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Acute Kidney Injury in Patients With Chronic Kidney Disease Undergoing Internal Carotid Artery Stent Implantation

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ABSTRACT

OBJECTIVES This study sought to investigate acute kidney injury (AKI) following carotid artery stenting (CAS).

BACKGROUND Few data exist on AKI following CAS.

METHODS This study evaluated 126 chronic kidney disease (CKD) patients who underwent CAS. The risk for contrast-induced AKI was defined by the Mehran score. Hemodynamic depression (i.e., periprocedural systolic blood pressure <90 mm Hg or heart rate <60 beats/min), AKI (i.e., an increase of ≥0.3 mg/dl in the serum creatinine concentration at 48 h), and 30-day major adverse events (including death, stroke, and acute myocardial infarction) were assessed.

RESULTS AKI occurred in 26 patients (21%). Although baseline kidney function and contrast volume were similar in the AKI group and the non-AKI group, the risk score was higher (10 ± 3 vs. 8 ± 3; p = 0.032), and hemodynamic depression (mostly due to hypotension) (65.5% vs. 35%; p = 0.005) was more common in the AKI group. The threshold of hemodynamic depression duration for AKI development was 2.5 min (sensitivity 54%, specificity 82%). Independent predictors of AKI were hemodynamic depression (odds ratio [OR]: 4.01; 95% confidence interval [CI]: 1.07 to 15.03; p = 0.009), risk score (OR: 1.29; 95% CI: 1.03 to 1.60; p = 0.024), and male sex (OR: 6.07; 95% CI: 1.18 to 31.08; p = 0.021). Independent predictors of 30-day major adverse events that occurred more often in the AKI group (19.5% vs. 7%; p = 0.058) were AKI (HR: 4.83; 95% CI: 1.10 to 21.24; p = 0.037) and hemodynamic depression (HR: 5.58; 95% CI: 1.10 to 28.31; p = 0.038).

CONCLUSIONS AKI in CKD patients undergoing CAS is mostly due to hemodynamic depression and is associated with a higher 30-day major adverse events rate. (J Am Coll Cardiol Intv 2015;8:1506–14) © 2015 by the American College of Cardiology Foundation.

Chronic kidney disease (CKD) has been associated with increased morbidity and mortality after coronary revascularization (1). In contrast, there are only limited and conflicting data on the impact of CKD in patients undergoing carotid revascularization (2,3). Although some data support the concept that CKD represents an independent predictor of unfavorable outcome even following carotid artery stenting (CAS) (3-6), others refute this association (2,7). A potential reason of these conflicting results is the paucity of data on post-procedural acute kidney injury (AKI). Indeed, small changes in serum creatinine (sCr) after surgery or interventional procedures are recognized as strong independent predictors for short- and long-term mortality (8). AKI following CAS may occur because of iodinated contrast media (CM) and hemodynamic depression. These 2 factors are not mutually exclusive but may act together in causing AKI. CM is a well-recognized cause of AKI. Hemodynamic depression, which occurs in 7% to 42% of patients undergoing coronary artery stenting (CAS) (9-12), might also

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have an important role in the pathogenesis of AKI (13).

In the present study on CKD patients undergoing CAS, we assessed the following: 1) the rate of AKI; 2) the role of CM and hemodynamic depression in the pathogenesis of AKI; and 3) the correlation between AKI and 30-day major adverse events (MAE)—death, stroke, and myocardial infarction.

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METHODS

PATIENT POPULATION. CKD patients (with estimated glomerular filtration rate [eGFR] ≤60 ml/min/1.73 m^2) scheduled for CAS at the Clinica Mediterranea from February 2, 2009 to September 17, 2013 were screened. Exclusion criteria were recent (≤48 h) administration of iodinated CM, dialysis, contraindication to aspirin and thienopyridines, and current enrollment in any other study. All patients who met the inclusion/exclusion criteria and signed an informed consent were included into the study. Patients were classified as symptomatic if they had experienced a recent transient ischemic attack, stroke, or transient monocular blindness ipsilateral to the study artery in the preceding 180 days before randomization. Otherwise, they were classified as asymptomatic.

STENTING TECHNIQUE. All patients were considered to be suitable for CAS, according to 2011 recommendations (14). All stenting procedures were performed according to the recommendations and without the induction of general anesthesia and/or sedation. A protection device was used in all instances. Balloon pre-dilation was performed only in case of failure of direct stenting. Self-expanding stents were used in all instances. Stents were classified according to alloy: 1) braided Elgiloy (Carotid Wallstent, Boston Scientific, Natick, Massachusetts); and 2) nitinol stents (X-Act and Acculink [Abbott Vascular Devices, Redwood City, California]; Precise [Cordis, Miami Lakes, Florida]; Crystallo Ideale [Medtronic Inc., Minneapolis, Minnesota]; Protegè (ev3, Plymouth, Minnesota); Sinus Carotid RX (Optimed, Ettlingen, Germany). Furthermore, stents were divided according to cell design: 1) closed cells: Carotid Wallstent and X-Act; 2) open cells: Precise and Protegè; and 3) hybrid: Crystallo Ideale, and Sinus Carotid RX. Balloon post-dilation was routinely performed with a 5.0-mm balloon. All patients received atropine (1.0 mg intravenously) before balloon post-dilation to minimize hemodynamic depression. Unfractionated heparin (10,000 IU) was administered intravenously at the beginning of the procedure. All patients received aspirin (100 mg/day) and clopidogrel pre-load (600 mg) 24 h before the procedure. After the procedure, clopidogrel was continued for at least 1 month, whereas aspirin was continued for life. The severity of stenosis was quantified using the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria (15). A baseline cranial computed tomogram was obtained in all patients. Neurologic evaluations were performed every 6 h or more frequently if the patient experienced any clinical deterioration.

