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Statins and Incidence of Contrast-Induced Acute Kidney Injury Following Coronary Angiography - Five Year Experience at a Tertiary Care Center☆

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ABSTRACT

Background: Role of statins in prevention of contrast-induced acute kidney injury (CI-AKI) in patients undergoing coronary angiography remains controversial. We studied the use of statins in decreasing CI-AKI following coronary angiography.

Methods: We reviewed all patients who underwent coronary angiography with or without PCI and had a follow-up creatinine from January 2012 to December 2016 at a single tertiary care center in the United States. CI-AKI was defined as 0.3 mg/dL absolute rise in creatinine. Patients who were on moderate to high-intensity statins or received moderate to high-intensity statins prior to coronary angiography were included in the statin group. Crude and adjusted odds ratios (AOR) were calculated using univariate multiple logistic regression analysis.

Results: Out of 2055 patients (females = 30.7%, mean age 58.0 ± 12.5 years, statin group = 886, non-statin group = 1169), 293 (14.3%) developed CI-AKI. Mean estimated glomerular filtration rate (eGFR) was not significantly different between the statin and the non-statin group (86.5 mL/min/1.73 m^2 vs 87.1 mL/min/1.73 m^2, $p = 0.65$). There was no significant difference in the incidence of CI-AKI between statin and non-statin group (14.4% vs 14.1%, $p = 0.83$). When adjusted for other risk factors, statin use was not significantly associated with decreased risk of CI-AKI (AOR) = 0.8, [95% confidence interval (CI) = 0.6–1.1, $p = 0.19$]. Results remained statistically non-significant on subgroup analysis of patients with acute coronary syndrome (ACS) (OR = 0.8, 95% CI = 0.6–1.2, $p = 0.27$), patients who had percutaneous coronary intervention (PCI) (OR = 1.1, 95% CI = 0.6–1.7, $p = 0.81$) and patients with eGFR < 60 mL/min/1.73 m^2 (OR = 0.9, 95% CI = 0.6–1.5, $p = 0.9$).

Conclusion: Statin use prior to coronary angiography is not associated with decreased incidence of CI-AKI.

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1. Introduction

Statin pretreatment reduces periprocedural myocardial infarction in patients undergoing percutaneous coronary intervention [1]. Statins have been extensively studied for their pleiotropic effects including anti-inflammatory, anti-oxidative, anti-thrombotic and endothelial function enhancement, which begins even before their lipid-lowering effects [2]. Renal medullary tissue inflammation, hypoxia, and oxidative stress are the major mechanisms of contrast-induced acute kidney injury (CI-AKI) [3–6]. This created interest in the role of statins for prevention of CI-AKI in patients undergoing coronary contrast procedures. Even after two decades of investigations, it is still unclear whether statins have any significant role in decreasing the occurrence of CI-AKI following coronary angiography.

According to the 2014 European Society of Cardiology percutaneous coronary intervention (PCI) guidelines, short-term, high-dose statin therapy for prevention of CI-AKI in patients with moderate-to-severe chronic kidney disease (CKD) is a class IIa recommendation [7]. But few recent large meta-analyses have found inconsistent findings on benefits of statins for reduction of CI-AKI [2,8]. The primary objective

Abbreviations: AA, African American; ACS, acute coronary syndrome; AOR, adjusted odds ratio; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI-AKI, contrast induced acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IABP, intra-aortic balloon pump; IRB, institutional research board; LVEF, left ventricular ejection fraction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

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of our study was to assess the role of statins in reducing the incidence of CI-AKI in patients undergoing coronary angiography with or without PCI in a tertiary care medical center in the United States.

2. Methods

2.1. Design and study population

In this retrospective study, we reviewed all patients who underwent coronary angiography with or without PCI ($n = 3367$) between January 2012 to December 2016 at a tertiary care medical center in the United States. Clinical and laboratory characteristics were obtained by chart review of electronic medical records. This study was approved by John H. Stroger Jr. Hospital of Cook County institutional research board (IRB). IRB waived the requirement for an informed consent because of retrospective chart review study design. This study entirely conforms in accordance with the Declaration of Helsinki. Patients with the end-stage renal disease on hemodialysis at the time of the procedure, age <18 and patients with no follow-up creatinine were excluded. A total of 2055 patients were included in the final statistical analysis. Based on whether the patients received statins prior to coronary angiography, the subjects were divided into statin and non-statin group. In-hospital clinical outcomes including the requirement for hemodialysis and length of hospital stay were also estimated.

