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Effect of No Prehydration vs Sodium Bicarbonate Prehydration Prior to Contrast-Enhanced Computed Tomography in the Prevention of Postcontrast Acute Kidney Injury in Adults With Chronic Kidney Disease
The Kompas Randomized Clinical Trial

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IMPORTANCE Prevention of postcontrast acute kidney injury in patients with stage 3 chronic kidney disease (CKD) by means of prehydration has been standard care for years. However, evidence for the need for prehydration in this group is limited.

OBJECTIVE To assess the renal safety of omitting prophylactic prehydration prior to iodine-based contrast media administration in patients with stage 3 CKD.

DESIGN, SETTING, AND PARTICIPANTS The Kompas trial was a multicenter, noninferiority, randomized clinical trial conducted at 6 hospitals in the Netherlands in which 523 patients with stage 3 CKD were randomized in a 1:1 ratio to receive no prehydration or prehydration with 250 mL of 1.4% sodium bicarbonate administered in a 1-hour infusion before undergoing elective contrast-enhanced computed tomography from April 2013 through September 2016. Final follow-up was completed in September 2017. Data were analyzed from January 2018 to June 2019.

INTERVENTIONS In total, 262 patients were allocated to the no prehydration group and 261 were allocated to receive prehydration. Analysis on the primary end point was available in 505 patients (96.6%).

MAIN OUTCOMES AND MEASURES The primary end point was the mean relative increase in serum creatinine level 2 to 5 days after contrast administration compared with baseline (noninferiority margin of less than 10% increase in serum creatinine level). Secondary outcomes included the incidence of postcontrast acute kidney injury 2 to 5 days after contrast administration, mean relative increase in creatinine level 7 to 14 days after contrast administration, incidences of acute heart failure and renal failure requiring dialysis, and health care costs.

RESULTS Of 554 patients randomized, 523 were included in the intention-to-treat analysis. The median (interquartile range) age was 74 (67-79) years; 336 (64.2%) were men and 187 (35.8%) were women. The mean (SD) relative increase in creatinine level 2 to 5 days after contrast administration compared with baseline was 3.0% (10.5) in the no prehydration group vs 3.5% (10.3) in the prehydration group (mean difference, 0.5; 95% CI, −1.3 to 2.3; $P < .001$ for noninferiority). Postcontrast acute kidney injury occurred in 11 patients (2.1%), including 7 of 262 (2.7%) in the no prehydration group and 4 of 261 (1.5%) in the prehydration group, which resulted in a relative risk of 1.7 (95% CI, 0.5-5.9; $P = .36$). None of the patients required dialysis or developed acute heart failure. Subgroup analyses showed no evidence of statistical interactions between treatment arms and predefined subgroups. Mean hydration costs were €119 (US $143.94) per patient in the prehydration group compared with €0 (US $0) in the no prehydration group ($P < .001$). Other health care costs were similar.

CONCLUSIONS AND RELEVANCE Among patients with stage 3 CKD undergoing contrast-enhanced computed tomography, withholding prehydration did not compromise patient safety. The findings of this study support the option of not giving prehydration as a safe and cost-efficient measure.

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Presently, the use of iodine-based contrast media (ICM) in radiologic imaging is extensive and indispensable. The iatrogenic acute deterioration of renal function after administration of ICM, in the absence of other possible explanations, is known as *postcontrast acute kidney injury* (PC-AKI) or, when a proper control population without administration of ICM is also analyzed, *contrast-induced acute kidney injury*.[1-5]

Postcontrast acute kidney injury is generally known to have a mild clinical course and most often is self-limiting without long-term effects. Despite this mild clinical course, PC-AKI preventive measures are advised by international guidelines in high-risk patients.[6] These guidelines generally recommend intravenous volume expansion with either isotonic saline or sodium bicarbonate.[2,5,7] The latter may be preferred because previous studies, including trials performed by our study group,[8] have demonstrated that administration of sodium bicarbonate 1 hour prior to ICM exposure in patients with chronic kidney disease (CKD) is noninferior to periprocedural saline hydration and is more practical and results in substantial health care savings.

