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Kidney Injury After Minimal Radiographic Contrast Administration in Patients With Acute Coronary Syndromes

Carlo Briguori, MD, PhD,[a] Cristina Quintavalle, MD, PhD,[b] Enrica Mariano, MD,[c] Alessandro D'Agostino, MD,[d] Mario Scarpelli, MD,[a] Amelia Focaccio, MD,[a] Giuseppe Biondi Zoccai, MD, MStat,[a,b,c,d,e] Salvatore Evola, MD,[d] Giovanni Esposito, MD, PhD,[f] Giuseppe Massimo Sangiorgi, MD, PhD,[c] Gerolama Condorelli, MD, PhD[g,h]

ABSTRACT

BACKGROUND Acute kidney injury (AKI) is common in patients with acute coronary syndromes (ACS) treated by percutaneous coronary intervention.

OBJECTIVES Contrast media (CM) volume minimization has been advocated for prevention of AKI. The DyeVert CM diversion system (Osprey Medical, Inc) is designed to reduce CM volume during coronary procedures.

METHODS In this randomized, single-blind, investigator-driven clinical trial conducted in 4 Italian centers from February 4, 2020 to September 13, 2022, 550 participants with ACS were randomly assigned in a 1:1 ratio to the following: 1) the contrast volume reduction (CVR) group (n = 276), in which CM injection was handled by the CM diversion system; and 2) the control group (n = 274), in which a conventional manual or automatic injection syringe was used. The primary endpoint was the rate of AKI, defined as a serum creatinine (sCr) increase ≥0.3 mg/dL within 48 hours after CM exposure.

RESULTS There were 412 of 550 (74.5%) participants with ST-segment elevation myocardial infarction (211 of 276 [76.4%] in the CVR group and 201 of 274 [73.3%] in the control group). The CM volume was lower in the CVR group (95 ± 30 mL vs 160 ± 23 mL; $P < 0.001$). Seven participants (1 in the CVR group and 6 in the control group) did not have postprocedural sCr values. AKI occurred in 44 of 275 (16%) participants in the CVR group and in 65 of 268 (24.3%) participants in the control group (relative risk: 0.66; 95% CI: 0.47-0.93; $P = 0.018$).

CONCLUSIONS CM volume reduction obtained using the CM diversion system is effective for prevention of AKI in patients with ACS undergoing invasive procedures. (REnal Insufficiency Following Contrast MEDIA Administration TriaL IV [REMEDIALIV]: NCT04714736) (J Am Coll Cardiol 2024;83:1059-1069) © 2024 by the American College of Cardiology Foundation.

Acute kidney injury (AKI) may occur in patients with acute coronary syndromes (ACSs) treated with percutaneous coronary intervention (PCI).[1-3] Although the pathogenesis of AKI in patients with ACS undergoing PCI is multifactorial,[4] the role of iodinated contrast media (CM) has been well established.[5] Volume expansion represents the cornerstone of contrast-associated AKI (CA-AKI) prevention.[6] However, all of the recommended volume expansion regimens have limited

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From the [a]Interventional Cardiology Unit, Mediterranea Cardiocentre, Naples, Italy; [b]Center for Experimental Endocrinology and Oncology (IEOS), National Research Council (CNR), Naples, Italy; [c]Department of Biomedicine and Prevention, Tor Vergata University, Rome, Italy; [d]Division of Cardiology, Paolo Giaccone University Hospital, Palermo, Italy; [e]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; [f]Department of Advanced Biomedical Science, Division of Cardiology, Federico II University of Naples, Naples, Italy; [g]Department of Molecular Medicine and Medical Biotechnology, Federico II University, Naples, Italy; and the [h]Scientific Institute for Research, Hospitalization, and Health Care-Mediterranean Neurological Institute (IRCCS Neuromed), Pozzilli, Italy.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AKI = acute kidney injury

BMI = body mass index

CA-AKI = contrast-associated acute kidney injury

CEC = Clinical Events Committee

CM = contrast media

CVR = contrast volume reduction

eGFR = estimated glomerular filtration rate

LVEDP = left ventricular end-diastolic pressure

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

RRT = renal replacement therapy

sCr = serum creatinine

STEMI = ST-segment elevation myocardial infarction

applicability in patients with ST-segment elevation myocardial infarction (STEMI) and in high-risk patients with non-ST-segment elevation myocardial infarction (NSTEMI) who are transferred to PCI-capable centers for emergency invasive treatment. Therefore, in this scenario, CM volume minimization is of the utmost importance in the attempt to prevent CA-AKI. The DyeVert system (Osprey Medical, Inc) is a device designed to reduce CM volume during coronary procedures while maintaining fluoroscopic image quality by diverting the excess CM before injection.[7]

The aim of REMEDIAL IV (Renal Insufficiency Following Contrast MEDIA Administration triaL IV; NCT04714736) was to test whether the use of this CM diversion system could effectively reduce the AKI rate in patients with ACS undergoing urgent invasive approaches.

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METHODS

PATIENT GROUP. The design of this multicenter, randomized, investigator-driven clinical trial was previously reported.[8] Patients with STEMI or high-risk NSTEMI requiring an urgent invasive approach were screened for inclusion or exclusion criteria (Supplemental Tables 1 to 3).[9-12] All participants or their legally authorized representatives provided written informed consent. The REMEDIAL IV trial was conducted at 4 Italian interventional cardiology centers (Supplemental Table 4), according to the principles of the Declaration of Helsinki[13] and Good Clinical Practice,[14] and was approved by the local Ethics Committees.

Participants were randomly assigned to either the contrast volume reduction (CVR) group or the control group.

