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High Plasma Exposure of Statins Associated With Increased Risk of Contrast-Induced Acute Kidney Injury in Chinese Patients With Coronary Artery Disease

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The role of statins in reducing the incidence of contrast-induced acute kidney injury (CI-AKI) remains controversial. We sought to evaluate the association between CI-AKI and high plasma exposure of statins in coronary artery disease (CAD) patients undergoing coronary angiography (CAG). This association was first evaluated in 1,219 patients with CAD receiving atorvastatin (AT) therapy and validated in 635 patients receiving rosuvastatin (RST) therapy. The plasma concentrations of statins were quantified using validated UPLC-MS/MS methods and CI-AKI incidence was assessed during the first 48 h postoperatively. Among all participants (n = 1,854), AKI occurred in 57 of 1219 (4.7%) in the AT cohort and 30 of 635 (4.7%) in the RST cohort. High plasma AT-all exposure was associated with increased risk of CI-AKI (odds ratio [OR]: 2.265; 95% confidence interval [CI]: 1.609-3.187; p < 0.0001). Plasma AT-all concentration in the CI-AKI group (22.40 \pm 24.63 ng/mL) was 2.6-fold higher than that in the control group $(8.60 \pm 9.65 \text{ ng/mL})$. High plasma RST exposure also significantly increased the risk of CI-AKI (OR: 2.281; 95% CI: 1.441–3.612; p = 0.0004). We further divided patients into two subgroups for each statin according to baseline renal function, and association between high plasma statin exposure and CI-AKI still remained highly significant in both subgroups. This study suggests for the first time that high plasma exposure of statins may significantly increase the risk of CI-AKI. Statins should be used with greater caution in CAD patients undergoing CAG to reduce the occurrence of CI-AKI.

Keywords: contrast-induced acute kidney injury, coronary angiography, atorvastatin, rosuvastatin, plasma exposure

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INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) is a known complication of intravascular administration of contrast media used in coronary angiography (CAG) and percutaneous coronary interventions (PCI) (Chalikias et al., 2016); and is associated with increased mortality, morbidity, healthcare expenditure, and prolonged hospital stay (Nash et al., 2002; Prasad et al., 2016). CI-AKI has become the third leading cause of iatrogenic renal failure in the United States (Prasad et al., 2016). Previous report indicated that even mild postoperative AKI is independently associated with an almost 5-fold increase in in-hospital death (Birnie et al., 2014). Clinically, the incidence of CI-AKI is greater in patients with cardiovascular diseases or pre-existing renal insufficiency (Goldenberg and Matetzky, 2005; Itoh et al., 2005; Ledneva et al., 2009). The reported incidence ranges from 2 to 50% (Aurelio and Durante, 2014).

Hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are potent inhibitors of cholesterol biosynthesis and exert beneficial effects in the primary and secondary prevention of coronary artery disease (CAD). The prophylactic benefit of statins in reducing the incidence of CI-AKI has been investigated in several observational (Khanal et al., 2005; Patti et al., 2008; Lev et al., 2009) and randomized studies (Patti et al., 2011); however, other studies have reported inconsistent and conflicting results (Argalious et al., 2010; Mithani et al., 2011; Billings et al., 2016; Park et al., 2016). Therefore, whether preoperative statin therapy has a preventive, neutral, or detrimental role on AKI remains unclear and hotly debated. To the best of our knowledge, no studies have evaluated the relationship between high plasma exposure of statins and the risk of CI-AKI.

Therefore, the objective of the current study was to systematically investigate the effects of high plasma exposure of widely prescribed statins (atorvastatin [AT] and rosuvastatin [RST]) and their metabolites on the incidence of CI-AKI in patients with CAD undergoing CAG.

METHODS

Ethics Statement

The present study was approved by the Medical Ethical Review Committee of Guangdong General Hospital and conducted according to the Declaration of Helsinki. All participants gave written informed consent in accordance with the Declaration of Helsinki.

Study Design and Patients

We conducted a prospective two-stage study to evaluate the effects of two statins on CI-AKI separately. In stage I (test set), 1,219 patients taking AT were recruited, including 1,023 patients without chronic kidney disease (CKD) and 196 patients with CKD. In stage II (validation set), 635 patients taking RST were enrolled for further validation; 531 of these were without CKD, whereas 104 were with CKD.

All patients were sequentially recruited in Guangdong General Hospital from January 2010 to December 2013 according to the same inclusion and exclusion criteria. Baseline information, including demographics, medical history, biochemical measurements, and medication was obtained from the hospital information database. Patients who underwent CAG and were diagnosed with CAD were included in the study.

The exclusion criteria included the followings: (1) age < 18 years or age > 80 years; (2) renal transplantation or dialysis; (3) liver insufficiency (defined as serum transaminase concentrations > 3 times the upper limit of normal [120 U/L], or a diagnosis of cirrhosis); (4) being pregnant or lactating; (5) advanced cancer or haemodialysis; (6) the concentrations of statins or their metabolites were lower than limit of detection (3:1 noise).

Coronary Angiography Procedure

CAG is performed to define the extent and severity of CAD in patients with suspected symptoms whose clinical characteristics and results of non-invasive testing indicate a high likelihood of CAD and who are amenable to, and candidates for, coronary revascularization (Fihn et al., 2014). Information derived from the CAG procedure will be took into consideration in patient management, and the risks and benefits of the procedure have been carefully considered and understood by the patients.

We used the Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score, an angiographic scoring system to determine the complexity, severity, and atherosclerotic burden of CAD (Sianos et al., 2005; Ikeda et al., 2012). SYNTAX score has been shown to independently predict MACE and longterm prognosis risks in stable CAD patients who underwent revascularization (Serruys et al., 2009; Mohr et al., 2013).

Images of coronary angiograms were obtained with Syngo Dynamics cardiovascular imaging software (Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania). The SYNTAX score was calculated for each patient using a computer program consisting of sequential and interactive self-guided questions according to the SYNTAX score calculator version 2.11. The SYNTAX score reflects a comprehensive anatomical assessment, and a low SYNTAX score was defined as \leq 22, an intermediate score as 23 to 32, and a high score as \geq 33.

Clinical Endpoint

The study endpoint was the diagnosis of postoperative CI-AKI. According to the Acute Kidney Injury Network criteria (Mehta et al., 2007), CI-AKI was diagnosed if a patient had an absolute increase in serum creatinine (sCr) concentration \geq 0.3 mg/dL (26.4 μ mol/L) from baseline or a relative increase \geq 50% (1.5-fold from baseline) in sCr concentration for more than 6 h within 48 h after surgery.

CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m² using the Modification of Diet in Renal Disease equation (National Kidney Foundation, 2002). SCr levels were measured upon admission and within 48 h after surgery. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol, creatine kinase (CK), creatine kinase MB (CKMB), and other standard clinical parameters were measured in the morning before the procedure.

Plasma Sample Preparation

Each eligible patients had been taking the same dose of AT or RST for at least 7 days prior to blood sampling. Statin dosage was prescribed by physician in accordance with patients' condition. Blood samples were obtained at 10–12 h post-dose in the morning before the CAG and collected in EDTA-coated tubes. Plasma was separated within 2 h by centrifugation at 3,000 rpm for 10 min at 4°C and then stored at -80° C until analysis.

Quantification of Plasma Concentrations of Statins and Their Metabolites

A reliable assay of ultra-performance liquid chromatography coupled with tandem mass spectrometry (UPLC–MS/MS) was developed and validated for the quantification of AT, its five metabolites, and internal standard (IS) carbamazepine in human plasma as described previously (Cai et al., 2017).

A sensitive UPLC-MS/MS assay was also developed and validated for the simultaneous quantification of RST, rosuvastatin lactone (RSTL), and N-desmethyl rosuvastatin (DM-RST) in human plasma. All the three analytes and the corresponding IS (carbamazepine) were extracted from 200 µL buffered human plasma (adding 100 μ L ammonium acetate of pH = 4.0 to 100 µL human plasma) by liquid–liquid extraction with ethyl acetate and then separated on an ACQUTY UPLC HSS T3 column (3.0 \times 100 mm, 1.8 μ m). The elution was performed at a rate of 0.3 mL/min using a mobile phase containing acetonitrile and 0.05% formic acid in water over a linear gradient of 30-85% acetonitrile. Mass detection was performed on a Waters Xevo TQ-S triplequadrupole mass spectrometer in positive electrospray ionization mode. The responses of RST, RSTL, and DM-RST were optimized at the m/z 482.1 \rightarrow 258.1, m/z464.1 \rightarrow 270.1, m/z 468.0 \rightarrow 258.0, respectively.

Statistical Analysis

The demographic and clinical characteristics were summarized using counts (percentages) for the categorical variables and mean (standard deviation, *SD*) for the continuous variables. As the ranges of the concentrations of statins and metabolites were skewed, logarithmic transformation was performed prior to analysis. AT-all is calculated amount of plasma AT concentration and equivalent concentrations of its two pharmacologically equipotent metabolites; this value represents overall therapeutic efficacy (Lennernas, 2003). Given that approximate 90% of plasma pharmacologically activity is accounted for RST, we only applied plasma RST concentration to represent the overall therapeutic efficacy (White, 2002).

Linear regression analysis was applied to evaluate the effects of the baseline demographic and clinical characteristics on the plasma concentrations of statins and metabolites. A univariate logistic regression analysis was conducted to evaluate the effects of plasma concentrations, baseline demographic, and clinical characteristics on the risk to CI-AKI and to calculate odds ratio (OR) and 95% confidence interval (CI). Variables with p < 0.05 were entered into the multivariate model, and only variables with p < 0.05 were retained in the model. P < 0.05 was considered statistically significant. Data analysis was performed using SAS 9.4 (SAS Inst, Cary, NC, USA).

Predictive Diagnostic Power of Variables for CI-AKI

In the study, the Daim package in R (version 3.2.3, http://www. R-project.org/) was used to construct the classification models. For each predictor variable, the true positive rate and false positive rate as a predictor of CI-AKI was evaluated by the receiver operating characteristic (ROC) curves using the area under the curve (AUC) as a measure of diagnostic effectiveness (Zweig and Campbell, 1993). First, every independent variable associated with CI-AKI were selected to construct the classifier for estimating the diagnostic effectiveness of a single predictor. Then, all significant variables were combined as a classifier for estimating the diagnostic effectiveness of variable combinations. The optimal cutoffs were calculated by selecting the data point that maximized the true positive rate and minimized the false positive rate.

RESULTS

Patient Characteristics and Their Effects on Plasma Statins and Metabolites Exposure

An overview of the enrolment of the patients is presented in **Figure 1**. In stage I, plasma concentrations of AT and its metabolites widely varied, which is consistent with published data (DeGorter et al., 2013). The concentrations of five metabolites were highly correlated with AT concentration (all r > 0.5, p < 0.0001). Among 1,219 patients with AT therapy, 21 (1.72%) were taking 10 mg AT, 1058 (86.79%) were 20 mg AT, and 140 (11.48%) were 40 mg AT compliance with prescription, respectively. Patients' baseline characteristics and their impacts on the AT concentration are summarized in **Table 1**.

Univariate linear regression analysis showed that plasma ATall concentration was affected by age, dosage, SYNTAX score, level of ALT, AST, Scr, eGFR, and other clinical parameters. Among these variables, increasing age (estimate = 0.0140, p < 0.0001), higher dosage (estimate = 0.0173, p = 0.0002), higher SYNTAX score (estimate = 0.0059, p = 0.0161), higher level of ALT (estimate = 0.0059, p = 0.0012), and Scr (estimate = 0.0012, p = 0.0008) were independently associated with a higher plasma AT-all concentration (**Table 1**).

In stage II, of the patients with RST therapy, 11 (1.74%) were taking 5 mg RST, 549 (86.73%) were 10 mg RST, 67 (10.58%) were 20 mg RST and 6 (0.95%) were 40 mg RST. Multiple linear regression analysis showed that plasma RST concentration was lower in patients with lower level of AST (estimate = -0.0059, p = 0.0286) and using angiotensin converting enzyme inhibitors (estimate = -0.3584, p = 0.0320) (**Table 2**).

Effects of Baseline Characteristics and Plasma Exposure of AT and Metabolites on CI-AKI

In patients receiving AT therapy in stage I, the clinical endpoint CI-AKI within 48 h after the surgery occurred in 57 (4.7%) patients. Univariate logistic analysis showed that higher plasma exposure of AT-all, AT and its five metabolites, SYNTAX core,



and other factors were associated with a higher risk of CI-AKI (**Table 3**). Multivariate analysis revealed that high plasma AT-all exposure (OR: 2.265; 95% CI: 1.609–3.187; p < 0.0001), diabetes (OR: 1.953; 95% CI: 1.030–3.704; p = 0.0403), high level of AST (OR: 1.009; 95% CI: 1.004–1.015; p = 0.0013), Scr (OR: 1.003; 95% CI: 1.001–1.006; p = 0.0118), eGFR (OR: 0.977; 95% CI: 0.964–0.991; p = 0.0017), and use of proton pump inhibitors (PPIs) (OR: 3.979; 95% CI: 1.828–8.659; p = 0.0005) were independent risk factors for CI-AKI (**Table 3**). Plasma AT-all concentration in patients with CI-AKI (22.40 ± 24.63 ng/mL) was 2.6-fold higher than that in controls (8.60 ± 9.65 ng/mL) (**Figure 2C**).

