Circulation: Cardiovascular Interventions
Volume 7, Issue 2, April 2014; Pages 216-224
https://doi.org/10.1161/CIRCINTERVENTIONS.113.000653

ORIGINAL ARTICLE

Prevention of Contrast-Induced Nephropathy With N-Acetylcysteine or Sodium Bicarbonate in Patients With ST-Segment–Myocardial Infarction

A Prospective, Randomized, Open-Labeled Trial

Per Thayssen, MD, DMSci, Jens Flensted Lassen, MD, PhD, Svend Eggert Jensen, MD, PhD, Knud Nørregaard Hansen, MD, Henrik Steen Hansen, MD, DMSci, Evald Høj Christiansen, MD, PhD, Anders Junker, MD, PhD, Jan Ravkilde, MD, DMSci, Leif Thuesen, MD, DMSci, Karsten Tange Veien, MD, and Lisette Okkels Jensen, MD, DMSci, PhD

BACKGROUND— Contrast-induced nephropathy (CIN) is a serious condition in patients with ST-segment–elevation myocardial infarction treated with primary percutaneous coronary intervention. We compared the risk of acute CIN and the influence of preventive strategies in patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention.

METHODS AND RESULTS— A total of 720 patients were randomized in the Prevention of Contrast-induced Nephropathy in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention (CINSTEMI) trial. Patients were randomly assigned in a 1:1:1:1 ratio to receive hydration with sodium chloride together with 1 of 4 prophylactic regimes (1) N-acetylcysteine (NAC), (2) sodium bicarbonate ($NaHCO_3$) infusion, (3) NAC in combination with $NaHCO_3$, or (4) hydration with sodium chloride infusion alone. Patients in cardiogenic shock were excluded. Acute CIN was defined as an increase in serum creatinine concentration >25% from the baseline value within a 3-day period. Overall, CIN occurred in 141 (21.9%) patients. The prevention treatment with NAC, $NaHCO_3$, or the combined NAC and $NaHCO_3$ did not reduce the rate of CIN significantly compared with hydration with intravenous sodium chloride infusion alone (20.1% versus 20.1% versus 20.8% versus 26.5%; *P*=NS). However, an increase in serum creatinine >25% from the baseline value to 30 day was significantly lower in patients treated with combined NAC and $NaHCO_3$ (18.7% versus 19.1% versus 9.2% versus 21.3%; *P*=0.033).

CONCLUSIONS— Treatment with NAC or $NaHCO_3$ did not reduce the rate of acute CIN significantly. Combined treatment with NAC and $NaHCO_3$ may reduce the risk of renal dysfunction after 30 days.

CLINICAL TRIAL REGISTRATION— URL: http://www.clinicaltrials.gov. Unique identifier: NCT01160627.

Key Words: contrast-induced nephropathy ■ ST-segment–elevation myocardial infarction

Contrast-induced nephropathy (CIN) is a well-known and important side effect to the use of contrast media when performing coronary angiography (CAG) or percutaneous coronary intervention (PCI). Defined as a relative increase in serum creatinine of ≥25% or an absolute rise of ≥44 μmol/L, this complication is low (<3%) in patients without known renal dysfunction or renal

risk factors, whereas it is ≤50% in patients with known renal risk factors and dysfunction.[1–3] In case of primary PCI, the risk of CIN is 10% to 20%.[4–6] Usually, CIN develops within the first 2 to 3 days with a peak in serum creatinine level 3 to 5 days after contrast exposure. In general, serum creatinine normalizes within 7 to 10 days after contrast exposure. However, in patients with ST-segment–elevation myocardial infarction (STEMI), after primary PCI the impaired renal function might persist in almost half of the patients with CIN.[7] The effect of contrast media on renal function is complex and not fully understood. Initially, a reduction in glomerular filtration occurs because of changes in intrarenal and systemic regulatory mechanisms.[8] Furthermore, an endothelial dysfunction, an erythrocyte aggregation with increased viscosity, and a decreased erythrocyte velocity are followed by a decreased oxygen tension together with a directly toxic effect on the tubular apparatus contributing to the reduction in renal function.[9] In patients with normal renal function and no renal risk factors, a transient increase in serum creatinine in general is spontaneously normalized.[10] However, this is not the case for patients with known reduced renal function or renal risk factors where a permanent reduction in renal function and a poorer prognosis may be the consequence.[11] To avoid these serious side effects of contrast administration, 2 precautions in general are recommended, namely to reduce the dose of contrast media as much as possible[3] and to ensure optimal hydration before and immediately after the procedure by administration of intravenous sodium chloride.[12] In addition to these general recommendations, several more specific pharmacological interventions have been proposed for the protection of renal function. Among these, antioxidant treatment with N-acetylcysteine (NAC) has been investigated in several trials without uniform results,[13,14] as well as intravenous sodium bicarbonate ($NaHCO_3$), which seems to prevent further deterioration in renal function in patients with known reduced kidney function.[15,16] Patients treated for STEMI with primary PCI are most often exposed for contrast media without preexisting knowledge of renal function, and the patients are in different conditions of hydration. Only a few studies[7,11,17] have investigated this problem in different settings. To investigate the degree of renal impairment and the possible preventive effect of NAC and intravenous $NaHCO_3$, alone or in combination, we initiated the present randomized and prospective study.

METHODS

Study Design

The study was designed as a randomized multicenter, open-labeled, 4-arm study where patients were randomly assigned in a 1:1:1:1 ratio into 4 groups: (1) standard treatment with intravenous sodium chloride (0.9%) alone giving ≥60 mL/h for a minimum of 6 hours, (2) standard treatment+NAC 1200 mg orally before PCI followed by 1200 mg daily during the next 48 hours, (3) standard treatment+isotonic $NaHCO_3$ (167 mmol/L) intravenously as 500 mL in the first hour followed by infusion of 100 mL per hour in the next 5 hours (in total 1000 mL), and (4) standard treatment+NAC as in group 2+isotonic $NaHCO_3$ intravenously as in group 3. Serum creatinine was measured at admission (day 0), the next morning (day 1), and the following 2 days (day 2 and day 3). Finally, the serum creatnine was measured at day 30 after the index procedure (Figure 1).