CVR group. In the CVR group, CM injection was handled by the CM diversion system.[7] During an injection, the device diverts a portion of the injected CM through a secondary fluid pathway controlled by a pressure-compensating diversion valve. This allows a decrease in CM overinjection and less aortic reflux (Supplemental Methods). The associated CM monitoring system displays the total injections (including tests/puffs) and CM volume injected (mL), split into attempted, delivered, and saved (the last reported both as an absolute value and as a percentage of the total).

Control group. CM injection in the control group was carried out by a conventional manual injection syringe or automatic injection device (ACIST Medical System). A new CM source bottle was used in all cases. Following the procedure, the CM remaining in the source bottle was measured using a graduated cylinder. The CM volume injected was than calculated as the difference between the total volume and the remaining CM volume. In this group, a nurse recorded all tests/puffs done by the second operator or technician.

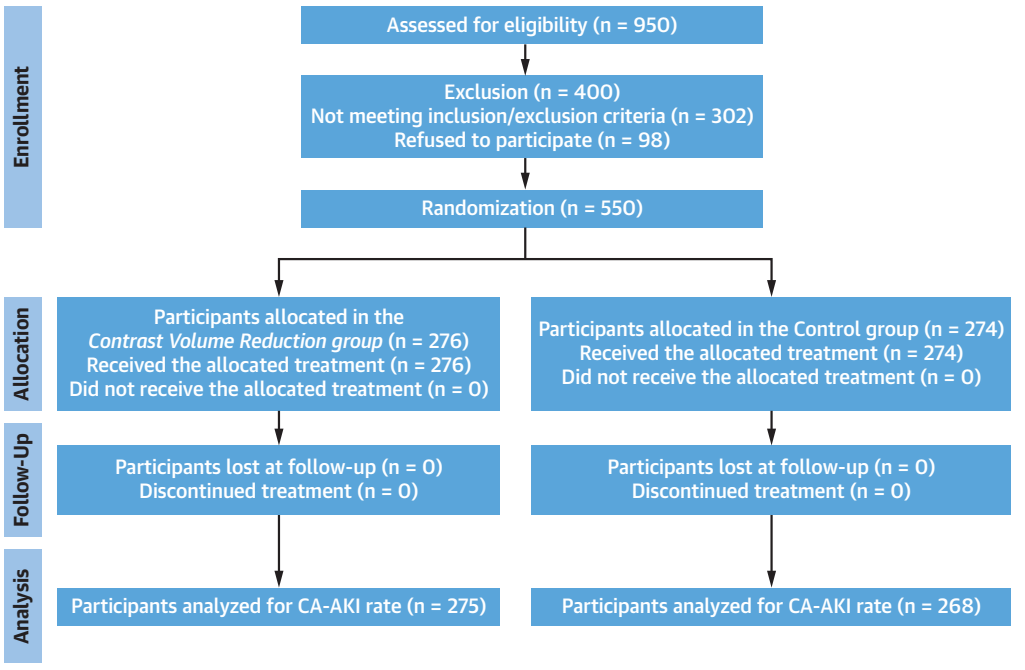
VOLUME-EXPANSION REGIMEN. Normal saline (3 mL/kg/h) was initiated as soon as the participants arrived in the cardiac catheterization laboratory. The infusion rate was adjusted according to the left ventricular end-diastolic pressure (LVEDP) estimated at the beginning of the procedure: 5 mL/kg/h for LVEDP ≤12 mm Hg, 3 mL/kg/h for LVEDP 13 to 18 mm Hg, and 1.5 mL/kg/h for LVEDP >18 mm Hg.[15] When deemed clinically contraindicated (Supplemental Table 5), volume expansion was not started. Volume expansion continued for at least 6 hours post-procedure. Total hydration >960 mL was considered the optimal cutoff volume to prevent CA-AKI.[16]

BIOMARKERS OF KIDNEY FUNCTION. Serum creatinine (sCr), cystatin C, blood urea nitrogen, sodium, and potassium values were measured at baseline and every day during the hospital stay; additional measurements were performed in all cases of deterioration of baseline renal function. The estimated glomerular filtration rate (eGFR) was calculated by applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[17] The risk for CA-AKI was evaluated according to the Mehran[18] and Gurm[19] scores (Supplemental Tables 6 and 7).

IODINATED CM. Iobitridol (Xenetix 350, 350 mg iodine/mL), a nonionic, low-osmolality (915 mOsm/kg water) CM was used in all instances. The following strategies were implemented for limiting CM volume[20]: 1) use of a 10-cm^3 syringe for injection; 2) avoidance of guide catheters with sideholes; 3) discouraging ''tests'' with ''puffs;'' and 4) avoiding left ventriculography. CM volume >3× eGFR is suggestive of an increased risk of CA-AKI.[21] Radiation exposure per patient was measured as follows: 1) dose rate (the amount of radiation delivered per unit time), expressed as grays (Gy); and 2) dose area product (DAP) (Gy/cm^2).

STUDY ENDPOINTS. The primary endpoint was the rate of CA-AKI, defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, as an increase in the sCr concentration ≥0.3 mg/dL

FIGURE 1 Flowchart of the Trial According to the Consolidated Standards of Reporting Trials Guidelines



One participant in the contrast volume reduction group and 6 participants in the control group were not analyzed for the primary endpoint because they died within 24 hours (range: 3-22 hours) after enrollment without at least 1 in-hospital postprocedural serum creatinine value. CA-AKI = contrast-associated acute kidney injury.

within 48 hours.[22] Secondary endpoints included the following: 1) the CM volume; 2) an increase in the sCr concentration ≥25% and/or ≥0.5 mg/dL within 72 hours after CM exposure; 3) the severity of AKI assessed according to the KDIGO criteria[22]; 4) changes in the serum cystatin C concentration at 24 and 48 hours after CM exposure; 5) the rate of acute renal failure requiring renal replacement therapy (RRT); 6) length of hospital stay; and 7) rate of in-hospital, 1-month, and 6-month major adverse events, including death, nonfatal myocardial infarction, RRT, sustained kidney injury, and major bleeding. Major bleeding was defined according to the Bleeding Academic Research Consortium (BARC) criteria.[23] Sustained kidney injury was defined as a persistent ≥25% eGFR reduction compared with baseline at the last available value during the follow-up.[24] All events were adjudicated by a Clinical Events Committee (CEC) blinded to treatment assignment.

