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AKIGUARD (Acute Kidney Injury GUARding Device) trial: in-hospital and one-year outcomes

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Aims **Contrast-induced acute kidney injury (CIAKI) in patients with chronic kidney disease undergoing coronary angiography or percutaneous coronary intervention is a common iatrogenic complication associated with increased morbidity and mortality. This study compares sodium bicarbonate/isotonic saline/*N*-acetylcysteine/vitamin C prophylaxis (BS-NAC) against high-volume forced diuresis with matched hydration in CIAKI prevention.**

Methods **One-hundred and thirty-three consecutive patients undergoing coronary angiography or percutaneous coronary intervention with estimated glomerular filtration rate less than 60 mL/min/1.73m^2 were randomized to the study group receiving matched hydration (MHG) or to the control group receiving BS-NAC. MHG received in vein (i.v.) 250 mL isotonic saline bolus, followed by a 0.5 mg/kg furosemide i.v. bolus to forced diuresis. A dedicated device automatically matched the isotonic saline i.v. infusion rate to the urinary output for 1 h before, during and 4 h after the procedure.**

Results **MHG had the lowest incidence of CIAKI (7 vs. 25%, $P = 0.01$), major adverse cardiac and cerebrovascular events at 1 year (7 vs. 32%, $P < 0.01$) and readmissions to cardiology/nephrology departments (8 vs. 25%, $P = 0.03$; hospitalization days 1.0 ± 3.8 vs. 4.9 ± 12.5, $P = 0.01$). Three months after the procedure the decrease in the estimated glomerular filtration rate was 0.02% for MHG versus 15% for the control group.**

Conclusion **Matched hydration was more effective than BS-NAC in CIAKI prevention. One-year follow-up showed that matched hydration was associated also with limited chronic kidney disease progression, major adverse cardiac and cerebrovascular events and hospitalizations.**

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Keywords: contrast media, contrast-induced acute kidney injury, coronary angiography, forced diuresis with matched hydration, percutaneous coronary intervention

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Introduction

Even in its milder forms chronic kidney disease (CKD) is an independent risk factor for coronary artery disease[1,2] affecting almost one-third of patients with acute coronary syndromes (ACS)[3,4] and favouring a higher cardiovascular morbidity[5] and mortality.[6] Coronary angiography or percutaneous coronary intervention (PCI) is challenging in this setting, because of an increased risk of contrast-induced acute kidney injury (CIAKI).[7–9] This iatrogenic complication is the third cause of hospital-acquired acute renal failure,[10,11] worsening the prognosis.[7,9,12] The current increase in coronary angiography/PCI in the elderly, affected by physiological renal function decline (8 mL/min/1.73 m^2 estimated glomerular filtration rate [eGFR] reduction/decade after 30 years of age[13]) makes CIAKI prevention an emerging cardiologic issue. Data on these high-risk patients are scant, as they are often excluded from clinical trials, thus possibly being underestimated.[14] CIAKI has more than 30 different definitions in the literature[15,16]; the most recent and comprehensive definition is in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,[17] that is, as a serum creatinine (sCr) increase of at least 0.3 mg/dL within 48 h or at least 50% within 7 days. CKD, diabetes, age, contrast media volume and reduced left ventricular ejection fraction are quoted as the most significant risk factors.[17,18] CIAKI critical consequences, lack of agreement on the most appropriate treatment and heterogeneous indications in the literature[17,19] prompted us to design the Acute Kidney Injury GUARding Device (AKIGUARD), a randomized and controlled trial on CIAKI prevention, aimed at testing the efficacy of high-volume forced diuresis with matched hydration compared with the sodium bicarbonate/isotonic saline/*N*-acetylcysteine/vitamin C (BS-NAC) prophylaxis routinely used in our institution.

