with an increased likelihood of needing a future kidney transplant. Because CARPEDIEM is able to achieve lower blood-flow rates than existing machines, dialysis access was achieved with a smaller (4 French) vascular catheter than is typically used in children receiving CRRT (6–7 French).[10] One of the most important improvements over the existing practice of adapting adult machines for use in very small children is the ability of CARPEDIEM to control ultrafiltration down to the millilitre. A major limitation of devices designed for adults and adapted to infants is the potential for errors in ultrafiltration volumes that would be trivial for an adult, but not for an infant.

Providers have become increasingly experienced in the care of children with kidney disease and new paediatric-specific technologies have become available over the past decade. In 2013, the National Institute of Diabetes and Digestive and Kidney Diseases convened a multidisciplinary workshop focused on systematically and prospectively studying kidney injury in neonates.[12] We hope that such efforts will translate into improved outcomes, both for children who need renal replacement therapy for acute kidney injury and for those who are developing end-stage kidney disease.[13,14]

In the case reported by Ronco and colleagues,[5] although the child survived to hospital discharge, she still had severe chronic kidney disease at the last follow-up. This outcome should motivate investigators to continue to develop new therapeutic strategies not only to manage existing kidney injury, but also to prevent permanent damage from occurring in the first place. Although the initial results with the new device are encouraging, more research will be needed to determine whether adequate solute clearance can be achieved in all patients with the low blood-flow rates and reduced-volume filters of CARPEDIEM.

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Hydration in contrast-induced acute kidney injury

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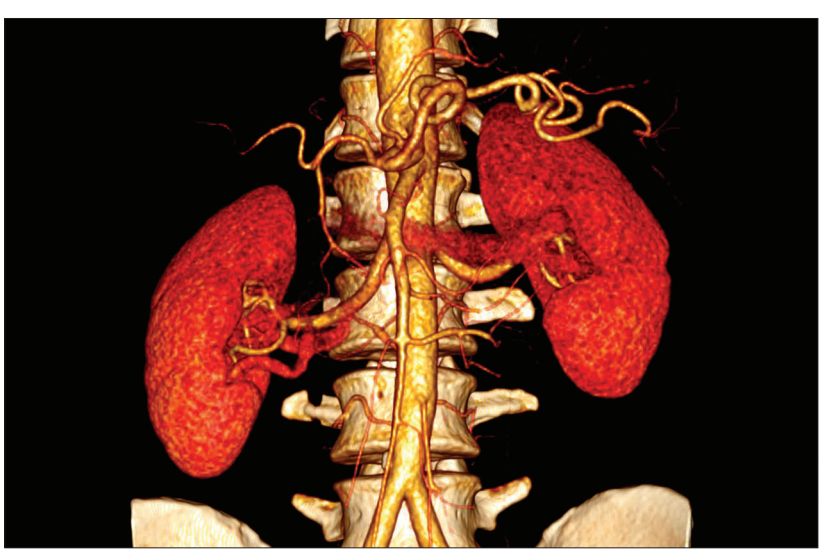
Contrast-induced acute kidney injury is associated with prolonged hospital stay, increased health-care costs, and raised risk of both further deterioration of kidney function and unfavourable clinical outcome.[1] A general consensus exists for the beneficial effect of hydration in preventing contrast-induced acute kidney injury. Hydration increases urine flow rates,[2] reduces the concentration of contrast media in the tubule, and expedites excretion of contrast media, thus reducing the length of time that tubular cells are exposed to the toxic effects of contrast media.[3] Although different hydration solutions and regimens have been suggested, choice of solution (eg, sodium bicarbonate *vs* sodium chloride) remains controversial.[4] The most widely

recommended hydration regimen is normal saline 1 mL/kg per h for 12 h before and 12 h after exposure to contrast media.[5] However, the limitations of this hydration regimen include preclusion in urgent or emergency settings, and suboptimum efficacy in patients at high or very high risk of kidney injury. The best possible hydration regimen should be decided according to a predefined clinical marker. Urine flow rate has been advocated as an ideal marker.[2]

In *The Lancet*, Somjot Brar and colleagues[6] propose an alternative marker: left ventricular end-diastolic pressure. In the POSEIDON trial they aimed to establish the efficacy of a novel fluid protocol based on this marker. Patients undergoing cardiac catheterisation with an estimated glomerular filtration rate of 60 mL/min per 1·73 m² or lower, and one or more of several risk factors (diabetes mellitus, history of congestive heart failure, hypertension, or age older than 75 years), were randomly allocated to left ventricular end-diastolic pressure-guided volume expansion or a control group. The trial's primary endpoint of contrast-induced acute kidney injury, as judged by a greater than 25% or 0·5 mg/dL increase in serum creatinine concentration, occurred less frequently in patients randomised to the left ventricular end-diastolic pressure-guided group (12 of 178 [6·7%]) than those in the control group (28 of 172 [16·3%]; relative risk 0·41, 95% CI 0·22–0·79). The 6-month rate of major adverse clinical events (a composite of all-cause mortality, myocardial infarction, or renal replacement therapy), was also lower in the left ventricular end-diastolic pressure-guided group (6 of 196 [3·1%]) than in the control group (19 of 200 [9·5%]; relative risk 0·32, 95% CI 0·13–0·79).

The strengths of this hydration regimen are that it leads to a substantial risk reduction in contrast-induced acute kidney injury and that it is suitable in both elective and acute settings. However, its weaknesses are that its use is limited to patients undergoing intra-arterial procedures and probably coronary interventions. The question of whether or not left ventricular end-diastolic pressure-guided treatment is necessary is also debatable. We should consider several points.

First, the proposed approach is based on the hypothesis that dosing the hydration regimen according to baseline left ventricular end-diastolic pressure should optimise volume expansion and both prevent contrast-induced acute kidney injury and mitigate the risk of pulmonary oedema. The primary endpoint of contrast-induced acute kidney injury occurred less frequently in the left ventricular end-diastolic pressure-guided group than in the control group, whereas the rate of pulmonary oedema was similar between the two groups. Six patients (three in each group) stopped receiving intravenous fluids early because of shortness of breath. This complication seems to be unrelated to baseline left ventricular end-diastolic pressure, which was low in two patients in the control group and in one patient in the left ventricular end-diastolic pressure-guided group, and high in one control group patient and in two in the left ventricular end-diastolic pressure-guided group. According to Frank–Starling curves, in ventricles with normal cardiac performance, a steep and positive association exists between increased left ventricular end-diastolic pressure and higher stroke volume. By contrast, in myocardial dysfunction, this relation is shifted to the right (ie, a higher filling pressure is needed to achieve the same cardiac output) and flattened so that continued increases in left heart filling pressure lead to a minimum increase in cardiac output at the possible expense of pulmonary oedema. Further studies are necessary to test this approach in patients with high left ventricular end-diastolic pressure, who have a heightened risk of both contrast-induced acute kidney injury and pulmonary oedema. In this trial, more



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than 50% of patients had normal left ventricular end-diastolic pressure and only 15% had high values.