STATISTICAL ANALYSIS. Treatment allocation to the 2 groups was determined by randomization in a 1:1 ratio. An independent statistician generated the randomization list with permuted blocks of 4 (Random Allocation Software version 1.0). The block size was not disclosed to the investigators. Participants were randomly assigned without stratification by STEMI vs NSTEMI. The expected CA-AKI rate in the control group was 19%.[1-3,16,25] A sample size of 261 participants in each group (a total of at least 522 randomized participants) was therefore needed to demonstrate an 8.5% difference between groups (ie, from 19% in the control group to 10.5% in the CVR group), with a 2-sided 95% CI and 80% power ($P < 0.05$), on the basis of the large sample normal approximation extended 0.07 from the observed difference in proportions.[16,26] Taking into account a dropout rate ≤5%, we recruited 550 participants. All principal analyses were performed on the basis of the intention-to-treat group, defined as all randomized participants, regardless of the treatment actually received.

Continuous variables are given as mean ± SD or median (Q1-Q3) and were compared using Student's *t*-test or the Mann-Whitney *U* test, respectively. The normality assumption was verified graphically (ie, by QQ plot) and was confirmed using the Shapiro-Wilk test. Categorical variables are reported as percentage and were analyzed by either the chi-square or Fisher

TABLE 1 Baseline Characteristics and Clinical Presentation of Participants Enrolled in the 2 Groups

	CVR Group (n = 276)	Control Group (n = 274)
Age, y	64 ± 13	65 ± 12
≥75	64 (23.0)	64 (23.5)
Male	220 (80.0)	202 (73.0)
Weight, kg	79 ± 17	78 ± 15
Height, m	1.69 ± 0.9	1.68 ± 0.2
Body mass index, kg/m^2	27 ± 7	27 ± 4
Blood pressure, mm Hg		
Systolic	125 ± 27	127±26
Diastolic	77 ± 17	77 ± 14
Mean	109 ± 20	110 ± 19
Diabetes mellitus	58 (21.0)	57 (21.0)
Insulin-treated	18 (6.5)	18 (6.5)
Peripheral artery disease	23 (8.0)	20 (7)
Systemic hypertension	154 (56)	165 (60.5)
Previous myocardial infarction	17 (6.1)	24 (8.8)
Previous TIA or stroke	13 (4.5)	6 (2.2)
Previous percutaneous coronary intervention	41 (15.0)	41 (15.2)
Previous coronary artery bypass surgery	8 (1.5)	6 (2.0)
Left ventricular ejection fraction, %	45 ± 10	45 ± 11
Type of myocardial infarction		
ST-segment elevation	211 (76.5)	201 (73.5)
Non-ST-segment elevation	65 (23.5)	73 (26.5)
Cardiac arrest	13 (4.7)	14 (5.0)
Cardiogenic shock	14 (5.0)	18 (6.5)
Stage A	2 (0.7)	2 (0.7)
Stage B	2 (0.7)	5 (1.8)
Stage C	10 (3.6)	11 (4.0)
Ongoing medical therapy		
ACE inhibitor	58 (21.0)	59 (21.5)
Angiotensin II receptor inhibitor	30 (11)	27 (10)
Diuretic agent	19 (7.0)	16 (6.0)
Beta-blocker	55 (20.0)	57 (21.0)
Statin	118 (43.0)	123 (45.0)
Serum creatinine, mg/dL	0.99 (0.82-1.18)	0.96 (0.82-1.19)
eGFR, mL/min/1.73 m^2	85 ± 34	84 ± 32
<60	54 (19.5)	62 (22.7)
Serum cystatin C, mg/dL[a]	1.00 (0.80.1.18)	1.01 (0.79-1.38)
Serum urea nitrogen, mg/dL	44.5 ± 23.7	44.6 ± 20.9
Serum sodium, mEq/L	138.7 ± 3.4	137.8 ± 7.1
Serum potassium, mEq/L	4.1 ± 0.7	4.0 ± 0.6
Hemoglobin, g/dL	14 ± 2	14 ± 2
C-reactive protein	5.0 (1.0-14.5)	5.0 (1.0-13.0)
Predicted risk for CA-AKI		
Gurm risk score	10 ± 9	10 ± 8
≥7	138 (50.0)	145 (53.0)
Mehran risk score	9 ± 3	9 ± 3
≥12	68 (25.0)	57 (21.0)

Values are mean ± SD, n (%), or median (Q1-Q3). [a]Cystatin C was available in 164 of 276 (58.6%) participants in the CVR group and in 162 of 274 (59.1%) in the control group.

ACE = angiotensin-converting enzyme; CA-AKI = contrast-associated acute kidney injury; CVR = contrast volume reduction; eGFR = estimated glomerular filtration rate; TIA = transient ischemic attack.

exact test, as appropriate. We calculated the relative risk (RR) and absolute risk difference and their 95% CIs for the primary and secondary endpoints. The inverse of the absolute risk difference yielded the number needed to treat to prevent 1 event. Logistic regression was performed to assess the interactions among CM volume, treatment group, and CA-AKI, as well as to explore the interplay of the CVR group, body mass index (BMI), and LVEDP. Variance inflation factor analysis was implemented to exclude collinearity. The Hosmer-Lemeshow goodness-of-fit test was assessed. To assess the impact of the 2 treatments on sCr and cystatin C, we used repeated measures analysis of variance models, after transforming sCr and cystatin C levels into natural logarithms (to overcome the problem of the non-normal distribution). A probability level <0.05 was considered significant. *P* values and 95% CIs for secondary endpoints have not been adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible. Statistical analyses were performed using SPSS for Windows software version 20.0 (IBM Corp) and Stata software version 11.2 for Windows (StataCorp, LP).