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Methods

Study design

The trial was designed to enrol consecutive patients undergoing coronary angiography/PCI in our cardiology department satisfying the inclusion criteria: eligibility for both procedures and eGFR of less than 60 mL/min/1.73 m^2 (computed according to the Chronic Kidney Disease EPIdemiology Collaboration [CKD-EPI] equation[20]). Exclusion criteria were primary PCI (emergency procedure), cardiogenic shock, acute heart failure, end-stage renal disease on haemodialysis, urinary tract infections within the last 3 months, benign prostatic hyperplasia and previously known difficulties in urinary catheterization. The trial lasted from October 2011 to April 2014. Enrolled patients were randomly subdivided into a study group receiving matched hydration (MHG) and a control group receiving BS-NAC.

The trial complied with the Declaration of Helsinki and subsequent modifications. Its research protocol was approved by the local ethical committee and accredited by AIFA (National Medicines Agency), registration number 340/352/70/2011. Adverse events, data/documents were monitored throughout the trial by the local pharmacovigilance organization for nonprofit trials, according to the Good Clinical Practice standards (European Parliament Directive 2001/20/EC). Written informed consent was obtained before enrolment.

Endpoints of the study

Our primary endpoint was incidence of CIAKI after coronary angiography/PCI as defined by the KDIGO guidelines,[17] that is an increase of sCr +0.3 mg/dL in 48 h or +50% in 7 days. Secondary endpoints were renal function (eGFR) evolution at 3 months, incidence of major adverse cardiac and cerebrovascular events (MACCE) and readmissions to cardiology/nephrology departments during the 1-year follow-up. MACCE were defined as: ACS, non-ACS event requiring revascularization with either PCI or coronary artery bypass grafting surgery (i.e. arrhythmias, unexplained syncope or chest pain), acute pulmonary oedema (APE), cardiogenic shock, transient ischemic attack (TIA), stroke, cardiovascular or cerebrovascular death.

Matched hydration and BS-NAC protocols

Matched hydration was to be performed with the RenalGuard System (PLC Medical System Inc., Milford, MA USA), a device designed to contrast CIAKI pathophysiology.[21] Such a device has a main console for real-time measurements of urinary output through a standard Foley catheter and an isotonic saline in vein (i.v.) infusion pump with an automatically matched rate to avoid hypovolemia/hypervolemia. BS-NAC was to be performed according to our hospital guidelines for CIAKI prevention issued on October 2008. Table 1 reports the main features of the two protocols.

An iodinated, nonionic, iso-osmolar contrast medium (iodixanol 320 mg/l) was used for all procedures. Blood samples were collected before procedure, on procedure day and daily for 72 postprocedural hours. Patients with less than 3 days of hospitalization were discharged with indication for sCr evaluation at 7 days. All patients had a 90-day sCr evaluation. All sCr evaluations were performed in our laboratory using the conventional alkaline picrate method (Jaffe).

Statistical analysis

Continuous variables, presented as means and standard deviations, were compared by nonparametric tests: Mann–Whitney's test was used for independent data and Wilcoxon's signed-rank test for paired data (pre–post evaluations). Categorical variables, presented as counts and percentages, were compared using the χ^2 test with Yates' correction or Fisher's exact test: the risk ratio was computed with its 95% confidence interval. All analyses were performed using the SPSS for Windows version 18.0 (SPSS, Inc., Chicago, Illinois, USA) and a two-sided significance level of 0.05 or less was considered statistically significant. The survival probability and freedom from adverse events were evaluated with the Kaplan–Meier curves compared by the Mantel–Cox test. The appropriate population size for reaching a test power of 0.8 and a confidence level of 95% was determined on the basis of previously reported CIAKI incidences.[9,18,22,23] Both the Fleiss and Kelsey procedures agreed on a minimum overall population of 120–130 patients. Randomization was based on a prearranged random sequence of numbers, with semen $2^{31}-1$, without duplicate exclusion.

Results

Among 133 enrolled patients, randomization placed 66 patients into the control group and 67 into the MHG. Consent was withdrawn shortly before the index procedure by 9 of 133 patients: one patient in the control group who asked to be discharged before coronary angiography and eight patients in the MHG, three because of discomfort/pain during urinary catheterization and five because of afterthoughts about receiving an experimental treatment and/or catheterization. Such patients, though excluded from the study, were anyway given traditional CIAKI prophylaxis. The remaining 124 patients (59 patients in the MHG and 65 in the control group) received the preestablished treatment protocol. A flow chart of the trial is shown in Fig. 1.