We measured sCr the day before the procedure and at 24 h, 48 h, and 1 week after CM administration. Additional measurements were performed in case of a deterioration of baseline renal function. We calculated eGFR by applying the Modification of Diet in Renal Disease formula (16). CKD was defined as an eGFR <60 ml/min/1.73 m^2. The risk for predicting contrast-induced AKI was calculated according to Mehran et al. (17).

Heart rate and blood pressure were assessed continuously during the procedure. After the procedure, patients were transferred to the post-interventional care unit, where heart rate and blood pressure were monitored continuously. Hemodynamic depression was defined as symptomatic or asymptomatic hypotension (systolic blood pressure <90 mm Hg) or bradycardia (heart rate <60 beats/min) at any time during or within the first 24 h after stent deployment (9,10,12,18). Treatment includes intravenous fluid boluses (≥500 ml), followed by the addition of dopamine (starting from 5 mg/kg/min). Patients who required continuous vasopressor infusion after CAS were considered to have persistent hemodynamic depression (9).

Contrast-induced AKI prophylaxis strategies were as follows: 1) in patients with eGFR 30 to 59 ml/min/1.73 m^2, hydration with sodium bicarbonate solution (154 mEq/l) plus high dose of N-acetylcysteine (NAC) (19); or 2) in patients with eGFR <30 ml/min/1.73 m^2, hydration with normal saline plus NAC controlled by the RenalGuard system (PLC Medical Systems, Franklin, Massachusetts) (19). Although the results on the use of NAC are conflicting, experimental studies demonstrated that NAC exerts its antioxidant properties preventing kidney cell death by inhibiting oxygen free radical production and thus stress kinases and apoptosis activation upon CM exposure (20). Iodixanol (Visipaque, GE Healthcare, Princeton, New Jersey) was used in all patients. In order to identify patients receiving a high-contrast load, the following weight- and creatinine-adjusted maximum contrast dose formula was used: 5 × kilograms of body

ABBREVIATIONS AND ACRONYMS

AKI = acute kidney injury
CAS = carotid artery stenting
CI = confidence interval(s)
CKD = chronic kidney disease
CM = contrast media
eGFR = estimated glomerular filtration rate
IQR = interquartile range
MAE = major adverse event(s)
NAC = N-acetylcysteine
OR = odds ratio(s)
sCr = serum creatinine

TABLE 1 Clinical Characteristics of the Global Population and of Patients With Versus Those Without AKI

	Global Population (n = 126)	AKI Group (n = 26)	Non-AKI Group (n = 100)	p Value
Age, yrs	76 ± 7	77 ± 5	75 ± 7	0.23
Male	95 (75.5)	22 (85)	73 (73)	0.059
Active smokers	15 (12)	6 (23)	9 (9)	0.085
Weight, kg	76 ± 13	75 ± 9	76 ± 10	0.54
Height, m	1.65 ± 0.8	1.66 ± 0.7	1.65 ± 087	0.25
Body-mass index, kg/m^2	28 ± 6	28 ± 3	27 ± 5	0.91
Blood pressure, mm Hg				
Systolic	138 ± 14	140 ± 35	136 ± 15	0.94
Diastolic	79 ± 5	80 ± 5	79 ± 6	0.21
Mean	90 ± 6	90 ± 5	89 ± 6	0.20
Heart rate, beats/min	73 ± 10	73 ± 11	72 ± 10	0.22
<60	6 (5)	2 (8)	4 (4)	0.60
Permanent pacemaker	6 (5)	2 (8)	4 (4)	0.53
Symptomatic carotid artery disease	40 (32)	9 (34.5)	31 (31)	0.53
LV ejection fraction, %	54 ± 10	48 ± 10	53 ± 10	0.33
Systemic hypertension	117 (93)	24 (92)	93 (93)	1.00
Hypercholesterolemia	82 (65)	14 (54)	68 (68)	0.25
Diabetes mellitus	55 (43.5)	14 (54)	41 (40.5)	0.29
Coronary artery disease	69 (55)	14 (54)	55 (55)	1.00
Contralateral carotid occlusion	17 (13.5)	2 (8)	15 (15)	0.35
Previous endarterectomy	5 (4)	1 (4)	4 (4)	1.00
Drugs				
Beta-blockers	31 (24.5)	7 (27)	24 (24)	0.80
Statins	105 (83)	22 (84.5)	83 (83)	1.00
Serum creatinine, mg/dl	1.49 (1.30, 1.70)	1.54 (1.27, 1.73)	1.54 (1.32, 1.83)	0.53
eGFR, ml/min/1.73 m^2	42 ± 12	43 ± 15	42 ± 12	0.53
Anemia†	50 (40)	16 (61.5)	34 (34)	0.014
Contrast nephropathy risk score*	9 ± 3	10 ± 3	8 ± 3	0.032
CIAKI, %	17 ± 7	21 ± 10	17 ± 7	0.026
Dialysis, %	0.5 ± 1.1	1.4 ± 2.5	0.4 ± 0.5	0.22
Volume of contrast media, ml	121 ± 50	116 ± 52	112 ± 48	0.69
Contrast ratio >1	96 (77)	22 (85)	74 (74)	0.21
Prophylaxis				
Sodium bicarbonate solution and NAC	121 (96)	26 (100)	95 (95)	0.58
RenalGuard therapy	5 (4)	0	5 (5)	