Although hydration protocols to prevent PC-AKI have been implemented in daily clinical practice for more than a decade, there is a lack of evidence for the effectiveness of these costly measures, and the magnitude of possible adverse effects, including volume overload in patients with congestive heart failure, is largely unknown. The safety of withholding hydration has been investigated in only a few recent randomized clinical trials in specific subgroups.[9,10] Given the low risk of PC-AKI, the question is whether it is useful to take preventive measures in patients with stage 3 CKD undergoing elective computed tomography (CT). To our knowledge, our study is the first that directly compares no prehydration with sodium bicarbonate prehydration prior to nonemergency contrast-enhanced CT (CECT) with intravenous ICM administration. In this multicenter randomized clinical trial, we studied whether no prehydration is noninferior to intravenous prehydration with 250 mL of 1.4% sodium bicarbonate in terms of renal safety in patients with stage 3 CKD undergoing CECT.

Key Points

Question Is it safe to omit prehydration with 1-hour sodium bicarbonate infusion in patients with stage 3 chronic kidney disease undergoing elective contrast-enhanced computed tomography?

Findings In this noninferiority randomized clinical trial that included 523 adults with stage 3 chronic kidney disease, the mean relative increase in serum creatinine level 2 to 5 days after intravenous contrast media administration compared with baseline was 3.0% in the no prehydration group vs 3.5% in the bicarbonate prehydration group.

Meaning Withholding short bicarbonate prehydration does not compromise renal safety in patients with stage 3 chronic kidney disease undergoing contrast-enhanced computed tomography.

Methods

Study Design and Population

The Kompas trial was a multicenter, open-label, noninferiority randomized clinical trial conducted in the Netherlands. Renal function was assessed in all outpatients undergoing nonemergency CECT by the referring physician of the 6 participating hospitals. Guidelines on the prevention of contrast-induced nephropathy that applied during the trial inclusion period included prescription of prophylactic hydration measures for all referred outpatients.[11] Inclusion criteria were patients with an estimated glomerular filtration rate (eGFR) of 30 to 44 mL/min/1.73 m^2 (CKD stage 3B) or with an eGFR of 45 to 59 mL/min/1.73 m^2 (CKD stage 3A) in the presence of diabetes or at least 2 of the following risk factors: peripheral artery disease, congestive heart failure, age older than 75 years, anemia, contrast volume greater than 150 mL, or use of nephrotoxic medication (eg, diuretics, nonsteroidal anti-inflammatory drugs, cyclosporin, tacrolimus, antiviral medication, amphotericin B, aminoglycosides, cisplatin, vancomycin). Patients with an eGFR less than 30 mL/min/1.73 m^2, age younger than 18 years, pregnancy, known allergy to ICM, kidney transplant less than 3 years prior, hemodynamic instability, or a planned contrast administration 7 days prior or 5 days after CECT were ineligible. The trial protocol was approved by the institutional review board of the Leiden University Medical Center and registered in the Netherlands Trial Register (https://www.trialregister.nl/trial/3605) and can be found in Supplement 1. All patients provided written informed consent prior to randomization. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Procedures

Patients were randomized in a 1:1 ratio to receive either no prehydration or prehydration by means of 250 mL of 1.4% sodium bicarbonate administered in a 1-hour infusion before CECT. This dose was based on 2 previous randomized clinical trials that demonstrated that prehydration using 250 mL of sodium bicarbonate is noninferior to saline hydration prior to and following contrast administration in patients with CKD.[9,12] Randomization was performed using Project Manager Internet Server (PROMISE) web-based software (Leiden University Medical Center) and was stratified for hospital of inclusion, presence of diabetes, and renal function. Baseline data were collected on sex, age, body mass index, blood pressure, smoking status, cause of CKD, renal function, and medication use. Also, information on comorbidity associated with an increased risk of PC-AKI, such as peripheral artery disease, coronary artery disease, atrial fibrillation, congestive heart failure, diabetes, multiple myeloma, and malignant neoplasm, was registered. Additionally, information regarding CECT indication, administered contrast volumes, temporary discontinuation of medication, and occurrence of adverse events was documented. The type of nonionic, isotonic contrast agent was used according to the clinical practice of the participating hospitals (eMethods in Supplement 2).