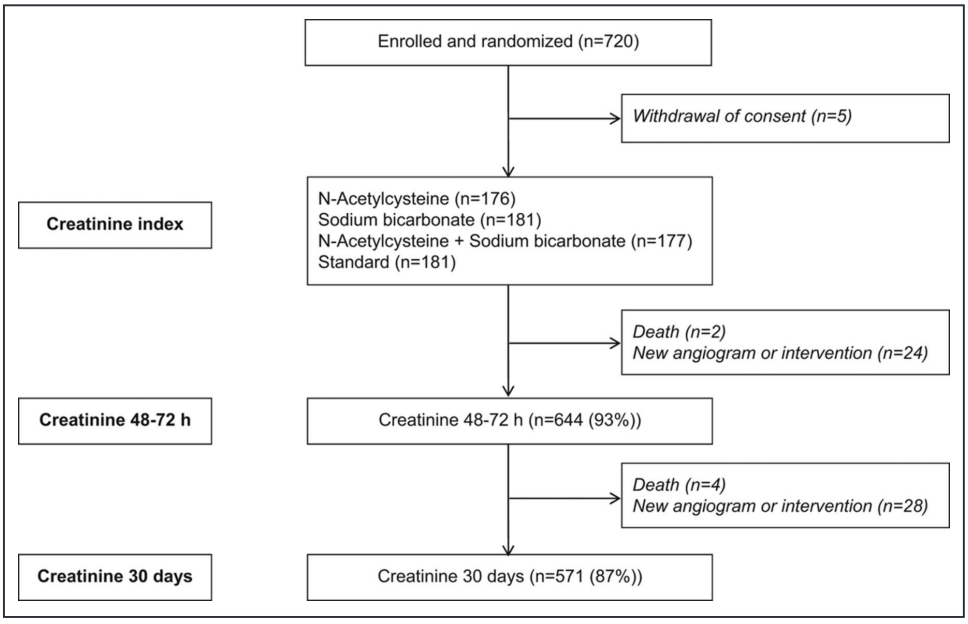

Figure 1. Trial flow diagram.

Patients

From May 2010 to March 2012, patients for the study were recruited from the 3 university hospitals in Western Denmark: Odense University Hospital, Aarhus University Hospital, Skejby, and Aalborg University Hospital. Eligible patients were all individuals aged ≥18 years being admitted for STEMI and having primary PCI performed within 12 hours from the onset of chest pain. Excluded from participation in the study were patients in cardiogenic shock, being unconscious, ventricular fibrillation or cardiac arrest before primary PCI, malignant disease, severe infection, or chronic treatment with dialysis. Excluded from the study after enrollment were patients having cardiac surgery or any other major surgery within 30 days after index PCI, or a new contrast media examination (ie, CAG or PCI) within 30 days. All patients were asked for participation after CAG when the indication for PCI was confirmed. Written informed consent was obtained before PCI. The study was approved by the Danish Medicines Agency (EUDRACT no. 2009-017642-32) and the Scientific Ethical Committee for Southern Denmark (jr. no. S-20090149).

Primary PCI

This was performed according to a common protocol for all 3 hospitals. The catheterization laboratory was notified when the diagnosis of STEMI was established, whether in the prehospital phase (tele-ECG transmission), at the referring hospital, or in the emergency room in 1 of the 3 university hospitals. All patients were admitted directly to the catheterization laboratory. All patients were pretreated with aspirin 600 mg, clopidogrel 300 mg or ticagrelor 180 mg, and heparine 10 000 IU. At the discretion of the PCI operator, this treatment was supplemented by glycoprotein IIB/IIIA receptor inhibitor or bivalirudine. The STEMI diagnose was ensured based on typical symptoms present <12 hours, characteristic ECG changes with ST-segment–elevation (≥0.1 mV in ≥2 standard leads or v4 through v6 or ≥0.2 mV in ≥2 contiguous precordial leads [v1 through v3]), or a presumed new developed left bundle branch block. Patients not belonging to the intake areas of the university hospitals were usually discharged within 24 hours to their local hospital, where the study-related blood test was taken at day 2 and day 3. For the 30-day serum creatinine blood sample test, a laboratory requisition was send to the patients 3 weeks after enrollment, and the patients had this blood test taken at a local hospital.

Randomization

Patients were enrolled by the investigators and randomly allocated to treatment groups after diagnostic CAG and before PCI. Block randomization by center was used to assign patients in a 1:1:1:1 to (1) standard treatment with intravenous sodium chloride (0.9%) alone, (2) standard treatment+NAC 1200 mg orally before the PCI followed by 1200 mg daily during the next 48 hours, (3) standard treatment+isotonic $NaHCO_3$ intravenously as 500 mL in the first hour followed by infusion of 100 mL per hour in the next 5 hours (in total 1000 mL), and (4) standard treatment+combined NAC (as in group 2)+isotonic $NaHCO_3$ intravenously (as in group 3). An independent organization computer generated the allocation sequence, stratified by sex and presence of diabetes mellitus. Patients were assigned to treatment through a Web-based Trial Partner randomization system. Although operators were not blinded, all individuals analyzing data were masked to treatment assignment.

End Points

The primary end point of the present study was CIN defined as a rise in serum creatinine of ≥25% from baseline value at admission to the value at day 3 (48–72 hours) after the index procedure. Secondary end points were (1) changes in serum creatinine from day 3 to day 30, (2) changes in serum creatinine from admission to day 30, (3) increase in serum creatinine of >25% from day 0 to day 30, and (4) increase in serum creatinine of >25% from day 0 to day 3 with a persistent increase in serum creatinine of >25% at day 30 compared with day 0. Intention-to-treat analyses were conducted after 3 days and 30 days of follow-up. Data monitoring was performed by the Good Clinical Practice unit at Odense University Hospital. An independent event committee, which was blinded to treatment group assignment during the adjudication process, reviewed all end points and source documents to adjudicate causes of death, reasons for hospitalization, diagnosis of myocardial infarction. Cine films were reviewed in the event committee to classify stent thrombosis and target vessel revascularization (either with PCI or coronary artery bypass grafting).

Definitions

The study end points were defined as follows:

CIN: a rise in serum creatinine of ≥25% from baseline value at admission to the value at day 3 (48–72 hours) after the index procedure. In patients who developed CIN, persistent renal damage was defined as persistence of increase in serum creatinine of ≥25% from baseline value at admission to the value at day 30.

The modification of diet in renal disease formula[18] was used to calculate the estimated creatinine clearance=$186 \times \text{standardized serum-creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if women).