Values are mean ± SD, n (%), or median (interquartile range). *According to Mehran et al. (17). †Anemia defined as baseline hematocrit <39% for male and <36% for female patients.

AKI = acute kidney injury; CIAKI = contrast-induced acute kidney injury; eGFR = estimated glomerular filtration rate; LV = left ventricular; NAC = N-acetylcysteine.

weight divided by sCr (mg/dl). When the "contrast ratio," that is the dichotomous variable obtained by dividing the actual amount of contrast received by the calculated maximum contrast dose, was >1, then the contrast dose was considered high (21).

STUDY OBJECTIVES. The outcome measures were as follow: 1) the development of AKI, defined as an increase in sCr concentration ≥0.3 mg/dl at 48 h after CAS or the need for dialysis (8); 2) the relationship between AKI and both CM volume and hemodynamic depression; and 3) the relationship between AKI and 30-day MAE, defined as death, stroke, and acute myocardial infarction. The severity of AKI was assessed according to the Acute Kidney Injury Network criteria: stage 1, an sCr increase ≥0.3 mg/dl or ≥1.5× to 1.9× from baseline; stage 2, an sCr increase ≥2.0× to 2.9× from baseline; and stage 3, an sCr increase ≥3.0× from baseline or the need for dialysis (8). Myocardial infarction was diagnosed in the occurrence of persistent ST-segment changes and/or new Q waves in 2 leads or the presence of elevated enzymes (including troponin >0.1 ng/ml). Neurological complications were classified as being among the following: 1) minor stroke, defined as a new neurological deficit that either resolves completely within 30 days or increased NIHSS (National Institute of Health Stroke Scale) by ≤3; and 2) major stroke, defined as a new neurological deficit that persists for >30 days and increased NIHSS by ≥4 (22). Bleeding was defined according to the Bleeding Academic Research Consortium criteria (23).

STATISTICAL ANALYSIS. Continuous variables are given as mean ± SD or median and interquartile range (IQR), when appropriate. Student *t* test and nonparametric Mann-Whitney tests were used to determine differences between mean values for normally and, respectively, not normally distributed variables. Categorical variables were reported as percentages and were analyzed by either chi-squared or Fisher exact tests, as appropriate. Receiver-operating characteristic curve was generated, and the area under the curve was calculated to evaluate the time threshold of hemodynamic depression for AKI development. Generalized linear model was performed to determine whether contrast volume and hemodynamic depression were independent predictors of AKI with and without adjustment for confounders selected according to the study hypothesis, literature, and significance ($p < 0.1$) at univariate analysis. Hosmer-Lemeshow goodness-of-fit test was assessed. Survival curves were generated using Kaplan-Meier analysis, and unadjusted comparisons between groups were compared with log-rank test. Cox proportional hazards model was used to provide hazard ratios with 95% confidence intervals (CI) and adjustment for previously selected risk factors (the same criteria reported herein). Potential interactions due to the therapy were evaluated. To correct for multiple testing, 200 bootstrap iterations were computed. For all tests, $p < 0.05$ was considered statistically significant. All p values are 2-sided. Data were analyzed with SPSS (version 13.0, SPSS, Inc., Chicago, Illinois) for Windows and Stata (version 11/SE, Stata Corp., College Station, Texas).

RESULTS

PATIENTS POPULATION. This study included 126 CKD patients (Table 1). Forty patients (32%) were symptomatic for carotid artery disease. Mean arterial pressure was 90 ± 6 mm Hg. Mean heart rate was 73 ± 10 beats/min, and 6 patients (4.8%) were bradycardic before the procedure.

CAROTID ARTERY STENTING PROCEDURE. Balloon pre-dilation was required in 9 patients (7%). The type of embolic protection device and self-expandable stent are reported in the Table 2. The procedure was technically successful in all patients. Hemodynamic depression occurred in 52 of 126 patients (41%) and was persistent in 15 of 126 patients (12%). Hemodynamic depression, which occurred in all instances during or following post-dilation, was due to hypotension alone in 46 of 52 patients (88.5%), bradycardia alone in 2 patients (4%), and both hypotension and bradycardia in 4 patients (7.5%). Vasopressor treatment was accomplished in 35 of these 52 patients (67%). Median duration of hemodynamic depression was 4 (interquartile range: 0, 556) min. Characteristics of patients with and without hemodynamic depression are reported in the Table 3. Patients with hemodynamic depression more often had lesions involving the bulb and smaller vessel size and less often had previous endarterectomy. Furthermore, patients with hemodynamic depression were more often treated with nitinol and open-cells stents (Table 3).