Second, in a retrospective observational study of rapid intra-arterial infusion of 5% dextrose before coronary angiography and frequency of contrast-induced acute kidney injury in high-risk patients,[7] the investigators administered 1 L of 5% dextrose through the common femoral artery sheath as a bolus at least 5 min before angiography. The primary endpoint of contrast-induced acute kidney injury occurred in 5·7% of patients in the control group and 1·4% in the treatment group. Dextrose infusion had no adverse haemodynamic consequences. Notably, mean left ventricular ejection fraction was 45% in the treatment group. This study suggests that high and quick volume expansion can be provided routinely, periprocedurally, without the need for guidance by left ventricular end-diastolic pressure.

Third, suboptimum efficacy of the common hydration regimen occurs more frequently in patients who are at high or very high risk of contrast-induced acute kidney injury. However, the participants enrolled in POSEIDON were at medium risk. According to the risk score proposed by Mehran and colleagues,[8] the expected rate of kidney injury is therefore roughly 14%, whereas, according to Gurm and colleagues,[9] it is 1–7%. Therefore, the proposed left ventricular end-diastolic pressure-guided hydration regimen should be tested in high-risk and very-high-risk patients.

Finally, high urine flow rate (≥150 mL/h) can reduce the incidence of contrast-induced acute kidney injury in several ways. When kidney function is normal, contrast medium is excreted quite quickly, within a few hours. In patients with chronic kidney disease, the excretion half-life might be more than 10 h.[10] Moreover, after glomerular filtration, the concentration of the filtered contrast medium increases to more than 100 times that in serum. If saline is infused at 1 mL/kg per h for 12 h in a healthy participant, the concentration of the filtered contrast media through the nephron is almost halved. If saline is infused at 5 mL/kg per h, the concentration of the filtered contrast medium through the nephron is reduced to about a tenth of the serum concentration. In this sense, it is important to consider that a high urine flow rate should be reached by maintenance of a constant intravascular volume to prevent hypovolaemia.[2] The RenalGuard system has been developed to enable optimum hydration therapy. This device allows achievement of high urine output while simultaneously balancing urine output and venous fluid infusion to prevent hypovolaemia.[11] Two trials have reported that RenalGuard therapy is more effective than is the conventional hydration regimen in preventing contrast-induced acute kidney injury.[12,13] Further studies are needed to compare left ventricular-guided versus RenalGuard system-guided hydration regimens.

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Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial

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Summary

Background **The administration of intravenous fluid remains the cornerstone treatment for the prevention of contrast-induced acute kidney injury. However, no well-defined protocols exist to guide fluid administration in this treatment. We aimed to establish the efficacy of a new fluid protocol to prevent contrast-induced acute kidney injury.**

Methods **In this randomised, parallel-group, comparator-controlled, single-blind phase 3 trial, we assessed the efficacy of a new fluid protocol based on the left ventricular end-diastolic pressure for the prevention of contrast-induced acute kidney injury in patients undergoing cardiac catheterisation. The primary outcome was the occurrence of contrast-induced acute kidney injury, which was defined as a greater than 25% or greater than 0·5 mg/dL increase in serum creatinine concentration. Between Oct 10, 2010, and July 17, 2012, 396 patients aged 18 years or older undergoing cardiac catheterisation with an estimated glomerular filtration rate of 60 mL/min per 1·73 m² or less and one or more of several risk factors (diabetes mellitus, history of congestive heart failure, hypertension, or age older than 75 years) were randomly allocated in a 1:1 ratio to left ventricular end-diastolic pressure-guided volume expansion (n=196) or the control group (n=200) who received a standard fluid administration protocol. Four computer-generated concealed randomisation schedules, each with permuted block sizes of 4, were used for randomisation, and participants were allocated to the next sequential randomisation number by sealed opaque envelopes. Patients and laboratory personnel were masked to treatment assignment, but the physicians who did the procedures were not masked. Both groups received intravenous 0·9% sodium chloride at 3 mL/kg for 1 h before cardiac catheterisation. Analyses were by intention to treat. Adverse events were assessed at 30 days and 6 months and all such events were classified by staff who were masked to treatment assignment. This trial is registered with ClinicalTrials.gov, number NCT01218828.**

Findings **Contrast-induced acute kidney injury occurred less frequently in patients in the left ventricular end-diastolic pressure-guided group (6·7% [12/178]) than in the control group (16·3% [28/172]; relative risk 0·41, 95% CI 0·22–0·79; p=0·005). Hydration treatment was terminated prematurely because of shortness of breath in three patients in each group.**

Interpretation **Left ventricular end-diastolic pressure-guided fluid administration seems to be safe and effective in preventing contrast-induced acute kidney injury in patients undergoing cardiac catheterisation.**

Funding **Kaiser Permanente Southern California regional research committee grant.**

Introduction

Acute kidney injury after cardiac catheterisation can result from several different causes, all of which can increase serum creatinine concentration, often in the absence of other clinical findings. A common cause is contrast-induced acute kidney injury, which is associated with increased morbidity, mortality, and health-care costs.[1–4] Although this mechanism of acute kidney injury has been well known for some time, treatment options remain scarce. No known treatments are available that can be implemented after acute kidney injury has occurred; therefore, the primary focus has been to identify preventive therapies. Many novel interventions have been assessed and so far none have been shown to be conclusively beneficial; however, intravascular volume expansion, preferably with isotonic saline (0·9%), is often recommended.[5–7] Nevertheless, as noted in existing guidelines, very little is known about the rate and duration of fluid administration around the time of contrast exposure.[8,9] So far, no trial has directly compared volume expansion with isotonic saline at different rates or durations in at-risk populations.[8] Not unexpectedly, these uncertainties might explain, in part, the non-uniform adoption of volume expansion strategies. For example, only 45% of patients undergoing coronary angiography received intravascular volume expansion with isotonic saline in a prospective observational study.[10]

The aim of the Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial was to investigative different rates of fluid administration guided by the left ventricular end-diastolic pressure in patients undergoing cardiac catheterisation. The left ventricular end-diastolic pressure is a haemodynamic

parameter that is routinely obtained during cardiac catheterisation and is a measure of intravascular volume status.