Statistical Analysis

The number of patients included in the study was based on previous trials with NAC and $NaHCO_3$. We assumed a rate of CIN of ≥25% in patients with hydration with sodium chloride only, 15% in patients treated with NAC, 8% in patients treated with $NaHCO_3$, and 4% in patients treated with combined NAC and $NaHCO_3$. To test this expected response with a power of 80%, a minimum of 125 patients in each of the 4 treatment groups had to be included. Thus, a minimum of 150 patients in each treatment group was prespecified for enrollment to compensate for withdrawal of consent or cardiac events with or without contrast within 30 days. Distributions of continuous variables in the 4 groups of patients, NAC, isotonic $NaHCO_3$, combined NAC+isotonic $NaHCO_3$, and standard treatment with saline, were compared using the Kruskal–Wallis test. Distributions of categorical variables were compared using the χ^2 test (primary end point: CIN defined as a rise in serum creatinine of ≥25% from baseline value at admission to the value at day 3). Serial creatinine concentrations and creatinine clearance were compared (secondary end point) within (index compared with day 3 and day 30, respectively) and between groups (at each time point) using a Kruskal–Wallis test. To account for multiple comparisons, the Bonferroni correction was used. Three treatments were compared with standard; thus a

significance level of 0.05/3=0.017 was used for pairwise comparisons. The statistical analysis was performed using SPSS version 20.0.

RESULTS

In total, 720 patients were enrolled and randomized, 5 patients were excluded because of withdrawal of consent. The patient characteristics were similar between the 4 groups (Table 1). Lesion characteristics and supplementary medication demonstrated no differences between the 4 groups (Table 2). In 26 patients, the primary end point CIN within 3 days was not assessed (death=2, new angiogram/PCI n=24), and in another 32 patients, the secondary end point with changes in serum creatinine from day 3 to day 30 was not assessed (death=4, new angiogram/PCI n=28). Baseline serum creatinine levels were obtained before angiography in 713 patients (99.7%). Serum creatinine levels were available at day 3 in 644 patients (93.4%), day 30 in 571 patients (86.9%), and at all 3 time points in 536 patients (81.8%). The flow diagram of the trial is provided in Figure 1.

Table 1. Characteristics of Patients (Table view)

	Valid Cases	NAC	$NaHCO_3$	NAC+$NaHCO_3$	Standard Treatment (Sodium Chloride)	*P* Value
No. of patients, n	715	176	181	177	181	
Male sex, n (%)	715	127 (72.2)	139 (76.8)	139 (78.5)	145 (80.1)	0.32
Age, y (interquartile range)	715	63.0 (55.0–70.8)	62.0 (52.0–75.0)	63.0 (53.5–73.0)	63.0 (55.0–72.0)	0.89
Smoking, n (%)	684	82 (48.8)	88 (51.2)	79 (46.5)	89 (51.1)	0.79
Body mass index, kg/m^2 (interquartile range)	661	26.5 (24.3–29.4)	26.1 (24.4–28.9)	26.4 (24.3–29.7)	26.6 (24.2–29.6)	0.91
Diabetes mellitus, n (%)	715	15 (8.5)	17 (9.4)	19 (10.7)	18 (9.9)	0.91
Hypertension, n (%)	695	58 (34.5)	62 (35.6)	68 (38.6)	58 (32.8)	0.71
Previous coronary artery bypass grafting, n (%)	704	1 (0.6)	2 (1.1)	1 (0.6)	3 (1.7)	0.67
Previous percutaneous coronary intervention, n (%)	693	23 (13.7)	20 (11.4)	17 (9.7)	13 (7.5)	0.28
Previous myocardial infarction, n (%)	692	21 (12.5)	18 (10.3)	14 (8.0)	14 (8.0)	0.44
Lipid-lowering therapy, n (%)	693	39 (23.2)	41 (23.4)	46 (26.3)	45 (25.7)	0.88
Serum creatinine level, mg/dL	713	0.84 (0.71–0.97)	0.87 (0.74–1.01)	0.88 (0.74–1.00)	0.87 (0.74–1.03)	0.19
Serum creatinine level, µmol/L	713	74.0 (63.0–86.0)	77.0 (65.0–89.0)	78.0 (65.5–88.9)	77.0 (65.0–91.0)	0.19
eGFR, mL/(min 1.73 m^2)	713	94.3 (76.7–109.8)	91.4 (75.7–110.5)	90.8 (76.5–107.8)	89.5 (76.4–105.3)	0.45
Hemoglobin A1c	660	0.057 (0.055–0.060)	0.058 (0.055–0.061)	0.058 (0.055–0.061)	0.058 (0.055–0.062)	0.49
Left ventricle ejection fraction, n (%)	647	50.0 (45.0–60.0)	50.0 (45.0–60.0)	50.0 (40.0–55.5)	50.0 (40.0–60.0)	0.39
Systolic blood pressure, mm Hg	667	130.0 (110.0–142.8)	130.0 (110.0–140.0)	130.0 (118.0–140.0)	120.0 (116.0–148.0)	0.96
Diastolic blood pressure, mm Hg	667	70.0 (60.0–80.0)	70.0 (60.0–80.0)	71.5 (60.0–80.0)	72.0 (60.0–80.0)	0.67

eGFR indicates estimated glomerular filtration rate; NAC, sodium bicarbonate; and $NaHCO_3$, sodium bicarbonate.

Table 2. Procedure Characteristics (Table view)

	Valid Cases	N-Acetylcysteine	Sodium Bicarbonate	N-Acetylcysteine+Sodium Bicarbonate	Standard Treatment (Sodium Chloride)	*P* Value
No. of patients, n	715	176	181	177	181	
Multivessel disease, n (%)	715	69 (39.2)	57 (31.5)	60 (33.9)	70 (38.7)	0.35
Infarct-related artery, n (%)	711					0.62
	Left anterior descending artery, n (%)		73 (41.5)	76 (42.2)	83 (47.2)	78 (43.6)
	Left circumflex artery, n (%)		23 (13.1)	26 (14.4)	27 (15.3)	29 (16.2)
	Right coronary artery, n (%)		80 (45.5)	77 (42.8)	65 (36.9)	69 (38.5)
	Left main, n (%)		0 (0.0)	1 (0.6)	1 (0.6)	3 (1.7)
Anterior STEMI or BBBMI, n (%)	674	63 (38.6)	73 (42.5)	82 (48.2)	71 (42.0)	0.26
Killip class, n (%)	715					0.35
	I		160 (98.2)	169 (98.3)	160 (94.1)	163 (96.4
	II		2 (1.2)	2 (1.2)	8 (4.7)	4 (2.7)
	III		1 (0.6)	1 (0.6)	2 (1.2)	2 (1.2)
Preintervention TIMI flow, n (%)	711					0.17
	Grade 0		96 (54.5)	83 (46.1)	90 (51.1)	91 (50.8)
	Grade 1		11 (6.2)	14 (7.8)	20 (11.4)	15 (8.4)
	Grade 2		31 (17.6)	27 (15.0)	16 (9.1)	29 (16.2)
	Grade 3		38 (21.6)	56 (31.1)	50 (28.4)	44 (24.6)
Sapheneous vein graft, n (%)	711	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	0.57
Stent number, n (%)	715					0.29
	0		14 (8.0)	10 (5.5)	14 (7.9)	12 (6.6)
	1		126 (71.6)	142 (78.5)	145 (81.9)	132 (72.9)
	2		33 (18.8)	23 (12.7)	17 (9.6)	33 (18.2)
	3+		3 (1.7)	3 (3.4)	1 (0.6)	4 (2.3)