Considering the impact of baseline renal function on CI-AKI, we further divided patients into two subgroups, which were patients without CKD and with CKD. In patients without CKD in stage Ia, CI-AKI occurred in 23 (2.2%) patients. In multivariate logistic model, only plasma AT-all exposure (OR: 2.381 95% CI: 1.459–3.884; p = 0.0005), male (OR: 0.327; 95% CI: 0.133–0.805; p = 0.0150), CK level (OR: 1.001; 95% CI: 1.000–1.001; p = 0.0030), and use of PPIs (OR: 10.128; 95% CI: 2.330–44.028; p = 0.0020) were retained in the model implying that they were independent risk factors for CI-AKI (Table S1). Plasma AT-all concentration in patients with CI-AKI (19.88 ± 23.69 ng/mL) was 2.5fold higher than that in controls (8.08 ± 8.57 ng/mL) (**Figure 2A**).

In patients with CKD in stage Ib, CI-AKI occurred in 34 (17.3%) patients, which is much higher than that in stage Ia. The association between high plasma AT-all exposure and CI-AKI remained highly significant. Multivariate logistic regression analysis revealed that high plasma AT-all exposure (OR: 5.377 95% CI: 2.403–12.032; p < 0.0001) was still an independent risk factors for CI-AKI (Table S2). Plasma AT-all concentration in patients with CI-AKI (24.10 ± 25.45 ng/mL) was 2.0-fold higher than that in controls (11.82 ± 14.29 ng/mL) (**Figure 2B**).

Effects of Baseline Characteristics and Plasma Exposure of RST and Metabolites on CI-AKI

To further confirm the predictive value of plasma statin concentration for CI-AKI, we assessed the association in patients who received RST treatment in stage II, and the association between high plasma statin exposure and CI-AKI remained highly significant. CI-AKI occurred in 30 (4.7%) patients who received RST treatment. Multivariate logistic regression analysis revealed that patients in the CI-AKI group had higher plasma RST exposure (OR: 2.281; 95% CI: 1.441–3.612; p = 0.0004), higher dosage (OR: 1.088; 95% CI: 1.015–1.167; p = 0.0175), and were with more diabetes (OR: 2.680; 95% CI: 1.153–6.230; p = 0.0220), heart failure (OR: 7.904; 95% CI: 3.032–20.606; p < 0.0001) (**Table 4**). RST plasma concentration in the CI-AKI group (8.28 ± 5.49 ng/mL) was 2.7-fold higher than that in the control group (3.04 ± 3.26 ng/mL) (**Figure 3C**).

Patients without CKD and with CKD were also analyzed separately. In patients without CKD in stage IIa, CI-AKI occurred in 17 (3.2%) patients. Plasma exposure of RST and DM-RST, dosage, hypertension, level of CK, and CKMB were entered into the multivariate logistic model, and only plasma RST exposure (OR: 3.556; 95% CI: 1.763–7.171; p = 0.0004), dosage (OR: 1.083; 95% CI: 1.000–1.173; p = 0.0493), and hypertension (OR: 3.492; 95% CI: 1.167–10.450; p = 0.0253) were retained in the model implying that they were independent risk factors for CI-AKI (Table S3). CI-AKI patients (7.61 ± 4.66 ng/mL) exhibited 2.5-fold higher plasma RST concentration than controls (3.04 ± 3.26 ng/mL) (**Figure 3A**).

In patients with CKD in stage IIb, CI-AKI occurred in 13 (12.5%) patients. Higher plasma exposure of RST and DM-RST were associated with a higher risk of CI-AKI. Multivariate analysis revealed that patients in the CI-AKI group had higher plasma DM-RST exposure (OR: 1.935; 95% CI: 1.056–3.547; p = 0.0327), and were with more heart failure (OR: 18.817; 95%

TABLE 1 | Patient characteristics and their effects on plasma concentration of AT-all.

Characteristics		Value N (%) or mean \pm SD	Plasma AT-all concentration, ng/mL				
				Univariat	e analysis	Multivariat	te analysis
			mean ± SD	Estimate	p-value	Estimate	<i>p</i> -value
DEMOGRAPHIC DATA							
Total number		1219	9.25 ± 11.19				
Age (years)		62.95 ± 10.00		0.0122	< 0.0001	0.0140	<0.0001
Sex	Female	297 (24.36)	9.89 ± 14.40	-0.0032	0.9633		
	Male	922 (75.64)	9.04 ± 9.94				
Dosage (mg)	10	21 (1.72)	4.23 ± 3.69	0.0197	< 0.0001	0.0173	<0.0001
	20	1058 (86.79)	8.72 ± 10.47				
	40	140 (11.48)	13.98 ± 15.27				
SYNTAX score		13.81 ± 12.19		0.0094	0.0001	0.0059	0.0161
MEDICAL HISTORY							
Arrhythmia	No	1104 (90.86)	9.08 ± 10.61	0.0707	0.4914		
	Yes	111 (9.14)	10.98 ± 15.86				
Diabetes	No	895 (73.66)	8.99 ± 10.56	0.0266	0.6924		
	Yes	320 (26.34)	9.99 ± 12.82				
Heart failure	No	1097 (90.29)	8.93 ± 10.46	0.1210	0.2261		
	Yes	118 (9.71)	12.24 ± 16.35				
Hypertension	No	499 (41.04)	8.40 ± 9.14	0.0881	0.1435		
<u> </u>	Yes	717 (58.96)	9.83 ± 12.41				
Hvperlipidemia	No	1073 (88.24)	9.36 ± 11.28	-0.0265	0.7734		
71	Yes	143 (11.76)	8.40 ± 10.57				
BIOCHEMICAL MEASUR	REMENTS	- (-)					
ALT. U/L		28.69 ± 16.80		0.0055	0.0017	0.0059	0.0012
AST. U/L		31.05 ± 30.42		0.0031	0.0014		
Scr. µmol/L		96.70 ± 81.69		0.0014	< 0.0001	0.0012	0.0008
eGFR. mL/min/1.73 m ²		91.26 + 72.98		-0.0013	0.0013		
CK. U/L		158.91 ± 408.68		0.0001	0.4328		
CKMB. U/L		8.82 + 13.67		0.0026	0.2603		
CHOL, mmol/L		4.32 ± 1.13		0.0318	0.2305		
LDLC, mmol/L		2.60 ± 0.94		0.0569	0.0739		
HDLC, mmol/L		0.99 ± 0.26		-0.1445	0.2058		
TRIG. mmol/L		1.58 ± 1.11		-0.0018	0.9463		
GLUC, mmol/L		6.66 ± 2.59		0.0267	0.0204		
Lpa. mg/L		295.05 ± 315.79		0.0003	0.0114		
APOA. a/L		1.06 ± 0.29		-0.3237	0.0048		
MEDICATION							
β-blockers	No	137 (11.27)	8.20 ± 8.00	0.0263	0.7787		
F	Yes	1079 (88 73)	9.38 ± 11.54				
ACEIs	No	467 (38 4)	9.46 ± 11.17	-0.0255	0.6761		
	Yes	749 (61 6)	9.11 ± 11.22	0.0200	0107.01		
CCBs	No	848 (69.74)	8.93 ± 10.17	-0.0102	0.8743		
	Yes	368 (30 26)	9.97 ± 13.25	2.0102	2.01.10		
PPIs	No	588 (48.36)	8.69 + 10.79	0.0550	0.3535		
-	Yes	628 (51.64)	9.77 ± 11.55				

Estimates were calculated by applying a linear regression model. Variables with P < 0.05 were entered into the multivariate model, and only variables with P < 0.05 were retained in the model ACEIs, angiotensin converting enzyme inhibitors; ALT, alanine aminotransferase; APOA, apolipoprotein a; AST, aspartate aminotransferase; CCBs, calcium channel blockers; CHOL, cholesterol; CK, creatine kinase; CKMB, creatine kinase MB; eGFR, estimated glomerular filtration rate; GLUC, glucose; HDLC, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Lpa, lipoprotein (a); PPIs, proton pump inhibitors; Scr, serum creatinine; SD, standard deviation; SYNTAX score, Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery score; TRIG, triglyceride.

TABLE 2 | Patient characteristics and their effects on plasma concentration of RST.

Characteristics	Value <i>N</i> (%) or mean ± <i>SD</i>		Plasma RST concentration, ng/mL				
				Univariate analysis		Multivariate analysis	
			mean ± SD	Estimate	p-value	Estimate	<i>p</i> -value
DEMOGRAPHIC DATA							
Total number		635	3.29 ± 3.57				
Age (years)		62.07 ± 10.50		0.0044	0.5810		
Sex	Female	164 (25.83)	3.67 ± 3.72	-0.2438	0.1992		
	Male	471 (74.17)	3.16 ± 3.51				
Dosage (mg)	5	11 (1.74)	2.79 ± 3.64	-0.0052	0.7932		
	10	549 (86.73)	3.19 ± 3.42				
	20	67 (10.58)	4.32 ± 4.57				
	40	6 (0.95)	2.40 ± 3.53				
SYNTAX score		14.19 ± 12.49		-0.0062	0.3671		
MEDICAL HISTORY							
Arrhythmia	No	584 (91.97)	3.20 ± 3.44	0.0445	0.8844		
	Yes	51 (8.03)	4.32 ± 4.73				
Diabetes	No	503 (79.21)	3.11 ± 3.33	0.2358	0.2498		
	Yes	132 (20.79)	3.97 ± 4.32				
Heart failure	No	591 (93.07)	3.14 ± 3.29	0.0189	0.9539		
	Yes	44 (6.93)	5.34 ± 5.90				
Hypertension	No	356 (56.06)	3.21 ± 3.50	0.0603	0.7189		
	Yes	279 (43.94)	3.40 ± 3.67				
Hyperlipidemia	No	566 (89.13)	3.27 ± 3.57	0.1139	0.6699		
	Yes	69 (10.87)	3.45 ± 3.63				
BIOCHEMICAL MEASUR	REMENTS						
ALT, U/L		29.27 ± 18.80		0.0021	0.6281		
AST, U/L		31.19 ± 30.87		-0.0064	0.0180	-0.0059	0.0286
Scr, µmol/L		88.66 ± 40.28		0.0007	0.7517		
eGFR, mL/min/1.73 m ²		98.55 ± 83.96		-0.0003	0.7818		
CK, U/L		146.90 ± 321.49		-0.0004	0.1253		
CKMB, U/L		7.99 ± 11.10		-0.0100	0.1901		
CHOL, mmol/L		4.53 ± 1.45		-0.1029	0.0753		
LDLC, mmol/L		2.77 ± 1.13		-0.2219	0.0029		
HDLC, mmol/L		1.00 ± 0.26		-0.3090	0.3473		
TRIG, mmol/L		1.67 ± 1.24		0.0994	0.1407		
GLUC, mmol/L		7.04 ± 3.20		-0.0251	0.3342		
Lpa, mg/L		275.42 ± 292.45		-0.0006	0.0658		
APOA, g/L		1.06 ± 0.27		0.1348	0.6887		
MEDICATION							
β-blockers	No	86 (13.54)	3.71 ± 4.11	-0.3353	0.1675		
	Yes	549 (86.46)	3.22 ± 3.48				
ACEIs	No	284 (44.72)	3.54 ± 3.59	-0.3823	0.0220	-0.3584	0.0320
	Yes	351 (55.28)	3.09 ± 3.55				
CCBs	No	455 (71.65)	3.35 ± 3.70	-0.0735	0.6904		
	Yes	180 (28.35)	3.15 ± 3.24				
PPIs	No	288 (45.35)	3.04 ± 3.18	0.1108	0.5070		
	Yes	347 (54.65)	3.49 ± 3.86				

Estimates were calculated by applying a linear regression model. Variables with P < 0.05 were entered into the multivariate model, and only variables with P < 0.05 were retained in the model.

RST, rosuvastatin; other abbreviations as in Table 1.

TABLE 3 | Effects of baseline characteristics and plasma concentrations of AT and its metabolites on CI-AKI in stage I.