Methods

Study design and participants

Between Oct 10, 2010, and July 17, 2012, all consecutive patients referred to the cardiac catheterisation laboratory at the Kaiser Permanente Medical Center in Los Angeles, CA, USA were screened to establish whether they met study criteria. The inclusion criteria included an estimated glomerular filtration rate (GFR) of 60 mL/min per 1·73 m² or lower; age 18 years or older; and at least one of the following: diabetes mellitus, history of congestive heart failure, hypertension (blood pressure >140/90 mm Hg or treatment with anti-hypertensive medication), or age older than 75 years. We calculated the estimated GFR with serum creatinine concentrations and the modification of diet in renal disease study equation:

$$186 \cdot 3 \times \text{serum creatinine level}^{-1 \cdot 154} \times \text{age}^{-0 \cdot 203}$$
$$[\times 0 \cdot 742 \text{ if female}]$$

We adjusted the obtained value for race by multiplying it by 1·21 for patients who identified themselves as black.

Exclusion criteria included inability to obtain consent from participants, emergency cardiac catheterisation (eg, primary percutaneous coronary intervention for ST-segment elevation myocardial infarction), renal replacement therapy, exposure to radiographic contrast media within the previous 2 days, allergy to radiographic contrast media, acute decompensated heart failure, severe valvular heart disease, mechanical aortic prosthesis, left ventricular thrombus, history of kidney or heart transplantation, and change in estimated GFR of 7·5% or more per day or a cumulative change of 15% or more during the preceding 2 or more days.

We randomly assigned eligible patients in a 1:1 ratio to either left ventricular end-diastolic pressure-guided therapy or a standard fluid administration protocol. We used the same fluid type—commercially available 0·9% sodium chloride—in all patients. A bolus infusion at 3 mL/kg for 1 h was given to all patients before the procedure. Before the administration of contrast media, we measured the left ventricular end-diastolic pressure by placing an angled 5-French or 6-French pigtail catheter in the mid-cavity of the left ventricle. We repositioned the catheter if necessary to minimise ventricular ectopy and calibrated the haemodynamic monitoring system in a standard manner. We recorded the left ventricular end-diastolic pressure with commercially available haemodynamic monitoring software (Xper; Phillips, Melbourne, FL, USA). Thereafter, the patient was randomly allocated to either left ventricular end-diastolic pressure-guided treatment or to the control group. In the former group, the fluid rate was adjusted according to the left ventricular end-diastolic pressure as follows: 5 mL/kg/h for left ventricular end-diastolic pressure lower than 13 mm Hg, 3 mL/kg/h for pressure of 13–18 mm Hg, and 1·5 mL/kg/h for pressure higher than 18 mm Hg. The control group was hydrated at 1·5 mL/kg per h. The fluid rate was set at the start of the procedure (before contrast exposure), continued for the duration of the procedure, and for 4 h post-procedure in both groups. Thus, both study groups received intravenous fluids for the same duration but at different rates. For patients who weighed more than 100 kg, the bolus and infusion rate were limited to those calculated for patients weighing 100 kg. All study participants received intra-arterial ioxilan (350 mg iodine/mL), which is a non-ionic, low-osmolar contrast medium.

We measured baseline serum creatinine concentrations on the day of cardiac catheterisation before fluid administration and contrast exposure. Patients were instructed to have their serum creatinine measured at least twice between days 1 and 4 post-procedure. We assessed serum creatinine concentrations until any increase resolved or reached a new baseline of renal function. Patients were given the same instructions for procedure preparation and post-procedure recovery. Before the procedure, patients were instructed to discontinue taking anticoagulants, non-steroidal anti-inflammatory drugs, and diuretics.

Randomisation and masking

Randomisation was stratified by diabetes mellitus status and N-acetylcysteine use. N-acetylcysteine use was defined as 600 mg twice daily for 2 days, starting the day before the index procedure, and use was at the discretion of the referring physician. If started, the 2-day course was completed. Four computer-generated concealed randomisation schedules, each with permuted block sizes of 4, were created. When an eligible patient had been enrolled, the research assistant used sealed opaque envelopes to allocate the patient to the next sequential randomisation number.

This study was partly blinded. Patients were not told which group they were randomly allocated to. The laboratory personnel processing the samples also had no knowledge of each patient's group assignment. The physicians who did the procedures were not masked. The procedure duration and contrast volume, which would probably represent any biases in contrast administration, were collected systematically. The contrast volume administered was measured in 1-mL increments, with the total established from the power injector used during the procedure. All procedures were done with the same injector type (ACIST CVi Contrast Delivery System [ACIST Medical Systems, Eden Prairie, MN, USA]). Procedure duration and fluoroscopy time were obtained from the computer systems integrated into the procedure rooms.

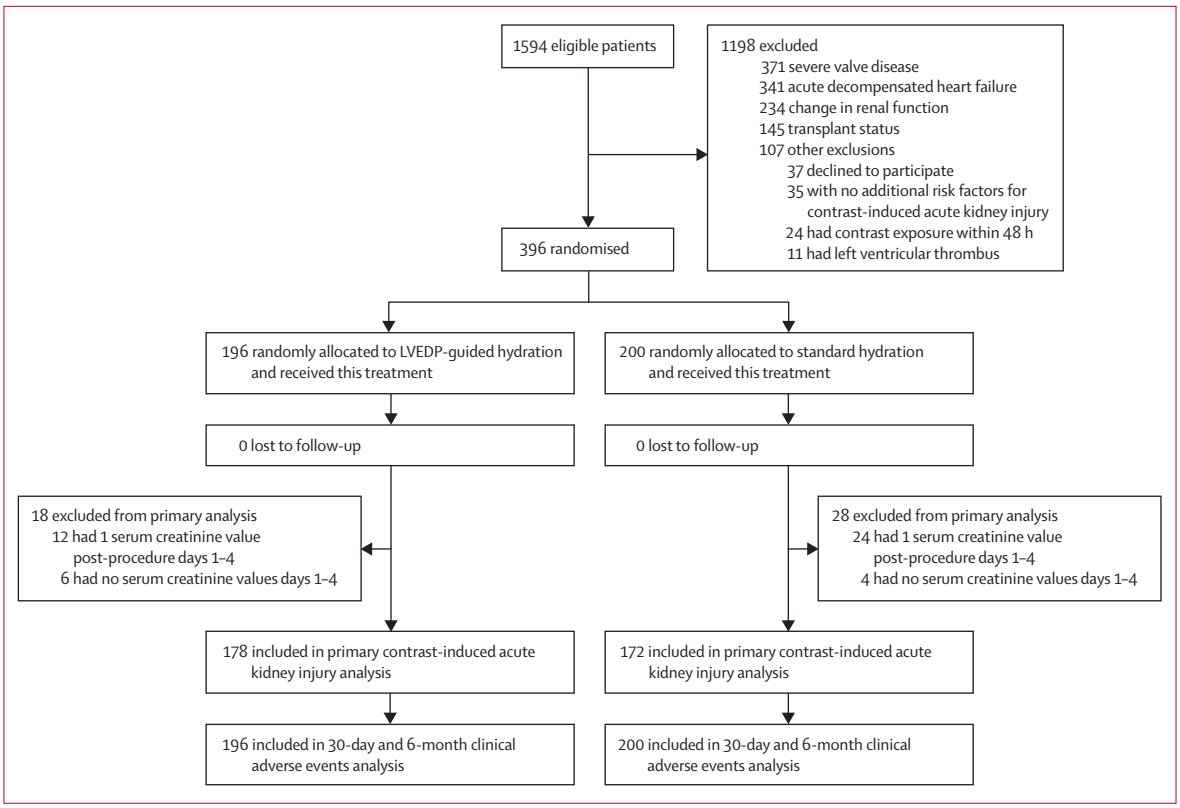

Figure 1: **Trial profile**
LVEDP=left ventricular end-diastolic pressure.