Serum creatinine levels and eGFR were determined by the participating centers prior to hydration and/or CECT. In individuals with missing baseline creatinine levels and stable renal function, the most recent value was used with a maximum duration of 1 month prior to CT. Patients were admitted to the hospital for the 1-hour infusion of prehydration. Patients were not instructed to increase their fluid intake prior to undergoing CECT. In some hospitals, it was common practice to advise patients to withhold food and beverages 3 hours prior to contrast administration to prevent vomiting. If a patient developed an indication for additional fluid administration for a reason other than PC-AKI prevention, this additional administration was allowed. Follow-up creatinine measurements were performed 2 to 5 days and 7 to 14 days after exposure to contrast agents. In patients who developed PC-AKI, serum sampling was repeated 2 months after CECT. The eGFR was calculated using the Modification of Diet in Renal Disease formula.[13,14]

Outcomes

The primary outcome was the mean relative increase (percentage) in serum creatinine level 2 to 5 days after contrast administration compared with baseline. Secondary outcomes were PC-AKI (defined as an increase in creatinine level greater than 25% or greater than 0.5 mg/dL [to convert to micromoles per liter, multiply by 88.4]) 2 to 5 days after contrast administration; mean relative increase in creatinine level 7 to 14 days after contrast administration; recovery of renal function in patients with PC-AKI after 2 months; acute heart failure; renal failure requiring dialysis; and presence of acute kidney injury according to the Acute Kidney Injury Network (AKIN) and the Risk, Injury, Failure, Loss, and End-stage Kidney Disease (RIFLE) classifications.[15,16] Subgroup analyses were performed for the primary end point and the secondary end point of PC-AKI 2 to 5 days after contrast administration in high-risk patients—namely, patients with an eGFR of 30 of 44 mL/min/1.73 m^2 with 2 or more risk factors for PC-AKI, patients with an eGFR of 30 to 44 mL/min/1.73 m^2 in combination with diabetes, and patients 75 years and older. Adverse events, such as hypersensitivity reactions to ICM, as well as treatment of complications and 1-year mortality were recorded. Also, we performed an economic evaluation (eMethods in Supplement 2).

Statistical Analyses

This study was designed as a noninferiority trial. As a consequence of the noninferiority design and the low risk of PC-AKI, our study was powered on a relative increase in serum creatinine level instead of PC-AKI for feasibility reasons, as has been done by other studies.[8,17] Based on a previous trial performed in the same clinical setting,[17] a mean (SD) increase in serum creatinine level of 2% (13) was anticipated in the prehydration group. No prehydration was considered noninferior to sodium bicarbonate prehydration when the difference in the mean relative increase in creatinine level between the 2 randomization groups was less than 10%. We chose this noninferiority margin because it is the margin at which the difference in creatinine level increase between the 2 groups becomes clinically relevant. Although a small increase in serum creatinine level was anticipated, we were willing to accept a maximum 10% higher increase in the no prehydration group. This is based on the mild clinical course of PC-AKI, which is characterized by a spontaneous recovery of renal function within a short time in almost all patients.[18]

The power calculation was based on the noninferiority criterion and expected increase in serum creatinine level following CECT. To detect a mean (SD) difference in relative creatinine level increase of 10% (20), it was calculated that approximately 250 individuals per randomization group were needed under the assumption of a true difference in creatinine level increase of 5% ($\alpha = .05$; $\beta = .20$). Accounting for a 15% loss to follow-up, we estimated that 575 patients would need to be enrolled.

Statistical analyses were performed according to the intention-to-treat principle using SPSS version 23.0 (IBM Corp). Categorical data are presented as absolute numbers and frequencies and continuous data as means and SDs or medians and interquartile ranges in cases of a nonnormal distribution. An independent-samples *t* test was used to analyze the mean relative differences in creatinine level increase between treatment and control arms at different time points in follow-up. Under the null hypothesis of equivalence, a 1-sided *P* value of noninferiority was calculated. A *P* value less than .025 was considered statistically significant for this analysis.

Using relative risk, statistical differences were tested for occurrence of PC-AKI, congestive heart failure, need for dialysis, and acute kidney injury according to AKIN and RIFLE classifications. Statistical significance was tested using the χ^2 test. For all secondary end point analyses, a 2-sided *P* value less than .05 indicated statistical significance. Data analysis was performed from January 2018 to June 2019.

Results

Of 554 patients randomized, 523 were included in the intention-to-treat analysis. The median (interquartile range) age was 74 (67-79) years; 336 (64.2%) were men and 187 (35.8%) were women. Patient characteristics at baseline were well balanced between both study arms (**Table 1**). From April 2013 through September 2016, a total of 554 patients were included and randomized. Withdrawal of consent after randomization occurred in 31 patients. Thus, 523 study patients were available for the intention-to-treat analysis, of which 262 patients (50.1%) had been randomized to the no prehydration group and 261 (49.9%) to receive prehydration with sodium bicarbonate prior to undergoing CECT (**Figure 1**).