	Valid Cases	N-Acetylcysteine	Sodium Bicarbonate	N-Acetylcysteine+Sodium Bicarbonate	Standard Treatment (Sodium Chloride)	*P* Value
Drug-eluting stent, n (%)	715	151 (85.8)	152 (84.0)	152 (85.9)	135 (80.4)	0.68
Final TIMI flow, n (%)	711					0.81
	Grade 0		3 (1.7)	1 (0.6)	2 (1.1)	3 (1.7)
	Grade 1		0 (0.0)	1 (0.6))	0 (0.0)	1 (0.6)
	Grade 2		3 (1.7)	5 (2.8)	7 (4.0)	7 (3.9)
	Grade 3		170 (96.6))	173 (96.1)	167 (94.9)	168 (93.9)
Procedure time, min (interquartile range)	715	19.0 (13.0–29.0)	18.0 (13.0–25.0)	19.0 (13.0–27.0)	18.8 (12.0–26.0)	0.566
Contrast, mL (interquartile range)	699	140.0 (110.0–180.0)	130.0 (110.0–180.0)	140.0 (110.0–180.0)	150.0 (110.0–180.0)	0.51
Glycoprotein IIb/IIIa receptor blocker, n (%)	715	68 (38.6)	68 (37.6)	81 (45.7)	78 (43.1)	0.37
Bivalirudin, n (%)	650	59 (37.8)	63 (38.0)	57 (35.4)	61 (36.5)	0.96
Thrombectomy, n (%)	715	41 (23.3)	39 (21.5)	43 (24.3)	40 (22.1)	0.93

BBBMI indicates bundle branch block myocardial infarction; STEMI, ST-segment–elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

Contrast-Induced Nephropathy

Baseline renal function and volume of contrast medium did not differ significantly between the 4 groups (Tables 1 and 2). The primary end point CIN occurred overall in 141 (21.9%) patients with no significant difference between the 4 groups: NAC n=32 (20.1%) versus isotonic $NaHCO_3$ n=33 (20.1%) versus combined NAC+isotonic $NaHCO_3$ n=33 (20.8%) versus standard treatment with sodium chloride n=43 (26.5%; *P*=0.430; Figure 2). CIN at day 3 did not differ significantly among patients with or without reduced creatinine clearance at baseline: creatinine clearance >60 mL/min n=132 (22.4%) versus creatinine clearance ≤60 mL/min n=9 (17.5%; *P*=0.360). The secondary end point, the change in serum creatinine concentration between admission (before angiography), day 3, and day 30, is shown in Table 3. Increase in serum creatinine of ≥25% from day 0 to day 30 (secondary end point) was seen in 97 (17.0%) patients, with a significant difference between the 4 groups: NAC n=28 (18.7%) versus isotonic $NaHCO_3$ n=27 (19.1%) versus combined NAC+isotonic $NaHCO_3$ n=13 (9.2%) versus standard treatment with sodium chloride n=29 (21.3%; *P*=0.033). Compared with standard therapy with sodium chloride, only treatment with combined NAC+isotonic $NaHCO_3$ reduced the risk of increase in serum creatinine of ≥25% from day 0 to day 30 significantly (*P*=0.005), which was significant after Bonferroni correction (Figure 3). In patients who developed CIN, persistent renal damage occurred in 55 (48.2%): NAC n=15 (57.7%) versus isotonic $NaHCO_3$ n=14 (56.0%) versus combined NAC+isotonic $NaHCO_3$ n=8 (29.6%) versus standard treatment with sodium chloride n=18 (50.0%; *P*=0.150). At day 30, the creatinine value was measured in 571 patients, and

the persistent renal damage in 55 patients constitutes 39% of all patients (n=141) with CIN within day 3. None of the patients had renal failure requiring dialysis.

Table 3. Change in Serum Creatinine and Creatinine Clearance (Table view)

	Index	Day 3	Day 30	*P* Value
Serum creatinine, μmol/L				
NAC, median (interquartile range)	74.0 (63.3−85.8)	80.0 (68.0−92.8)	81.5 (69.0−92.0)	<0.001
$NaHCO_3$, median (interquartile range)	78.5 (65.0−89.0)	84.0 (72.0−95.8)	81.5 (72.3−96.8)	<0.001
NAC+$NaHCO_3$, median (interquartile range)	77.0 (66.0−88.0)	86.0 (75.0−98.0)	82.0 (73.3−93.0)	<0.001
Standard treatment (sodium chloride), median (interquartile range)	77.0 (65.0−90.0	83.0 (73.0−99.0)	82.0 (73.0−97.0)	<0.001
P value	0.467	0.063	0.546	
Creatinine clearance, mL/min				
NAC, median (interquartile range)	94.9 (76.8−109.6)	85.1 (73.9−97.0)	82.8 (73.8−96.4)	<0.001
$NaHCO_3$, median (interquartile range)	89.8 (76.1−108.4)	81.6 (70.5−93.7)	81.5 (69.0−99.1)	<0.001
NAC+$NaHCO_3$, median (interquartile range)	92.2 (76.5−107.6)	81.1 (69.9−93.0)	82.7 (73.5−95.8)	<0.001
Standard treatment (sodium chloride) median, (interquartile range)	90.9 (77.5−103.8)	80.2 (68.8−94.7)	81.8 (67.3−94.9)	<0.001
P value	0.881	0.414	0.948	

NAC indicates N-acetylcysteine; and $NaHCO_3$, sodium bicarbonate.