AKI. AKI occurred in 26 patients (21%) (Tables 1 and 2). The majority of these patients (21 of 26 [81%]) experienced a stage 1 AKI, and only 5 of 26 (19%) had a stage 2 AKI. Patients in the AKI group were more often male, active smokers, anemic, and had a high Mehran risk score. Balloon pre-dilation was more frequent (15% vs. 5%; p = 0.086) and mean stent diameter was larger (9.68 ± 0.69 vs. 9.36 ± 0.96; p = 0.022) in the AKI group. Furthermore, the implantation of a nitinol stent was more frequent in the AKI group (96% vs. 79%; p = 0.044). Baseline eGFR, CM volume, and prophylactic strategies for contrast-induced AKI were similar in the AKI and non-AKI groups (Table 1). Changes in intraprocedural systolic and mean blood pressure in AKI and non-AKI groups are represented in Figure 1. Hemodynamic depression occurred in 17 of 26 patients (65.5%) in the AKI group versus 35 of 100 patients (35%) in the non-AKI group (odds ratio [OR]: 3.50; 95% CI: 1.42 to 8.68; p = 0.005). Similarly, persistent hemodynamic depression was more common in the AKI group (10 of 26 [38.5%] vs. 5 of 100 [5%]; OR: 11.87; 95% CI: 3.59 to 39.31; p < 0.001). Median duration of hemodynamic depression was longer in the AKI group than non-AKI group (630 [IQR: 0 to 1440] vs. 3 [IQR: 0 to 4.5] min; p < 0.001). A significant positive correlation was observed between duration of hemodynamic depression and absolute difference of serum creatinine between post-procedural and baseline values (r = 0.55; p < 0.001) (Figure 2). By receiver-operating characteristic analysis, 2.5 min was the threshold of hemodynamic depression duration (54% sensitivity and 82% specificity) for AKI development (Figure 3). Vasopressor treatment was more common in the AKI group (13 of

TABLE 2 Angiographic and Procedural Characteristics of the Global Population and of Patients With Versus Those Without AKI

	Global Population (n = 126)	AKI Group (n = 26)	Non-AKI Group (n = 100)	p Value
Right internal carotid artery	71 (56%)	17 (65%)	54 (54%)	0.18
Left internal carotid artery	55 (44)	9 (35)	46 (46)	
Eccentric	89 (72.5)	21 (80)	68 (68)	0.14
Ulceration	18 (14)	6 (23)	12 (12)	0.14
Calcification	29 (23)	5 (19)	24 (24)	0.60
Involvement of the bulb	72 (57)	14 (53)	58 (58)	0.95
Reference vessel diameter, mm	6.03 ± 0.77	6.06 ± 0.59	5.94 ± 0.77	0.59
Minimal lumen diameter, mm	1.57 ± 0.79	1.71 ± 0.03	1.54 ± 0.75	0.45
Diameter stenosis, %	77 ± 12	74 ± 15	78 ± 12	0.64
Pre-dilation	9 (7)	4 (15)	5 (5)	0.086
Post-dilation	126 (100)	26 (100)	100 (100)	1.00
Balloon diameter	5.32 ± 0.38	5.30 ± 0.35	5.34 ± 0.35	0.72
Balloon-to-artery ratio	0.90 ± 0.12	0.89 ± 0.10	0.92 ± 0.12	0.61
Stent diameter, mm	9.36 ± 0.96	9.68 ± 0.69	9.27 ± 0.97	0.022
Stent length, mm	37 ± 4	37 ± 4	37 ± 4	0.72
Maximal inflation pressure, atm	14 ± 3	14 ± 2	14 ± 3	0.18
Stent-to-vessel ratio	1.55 ± 0.17	1.58 ± 0.17	1.54 ± 0.26	0.77
Stent type				0.21
Wallstent	22 (17.5)	1 (3.8)	21 (21)	
Acculink	31 (24.5)	7 (27)	24 (24)	
Protegè	42 (33)	11 (42)	31 (31)	
Sinus Carotid RX	8 (6)	2 (7.7)	6 (6)	
Crystallo Ideale	10 (8)	4 (15.5)	6 (6)	
Precise	12 (9.5)	1 (3.8)	11 (11)	
X-Act	1 (0.8)	0	1 (1)	
Braided Elgiloy	22 (17.5)	1 (4)	21 (21)	0.044
Nitinol	104 (82.5)	25 (96)	79 (79)	
Closed cell	23 (18)	1 (4)	22 (20)	0.13
Open cell	85 (67.5)	19 (73)	66 (66)	
Hybrid cell	18 (14.5)	6 (23)	12 (12)	
Protection device				0.41
SpideRX*	74 (59)	19 (73)	55 (55)	
Emboshield†	14 (11)	2 (7.7)	12 (12)	
EPI filter‡	21 (16.5)	2 (7.7)	19 (19)	
RX Accunet†	2 (1.5)	1 (3.8)	1 (1)	
Angioguard RX§	11 (9)	1 (3.8)	10 (10)	
Mo.Ma‖	4 (3)	1 (3.8)	3 (3)	

Values are n (%) and mean ± SD. *SpideRX (Covidien, Mansfield, Massachusetts). †Emboshield and RX Accunet (Abbott Vascular Devices, Redwood City, California). ‡EPI filter (Boston Scientific, Natick, Massachusetts). §Angioguard RX (Cordis, Miami Lakes, Florida). ‖Mo.Ma (Medtronic Inc., Minneapolis, Minnesota).
AKI = acute kidney injury.