<table-container>kl%)or means 20kl%)or means 20Refers 0PalentRefers 0PalentEnduration10250.39 ± 6.071.040 (1.010-1.071)0.00450.59 ± 6.0750.59 ± 7.0750.59 ±</table-container>	Characteristics		Without CI-AKI	Without CI-AKI With CI-AKI		Univariate analysis		Multivariate analysis	
Determining 1102 57 Total number 67.79 0.0094 0.0792 0.0794 Sex Findle 284 (24.44) 13.22.81) 1.058 (0.591-20.692) 0.7792 Dearge (rig) 10 19(16.44) 2 (3.51) 1.022 (0.988-1.059) 0.2288 20 1018 (87.19) 40 (75.69) 40 (77.59) 0.0006 1.0006 (1.015-1.057) 0.0006 SNTAX accos 13.84 ± 12.33 10.38 ± 12.23 1.038 (1.015-1.057) 0.0006 PCI No 398 (43.43) 17 (23.82) 1.180 (0.455-2.814) 0.7002 MBOLAL Higgs 11.89 (0.457-2.814) 0.7002 1.853 (1.030-3.704) 0.0403 Yes 705 (80.70) 61 (105.37) 0.0002 1.853 (1.030-3.704) 0.0403 Yes 105 (80.70) 61 (75.31) 0.0002 0.0239 1.953 (1.030-3.704) 0.0403 Yes 105 (80.71) 2.37 (3.74,4) 3.300 (1.747-6.232) 0.0002 1.953 (1.030-3.704) 0.0403 Yes 105 (80.71) 6.37 (80.71) 6			N (%) or mean \pm SD	N (%) or mean \pm SD	OR (95% CI)	P-Value	OR (95% CI)	P-Value	
Tatiah mutaki11257Age62.78 ± 10.0360.39 ± 8.71.008 10.51-2.0020.0702SaxFenda241 24.4113 (22.81)1.008 10.51-2.0020.772Main47.0 (5.84)44.0 (7.18)0.220 (385-1.508)0.2281Main10 19 (16.4)2.63.511.022 (0.985-1.508)0.2081Main10 10 10.4110.75.40.00000.0000SMTWace10.54 ± 12.1319.38 ± 12.231.030 (10.16-1.007)0.0000MEDCALHSTON10.99 (94.34)17.72.821.120 (0.089-21.98)0.4873ArmformaNo10.058 (90.07)6.100.590.00001.003 (1.020-3.700)0.0016MartineNo10.058 (90.07)6.100.590.00201.003 (1.020-3.700)0.0016MartineNo10.058 (90.07)6.100.590.00201.003 (1.020-3.700)0.0016MartineNo10.058 (90.07)22.08.600.02200.0021MartineNo10.058 (90.07)0.00150.00160.0016No10.059 (90.01.02)0.00160.00160.00160.0016No10.058 (90.07.100)0.00160.00160.00160.0016No10.058 (90.07.100)0.00160.00160.00160.0016No10.058 (90.07.100)0.00160.00160.00160.0016No10.058 (90.07.100)0.00160.00160.00160.0016No10.058 (90.07.100)0.00160.00160.00160.0016<	DEMOGRAPHIC DATA								
Age E07.94 10.90 10.90 10.90 10.90 10.90 Sax Ferrade 284 24.94 1312.251 1.056 0.07792	Total number		1162	57					
SaxParale28 (47.49)13 (22.81)1.006 (0.581-2.002)0.772Dasage (mg)1019 (1.64)2 (3.51)1.022 (0.366-1.059)0.226820103 (07.19)40 (77.89)0.026 (0.161-0.07)0.005300103 (07.19)13.83 ± 12.231.036 (1.061-0.107)0.005SWINZ score13.94 ± 12.1313.83 ± 12.231.036 (0.169-0.107)0.005PCINo390 (94.39)17 (29.87)1.230 (0.689-2.198)0.4837ArrythmiaNo1053 (0.003)61 (0.53)0.4837ArrythmiaNo1053 (0.003)61 (0.53)0.00301.810 (1.07-3.12)0.033DabelesNo800 (47.27)22 (38.6)0.00210.0023Yea1069 (0.57)1.614 (1.007-3.12)0.0031.853 (1.003-3.704)0.0403HayntrainNo1064 (10.2)43 (76.4)3.300 (1.747-6.222)0.0023Yea104 (81.02)43 (76.4)3.300 (1.747-6.222)0.0021Yea104 (81.02)61 (89.47)0.878 (0.370-2.083)0.767HyperbraineNo494 (14.70)0.678 (0.370-2.083)0.767Yea102 (28.18)61 (89.47)1.006 (1.061-1.02)0.0013Sci, mail103 (1.12-1.14)1.006 (1.061-1.02)0.0014Yea103 24 (14.77)1.006 (1.061-1.02)0.0014Yea104 (1.02)1.017 ± 1.201.006 (1.061-1.02)0.0116Sci, mail103 (1.12-1.14)1.006 (1.061-1.02)0.0116Yea <td>Age</td> <td></td> <td>62.78 ± 10.03</td> <td>66.39 ± 8.97</td> <td>1.040 (1.010–1.071)</td> <td>0.0084</td> <td></td> <td></td>	Age		62.78 ± 10.03	66.39 ± 8.97	1.040 (1.010–1.071)	0.0084			
Main Dasage (mg)Main 19 (1.64)4 (77.16) 2 (0.3961-0.56)0.2268	Sex	Female	284 (24.44)	13 (22.81)	1.095 (0.581–2.062)	0.7792			
Decage (mg) 10 19 (1 e4) 2 (3 x) 1.022 (0.986 - 1.059) 0.2288 40 130 (1714) 10(17.4)		Male	878 (75.56)	44 (77.19)					
No 40138 (11.18)45 (78.98)SYNTX score13.84 ± 12.1319.39 ± 12.231.038 (1.015 - 1.067)0.0006SYNTX score13.84 ± 12.1319.39 ± 12.231.038 (1.015 - 1.067)0.0006MEUCAL HISTORY12.20 (0.686 - 2.180)0.4837.PCINo399 (44.37)1.180 (0.495 - 2.814)0.70381.953 (1.030 - 3.704)0.0403Yes1053 (00.7)61105.30DebetesNo290 (6.27)32 (61.4)1.181 (1.047 - 3.122)0.0203Yes1054 (1.70)43 (73.44)3.300 (1.747 - 6.233)0.0022Haurt falureNo1024 (8.17)15.08 (4.7)0.878 (0.370 - 2.083)0.7673HyperfolomiaNo1024 (8.17)15.08 (1.037 - 3.082)0.0230HyperfolomiaNo1024 (8.17)15.08 (1.037 - 2.08)0.7673HyperfolomiaNo1022 (8.17)1.009 (1.000 - 1.023)0.0013Soft_MovilNo1022 (8.18)51.72 (3.52)0.081 (0.37 - 0.23)0.7673 <td< td=""><td>Dosage (mg)</td><td>10</td><td>19 (1.64)</td><td>2 (3.51)</td><td>1.022 (0.986–1.059)</td><td>0.2268</td><td></td><td></td></td<>	Dosage (mg)	10	19 (1.64)	2 (3.51)	1.022 (0.986–1.059)	0.2268			
PAP10 (P1.19)P10 (P1.29)P10 (P1.29)<		20	1013 (87.18)	45 (78.95)					
SWNTA score 18.84 ± 12.13 19.88 ± 12.23 1.036 (1.015-1.057) 0.0006 MEDICAL HISTORY V V V N 0.483 0.4837 V N PCI No 105 (8.07) 17 (29.82) 1.250 (0.689-2.194) 0.4837 V N N 105 (8.07) 6 (10.53) Diabeles No 2080 (74.27) 36 (81.4) 1.814 (1.047-3.142) 0.035 1.853 (1.039-3.704) 0.0403 Meat falure No 1064 (91.02) 43 (75.49) 3.300 (1.747-6.232) 0.0002		40	130 (11.19)	10 (17.54)					
MEDICAL HISTORY PCI No 399 (43.4) 17 (29.82) 1.230 (0.889-2.198) 0.4837 PCI Yes 763 (65.66) 40 (70.18) 0.7032 Arhythmia No 1053 (90.03) 51 (84.7) 1.180 (0.489-2.198) 0.4837 Diabetes No 660 (74.27) 35 (61.4) 1.814 (1.047-3.142) 0.0336 1.963 (1.030-3.704) 0.0403 Hypertansion No 1054 (91.02) 43 (75.44) 3.300 (1.747-6.232) 0.0002 Hypertansion No 104 (9.89) 14 (24.56) 0.878 (0.370-2.003) 0.7673 Hypertansion No 1022 (98.18) 51 (98.47) 0.878 (0.370-2.003) 0.7673 SIOCHEMICAL MEASUREMENTS 23.63 ± 74.59 52.43 ± 27.84 1.005 (1.003-1.012) 0.0001 0.0001 (1.004-1.015) 0.0013 Soft, Jul. 30.34 ± 27.9 45.42 ± 70.84 1.008 (1.003-1.012) 0.0001 0.0077 (0.964-0.991) 0.0011 Soft, Jul. 30.34 ± 23.9 25.44 ± 28.27 1.003 (1.002-1.012) 0.0001 0.0917 (0.964-0.991) <	SYNTAX score		13.54 ± 12.13	19.38 ± 12.23	1.036 (1.015–1.057)	0.0006			
PCI No 399 (94.34) 17 (29.2) 1.230 (0.685-2.198) 0.4837 ''es 763 (65.66) 40 (70.16)	MEDICAL HISTORY								
\begin \ben \begi \begin \begin \begin \begin \begin \b	PCI	No	399 (34.34)	17 (29.82)	1.230 (0.689–2.198)	0.4837			
AnthythmiaNo1053 (00.63)1180 (0.496-2.814)0.7062'Yes1058 (0.07)6 (10.53)0.3031.953 (1.030-3.704)0.0403'Yes2080 (26.73)22 (28.6)0.0020.002'Yes1054 (91.02)43 (75.44)3.300 (1.747-6.232)0.02300.274HypettensionNo484 (41.76)15 (26.32)0.0301 (1.747-6.232)0.02300.274'Yes675 (56.24)42 (73.69)0.378 (0.370-2.08)0.76730.7673'Yes675 (56.24)106 (1.050 -0.01811.009 (1.004-1.015)0.018'Yes0.364 ± 26.7945.42 ± 70.841.005 (0.900-1.02)0.49600.0173Scr, mol/L10.364 ± 26.7945.42 ± 70.841.006 (1.000-1.012)0.0181.009 (1.004-1.015)0.01186GFE, mL/min/1.73 m²93.03 ± 73.9055.17 ± 35.250.958 (0.484-0.968)<0.001		Yes	763 (65.66)	40 (70.18)					
Yes 105 (8.07) 6 (10.53) Dabotes No 860 (74.27) 35 (61.4) 1.14 (1.047-3.142) 0.0336 1.953 (1.050-3.704) 0.0403 Heart failure No 1054 (91.02) 43 (75.44) 3.300 (1.747-6.232) 0.0020 Hypertansion No 444 (41.76) 15 (25.32) 2.008 (1.101-3.662) 0.0230 Hypertansion No 424 (41.76) 41 (72.68) 0.0770-2.083 0.7673 Hypertansion No 426 (21.68) 42 (73.68) 0.7670 0.4900 Yes 675 (68.24) 42 (73.68) 0.0709-1.020 0.4900 0.0011 Strup Vic 30.31 ± 10.79 45.42 ± 70.84 1.006 (1.005-1.012) 0.0011 0.0021 0.077 (0.964-0.991) 0.0118 Scr. µmol/L 90.37 ± 47.95 226.43 ± 282.21 1.006 (1.005-1.012) 0.0011 0.0021 0.977 (0.964-0.991) 0.0118 GGFR, µmin/L, 73 m ² 90.37 ± 47.95 226.43 ± 282.21 1.006 (1.002-1.012) 0.021 0.977 (0.964-0.991) 0.017 CK, UL, U,	Arrhythmia	No	1053 (90.93)	51 (89.47)	1.180 (0.495–2.814)	0.7092			
Diabetes No 860 (74.27) 35 (1.303-3.704) 0.0403 Ves 298 (25.73) 22 (38.6) .		Yes	105 (9.07)	6 (10.53)					