Protocol violations occurred for 23 patients (4.4%), of which 14 (5.3%) had been randomized to the no prehydration group and 9 (3.4%) to the prehydration group (eTable 1 in Supplement 2). In the no prehydration group, 1 patient received saline prior to and after CECT, 1 patient received saline only prior to CECT and 1 patient did not meet the inclusion criteria of the trial. In the prehydration group, 1 patient did not receive prehydration and 1 patient received hydration other than the study-mandated protocol (1 L of saline posthydration). Finally, 1 patient was randomized while ineligible be-

Table 1. Baseline Study Participant Characteristics

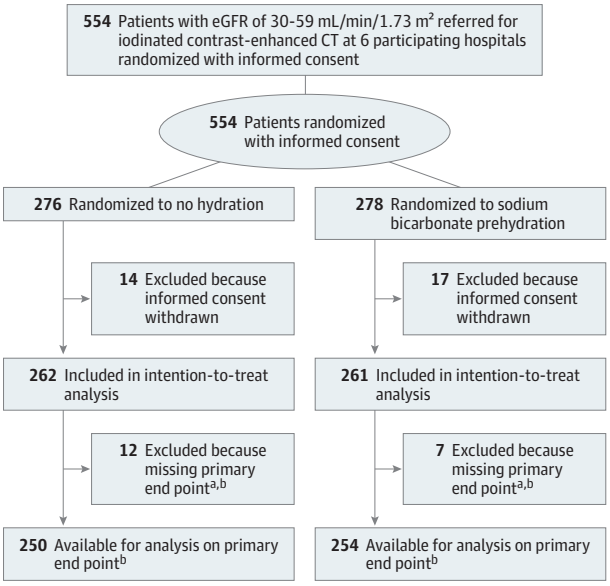
Characteristic	No. (%)	
	No Prehydration Group (n = 262)	Sodium Bicarbonate Prehydration Group (n = 261)
Male	170 (64.9)	166 (63.6)
Age, median (IQR), y	74 (67-80)	73 (67-78)
BMI, median (IQR)[a]	27.7 (24.7-30.9)	27.2 (24.4-30.0)
MDRD group, mL/min/1.73 m^2		
eGFR 30-44	130 (49.6)	137 (52.5)
eGFR 45-59	132 (50.4)	124 (47.5)
Serum creatinine at randomization, mean (SD), mg/dL	1.43 (0.27)	1.41 (0.26)
Hemoglobin, mean (SD), g/dL	12.9 (1.8)	12.7 (1.6)
Comorbidity		
Diabetes	103 (39.3)	104 (39.8)
Atrial fibrillation	19 (7.3)	25 (9.6)
Coronary artery disease	92 (35.4)	81 (31.0)
Heart failure	39 (14.9)	43 (16.5)
Peripheral artery disease	92 (35.2)	90 (34.5)
Multiple myeloma	0	7 (2.7)
CKD cause		
Nephrosclerosis/hypertension	104 (39.7)	104 (39.8)
Diabetic nephropathy	71 (27.1)	65 (24.9)
Cystic kidneys	6 (2.3)	6 (2.3)
Acute tubular necrosis	4 (1.5)	3 (1.1)
Renal malignant neoplasm, nephrectomy	20 (7.6)	24 (9.2)
Other	57 (21.8)	59 (22.6)
History of smoking		
Current	43 (16.4)	62 (23.8)
In the past	128 (48.9)	131 (50.2)
Medication use		
Statin	177 (67.6)	159 (60.9)
Metformin	78 (29.8)	73 (28.0)
ACE inhibitor	91 (34.7)	95 (36.4)
Angiotensin receptor blocker	96 (36.6)	74 (28.5)
NSAID	13 (5.0)	8 (3.1)
Aminoglycoside	0	0
Diuretic	138 (52.7)	120 (46.0)
Chemotherapy	5 (1.9)	5 (1.9)
Other nephrotoxic medication	6 (2.3)	15 (5.7)

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; NSAID, nonsteroidal anti-inflammatory drug.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4. To convert hemoglobin to grams per liter, multiply by 10.

[a] Calculated as weight in kilograms divided by height in meters squared.

Figure 1. Trial Flowchart



CT indicates computed tomography; eGFR, estimated glomerular filtration rate.

[a] No blood samples obtained at baseline and/or during follow-up 2 to 5 days after contrast-enhanced CT.

[b] Protocol violations are summarized in eTable 1 in Supplement 2.

cause of unstable renal function 2 months prior to inclusion. One patient received, in addition to sodium bicarbonate according to protocol, 2 L of 5% glucose after CECT because of hypoglycemia. This was not deemed a protocol violation.

