jraas

Journal of the Renin-Angiotensin-Aldosterone System
April-June 2017: 1–8

DOI: 10.1177/1470320317708894
journals.sagepub.com/home/jra
SAGE

Intensity of hydration changes the role of renin–angiotensin–aldosterone system blockers in contrast-induced nephropathy risk after coronary catheterisation in patients with chronic kidney disease

Xiao-sheng Guo[1], Deng-xuan Wu[2], Wei-jie Bei[1], Hua-long Li[1], Kun Wang[3], Ying-ling Zhou[1], Chong-yang Duan[4], Shi-qun Chen[1], Dan Lian[1], Li-wen Li[1], Yong Liu[1], Ning Tan[1] and Ji-yan Chen[1]

Abstract

Objective: This study evaluated the potential effect of hydration intensity on the role of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) on contrast-induced nephropathy in patients with renal insufficiency.
Methods: All eligible patients were included and stratified according to hydration intensity defined as saline hydration volume to body weight tertiles: <10.21 mL/kg, 10.21 to <17.86 mL/kg, and ⩾17.86 mL/kg.
Results: In total, 84 (6.7%) of 1254 patients developed contrast-induced nephropathy: 6.2% in the ACEI/ARB group versus 10.8% in the non-ACEI/ARB group (P=0.029), with an adjusted odds ratio (OR) of 0.89 (95% confidence interval (CI) 0.46–1.73, P=0.735). The incidence of contrast-induced nephropathy was lower in the ACEI/ARB group than in the non-ACEI/ARB group in the second tertile (P=0.031), while not significantly different in the first (P=0.701) and third (P=0.254) tertiles. ACEIs/ARBs were independently associated with a lower contrast-induced nephropathy risk (OR 0.26, 95% CI 0.09–0.74, P=0.012) and long-term all-cause death (hazard ratio 0.461, 95% CI 0.282–0.755, P=0.002) only in the second hydration volume to body weight tertile.
Conclusion: The effects of ACEIs/ARBs on contrast-induced nephropathy risk vary according to saline hydration intensity in chronic kidney disease patients, and may further reduce contrast-induced nephropathy risk in patients administered moderate saline hydration.

Keywords

Contrast-induced nephropathy, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, saline hydration, coronary catheterisation

Date received: 31 December 2016; accepted: 13 April 2017

Introduction

Contrast-induced nephropathy (CIN) is a common complication after coronary catheterization, with an incidence of as high as 20–40% in patients with renal insufficiency, and is associated with increased in-hospital and long-term clinical outcome, as well as prolonged hospital stay and raised healthcare costs.[1–3] Avoiding the use of nephrotoxic drugs is one of the most fundamental preventive strategies for CIN.

It is a common practice in many centres to prescribe angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for patients with coronary artery disease before and after coronary

[1]Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China
[2]Department of Cardiology, Panzhihua Central Hospital, China
[3]Department of Graduate School, Southern Medical University, China
[4]Department of Biostatistics, Southern Medical University, China

The first two authors are the joint first authors of this work.

Corresponding author:
Ji-yan Chen, Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, 510100, China.
Email: chenjiyandr@126.com

angiography because it reduces morbidity and mortality rates in the long term.[4,5] But the role of the periprocedural use of ACEIs/ARBs on preventing CIN remains controversial, as the available literature is conflicting and inconclusive. Bainey et al. found that ACEIs/ARBs demonstrated a reduction of the post-procedural rise of creatinine in patients with moderate renal insufficiency undergoing cardiac catheterisation, although not reducing the rate of CIN.[6] The European Society of Cardiology guidelines on myocardial revascularisation have recommended optimal medical therapy including ACEIs as a preventive strategy of CIN for chronic kidney disease (CKD) patients (class I, level A).[7] On the other hand, some studies have revealed neither beneficial nor adverse effects with the use of these drugs prior to contrast administration in patients with and without CKD.[8–10] Moreover, a meta-analysis even showed that discontinuation of ACEIs/ARBs could reduce the incidence of CIN.[11] Thus, paradoxical opinions exist among clinicians as to whether the administration of ACEIs/ARBs should be discontinued prior to coronary catheterisation, especially in patients with reduced renal function. The varying conclusions might be because of differences in characteristics of study populations and interventions in studies. Similar to ACEIs/ARBs, the protective effect of saline hydration on CIN has been partly attributed to the inhibition of the renin–angiotensin–aldosterone system (RAAS).[12] We hypothesised that saline hydration may further influence the circulatory volume and the renal blood flow after the administration of ACEIs/ARBs, thus affecting the development of CIN.

Previous studies did not analyse the effect of ACEIs/ARBs under various doses of saline hydration. Therefore, we conducted this study to evaluate the potential effect of hydration intensity on the role of ACEIs/ARBs on the risk of CIN in patients with CKD.