Yes 298 (25.7) 22 (38.6) Heart failure No 1054 (91.02) 43 (75.44) 3.03 (1.747-6.23) 0.002 Hypertipidemia No 484 (41.76) 15 (26.32) 2.008 (1.101-3.682) 0.0230 Hypertipidemia No 428 (41.76) 51 (82.4) 0.0270 0.0230 Hypertipidemia No 428 (41.76) 51 (82.4) 0.0770 0.0763 Hypertipidemia No 426 (22.16) 51 (83.4) 0.0771 ± 19.10 1.005 (0.990-1.020) 0.4960 AT, U/L 30.34 ± 26.79 45.42 ± 70.84 1.008 (1.003-1.012) 0.001 1.009 (1.004-1.015) 0.0118 GGFR, m/Lmin/1.73 m ² 90.37 ± 47.95 225.43 ± 282.21 1.008 (1.003-1.012) 0.0001 1.009 (1.004-1.015) 0.0118 GGFR, m/Lmin/1.73 m ² 90.37 ± 47.95 225.43 ± 282.21 1.000 (1.000-1.010) 0.0261 1.009 (1.004-1.015) 0.0118 GGFR, m/Lmin/1.73 m ² 90.37 ± 47.95 297.94 ± 991.87 1.000 (1.000-1.010) 0.0261 1.001 (1.002-1.021) 0.001 1.001 (1.002-1.010) 0.02	Diabetes	No	860 (74.27)	35 (61.4)	1.814 (1.047–3.142)	0.0336	1.953 (1.030–3.704)	0.0403	
Hear failure No 1054 (91.02) 43 (75.44) 3.300 (1.747-6.232) 0.0002 Hypertension No 404 (41.76) 15 (26.32) 2.008 (1.101-3.662) 0.0230 Hypertipidemia No 1022 (88.18) 51 (89.47) 0.876 (0.370-2.083) 0.7673 BIOCHEMICAL MEASURENTS 610.53) 610.53 0.0001 0.0001 0.0030 (1.004-1.015) 0.013 Sor, µno/L Ves 03.03 ± 26.79 45.42 ± 70.84 1.008 (1.005-1.012) 0.0460 1.009 (1.004-1.015) 0.013 Sor, µno/L 03.03 ± 26.79 0.25.43 ± 282.21 1.000 (1.005-1.012) 0.001 1.003 (1.01-1.005) 0.011 a67R, mL/mir/1.73 m ² 93.03 ± 73.90 55.17 ± 35.25 0.958 (0.948-0.968) <0.001		Yes	298 (25.73)	22 (38.6)					
Yee 104 (8.98) 14 (24.56) Hypertension No 484 (41.76) 15 (26.32) 0.008 (1.101-6.06) 0.767 Hypertipidemia No 070 (68.24) 42 (7.68) 0.778 (0.370-2.08) 0.767 Hypertipidemia No 1022 (88.18) 51 (99.47) 0.878 (0.370-2.08) 0.767 3 BIOELENELENELENELENELENEL 30.34 ± 26.79 45.42 ± 70.84 1.005 (0.990-1.02) 0.4080 1.009 (1.004-1.015) 0.0118 GSFL, mu/L 30.34 ± 26.79 45.42 ± 70.84 1.008 (1.003-1.012) 0.001 1.009 (1.004-1.015) 0.0118 GSFL, mu/L/1.73 m ² 90.37 ± 47.99 225.43 ± 282.21 1.008 (1.003-1.012) 0.001 1.009 (1.004-1.015) 0.0118 GSFL, mu/L/1.73 m ² 90.37 ± 47.99 227.043 ± 28.20 (0.948-0.968) <.00001	Heart failure	No	1054 (91.02)	43 (75.44)	3.300 (1.747–6.232)	0.0002			
Hypertension No 484 (41.76) 15 (26.32) 2.008 (1.101-3.662) 0.0230 Yes 675 (58.24) 42 (73.68) 5.188.47) 0.878 (0.370-2.083) 0.7673 Hyperipiolemia Yes 137 (11.82) 6 (10.53) 0.7673 0.4900 EDOCENTICAL MEASUREMENTS 28.62 ± 16.69 0.452 ± 70.84 1.008 (1.005-1.012) 0.0011 1.009 (1.004-1.015) 0.0173 Scr, µmol/L 90.37 ± 74.95 225.43 ± 282.21 1.008 (1.005-1.012) 0.001 0.071 (0.964-0.911) 0.017 CK, U/L 90.37 ± 74.95 225.43 ± 282.21 1.008 (1.005-1.012) 0.001 0.001 0.017 0.017 CK, U/L 90.37 ± 74.95 225.43 ± 282.21 1.008 (1.005-1.012) 0.021 0.017 0.017 0.017 0.017 0.017 0.017 0.017 0.017 0.017 0.011 0.0271 0.0261 0.027 0.0271 0.0241 0.001 0.017 0.011 0.017 0.017 0.017 0.017 0.017 0.017 0.017 0.017 0.017 <td></td> <td>Yes</td> <td>104 (8.98)</td> <td>14 (24.56)</td> <td></td> <td></td> <td></td> <td></td>		Yes	104 (8.98)	14 (24.56)					
Yes 675 (68.24) 42 (73.68) 51 (89.47) 0.878 (0.370-2.08) 0.7673 Hypenipidemia Yes 01022 (88.18) 51 (89.47) 0.878 (0.370-2.08) 0.7673 BIOCHEMICAL MEASUREMENTS E E E E E Str, U/L 28.86 ± 16.69 30.17 ± 19.10 1.006 (1.909-1.020) 0.4960 1.009 (1.004-1.015) 0.0013 Scr, µrol/L 30.34 ± 26.79 45.42 ± 27.0.84 1.008 (1.005-1.012) 0.0001 1.003 (1.001-1.006) 0.0118 Scr, µrol/L 30.34 ± 26.79 45.42 ± 27.0.84 1.008 (1.000-1.001) 0.021 0.001 0.031 (1.001-1.006) 0.0118 Scr, µrol/L 93.03 ± 73.90 55.17 ± 35.25 0.968 (0.948-0.968) <0.0001 0.977 (0.964-0.991) 0.017 CKUL, µrol/L 55.8 ± 11.80 13.46 ± 32.79 1.013 (1.002-1.001) 0.024 1.002 (1.004-1.015) 0.017 CKUL, µrol/L 2.60 ± 0.95 2.54 ± 0.89 0.955 (0.892-1.140) 0.0247 1.012 0.2574 1.012 0.2574 LDLC, mmol/L 0.99 ± 0.26	Hypertension	No	484 (41.76)	15 (26.32)	2.008 (1.101–3.662)	0.0230			
Hyperlipidemia YesNo1022 (88.18) 137 (11.82)51 (89.47) 6 (10.53)0.878 (0.370-2.083) 0.76730.7673BIOCHEMCAL MEXTERNETALT, U/L28.62 ± 16.6930.17 ± 19.101.005 (0.990-1.020) 1.003 (1.003-1.012)0.0018 0.00181.009 (1.004-1.015) 0.00180.0013 0.0011SSR, U/L30.34 ± 26.7945.42 ± 70.841.008 (1.003-1.012) 0.00180.0011 0.002100.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.00110.0011 0.002410.0011 0.002410.0011 0.002410.0011 0.002410.0011 0.002410.0011 0.002410.0011 0.002410.0011 0.002410.0011 0.002410.0011 0.002410.002410.0011 0.002410.002410.0011 0.002410.002410.0011 0.002410.002410.0011 0.002410.002410.002410.002410.002410.002410.0011 0.00241		Yes	675 (58.24)	42 (73.68)					
Yes 137 (11.82) 6 (10.53) EIOCHEMICAL MEASUREMENTS 28.62 ± 16.69 30.17 ± 19.10 1.005 (0.990-1.020) 0.4960 AST, U/L 28.62 ± 16.69 30.17 ± 19.10 1.008 (1.003-1.012) 0.0018 1.009 (1.004-1.015) 0.0013 Sor, µmol/L 90.37 ± 47.95 225.43 ± 282.21 1.008 (1.005-1.012) <.0001	Hyperlipidemia	No	1022 (88.18)	51 (89.47)	0.878 (0.370-2.083)	0.7673			
BIOCHEMICAL MEASUREMENTS ALT, U/L 28.62 ± 16.69 30.17 ± 19.10 1.005 (0.990-1.020) 0.4960 AST, U/L 30.34 ± 26.79 45.42 ± 70.84 1.008 (1.003-1.012) 0.0018 1.009 (1.004+1.015) 0.0013 Scr, µnol/L 90.37 ± 47.95 225.43 ± 282.21 1.008 (1.002-1.012) <0.0001		Yes	137 (11.82)	6 (10.53)					
AI, U/L 28.62 ± 16.69 30.17 ± 19.10 1.005 (0.990-1.020) 0.4960 AST, U/L 30.34 ± 26.79 45.42 ± 70.84 1.008 (1.003-1.012) 0.0018 1.009 (1.004-1.015) 0.0113 SCr, µmol/L 90.37 ± 47.95 225.43 ± 282.21 1.008 (1.005-1.012) <0.0011	BIOCHEMICAL MEAS	UREMENTS							
AST, U/L 30.34 ± 26.79 45.42 ± 70.84 1.008 (1.003-1.012) 0.0018 1.009 (1.004-1.015) 0.0013 Sr, µmol/L 90.37 ± 47.95 225.43 ± 282.21 1.008 (1.005-1.012) <0.0001	ALT, U/L		28.62 ± 16.69	30.17 ± 19.10	1.005 (0.990–1.020)	0.4960			
Scr. μmol/L 90.37 ± 47.95 225.43 ± 282.21 1.008 (1.005-1.012) <0.0011 1.003 (1.001-1.006) 0.0118 eGFR, mL/min/1.73 m ² 93.03 ± 73.90 55.17 ± 35.25 0.958 (0.948-0.968) <0.0001 0.977 (0.964-0.991) 0.0017 CK, U/L 151.84 ± 353.97 297.94 ± 991.87 1.000 (1.000-1.001) 0.0241 0.997 (0.964-0.991) 0.0017 CKMB, U/L 8.58 ± 11.80 13.46 ± 32.79 1.013 (1.002-1.004) 0.0247 0.964 CHOL, mmol/L 2.60 ± 0.95 2.54 ± 0.89 0.925 (0.689-1.240) 0.6012 0.975 LDC, mmol/L 0.99 ± 0.26 0.92 ± 0.26 0.292 (0.092-0.922) 0.0358 0.995 HDLC, mmol/L 1.59 ± 1.12 1.52 ± 0.76 0.935 (0.702-1.247) 0.6481 0.975 GLUZ, mmol/L 1.09 ± 310.42 356.40 ± 0.59 1.043 (0.950-1.144) 0.3780 0.995 Lpa, mg/L 1.07 ± 0.29 0.99 ± 0.24 0.343 (0.102-1.154) 0.0839 0.995 Mo 137 (11.82 0 (0 4.752 (0.897-∞) 0.0019 995 91.924	AST, U/L		30.34 ± 26.79	45.42 ± 70.84	1.008 (1.003–1.012)	0.0018	1.009 (1.004–1.015)	0.0013	
eGFR, mL/min/1.73 m ² 93.03 ± 73.90 55.17 ± 35.25 0.958 (0.948-0.968) <0.0001 0.977 (0.964-0.991) 0.017 CK, U/L 151.84 ± 353.97 297.94 ± 991.87 1.000 (1.000-1.001) 0.0261 CKMB, U/L 8.58 ± 11.80 13.46 ± 32.79 1.013 (1.002-1.024) 0.0247 CHOL, mmol/L 4.33 ± 1.14 4.15 ± 1.03 0.865 (0.672-1.112) 0.2574 LDLC, mmol/L 2.60 ± 0.95 2.64 ± 0.89 0.925 (0.689-1.240) 0.6012 HDLC, mmol/L 0.99 ± 0.26 0.92 ± 0.26 0.929 (0.092-0.922) 0.0358 TRIG, mmol/L 1.59 ± 1.12 1.52 ± 0.76 0.935 (0.702-1.247) 0.6481 GLUC, mmol/L 6.64 ± 2.59 6.96 ± 2.69 1.043 (0.950-1.144) 0.3780 Lpa, mg/L 291.99 ± 310.42 356.40 ± 408.46 1.001 (1.000-1.001) 0.1795 APOA, g/L 1.07 ± 0.29 0.99 ± 0.24 0.343 (0.102-1.154) 0.0839 CM volume, mL 184.34 ± 68.01 144.86 ± 51.83 0.999 (0.94-1.005) 0.7531 MEDICATION ACEIs No 137 (11.82) 0 (0) 4.752 (0.897-∞) 0.0019 Yes 1022 (88.18) 57 (100) ACEIs No 450 (38.83) 17 (29.82) 1.493 (0.836-2.666) 0.1750 Yes 370 (961.17) 40 (70.18) CCBS No 818 (70.58) 30 (52.63) 2.159 (1.264-3.687) 0.0048 Yes 370 (961.17) 40 (70.18) CCBS No 578 (49.87) 10 (17.54) 4.676 (2.340-9.343) <0.001 3.979 (1.828-8.659) 0.0050 Yes 361 (20.13) 77 (82.24) PIS No 578 (49.87) 10 (17.54) 4.676 (2.340-9.343) <0.001 3.979 (1.828-8.659) 0.0055 Yes 361 (50.13) 47 (82.46) PLASMA CONCENTERIU PLASMA CONCENTERIU ALASMA CONCENTERIU 2.47, ng/mL 3.50 ± 3.39 8.03 ± 9.79 2.300 (1.678-3.153) <0.0001	Scr, µmol/L		90.37 ± 47.95	225.43 ± 282.21	1.008 (1.005–1.012)	< 0.0001	1.003 (1.001–1.006)	0.0118	