Baseline creatinine values were missing in 29 of 523 patients (5.5%). In 10 patients (5 in the no prehydration group and 5 in the prehydration group), the most recent creatinine value within 1 month prior to CECT was extracted from the hospital electronic patient medical record and used for analysis. In the remaining 19 patients, creatinine values for analysis of primary outcome were missing (Figure 1). In 267 of 523 participants (51.1%), the eGFR was 30 to 44 mL/min/1.73 m^2, and in the remaining 256 patients (48.9%), the eGFR was 45 to 59 mL/min/1.73 m^2. The CECT characteristics are summarized in **Table 2**.

A total of 523 patients were included in the intention-to-treat analysis. Assessment of the primary outcome was possible in 504 of 523 patients (96.4%), of which 250 (49.6%) were in the no prehydration group and 254 (50.4%) were in the prehydration group. The mean (SD) relative increase in creatinine level 2 to 5 days after contrast administration compared with baseline was 3.0% (10.5) in the no prehydration group compared with 3.5% (10.3) in the prehydration group (mean difference, 0.5%; 95% CI, −1.3 to 2.3; $P < .001$ for noninferiority) (**Table 3**). The mean relative change in eGFR is described in the eResults in Supplement 2. Postcontrast acute kidney injury within 2 to 5 days after contrast administration occurred in 7 patients (2.7%) in the no prehydration group vs 4 patients (1.5%) in the prehydration group (relative risk, 1.7; 95% CI, 0.5-5.9; $P = .36$; risk difference, 1.2%). The mean (SD) relative increase in creatinine level 7 to 14 days after contrast administration compared with baseline was 3.5% (13.4) in the no prehydration group compared with 3.5% (13.0) in the prehydration group (mean difference, 0%; 95% CI, −2.3 to 2.3; $P < .001$ for noninferiority). An alternative cause for the deterioration of renal function could not be identified in these

Table 2. Procedural Characteristics

Characteristic	No Prehydration Group (n = 262)			Sodium Bicarbonate Prehydration Group (n = 261)		
	No. (%)	Administered Iodine Dose, Median (IQR), gI	Administered Contrast Volume, Mean (SD), mL	No. (%)	Administered Iodine Dose, Median (IQR), gI	Administered Contrast Volume, Mean (SD), mL
CECT type						
Abdomen	40 (15.3)	32 (30-38)	110 (19)	41 (15.7)	32 (30-38)	107 (19)
Thorax	14 (5.3)	24 (20-30)	84 (19)	17 (6.5)	29 (24-35)	94 (24)
Thorax-abdomen	59 (22.5)	35 (30-43)	113 (17)	61 (23.4)	36 (30-44)	113 (18)
Angiography	100 (38.2)	32 (30-36)	101 (15)	96 (36.8)	32 (30-36)	101 (20)
Other	38 (14.5)	36 (30-39)	115 (18)	40 (15.3)	36 (30-36)	108 (21)
CT canceled or nonenhanced	11 (4.2)	NA	NA	6 (2.2)	NA	NA
CECT indication						
PAD	57 (21.8)	32 (32-36)	107 (13)	58 (22.2)	32 (30-37)	106 (16)
Malignant neoplasm	108 (41.2)	35 (30-43)	112 (18)	118 (45.2)	35 (30-43)	109 (20)
Aortic aneurysm/(T)EVAR	36 (13.7)	30 (27-32)	95 (14)	33 (12.6)	30 (26-37)	97 (19)
Other	51 (19.5)	30 (30-37)	106 (23)	48 (18.4)	30 (27-36)	101 (27)
Intravenous ICM						
Iopromide	132 (50.4)	NA	NA	136 (52.1)	NA	NA
Iodixanol	40 (15.3)	NA	NA	44 (16.9)	NA	NA
Iohexol	51 (19.5)	NA	NA	48 (18.4)	NA	NA
Iobitridol	28 (10.7)	NA	NA	27 (10.3)	NA	NA
Nephrotoxic drugs						
No	41 (15.6)	NA	NA	55 (21.1)	NA	NA
Yes	221 (84.4)	NA	NA	206 (78.9)	NA	NA
Temporarily discontinued	118 (45.0)	NA	NA	106 (40.6)	NA	NA

Abbreviations: CECT, contrast-enhanced computed tomography; gI, grams of iodine; ICM, iodine-based contrast media; IQR, interquartile range; NA, not applicable; PAD, peripheral artery disease; (T)EVAR, (thoracic) endovascular aneurysm repair.