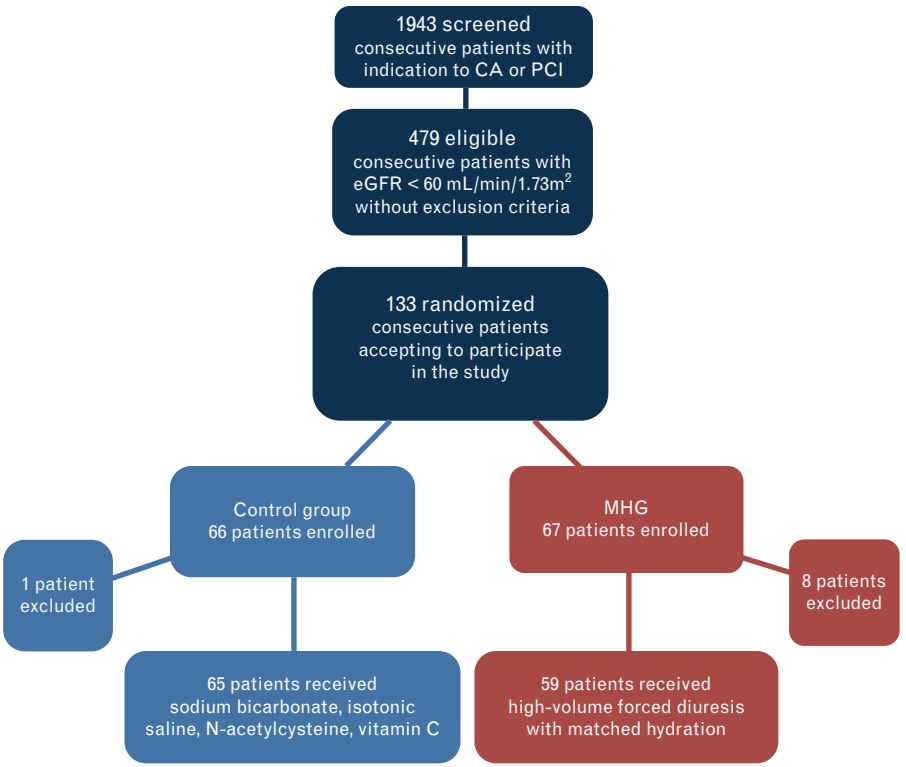
Table 2 shows that the baseline of patients in the study and control group is homogenous. MHG patients received 4033 ± 1405 (range: 2140–9420) mL of isotonic saline i.v. infusion, matched with diuresis over a period of 6:55 ± 1:17 (5:00–10:15) hours. Corresponding diuresis over the same period was 3822 ± 1368 (1900–9173) mL, with a diuresis rate of 553 ± 188 mL/h. Thirty-three

Table 1 **Matched hydration and BS-NAC treatment protocol**

	Before coronary angiography/PCI	During and after coronary angiography/PCI
Matched hydration	Urinary catheterization/peripheral venous access is placed 90 min before procedure. After device connection, a 250 mL i.v. isotonic saline bolus is given in 30 min, followed by 0.5 mg/kg i.v. furosemide to forced diuresis. Isotonic saline i.v. infusion proceeds automatically, rate-matched with diuresis. *If diuresis rate <300 mL/h, further furosemide boli are needed.*	The device remains operative during and for 4 h after procedure, it is then disconnected and the urinary catheter/venous access removed.
BS-NAC	1000 mL isotonic saline i.v. administration 12 h before procedure (rate-adjusted according to LVEF*: 20–40 mL/h if LVEF < 30%, 80–120 mL/h if LVEF 30–50%, 200 mL/h if LVEF >50%). *Plus* 3 mL/kg/h 1.4% SB solution i.v. infusion for 1 h before procedure *Plus* 5000 mg p.o. Vitamin C *Plus* 1200 mg p.o. *N*-acetylcysteine	1 mL/kg/h 1.4% SB solution i.v. infusion for 6 h after procedure *Plus* 5000 mg p.o. Vitamin C the following day *Plus* 1200 mg p.o. *N*-acetylcysteine the following day

* Infusion rate was adjusted according to our hospital guidelines for contrast-induced acute kidney injury prevention.BS-NAC, sodium bicarbonate/isotonic saline/*N*-acetylcysteine/vitamin C; i.v., intravenous; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; p.o., per os; SB, sodium bicarbonate.