Methods

Subjects

All eligible patients in the Predictive Value of Contrast Volume to Creatinine Clearance Ratio (PRECOMIN, ClinicalTrials.gov NCT01400295) study were included in the present analysis. In this prospective observational study, the data were reviewed of all consecutive patients who had undergone coronary catheterisation between January 2010 and October 2012, at the Guangdong Cardiovascular Institute of the Guangdong Academy of Medical Sciences, Guangdong General Hospital. The eligibility criteria were patients 18 years or older, creatinine clearance rate (CrCl) between 15 mL/minute and 60 mL/minute, and agreement to stay in the hospital for at least 2 days after coronary catheterisation. The exclusion criteria included pregnancy, lactation, contrast medium (CM) or ACEI/ARB allergy, renal artery stenosis, hyperkalemia, systolic blood pressure (SBP) less than 90 mmHg, renal replacement, CM exposure within 7 days before or 3 days after the procedure, cardiovascular surgery, malignancy, and no isotonic saline for hydration. Finally, 1254 patients were included in the analyses. The institutional study protocol was approved by the Guangdong General Hospital ethics committee. Written informed consent was obtained from all patients before the procedure.

Procedures and hydration

Coronary catheterisation was performed by experienced interventional cardiologists according to standard clinical practice via the femoral or radial approach, using standard devices. All patients received non-ionic, low-osmolarity contrast agents (either iopamiron or iopromide, both 370 mg I/mL). The contrast dose was based on the need for the procedure. Pharmacotherapy and behavioural interventions were administered at the discretion of the clinicians according to the clinical practice guidelines. Isotonic saline hydration was performed at the rate of 1 mL/kg per hour (0.5 mL/kg per hour in the case of left ventricular ejection fraction (LVEF) <40% or severe congestive heart failure) for at least 2–12 hours before and 6–24 hours after the procedure.[2] Serum creatinine (SCr) concentrations were measured in all patients at admission and on days 1, 2 and 3 after the procedure. CrCl was calculated using the Cockcroft–Gault formula. The hydration volume of isotonic saline 12 hours before and 24 hours after the procedure was recorded, and the hydration volume-to-weight (HV/W) ratio was calculated to indicate the adjusted intensity of hydration. Patients were stratified into low, moderate and high hydration groups according to tertiles of baseline HV/W: <10.21 mL/kg, 10.21 to <17.86 mL/kg, and ⩾17.86 mL/kg.

Endpoints

The primary endpoint was the occurrence of CIN, defined as an absolute increase in SCr by 0.5 mg/dL or greater (44.8 mmol/L) from the baseline value within 48–72 hours after CM exposure. Other endpoints were: in-hospital all-cause death; combined major adverse clinical events (MACEs) including all-cause death, non-fatal recurrent myocardial infarction, target vessel revascularisation, acute heart failure, arrhythmia, stroke and renal replacement therapy.

Statistical analysis

All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC, USA), and statistical significance was considered if the P value was less than 0.05 (two-tailed). Continuous variables are described as means ± standard

deviation or median (if not normally distributed), while categorical variables are presented as absolute values (percentages). To identify differences in baseline characteristics between the ACEI/ARB and non-ACEI/ARB groups, Student's *t*-test or the Wilcoxon rank sum test were used for continuous variables, and the Pearson chi-square test or Fisher's exact test were applied for categorical variables, as appropriate. The association between ACEI/ARB treatment and CIN occurrence was assessed by using logistic regression analysis after adjusting for potential confounding variables; the variables included either exhibited a statistically significant difference from baseline or were considered to have an important effect on the endpoints based on findings from clinical practice or previous studies. The in-hospital and long-term clinical outcomes between groups were compared using the log-rank test and Kaplan–Meier survival method. Cox regression analysis was conducted to determine the risk factors for follow-up death and MACEs and to determine the relationship between the accumulated risk of adverse events and the periprocedural administration of ACEIs/ARBs.

Results

Of the 1254 consecutive CKD patients (mean CrCl, 45.1±10.5ml/min), 1094 were treated with ACEIs/ARBs during the periprocedural period and the other 160 were non-users. Compared to the non-ACEI/ARB group, the ACEI/ARB group in the first tertile (HV/W <10.21 mL/kg, 375 patients) had a higher body weight (61.2±8.5 kg vs. 58.0±5.5 kg, P=0.001), LVEF (58.3±12.8% vs. 52.5±14.4%, P=0.012), contrast volume (129.1±66.3 ml vs. 93.3±52.6 ml, P<0.001), and lower HV/W ratio (8.2±1.4 vs. 8.5±0.7 ml/kg, P=0.019), and a greater proportion had hypertension (67.7% vs. 51.2%, P=0.03). The ACEI/ARB group in the second tertile (10.21≤ HV/W <17.86 mL/kg, 369 patients) had fewer patients older than 75 years (7.3% vs. 9.3%, P=0.017), higher SBP (132.1±21.9 mmHg vs. 121.7±22.4 mmHg, P=0.001), and diastolic blood pressure (DBP, 75.0±12.0 mmHg vs. 69.8±10.6 mmHg, P=0.003), and a lower proportion of patients had anaemia (43.8% vs. 61.5%, P=0.017). The ACEI/ARB group in the third tertile (HV/W ⩾17.86 mL/kg, 350 patients) had higher SBP (132.1±21.0 mmHg vs. 114.0±26.5 mmHg, P<0.001) and DBP (74.5±10.7 mmHg vs. 65.0±15.3 mmHg, P<0.001) and a lower Mehran risk score (8.0±4.7 vs. 11.0±6.6, P<0.001), HV/W ratio (26.4±8.6 mL/kg vs. 32.1±17.3 mL/kg, P=0.012), baseline SCr (113.6±38.4 vs. 142.3±69.7, P=0.002), and proportion of CrCl <30 mL/minute (14.6% vs. 36.5%, P<0.001) and incidence of chronic heart failure (CHF) (24.6% vs. 41.3%, P=0.006). The other demographic, laboratory and procedural characteristics, such as gender, triglyceride, uric acid and stent number, were similar between the two groups for all tertiles (Table 1).