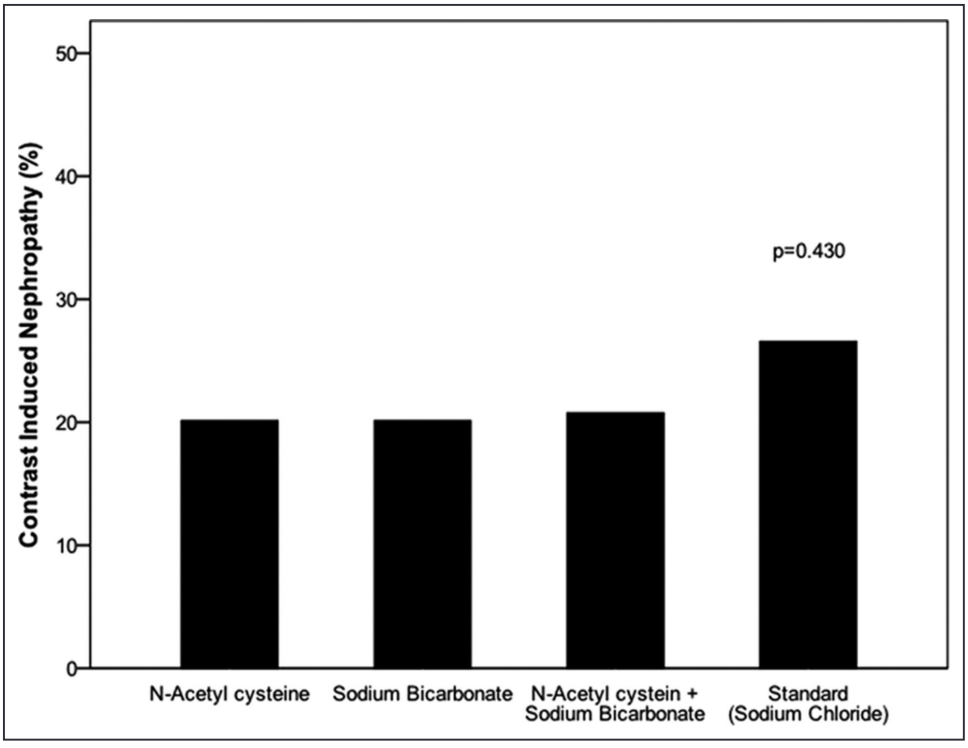

Figure 2. Rate of contrast-induced nephropathy at day 3 in patients treated with N-acetylcysteine (NAC), isotonic sodium bicarbonate ($NaHCO_3$), combined NAC+isotonic $NaHCO_3$, and standard treatment with sodium chloride.

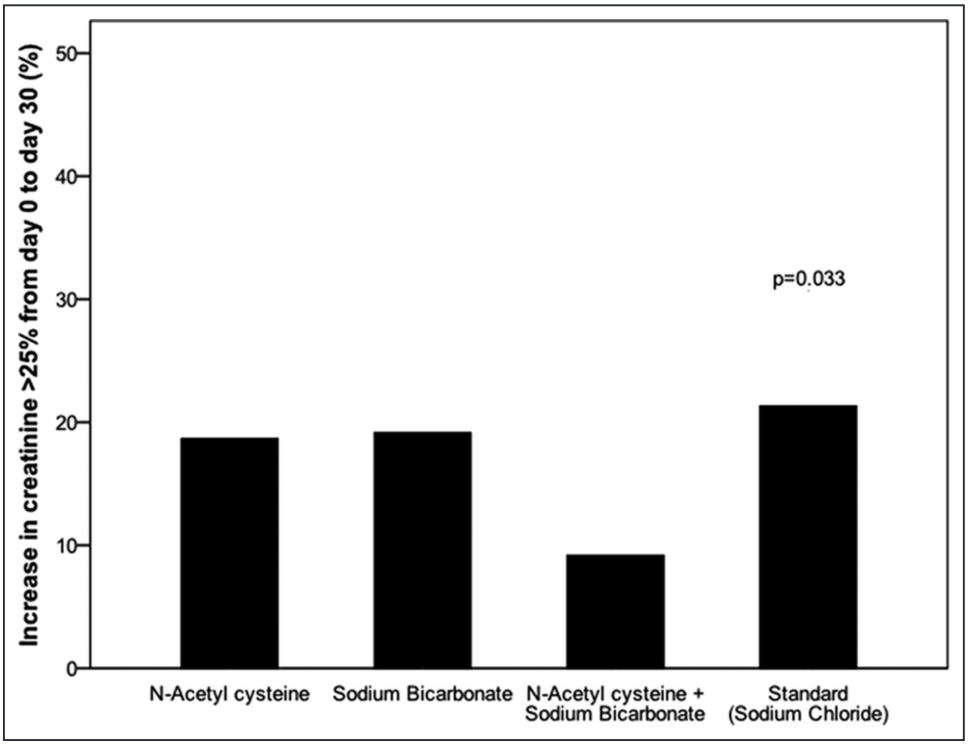

Figure 3. Rate of >25 increase in serum after 30 days compared with baseline in patients treated with N-acetylcysteine (NAC), isotonic sodium bicarbonate ($NaHCO_3$), combined NAC+isotonic $NaHCO_3$, and standard treatment with sodium chloride.

Clinical Outcome

Within 3 days, 2 (0.3%) patients died (cardiac death), 3 (0.3%) patients had an acute definite stent thrombosis, 3 (0.3%) patients had a new myocardial infarction, 3 (0.3%) patients had a target lesion revascularization, and 4 patients (0.6%) had a target vessel revascularization. Eleven patients (1.5%) had a new angiogram for a clinical reason without intervention and 9 (1.3%) patients had a nonculprit artery PCI. Two patients (0.3%) had pulmonary edema within 24 hours; both patients were randomized to treatment with combined NAC+isotonic $NaHCO_3$. Within 30 days, 6 (0.6%) patients died (cardiac death), 3 (0.3%) patients had an acute definite stent thrombosis, 1 (0.1%) patient had a subacute definite stent thrombosis, 6 (0.6%) patients had a new myocardial infarction, 7 (1.0%) patients had a target lesion revascularization, and 11 patients (1.5%) had a target vessel revascularization. Twenty patients (2.8%) had a new angiogram for a clinical reason without intervention, and 24 (3.3%) patients had a nonculprit artery PCI. A composite major adverse cardiac event rate (cardiac death, myocardial infarction, target vessel revascularization) at 30-month follow-up was 1.8%: NAC n=0 (0.0%) versus isotonic $NaHCO_3$ n=6 (3.6%) versus combined NAC+isotonic $NaHCO_3$ n=3 (1.7%) versus standard treatment with sodium chloride n=4 (2.2%; *P*=0.127).