Fig. 1



Acute Kidney Injury GUARding Device (AKIGUARD) trial flow chart.

Table 2 Baseline risk factors, characteristics and clinical indications to coronary angiography or percutaneous coronary intervention

	Population ($n=124$)	MHG ($n=59$)	Control group ($n=65$)	P
Age (years)	75 ± 9	76 ± 9	75 ± 8	0.28
Female	32 (26%)	13 (22%)	19 (29%)	0.41
Body Mass Index	25 ± 4	25 ± 4	25 ± 4	0.67
LVEF on admission (%)	52 ± 13	53 ± 10	50 ± 14	0.34
Smokers	10 (8%)	3 (5%)	7 (11%)	0.33
Hypertension	104 (84%)	49 (83%)	55 (85%)	0.99
Diabetes	44 (35%)	22 (37%)	22 (34%)	0.71
Dyslipidemia on statin treatment	64 (52%)	31 (53%)	33 (51%)	0.86
Total cholesterol (mg/dL)	155 ± 37	165 ± 38	149 ± 36	0.10
LDL cholesterol (mg/dL)	90 ± 30	93 ± 31	87 ± 29	0.38
Triglycerides (mg/dL)	116 ± 49	124 ± 52	112 ± 47	0.28
Baseline sCr (mg/dL)	1.48 ± 0.42	1.54 ± 0.43	1.42 ± 0.41	0.07
Baseline eGFR (mL/min/1.73m^2)*	44 ± 12	42 ± 11	45 ± 13	0.13
Kidney graft	4 (3%)	2 (3%)	2 (3%)	0.99
Solitary kidney	4 (3%)	2 (3%)	2 (3%)	0.99
Prior coronary angiography or PCI	79 (64%)	40 (68%)	39 (60%)	0.45
Prior CABG	19 (15%)	7 (12%)	12 (18%)	0.33
Prior AMI	35 (28%)	11 (19%)	16 (25%)	0.52
Diuretics*	82 (66%)	37 (63%)	45 (69%)	0.46
CCBs*	29 (23%)	11 (19%)	18 (28%)	0.29
ACE inhibitors*	67 (54%)	33 (56%)	34 (52%)	0.72
ARBs*	28 (23%)	9 (15%)	19 (29%)	0.09
CIAKI risk score†	9.6 ± 4.2	9.8 ± 4.1	9.5 ± 4.3	0.56
Contrast volume (mL)	156 ± 83	172 ± 93	157 ± 73	0.50
Multivessel lesions	61 (49%)	26 (44%)	35 (54%)	0.29
PCI with stent implantation	58 (47%)	29 (49%)	29 (45%)	0.72
Coronary angiography indication: NSTEMI or unstable angina	49 (40%)	28 (47%)	21 (32%)	0.12
Coronary angiography indication: subacute AMI	3 (2%)	1 (2%)	1 (2%)	0.52
Coronary angiography indication: STEMI-staged PCI in severe nonculprit stenosis	6 (5%)	3 (5%)	3 (5%)	0.77
Coronary angiography indication: elective PCI	3 (2%)	1 (2%)	2 (3%)	0.93
Coronary angiography indication: stable angina	20 (16%)	11 (19%)	9 (14%)	0.63
Coronary angiography indication: instrumental ischemia	11 (9%)	4 (7%)	7 (11%)	0.64
Coronary angiography indication: arrhythmia	4 (3%)	1 (2%)	3 (5%)	0.68
Coronary angiography indication: syncope	3 (2%)	1 (2%)	2 (3%)	0.93
Coronary angiography indication: heart failure	26 (21%)	10 (17%)	16 (25%)	0.41