RESULTS

PATIENT GROUP. From February 4, 2020 to September 13, 2022, the study enrolled 550 participants (Figure 1). The clinical and biochemical characteristics of the 2 groups were well matched (Table 1). Details on PCI are reported in Table 2. Automatic injection was used in 21 (7.6%) participants in the CVR group and in 20 (7.3%) participants in the control group ($P = 1.00$). The CM diversion system was not turned off under any circumstances as a result of inadequate/poor image quality or other device-related reasons.

VOLUME EXPANSION. Mean 24-hour volume expansion was similar in the 2 groups (1,691 ± 473 mL in the CVR group vs 1,669 ± 517 mL in the control group; $P = 0.61$). Volume expansion was >960 mL in 257 (93.2%) participants in the CVR group and in 254 (92.5%) participants in the control group ($P = 0.74$). Periprocedural intravenous furosemide was administered in 78 (28%) participants in the CVR group and in 85 (31%) participants in the control group ($P = 0.45$). Daily diuresis was similar in the 2 groups at 24 hours (CVR group 1,613 ± 794 mL vs control group 1,577 ± 799 mL; $P = 0.59$), 48 hours (2,061 ± 936 mL vs

2,112 ± 855 mL; $P = 0.52$), and 72 hours (2,153 ± 958 mL vs 2,130 ± 8,932 mL; $P = 0.80$).

PRIMARY ENDPOINT. Seven participants (1 in the CVR group and 6 in the control group) did not have at least 1 postprocedural sCr value because they died within 24 hours (range: 3-22 hours) after enrollment (Supplemental Table 8). All other participants had at least 2 postprocedural sCr values (ie, at 24 and 48 hours), and 3 or more values were available for 539 (98%) participants (**Figure 2A**, Supplemental Figure 1). AKI occurred in 44 of 275 (16%) participants in the CVR group and in 65 of 268 (24.3%) participants in the control group (RR: 0.66; 95% CI: 0.47-0.93; $P = 0.018$) (**Figure 2B**). The absolute risk difference was −8.3% (Q1-Q3: −0.14% to −0.01%). The number needed to treat to prevent 1 event with the CM diversion system was 12. AKI occurred in 35 of 109 (32.1%) participants with eGFR <60 mL/min/1.73 m^2 (CVR group 12 of 53 [22.6%] vs control group 23 of 56 [41%]; RR: 0.55; 95% CI: 0.30-0.99; $P = 0.045$) and in 74 of 434 (17%) participants with eGFR ≥60 mL/min/1.73 m^2 (CVR group 32 of 222 [14.4%] vs control group 42 of 212 [18.8%]; RR: 0.72; 95% CI: 0.47-1.10; $P = 0.13$).

SENSITIVITY ANALYSIS AND SECONDARY ENDPOINTS. When considering all enrolled participants and including the only participant in the CVR group who died within 24 hours with AKI, and the 6 participants in the control group who died within 24 hours without events, AKI occurred in 45 of 276 (16.3%) participants in the CVR group and in 65 of 274 (23.7%) in the control group (RR: 0.68; 95% CI: 0.49-0.96; $P = 0.031$). CM volume was lower in the CVR group than in the control group (95 ± 30 mL vs 160 ± 23 mL; $P < 0.001$) (**Figure 3A**). A CM volume >3× eGFR was reported in 25 (10.7%) participants in the CVR group and in 62 (22.7%) participants in the control group ($P < 0.001$). In the CVR group, the mean absolute and percentage of CM volume saved were 59.8 ± 37.3 mL and 38.1% ± 9.4%, respectively. This finding was similar in the subgroup of participants who underwent automatic injection (36.7% ± 8.2%). The number of injections per patient was similar in the 2 groups (CVR group 37 ± 25 vs control group 33 ± 2; $P = 0.072$). The association between CM volume and CA-AKI was also confirmed by graphic analysis (**Figure 3B**). An exploratory analysis appraising the interactions among CA-AKI, CM volume, and CVR group is reported in Supplemental Table 9.

In a multivariable logistic regression model including CVR group, low BMI (≤24.9 kg/m^2), and increased LVEDP (18 mm Hg or more), the CVR group was still significantly associated with a lower risk of CA-AKI (OR: 0.53; 95% CI: 0.34-0.82; $P = 0.005$), with low BMI and high LVEDP also significantly associated with CA-AKI (OR: 2.07; 95% CI: 1.10-3.91; $P = 0.025$; and OR: 2.43; 95% CI: 1.56-3.79; $P < 0.001$, respectively), without a significant interaction between the CVR group and either of these clinical variables ($P = 0.716$ and $P = 0.423$, respectively) (Supplemental Figure 2). The distribution of different cutoffs of sCr and cystatin C increase is reported in **Table 3**. The kinetics of cystatin C are represented in Supplemental Figure 3.