2.2. Definitions

AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines as ≥0.3 mg/dL absolute rise in creatinine from baseline within 48 h of exposure to contrast [9]. Patients who were on moderate to high-intensity statin therapy or who received them prior to coronary angiography were included in the statin group. All other patients who were on low intensity statin therapy or who were not on any statins at the time of coronary angiography were included in the non-statin group. Atorvastatin 20–80 mg, Rosuvastatin 10–20 mg, Simvastatin 20–80 mg, Pravastatin 40–80 mg and Lovastatin 40–80 mg were recognized as moderate to high-intensity statins [10]. Low-osmolar or iso-osmolar non-ionic contrast agents were used for all angiographic purposes.

2.3. Statistical analysis

Continuous variables were expressed as the mean ± standard deviation and compared using independent sample *t*-test. Categorical variables were expressed as numbers with percentages and compared using Pearson chi-square test. Independent predictors of CI-AKI were identified using logistic regression analysis. The independent association of statin use with incidence of CI-AKI was evaluated by binary logistic regression model adjusted for following co-variables including age, race/ethnicity, prior chronic kidney disease, prior heart failure, diabetes mellitus, hypertension, preprocedural anemia, periprocedural drop in hemoglobin, intra-aortic balloon pump (IABP) use, acute coronary syndrome (ACS) as index clinical presentation and presence of cardiogenic shock. Subgroup analysis was carried out to assess whether statin use was associated with decreased incidence of CI-AKI in high risk groups like patients presenting with ACS, patients with significant CKD and those who underwent PCI. All p values are 2-sided and a p-value < 0.05 was considered as statistically significant in all case. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline characteristics

A total of 2055 patients who underwent coronary angiography were included in the final analysis. Baseline demographics, clinical profile and in-hospital outcomes of the patients included in statin and non-statin groups are provided in Table 1. The mean age was 58.0 ± 12.5 years with 30.7% being females. Almost two-thirds of the patients ($n = 1392$, 67.7%) presented with ACS and about one-third of the patients ($n = 695$, 33.8%) underwent PCI. In the statin group, 341 (38.5%) patients underwent PCI whereas 354 (30.3%) patients from non-statin group had PCI. The study includes 16.1% ($n = 331$) patients with moderate to severe CKD defined by a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 and 14.7% ($n = 303$) patients with moderate to severe anemia defined by a hemoglobin (Hb) between 7.1 g/dL to 11.0 g/dL. Out of 2055 patients, 14.3% ($n = 293$) developed CI-AKI. We did not find any significant difference in mean contrast volume (136.2 mL vs 126.6 mL, $p = 0.06$), preprocedural baseline creatinine (1.1 mg/dL vs 1.0 mg/dL, $p = 0.21$) and number of patients with various stages of CKD between the statin and the non-statin groups. Statin group had significantly larger proportion of patients with cardiac risk factors like diabetes mellitus, hypertension and prior history of stroke, coronary artery disease (CAD) or coronary artery bypass grafting (CABG) when compared to the non-statin group.

3.2. Predictors of CI-AKI

Significant predictors of CI-AKI identified from our study cohort are listed in Table 2. The patients who developed CI-AKI were older (60.8 vs 57.5 years, $p < 0.001$), more likely African American (58.4% vs 44.0%, $p < 0.001$) and had a higher prevalence of hypertension (81.2% vs 73.8%, $p = 0.01$), diabetes mellitus (42.3% vs 35.1%, $p = 0.02$), heart failure (36.2% vs 20.1%, $p < 0.001$), baseline CKD stage 3 (25.6% vs 10.6%, $p < 0.001$), CKD stage 4 (8.5% vs 1.6%, $p < 0.001$) and CKD stage 5 (2.0% vs 0.5%, $p < 0.001$). Cardiogenic shock (6.5% vs 2.0%, $p < 0.001$) and IABP use (2.7% vs 1.0%, $p = 0.02$) prior or within 24 h of PCI were seen more in the CI-AKI group over the non-CI-AKI group. The patients with baseline GFR < 60 mL/min/1.73 m^2 were at 3.6 to 6.1 times higher risk of CI-AKI and those with preprocedural anemia were associated with 5 times increased risk of CI-AKI following coronary angiography.