* on treatment at hospital admission. † estimated according to Mehran score(18).ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; ARBs, angiotensin-II receptor blockers; CABG, coronary artery bypass grafting surgery; CCBs, calcium channel blockers; CIAKI, contrast-induced acute kidney injury; eGFR, estimated glomerular filtration rate; LDL, low-density lipoproteins; LVEF, left ventricular ejection fraction; MHG, study group receiving high-volume forced diuresis with matched hydration; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; sCr, serum creatinine; STEMI, ST-segment elevation myocardial infarction.

patients (56%) necessitated a second furosemide bolus and three (5%) a third furosemide bolus to reach the diuresis target. The additional diuretic dose was 19 ± 23 mg. Control group patients received a total of 637 ± 128 (180–1062) mL 1.4% sodium bicarbonate (213 ± 41 mL before procedure and 425 ± 89 mL afterwards) and 10 g of vitamin C, 2.4 g of *N*-acetylcysteine and a preprocedural hydration with 1000 mL of isotonic saline, at protocol rates and volumes (Table 1).

The required amount of contrast media was 193 ± 92 mL in urgent procedures (i.e. non-ST-segment elevation myocardial infarction or unstable angina, ST-segment elevation myocardial infarction-staged PCI in severe nonculprit stenosis and subacute myocardial infarction) versus 140 ± 66 mL ($P<0.01$) in elective procedures. There were no differences between MHG and control group as to the proportion of urgent procedures (54% in the MHG vs. 40% in the control group, $P=0.15$). Gurm *et al.*[24] set maximum desirable contrast media limits at three times the estimated eGFR and our limits differed very slightly in the nonurgent subset. Conversely, this limit was necessarily exceeded in the urgent subset, because of the intrinsic timing and complexity of PCI.

Postprocedural contrast-induced acute kidney injury

CIAKI incidence after coronary angiography/PCI in the two samples was significantly different: 16/65 (25%) control group patients versus 4/59 (7%) MHG patients ($P=0.01$, risk ratio = 3.6 with 95% confidence interval 1.3–10.2). Severe CIAKI (stage II or III according to the KDIGO criteria[17]) was diagnosed in 5 out of 16 (31%) control group patients against 0 of 4 in the MHG. As to CIAKI definition, considering the '+0.3 in 48 h' criterion alone, 16/65 (25%) patients in the control group would have been diagnosed with CIAKI and 4/59 (7%) in the MHG ($P=0.01$). Using the '+50% in 7 days' criterion, there would have been 4/65 (6%) in the control group versus 2/59 (3%) patients in the MHG ($P=0.77$).

Kidney function variation at 3 months

The eGFR at 3 months in the control |group was significantly lower than that at baseline, dropping from 45 ± 13 to

39 ± 16 mL/min/1.73m^2 ($P < 0.01$) with a mean 15% decrease, whereas in the MHG it had barely a 0.02% variation, from 42 ± 11 to 42 ± 15 mL/min/1.73m^2 ($P = 0.57$). Postprocedural CIAKI influenced these values: eGFR at 3 months was remarkably lower in CIAKI patients compared with those without (28 ± 14 vs. 43 ± 15 mL/min/1.73m^2, $P < 0.01$). When the eGFR pre-post values were compared within each subgroup, a stronger eGFR reduction was observed ($P < 0.01$) in CIAKI patients than in those without ($P = 0.15$).

One-year follow-up: major adverse cardiac and cerebrovascular events and hospital readmissions after discharge

During the 12-month follow-up, a total of 12 patients (10%) deceased, 8 (12%) in the control group and 4 (7%) in the MHG ($P = 0.46$), whereas 4 patients (3%), 2 in the control group and 2 in the MHG, were not available for the survey, leaving 108 patients. Twenty-five MACCE were observed, defined as aforementioned. Table 3 illustrates how they were distributed between the two groups: 4 in the MHG and 21 in the control group ($P < 0.01$). Figure 2a reports the Kaplan–Meier curves of freedom from MACCE in both arms: at 1 year the freedom probability was 93% in the MHG whereas it was 75% in the control group ($P < 0.01$). Noteworthy was the fact that the control group not only had the highest incidence of CIAKI but also of MACCE during the follow-up, as illustrated by Fig. 2b. Figure 2b reports the freedom curves for CIAKI and non-CIAKI patients, with a statistically significant difference ($P < 0.01$) in favour of patients without CIAKI.