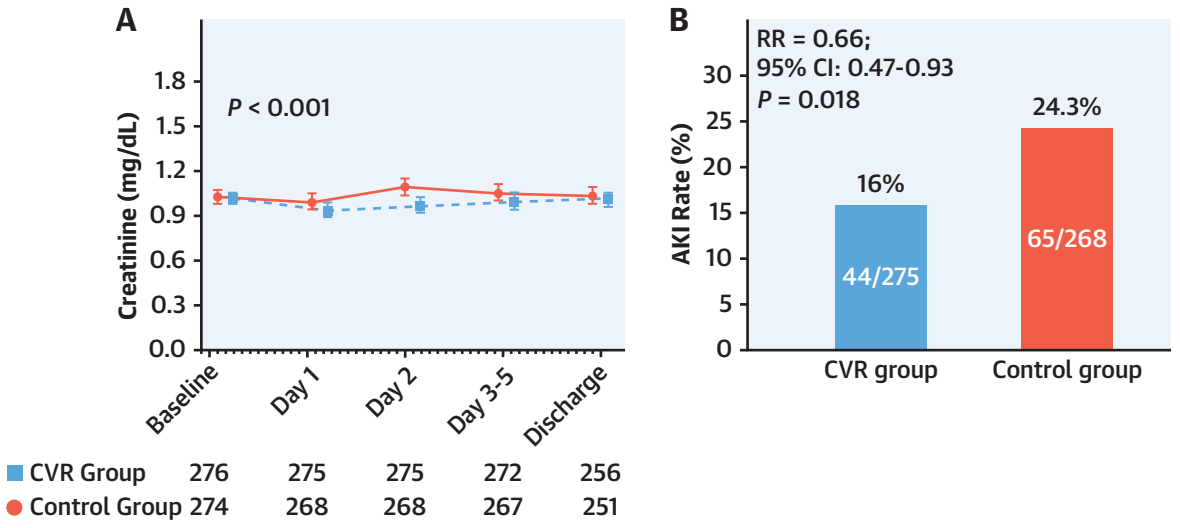
TABLE 2 Procedural Characteristics of Participants Enrolled in the 2 Groups

	CVR Group (n = 276)	Control Group (n = 274)
Coronary angiography attempted	276 (100)	274 (100)
Coronary angiography completed	276 (100)	274 (100)
PCI attempted	243 (88.0)	235 (85.7)
PCI completed	243 (88.0)	235 (85.7)
Radial approach	265 (96.5)	268 (98.5)
Symptom onset to treatment, min	306 (192-564)	300 (192-540)
ST-segment elevation myocardial infarction	240 (132-498)	240 (126-420)
Non-ST-segment elevation myocardial infarction	426 (198-570)	330 (198-492)
Door-to-balloon time, min[a]	40 (17-60)	45 (20-69)
Left ventricular end-diastolic pressure, mm Hg	17 ± 6	16 ± 7
≤12	73 (26.0)	86 (31.5)
13-18	96 (35.0)	103 (38.0)
>18	107 (39.0)	85 (31.0)
Mechanical assist device	14 (5.0)	16 (5.8)
Intra-aortic balloon pump	1 (0.3)	1 (0.4)
Impella CP (Abiomed)	13 (4.7)	15 (5.4)
Vasopressor agents	22 (8.0)	29 (10.6)
Norepinephrine	11 (4.0)	23 (8.4)
Epinephrine	11 (4.0)	6 (2.2)
Multivessel disease	115 (41.5)	112 (41.0)
Vessels treated	292	290
Left main coronary artery	14 (4.8)	16 (5.5)
Left anterior descending artery	144 (49.3)	140 (48.2)
Left circumflex artery	39 (13.3)	38 (13.1)
Right coronary artery	82 (28.1)	81 (27.9)
Others	13 (4.5)	15 (5.1)
Number of lesions treated per patient	1.37 ± 0.58	1.31 ± 0.59
Total stent length, mm	42.8 ± 27.4	41.8 ± 31.2
Multivessel stenting	50/243 (20.5)	52/235 (22.1)
Number of stents implanted	1.56 ± 0.95	1.53 ± 0.91
0	3/243 (1.2)	2/235 (0.9)
1	146/243 (60.0)	139/235 (59.1)
2	57/243 (23.5)	67/235 (28.5)
≥3	37/243 (15.3)	27/235 (11.5)
Radiation exposure		
Dose rate, Gy	1.38 ± 1.07	1.53 ± 1.32
Dose area product, Gy/cm^2	112 ± 94	118 ± 108
Fluoroscopic time, min	14 ± 10	14 ± 11

Values are n (%), median (Q1-Q3), mean ± SD, n, or n/N (%). [a]In participants with ST-segment elevation myocardial infarction.

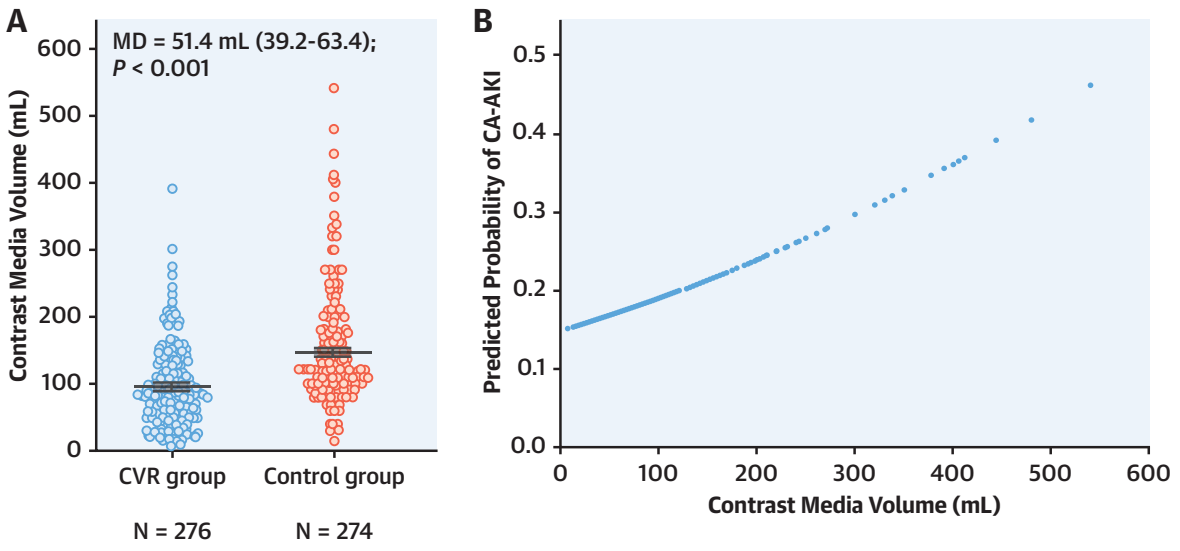
CVR = contrast volume reduction; PCI = percutaneous coronary intervention.