$\begin{array}{c c c c c c } CK, U/L & 151.84 \pm 353.97 & 297.94 \pm 991.87 & 1.000 (1.000 -1.001) & 0.0261 \\ \hline timesmaplinesmaplicesmaplinesmaplinesmaplinesmaplinesmaplinesmaplinesmaplinesmaplikesmaplinesmaplikes$	eGFR, mL/min/1.73 m ²		93.03 ± 73.90	55.17 ± 35.25	0.958 (0.948–0.968)	< 0.0001	0.977 (0.964–0.991)	0.0017	
CKMB, U/L 8.58 ± 11.80 13.46 ± 32.79 1.013 (1.002-1.024) 0.0247 CHOL, mmol/L 4.33 ± 1.14 4.15 ± 1.03 0.865 (0.672-1.112) 0.2574 LDLC, mmol/L 2.60 ± 0.95 2.54 ± 0.89 0.925 (0.689-1.240) 0.6012 HDLC, mmol/L 0.99 ± 0.26 0.92 ± 0.26 0.292 (0.092-0.922) 0.0358 TRIG, mmol/L 1.59 ± 1.12 1.52 ± 0.76 0.935 (0.702-1.247) 0.6481 GLUC, mmol/L 6.64 ± 2.59 6.96 ± 2.69 1.043 (0.950-1.144) 0.3780 Lpa, mg/L 291.99 ± 310.42 3564.0 ± 408.46 1.001 (1.000-1.001) 0.1795 APOA, g/L 1.07 ± 0.29 0.99 ± 0.24 0.343 (0.102-1.154) 0.0839 CM volume, mL 148.43 ± 66.01 144.86 ± 51.83 0.999 (0.94+1.005) 0.7531 MEDICATION 1 172 (2.88.18) 57 (100) 57 ACEIs No 431 (0.758) 30 (52.63) 2.159 (1.264-3.687) 0.0018 Yes 709 (61.17) 40 (70.18)	CK, U/L		151.84 ± 353.97	297.94 ± 991.87	1.000 (1.000-1.001)	0.0261			
$\begin{array}{llllllllllllllllllllllllllllllllllll$	CKMB, U/L		8.58 ± 11.80	13.46 ± 32.79	1.013 (1.002–1.024)	0.0247			
LDLC, mmol/L 2.60 ± 0.95 2.54 ± 0.89 $0.925 (0.889-1.240)$ 0.6012 HDLC, mmol/L 0.99 ± 0.26 0.92 ± 0.26 $0.292 (0.092-0.922)$ 0.0358 TRIG, mmol/L 1.59 ± 1.12 1.52 ± 0.76 $0.935 (0.702-1.247)$ 0.6481 GLUC, mmol/L 6.64 ± 2.59 6.96 ± 2.69 $1.043 (0.950-1.144)$ 0.3780 Lpa, mg/L 291.99 ± 310.42 356.40 ± 408.46 $1.001 (1.000-1.001)$ 0.1795 APOA, g/L 1.07 ± 0.29 0.99 ± 0.24 $0.343 (0.102-1.154)$ 0.0839 CM volume, mL 148.43 ± 68.01 144.86 ± 51.83 $0.999 (0.994-1.005)$ 0.7531 MEDICATION V $1022 (88.18)$ $57 (100)$ $.5731$ ACEIs No $137 (11.82)$ $0 (0)$ $4.752 (0.897-\infty)$ 0.0019 CCBs No $181 (70.58)$ $30 (52.63)$ $2.159 (1.264-3.687)$ 0.0048 Yes $709 (61.17)$ $40 (70.18)$ $.57 (100)$ $.57 (49.87)$ 0.005 $.58 (50.13)$ $.57 (49.87)$ 0.007 $.59 (53.94, 62.63)$ $.50 (53.40-9.343)$ $.50 (0.001$ $.3979 (1.828-8.659)$ </td <td>CHOL, mmol/L</td> <td></td> <td>4.33 ± 1.14</td> <td>4.15 ± 1.03</td> <td>0.865 (0.672–1.112)</td> <td>0.2574</td> <td></td> <td></td>	CHOL, mmol/L		4.33 ± 1.14	4.15 ± 1.03	0.865 (0.672–1.112)	0.2574			
HDLC, mmol/L 0.99 ± 0.26 0.92 ± 0.26 0.292 (0.092-0.92) 0.0358 TRIG, mmol/L 1.59 ± 1.12 1.52 ± 0.76 0.935 (0.702-1.247) 0.6481 GLUC, mmol/L 6.64 ± 2.59 6.96 ± 2.69 1.043 (0.950-1.144) 0.3780 Lpa, mg/L 291.99 ± 310.42 356.40 ± 408.46 1.001 (1.000-1.001) 0.1795 APOA, g/L 1.07 ± 0.29 0.99 ± 0.24 0.343 (0.102-1.154) 0.0839 CM volume, mL 148.43 ± 68.01 144.86 ± 51.83 0.999 (0.994-1.005) 0.7531 MEDICATION 1707 ± 0.29 0.09 4.752 (0.897-∞) 0.0019 Yes 1022 (88.18) 57 (100)	LDLC, mmol/L		2.60 ± 0.95	2.54 ± 0.89	0.925 (0.689–1.240)	0.6012			
TRIG, mmol/L 1.59 ± 1.12 1.52 ± 0.76 $0.935 (0.702 - 1.247)$ 0.6481 GLUC, mmol/L 6.64 ± 2.59 6.96 ± 2.69 $1.043 (0.950 - 1.144)$ 0.3780 Lpa, mg/L 291.99 ± 310.42 356.40 ± 408.46 $1.001 (1.000 - 1.001)$ 0.1795 APOA, g/L 1.07 ± 0.29 0.99 ± 0.24 $0.343 (0.102 - 1.154)$ 0.0839 CM volume, mL 148.43 ± 68.01 144.86 ± 51.83 $0.999 (0.994 - 1.005)$ 0.7531 MEDICATION β-blockersNo $137 (11.82)$ $0 (0)$ $4.752 (0.897 - \infty)$ 0.0019 ACEIsNo $450 (38.83)$ $17 (29.82)$ $1.493 (0.836 - 2.666)$ 0.1750 CCBsNo $450 (38.83)$ $17 (29.82)$ $1.493 (0.836 - 2.666)$ 0.001 Yes $709 (61.17)$ $40 (70.18)$ 0.0048 CCBsNo $818 (70.58)$ $30 (52.63)$ $2.159 (1.264 - 3.687)$ 0.0048 Yes $341 (29.42)$ $27 (47.37)$ 0.0001 $3.979 (1.828 - 8.659)$ 0.0050 PISA CONCENTRATIONPLASMA CONCENTRATIONAf, ng/mL 3.95 ± 5.39 10.28 ± 12.14 $2.224 (1.697 - 2.915)$ <0.0001 A 3.95 ± 5.39 10.28 ± 12.14 $2.224 (1.697 - 2.915)$ <0.0001	HDLC, mmol/L		0.99 ± 0.26	0.92 ± 0.26	0.292 (0.092-0.922)	0.0358			
GLUC, mmol/L 6.64 ± 2.59 6.96 ± 2.69 $1.043 (0.950-1.144)$ 0.3780 Lpa, mg/L 291.99 ± 310.42 356.40 ± 408.46 $1.001 (1.000-1.001)$ 0.1795 APOA, g/L 1.07 ± 0.29 0.99 ± 0.24 $0.343 (0.102-1.154)$ 0.0839 CM volume, mL 148.43 ± 68.01 144.86 ± 51.83 $0.999 (0.994-1.005)$ 0.7531 MEDICATION Image: state st	TRIG, mmol/L		1.59 ± 1.12	1.52 ± 0.76	0.935 (0.702–1.247)	0.6481			
Lpa, mg/L 291.99 ± 310.42 356.40 ± 408.46 $1.001 (1.000-1.001)$ 0.1795 APOA, g/L 1.07 ± 0.29 0.99 ± 0.24 $0.343 (0.102-1.154)$ 0.0839 CM volume, mL 148.43 ± 68.01 144.86 ± 51.83 $0.999 (0.994-1.005)$ 0.7531 MEDICATION β -blockersNo $137 (11.82)$ $0 (0)$ $4.752 (0.897-\infty)$ 0.0019 γ es $1022 (88.18)$ $57 (100)$ ACEIsNo $450 (38.83)$ $17 (29.82)$ $1.493 (0.836-2.666)$ 0.1750 γ es $709 (61.17)$ $40 (70.18)$ CCBsNo $818 (70.58)$ $30 (52.63)$ $2.159 (1.264-3.687)$ 0.0048 γ es $341 (29.42)$ $27 (47.37)$ PIsNo $578 (49.87)$ $10 (17.54)$ $4.676 (2.340-9.343)$ <0.001 $3.979 (1.828-8.659)$ 0.0005 PLASMA CONCENTRATION A (0.95 ± 5.39) 10.28 ± 12.14 $2.224 (1.697-2.915)$ <0.0001 2-AT, ng/mL 3.50 ± 3.39 8.03 ± 9.79 $2.300 (1.678-3.153)$ <0.0001	GLUC, mmol/L		6.64 ± 2.59	6.96 ± 2.69	1.043 (0.950–1.144)	0.3780			
$\begin{array}{llllllllllllllllllllllllllllllllllll$	Lpa, mg/L		291.99 ± 310.42	356.40 ± 408.46	1.001 (1.000-1.001)	0.1795			
CM volume, mL 148.43 ± 68.01 144.86 ± 51.83 0.999 (0.994–1.005) 0.7531 MEDICATION <th< td=""><td>APOA, g/L</td><td></td><td>1.07 ± 0.29</td><td>0.99 ± 0.24</td><td>0.343 (0.102–1.154)</td><td>0.0839</td><td></td><td></td></th<>	APOA, g/L		1.07 ± 0.29	0.99 ± 0.24	0.343 (0.102–1.154)	0.0839			
$\begin{tabular}{ c c c c } \hline \textbf{MEDICATION} & & & & & & & & & & & & & & & & & & &$	CM volume, mL		148.43 ± 68.01	144.86 ± 51.83	0.999 (0.994–1.005)	0.7531			
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	MEDICATION								
Yes 1022 (88.18) 57 (100) ACEIs No 450 (38.83) 17 (29.82) 1.493 (0.836-2.666) 0.1750 Yes 709 (61.17) 40 (70.18)	β-blockers	No	137 (11.82)	0 (0)	4.752 (0.897–∞)	0.0019			
ACEIs No 450 (38.83) 17 (29.82) 1.493 (0.836–2.666) 0.1750 Yes 709 (61.17) 40 (70.18)		Yes	1022 (88.18)	57 (100)					
Yes 709 (61.17) 40 (70.18) CCBs No 818 (70.58) 30 (52.63) 2.159 (1.264–3.687) 0.0048 Yes 341 (29.42) 27 (47.37) PPIs No 578 (49.87) 10 (17.54) 4.676 (2.340–9.343) <0.0001	ACEIs	No	450 (38.83)	17 (29.82)	1.493 (0.836–2.666)	0.1750			
No 818 (70.58) 30 (52.63) 2.159 (1.264–3.687) 0.0048 Yes 341 (29.42) 27 (47.37)		Yes	709 (61.17)	40 (70.18)					
Yes 341 (29.42) 27 (47.37) PPIs No 578 (49.87) 10 (17.54) 4.676 (2.340–9.343) <0.0001	CCBs	No	818 (70.58)	30 (52.63)	2.159 (1.264–3.687)	0.0048			
PPIs No 578 (49.87) 10 (17.54) 4.676 (2.340–9.343) <0.0001 3.979 (1.828–8.659) 0.0005 PLASMA CONCENTRATION 47 (82.46) 47 (82.46) 581 (50.13) 47 (82.46) 581 (50.13) 10.28 ± 12.14 2.224 (1.697–2.915) <0.0001 3.979 (1.828–8.659) 0.0005 PLASMA CONCENTRATION 3.95 ± 5.39 10.28 ± 12.14 2.224 (1.697–2.915) <0.0001 <0.0001 2-AT, ng/mL 3.50 ± 3.39 8.03 ± 9.79 2.300 (1.678–3.153) <0.0001		Yes	341 (29.42)	27 (47.37)					
Yes 581 (50.13) 47 (82.46) PLASMA CONCENTRATION Image: Concentration of the state of the s	PPIs	No	578 (49.87)	10 (17.54)	4.676 (2.340–9.343)	<0.0001	3.979 (1.828–8.659)	0.0005	
PLASMA CONCENTRATION AT, ng/mL 3.95 ± 5.39 10.28 ± 12.14 2.224 (1.697-2.915) <0.0001		Yes	581 (50.13)	47 (82.46)					
AT, ng/mL 3.95 ± 5.39 10.28 ± 12.14 2.224 (1.697-2.915) <0.0001 2-AT, ng/mL 3.50 ± 3.39 8.03 ± 9.79 2.300 (1.678-3.153) <0.0001	PLASMA CONCENTRA	ATION							
2-AT, ng/mL 3.50 ± 3.39 8.03 ± 9.79 2.300 (1.678–3.153) <0.0001	AT, ng/mL		3.95 ± 5.39	10.28 ± 12.14	2.224 (1.697–2.915)	< 0.0001			
	2-AT, ng/mL		3.50 ± 3.39	8.03 ± 9.79	2.300 (1.678–3.153)	< 0.0001			