TABLE 3 Characteristics of Patients With Versus Those Without Hemodynamic Depression

	Hemodynamic Depression Group (n = 52)	Non-Hemodynamic Depression Group (n = 74)	p Value
Age, yrs	76 ± 7	76 ± 7	0.80
Male	37 (71)	58 (78)	0.26
Blood pressure, mm Hg			
Systolic	137 ± 16	134 ± 14	0.39
Diastolic	79 ± 5	78 ± 6	0.68
Mean	90 ± 6	90 ± 6	0.49
Heart rate, beats/min	74 ± 9	71 ± 11	0.19
<60	2 (4)	4 (5)	0.60
Permanent pacemaker	2 (4)	4 (5)	0.60
LV ejection fraction, %	52 ± 12	55 ± 9	0.51
Diabetes mellitus	19 (36.5)	26 (35)	1.00
Contralateral carotid occlusion	10 (20)	7 (9.5)	0.18
Previous endarterectomy	0	5 (6.5)	0.041
Beta-blockers	13 (26)	18 (24)	0.96
eGFR, ml/min/1.73 m^2	42 ± 12	42 ± 12	0.87
Contrast nephropathy risk score*	9 ± 4	9 ± 3	0.77
Volume of contrast media, ml	118 ± 48	109 ± 49	0.31
Contrast ratio >1	41 (79.5)	55 (74.5)	0.73
Reference vessel diameter, mm	5.85 ± 0.64	6.17 ± 0.84	0.066
Diameter stenosis, %	75 ± 13	79 ± 12	0.15
Pre-dilation	5 (9.5)	4 (5.5)	0.48
Post-dilation	52 (100)	74 (100)	1.00
Balloon diameter	5.28 ± 0.41	5.35 ± 0.36	0.074
Balloon-to-artery ratio	0.92 ± 0.10	0.89 ± 0.13	0.28
Stent diameter, mm	9.39 ± 0.98	9.33 ± 0.96	0.74
Stent length, mm	38 ± 4	37 ± 5	0.49
Maximal inflation pressure, atm	14 ± 2	15 ± 3	0.18
Stent-to-vessel ratio	1.59 ± 0.27	1.52 ± 0.27	0.28
Eccentric	38 (73)	51 (69)	0.69
Calcification	10 (19)	19 (26)	0.34
Involvement of the bulb	38 (74)	34 (45)	0.003
Stent type			0.099
Wallstent	3 (5.5)	19 (25.5)	
Acculink	13 (25)	18 (24.5)	
Protegè	22 (42.5)	20 (27)	
Sinus Carotid RX	4 (7.7)	4 (5.5)	
Crystallo Ideale	4 (7.7)	6 (8)	
Precise	6 (11.5)	6 (8)	
X-Act	0	1 (1.5)	
Braided Elgiloy	3 (5.5)	19 (25.5)	0.002
Nitinol	49 (94.5)	55 (74.5)	
Closed cell	3 (5.5)	20 (27)	0.015
Open cell	41 (79)	44 (59.5)	
Hybrid cell	8 (15.5)	10 (13.5)	

Values are mean ± SD or n (%). *According to Mehran et al. (17).
Abbreviations as in Table 1.

26 [50%] vs. 22 of 100 patients [22%]; p = 0.007). Independent predictors of AKI were hemodynamic depression (OR: 4.01; 95% CI: 1.07 to 15.03; p = 0.009), risk score (OR: 1.29; 95% CI: 1.03 to 1.60; p = 0.024), and male sex (OR: 6.07; 95% CI: 1.18 to 31.08; p = 0.021) (Table 4).

IN-HOSPITAL AND 30-DAY MAE. In-hospital and 30-day MAE occurred in 12 patients (9.5%) and were more common in the AKI group than in the non-AKI group (5 of 26 [19.5%] vs. 7 of 100 [7%]; OR: 6.39; 95% CI: 1.01 to 40.48; p = 0.058) (Table 5, Figure 4). The higher MAE events rate in the AKI group was driven by the higher death rate (3 of 26 [11.5%] vs. 2 of 100 [2%]; p = 0.026), whereas the rate of neurological complication was similar in the 2 groups (Table 5). Major bleeding occurred in 1 patient in the AKI group (3.8%) and in none in the non-AKI group (p = 0.21). Independent predictors of 30-day MAE were AKI (HR: 4.83; 95% CI: 1.10 to 21.24; p = 0.037) and hemodynamic depression (HR: 5.58; 95% CI: 1.10 to 28.31; p = 0.038) (Table 6). Hemodynamic depression ≥2.5 min occurred in 5 of 12 patients (41.5%) with MAE and in 14 of 114 patients (12.5%) without MAE (OR: 5.01; 95% CI: 1.42 to 18.29; p = 0.019).

