation with 24 h sodium chloride 0.9% is more effective than 7 h sodium bicarbonate in the prevention of CIN and seems therefore to be the regimen of choice whenever maximal protection is desired and logistics permits. The short-term sodium bicarbonate regimen seems to be an attractive alternative for all other patients, including those undergoing outpatient procedures.

Funding

This study was supported by the University Hospital of Basel, Switzerland, and the Swiss National Science Foundation (grant number PP00B-102853). The study medications were provided by B Braun (Sempach, Switzerland), Bichsel (Interlaken, Switzerland), and Salmon (Basel, Switzerland). The sponsors had no role in study design, data analysis, or interpretation.

Conflict of interest: none declared.

References

1. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. *J Am Med Assoc* 1996;**275**:1489–1494.

2. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 1983;**74**:243–248.
3. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR Jr. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002;**105**:2259–2264.
4. Mueller C. Prevention of contrast-induced nephropathy with volume supplementation. *Kidney Int* 2006;**69**:S16–S19.
5. Bakris GL, Lass N, Gaber AO, Jones JD, Burnett JC Jr. Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. *Am J Physiol* 1990;**258**:F115–F120.
6. Marenzi G, Marana I, Lauri G, Assanelli E, Grazi M, Campodonico J, Trabattoni D, Fabbiocchi F, Montorsi P, Bartorelli AL. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med* 2003; **349**:1333–1340.
7. Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, De Metrio M, Galli S, Fabbiocchi F, Montorsi P, Veglia F, Bartorelli AL. *N*-Acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med* 2006;**354**: 2773–2782.
8. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994;**331**:1416–1420.
9. Stone GW, McCullough PA, Tumlin JA, Lepor NE, Madyoon H, Murray P, Wang A, Chu AA, Schaer GL, Stevens M, Wilensky RL, O'Neill WW. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *J Am Med Assoc* 2003;**290**:2284–2291.
10. Birck R, Krzossok S, Markowetz F, Schnulle P, van der Woude FJ, Braun C. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *Lancet* 2003; **362**:598–603.
11. Hoffmann U, Fischereder M, Kruger B, Drobnik W, Kramer BK. The value of *N*-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. *J Am Soc Nephrol* 2004;**15**:407–410.
12. Bader BD, Berger ED, Heede MB, Silberbaur I, Duda S, Risler T, Erley CM. What is the best hydration regimen to prevent contrast media-induced nephrotoxicity? *Clin Nephrol* 2004;**62**:1–7.
13. Trivedi HS, Moore H, Nasr S, Aggarwal K, Agrawal A, Goel P, Hewett J. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron Clin Pract* 2003;**93**:C29–34.
14. Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA 3rd, Rittase RA, Norton HJ, Kennedy TP. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *J Am Med Assoc* 2004;**291**:2328–2334.
15. Siegel RE. Prevention of contrast-induced nephropathy with sodium bicarbonate. *J Am Med Assoc* 2004;**292**:1428; author reply 1428–1429.
16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**:461–470.
17. Levey AS. Measurement of renal function in chronic renal disease. *Kidney Int* 1990; **38**:167–184.
18. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;**29**:2388–2442.
19. Davidson C, Stacul F, McCullough PA, Tumlin J, Adam A, Lameire N, Becker CR. Contrast medium use. *Am J Cardiol* 2006;**98**:42K–58K.
20. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002;**162**:329–336.
21. Schwab SJ, Hlatky MA, Pieper KS, Davidson CJ, Morris KG, Skelton TN, Bashore TM. Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. *N Engl J Med* 1989;**320**:149–153.
22. Spargias K, Alexopoulos E, Kyrzopoulos S, Iokovis P, Greenwood DC, Manginas A, Voudris V, Pavlides G, Buller CE, Kremastinos D, Cokkinos DV. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 2004;**110**: 2837–2842.
23. Zoungas S, Ninomiya T, Huxley R, Cass A, Jardine M, Gallagher M, Patel A, Vasheghani-Farahani A, Sadigh G, Perkovic V. Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. *Ann Intern Med* 2009;**151**:631–638.
24. Recio-Mayoral A, Chaparro M, Prado B, Cozar R, Mendez I, Banerjee D, Kaski JC, Cubero J, Cruz JM. The reno-protective effect of hydration with sodium bicarbonate plus *N*-acetylcysteine in patients undergoing emergency percutaneous coronary intervention: the RENO Study. *J Am Coll Cardiol* 2007;**49**:1283–1288.
25. Briguori C, Airoldi F, D'Andrea D, Bonizzoni E, Morici N, Focaccio A, Michev I, Montorfano M, Carlino M, Cosgrave J, Ricciardelli B, Colombo A. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation* 2007;**115**:1211–1217.
26. Masuda M, Yamada T, Mine T, Morita T, Tamaki S, Tsukamoto Y, Okuda K, Iwasaki Y, Hori M, Fukunami M. Comparison of usefulness of sodium bicarbonate versus sodium chloride to prevent contrast-induced nephropathy in patients undergoing an emergent coronary procedure. *Am J Cardiol* 2007;**100**:781–786.
27. Ozcan EE, Guneri S, Akdeniz B, Akyildiz IZ, Senaslan O, Baris N, Aslan O, Badak O. Sodium bicarbonate, *N*-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy. A comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled trial. *Am Heart J* 2007;**154**:539–544.
28. Pakfetrat M, Nikoo MH, Malekmakan L, Tabandeh M, Roozbeh J, Nasab MH, Ostovan MA, Salari S, Kafi M, Vaziri NM, Adl F, Hosseini M, Khajehdehi P. A comparison of sodium bicarbonate infusion versus normal saline infusion and its combination with oral acetazolamide for prevention of contrast-induced nephropathy: a randomized, double-blind trial. *Int Urol Nephrol* 2009;**41**:629–634.
29. Maioli M, Toso A, Leoncini M, Gallopin M, Tedeschi D, Micheletti C, Bellandi F. Sodium bicarbonate versus saline for the prevention of contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *J Am Coll Cardiol* 2008;**52**:599–604.
30. Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, Ree M, Shah AI, Burchette RJ. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. *J Am Med Assoc* 2008;**300**:1038–1046.
31. From AM, Bartholmai BJ, Williams AW, Cha SS, Pflueger A, McDonald FS. Sodium bicarbonate is associated with an increased incidence of contrast nephropathy: a retrospective cohort study of 7977 patients at mayo clinic. *Clin J Am Soc Nephrol* 2008;**3**:10–18.
32. Meier P, Ko DT, Tamura A, Tamhane U, Gurm HS. Sodium bicarbonate-based hydration prevents contrast-induced nephropathy: a meta-analysis. *BMC Med* 2009;**7**:23.
33. From AM, Bartholmai BJ, Williams AW, Cha SS, McDonald FS. Mortality associated with nephropathy after radiographic contrast exposure. *Mayo Clin Proc* 2008;**83**:1095–1100.
34. Breidthardt T, Mebazaa A, Mueller CE. Predicting progression in nondiabetic kidney disease: the importance of cardiorenal interactions. *Kidney Int* 2009;**75**: 253–255.
35. Van Pottelbergh G, Van Heden L, Mathei C, Degryse J. Methods to evaluate renal function in elderly patients: a systematic literature review. *Age Ageing* 2010;**39**: 542–548.
36. Gaspari F, Perico N, Ruggenenti P, Mosconi L, Amuchastegui CS, Guerini E, Daina E, Remuzzi G. Plasma clearance of nonradioactive iohexol as a measure of glomerular filtration rate. *J Am Soc Nephrol* 1995;**6**:257–263.