Outcomes

The primary endpoint of a greater than 25% or 0·5 mg/dL increase in the serum creatinine concentration was calculated with a baseline value obtained before the procedure and the highest post-procedure value on days 1–4 in patients with two or more post-procedure serum creatinine values. Secondary endpoints were components of the primary endpoint and the occurrence of major adverse events, with the latter defined as a composite of all-cause mortality, myocardial infarction, or renal replacement therapy, at 30 days and 6 months. Myocardial infarction was defined according to the European Society of Cardiology–American College of Cardiology Foundation–American Heart Association–World Heart Federation consensus document and excluded periprocedural events related to the index procedure.[11] The safety endpoints included clinical sequelae of fluid administration and left ventricular end-diastolic pressure measurement, such as pulmonary oedema or sustained ventricular arrhythmias. All adverse events were classified and confirmed by personnel who were masked to treatment assignment.

In post-hoc analyses, the rate of contrast-induced acute kidney injury, defined as an increase in serum creatinine concentration of 0·3 mg/dL or more, was calculated by treatment assignment. The frequency of persistent renal impairment, defined as a more than 15% increase in serum creatinine above baseline, was also assessed by treatment assignment and in patients with contrast-induced acute kidney injury. Serum creatinine samples were obtained 2–8 weeks after the index procedure and the first serum creatinine value during this period was used in analyses.

Statistical analysis

Continuous data are reported as mean (SD) or median (IQR), as appropriate. Categorical data are presented as absolute values and percentages. Continuous variables were compared with the Wilcoxon rank sum test, and the χ^2 or Fisher's exact test was used for categorical variables.

We compared the event rates of contrast-induced acute kidney injury for the left ventricular end-diastolic pressure-guided and control groups with Pearson's χ^2 test. We calculated the relative risk and absolute risk difference, and their 95% CIs, for the primary contrast-induced acute kidney injury endpoint and the secondary clinical composite adverse events endpoint. The inverse of the absolute risk difference yielded the number needed to treat to prevent one contrast-induced acute kidney injury event. We used logistic regression with interaction testing to assess whether the recorded treatment effect was consistent across prespecified subgroups. We

compared the occurrence of major adverse events with the Kaplan-Meier method and the log-rank test.

We studied the association between volume of fluid administered and the occurrence of contrast-induced acute kidney injury by dividing the study cohort into tertiles by volume of normal saline administered. We used logistic regression to calculate the odds ratio (and 95% CI) for total volume of normal saline administered for the contrast-induced acute kidney injury endpoint.

We designed this study to assess superiority of the left ventricular end-diastolic pressure-guided fluid administration strategy over the standard approach. We calculated the necessary sample size on the basis of previous trial data suggesting that 18% of the control group and 8% of the left ventricular end-diastolic pressure-guided treatment group would develop contrast-induced acute kidney injury.[5] We also estimated that 10% of patients would have fewer than two serum creatinine values post-procedure, based on previous contrast-induced acute kidney injury prevention trials enrolling both inpatients and outpatients undergoing cardiac procedures.[5,6] On the basis of these assumptions, a χ^2 analysis suggested that 390 patients would be needed to detect a statistically significant difference, with 80% power and a two-sided α of 0·05.

We did post-hoc sensitivity analyses to assess the significance of minor imbalances between the groups in baseline clinical and procedural characteristics, for which we used logistic regression for the contrast-induced acute kidney injury endpoint and the Cox proportional hazards model for major adverse events at 6 months. Candidate variables were known or suspected contrast-induced acute kidney injury prognostic factors. Logistic regression model goodness of fit was satisfied by the Hosmer-Lemeshow goodness of fit test, and log-log plots and Schoenfeld residuals confirmed that the proportionality assumption was satisfied for the Cox proportional hazards model.

Analyses were done with Stata version 12.0 and R version 2.15.3. All tests were two-tailed, with differences reported as significant if the p value was less than 0·05. The study was approved by the institutional review board of Kaiser Permanente Southern California; all consecutive, eligible patients provided written informed consent. This trial is registered with ClinicalTrials.gov, number NCT01218828.

Role of the funding source

The funder was not involved in the trial design, patient recruitment; data collection, analysis, interpretation, or presentation; writing or editing of the report; or the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 1594 eligible patients, 396 were enrolled and randomly assigned to the left ventricular end-diastolic pressure-guided treatment group (n=196) or the control group (n=200) (figure 1). All randomly assigned patients received their allocated treatment. Demographics, clinical, haemodynamic, and procedural characteristics

	LVEDP-guided hydration group (n=196)	Control group (n=200)
Age (years)*	71 (9)	72 (8)
Female sex	70 (36%)	81 (41%)
Race		
Black	27 (14%)	28 (14%)
Asian	28 (14%)	29 (15%)
Latino/Hispanic	17 (9%)	24 (12%)
White	111 (57%)	113 (57%)
Left ventricular end-diastolic pressure (mm Hg)	12 (7)	12 (7)
Left ventricular end-diastolic pressure category		
<13 mm Hg	113 (58%)	108 (54%)
13–18 mm Hg	52 (27%)	62 (31%)
>18 mm Hg	31 (16%)	30 (15%)
Renal function		
Estimated GFR (mL/min/1·73 m^2)	48 (9)	48 (9)
Serum creatinine concentration (mg/dL)	1·4 (0·4)	1·4 (0·3)
Blood pressure (mm Hg)		
Systolic	136 (20)	134 (21)
Diastolic	69 (12)	68 (13)
Weight (kg)	86 (20)	83 (18)
Height (cm)	169 (12)	170 (26)
BMI (kg/m^2)	30 (6)	29 (6)
Medical history		
Diabetes mellitus	102 (52%)	101 (51%)
Dyslipidaemia (use of statin therapy or LDL>160 mg/dL)	181 (92%)	190 (95%)
Congestive heart failure†	31 (16%)	50 (25%)
Hypertension	193 (99%)	195 (98%)
Previous percutaneous coronary intervention	79 (40%)	70 (35%)
Previous coronary artery bypass graft	38 (19%)	35 (18%)
Laboratory data		
Haemoglobin concencration (g/dL)	12·7 (1·8)	12·7 (2·1)
Platelets (×10^3/μL)	213 (67)	210 (66)
LDL concentration (mg/dL)	89 (38)	89 (33)
HDL concentration (mg/dL)	45 (12)	47 (13)
Haemoglobin A_{1c} (%)	7·2% (1·2%)	7·1% (1·4%)
Medications		
HMG-CoA reductase inhibitors	155 (79%)	146 (73%)
Aspirin	167 (85%)	168 (84%)
Insulin	48 (25%)	60 (30%)
N-acetylcysteine	75 (38%)	74 (37%)
Procedural details		
Contrast total (mL)	104 (84–187)	112 (79–209)
Procedure duration (min)	26 (18–48)	30 (17–54)
Fluoroscopy duration (min)	5·0 (2·6–11·4)	6·1 (2·5–11·4)
Percutaneous coronary intervention*	47 (24%)	65 (33%)
Acute coronary syndrome	77 (39%)	89 (45%)