During the follow-up, 16 patients (25%) in the control group and 5 (8%) in the MHG were readmitted in the cardiology or nephrology department ($P = 0.03$). Figure 3 reports the Kaplan–Meier curves for freedom from readmission: freedom at 1 year was 91% in the MHG, whereas it was 74% in the control group ($P = 0.02$). The cumulative hospitalization within 1-year post coronary angiography/PCI was 1 ± 3.8 days for the MHG and 4.9 ± 12.5 days for the control group ($P = 0.01$). Two patients in the control group (3%) and none in the MHG were started on haemodialysis within 1 year after coronary angiography/PCI.

Table 3 Major adverse cardiac and cerebrovascular events occurrence during the 12-month follow-up

	Population	MHG	Control group
ACS	6	1	5
Non-ACS event requiring PCI or CABG	3	1	2
APE or cardiogenic shock	6	1	5
TIA or stroke	2	0	2
Cardiovascular death	8	1	7
Cerebrovascular death	0	0	0
Overall	25	4	21

ACS, acute coronary syndrome; APE, acute pulmonary oedema; CABG, coronary artery bypass grafting surgery; MHG, study group receiving high-volume forced diuresis with matched hydration; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Intention-to-treat analysis

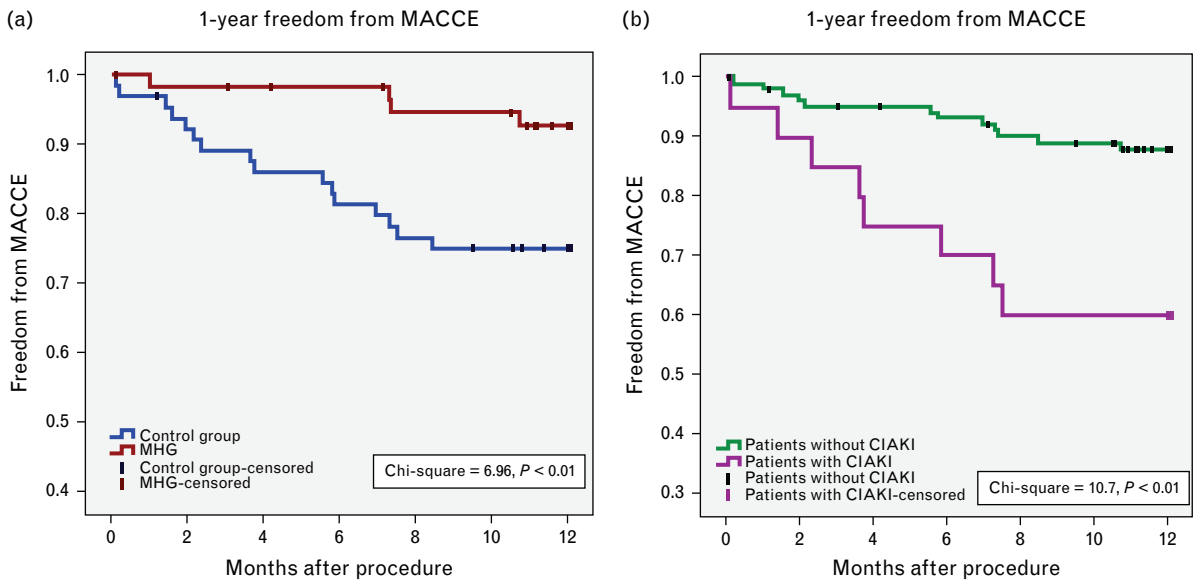
According to the intention-to-treat analysis (Table 4) performed on 133 patients (the nine excluded patients were added), the baseline CIAKI risk score[18] remained similar between the two groups: 9.8 ± 4 in the MHG and 9.4 ± 4.3 in the control group ($P = 0.46$). As to the incidence of postprocedural CIAKI, it would have been 16/66 (24%) within the control group compared with 4/67 (6%) within the MHG ($P = 0.01$). Among the eight excluded MHG patients, there were not any CIAKI events. The MACCE occurrence during the follow-up would have been 7/67 (10%) within the MHG versus 21/66 (32%) within the control group ($P < 0.01$).