Overall, 6.2% (67/1094) patients developed CIN in the ACEI/ARB group and 10.8% (17/160) in the non-ACEI/ARB group, respectively. The incidences of CIN were significantly lower in patients treated with periprocedural ACEIs/ARBs than non-users (6.2% vs. 10.8%, P=0.029). Similar results were also obtained for the rates of in-hospital death (2.9% vs. 7.5%, P=0.003) and arrhythmia (6.0% vs. 11.9%, P=0.005). However, there were no significant differences between the two groups in the rates of MACEs (11.1% vs. 16.3%, P=0.057) and other in-hospital adverse events such as renal replacement therapy (1.4% vs. 3.1%, P=0.098; Table 2).

Multivariate logistic regression analysis indicated that periprocedural ACEI/ARB administration had no significant effect on the risk of CIN (odds ratio (OR) 0.89, 95% confidence interval (CI) 0.46–1.73, P=0.735) after adjusting for potential confounding risk factors (age >75 years, CrCl <30 mL/minute, CHF, contrast volume, anaemia, SBP, DBP and HV/W). Age greater than 75 years (P=0.045), CrCl less than 30 mL/minute (P<0.001) and CHF (P<0.001), and contrast volume (P=0.021) were risk factors for CIN occurrence in this population (Table 3).

The periprocedural administration of ACEIs/ARBs significantly reduced the incidence of CIN in the second tertile (5.44% vs. 13.21%, P=0.031). In addition, the incidence of CIN in patients treated with periprocedural ACEIs/ARBs compared to that of non-users was not significantly different in the first tertile (3.51% vs. 2.38%, P=0.701) and in the third tertile (9.7% vs. 14.75%, P=0.254; Figure 1).

Consistent with the results mentioned above, multivariate logistic regression analysis revealed that the periprocedural administration of ACEIs/ARBs significantly reduced the risk of CIN after coronary catheterisation in CKD patients only in the second tertile after adjusting for age greater than 75 years, CrCl less than 30 mL/minute, CHF, contrast volume, anaemia, SBP, DBP and HV/W ratio (OR 0.26, 95% CI 0.09–0.74, P=0.012; Figure 2).

The median follow-up period was 2.59 years (interquartile range 1.84–3.44 years) and was continued for all patients who survived until discharge. Patients treated with periprocedural ACEIs/ARBs demonstrated a lower incidence of all-cause death in the second tertile (14.5% vs. 26.2%, P=0.043) and MACEs in the first (6.8% vs. 16.7%, P=0.027) and second tertiles (15.2% vs. 28.6%, P=0.023; Figure 3).

On multivariable Cox proportional hazard regression analysis, periprocedural ACEI/ARB administration significantly reduced the risk of death (hazard ratio (HR) 0.426, 95% CI 0.207–0.877, P=0.02) and MACEs (HR 0.43, 95% CI 0.216–0.856, P=0.016) only in the second tertile after adjusting for age greater than 75 years, DM, CrCl, CHF, SBP and HV/W ratio. In addition, age greater than 75 years, DM and CrCl were independent risk factors for long-term death and MACEs after coronary catheterisation in the second HV/W tertile (Figure 4).

Table 1. Baseline characteristics of the ACEI/ARB group and non-ACEI/ARB group in HV/W tertiles.