(Continued)

TABLE 3 | Continued

Characteristics	Without CI-AKI	With CI-AKI <i>N</i> (%) or mean ± <i>SD</i>	Univariate analysis		Multivariate analysis	
	N (%) or mean \pm SD		OR (95% CI)	P-Value	OR (95% CI)	P-Value
4-AT, ng/mL	1.28 ± 1.94	4.43 ± 5.95	2.503 (1.942–3.226)	<0.0001		
ATL, ng/mL	3.91 ± 6.02	10.11 ± 12.06	1.959 (1.533–2.503)	< 0.0001		
2-ATL, ng/mL	8.94 ± 9.70	17.58 ± 14.77	2.033 (1.518–2.724)	< 0.0001		
4-ATL, ng/mL	1.66 ± 2.32	4.03 ± 5.24	2.246 (1.721–2.932)	< 0.0001		
AT-all, ng/mL	8.60 ± 9.65	22.40 ± 24.63	2.826 (2.075–3.851)	< 0.0001	2.265 (1.609–3.187)	< 0.0001

ORs (95% CI) were calculated by applying a logistic regression model. Variables with P < 0.05 were entered into the multivariate model, and only variables with P < 0.05 were retained in the model.

2-AT, 2-hydroxy atorvastatin; 2-ATL, 2-hydroxy atorvastatin lactone; 4-AT, 4-hydroxy atorvastatin; 4-ATL, 4-hydroxy atorvastatin lactone; AT, atorvastatin; ATL, atorvastatin lactone; CI, confidence interval; CI-AKI, contrast induced acute kidney injury; CM volume, contrast media volume; OR, odds ratio; PCI, percutaneous coronary intervention; other abbreviations as in **Table 1**.



receiver operating characteristic; Scr, serum creatinine; other abbreviations as in **Figure 1**.

CI: 4.334–81.701; p < 0.0001) (Table S4). CI-AKI patients (9.15 ± 6.51 ng/mL) exhibited 3.0-fold higher plasma RST concentration than controls (3.05 ± 3.28 ng/mL) (**Figure 3B**).

Predictive Diagnostic Power of Plasma AT and RST Exposure for CI-AKI

To better predict occurrence of CI-AKI, we developed a prognostic classifier combining clinical characteristics and plasma concentrations. In stage I, the AUCs of AT-all, in groups

without and with CKD, performed similar characteristics (0.70 and 0.73, respectively) (**Figures 2D,E**). The AUC of plasma ATall exposure for all patients in stage I was 0.76. A cutoff of 10.73 ng/mL performed high true positive rate (70%) and low false positive rate (25%) (**Figure 2F**). Predictive value of use of PPIs, diabetes, level of Scr, AST, and eGFR for CI-AKI, as determined by the ROC curves, were insufficient with AUC varying between 0.23 and 0.75. However, predictive effectiveness of combined variables was substantially increased to 0.86.

TABLE 4 | Effects of baseline characteristics and plasma concentrations of RST and its metabolites on CI-AKI in stage II.