FIGURE 2 Trends in Serum Creatinine Concentrations and Incidence of AKI



(A) Trends in serum creatinine concentrations. Serum creatinine concentrations (geometric means with their 95% CIs) at baseline, day 1, day 2, and days 3 to 5 after contrast media administration in the contrast volume reduction (CVR) group (dashed line and closed square) and in the control group (continuous line and closed circle). (B) Incidence of acute kidney injury (AKI). Contrast volume reduction group = blue bar; control group = red bar. The absolute risk difference was −8.3% (Q1-Q3: −0.14% to −0.01%). The number needed to treat to prevent 1 event with the contrast media diversion system was 12. RR = relative risk.

FIGURE 3 Contrast Media Volume



(A) Cumulative distribution of contrast media volume by group. Dotted line = mean; error bars = standard error of mean. Differences in means (MD) with 95% CIs are reported on top. (B) Association between contrast media volume and contrast-associated acute kidney injury (CA-AKI). CVR = contrast volume reduction.

The distribution of AKI stage was similar in the 2 groups (Supplemental Table 10). RRT occurred in 7 of 276 (2.5%) participants in the CVR group vs 14 of 274 (5.1%) participants in the control group (RR = 0.50; 95% CI: 0.20-1.23; $P = 0.13$). Length of hospital stay was 6.7 ± 6.1 days in the CVR group vs 6.6 ± 4.6 days in the control group ($P = 0.78$). In contrast, the length of hospital stay was longer in participants who experienced AKI (11.1 ± 9.8 days vs 5.6 ± 2.7 days; $P < 0.001$). The in-hospital death rate was 6.9% (19 of 276) in the CVR group vs 7.7% (21 of 274) in the control group (RR: 0.89; 95% CI: 0.49-1.63; $P = 0.72$). The in-hospital death rate was higher in participants who experienced AKI (26 of 109 [23.8%] vs 7 of 434 [1.6%]; RR: 14.8; 95% CI: 6.59-33.1; $P < 0.001$).

The 1-month and 6-month major adverse cardiac and kidney event rates are reported in Table 4. Sustained kidney damage was lower in the CVR group than in the control group. Sustained kidney damage occurred in 22 of 116 (18.9%) participants with eGFR <60 mL/min/1.73 m^2 (CVR group 6 of 54 [11.1%] vs control group 16 of 62 [25.8%]; RR: 0.43; 95% CI: 0.18-1.02; $P = 0.056$) and in 33 of 434 (7.6%) participants with eGFR ≥60 mL/min/1.73 m^2 (CVR group 11 of 222 [4.9%] vs control group 22 of 212 [10.4%]; RR: 0.47; 95% CI: 0.23-0.96; $P = 0.038$). Among the 109 participants who had AKI, 37 (33.9%) experienced sustained kidney damage at 6 months. More specifically, AKI and eventual sustained kidney damage occurred in 19 of 434 (4.4%) participants with baseline eGFR ≥60 mL/min/1.73 m^2 and in 18 of 116 (15.5%) participants with eGFR <60 mL/min/1.73 m^2.

TABLE 3 Distribution of the Changes in Serum Creatinine and Cystatin C Levels

	CVR Group	Control Group	Relative Risk (95% CI)	*P* Value
Changes in creatinine				
Increase ≥0.3 mg/dL at 48 h	44/275 (16)	65/268 (24.3)	0.59 (0.39-0.91)	0.018
Increase ≥0.5 mg/dL or ≥25% at 72 h	52/272 (19.1)	72/267 (26.9)	0.71 (0.51-0.97)	0.032[a]
Changes in cystatin C				
Increase ≥10% at 24 h	23/164 (19.8)	50/162 (30.5)	0.56 (0.33-0.93)	0.030[a]
Increase ≥25% at 24 h	8/164 (5)	16/162 (10)	0.50 (0.21-1.12)	0.092[a]
Increase ≥10% at 48 h	20/163 (12.2)	35/156 (22.4)	0.54 (0.32-0.89)	0.018[a]
Increase ≥25% at 48 h	10/163 (6.1)	19/156 (12.1)	0.50 (0.24-1.04)	0.067[a]

Values are n/N(%) unless otherwise indicated. [a]No corrections for multiple testing were applied.
CVR = contrast volume reduction.