Data are mean (SD), n (%), or median (IQR). LVEDP=left ventricular end-diastolic pressure. GFR=glomerular filtration rate. LDL=low-density lipoprotein. HDL=high-density lipoprotein. *p=0·05–0·10. †p=0·01–0·05.

Table 1: **Baseline characteristics of the study population**

were well balanced between the groups (table 1). The mean age of the cohort was 71 years, 38% were women, and 43% identified themselves as non-white. The prevalence of diabetes was 51% overall and was similar between groups. Participants randomly allocated to the control group were more likely to have a history of congestive heart failure and undergo percutaneous coronary intervention than were those in the left ventricular end-diastolic pressure-guided group. On post-contrast exposure days 1–4, at least one serum creatinine value was available for 98% (386/396) of participants and at least two values were available for 88% (350/396) of patients. 30-day and 6-month clinical follow-up was complete for all patients.

Baseline renal function and haemodynamic parameters were similar between groups. The mean (SD) estimated GFR was 48 (9) mL/min per 1·73 m² in both study groups. The mean left ventricular end-diastolic pressure was 12 (7) mm Hg with a range of 1–39 mm Hg and was similar between groups (p=0·29). The percentage of patients with a left ventricular end-diastolic pressure of 18 mm Hg or below was 85% (335/396) and those with a pressure higher than 18 mm Hg was 15% (61/396); the percentages were also similar between the groups (p=0·829). The total mean (SD) volume of normal saline administered was 1727 (583) mL in the left ventricular end-diastolic pressure-guided group versus 812 (142) mL in the control group (p<0·0001) (figure 2). Outpatient or ambulatory procedures were done in 58% (230/396) of the cohort and the rate was similar between groups (61% [119/196] in the left ventricular end-diastolic pressure-guided group and 56% [111/200] in the control group; p=0·29) .

The overall incidence of contrast-induced acute kidney injury was 11·4% (40/350)—it was 6·7% (12/178) in the left ventricular end-diastolic pressure-guided treatment group versus 16·3% (28/172) in the control group (p=0·005). The relative risk was 0·41 (95% CI 0·22–0·79)

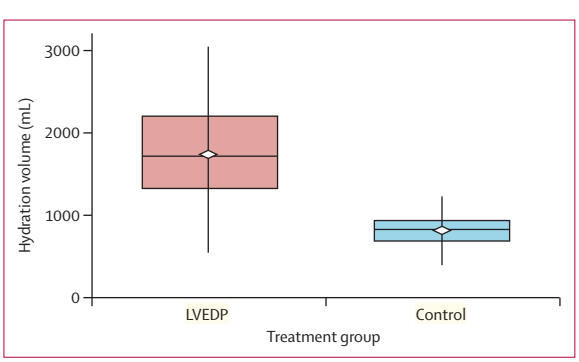

Figure 2: **Hydration volumes of normal saline administered in each group**
The box for each group represents the 25th percentile to the 75th percentile of the data (ie, the IQR). The line in the middle of the box indicates the median (50th percentile) of the data. The whiskers start from the edge of the box and extend to the furthest datapoint that is within 1·5-times the IQR. The diamonds represent the mean volume of fluid administered. LVEDP=left ventricular end-diastolic pressure.

and the absolute risk difference was –9·5% (–2·9 to –16·2%). The number needed to treat to prevent one contrast-induced acute kidney injury event with the left ventricular end-diastolic pressure-guided treatment was 11 patients. The results were qualitatively similar to other measures of contrast-induced acute kidney injury (table 2) and across prespecified patient subgroups (table 3). No significant interactions occurred between treatment assignment by subgroup (table 3). The results were also consistent in patients with more severe renal impairment. In participants with an estimated GFR of 45 mL/min per 1·73 m² or lower, the incidence of contrast-induced acute kidney injury with left ventricular end-diastolic pressure-guided treatment was 8% (5/60) compared with 23% (14/61) in the control group, and the corresponding relative risk was 0·36 (95% CI 0·14–0·95, p=0·03). The distribution of peak serum creatinine values on different days post-procedure was as follows: day 1, 16%; day 2, 42%; day 3, 34%; and day 4, 8%. The day on which the peak serum creatinine occurred (day 2) was the same in both study groups (p=0·98).

Patients who received larger volumes of normal saline had a lower rate of contrast-induced acute kidney injury than did those given smaller volumes. Per protocol, patients with a left ventricular end-diastolic pressure of 18 mm Hg or below in the treatment group received fluids at a higher rate than did those in the control group. In these patients, the rate of contrast-induced acute kidney injury was 5·3% (8/152) in the treatment group versus 14·4% (21/146) in the control group (relative risk 0·37, 95% CI 0·17–0·80; p=0·008). Moreover, the odds of contrast-induced acute kidney injury decreased by 9% for every additional 100 mL of normal saline administered (odds ratio 0·91, 95% CI 0·89–0·94; p=0·01). A graded association was also recorded: increasing volumes of fluid administered during the study period were associated with reduced rates of contrast-induced acute kidney injury. The full study cohort was divided into tertiles on the basis of the volume of isotonic saline received. The volume of fluid in each tertile was: tertile 1 448–874 mL, tertile 2 874–1512 mL, and tertile 3 1512–3055 mL. The corresponding rates of contrast-induced acute kidney injury were 17% (20/117) for tertile 1, 11% (13/117) for tertile 2, and and 6% (7/116) for tertile 3 (p=0·03).