11 patients. Renal function was reassessed 2 months after CECT in 8 of 11 patients. In 5 patients, renal function had completely recovered (3 patients in the no prehydration group and 2 in the prehydration group). In the remaining 3 patients, all in the no prehydration group, deterioration of kidney function persisted (mean decrease in eGFR, 3 mL/min/1.73 m^2). One of 3 patients in whom renal function was not reassessed at 2 months died within the follow-up period because of multiorgan failure owing to sepsis. However, recovery of kidney function had already occurred at follow-up 7 days after contrast administration. In another patient with missing follow-up at 2 months, renal function had recovered within 2 weeks. One patient was lost to follow-up.

Rates of acute kidney injury according to the AKIN and RIFLE classifications are summarized in Table 3. No patient developed a need for dialysis or acute heart failure resulting from volume overload or any other complications of the prehydration. Two patients developed acute self-limiting rash following administration of 370 mgI/mL iopromide. No evidence of statistical interactions between treatment arms and predefined subgroups was found on the primary outcome and the outcome of PC-AKI (**Figure 2**).

No patient required dialysis at 1-year follow-up. Mortality rates were 9.9% (26 of 262) in the no prehydration group and 9.6% (25 of 261) in the prehydration group (P = .89); all patients died of causes unrelated to PC-AKI. Additional costs directly associated with the management with 1-hour infusion of prehydration with sodium bicarbonate were estimated at €119 (US $143.94) per patient compared with €0 (US $0) in the no prehydration group (P < .001). Average total hospital costs in the 2 months following randomization were estimated at €1243 (US $1386.92) in the no prehydration group and €1315 (US $1467.26) in the prehydration group (P = .80). The results of the cost-effectiveness analysis are described further in eTable 2 and the eFigure in Supplement 2.

Discussion

We performed a prospective noninferiority randomized clinical trial that contributes to the current state of knowledge concerning PC-AKI. To our knowledge, the current study is the first that directly compared no prehydration with a 1-hour sodium bicarbonate prehydration regimen prior to CECT using intravenous ICM administration. This study, with almost complete follow-up, shows that withholding prehydration is noninferior to administering prehydration with sodium bicarbonate in terms of renal safety in patients with stage 3 CKD undergoing CECT. Concerning the secondary outcome of PC-AKI within 2 to 5 days after contrast administration, the absolute differences between treatment groups are small (7 of 262 patients [2.7%] in the no prehydration group vs 4 of 261 patients [1.5%] in the prehydration group). The effect of prehydration therapy on PC-AKI incidence did not differ significantly between high-

Table 3. Primary and Secondary Outcomes

Outcome	No. (%)		Treatment Effect (95% CI)	*P* Value
	No Prehydration Group (n = 262)	Sodium Bicarbonate Prehydration Group (n = 261)		
Primary Outcome[a]				
Relative increase in serum creatinine level 2-5 d after CECT, mean (SD), %	3.0 (10.5)	3.5 (10.3)	0.5 (−1.3 to 2.3)	<.001[b]
Secondary Outcomes[c]				
Relative increase in serum creatinine level 7-14 d after CECT, mean (SD), %	3.5 (13.4)	3.5 (13.0)	0 (−2.3 to 2.3)	<.001[b]
PC-AKI 2-5 d after CECT, No./total No. (%)	7/262 (2.7)	4/261 (1.5)	1.7 (0.5 to 5.9)	.36
Follow-up 2 mo after contrast administration, No./total No. (%)				
Persisting decline of renal function	3/7 (43)	0/4	NA	NA
Renal function recovery	3/7 (43)	2/4 (50)	0.9 (0.2 to 3.1)	.82
Missing	1/7 (14)	2/4 (50)	NA	NA
AKIN classification[d,e]				
Not applicable	255 (97.3)	250 (95.8)	NA	NA
Stage 1	5 (1.9)	6 (2.3)	1.2 (0.4 to 3.9)	.76
Stage 2	0	0	NA	NA
Stage 3	2 (0.8)	2 (0.8)	1.0 (0.1 to 7.0)	>.99
RIFLE classification[d,f]				
Not applicable	259 (98.9)	257 (98.5)	NA	NA
Risk	1 (0.4)	2 (0.8)	2.0 (0.2 to 22.0)	.62
Injury	0	0	NA	NA
Failure	2 (0.8)	2 (0.8)	1.0 (0.1 to 7.1)	>.99
Loss of kidney function	0	0	NA	NA
End-stage kidney disease	0	0	NA	NA
Complications				
Heart failure	0	0	NA	NA
Dialysis within 1-y follow-up	0	0	NA	NA

Abbreviations: AKIN, Acute Kidney Injury Network; CECT, contrast-enhanced computed tomography; NA, not applicable; PC-AKI, postcontrast acute kidney injury; RIFLE, Risk, Injury, Failure, Loss, and End-stage Kidney Disease.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

[a] Treatment effects calculated as risk differences.