DISCUSSION

The present randomized, open-labeled study in patients with STEMI demonstrates an overall rise in serum creatinine >25% in 22% of the patients from admission to day 3 without any difference in patients treated prophylactic with NAC, $NaHCO_3$, NAC+$NaHCO_3$, or hydration with sodium chloride. However, at 30 days, the group treated with the combination of NAC+$NaHCO_3$ had a significantly lower rate of increase in serum creatinine >25% compared with standard treatment, or treatment with either NAC or $NaHCO_3$ alone. After 30 days, half of the patients with CIN had persistent impaired renal function. Although patients in cardiogenic shock, severe general or infectious disease, and dialysis-treated patients were excluded in the present study, the overall average rise in serum creatinine >25% from admission to day 3 was of the same magnitude as found by others in patients

with STEMI.[4,7,17] The reason for contrast-induced renal impairment still remains unclear, but vasoconstriction because of tubular damage and oxidative stress, which together with increased interstitial renal pressure, lead to medullary hypoperfusion, and lowered glomerular filtration may contribute significantly.[19] These changes occur because of cytotoxity and increased viscosity of the contrast media. In the present study, almost all patients had Iodixanol (visipaque), a nonionic, dimeric, and iso-osmolar contrast medium, which is shown to have a low nephrotoxic effect in different subsets of patients with or without impaired renal function,[20,21] but the matter of which type of contrast media that is most kidney-friendly is still under debate.[22] The relationship between impaired renal function after contrast media and prognosis has been well documented with a poorer prognosis for an impaired kidney function, as well in patients with precontrast-impaired kidney function.[23–25] Many efforts have, therefore, been done to find regimens or drugs to prevent CIN. To find an effective prevention of CIN is, in particular, important in patients with STEMI treated with primary PCI in whom knowledge of possible kidney risk factors or disease is not present before injecting contrast media to the coronary arteries. In the present study, we have examined the preventive effect on the kidney function using either NAC, $NaHCO_3$, or both and compared the possible efficacy to standard treatment with sodium chloride intravenously alone. In addition, the use of contrast media was reduced as much as possible, being in average 140 mL per procedure, because of the fact that the degree of impaired kidney function is depending on the dose of contrast used.[26] In accordance with the previous studies,[12,27] our patients in the standard group and in the NAC group did have a sodium chloride infusion to keep them well hydrated during and after the PCI procedure, whereas this was done by isotonic $NaHCO_3$ in the other 2 groups. NAC is a potent antioxidant and by this supposed to prevent a direct oxidative tissue damage in the kidney.[28] A possible beneficial clinical effect has been investigated in several studies in patients with chronic nephropathy showing different results.[13,29,30] Only in 2 studies, the effect has been investigated in patients with primary PCI.[5,30] In agreement with the results from the present study, no beneficial effect on the occurrence of CIN using high-dose NAC could be proven, although patients in the study of Thiele et al[5] included severely ill patients in hemodynamic deranged condition. Thiele et al[5] found an occurrence of CIN in 14% of NAC-treated patients, despite using a slightly higher contrast volume and enrolling patients in Killip class 4 and patients treated with intra-aortic balloon pump. Whether patients with cardiogenic shock may benefit more from treatment with NAC cannot be addressed from the data from the study by Thiele et al[5] or our studies.

$NaHCO_3$ is an alkalinizing agent with alkalinizing effect on the renal tubular fluid and is by this theoretically able to reduce oxidative tissue damage in the kidney induced by contrast media. In patients with STEMI, a regimen with preprocedure and postprocedure hydration therapy with $NaHCO_3$ appeared to be more efficacious than postprocedure hydration only with isotonic sodium chloride.[27] This is in accordance with our study. Although we did not find a significant reduction in CIN in $NaHCO_3$-treated patients, the rate of CIN was numerically lower in $NaHCO_3$-treated patients compared with patients hydrated with sodium chloride only. Furthermore, Merten et al[15] demonstrated in a randomized setting, comparing hydration with isotonic sodium chloride or isotonic $NaHCO_3$ in patients with impaired renal function undergoing either CAG or PCI, a significant reduction of CIN from 13.8% in the sodium chloride group to 1.7% in the $NaHCO_3$ group. This is in contrast to our results, but patients characteristics were different because the patients enrolled in our study did not have a known impaired renal function and the hydration protocols differed with respect to the hydration with sodium chloride.

From a theoretical point of view, the combination of NAC and $NaHCO_3$ might be the superior strategy because these drugs in combination may exert a potent antioxidative effect and by this reduce the harmful consequence of contrast media. In the present study, this could not be proven in the acute phase after primary PCI, but at long-term follow-up at 30 days, a significant reduction in serum creatinine was observed in the group with NAC+$NaHCO_3$ compared with standard treatment. A

similar beneficial result has been reported by Briguori et al[16] in patients with chronic kidney disease, where a significantly lower proportion of patients with CIN was observed in the group treated with NAC+$NaHCO_3$ compared with the group treated with isotonic sodium chloride+$NaHCO_3$ 2 days after contrast exposure. A meta-analysis reviewing 10 randomized controlled studies, mostly in patients with chronic kidney disease, showed significantly fewer patients with CIN in the group with NAC+$NaHCO_3$ compared with sodium chloride+$NaHCO_3$ when defined as an increase of 0.5 mg/dL but not when defined as a 25% increase in serum creatinine.[31] A beneficial effect of intravenous $NaHCO_3$+NAC was also demonstrated in the study of Recio-Mayoral et al[32] in patients undergoing PCI for acute coronary syndromes, showing a significant lower occurrence of CIN within the first week after index PCI. In that study, CIN was defined as an increase in serum creatinine of >0.5 mg/dL, but the protective effect was also present using the definition for CIN as an increase in serum creatinine of >25% from baseline. In a recent study by Leone et al,[33] a group of urgent PCI patients had kidney protection with high-dose NAC+$NaHCO_3$ and was compared with a historic control group being treated with high-dose NAC+isotonic sodium chloride. Defining CIN as an increase of >25% in serum creatinine, they found a significant reduction in both in-hospital death and occurrence of CIN, the latter reduced from 14.1% to 8.0% 2 days after contrast exposure by the treatment with NAC+$NaHCO_3$. In the present study, we did not observe any difference at 3 day but first at 30-day follow-up. The reason for this is unexplained, and this secondary end point result is hypothesis generating and merits formal confirmation. Also, after 30 days, overall one fifth of the patients had impaired renal function, and half of the patients with CIN had persistent impaired renal function. The same was found in a retrospective observational registry,[7] where half of the patients with CIN within 2 days had persistent impaired renal function, and these patients experienced more adverse clinical events that patients who did not develop CIN. Recently Maioli et al[34] found that persistent renal damage occurred in ≈20% of patients 3 months after contrast exposure in patients with reduced creatinine clearance at the time of the contrast exposure. This may indicate that CIN is not always a transient impairment of the renal function but rather a direct cause of worsening renal function.