	Total (*n*=1254)	1st Tertile (<10.21 ml/kg)			2nd Tertile (10.21 to <17.86 ml/kg)			3rd Tertile (⩾17.86 ml/kg)		
		ACEI/ARB (*n*=375)	No ACEI/ ARB (*n*=43)	*P* value	ACEI/ARB (*n*=369)	No ACEI/ ARB (*n*=54)	*P* value	ACEI/ARB (*n*=350)	No ACEI/ ARB (*n*=63)	*P* value
Demographics										
Age, years	71.1 ± 8.0	69.9 ± 7.7	67.4 ± 9.8	0.113	71.2 ± 7.8	73.4 ± 8.1	0.053	72.2 ± 8.1	71.7 ± 8.0	0.648
Age >75 years	385 (30.7%)	82 (21.9%)	9 (20.9%)	0.888	27 (7.3%)	5 (9.3%)	0.017	128 (36.6%)	23 (36.5%)	0.992
Female, %	374 (29.8%)	102 (27.2%)	12 (27.9%)	0.921	101 (27.4%)	15 (27.8%)	0.950	122 (34.9%)	22 (34.9%)	0.992
Smoking	393 (31.3%)	113 (30.1%)	14 (32.6%)	0.743	126 (34.1%)	15 (27.8%)	0.354	105 (30.0%)	20 (31.7%)	0.781
Weight, kg	59.2 ± 9.4	61.2 ± 8.5	58.0 ± 5.5	0.001	60.2 ± 9.9	58.3 ± 9.3	0.188	56.8 ± 9.6	57.1 ± 8.8	0.801
SBP at admission, mmHg	130.9 ± 22.6	133.1 ± 22.2	128.8 ± 26.10	0.239	132.1 ± 21.9	121.7 ± 22.4	0.001	132.1 ± 21.0	114.0 ± 26.5	<.001
DBP at admission, mmHg	74.1 ± 11.9	74.9 ± 11.6	74.6 ± 12.8	0.901	75.0 ± 12.0	69.8 ± 10.6	0.003	74.5 ± 10.7	65.0 ± 15.3	<.001
Mehran score	7.3 ± 4.8	6.0 ± 4.1	6.3 ± 4.0	0.645	7.3 ± 4.7	8.4 ± 4.0	0.099	8.0 ± 4.7	11.0 ± 6.6	<.001
Medical history										
Hypertension, %	844 (67.3%)	254 (67.7%)	22 (51.2%)	0.030	249 (67.5%)	30 (55.6%)	0.084	250 (71.4%)	39 (61.9%)	0.129
CHF, %	294 (23.5%)	64 (17.1%)	10 (23.8%)	0.282	92 (25.0%)	16 (29.6%)	0.467	86 (24.6%)	26 (41.3%)	0.006
Diabetes mellitus, %	331 (26.4%)	94 (25.1%)	8 (18.6%)	0.346	104 (28.2%)	13 (24.1%)	0.528	94 (26.9%)	18 (28.6%)	0.778
Anaemia, %	594 (47.9%)	161 (43.4%)	22 (53.7%)	0.209	160 (43.8%)	32 (61.5%)	0.017	181 (52.0%)	38 (61.3%)	0.177
Hyperlipidaemia, %	137 (10.9%)	48 (12.8%)	5 (11.6%)	0.827	31 (8.4%)	6 (11.1%)	0.510	39 (11.1%)	8 (12.7%)	0.720
Laboratory variables										
Serum creatinine, mmol/L	112.8 ± 39.8	107.5 ± 30.8	107.1 ± 27.4	0.936	113.1 ± 41.4	112.2 ± 39.8	0.874	113.6 ± 38.4	142.3 ± 69.7	0.002
CrCl <30 mL/min	126 (10.0%)	17 (4.5%)	3 (7.0%)	0.477	27 (7.3%)	5 (9.3%)	0.614	51 (14.6%)	23 (36.5%)	<.001
log (NT-proBNP)	6.6 ± 1.8	6.2 ± 1.8	6.7 ± 1.8	0.160	6.7 ± 1.7	6.5 ± 2.2	0.572	6.9 ± 1.7	6.7 ± 1.6	0.472
LVEF, %	55.9 ± 13.1	58.3 ± 12.8	52.5 ± 14.4	0.012	55.7 ± 13.6	55.2 ± 11.8	0.803	54.0 ± 12.7	56.6 ± 11.9	0.158
Haematocrit, %	37.0 ± 5.0	40.0 ± 4.0	37.0 ± 5.0	0.090	38.0 ± 5.0	36.0 ± 5.0	0.148	37.0 ± 5.0	36.0 ± 6.0	0.145
HbA1c, %	6.6 ± 1.3	6.6 ± 1.5	6.4 ± 1.1	0.463	6.5 ± 1.2	6.8 ± 1.5	0.344	6.5 ± 1.3	6.5 ± 1.1	0.744
TC, mmol/L	4.3 ± 1.0	4.3 ± 1.0	4.6 ± 1.3	0.236	4.2 ± 1.0	4.2 ± 1.2	0.991	4.4 ± 1.0	4.5 ± 1.0	0.673
TG, mmol/L	1.4 ± 0.9	1.4 ± 0.8	1.6 ± 1.5	0.455	1.2 ± 0.6	1.3 ± 0.5	0.348	1.4 ± 1.2	1.6 ± 1.4	0.634
UA, μmol/L	404.9 ± 129.8	408.1 ± 107.0	406.7 ± 104.1	0.943	398.1 ± 141.0	382.4 ± 109.0	0.500	406.2 ± 138.3	437.9 ± 160.7	0.162
Procedural characteristics										
Contrast volume, mL	131.5 ± 65.9	129.1 ± 66.3	93.3 ± 52.6	<.001	132.7 ± 66.5	123.2 ± 62.5	0.324	140.2 ± 64.8	124.2 ± 66.7	0.074
Stent number	1.8 ± 3.2	2.0 ± 5.6	1.4 ± 1.2	0.075	1.7 ± 1.3	1.8 ± 1.2	0.411	1.7 ± 1.3	1.5 ± 1.1	0.267
HV/W, mL/kg	16.6 ± 10.1	8.2 ± 1.4	8.5 ± 0.7	0.019	14.2 ± 2.2	14.5 ± 2.3	0.372	26.4 ± 8.6	32.1 ± 17.3	0.012

Values are presented as means ± standard deviation or *n* (%).

ACEI/ARB: angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; CHF: chronic heart failure; CrCl: creatinine clearance; DBP: diastolic blood pressure; HbA1c: haemoglobin A1c; HV/W: hydration volume-to-weight ratio; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride; UA: uric acid.

Table 2. In-hospital events of the ACEI/ARB group and the non-ACEI/ARB group.