[b] *P* for noninferiority.

[c] Treatment effects calculated as relative risks.

[d] Serum creatinine measurement 2 to 5 days after CECT.

[e] AKIN stage 1 was defined as an increase of greater than 0.3 mg/dL or 150% to 200% from baseline serum creatinine level. Stage 2 was defined as a 2-fold to 3-fold increase in creatinine level from baseline. Stage 3 was defined as a creatinine level increase of 4.0 mg/dL or more or greater than 300% from baseline, or renal replacement therapy.

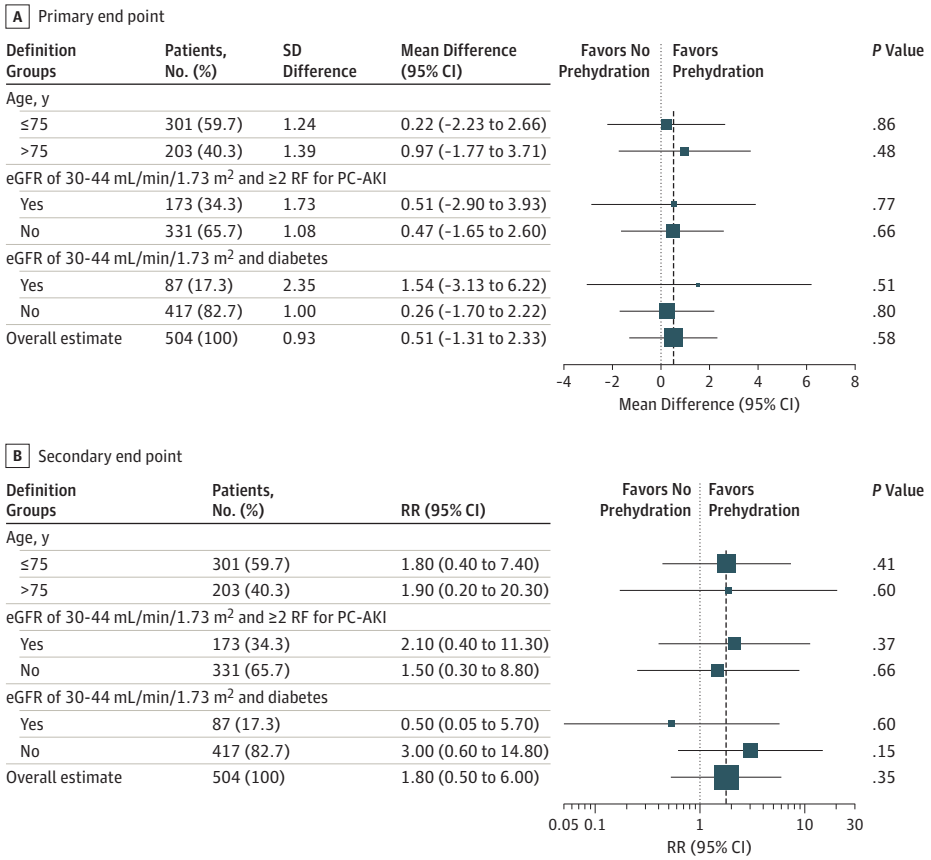
[f] RIFLE risk classification was based on a 150% or greater increase in creatinine level or greater than 25% decrease in estimated glomerular filtration rate. RIFLE injury was defined as a greater than 200% increase in creatinine level or greater than 50% decrease in estimated glomerular filtration rate. RIFLE failure was defined as a greater than 300% or 0.5 mg/dL or greater increase in creatinine level or greater than 75% decrease in estimated glomerular filtration rate.

risk subgroups, showing no evidence for heterogeneity in the results. Importantly, omission of prehydration therapy did not lead to aggravated health care expenses in the 2 months following randomization.

Strategies to prevent PC-AKI, including discontinuing nephrotoxic agents, preventing patients from being in a hypovolemic state by means of volume expansion, and alkalinizing urine by means of infusion of sodium bicarbonate, have become the standard care for years. The risk of renal failure induced by ICM may be overstated in the literature and overestimated by clinicians.[19-21] In this light, the use of certain interventions that improve quality of life or are even lifesaving could be withheld because of an inflated concern of PC-AKI.