DISCUSSION

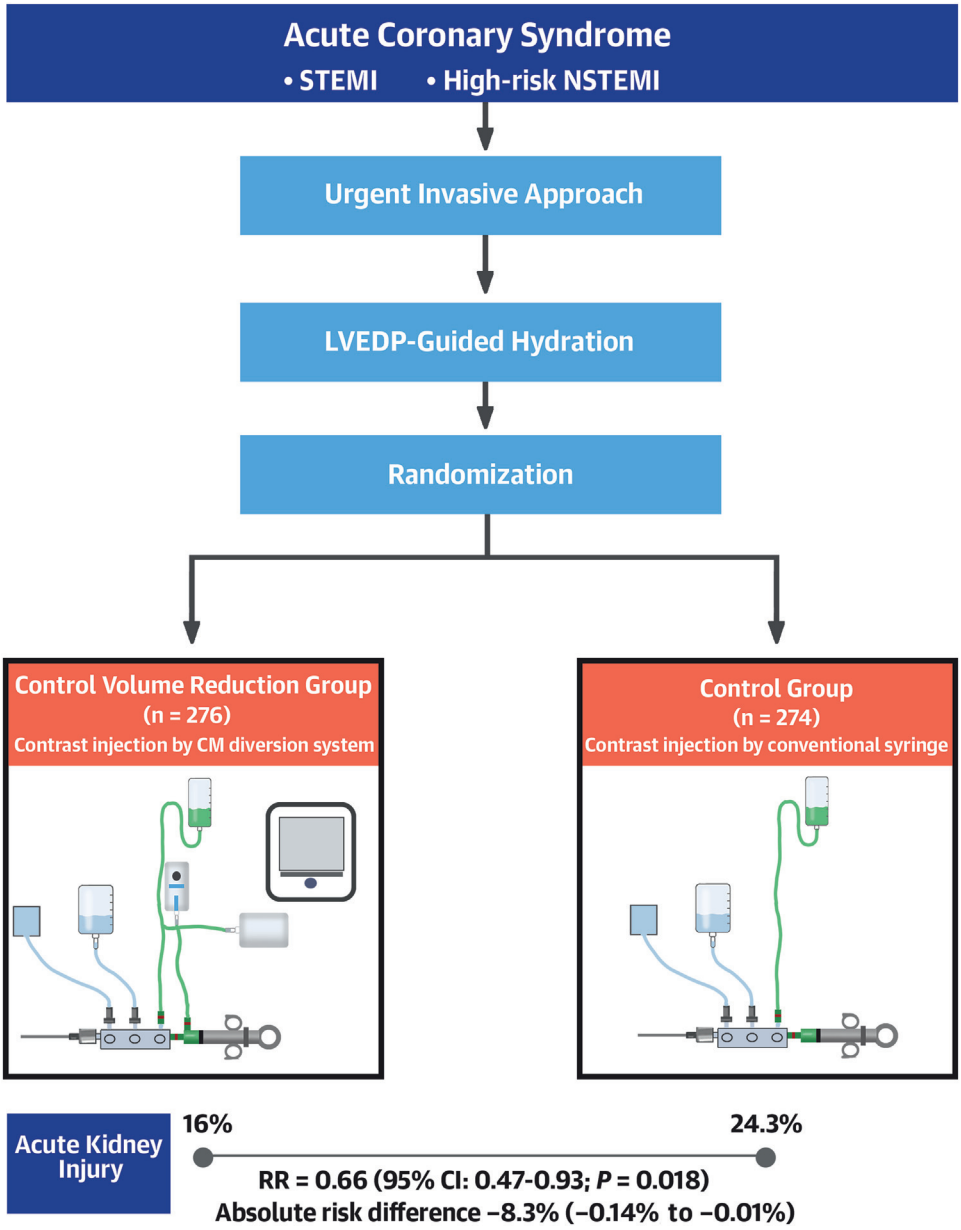
Patients with ACS are at high risk of AKI, even if baseline kidney function is preserved.[1-3,5] AKI has been associated with persistent kidney function deterioration and higher rates of in-hospital and long-term adverse cardiac and renal events.[1,18] The pathogenesis of AKI in the setting of ACS is multifactorial. Age, unstable hemodynamic conditions, comorbidities, preexisting chronic kidney disease, dehydration, and the administration of nephrotoxic drugs and CM may concur in the development of AKI.[4] Recently, the role of iodinated CM has been questioned because the studies linking CM use to AKI in the setting of ACS lack a control group in which CM was not administered, thus making it impossible to distinguish CA-AKI from CM-independent AKI. Caspi et al[27] reported in an observational nonrandomized study that the AKI rate was similar in STEMI patients with and without CM exposure. At present, it is unethical and unrealistic to design a randomized, controlled study to assess the AKI rate in patients with ACS treated by invasive vs medical approaches. A way to overcome this issue would be to test whether strategies for CM minimization are associated with a reduction in AKI rate. Indeed, both nonlinear and linear relationships between CM volume and AKI have been reported.[21,26,28] Gurm et al[28] suggested that a 30% reduction in CM volume could translate into a 12.8% reduction in AKI. Ultralow-CM or zero-CM procedures have been advocated, and several CM-sparing strategies have been proposed.[20] All of these strategies are, however, "operator-dependent." The CM diversion system is an additional, "operator-independent" tool contributing to the CM-sparing approach. Use of

TABLE 4 Major Adverse Cardiac and Kidney Events at 1 and 6 Months[a]

	CVR Group (n = 276)	Control Group (n = 274)	Relative Risk (95% CI)	*P* Value
1 month				
Cumulative major adverse events	32 (11.5)	45 (16.5)	0.70 (0.46-1.07)	0.10
Death	20 (7.2)	23 (8.4)	0.86 (0.48-1.53)	0.63
Myocardial infarction	7 (2.5)	3 (1.1)	2.31 (0.60-8.86)	0.22
Dialysis	7 (2.5)	14 (5.1)	0.49 (0.20-1.21)	0.12
Sustained kidney damage[b]	15 (5.4)	37 (13.5)	0.40 (0.22-0.71)	0.002
Major bleeding (BARC 3/5)	5 (1.8)	6 (2.2)	0.82 (0.25-2.67)	0.77
6 months				
Cumulative major adverse events	41 (14.9)	55 (20.1)	0.74 (0.51-1.07)	0.11
Death	25 (9.0)	29 (10.5)	0.85 (0. 51-1.42)	0.57
Myocardial infarction	9 (3.2)	5 (1.8)	1.78 (0.60-5.26)	0.42
Dialysis	7 (2.5)	14 (5.1)	0.49 (0.20-1.21)	0.12
Sustained kidney damage[c]	17 (6.1)	38 (13.8)	0.44 (0.25-0.76)	0.003
Major bleeding (BARC 3/5)	7 (2.5)	8 (2.9)	0.86 (0.32-2.36)	0.78