h (%) or mean ± 50 Ø (%) or mean ± 50 Ø (8) (%) P-Value Ø (8)% C) P-Value DEMOSET 503 30 300 <	Characteristics		Without CI-AKI	With CI-AKI	Univariate analysis		Multivariate analysis	
DEMOGRAPHIC Data 605 30 Total runner 60.5 30 Age 61.89 ± 10.53 64.02 ± 9.49 1.020 (0.083-1.056) 0.2965 Sex Fermine 10 (20.61) 3 (10) 2.284 (0.977-10.020) 0.0546 Desege (rm) 5 11.182 0 (9) 1.065 (1.007-1.127) 0.0265 1.088 (1.015-1.167) 0.0175 20 61 (10.08) 6 (20.67) 2.20 (0.065-4.023) 0.0006 SWTMX core 14.08 ± 12.57 15.30 ± 10.30 1.014 (0.866-1.012) 0.3440 MEDICAL INSTORY 67 (92.07) 2.70 (9) 1.200 (0.378-4.000) 0.0824 Virea 36 (55.4) 2 (73.35) - - - Arityftmin No 257 (42.07) 2.70 (9) 1.200 (0.378-4.000) 0.0007 2.680 (1.153-6.230) 0.0220 Holdebees No 257 (42.07) 1.70 (9) 1.200 (0.378-4.010) 0.0007 7.90 (0.289-1.016) - Holdebees No 257 (42.07) 1.100 (0.335 (4.14-22.814) <			N (%) or mean \pm SD	N (%) or mean \pm SD	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Tarial number 005 30 Age 61.08 ± 10.23 64.02 ± 9.0 1.020 10.68.1.059 0.2305 Sax Fennale 161 (26.13) 3 (10) 3.264 (0.977-10.304) 0.056 Obesge (ng) 5 11 (182) 0.0 1005 (1.007-1.127) 0.0285 1.088 (1.016-1.167) 0.175 20 0 (10 0.058) 1 (3.33) 5 5 5 5 5 VITAV score 1 (3.64 ± 12.57) 1 (3.03) 5 7 1.088 (1.156-6.23) 0.0000 VITAV score 203 (16.058) 1 (3.33) 5 7 0.0688 2 VITAV score 1 (3.64 ± 10) 1.200 (0.378-4.000) 0.0000 2.680 (1.163-6.320) 0.0020 Mem 5 (26.07) 2.7 (0.0 1.200 (0.378-4.000) 0.0007 2.680 (1.163-6.320) 0.0020 Mis 5 (26.07) 2.7 (0.0 1.200 (0.378-4.000) 0.0007 2.680 (1.163-6.320) 0.0020 Mis 5 (26.07) 2.7 (0.0 3.030 (0.41-0.22) 0.0000 2.680 (1.163-6	DEMOGRAPHIC DATA							
Aga In 18 (PAGE) 1.02 (0.038-1.053) 0.2005 Ser. Fermal 18 (PAGE) 3.10 3.284 (0.977-10.904) 0.0644 Desage (mg) 5 11 (PAGE) 220 (6.7) 22 (6.87) 0.02 (6.1) 0.0251 0.0264 0.0264 Desage (mg) 5 11 (PAGE) 0.02 (6.87) 0.200 (0.88-1.027) 0.0264 </td <td>Total number</td> <td></td> <td>605</td> <td>30</td> <td></td> <td></td> <td></td> <td></td>	Total number		605	30				
SaxFinale141 (128)3 (10)3.284 (1397-10304)0.0548Mala444 (7339)27 (00)1.085 (1.007-1.127)0.02831.038 (1.015-1.167)0.0175Dasage (mg)561 (10.08)6 (00)0.01750.0175206 (1.028 (1.037 - 11.237)0.02831.014 (0.988-1.042)0.0494 <td< td=""><td>Age</td><td></td><td>61.98 ± 10.53</td><td>64.02 ± 9.89</td><td>1.020 (0.983–1.058)</td><td>0.2995</td><td></td><td></td></td<>	Age		61.98 ± 10.53	64.02 ± 9.89	1.020 (0.983–1.058)	0.2995		
$ \begin{array}{ c c c c c } & Mathebreak Ma$	Sex	Female	161 (26.61)	3 (10)	3.264 (0.977-10.904)	0.0546		
Densign (mg) 5 11 (1.82) 0.00 1.065 (1.007-1.127) 0.0285 1.088 (1.015-1.167) 0.0175 20 61 (10.08) 6 (20) -		Male	444 (73.39)	27 (90)				
1012	Dosage (mg)	5	11 (1.82)	O (O)	1.065 (1.007–1.127)	0.0285	1.088 (1.015–1.167)	0.0175
40 61 (10.06) 6 (20) 40 5 0.83) 1 (3.3) SYNTAX acore 14.08 ± 12.57 16.30 ± 10.30 1.014 (0.896-1.042) 0.3440 MEDICAL HISTORY 19 3.03 (55.54) 2.2 (73.3) 0.0508 5.4 PCI No 0.557 (20.07) 2.70 (0.966-5.023) 0.0607 2.680 (1.153-6.230) 0.0220 Maynomia No 657 (20.07) 2.70 (0.90 1.290 (0.378-4.406) 0.007 2.680 (1.153-6.230) 0.0220 No 647 (733) 3 (161 (1.14-2.54.4) 0.001 7.504 (3.032-20.606) <0.0220		10	528 (87.27)	23 (76.67)				
+0 $5, 0.8.3$ $1 (3.3)$ NUAR scoreNUAR scoreNUAR scoreNO $2 (0.20) (44.40)$ $8 (26.67)$ $2.202 (0.966-5.02)$ 0.008 No $336 (55.5)$ $22.7 (3.3)$ ArhythmiaNo $557 (92.07)$ $27 (90)$ $1.200 (0.378-4.406)$ 0.6846 No $487 (80.5)$ $16 (53.33)$ $3.611 (1.714-7.606)$ 0.0007 $2.680 (1.153-6.230)$ 0.0220 Plant laireNo $557 (92.67)$ $19 (93.33)$ $10.035 (4.41+2.2814)$ <0.0001 $7.904 (3.022-20.606)$ <0.0001 HypertensionNo $552 (42.64)$ $21 (70)$ $<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<><<<<<<<><<<<<<><<<<<><<<<<<<><<<<><<<<<<<><<<<><<<<<<<<><<<<<><<<<<<<<<<<<<><<<<><<<<><$		20	61 (10.08)	6 (20)				
SYNTRX code 16.18 ± 12.57 16.30 ± 1.030 1.014 (0.988-1.0.2) 0.340 MEDIGAL HISTOR 760 269 (44.46) 8 (76.67) 2.202 (0.965-5.023) 0.6618 Yes 326 (55.54) 22 (73.33) 2.202 (0.965-5.023) 0.6618 Yes 48 (7.93) 3 (16) 0.6548 0.6544 Yes 118 (19.6) 14 (66.57) 0.0007 2.680 (1.153-6.230) 0.0220 No 572 (24.55) 19 (63.33) 0.335 (4.14-22.614) <0.001		40	5 (0.83)	1 (3.33)				
MEDICAL HISTORY PCI No 028 (44.46) 8 (26.67) 2.202 (0.965-5.02) 0.0606 Yes 336 (55.54) 22 (73.33)	SYNTAX score		14.08 ± 12.57	16.30 ± 10.90	1.014 (0.986–1.042)	0.3440		
$ \begin{array}{ c c c } \mbox{No} & 262 (4.4.46) & 2.22 (2.0.266-5.023) & 0.0068 \\ \mbox{No} & 366 (55.54) & 22.7 (3.3) \\ \mbox{No} & 457 (92.67) & 27 (90) & 1.290 (0.378-4.406) & 0.6848 \\ \mbox{No} & 487 (90.5) & 16 (50.33) & 3.611 (1.714-7.606) & 0.0007 & 2.680 (1.153-6.230) & 0.0220 \\ \mbox{No} & 487 (90.5) & 14 (46.67) & & & & & & & & & & & & & & & & & & &$	MEDICAL HISTORY							
Visis 335 (65.54) 22 (7.33) Arinydminia No 557 (82.07) 27 (80) 1.290 (0.376-4.406) 0.684 Visis 48 (7.93) 3 (10) 2.680 (1.153-6.230) 0.0220 Visis 118 (195) 144 (46.67) -	PCI	No	269 (44.46)	8 (26.67)	2.202 (0.965–5.023)	0.0608		
Arthythmia No 557 (82.07) 27 (90) 1.280 (0.378-4.40c) 0.6848 Vies 4487 (80.5) 16 (53.33) 3.611 (1.714-7.60c) 0.0007 2.680 (1.153-6.230) 0.0220 Vies 118 (19.5) 14 (46.67) .0001 7.904 (3.032-20.600) <0.0001		Yes	336 (55.54)	22 (73.33)				
Yes 48 (7.39) 3 (10) Diabetes Yes 118 (19.5) 14 (46.67) 0.0007 2.680 (1.153-6.230) 0.0220 Heart failure No 572 (94.58) 19 (96.33) 10.035 (4.41-4-28.14) <0.0001	Arrhythmia	No	557 (92.07)	27 (90)	1.290 (0.378–4.406)	0.6848		
Diabetes No 487 (80.5) 16 (85.33) 3.611 (1.714-7.600) 0.0007 2.680 (1.153-6.230) 0.0220 Heart failure No 572 (94.55) 19 (63.33) 10.035 (4.414-22.814) <0.0001 7.904 (3.032-20.606) <0.0001 Hypertension No 33 (5.46) 11 (86.67) <0.0001 7.904 (3.032-20.606) <0.0001 <0.0001 7.904 (3.032-20.606) <0.0001 <0.0001 7.904 (3.032-20.606) <0.0001 <0.0001 7.904 (3.032-20.606) <0.0001 <0.0001 <0.0001 <0.0001 <0.0001 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011 <0.0011<		Yes	48 (7.93)	3 (10)				
Yes 118 (19.5) 114 (46.67) Heart failure No 57 (94.55) 19 (63.33) 10.035 (4.414-22.814) <0.0001	Diabetes	No	487 (80.5)	16 (53.33)	3.611 (1.714–7.606)	0.0007	2.680 (1.153–6.230)	0.0220
Heart failure No 572 (94.55) 19 (83.33) (1035 (4.41–22.814) <0.0001 7.904 (3.032–20.606) <0.0001 Hypertension No 347 (57.36) 9 (30) 3.138 (1.41–6.965) 0.0049 Hypertension No 539 (80.09) 27 (80) 0.907 (0.266–3.073) 0.8760 BIOCHEMICAL MEASUREMENTS 28.09 ± 14.23 0.997 (0.977–1.018) 0.7031 AST, UL 31.01 ± 30.52 34.78 ± 37.62 1.003 (0.994–1.012) 0.5190 Scr. µmol/L 87.70 ± 40.27 107.88 ± 36.01 1.007 (1.001–1.013) 0.0148 GGFR, mL/min/1.73 m ² 99.77 ± 85.57 74.08 ± 31.24 0.981 (0.968–0.994) 0.0043 CK UL 143.38 ± 311.70 215.29 ± 475.95 1.000 (1.000–1.011) 0.2571 CK ML, UL 7.91 ± 10.58 9.66 ± 13.47 1.009 (0.867–1.328) 0.4683 LDC, mmol/L 1.06 ± 0.28 0.99 ± 0.22 0.952 (0.244–4.08) 0.4464 CHOL, mmol/L 1.07 ± 1.26 1.55 ± 1.02 0.898 (0.610–1.323) 0.5683 LDC, mmol/L 1.06 ± 0.28 0.		Yes	118 (19.5)	14 (46.67)				
Wes33 (5.45)11 (36.67)HypertensionNo347 (67.36)9 (30)3.138 (1.414-6.966)0.0049HypertipidemiaNo539 (89.09)27 (90)0.907 (0.268-3.073)0.8760BOCHEMICAL MEASUFEWENTS3 (10)3 (10)1000.997 (0.977-1.018)0.7931ATL, UA29.31 ± 19.0028.39 ± 14.230.997 (0.977-1.018)0.7931AST, U/L31.01 ± 30.5234.78 ± 37.621.003 (0.994-1.012)0.5190Ser, µmo/L87.70 ± 40.27107.88 ± 38.011.007 (1.001-1.013)0.0148eGFR, mL/min/1.73 m²99.77 ± 85.5774.08 ± 31.240.981 (0.968-0.994)0.0043CK, U/L1.43.38 ± 311.70215.29 ± 475.551.000 (1.000-1.010)0.2571CKMB, U/L7.94 ± 1.434.39 ± 1.780.928 (0.699-1.230)0.6018CHOL, mmo/L4.54 ± 1.434.39 ± 1.780.928 (0.699-1.230)0.6018LDLC, mmo/L1.06 ± 0.280.99 ± 0.220.952 (0.224-4.038)0.9465GLUC, mmo/L7.03 ± 3.207.17 ± 3.281.103 (0.098-1.130)0.8163Lpa, mg/L7.03 ± 3.207.17 ± 3.281.013 (0.098-1.030)0.8163Lpa, mg/L7.03 ± 3.207.17 ± 3.281.013 (0.098-1.030)0.8163Lpa, mg/L1.06 ± 0.281.02 ± 0.31.660.07100.8253CM volume, mL112.23 ± 60.231.02 ± 0.331.660.0691Hyber K273.94 ± 290.340.101 ± 49.860.997 (0.988-1.004)0.3339CM Sa (2406.61)25 (83.33)<	Heart failure	No	572 (94.55)	19 (63.33)	10.035 (4.414–22.814)	<0.0001	7.904 (3.032–20.606)	<0.0001
Hypertension No 347 (57.36) 9 (30) 3.138 (1.14-6.965) 0.0049 Yes 256 (42.64) 21 (70)		Yes	33 (5.45)	11 (36.67)				
Yes 258 (42.84) 21 (70) Hyperipidemia Yes 66 (10.91) 3 (10) EIOCENTICAL MEASUREMENTS 3 (30) 0.997 (0.977-1.018) 0.7931 AST, U/L 29.31 ± 19.00 28.39 ± 14.23 0.997 (0.977-1.018) 0.7931 Scr. µmol/L 87.70 ± 40.27 107.88 ± 36.01 1.007 (1.001-1.013) 0.0148 6GFR, mL/min/1.73 m ² 99.77 ± 85.57 74.08 ± 31.24 0.981 (0.968-0.994) 0.0043 CK, U/L 7.91 ± 10.98 9.65 ± 13.47 1.009 (1.001-1.013) 0.0148 CHOL, mmol/L 7.91 ± 10.98 9.65 ± 13.47 1.009 (0.967-1.032) 0.4164 CHOL, mmol/L 7.91 ± 1.13 2.69 ± 1.42 0.931 (0.657-1.318) 0.6853 LDLC, mmol/L 1.67 ± 1.26 1.55 ± 1.02 0.886 (0.61-3.23) 0.5858 GIUC, mmol/L 1.67 ± 1.26 1.55 ± 1.02 0.886 (0.61-1.323) 0.5853 GIUC, mmol/L 1.67 ± 1.26 1.05 ± 0.21 0.501 (0.109-2.306) 0.3752 CM oume, mL 112.23 ± 60.23 1.012 ± 0.21 0.501 (0.109-2.306) 0.375	Hypertension	No	347 (57.36)	9 (30)	3.138 (1.414–6.965)	0.0049		
Hyperingioemia No S59 (83.09) 27 (90) 0.907 (0.288-3.07.3) 0.8740 BIOCHEMICAL MEASUREMENTS BIOCHEMICAL MEASUREMENTS AIT, U/L 29.31 ± 10.00 28.39 ± 14.23 0.997 (0.977-1.018) 0.7931 AST, U/L 31.01 ± 30.52 34.78 ± 37.62 1.003 (0.994-1.012) 0.5190 S7, U/L 31.01 ± 30.52 34.78 ± 37.62 1.003 (0.994-1.012) 0.0148 GFR, mL/min/1.73 m ² 99.77 ± 85.57 74.08 ± 31.24 0.981 (0.968-0.994) 0.0043 CK, U/L 143.38 ± 311.70 215.29 ± 475.95 1.000 (0.007-1.001) 0.2571 CKMB, U/L 7.91 ± 10.98 36.65 ± 1.347 1.009 (0.987-1.318) 0.6853 CKMB, U/L 1.00 ± 0.26 0.99 ± 0.22 0.952 (0.224-4.036) 0.9466 CMIMUL 1.00 ± 0.26 0.99 ± 0.22 0.958 (0.610-1.323) 0.6853 GLUC, mmol/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109-2.306) 0.5752 CHOL, mmol/L 1.06 ± 0.28		Yes	258 (42.64)	21 (70)	/			