Persistent renal impairment, based on serum creatinine measurements taken 2–8 weeks after the index procedure, was recorded in 3·4% (6/178) of patients in the left ventricular end-diastolic pressure-guided group and in 7·0% (12/172) of those in the control group; the corresponding relative risk was 0·48 (95% CI 0·19–1·26) and the risk difference was –3·6 (95% CI –8·2 to 1·0; p=0·13). Persistent renal impairment was recorded in 46% (18/39) of patients who developed contrast-induced acute kidney injury. One patient in the control group died before a follow-up serum creatinine could be measured. The frequency of

	LVEDP hydration-guided group	Control group	Relative risk (95% CI)	Risk difference (95% CI)	p value
Primary endpoint					
>25% or 0·5 mg/dL increase in serum creatinine	12/178 (6·7%)	28/172 (16·3%)	0·41 (0·22–0·79)	–9·5 (-2·9 to –16·2)	0·005
Secondary endpoints					
>25% increase in serum creatinine	12/178 (6·7%)	27/172 (15·7%)	0·43 (0·22–0·82)	–9·0 (–2·5 to –15·5)	0·008
>0·5 mg/dL increase in serum creatinine	5/178 (2·8%)	11/172 (6·4%)	0·44 (0·16–1·24)	–3·6 (–8·0 to 0·8)	0·11
Sensitivity analyses					
≥0·3 mg/dL increase in serum creatinine	24/178 (13·5%)	43/172 (25·0%)	0·54 (0·34–0·85)	–11·5 (–3·3 to –19·7)	0·006
>25% or 0·5 mg/dL increase in serum creatinine in participants with ≥1 serum creatinine value available	12/190 (6·3%)	28/196 (14·3%)	0·44 (0·23–0·84)	–8·0 (–2·0 to –14·0)	0·01

Data are n/N (%). LVEDP=left ventricular end-diastolic pressure.

Table 2: **Occurrence of contrast-induced acute kidney injury**

persistent renal impairment was similar between treatment groups—it was 50% (6/12) in the left-ventricular end-diastolic pressure group and 44% (12/27) in the control group (p=0·75).

We aimed to recruit 350 participants with at least two serum creatinine samples available post-procedure. Since we anticipated that 10% of participants would have less than two values, we recruited 396 patients to account for this rate of attrition.[5,6] The actual recorded attrition rate of 11·6% was similar to our estimate. In analyses of 98% of randomised patients in whom one or more serum creatinine measurements were available, we recorded no qualitative differences in the contrast-induced acute kidney injury event rate, relative risk, risk difference, or number needed to treat compared with the analyses that needed at least two serum creatinine values (table 2).

Table 4 shows the major adverse clinical events by treatment group. At 30 days, the rate of major adverse events was lower, although not significantly so, in the left ventricular end-diastolic pressure group. At 6 months, the composite major adverse event endpoint was reported in 3·1% (6/196) of patients in the left ventricular end-diastolic pressure-guided treatment group compared with 9·5% (19/200) in the control group; the corresponding relative risk was 0·32 (95% CI 0·13–0·79; p=0·008) (figure 3). All-cause mortality and myocardial infarction at 6 months were also significantly lower in the left ventricular end-diastolic pressure-guided treatment group than in the control group (table 4). The number needed to treat to prevent one major adverse event with the left ventricular end-diastolic pressure-guided treatment was 16 patients.

We also reported the rate of major adverse events by contrast-induced acute kidney injury status. In patients with contrast-induced acute kidney injury, the rate of major adverse events was 25% (10/40), whereas it was 3·5% (11/310) in patients without such injury. The corresponding relative risk for the composite major adverse event endpoint in patients with contrast-induced acute kidney injury was 7·1 (95% CI 3·2–15·5; p<0·0001). Patients who developed contrast-induced acute kidney injury had a higher rate of all-cause mortality (p=0·002), myocardial infarction (p=0·02), and need for renal replacement therapy (p=0·0002) than did those who did not develop kidney injury. Renal replacement therapy was needed only for patients who previously developed contrast-induced acute kidney injury after the index cardiac procedure.

	LVEDP hydration-guided group	Control group	Relative risk (95% CI)	p value for heterogeneity
Diabetes				0·19
No	1/87 (1·1%)	8/82 (9·8%)	0·12 (0·02–0·92)	..
Yes	11/91 (12·1%)	20/90 (22·2%)	0·54 (0·28–1·07)	..
Sex				0·53
Male	4/116 (3·4%)	11/101 (10·9%)	0·32 (0·10–0·96)	..
Female	8/62 (12·9%)	17/71 (23·9%)	0·54 (0·25–1·16)	..
N-acetylcysteine				0·63
User	4/66 (6·1%)	12/67 (17·9%)	0·34 (0·11–1·00)	..
Non-user	8/112 (7·1%)	16/105 (15.2%)	0·47 (0·21–1·05)	..
Contrast volume				0·73
>100 mL	8/94 (8·5%)	20/93 (21·5%)	0·40 (0·18–0·85)	..
≤100 mL	4/84 (4·8%)	8/79 (10·1%)	0·47 (0·15–1·50)	..

Data are n/N (%) unless otherwise indicated. LVEDP=left ventricular end-diastolic pressure.

Table 3: **Occurrence of contrast-induced acute kidney injury in prespecified patient subgroups**

In total, six patients (1·5%)—three in each group—terminated the intravenous fluids early, the reason for which was shortness of breath in all six patients. In these patients, the left ventricular end-diastolic pressure values in the guided treatment group were 3, 7, and 26 mm Hg, and those in the control group were 3, 23, and 31 mm Hg. One patient in each group received treatment with an intravenous diuretic. No cases of ventricular arrhythmias or other complications associated with left ventricular end-diastolic pressure measurements were reported.

We assessed the effect of minor imbalances in baseline characteristics and procedural variables with logistic regression for the contrast-induced acute kidney injury endpoint and Cox proportional hazards model for major adverse events at 6 months. The models included

	LVEDP-guided group (n=196)	Control group (n=200)	Relative risk (95% CI)	Risk difference (95% CI)	p value
At 30 days					
All-cause mortality	0	3 (1·5%)	..	..	0·25
Myocardial infarction	1 (0·5%)	4 (2·0%)	..	..	0·37
Renal replacement therapy	1 (0·5%)	3 (1·5%)	..	..	0·62
Cumulative major adverse events	2 (1·0%)	8 (4·0%)	0·26 (0·05–1·19)	–3·0 (–6·0 to 0·1)	0·11
At 6 months					
All-cause mortality	1 (0·5%)	8 (4·0%)	..	..	0·037
Myocardial infarction	4 (2·0%)	13 (6·5%)	..	..	0·029
Renal replacement therapy	1 (0·5%)	4 (2·0%)	..	..	0·37
Cumulative major adverse events	6 (3·1%)	19 (9·5%)	0·32 (0·13–0·79)	–6·4 (–11·2 to –1·7)	0·008

Data are n (%). LVEDP=left ventricular end-diastolic pressure.