Discussion

CIAKI preventive measures, that is hydration and antioxidative agents such as *N*-acetylcysteine or vitamin C, are aimed at counteracting contrast media-induced vasoconstriction and oxidative stress. Hydration may be obtained either with isotonic saline or sodium bicarbonate solutions,[17] the latter having both a hydration and antioxidative effect.[25] As renal medulla hypoperfusion is the mechanism underlying CIAKI, diuretics alone are not advisable as they would worsen massive volume depletion.[26] However, if the fluid loss is offset by an adequate fluid intake, a virtuous circle can be established, accelerating urinary flow and improving contrast media renal clearance. The Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) study[21] demonstrated that a diuresis rate of greater than 150 mL/h led to a lower CIAKI incidence. Two more recent clinical trials reported favourably on matched hydration.[22,23] This novel method permits a massive hydration; traditional hydration protocols have instead limited infusion rates for avoiding circulatory overload and this may lead to an insufficient contrast media clearance along with a limited protection from vasoconstriction and oxidative stress.

AKIGUARD demonstrated the advantages of matched hydration over BS-NAC (control group) in meeting both primary and secondary endpoints. Noteworthy is the fact that the amount of sodium bicarbonate administered to the patients in the control group was strictly dependent on their body weight, whereas the hydration volumes administered to the MHG patients depended on their diuresis rate; this difference may be of use in the set-up of future BS-NAC protocols. The treatment protocol for the MHG and the 300 mL/h preprocedural threshold (Table 1) was arbitrarily chosen based on previous literature studies[22,23]; however, as almost 60% of our patients needed additional diuretic boluses, this finding could be useful for planning further investigations and protocol improvements.

Fig. 2



(a/b) Kaplan–Meier curves (freedom from major adverse cardiac and cerebrovascular events [MACCE]): (a) 1-year freedom from MACCE within matched hydration group (MHG) and control group; (b) 1-year freedom from MACCE within patients with post-procedural CIAKI and patients without post-procedural CIAKI.

The follow-up monitoring confirmed the better trend in the MHG patients. There was a significant difference in CKD progression between the two groups at 3 months after discharge. The freedom from MACCE within 1 year was significantly higher in the MHG than in the control group.

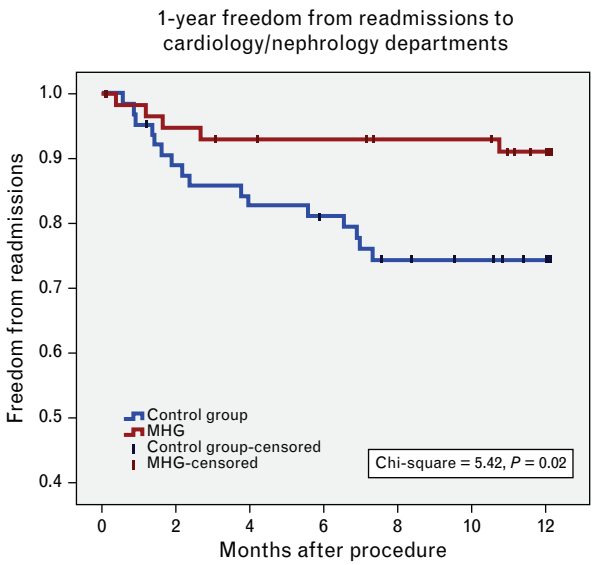
A direct comparison of the CIAKI incidence observed in our trial with other studies is not easy. The definition of CIAKI evolved over the years, tending to be more sensitive for milder forms; moreover, different studies used heterogeneous prophylaxes and considered different risk factors.[17] The studies most similar to ours report a CIAKI incidence in patients on i.v. hydration with isotonic saline or sodium bicarbonate between 18 and 37%[9,18,22,23]: the 25% CIAKI incidence observed in our control group falls right in the middle of this bracket. The 7% incidence we observed in the MHG is similar to the outcome of the two previous trials testing the same device, that is 4.6% in the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial[23] (compared with 18% in controls on simple isotonic saline hydration) and 11% in the Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II)[22] (compared with 21% in controls on sodium bicarbonate and *N*-acetylcysteine). Although these two studies used the same device as ours, comparison is not straightforward as the MYTHOS trial applied the older CIAKI definition '+0.5 or +25% in 72 hours': by this criterion the CIAKI incidence in our study would have been 3/59 (5%) patients in the MHG compared with 12/65 (18%) patients in the control group ($P = 0.04$). The REMEDIAL II excluded patients with eGFR higher than 30 mL/min/1.73m^2, a CIAKI risk score less than 11 and those with acute myocardial infarction. As to the follow-up, only the REMEDIAL II assessed the patients' clinical evolution after discharge, but limiting the period of observation to 1 month, during which no significant difference was found for MACE defined as death, APE or dialysis.