Limitations

Like most PCI trials, the Prevention of Contrast-induced Nephropathy in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention (CINSTEMI) trial was designed as a single-blinded study, but we think that the lack of double-blindness would not influence the results because all end points were objective and determined by an event committee, who was blinded to treatment group assignment during the adjudication process. The diagnostic angiogram was performed just before the randomization and initiation of the prophylactic treatment. However, we do not think that this treatment of prophylactic regimes delay of minutes would have influenced on the results in a STEMI population. Patients in cardiogenic shock or with prehospital cardiac arrest were excluded from the study because these clinical circumstances by themself may influence creatinine levels the first days after the index primary PCI. Because we excluded these patients, the results from the CINSTEMI cannot be extrapolated to patients with STEMI and cardiogenic shock or prehospital cardiac arrest. In a population without known renal insufficiency, the baseline creatinine level would be expected to be lower compared with patients with preexisting renal insufficiency. With the end point definition used in the present study, which is comparable with the literature, a 25% increase in serum creatinine at day 3 requires a smaller absolute increase in patients with a normal or low baseline creatinine compared with patients with renal insufficiency or increased creatinine level. In this way, our study differs from studies where patients with known renal insufficiency are examined, and our results cannot be extrapolated to a population with known renal insufficiency. Furthermore, the results in the present STEMI population cannot be generalized to

patients with stable angina pectoris, where proper lead times could be available for treatment with prophylactic regimes.

Conclusions

Treatment with NAC or $NaHCO_3$ did not reduce the rate of acute CIN significantly. However, combined treatment with NAC and $NaHCO_3$ may reduce the risk of renal dysfunction after 30 days.

WHAT IS KNOWN

- Contrast-induced nephropathy is a serious condition in patients with ST-segment–elevation myocardial infarction treated with primary percutaneous coronary intervention.
- Usually, contrast-induced nephropathy develops within the first 2 to 3 days with a peak in serum creatinine level 3 to 5 days after contrast exposure.
- To avoid these serious side effects of contrast administration, 2 precautions in general are recommended to reduce the dose of contrast media as much as possible and to ensure optimal hydration before and immediately after the procedure.

What the Study Adds

- Contrast-induced nephropathy occurred overall in 21.9% patients with no significant difference between 4 prophylactic regimes (1) N-acetylcysteine, (2) sodium bicarbonate infusion, (3) N-acetylcysteine in combination with sodium bicarbonate, or (4) hydration with sodium chloride infusion alone.
- An increase in serum creatinine >25% from the baseline value to 30 day was significantly lower in patients treated with combined N-acetylcysteine and sodium bicarbonate.
- Contrast-induced nephropathy at day 3 did not differ significantly among patients with (creatinine clearance ≤60 mL/min) or without reduced creatinine clearance (creatinine clearance >60 mL/min) at baseline.

ARTICLE INFORMATION

Received April 11, 2013; accepted February 20, 2014.

The Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.113.000653/-/DC1.

Correspondence

Correspondence to Per Thayssen, MD, DMSci, Department of Cardiology, Odense University Hospital, Sdr. Blvd 29, 5000 Odense C, Denmark. E-mail per.thayssen@rsyd.dk

Affiliations

From the Department of Cardiology, Odense University Hospital, Odense, Denmark (P.T., K.N.H., H.S.H., A.J., K.T.V., L.O.J.); Department of Cardiology, Aarhus University Hospital, Skejby, Denmark (J.F.L., E.H.C., L.T.); and Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark (S.E.J., J.R.).

Disclosures

Dr Thayssen has received an unrestricted grant to his institution from Medtronic, Terumo, and Cordis. Dr Jensen has received an unrestricted grant form Terumo and honoraria from AstraZeneca. The other authors report no conflicts.

APPENDIX

Please see the Data Supplement for additional information regarding CINSTEMI.

REFERENCES

1. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int Suppl*. 2006;*100*:S11–S15. Crossref.
2. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;*105*:2259–2264. Crossref. PubMed.
3. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997;*103*:368–375. Crossref. PubMed.
4. Marenzi G, Lauri G, Assanelli E, Campodonico J, De Metrio M, Marana I, Grazi M, Veglia F, Bartorelli AL. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol*. 2004;*44*:1780–1785. Crossref. PubMed.
5. Thiele H, Hildebrand L, Schirdewahn C, Eitel I, Adams V, Fuernau G, Erbs S, Linke A, Diederich KW, Nowak M, Desch S, Gutberlet M, Schuler G. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) Trial. *J Am Coll Cardiol*. 2010;*55*:2201–2209. PubMed.
6. Bolognese L, Falsini G, Schwenke C, Grotti S, Limbruno U, Liistro F, Carrera A, Angioli P, Picchi A, Ducci K, Pierli C. Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced nephropathy and tissue reperfusion in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the Contrast Media and Nephrotoxicity Following Primary Angioplasty for Acute Myocardial Infarction [CONTRAST-AMI] Trial). *Am J Cardiol*. 2012;*109*:67–74. PubMed.
7. Wi J, Ko YG, Kim JS, Kim BK, Choi D, Ha JW, Hong MK, Jang Y. Impact of contrast-induced acute kidney injury with transient or persistent renal dysfunction on long-term outcomes of patients with acute myocardial infarction undergoing percutaneous coronary intervention. *Heart*. 2011;*97*:1753–1757. Crossref. PubMed.
8. Detrenis S, Meschi M, Musini S, Savazzi G. Lights and shadows on the pathogenesis of contrast-induced nephropathy: state of the art. *Nephrol Dial Transplant*. 2005;*20*:1542–1550. Crossref. PubMed.
9. Tumlin J, Stacul F, Adam A, Becker CR, Davidson C, Lameire N, McCullough PA; CIN Consensus Working Panel. Pathophysiology of contrast-induced nephropathy. *Am J Cardiol*. 2006;*98*(6A):14K–20K. Crossref. PubMed.
10. Goldenberg I, Matetzky S. Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies. *CMAJ*. 2005;*172*:1461–1471. Crossref. PubMed.
11. Sgura FA, Bertelli L, Monopoli D, Leuzzi C, Guerri E, Spartà I, Politi L, Aprile A, Amato A, Rossi R, Biondi-Zoccai G, Sangiorgi GM, Modena MG. Mehran contrast-induced nephropathy risk score predicts short- and long-term clinical outcomes in patients with ST-elevation-myocardial infarction. *Circ Cardiovasc Interv*. 2010;*3*:491–498. Crossref. PubMed.
12. 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. Crossref. PubMed.
13. Goldenberg I, Shechter M, Matetzky S, Jonas M, Adam M, Pres H, Elian D, Agranat O, Schwammenthal E, Guetta V. Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography. A randomized controlled trial and review of the current literature. *Eur Heart J*. 2004;*25*:212–218. Crossref. PubMed.
14. Briguori C, Colombo A, Violante A, Balestrieri P, Manganelli F, Paolo Elia P, Golia B, Lepore S, Riviezzo G, Scarpato P, Focaccio A, Librera M, Bonizzoni E, Ricciardelli B. Standard vs double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. *Eur Heart J*. 2004;*25*:206–211. Crossref. PubMed.
15. Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA, Rittase RA, Norton HJ, Kennedy TP. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA*. 2004;*291*:2328–2334. Crossref. PubMed.