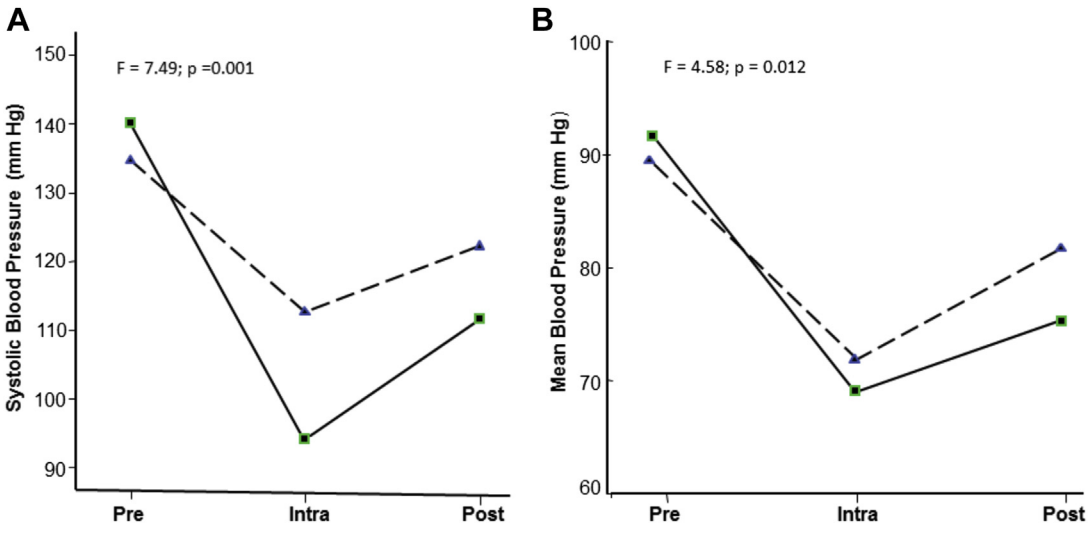
DISCUSSION

The main results of the current study addressing AKI in CKD patients undergoing CAS are as follow: 1) AKI rate is higher than expected; 2) hemodynamic depression (mostly due to hypotension), but not CM volume, represents an independent predictor of AKI; and 3) AKI is associated with a higher 30-day MAE rate.

AKI FOLLOWING CAS. The observed AKI rate (21%) was higher than expected. The reported low (<1%) contrast-induced AKI in previous studies may be explained by the following: 1) CAS is generally avoided in patients with severe renal dysfunction (14), and/or 2) AKI is under-reported. In our population, according to the Mehran risk score (17), the predicted risk for contrast-induced AKI was approximately 17%. This risk score, although developed in patients undergoing CM exposure for coronary interventions, is an independent predictor of AKI even in CKD patients undergoing CAS.

PATHOPHYSIOLOGY OF AKI AFTER CAS. Our results suggest a prevalent role of hemodynamic depression in the pathophysiology of AKI following CAS. The lack of significant differences in both traditional risk factors for AKI (i.e., baseline eGFR, diabetes mellitus, age, contrast media volume) and the Mehran risk score between patients with versus those without hemodynamic depression reinforces the independent role of hemodynamic depression in the pathophysiology of AKI in this clinical setting. Hemodynamic depression after CAS almost always was due to hypotension (alone and/or associated to bradycardia). This results from baroreceptor

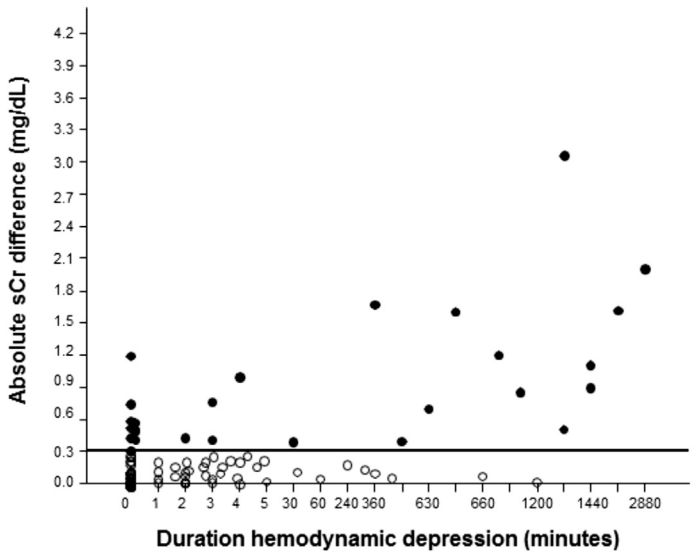
FIGURE 1 Systolic and Mean Blood Pressure in Patients With and Without AKI



Systolic **(A)** and mean blood pressure **(B)** before, during, and after the procedure in patients with **(solid line)** and without **(dashed line)** acute kidney injury (AKI). Post hoc test adjusted p value was assessed by repeated measures analysis of variance model.