Table 4 Intention-to-treat analysis of primary and secondary endpoints

	Population ($n = 124 + 9$)	MHG ($n = 59 + 8$)	Control group ($n = 65 + 1$)	*P*
Postprocedural CIAKI	20 (15%)	4 (6%)	16 (24%)	0.01
MACCE in 12 months	28 (21%)	7 (10%)	21 (32%)	0.01
Readmissions to cardiology/nephrology departments in 12 months	25 (19%)	9 (13%)	16 (24%)	0.17
Cumulative hospitalization in 12 months (days)	3.14 ± 9.5	1.57 ± 4.6	4.7 ± 12.5	0.09
3 months eGFR variation	−9%	−1%	−16%	–
P-value (Wilcoxon test between baseline and 3-months evaluation)	<0.01	0.58	<0.01	–

CIAKI, contrast-induced acute kidney injury; eGFR, estimated glomerular filtration rate; MACCE, major adverse cardiac and cerebrovascular events; MHG, study group receiving high-volume forced diuresis with matched hydration.

Fig. 3



Kaplan–Meier curves (freedom from readmissions to cardiology/nephrology departments) comparing matched hydration group (MHG) with control group.

The possible relation between CIAKI following the procedure and MACCE during follow-up remains a challenging issue, with current literature reporting numerous indications in favour of some connection: after a single and transient CIAKI episode a dramatic increase in cardiovascular events and cerebrovascular events has been observed,[5,27,28] and even a 13-fold increased death risk after 1 month and a 6-fold increased risk after 1 year.[7] The most accredited hypothesis is an accelerated progression of renal dysfunction[29,30] enhancing vascular, endothelial and atherosclerotic damage evolution.[27] Our results on the freedom from MACCE illustrated in Fig. 2 lend support to this scenario.

Study limitations

The present trial is monocentric and, therefore, our observations are limited to our hospital catchment area. During the initial screening phase, a number of eligible patients refused the enrolment mainly because of concerns about bladder catheterization: some of them were in an urgent coronary angiography/PCI setting, concerned about receiving a 'randomized' treatment, whereas some other was concerned about bladder catheterization without a strict clinical indication. The wide applicability of the matched hydration strategy in the general high-risk population is, still, not affected by this bias, as the refusal was mainly related to the study design itself. As to the number of unexpectedly excluded patients in the MHG, due to consent withdrawal, it may have been considered a potential source of bias, though our intention-to-treat analysis cleared up this question. The coronary angiography and PCI procedures in the urgency setting did necessitate larger amounts of contrast media and this might have influenced the CIAKI rates as aforementioned. As blinding both the patients and the doctors was not feasible, the AKIGUARD study is open-label even if anonymous Case Report Forms were used and staff was assigned to separate roles.

Conclusion

The data from this trial show that matched hydration is well tolerated, feasible and it can effectively reduce CIAKI incidence in high-risk patients undergoing coronary angiography or PCI. The beneficial effects extend to the 1-year follow-up, with improvements in slowing down CKD progression and lowering the MACCE rate, consequently reducing the number and duration of hospital readmissions.

Acknowledgements

There are no conflicts of interests.

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