3.3. Statin use and incidence of CI-AKI

The statin group had a total of 886 (43.1%) patients. There was no difference in the incidence of CI-AKI between the statin and non-statin group (14.4% versus 14.1%, $p = 0.83$). When adjusted for other confounding variables, statin use was not associated with significantly decreased incidence of CI-AKI [adjusted odds ratio (AOR) = 0.8, 95% CI = 0.6–1.1, $p = 0.19$]. Results of subgroup analysis for specific high-risk groups with ACS at clinical presentation, baseline eGFR < 60 mL/min/1.73 m^2 and those who underwent PCI are provided in Table 3. Results from sub group analysis remained statistically non-significant in ACS subgroup (OR = 1.2, 95% CI = 0.9–1.7, $p = 0.2$), subgroup of patients with eGFR < 60 mL/min/1.73 m^2 (OR = 0.81, 95% CI = 0.6–1.7, $p = 0.15$) and PCI subgroup (OR = 0.9, 95% CI = 0.6–1.5, $p = 0.9$).

3.4. In-hospital outcomes

3.8% of patients who developed CI-AKI required hemodialysis versus 0.1% of the non-CI-AKI group ($p < 0.001$). Mean hospital stay was significantly longer in patients with CI-AKI when compared to the non-CI-AKI patient group (6.7 days vs 4.5 days, $p < 0.001$).

4. Discussion

Pleiotropic effects of statins have been a long time clinical interest in preventing CI-AKI [2]. However, it is unclear whether these preclinical benefits of statins translate well into clinical medicine. We assessed the role of statins in reducing the incidence of CI-AKI in patients who underwent coronary angiography in a tertiary care medical center

Table 1
Baseline clinical characteristics and in-hospital outcomes.

Baseline characteristics and outcomes	Subgroups	Total ($n = 2055$)	Prior statin use		p value
			Statin group ($n = 886$)	No statin group ($n = 1169$)	
Mean age in years		58.0 ± 12.5	59.3 ± 9.7	57.0 ± 14.0	0.00
Female		631 (30.7%)	289 (32.6%)	342 (29.3%)	0.06
Race/ethnicity	African American	946 (46.0%)	386 (43.6%)	560 (48.0%)	0.14
	Caucasian	459 (22.3%)	201 (22.7%)	258 (22.1%)	
	Hispanic	380 (18.5%)	167 (18.8%)	213 (18.2%)	
	Asian	247 (12.0%)	123 (13.9%)	124 (10.6%)	
Current smoking		868 (42.2%)	346 (39.1%)	522 (44.7%)	0.01
Hypertension		1539 (74.9%)	765 (86.3%)	774 (66.2%)	0.00
Diabetes mellitus		743 (36.2%)	460 (51.9%)	283 (24.2%)	0.00
Prior CAD, stroke or CABG		643 (31.3%)	509 (57.4%)	134 (11.5%)	0.00
Prior heart failure		461 (22.4%)	237 (26.7%)	224 (19.2%)	0.00
Mean LVEF (%)		48.6 ± 17.2	48.8 ± 16.8	48.5 ± 17.6	0.70
Statin use		886 (43.1%)	758 (43.0%)	128 (43.7%)	0.83
Prior CKD (eGFR in mL/min/1.73 m^2)	No CKD (eGFR > 90)	927 (45.1%)	394 (44.5%)	533 (45.6%)	0.71
	Stage 2 (eGFR 61 to 90)	797 (38.8%)	339 (38.3%)	458 (39.2%)	
	Stage 3 (eGFR 31 to 60)	262 (12.7%)	120 (13.5%)	142 (12.1%)	
	Stage 4 (eGFR 15 to 30)	54 (2.6%)	27 (3.0%)	27 (2.3%)	
	Stage 5 (eGFR <15)	15 (0.7%)	6 (0.7%)	9 (0.8%)	
Clinical presentation	Stable angina	303 (14.7%)	187 (21.1%)	116 (9.9%)	0.00
	Unstable angina	512 (24.9%)	239 (27.0%)	273 (23.4%)	
	NSTEMI	682 (33.2%)	284 (32.1%)	398 (34.0%)	
	STEMI	198 (9.6%)	58 (6.5%)	140 (12.0%)	
	Heart failure	322 (15.7%)	103 (11.6%)	219 (18.7%)	
Cardiogenic shock at presentation or within 24 h		55 (2.7%)	19 (2.1%)	36 (3.1%)	0.12
IABP use		26 (1.3%)	10 (1.1%)	16 (1.4%)	0.39
No PCI		1360 (66.2%)	545 (61.5%)	815 (69.7%)	0.02
PCI with number of coronary stents	1	526 (25.6%)	260 (29.3%)	266 (22.8%)	0.02
	2	142 (6.9%)	69 (7.8%)	73 (6.2%)	
	3	23 (1.1%)	9 (1.0%)	14 (1.2%)	
	4	4 (0.2%)	3 (0.3%)	1 (0.1%)	
Mean contrast volume (mL)		130.1 ± 89.0	136.2 ± 92.2	126.6 ± 85.5	0.06
Contrast volume use (mL)	<100	1030 (50.1%)	387 (43.7%)	643 (55.0%)	0.00
	101–200	652 (31.7%)	316 (35.7%)	336 (28.7%)	
	201–300	285 (13.9%)	135 (15.2%)	150 (12.8%)	
	301–400	64 (3.1%)	35 (4.0%)	29 (2.5%)	
	>400	24 (1.2%)	13 (1.5%)	11 (0.9%)	
Mean baseline Hb (g/dL)		13.1 ± 2.0	13.0 ± 2.0	13.3 ± 2.0	0.00
Anemia severity	Mild (Hb 11.1 g/dL–13 g/dL)	606 (29.5%)	283 (31.9%)	323 (27.6%)	0.02
	Moderate (Hb 9.1 g/dL–11.0 g/dL)	224 (10.9%)	109 (12.3%)	115 (9.8%)	
	Severe (Hb 7.0 g/dL–9.0 g/dL)	76 (3.7%)	34 (3.8%)	42 (3.6%)	
Mean GFR (mL/min/1.73 m^2)		86.8 ± 30.6	86.5 ± 32.3	87.1 ± 29.3	0.65
Mean pre-procedural creatinine (mg/dL)		1.1 ± 0.6	1.1 ± 0.6	1.0 ± 0.5	0.21
Requirement for new hemodialysis		13 (0.6%)	5 (0.6%)	8 (0.7%)	0.48
Requirement for blood transfusion		32 (1.6%)	15 (1.7%)	17 (1.5%)	0.40
Mean length of hospital stay in days		4.8 ± 4.8	4.9 ± 4.8	4.7 ± 4.7	0.40