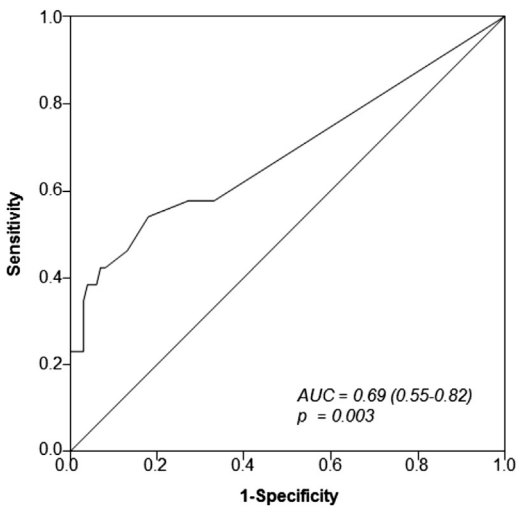
stimulation that occurs particularly at the time of balloon inflation in the region of the carotid sinus (24). Furthermore, nitinol stents are associated with a higher risk of hemodynamic depression. This finding might be explained by their higher outward radial expansion force than that of the braided Elgiloy stents, thereby exerting higher pressure on the carotid sinus. Given that the carotid sinus has its main role in short-term blood pressure regulations, this finding might be explained by continuing post-deployment expansion of self-expanding stents (25). Hemodynamic depression has been associated with an increased risk of developing major periprocedural adverse clinical events, including death and stroke (9,26). In the CAS arm of the CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial), patients who had stroke more often experienced hemodynamic depression requiring treatment (27,28). Intraoperative hemodynamic depression has the potential to cause an ischemia-reperfusion injury, which, in turn, may substantially contribute to post-operative AKI (13). The putative major mechanism of peri-operative AKI is a decrease in kidney perfusion with associated ischemia and activation of inflammatory mediators, adhesion molecules, platelets, and thromboxane (29,30). It has been demonstrated an independent, graded relationship between the length of time spent with a mean blood pressure <55 mm Hg (13) or <60 mm Hg (31) and AKI. Furthermore, the longer the time with a mean blood pressure <55

FIGURE 2 Relationship Between Duration of Hemodynamic Depression and Absolute Change in sCr Levels



Relationship between duration of hemodynamic depression (minutes) and absolute change in serum creatinine (sCr) levels from baseline to peak value after contrast media exposure. **Open circles** represent patient without acute kidney injury (AKI); **closed circles** represent patients with AKI.

FIGURE 3 ROC Curves of Duration of Hemodynamic Depression for AKI Diagnosis



Receiver-operating characteristic (ROC) curves of duration of hemodynamic depression (min) for the diagnosis of acute kidney injury (AKI). AUC = area under the curve.

mm Hg, the higher the risk of 30-day death after surgery (13). In the current study, we identified 2.5 min as the threshold of hemodynamic depression duration with a 54% sensitivity and 82% specificity for AKI development (**Figure 3**). In healthy animals, renal blood flow is maintained (autoregulated) down to a mean blood pressure <70 mm Hg (32). It may be, however, that in CKD patients the autoregulation pathway becomes impaired. As such, optimizing peri-operative hemodynamics may mitigate or prevent this complication. This theory is supported by the observation that strategies preventing peri-operative hypotension are effective in reducing the incidence of AKI (33). Although we adopted the systematic use of atropine before balloon post-dilation, the rate of hemodynamic depression is still high. Additional strategies, therefore, should be implemented to prevent this complication in CKD patients.

TABLE 4 Independent Predictors of AKI

	Multivariable Analysis			
	OR	95% CI	p Value	Bootstrap p Value*
Hemodynamic depression	4.01	1.07-15.03	0.009	0.039
Risk score	1.29	1.03-1.60	0.024	0.034
Male	6.07	1.18-31.18	0.021	0.030
Stent diameter	1.71	0.66-4.38	0.129	0.262
Nitinol stent	0.23	0.04-1.33	0.199	0.101
Pre-dilation	2.73	0.39-18.76	0.267	0.308
eGFR	1.02	0.93-1.11	0.381	0.381
Contrast media volume	0.99	0.98-1.01	0.738	0.637

*For the adjusted p values, bootstrap sampling method (200 repetitions) was employed. Hosmer-Lemeshow goodness-of-fit p = 0.71.

CI = confidence interval; eGFR = estimated glomerular filtration rate; OR = odds ratio.

Unlike coronary interventions, the impact of CM seems to be attenuated in CAS, due to the dominant role of hemodynamic depression (17,34). Our data may be interpreted in the following ways: 1) by the limited power of the study (due to the small sample size) to find significant difference in contrast volume between the AKI and non-AKI groups; 2) by taking into account the systematic adoption of the recommended prophylactic strategies to prevent CM-induced kidney damage, and the systematic use of atropine to prevent hemodynamic depression; and 3) by the possibility that hemodynamic depression may increase the nephrotoxic potential of CM. Hemodynamic depression, by impairing renal circulation, may prolong the time for CM elimination and, therefore, increase the risk of CM-induced tubular epithelial cells apoptosis (20). The high AKI rate observed in the present study may support this hypothesis.