Table 4: **Major adverse events at 30 days and 6 months**

prognostic factors that were judged to have a potential clinically meaningful baseline imbalance between the treatment groups. Binary variables included were history of congestive heart failure and percutaneous coronary intervention status when the absolute difference between groups was greater than 5%. Both factors selected have been associated with the development of contrast-induced acute kidney injury in either observational studies or risk prediction models.[1,2,12,13] The odds ratio for contrast-induced acute kidney injury without the imbalance variables was 0·37 (95% CI 0·18–0·74) and that with the imbalance variables was 0·40 (0·19–0·81). Similarly, the hazard ratio for 6-month major adverse events without the imbalance covariates was 0·31 (95% CI 0·13–0·78) and that with the imbalance covariates was 0·35 (0·14–0·89). Thus, the minor imbalances between treatment groups do not have a meaningful effect on the results. We investigated the effect of a dilutional effect of volume expansion on serum creatinine measurement and showed it to be negligible. Improvement in serum creatinine of 20% or more post-contrast exposure was 3·0% (6/178) in the left ventricular end-diastolic pressure group and 0·6% (1/172) in the control group (p=0·12).

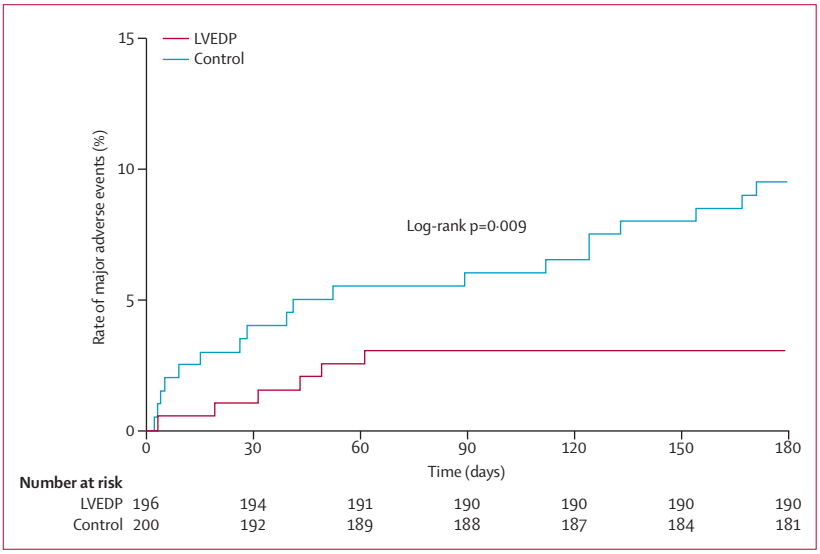

Figure 3: **Rate of major adverse events in each group**
The graph shows the 6-month rate of major adverse events, defined as a composite of all-cause mortality, myocardial infarction, or dialysis. LVEDP=left ventricular end-diastolic pressure.

Discussion

Our study is the first randomised trial to compare different rates of volume expansion with normal saline for the prevention of contrast-induced acute kidney injury in both the treatment and control groups (panel). The rate of fluid administration in the treatment group was guided by the left ventricular end-diastolic pressure, a haemodynamic parameter that can be used to establish intravascular volume status. The main findings of the POSEIDON trial were that in patients with stable renal insufficiency undergoing cardiac catheterisation and who were followed up for 6 months post-procedure, left ventricular end-diastolic pressure-guided fluid administration as compared with standard treatment resulted in a significant 68% relative reduction (a 9·5% absolute reduction) in the primary endpoint of contrast-induced acute kidney injury, and a significant 59% relative reduction (a 6·4% absolute reduction) in major adverse clinical events.

Haemodynamic data are obtained in various clinical settings to assess volume status and guide medical therapy, including the administration of intravenous fluids.[15–20] Without these data, assessment of a patient's intravascular volume status, and thus their ability to tolerate high rates of fluid administration, is difficult. The left ventricular end-diastolic pressure-guided fluid administration protocol provides a framework for targeted intravascular volume expansion. Through linkage of the rate of fluid administration to the left ventricular end-diastolic pressure, the treatment group was able to receive roughly twice the volume of normal saline with a similar rate of fluid termination than the control group. Furthermore, the left ventricular

end-diastolic pressure was assessed safely in all patients. The sustained administration of normal saline at 3 or 5 mL/ kg per h for at least 5 h are the highest hydration rates studied in a contrast-induced acute kidney injury prevention trial so far. Thus, despite more aggressive volume expansion with left ventricular end-diastolic pressure-guided therapy than with standard hydration treatment, intravenous fluids were terminated at a similarly low rate in both study groups, which suggests that higher rates can be tolerated.

The mechanisms underlying these favourable treatment effects are probably multifactorial. Volume expansion with normal saline might reduce contrast-mediated injury by expanding plasma volume, reducing renin activation and loss of nitric oxide, reducing production of reactive oxygen species, and through dilution of contrast within the tubular lumen.[21,22] The consequent decrease in renin and vasopressin might increase urine flow rates that can reduce the contrast medium concentration in tubular fluid. In an animal model, hydration lessened the rise in urine viscosity due to contrast medium, which speeds up excretion of contrast medium and leads to preservation of renal function.[23] Because of the exponential concentration–viscosity association, we postulate that more rapid rates of fluid administration could further attenuate the rise in urine viscosity due to contrast administration, helping contrast excretion and shortening the period of exposure of tubular cells to contrast media.[24] In support of this idea, we noted that the volume of fluid administered was significantly associated with the development of contrast-induced acute kidney injury.

The preservation of renal function with left ventricular end-diastolic pressure-guided therapy had a beneficial effect on clinical outcomes, as shown by the significant reduction in the 6-month composite major adverse events, including a significant decrease in rates of death and myocardial infarction compared with the control group. Furthermore, patients who developed contrast-induced acute kidney injury had a sevenfold increase in the rate of the composite major adverse events endpoint, and a significant increase in each of the components including death, myocardial infarction, and renal replacement therapy. All patients with new-onset dialysis during the follow-up period had previously developed contrast-induced acute kidney injury after the index procedure. Our results are consistent with previous reports that showed an association between contrast-induced acute kidney injury after coronary angiography or percutaneous coronary intervention and increases in mortality and myocardial infarction.[1,3,13,25] The rate of major adverse events was lower in the left ventricular end-diastolic pressure group than in the control group at 30 days, although this difference was not significant. Some studies suggest that episodes of acute kidney injury might further accelerate the rate of decline in kidney function, which could increase the long-term risks of major adverse events following coronary angiography.[26] This increase in risk could partly explain the continued accrual of more major adverse events in the control group than in the left ventricular end-diastolic pressure-guided therapy group beyond 30 days. These findings emphasise the importance of longer term follow-up in contrast-induced acute kidney injury prevention trials.