Sodium bicarbonate hydration has been the subject of several recent randomized clinical trials and reviews.[8,9,17,22-28] Weisbord et al[23] reported no benefit of periprocedural administration of intravenous isotonic sodium bicarbonate over intravenous isotonic sodium chloride among patients with impaired kidney function undergoing angiography. Prehydration with 250 mL of sodium bicarbonate has previously been shown to be noninferior to prehydration with 1 L of saline and posthydration with 1 L of saline in the prevention of PC-AKI in a noninferiority trial conducted by our study group.[17] Because volume overload can lead to cardiac decompensation, the profoundly reduced volume of fluid administration (250 mL of sodium bicarbonate vs 2 L of saline) was an important advantage, especially in patients with known heart failure. International guidelines, including the Kidney Disease: Improving Global Outcomes clinical practice guideline, and the Dutch national guidelines have recommended sodium bicarbonate prehydration for more than a decade with a class 1A level of recommendation.[2,3,7,29]

Figure 2. Subgroup Analyses



A, Effect size estimate for the primary end point in subgroups. Subgroup analyses were performed on the primary outcome of a relative increase in serum creatinine level 2 to 5 days after intravenous contrast administration. Effect size is calculated as the difference in the mean relative increase in serum creatinine level between both randomization groups. Baseline creatinine clearance was calculated using the Modification of Diet in Renal Disease formula. There were no statistically significant interactions in the various subgroups. The dashed line represents the point estimate of the entire study population. The predefined noninferiority margin was 10%. B, Forest plot of the secondary outcome of risk of postcontrast acute kidney injury (PC-AKI). Subgroup analyses were performed on the secondary outcome of risk of PC-AKI 2 to 5 days after contrast administration in subgroups, calculated as relative risk (RR). eGFR indicates estimated glomerular filtration rate; RF, risk factors.

However, the efficacy of nephroprotective hydration vs no prophylactic measures has only been investigated in a few recent randomized clinical trials.[9,10] The trial conducted by our study group[9] included 138 patients with stage 3 CKD requiring nonelective intravenous contrast procedures. Postcontrast acute kidney injury occurred in 6 of 67 (9%) in the no hydration group and 5 of 71 (7%) in the 1-hour sodium bicarbonate prehydration group (relative risk, 1.29; 95% CI, 0.41-4.03). In the current trial, we found a lower PC-AKI incidence. The difference is likely caused by the nonelective setting vs the elective setting of our current study population. In patients with stage 3 CKD undergoing elective CECT, Nijssen et al[10] reported PC-AKI in 8 of 307 patients (2.6%) receiving no hydration vs 8 of 296 (2.7%) receiving 1 L of saline prehydration and 1 L of saline posthydration. These results are in agreement with our findings. Both trials[9,10] revealed no significant benefits of fluid expansion vs no hydration in patients with stage 3 CKD, whereas hydration is accompanied with significant health care costs and possible adverse effects.

Limitations

Our study had limitations. First, because serum creatinine level was assessed only in patients with CKD undergoing elective CECT with intravenous ICM administration, our results cannot be extrapolated to angiography with intra-arterial ICM administration or to acute interventions, such as percutaneous transluminal (coronary) interventions. Second, for feasibility reasons, our study was powered on a relative increase in serum creatinine level instead of PC-AKI, as has been done by many other studies.[8,9,17,30-35] This is a consequence of the noninferiority design and the low risk of PC-AKI in this clinical setting. Indeed, risks of PC-AKI were low in our study, and no long-term adverse effects of ICM administration were recorded. Third, we did not perform blinding. However, actions for blinding for treatment are not feasible in this setting, nor would it have provided additional value because patients and health care professionals did not influence the primary outcome. Fourth, the contrast agent used was selected according to the clinical practice of the participating hospitals and not mandated by the protocol. However, we believe this is a positive feature of the trial because it best approximates daily clinical practice, considering that on a national and international level, the use of contrast agents may vary per hospital.

Conclusions

In the present study, we demonstrate that withholding hydration prior to CECT is noninferior with respect to the relative increase in serum creatinine level compared with 1-hour in-

fusion of sodium bicarbonate prehydration in patients with stage 3 CKD. Omission of prophylactic measures did not lead to increased health care expenses during the 2 months' follow-up. Based on these results, we believe that our study provides sufficient evidence that preventive hydration can be withheld in this population.

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