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

Kevin R. Bainey, MD, MSc,[a] Sherali Rahim, MD,[b] Krystal Etherington, BSc,[b] Michael L. Rokoss, MD,[b] Madhu K. Natarajan, MD, MSc,[b] James L. Velianou, MD,[b] Sonya Brons, RN,[b] and Shamir R. Mehta, MD, MSc[b], for the CAPTAIN Investigators ***Alberta, and Ontario, Canada***

Background It is unclear if holding angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) prior to coronary angiography reduces contrast-induced acute kidney injury (AKI). We undertook a randomized trial to investigate the effect of holding ACEI/ARB therapy prior to coronary angiography on the incidence of AKI.

Methods We randomly assigned 208 patients with moderate renal insufficiency (creatinine ≥ 1.7 mg/dL within 3 months and/or documented creatinine ≥ 1.5 mg/dL within 1 week before cardiac catheterization) to hold ACEI/ARB ≥24 hours preprocedure or continue ACEI/ARB. The primary outcome was the incidence of AKI defined as an absolute rise in serum creatinine of ≥0.5 mg/dL from baseline and/or a relative rise in serum creatinine of ≥25% compared with baseline measured at 48 to 96 hours postcardiac catheterization.

Results All patients were taking an ACEI (72.1%) or ARB (27.9%) prior to randomization. At 48 to 96 hours, the primary outcome occurred in 18.4% of patients who continued ACEI/ARB compared with 10.9% of the patients who held ACEI/ARB (hazard ratio 0.59, 95% CI 0.30-1.19, $P = .16$). In a prespecified secondary outcome, there was a lower rise in mean serum creatinine after the procedure in patients who held ACEI/ARB (0.3 ± 0.5 vs 0.1 ± 0.3 mg/dL, $P = .03$). The clinical composite of death, myocardial infarction, ischemic stroke, congestive heart failure, rehospitalization for cardiovascular cause, or need for dialysis preprocedure occurred in 3.9% who continued ACEI/ARB compared with 0% who held the ACEI/ARB (hazard ratio 0.11, 95% CI 0.01-2.96, $P = .06$).

Conclusion In this pilot study of patients with moderate renal insufficiency undergoing cardiac catheterization, withholding ACEI/ARB resulted in a non-significant reduction in contrast-induced AKI and a significant reduction in postprocedural rise of creatinine. This low cost intervention could be considered when referring a patient for cardiac catheterization. (Am Heart J 2015;170:110-6.)

From the [a]Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada, and [b]Interventional Cardiology Research Group and Division of Cardiology, Department of Medicine, McMaster University, and Hamilton Health Sciences Hamilton, Ontario, Canada.

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Reprint requests: Shamir R. Mehta, MD, MSc, FRCPC, FACC, FESC, David Braley Cardiac, Vascular and Stroke Institute, Hamilton General Hospital, Room 3-119, 237 Barton St East, Hamilton, ON, Canada L8L 2X2.
E-mail: smehta@mcmaster.ca
0002-8703

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Blockers of the renin-angiotensin system reduce cardiovascular events in individuals at high risk.[1-3] Patients prescribed an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) are often referred for cardiac catheterization, a procedure that requires the use of iodine-based contrast media. Acute kidney injury (AKI) can occur after exposure to contrast media, and this risk is increased in patients who have preexisting renal insufficiency. The development of contrast-induced AKI has been associated with adverse

Table I. Baseline characteristics

Variable	Continue (n = 102)	Hold (n = 106)	*P*
Demographic characteristics			
Age (y), mean (SD)	72.4 (8.4)	73.2 (9.1)	.5600
Female sex (%)	26.5	26.4	1.0000
Medical history (%)			
Diabetes mellitus	55.9	51.9	.5806
Hypertension	94.1	87.7	.1488
Liver cirrhosis	1.0	0.9	1.0000
Congestive heart failure	11.8	16.0	.4266
Ejection fraction (%), median (interquartile range)	50.0 (42.0-55.0)	50.0 (35.0-55.0)	.2023
ACS presentation (%)	2.0	2.8	.989
Medications prior to cardiac catheterization (%)			
Aspirin	80.4	77.4	.6145
Clopidogrel	27.5	24.5	.6392
COX II inhibitors	1.0	0.0	.4904
Calcium-channel blockers	39.2	34.9	.5668
Other NSAIDS	5.9	2.8	.3250
Loop diuretics	26.5	34.0	.2910
Thiazide diuretics	17.6	14.2	.5704
β-Blockers	59.8	67.9	.2494
Spironolactone	2.0	5.7	.2802
Statins	78.4	75.5	.6258
Oral hypoglycemics	21.6	22.6	.8689
Insulin	24.5	14.2	.0779
Thiazolidinediones	2.9	1.9	.6785
ACEI/ARB	100.0	100.0	.9999