Values are n (%) unless otherwise indicated. [a]No corrections for multiple testing were applied. [b]Median time from contrast media administration to the serum creatinine measurement used to assess sustained kidney damage at 1 month was 30 days (Q1-Q3: 28-30 days) in the CVR group (n = 275) and 30 days (Q1-Q3: 26-30 days) in the control group (n = 268; $P = 0.48$). [c]Median time from contrast media administration to the serum creatinine measurement used to assess sustained kidney damage at 6 months was 174 days (Q1-Q3: 143-180 days) in the CVR group (n = 275) and 174 days (Q1-Q3: 161-192 days) in the control group (n = 268; $P = 0.47$).
BARC = Bleeding Academic Research Consortium; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION Schematic Representation of the Study Design and Results



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Participants were randomly assigned in a 1:1 ratio to the following: 1) the contrast volume reduction (CVR) group, in which contrast media (CM) injection was handled by the contrast media diversion system; and 2) the control group, in which a conventional manual or automatic injection syringe was used. The primary endpoint was acute kidney injury, defined as a serum creatinine increase ≥0.3 mg/dL within 48 hours after contrast media exposure. LVEDP = left ventricular end-diastolic pressure; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

the CM diversion system resulted in a 41% reduction in CM volume.[7,29]

The CM volume administered during an invasive procedure in patients with ACS is, on average, 138 to 425 mL.[1-3,5,16] In a pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trials, the CM volume was 232 mL in the CA-AKI group and 220 mL in the group without CA-AKI.[1] In a group of patients with STEMI, Marenzi et al[5] reported a mean CM volume of 216 ± 73 mL in the group without CA-AKI and 425 ± 148 mL in the CA-AKI group. In the MATRIX (Minimizing Adverse Hemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial, the mean CM volume was 183 ± 104 mL in the radial access group and 183 ± 110 mL in the femoral access group.[2] In the present study, the CM volume administered in the control group was 160 ± 23 mL, which is one of the lowest values reported in this setting. This finding supports the fact that strategies for CM minimization have been implemented. Moreover, the CM volume administered in the CVR group was 95 ± 30 mL. The current REMEDIAL IV study therefore supports the observation that, on top of all strategies recommended for CM minimization, the CM diversion system is effective in limiting the CM volume, even in patients with ACS. This CM volume saving was associated with a significant reduction in the CA-AKI rate (the absolute risk difference was −8.3%) (**Central Illustration**). This finding supports the concept that CM volume is an important determinant of AKI in patients with ACS and emphasizes the need to implement all strategies effective for CM minimization, including the CM diversion system.

Volume expansion represents a widely accepted prophylactic strategy for CA-AKI. At present, there is no consensus on how volume expansion should be carried out, especially in patients with ACS. The most commonly recommended regimen is normal saline infusion at 1 mL/kg/h (0.5 mL/kg/h if the left ventricular ejection fraction is ≤35% or the patient is in NYHA functional class >II) from 12 hours before to 24 hours after CM exposure.[6] This regimen, however, is not suitable in urgent/emergency settings. Maioli et al[16] suggested early rapid hydration (3 mL/kg/h, starting in the emergency department) followed by infusion of 1 mL/kg/h for 12 hours. However, this forced volume expansion regimen is contraindicated in patients with ACS with unstable hemodynamic conditions. The concept of a tailored volume expansion strategy has been increasingly accepted. In the present trial, we adopted the LVEDP-guided protocol[15] because it is simple and easy to implement in patients with ACS undergoing an urgent invasive approach, as also recently demonstrated in the ATTEMPT (Aggressive hydraTion in patients with STEMI undergoing pPCI to prevenT Contrast-Induced Acute Kidney Injury) trial.[30] Notably, although CM minimization appeared safe and effective in all subgroups, without significant statistical interactions for BMI and LVEDP, it is evident that its use should be particularly beneficial in those subjects at higher risk of CA-AKI such as those with low BMI and/or high LVEDP.

STUDY LIMITATIONS. The lack of blinding and the relatively small number of participating centers may have influenced decisions on the number of injections and amount of CM volume used. Indeed, the physicians who performed the procedure were not masked. However, the laboratory personnel processing the samples and the members of the CEC were blinded to the treatment group. CM injection was handled by manual syringe in most participants. Automatic injection was used in ≈7% of participants. Therefore, although the amount of CM saved was similar, irrespective of the injection strategy, we should be cautious about extending these results to participants receiving automatic injections. The systematic use of the CM diversion system comes at a price. However, AKI is associated with a longer hospital stay. Future cost-benefit analysis studies will clarify the economic impact of the CM diversion system. Finally, although the use of the CM diversion system is quite simple and we did not find any delay in starting the procedure directly as a result of preparation of this device, we should acknowledge that its use in an emergency setting may require a short training period so as not to slow down the intervention itself.

CONCLUSIONS

The current study suggests that, in patients with ACS requiring an urgent invasive approach, CM minimization obtained by the CM diversion system is associated with a significant reduction in the AKI rate.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose. The company providing the DyeVert system (Osprey Medical, Inc) was not involved in the trial design and conduction.

ADDRESS FOR CORRESPONDENCE: Dr Carlo Briguori, Department of Interventional Cardiology, Mediterranea Cardiocentro, Via Orazio, 2, I-80121 Naples, Italy. E-mail: carlobriguori@clinicamediterranea.it.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Minimizing radiographic contrast exposure reduces the incidence of kidney injury in patients with acute coronary syndromes undergoing coronary angiographic intervention.

TRANSLATIONAL OUTLOOK: Additional studies are needed to evaluate the impact of minimizing contrast exposure on other clinical events in patients with ACS undergoing percutaneous revascularization.

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KEY WORDS contrast media, myocardial infarction, percutaneous coronary intervention

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.