Variables	ACEI/ARB (*n*=1094)	No ACEI/ARB (*n*=160)	*P* value
CIN	67 (6.2%)	17 (10.8%)	0.029
Death	32 (2.9%)	12 (7.5%)	0.003
Renal replacement therapy	15 (1.4%)	5 (3.1%)	0.098
Acute heart failure	56 (5.1%)	9 (5.6%)	0.791
Non-fatal recurrent MI	9 (0.8%)	0 (0.0%)	0.249
Target vessel revascularisation	3 (0.3%)	0 (0.0%)	0.529
Arrhythmia	65 (6.0%)	19 (11.9%)	0.005
Stroke	9 (0.8%)	2 (1.3%)	0.590
MACEs	121 (11.1%)	26 (16.3%)	0.057

Values are reported as *n* (%).
ACEI/ARB: angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; CIN: contrast-induced nephropathy; MI: myocardial infarction; MACEs: major adverse clinical events (all-cause death, non-fatal recurrent myocardial infarction, acute heart failure, arrhythmia, stroke and renal replacement therapy).

Table 3. Multivariate analyses for the association between ACEIs/ARBs and CIN risk.

Variables	OR	95% CI	*P* value
ACEI/ARB	0.89	0.46~1.73	0.735
Age >75 years	1.66	1.01~2.72	0.045
CrCl <30 mL/min	4.29	2.44~7.54	0.000
CHF	3.25	2.01~5.25	0.000
Contrast volume	1.00	1.00~1.01	0.021
Anaemia	0.99	0.61~1.61	0.979
SBP	0.99	0.98~1.01	0.349
DBP	1.00	0.98~1.03	0.855
HV/W	1.02	1.00~1.04	0.068

ACEI/ARB: angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; CI: confidence interval; CrCl: creatinine clearance; CHF: chronic heart failure; DBP: diastolic blood pressure; HV/W: hydration volume-to-weight ratio; OR: odds ratio; SBP: systolic blood pressure.

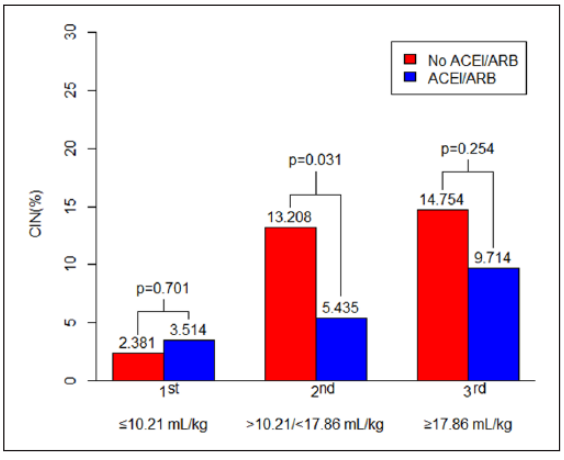

Figure 1. Incidence of CIN in the ACEI/ARB group and the non-ACEI/ARB group according to HV/W tertiles.
ACEI/ARB: angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; CIN: contrast-induced nephropathy; HV/W: hydration volume to body weight.

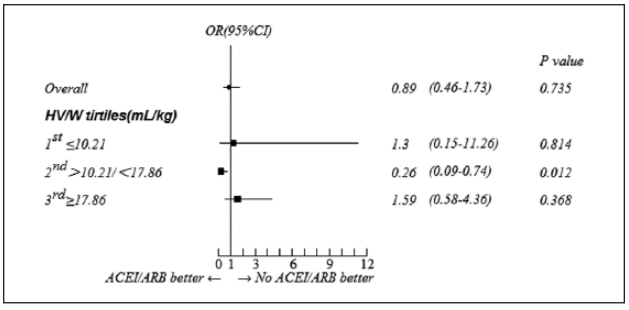

Figure 2. Multivariate analysis for association between periprocedural administration of ACEI/ARB and CIN risk based on HV/W tertiles. (OR were adjusted for age >75 years, CrCl <30 mL/minute, CHF, contrast volume, anaemia, SBP, DBP and HV/W.).
ACEI/ARB: angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; CIN: contrast-induced nephropathy; CrCl: creatinine clearance rate; CHF: chronic heart failure; CI: confidence interval; DBP: diastolic blood pressure; HV/W: hydration volume to body weight; OR: odds ratio; SBP: systolic blood pressure.

Discussion

The key finding of our study was that the effect of ACEIs/ARBs on CIN in CKD patients varied according to the intensity of hydration. ACEIs/ARBs presented as a preventive factor for CIN and significantly reduced CIN risk by more than 70% in the second HV/W tertile with moderate intensity hydration, but showed neither adverse nor beneficial effects with a non-significant trend towards higher CIN risk in the first and third tertiles after adjusting for potential confounding factors. Therefore, ACEIs/ARBs prescribed during the periprocedural period may reduce CIN incidence in CKD patients administered moderate-intensity saline hydration. To our knowledge, this is the first study that investigated the effect of the periprocedural use of ACEIs/ARBs on the risk of CIN at particular saline hydration levels in a prospective observational manner.