16. 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. Crossref. PubMed.
17. Osherov AB, Roguin A, Aronson D, Grenadier E, Kerner A, Boulus M, Kapeliovich M, Hani A, Hammerman H, Beyar R, Nikolsky E. Impact of platelet glycoprotein IIb/IIIa receptor inhibitors on renal function in patients with ST-segment elevation myocardial infarction treated with primary or rescue percutaneous coronary intervention. *EuroIntervention*. 2009;*5*:604–609. Crossref. PubMed.
18. Hallan S, Asberg A, Lindberg M, Johnsen H. Validation of the Modification of Diet in Renal Disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. *Am J Kidney Dis*. 2004;*44*:84–93. Crossref. PubMed.
19. Seeliger E, Sendeski M, Rihal CS, Persson PB. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. *Eur Heart J*. 2012;*33*:2007–2015. Crossref. PubMed.
20. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ; Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media Study Investigators. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med*. 2003;*348*:491–499. Crossref. PubMed.
21. Davidson CJ, Laskey WK, Hermiller JB, Harrison JK, Matthai W, Vlietstra RE, Brinker JA, Kereiakes DJ, Muhlestein JB, Lansky A, Popma JJ, Buchbinder M, Hirshfeld JW Randomized trial of contrast media utilization in high-risk PTCA: the COURT trial. *Circulation*. 2000;*101*:2172–2177. Crossref. PubMed.
22. Reed M, Meier P, Tamhane UU, Welch KB, Moscucci M, Gurm HS. The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials. *JACC Cardiovasc Interv*. 2009;*2*:645–654. Crossref. PubMed.
23. Sadeghi HM, Stone GW, Grines CL, Mehran R, Dixon SR, Lansky AJ, Fahy M, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Stuckey TD, Turco M, Carroll JD. Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. *Circulation*. 2003;*108*:2769–2775. Crossref. PubMed.
24. McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, Tumlin J; CIN Consensus Working Panel. Risk prediction of contrast-induced nephropathy. *Am J Cardiol*. 2006;*98*(6A):27K–36K. Crossref. PubMed.
25. Cardarelli F, Bellasi A, Ou FS, Shaw LJ, Veledar E, Roe MT, Morris DC, Peterson ED, Klein LW, Raggi P. Combined impact of age and estimated glomerular filtration rate on in-hospital mortality after percutaneous coronary intervention for acute myocardial infarction (from the American College of Cardiology National Cardiovascular Data Registry). *Am J Cardiol*. 2009;*103*:766–771. Crossref. PubMed.
26. Marenzi G, Assanelli E, Campodonico J, Lauri G, Marana I, De Metrio M, Moltrasio M, Grazi M, Rubino M, Veglia F, Fabbiocchi F, Bartorelli AL. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. *Ann Intern Med*. 2009;*150*:170–177. Crossref. PubMed.
27. Maioli M, Toso A, Leoncini M, Micheletti C, Bellandi F. Effects of hydration in contrast-induced acute kidney injury after primary angioplasty: a randomized, controlled trial. *Circ Cardiovasc Interv*. 2011;*4*:456–462. Crossref. PubMed.
28. Briguori C, Marenzi G. Contrast-induced nephropathy: pharmacological prophylaxis. *Kidney Int Suppl*. 2006;*100*:S30–S38. Crossref.
29. 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. Crossref. PubMed.
30. Tanaka A, Suzuki Y, Suzuki N, Hirai T, Yasuda N, Miki K, Fujita M, Tanaka T. Does N-acetylcysteine reduce the incidence of contrast-induced nephropathy and clinical events in patients undergoing primary angioplasty for acute myocardial infarction? *Intern Med*. 2011;*50*:673–677. Crossref. PubMed.
31. Brown JR, Block CA, Malenka DJ, O'Connor GT, Schoolwerth AC, Thompson CA. Sodium bicarbonate plus N-acetylcysteine prophylaxis: a meta-analysis. *JACC Cardiovasc Interv*. 2009;*2*:1116–1124. Crossref. PubMed.

32. Recio-Mayoral A, Chaparro M, Prado B, Cózar R, Méndez 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. Crossref. PubMed.

33. Leone AM, De Caterina AR, Sciahbasi A, Aurelio A, Basile E, Porto I, Trani C, Burzotta F, Niccoli G, Mongiardo R, Mazzari MA, Buffon A, Panocchia N, Romagnoli E, Lioy E, Rebuzzi AG, Crea F. Sodium bicarbonate plus N-acetylcysteine to prevent contrast-induced nephropathy in primary and rescue percutaneous coronary interventions: the BINARIO (BIcarbonato e N-Acetil-cisteina nell'infaRto mIocardico acutO) study. *EuroIntervention*. 2012;*8*:839–847. Crossref. PubMed.

34. Maioli M, Toso A, Leoncini M, Gallopin M, Musilli N, Bellandi F. Persistent renal damage after contrast-induced acute kidney injury: incidence, evolution, risk factors, and prognosis. *Circulation*. 2012;*125*:3099–3107. Crossref. PubMed.