serving a diverse patient population in the United States. We found that use of moderate to high-intensity statin pretreatment in patients undergoing coronary angiography with or without PCI is not associated with a significant reduction in the incidence of CI-AKI. We believe this could be because our study has a larger proportion of patients with moderate to severe CKD and significant anemia who share a relatively higher risk profile for development of CI-AKI. Both CKD and anemia emerged as strong independent predictors of CI-AKI following angiography in this study. Our findings regarding statin use are in contrast to the recent meta-analysis by Giacoppo et al., where they concluded that statin use was beneficial in preventing CI-AKI [2]. Study heterogeneity arising from the inclusion of studies from nearly two decades with wide variability in patient demographics and clinical profile could influence the results of this meta-analysis [11]. On the other hand, our study findings correlate with and support the interpretations of Thomson et al. in their large meta-analysis, where there was no statistical evidence to support the use of statins for decreasing the incidence of CI-AKI in patients with CKD stage 3 and worse (GFR < 60 mL/min/1.73 m^2) [8]. In another meta-analysis by Wang et al., statins were found to be effective in preventing CI-AKI in CKD patients undergoing coronary contrast procedures, but the results were driven in favor of statins mainly by a single study by Han et al. which included patients with GFR up to 89 mL/min/1.73 m^2 [12,13]. Our study underlines the fact that we lack strong clinical evidence to support the use of statins for reducing the incidence of CI-AKI, especially in advanced CKD patients. The lack of reno-protective benefits of statins in advanced CKD patients could be due to two reasons. One, because, patients having advanced CKD with underlying irreversible kidney damage may not have significant healthy renal tissue for the pleiotropic effects of statins to act on. Two, the risk of CI-AKI

Table 2
Predictors of contrast-induced acute kidney injury.

Variables		OR	95% CI	p-Value
African American		1.8	1.3–2.6	<0.001
Hypertension		1.5	1.1–2.1	0.01
Diabetes mellitus		1.4	1.1–1.7	0.02
Prior heart failure		2.2	1.7–2.9	<0.001
Intra-aortic balloon pump use		2.7	1.2–6.3	0.02
Acute coronary syndrome		1.8	1.4–2.3	<0.001
Cardiogenic shock		3.3	1.9–5.9	<0.001
Chronic kidney disease	Stage 3	3.6	2.5–5.1	<0.001
	Stage 4	7.8	4.4–14.0	<0.001
	Stage 5	6.1	2.1–17.4	<0.001
Preprocedural anemia		5.3	3.8–7.3	<0.001
Periprocedural hemoglobin drop		1.3	1.1–1.7	0.03

Table 3
Subgroup analysis of association of statin use and CI-AKI following coronary angiography.