The use of ACEIs/ARBs was reported to be a risk factor for CIN in some previous studies in which the details

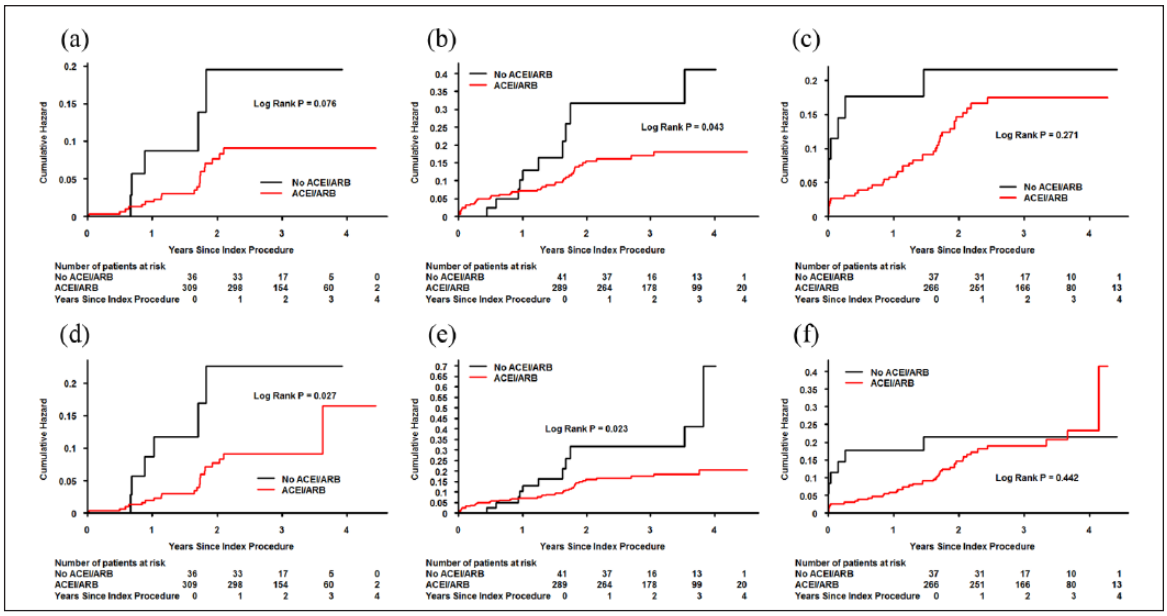

Figure 3. Kaplan–Meier curves for the cumulative probability of follow-up all-cause death (a, b and c for the first, second and third tertiles) and MACEs (d, e and f for the first, second and third tertiles).
ACEI/ARB: angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; MACEs: major adverse clinical events.

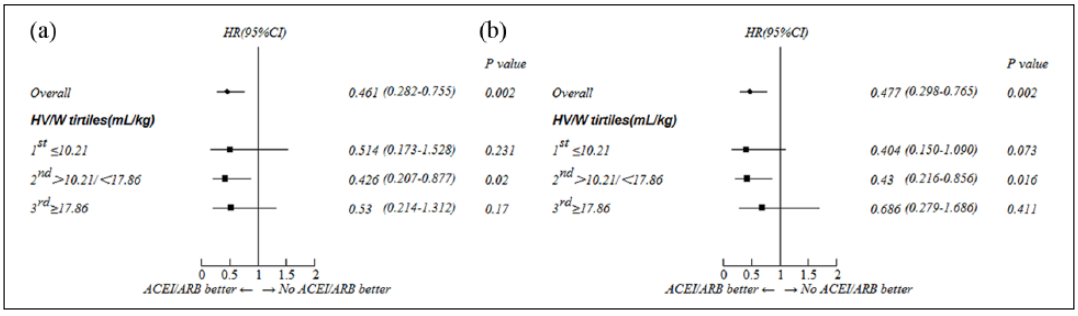

Figure 4. Multivariate Cox regression analysis of risk factors for follow-up all-cause death (a) and MACEs (b) according to HV/W tertiles. HR were adjusted for age greater than 75 years, DM, CrCl, CHF, SBP and HV/W.
ACEI/ARB: angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; CrCl: creatinine clearance rate; CHF: chronic heart failure; CI: confidence interval; DM: diabetes mellitus; HV/W: hydration volume to body weight; HR: hazard ratio; MACEs: major adverse clinical events; SBP: systolic blood pressure.

on hydration were not detailed. Toprak et al.[13] performed a randomised controlled study on the effect of periprocedural captopril on CIN in 80 patients with SCr less than 2 mg/dL. Compared with patients treated without ACEIs/ARBs, those treated with captopril had a significantly higher CIN incidence (8.3% vs. 3%, P=0.02). Similar results were observed in elderly patients and patients with imparied renal function.[14,15] Accordingly, some researchers suggested withdrawing these drugs during the periprocedural period in CIN high-risk patients.

However, other studies reported neutral or even contradicting results. Rosenstock et al., in a randomised controlled study on patients at stages 3–4 CKD (n=281), compared the effect of continuing or discontinuing of long-term ACEI/ARB therapy before and 24 hours after the procedure with no ACEI/ARB therapy on CIN development. No difference in CIN incidence was detected among the three groups (6.2%, 3.7% and 6.3%, P=0.66), and thus the authors concluded that patients at stages 3–4 CKD undergoing percutaneous coronary intervention do not need to withdraw ACEIs/ARBs during the periprocedural period.[10] Another randomised controlled study conducted among 208 patients with moderate renal insufficiency by Bainey et al. indicated that continued ACEIs/ARBs caused a lower increase in mean SCr after the procedure in patients who continued ACEIs/ARBs (0.3±0.5 vs. 0.1±0.3 mg/dL, P=0.03) while not increasing the rate of CIN.[6] So they suggested withholding this low-cost intervention before cardiac catheterisation.