Abbreviations: *ACS*, Acute coronary syndrome; *COX*, cyclooxygenase; *NSAIDS*, nonsteroidal anti-inflammatory drugs.

clinical events which has prompted investigation for preventative strategies.[4-6]

Currently, it is unclear if the use of ACEI or ARBs is independently associated with an increased risk of contrast-induced AKI. Continuation of the ACEI/ARB during cardiac catheterization may prevent medullary ischemia induced by angiotensin II after contrast administration.[7] Alternatively, ACEI/ARBs can decrease the glomerular filtration rate (GFR) resulting in an increase in serum creatinine and predisposition toward contrast-induced AKI.[8-10] As such, the use of holding the ACEI/ARB prior to cardiac catheterization in patients at risk for AKI has not been firmly established. Given this uncertainty, we designed a pilot randomized trial to determine whether holding the ACEI/ARB prior to cardiac catheterization reduces the incidence of contrast-induced AKI in patients with chronic kidney disease.

Methods

Patients

The CAPTAIN trial was a randomized, parallel-group, single-center pilot study with blinded adjudication of outcomes. From July 2006 through March 2012, a total of 208 patients underwent randomization (ClinicalTrials.gov identifier NCT0031252).

Patients were eligible for the CAPTAIN study if they presented to Hamilton General Hospital for cardiac catheterization on an ACEI or ARB and were scheduled for coronary angiography more than 24 hours from enrollment, with evidence of chronic kidney disease defined as documented serum creatinine ≥ 1.7 mg/dL (150 μmol/L) within 3 months before cardiac catheterization and/or documented serum creatinine ≥ 1.5 mg/dL (132 μmol/L) within 1 week before cardiac catheterization. Patients were excluded if they had end-stage renal disease (chronic kidney disease stage ≥4 or on dialysis), required emergency cardiac catheterization with insufficient time to hold the ACEI, or had acute pulmonary edema.

The trial was approved by the local institutional review board, and all patients provided written informed consent. The trial was funded and coordinated by the Interventional Cardiology Research Group at McMaster University and Hamilton Health Sciences.

Randomization and study treatments

Permuted-block randomization was performed with the use of a central 24-hour computerized interactive voice-response system located at the Population Health Research Institute, McMaster University and Hamilton Health Sciences. Among the patients who were randomly assigned to the hold ACEI/ARB group, the renin-angiotensin blocker was held at least 24 hours before the procedure and up to 96 hours after the procedure (restarted after postprocedure creatinine is measured). Patients who were assigned to the continue ACEI/ARB group carried on with their renin-angiotensin blocker before and after the procedure.

Both groups received intravenous normal saline at 3 mL/kg per hour for at least 1 hour immediately before radiocontrast injection, then intravenous normal saline at 1 mL/kg per hour during the contrast exposure and 6 hours after the procedure or until discharge from hospital. Intravenous normal saline was discontinued if raised left ventricular end-diastolic pressures were noted. All patients were given a prescription for *N*-acetylcysteine 600 mg to be taken orally twice daily the day before and the day of the procedure, as was recommended at the time the study was designed.

A phone call from the study nurse was performed at least 24 hours prior to cardiac catheterization to remind patients to stop any nonsteroidal anti-inflammatory drugs or metformin prior to the procedure, remind patients to take *N*-acetylcysteine prior to the procedure, and provide instructions to either hold or continue their ACEI/ARB.

Immediately before cardiac catheterization, patients had baseline serum creatinine measured. Serum creatinine levels were obtained 72 ± 24 hours postprocedure. After the postprocedure creatinine level, patients in the "hold ACEI/ARB" treatment group resumed their renin-angiotensin blocker.