Category	Subgroups (*n*)	Total incidence of AKI (%)	AKI incidence in statin vs non-statin group		OR	95% CI	*p* value
			Statin group	Non-statin group			
ACS at clinical presentation	Non-ACS (663)	114 (17.2%)	55 (48.2%)	59 (51.8%)	1.1	0.7–1.7	0.6
	ACS (1392)	179 (12.9%)	83 (46.4%)	96 (53.6)	1.2	0.9–1.7	0.2
Baseline CKD based on eGFR	eGFR ≥ 60 mL/min/1.73 m^2 (1724)	187 (10.8%)	88 (47.1%)	99 (52.9%)	1.2	0.9–1.7	0.2
	eGFR < 60 mL/min/1.73 m^2 (331)	106 (32.0%)	50 (47.2%)	56 (52.8%)	1.1	06–1.7	0.81
PCI	No PCI (1360)	195 (14.3%)	90 (46.2%)	105 (53.8%)	1.3	0.9–1.8	0.06
	PCI (695)	98 (14.1%)	48 (49.0%)	50 (51.0%)	0.9	0.6–1.5	0.9

associated with preexisting advanced CKD and significant anemia probably offset the minor benefits of statins.

Interestingly, another probable reason for our finding of statins not being beneficial for reducing CI-AKI in our study could be because of greater representation of African American (AA) patients. Our study shows that being of AA origin is independently associated with increased risk of CI-AKI following coronary contrast exposure (Table 2). This is further supported by Grams et al. in their large community-based study, where they found that AA patients are at 30% additional risk of acute kidney injury adjusted for other known clinical risk factors [14]. APOL1 gene variations are implicated in the progressive decline of GFR in CKD patients of AA origin, but their role in the development of AKI is yet to be characterized by preclinical and clinical studies [15]. Also, most of the clinical evidence regarding the use of statins for prevention of CI-AKI is from east Asian countries with some sub-groups from European countries, with gross under-representation of AA patients [8,12,13,16]. This creates ambiguity regarding the generalizability of these study findings. Further epidemiological and multicenter, prospective clinical studies which include AA patients and other minority populations are necessary to assess the role of preprocedural statin use for prevention of CI-AKI.

Prior clinical studies suggested that the effect of statins in decreasing CI-AKI was more pronounced in patients with ACS rather than non-ACS clinical presentation [17,18]. In our subgroup analysis, statins failed to show any significant reduction in the incidence of CI-AKI in either ACS or non-ACS clinical presentations. This could be because we included patients with high-risk factors for CI-AKI like prior CKD, anemia and ST-elevation myocardial infarction (STEMI) who were mostly excluded in previous studies and randomized controlled trials [8]. Also in our subgroup analysis based on baseline eGFR level and whether patients underwent PCI or not, statin group consistently did not show any significant difference in incidence of CI-AKI when compared to the non-statin group. This reemphasizes the uncertainty of clinical utility of statins to decrease the occurrence of CI-AKI following coronary angiography even in high risk groups like ACS at clinical presentation, CKD with eGFR < 60 mL/min/1.73 m^2 and those patients who underwent PCI.

AKI is the foremost trigger for progressive decline in renal function in any patient with pre-existing CKD. Currently, there are only limited proven preventive strategies like intravenous hydration to use in high-risk groups to reduce the incidence of CI-AKI. This reiterates the clinical importance of better risk stratification and timely correction of potentially reversible risk factors rather than focusing on medical therapy like statins with doubtful clinical utility for decreasing incidence of CI-AKI [19,20]. Further multicenter, prospective clinical studies are necessary for evaluation of pleiotropic benefits of statins in reduction of CI-AKI in high-risk patients undergoing coronary angiography.

4.1. Limitations

This study has several limitations because of retrospective observational study design. First, the observed associations could be influenced by unknown confounders because of no randomization and hence causality cannot be assessed. Second, selection bias arises because of exclusion of patients without post-procedural laboratory results. Third, long-term outcomes of subjects could not be studied because of data unavailability and outcomes studied were restricted to the length of hospital stay and need for hemodialysis. Fourth, our findings are not adjusted for procedural characteristics, duration of statin therapy and use of reno-protective strategies. Fifth, the temporal relationship between statin use and time of coronary angiography and its significance could not be studied because of retrospective nature of the study design.

5. Conclusion

We found that use of moderate to high-intensity statin prior to coronary angiography with or without PCI is not significantly associated with decreased incidence of CI-AKI. Further prospective multicenter investigations are required in high-risk groups to reassess the role of statins in the prevention of CI-AKI.

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