The most recent meta-analysis regarding ACEIs/ARBs on CIN risk including 14 studies (15,447 subjects) indicated

that ACEI/ARB treatment significantly increased the risk of CIN in seven observational studies (OR 1.84, 95% CI 1.19–2.85, P=0.006) but not in the randomised controlled trials (OR 0.88, 95% CI 0.41–1.90, P=0.74).[16] The conflicting results that lead to paradoxical opinions among clinicians may be due to differences in characteristics of study populations and interventions such as isotonic saline hydration that are reported to affect renal haemodynamics and thus decrease CIN risk partly by inhibiting the RAAS.

Renal medullary hypoxia resulting from alternation in renal haemodynamics such as the reduction in renal blood flow secondary to renal artery vasoconstriction after CM exposure was considered the main pathophysiology of CIN.[17,18] There was rapid renal vasodilatation followed by prolonged vasoconstriction after CM exposure, associated with increased intrarenal vascular resistances, decreased renal blood flow, and reduced glomerular filtration rate (GFR), which may partly result from and be further aggravated by the activated RAAS.[19–21] Both ACEIs and ARBs are RAAS blockers that prevent vasoconstriction, reduce the generation of reactive oxygen species, and increase the synthesis of nitric oxide by inhibiting angiotensin II.[22,23] Experimental data suggest an important role of RAAS activation in contrast-induced intrarenal vasoconstriction and renal tubular cell apoptosis, and the blockade of angiotensin II decreased the duration of renal vasoconstriction and renal tissue injury following CM exposure.[24] However, the decrease in renal vascular resistance is predominant on the efferent arteriole of the glomerule rather than the afferent arteriole, and therefore the GFR may be further decreased by reducing the intraglomerular pressure.[25] The decreased GFR may not only prolong the excretion of CM, but also further affect renal tubulodynamics, increasing the duration of CM exposure, nullifying the increase in renal perfusion, and even reducing renal blood flow in the case of hypovolaemia.

Isotonic saline hydration is a well proved and widely accepted preventive strategy for CIN decreasing the direct toxic effects of CM on the renal tubules by diluting CM, countering against renal vasoconstriction by downregulating tubuloglomerular feedback to inhibit the RAAS, and decreasing the release of vasoconstrictors and production of reactive oxygen species.[26] The effects of isotonic saline hydration on renal haemodynamics may prevent the deleterious effect of ACEIs/ARBs on GFR and further increase renal blood flow through volume expansion and sodium load.[27] Therefore, we propose that ACEIs/ARBs may reduce the incidence of CIN when treated with a certain intensity of periprocedural isotonic saline hydration, while increasing the risk of CIN occurrence in the case of insufficient hydration accompanying pre-existing hypovolaemia, and have no effect on CIN if the hydration intensity is sufficient to inhibit the RAAS completely. However, none of the studies mentioned above investigated the effect of ACEIs/ARBs on CIN under different hydrations.

In our present observational study, saline hydration strategies were based on the judgement of clinicians. Patients with hypovolaemia or a higher risk of CIN received a higher intensity of saline hydration. Therefore, a trend towards increased CIN incidence with increasing HV/W level was observed, and patients in the first HV/W tertile with a mean LVEF of 55.9% should be adequate in circulating volume. Consistent with our hypothesis, the periprocedural administration of ACEIs/ARBs was a protective factor for CIN prevention in the second tertile, and there was no effect in the other two tertiles. In addition, we observed a significant protective effect of periprocedural ACEI/ARB treatment on the long-term all-cause death and MACEs in the second HV/W tertile. That may be attributed to a reduced incidence of CIN, which has been well proved to be associated with worse long-term clinical outcomes.

The present study has several limitations. First, this is a retrospective analysis of prospective study data, and hence causality would need to be confirmed in future randomised controlled trials. Second, the incidence of CIN may have been underestimated because SCr was not monitored continuously, as the peak value of SCr after CM exposure could not be predicted. Finally, variation in the measurement times may have led to reduced precision of the results.

Conclusion

Our study results indicate that in patients undergoing coronary angiography or intervention with CKD, the effect of the periprocedural administration of ACEIs/ARBs on the risk of CIN varied according to isotonic saline hydration intensity. When a moderate intensity of saline hydration was administered concomitantly during the periprocedural period, ACEI/ARB use was associated with a significant reduction in CIN incidence and improvement in long-term outcomes. Thus, we recommend patients with CKD to be prescribed ACEIs/ARBs when administrated moderate hydration in order to prevent CIN.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by a grant from the Science and Technology Planning Project of Guangdong Province (grant no. 2008A030201002), Guangdong Cardiovascular Institute; Guangdong Provincial Cardiovascular Clinical Medicine Research Fund (grant no. 2009X41). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the article; the work was not funded by any industry sponsors.