AKI AND PROGNOSIS IN CKD PATIENTS UNDERGOING CAS. CKD has been well described as an independent predictor of mortality in patients undergoing vascular operations (35) and coronary artery revascularizations (36). Controversies still exist on the prognostic association between CKD and both surgical and percutaneous revascularization for carotid artery stenosis (2,3,7). Possible explanations are the limited data available on CKD patients enrolled in the major trials and the lack of systematic evaluation of post-procedural AKI. Indeed, no data on CKD patients have been reported in several trials (27,37–39). In the SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial (40), only 6% of patients in the CAS arm had CKD. The most important data comes from the CARE (Carotid Artery Revascularization and Endarterectomy) registry (2), where CKD occurred in 37.5% of patients. The majority (63%) of these CKD patients underwent CAS. Although patients with CKD treated by CAS had worse unadjusted in-hospital and 30-day outcomes (mainly driven by higher stroke rates), this association was no longer significant after adjustment for patients' baseline characteristics (2). Indeed, worse kidney function was associated with older age and a significantly higher prevalence of comorbidities. Therefore, it has been proposed that CKD may only be a marker for more advanced disease and more comorbidities

TABLE 5 MAE at 1 Month in the Global Population and in Patients With Versus Those Without AKI

	Global Population (n = 126)	AKI Group (n = 26)	Non-AKI Group (n = 100)	p Value
Cumulative MAE	12 (9.5)	5 (19.5)	7 (7)	0.058
Death	5 (4)	3 (11.5)	2 (2)	0.026
Any neurological complication	7 (5.5)	2 (7.6)	5 (6.5)	0.63
Minor stroke	6 (4.8)	1 (3.8)	5 (5)	0.045
Major stroke	1 (0.7)	1 (3.8)	0	0.58
Myocardial infarction	0	0	0	–

Values are n (%).
AKI = acute kidney injury; MAE = major adverse events.

TABLE 6 Independent Predictors of 30-Day MAE

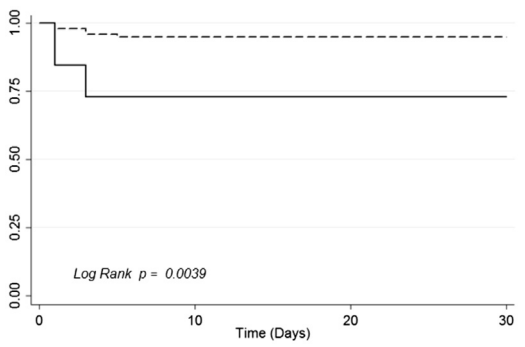
	Multivariable Analysis		
	HR	95% CI	p Value*
AKI	4.83	1.10–21.24	0.037
Hemodynamic depression	5.58	1.10–28.31	0.038
eGFR	1.06	1.00–1.12	0.061
Age	1.12	0.99–1.26	0.071
Male	0.42	0.09–1.92	0.263

*For the adjusted p values, bootstrap sampling method (200 reps) was employed. Hosmer-Lemeshow goodness-of-fit p = 0.44.
HR = hazard ratio; other abbreviations as in Tables 1, 4, and 5.

(3). The present study suggests another possible explanation: the unfavorable prognosis following CAS is mostly limited to CKD patients experiencing post-procedural AKI. Further studies, however, are needed to test whether strategies preventing AKI may improve outcomes following CAS in CKD patients.

STUDY LIMITATIONS. This is a single-center, observational study, with the intrinsic shortcoming of potentially limited external validity and intrinsic bias. The small sample size represents a further limitation. Although hypotension is recognized as an important factor in the development of post-operative complications, there is uncertainty in how to optimally define intraoperative hypotension (41). In a clinical perspective, the low sensitivity of hemodynamic depression time represents an important limitation. Indeed, given the short threshold time, a high sensitivity would have been a more clinically useful marker. However, the observed graded relationship between the length of time spent with hemodynamic depression and AKI highlights the importance of limit hemodynamic depression time as much as possible (13). The present results refer only to patients with CKD. Additional studies are needed to assess the role of hemodynamic depression and CM volume in the occurrence of AKI and MAE in non-CKD patients undergoing CAS.

FIGURE 4 Kaplan-Meier Curves of 30-Day MAE in Patients With and Without AKI



Kaplan-Meier curves of 30-day major adverse events (MAE) in patients with **(continuous line)** and without **(dotted line)** acute kidney injury (AKI). Unadjusted log rank p value = 0.0039.

CONCLUSIONS

The current study addressing AKI in CKD patients undergoing CAS suggests the following: 1) AKI rate is higher than expected; 2) hemodynamic depression (mostly due to hypotension) but not CM volume represents an independent predictor of AKI; and 3) AKI is associated with a higher 30-day MAE rate.

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PERSPECTIVES

WHAT IS KNOWN? AKI following CAS may occur because of iodinated CM and hemodynamic depression.

WHAT IS NEW? In CKD patients, undergoing CAS, hemodynamic depression but not CM volume represents an independent predictor of AKI, and AKI is associated with a higher 30-day MAE rate.

WHAT IS NEXT? Further studies are needed to assess whether preventing hemodynamic depression will reduce the AKI rate and therefore improve outcome following CAS.

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