As noted in current guidelines, no clear evidence exists to guide the choice of optimum rate or duration

***Panel:* Research in context**

Systematic review

We searched PubMed on March 31, 2014, with combinations of the medical subject heading (MeSH) search terms "contrast media" and "fluid therapy" and the keywords "saline", "hydration", "coronary angiography", "percutaneous coronary intervention", "end diastolic", and "LVEDP." We searched for reports published in English with no date restrictions to identify randomised trials that compared fluid administration with normal saline at either different rates or durations in patients at risk for contrast-induced acute kidney injury. We did not identify any randomised studies meeting these criteria. Our search yielded one study comparing a single 300 mL bolus of normal saline versus a 24-h infusion period in 39 participants with normal renal function.[14]

Interpretation

Despite being a frequently recommended treatment, little remains known regarding the best possible rate and duration of normal saline administration for the prevention of contrast-induced acute kidney injury. Substantial emphasis has been placed on pharmacological interventions to prevent contrast-induced acute kidney injury, despite the widespread recognition of the importance of intravascular volume expansion and paucity of clinical trial data to guide peri-procedural fluid administration. The POSEIDON trial is the first randomised trial to directly compare different normal saline fluid administration protocols and to use the left ventricular end-diastolic pressure, a measure of intravascular volume status, to further personalise treatment. The sustained administration of normal saline of up to 5 mL/kg per h in some patients, guided by the left ventricular end-diastolic pressure, represents the highest rates studied in a contrast-induced acute kidney injury prevention trial so far. Left ventricular end-diastolic pressure-guided intravenous fluid administration significantly reduced the rates of contrast-induced acute kidney injury and major adverse clinical events at 6 months after cardiac catheterisation. The results were consistent across various definitions of contrast-induced acute kidney injury and in sensitivity analyses. The left ventricular end-diastolic pressure-guided strategy is a practical protocol that can be readily integrated into existing patterns of care, is not expensive, does not require prolonged hospital stay, and the findings are applicable to patients undergoing either ambulatory or hospital-based cardiac catheterisation.

of volume expansion with normal saline.[8] So far, no randomised trial has directly compared different durations or rates of volume expansion using normal saline in both treatment groups. In the absence of appropriately designed randomised trials, strategies of fluid administration have had substantial controversy and variability. For example, some advocate for 36 h of peri-procedural administration of isotonic saline, albeit at lower rates.[27] Studies cited in support of this recommendation did not compare longer versus shorter hydration periods with isotonic saline but compared a combination of different fluid types, durations, and rates of fluid administration, and adjunctive pharmacological interventions to prevent contrast-induced acute kidney injury and yielded conflicting results.[5,28–30] Although longer durations of volume expansion with normal saline might be more effective in some patients, this idea needs further validation in future trials. Moreover, a prolonged hydration period of 36 h can be logistically difficult to implement.[27] In the present study, more than 50% of the patients underwent ambulatory procedures for whom a total hydration period of 36 h would have necessitated admission to hospital both pre-procedure and post-procedure, leading to increased costs.

In recent contrast-induced acute kidney injury trials, investigators have increasingly selected durations of fluid administration that are suitable for a broad group of patients and can be integrated into existing workflows. At least 15 such trials have administered intravenous fluids of differing types at 1–1·5 mL/kg per h, started at least 1 h before and continued for 3–6 h after contrast administration—a regimen similar to that used in the control group of our study.[31,32] Similarly, we sought to develop a fluid administration protocol that is generalisable to ambulatory and hospital-based procedures, and that is practical, feasible, and can be readily integrated into existing patterns of care.

The study population was at a moderate to high risk of contrast-induced acute kidney injury since all patients had an estimated GFR 60 mL/min per 1·73 m² or less and one additional contrast-induced acute kidney injury risk factor, the prevalence of hypertension was 98%, and 51% of participants had diabetes. The recorded rate of contrast-induced acute kidney injury in the control group was similar to the expected rate and to results from previous trials with similar at-risk patients.[5,33,34] Hence, differences in outcomes between study groups are probably due to more aggressive volume expansion with left ventricular end-diastolic pressure-guided treatment and the resultant reduction in the contrast-induced acute kidney injury rate, rather than a greater than expected event rate in the control group.

Although there were minor imbalances between treatment groups, these did not have a notable effect on the contrast-induced acute kidney injury or 6-month major adverse events endpoints. The results that took these imbalances into consideration were qualitatively similar to the primary results. We also assessed the effect of missing serum creatinine values. In participants with at least one or at least two serum creatinine samples, the event rates, measures of association (relative risk or risk difference), and number needed to treat were similar. If we restricted the study population to patients who were admitted to hospital, this approach would have minimised the frequency of missing serum creatinine values. However, it would have also limited the generalisability of the trial by excluding the many patients who undergo elective or ambulatory procedures.

Our study does have some important limitations that we should discuss. The strategy of more aggressive volume expansion is not suitable for all patients, especially those with acute decompensated heart failure or severe valvular heart disease; such patients were excluded from our trial. Preventive strategies for these groups remain scarce. Although left ventricular end-diastolic pressure provides a safe and accurate assessment of intravascular volume status, it is only available in patients undergoing cardiac catheterisation. A reliable non-invasive measure of intravascular volume status could allow for more aggressive volume expansion in patients in whom left ventricular end-diastolic pressure is not routinely measured and could also allow for the initiation of fluids at a higher rate before contrast administration. Further research is needed in this promising area. Our study was partly blinded, but physicians undertaking the procedures could have established the fluid rate and thus the patient's randomisation. However, this situation is unlikely to have biased results since the procedure duration, fluoroscopy time, and contrast volumes were similar between groups. Additionally, the laboratory personnel processing the samples were masked to the patient's treatment assignment and the clinical endpoints were adjudicated by personnel who were masked to treatment assignment.

In conclusion, the results of this study suggest that intravenous administration of normal saline, guided by the left ventricular end-diastolic pressure, is well tolerated and could substantially reduce the incidence of contrast-induced acute kidney injury and major adverse clinical events in patients undergoing cardiac catheterisation.

Contributors

SSB had full access to the data and takes responsibility for the integrity of the data and accuracy of the analysis. SSB came up with the study concept, designed and supervised the study, and secured funding. SSB, MJ, VA, PM, NM, and AY-JS developed the study protocol. LS, KK, AY-JS, AD, and NM gathered the data. SSB, PM, VA, AY-JS, NM, LS, KK, and AD analysed and interpreted the data. SSB, PM, AY-JS, and NM drafted the report. SSB, PM, VA, AY-JS, NM, MJ, LS, KK, and AD critically revised the report. SSB, AY-JS, PM, and AD did the statistical analyses. SSB, PM, VA, AY-JS, NM, LS, KK, and AD provided administrative, technical, and material support.

Declaration of interests

We declare no competing interests.

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