References

1. Gami AS and Garovic VD. Contrast nephropathy after coronary angiography. *Mayo Clin Proc* 2004; 79: 211–219.
2. Gruberg L, Mintz GS, Mehran R, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol* 2000; 36: 1542–1548.
3. Qian G, Fu Z, Guo J, et al. Prevention of contrast-induced nephropathy by central venous pressure-guided fluid administration in chronic kidney disease and congestive heart failure patients. *JACC Cardiovasc Interv* 2016; 9: 89–96.
4. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the Management of Stable Coronary Artery Disease of the European Society of Cardiology. *Eur Heart J* 2013; 34: 2949–3003.
5. King SR, Smith SJ, Hirshfeld JJ, et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation* 2008; 117: 261–295.
6. Bainey KR, Rahim S, Etherington K, et al. Effects of withdrawing vs continuing renin–angiotensin blockers on incidence of acute kidney injury in patients with renal insufficiency undergoing cardiac catheterization: results from the Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker and Contrast Induced Nephropathy in Patients Receiving Cardiac Catheterization (CAPTAIN) trial. *Am Heart J* 2015; 170: 110–116.
7. Kolh P, Wijns W, Danchin N, et al. Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg* 2010; 38 (Suppl): S1–S52.
8. Zhou S, Wu C, Song Q, et al. Effect of angiotensin-converting enzyme inhibitors in contrast-induced nephropathy: a meta-analysis. *Nephron* 2016; 133: 1–14.
9. Spatz C, Saadulla L, Lapsiwala A, et al. Effect of renin–angiotensin–aldosterone system blockade therapy on incidence of contrast-induced nephropathy in patients with chronic kidney disease. *Iran J Kidney Dis* 2012; 6: 432–436.
10. Rosenstock JL, Bruno R, Kim JK, et al. The effect of withdrawal of ACE inhibitors or angiotensin receptor blockers prior to coronary angiography on the incidence of contrast-induced nephropathy. *Int Urol Nephrol* 2008; 40: 749–755.
11. Jo SH, Lee JM, Park J, et al. The impact of renin–angiotensin–aldosterone system blockade on contrast-induced nephropathy: a meta-analysis of 12 studies with 4,493 patients. *Cardiology* 2015; 130: 4–14.
12. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002; 162: 329–336.
13. Toprak O, Cirit M, Bayata S, et al. [The effect of pre-procedural captopril on contrast-induced nephropathy in patients who underwent coronary angiography]. *Anadolu Kardiyol Derg* 2003; 3: 98–103.
14. Umruddin Z, Moe K and Superdock K. ACE inhibitor or angiotensin II receptor blocker use is a risk factor for contrast-induced nephropathy. *J Nephrol* 2012; 25: 776–781.
15. Cirit M, Toprak O, Yesil M, et al. Angiotensin-converting enzyme inhibitors as a risk factor for contrast-induced nephropathy. *Nephron Clin Pract* 2006; 104: c20–c27.
16. Wu Z, Zhang H, Jin W, et al. The effect of renin–angiotensin–aldosterone system blockade medications on contrast-induced nephropathy in patients undergoing coronary angiography: a meta-analysis. *PLoS One* 2015; 10: e129747.
17. McCullough PA, Choi JP, Feghali GA, et al. Contrast-induced acute kidney injury. *J Am Coll Cardiol* 2016; 68: 1465–1473.
18. Seeliger E, Sendeski M, Rihal CS, et al. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. *Eur Heart J* 2012; 33: 2007–2015.
19. Persson PB, Hansell P and Liss P. Pathophysiology of contrast medium-induced nephropathy. *Kidney Int* 2005; 68: 14–22.
20. Detrenis S, Meschi M, Musini S, et al. Lights and shadows on the pathogenesis of contrast-induced nephropathy: state of the art. *Nephrol Dial Transplant* 2005; 20: 1542–1550.
21. Sendeski M, Patzak A and Persson PB. Constriction of the vasa recta, the vessels supplying the area at risk for acute kidney injury, by four different iodinated contrast media, evaluating ionic, nonionic, monomeric and dimeric agents. *Invest Radiol* 2010; 45: 453–457.
22. Brewster UC and Perazella MA. The renin–angiotensin–aldosterone system and the kidney: effects on kidney disease. *Am J Med* 2004; 116: 263–272.
23. Munzel T and Keaney JJ. Are ACE inhibitors a "magic bullet" against oxidative stress? *Circulation* 2001; 104: 1571–1574.
24. Duan SB, Wang YH, Liu FY, et al. The protective role of telmisartan against nephrotoxicity induced by X-ray contrast media in rat model. *Acta Radiol* 2009; 50: 754–759.
25. Larson TS, Hudson K, Mertz JI, et al. Renal vasoconstrictive response to contrast medium. The role of sodium balance and the renin–angiotensin system. *J Lab Clin Med* 1983; 101: 385–391.
26. Azzalini L, Spagnoli V and Ly HQ. Contrast-induced nephropathy: from pathophysiology to preventive strategies. *Can J Cardiol* 2016; 32: 247–255.
27. Gu GQ, Lu R, Cui W, et al. Low-dose furosemide administered with adequate hydration reduces contrast-induced nephropathy in patients undergoing coronary angiography. *Cardiology* 2013; 125: 69–73.