Ves 66 (10.91) 3 (10) BIOCHEMICAL MEASUREMENTS ALT, U/L 29.31 ± 19.00 28.39 ± 14.23 0.997 (0.977-1.018) 0.7931 AST, U/L 31.01 ± 30.52 34.78 ± 37.62 1.003 (1.0094-1.012) 0.5190 Scr, µmol/L 87.70 ± 40.27 107.88 ± 36.01 1.007 (1.001-1.013) 0.0148 GFR, mL/min/1.73 m ² 99.77 ± 85.57 74.08 ± 31.24 0.981 (0.988-0.994) 0.0043 CK, U/L 143.38 ± 311.70 215.29 ± 475.95 1.000 (1.000-1.001) 0.2571 CKMB, U/L 7.91 ± 10.98 9.65 ± 13.47 1.009 (0.897-1.032) 0.4164 CHOL, mmol/L 4.54 ± 1.43 4.39 ± 1.78 0.928 (0.899-1.230) 0.6018 LDC, mmol/L 1.00 ± 0.26 0.99 ± 0.22 0.952 (0.224-4.036) 0.9465 HDLC, mmol/L 1.02 ± 0.28 0.101 (0.999-1.030) 0.8163 Lpa, mg/L 27.79 ± 1.26 1.55 ± 1.02 0.898 (0.610-1.323) 0.5863 Lpa, mg/L 1.02 ± 0.28 0.013 (0.999-1.030) 0.8163 Lpa, mg/L 1.02 ± 0.28 0.010 (0.9	Hyperlipidemia	No	539 (89.09)	27 (90)	0.907 (0.268–3.073)	0.8760		
BIOLEMICAL MEASUREMENTS ALT, U/L 29.31 ± 19.00 28.39 ± 14.23 0.997 (0.977-1.018) 0.7931 AST, U/L 31.01 ± 30.52 34.78 ± 37.62 1.003 (0.994-1.012) 0.5190 Scr, µmol/L 67.70 ± 40.27 107.88 ± 36.01 1.007 (1.001-1.013) 0.0148 eGFR, mL/min/1.73 m ² 99.77 ± 85.57 74.08 ± 31.24 0.981 (0.980-0.994) 0.0043 CK, U/L 143.38 ± 311.70 215.29 ± 475.95 1.0009 (1.000-1.001) 0.2571 CK, MB, U/L 7.91 ± 10.98 9.65 ± 13.47 1.009 (0.987-1.032) 0.4164 CHOL, mmol/L 4.54 ± 1.43 4.39 ± 1.78 0.282 (0.699-1.230) 0.6018 LDLC, mmol/L 1.00 ± 0.26 0.99 ± 0.22 0.952 (0.224-4.036) 0.9465 TRIG, mmol/L 1.06 ± 0.26 0.99 ± 0.22 0.952 (0.224-4.036) 0.9465 CLUC, mmol/L 1.00 ± 0.26 0.99 ± 0.22 0.952 (0.224-4.036) 0.9465 CHOL, mmol/L 1.073 ± 3.20 7.17 ± 3.28 1.013 (0.908-1.130) 0.8163 Lpa, mg/L 7.03 ± 3.20 1.10 ± 49.86 0.99		Yes	66 (10.91)	3 (10)				_
AT, U/L 29.31 ± 19.00 28.39 ± 14.23 0.997 (1.016) 0.7831 AST, U/L 10.11 ± 30.52 34.78 ± 37.62 1.003 (0.994 - 1.012) 0.5190 Scr, µmol/L 87.70 ± 40.27 107.88 ± 36.01 1.007 (1.001 - 1.013) 0.0148 eGFR, mL/min/1.73 m ² 99.77 ± 85.57 74.08 ± 31.24 0.981 (0.968 - 0.994) 0.0043 CK, U/L 143.38 ± 31.70 215.29 ± 475.95 1.000 (1.000 - 1.001) 0.2571 CKMB, U/L 7.91 ± 10.98 9.65 ± 13.47 1.009 (0.987 - 1.032) 0.4164 CHOL, mmol/L 4.54 ± 1.43 4.39 ± 1.78 0.928 (0.699 - 1.230) 0.6018 LDLC, mmol/L 1.06 ± 1.26 1.55 ± 1.02 0.989 (0.610 - 1.323) 0.5858 GLUC, mmol/L 1.06 ± 0.28 0.99 ± 0.22 0.952 (0.224 - 4.036) 0.9463 Lpa, mg/L 7.03 ± 3.20 7.17 ± 3.28 1.013 (0.908 - 1.001) 0.6253 GLUC, mmol/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109 - 2.088) 0.3752 CM volume, mL 112.34 ± 60.23 1.02 ± 0.21 0.501 (0.109 - 2.088) 0.3752 CM volume, mL 126.4 (86.51) 25 (86.33) <td< td=""><td></td><td>JREMENIS</td><td>00.01 10.00</td><td>00.00 + 14.00</td><td>0.007 (0.077, 1.010)</td><td>0.7001</td><td></td><td></td></td<>		JREMENIS	00.01 10.00	00.00 + 14.00	0.007 (0.077, 1.010)	0.7001		
Ab. 1, 0L 31, 01 ± 30, 32 34, 78 ± 37, 82 1, 103 (0, 394-1, 0, 12) 0, 31 (0) eGFR, mL/min/1, 73 m ² 99, 77 ± 85, 57 74, 08 ± 31, 24 0, 981 (0, 968-0, 994) 0, 0043 CK, U/L 143, 38 ± 311, 70 215, 29 ± 475, 95 1, 000 (1, 000-1, 001) 0, 2571 CKMB, U/L 7, 91 ± 10, 98 9, 66 ± 13, 47 1, 009 (0, 987-1, 032) 0, 4164 CHOL, mmol/L 4, 54 ± 1, 43 4, 39 ± 1, 78 0, 928 (0, 699-1, 230) 0, 6018 LDC, mmol/L 1, 00 ± 0, 26 0, 99 ± 0, 22 0, 952 (0, 224-4, 036) 0, 9465 TRIG, mmol/L 1, 00 ± 0, 26 0, 99 ± 0, 22 0, 952 (0, 224-4, 036) 0, 9465 LDC, mmol/L 1, 00 ± 0, 26 0, 99 ± 0, 22 0, 952 (0, 224-4, 036) 0, 9465 HDLC, mmol/L 1, 00 ± 0, 26 0, 99 ± 0, 22 0, 952 (0, 224-4, 036) 0, 9465 GLUC, mmol/L 1, 00 ± 0, 26 0, 99 ± 0, 22 0, 952 (0, 224-4, 036) 0, 9465 Lop, mpL 1, 00 ± 0, 28 1, 02 ± 0, 21 0, 501 (0, 109-2, 308) 0, 6253 APOA, g/L 1, 06 ± 0, 28 1, 02 ± 0, 21 0, 501 (0, 109-2, 308) 0, 3752 CM volume	ALI, U/L		29.31 ± 19.00	28.39 ± 14.23	0.997 (0.977-1.018)	0.7931		
Sch, Jindoll, 67,76 ± 40,27 107,86 ± 33,01 1.007 (1.001-1.01.5) 0.0148 eGFR, mL/min/1.73 m ² 99,77 ± 85,57 74,08 ± 31.24 0.981 (0.968-0.994) 0.0043 CK, U/L 143.38 ± 311.70 215,29 ± 475,55 1.000 (1.000-1.011) 0.2571 CKMB, U/L 7.91 ± 10.98 9.65 ± 13.47 1.009 (0.987-1.032) 0.4164 CHOL, mmol/L 4.54 ± 1.43 4.39 ± 1.78 0.928 (0.699-1.230) 0.6018 LDLC, mmol/L 1.00 ± 0.26 0.99 ± 0.22 0.952 (0.224-4.036) 0.9465 TRIG, mmol/L 1.67 ± 1.26 1.55 ± 1.02 0.988 (0.610-1.323) 0.5858 GLUC, mmol/L 7.03 ± 3.20 7.17 ± 3.28 1.013 (0.908-1.130) 0.8163 Lpa, mg/L 273.94 ± 290.34 301.20 ± 331.66 1.000 (0.999-1.001) 0.6253 APOA, g/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109-2.308) 0.3752 CM volume, mL 112.23 ± 60.23 101.94 ± 9.86 0.997 (0.899-1.004) 0.3839 MED/CATION Yes 524 (86.61) 25 (83.33) 0.4021 0.301 CCBs No 274 (45.29) 10 (33.33)	ASI, U/L		31.01 ± 30.52	34.78 ± 37.02	1.003 (0.994-1.012)	0.5190		
early intrinier 1/3 m 39.77 ± 0.0.0 74.05 ± 01.24 0.0061 (0.00-1.001) 0.2571 CK, U/L 143.38 ± 311.70 215.29 ± 475.95 1.000 (1.000-1.001) 0.2571 CKMB, U/L 7.91 ± 10.98 9.66 ± 13.47 1.009 (0.987-1.032) 0.4164 CHOL, mmol/L 4.54 ± 1.43 4.39 ± 1.78 0.928 (0.699-1.230) 0.6018 LDLC, mmol/L 1.00 ± 0.26 0.99 ± 0.22 0.952 (0.224-4.036) 0.9465 FIRG, mmol/L 1.67 ± 1.26 1.55 ± 1.02 0.988 (0.610-1.323) 0.5858 GLUC, mmol/L 7.03 ± 3.20 7.17 ± 3.28 1.013 (0.908-1.130) 0.8163 Lpa, mg/L 7.03 ± 4.290.34 301.20 ± 331.66 1.000 (0.999-1.001) 0.6253 APOA, g/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109-2.308) 0.3752 CM volume, mL 112.32 ± 60.23 101.09 ± 49.86 0.997 (0.989-1.004) 0.3839 MEDICATION ************************************	SCI, μ mol/L		87.70 ± 40.27	107.00 ± 30.01	1.007 (1.001 - 1.013)	0.0148		
ON, DL 143.53 ± 31.17.0 213.29 ± 143.53 1.000 (1000+1.001) 0.23.11 CKMB, U/L 7.91 ± 10.98 9.65 ± 13.47 1.009 (0.987-1.032) 0.4164 CHOL, mmol/L 4.54 ± 1.43 4.39 ± 1.78 0.928 (0.699-1.230) 0.6018 LDLC, mmol/L 2.77 ± 1.11 2.69 ± 1.42 0.931 (0.657-1.318) 0.6853 HDLC, mmol/L 1.00 ± 0.26 0.99 ± 0.22 0.952 (0.224-4.036) 0.9465 TRIG, mmol/L 1.67 ± 1.26 1.55 ± 1.02 0.888 (0.610-1.323) 0.5858 GLUC, mmol/L 1.67 ± 1.26 1.55 ± 1.02 0.888 (0.610-1.323) 0.5858 GLUC, mmol/L 1.63 ± 0.20 7.17 ± 3.28 1.013 (0.906-1.130) 0.8163 Lpa, mg/L 7.03 ± 3.20 7.17 ± 3.28 1.013 (0.999-1.001) 0.6253 APOA, g/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109-2.308) 0.3752 CM volume, mL 112.23 ± 60.23 101.09 ± 49.86 0.997 (0.899-1.004) 0.3839 MEDICATION Yes 524 (86.61) 25 (83.33) 0.40691 0.6091 CCBs No 81(1.3.39) 5 (16.67) 0.773 (0.288-2.076) <td></td> <td></td> <td>99.77 ± 00.07</td> <td>74.00 ± 31.24</td> <td>1.000 (1.000, 1.001)</td> <td>0.0043</td> <td></td> <td></td>			99.77 ± 00.07	74.00 ± 31.24	1.000 (1.000, 1.001)	0.0043		
CMML 1.91 ± 10.30 5.00 ± 10.347 1.005 (0.367 + 1.032) 0.4104 CHOL, mmol/L 4.54 ± 1.43 4.39 ± 1.78 0.928 (0.699 - 1.230) 0.6018 LDC, mmol/L 1.00 ± 0.26 0.99 ± 0.22 0.952 (0.224 - 4.036) 0.9465 TRIG, mmol/L 1.67 ± 1.26 1.55 ± 1.02 0.898 (0.610 - 1.323) 0.5858 GLUC, mmol/L 7.03 ± 3.20 7.17 ± 3.28 1.013 (0.908 - 1.130) 0.8163 Lpa, mg/L 273.94 ± 290.34 301.20 ± 331.66 1.000 (0.999 - 1.001) 0.6253 APOA, g/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109 - 2.308) 0.3752 CM volume, mL 112.23 ± 60.23 101.09 ± 49.86 0.997 (0.988 - 1.004) 0.3839 MEDICATION ************************************	CKMR II/		7.01 ± 10.09	213.29 ± 473.93	1.000 (1.000-1.001)	0.2371		
OrlOC, mmol/L 2.77 ± 1.11 2.69 ± 1.42 0.931 (0.657-1.20) 0.0010 LDLC, mmol/L 1.00 ± 0.26 0.99 ± 0.22 0.952 (0.224-4.036) 0.9465 TRIG, mmol/L 1.67 ± 1.26 1.55 ± 1.02 0.898 (0.610-1.323) 0.5858 GLUC, mmol/L 7.03 ± 3.20 7.17 ± 3.28 1.013 (0.908-1.130) 0.8163 Lpa, mg/L 273.94 ± 290.34 301.20 ± 331.66 1.000 (0.999-1.001) 0.6253 APOA, g/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109-2.308) 0.3752 CM volume, mL 112.23 ± 60.23 101.09 ± 49.86 0.997 (0.389-1.004) 0.3839 MEDICATION *** *** *** *** β-blockers No 81 (13.39) 5 (16.67) 0.773 (0.288-2.076) 0.6091 Yes 524 (86.61) 25 (83.33) *** *** *** ACEIs No 871 (45.29) 10 (33.33) 1.656 (0.762-3.596) 0.2028 Yes 331 (54.71) 20 (66.67) *** *** *** CCBs No 432 (71.4) 23 (76.67) 0.760 (0.320-1.804) 0.5339 <td>CHOL mmol/l</td> <td></td> <td>1.91 ± 10.90 1.51 ± 1.13</td> <td>9.03 ± 13.47</td> <td>0.928 (0.699-1.230)</td> <td>0.4104</td> <td></td> <td></td>	CHOL mmol/l		1.91 ± 10.90 1.51 ± 1.13	9.03 ± 13.47	0.928 (0.699-1.230)	0.4104		
LLC, mmol/L 1.00 ± 0.26 0.99 ± 0.22 0.952 (0.224-4.036) 0.9465 TRIG, mmol/L 1.67 ± 1.26 1.55 ± 1.02 0.898 (0.610-1.323) 0.5858 GLUC, mmol/L 7.03 ± 3.20 7.17 ± 3.28 1.013 (0.908-1.130) 0.8163 Lpa, mg/L 273.94 ± 290.34 301.20 ± 331.66 1.000 (0.999-1.001) 0.6253 APOA, g/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109-2.308) 0.3752 CM volume, mL 112.23 ± 60.23 101.09 ± 49.86 0.997 (0.989-1.004) 0.3839 MEDICATION ************************************			4.34 ± 1.43 2.77 + 1.11	4.59 ± 1.70 2.69 ± 1.42	0.928 (0.099-1.230)	0.6853		
Index 1 1.65 ± 0.25 0.63 ± 0.12 0.63 ± 0.124 0.63 ± 0.024 0.6424 TRIG, mmol/L 1.67 ± 1.26 1.55 ± 1.02 0.898 (0.610–1.323) 0.5658 GLUC, mmol/L 7.03 ± 3.20 7.17 ± 3.28 1.013 (0.098–1.130) 0.8163 Lpa, mg/L 273.94 ± 290.34 301.20 ± 331.66 1.000 (0.999–1.001) 0.6253 APOA, g/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109–2.308) 0.3752 CM volume, mL 112.23 ± 60.23 101.09 ± 49.86 0.997 (0.989–1.004) 0.3839 MEDICATION # 112.23 ± 60.23 101.09 ± 49.86 0.997 (0.989–1.004) 0.3839 MEDICATION # 112.23 ± 60.23 101.09 ± 49.86 0.997 (0.989–1.004) 0.3839 MEDICATION # 112.23 ± 60.23 101.09 ± 49.86 0.997 (0.989–1.004) 0.3839 MEDICATION # 112.23 ± 60.23 101.09 ± 0.816 0.977 (0.989–1.004) 0.3839 MEDICATION # 10 (33.33) 1.656 (0.762–3.596) 0.2028 0.6091 CCBs No 274 (45.29) 10 (33.33) 1.656 (0.762–3.596) 0.2028 0.994	HDLC mmol/L		1.00 ± 0.26	2.09 ± 0.42	0.957 (0.007–1.010)	0.0000		
Mind, Mindel 1.03 ± 1.25 1.05 ± 1.02 0.0305 (0.01 + 1.02) 0.0306 GLUC, mmol/L 7.03 ± 3.20 7.17 ± 3.28 1.013 (0.908 - 1.130) 0.8163 Lpa, mg/L 273.94 ± 290.34 301.20 ± 331.66 1.000 (0.999 - 1.001) 0.6253 APOA, g/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109 - 2.308) 0.3752 CM volume, mL 112.23 ± 60.23 101.09 ± 49.86 0.997 (0.989 - 1.004) 0.3839 MEDICATION ************************************	TRIG_mmol/l		1.00 ± 0.20 1.67 ± 1.26	0.39 ± 0.22 1.55 + 1.02	0.898 (0.610-1.323)	0.5400		
Lpa, mg/L 273.94 ± 290.34 301.20 ± 331.66 1.000 (0.999-1.001) 0.6253 APOA, g/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109-2.308) 0.3752 CM volume, mL 112.23 ± 60.23 101.09 ± 49.86 0.997 (0.989-1.004) 0.3839 MEDICATION MEDICATION Kes 524 (86.61) 25 (83.33) ACEIs No 271.44 (45.29) 10 (33.33) 1.656 (0.762-3.596) 0.2028 Yes 331 (54.71) 20 (66.67) 2000000000000000000000000000000000000	GLUC mmol/l		7.03 ± 3.20	7.17 ± 3.28	1.013 (0.908-1.130)	0.8163		
APOA, g/L 1.06 ± 0.28 1.02 ± 0.21 0.501 (0.109-2.308) 0.3752 CM volume, mL 112.23 ± 60.23 101.09 ± 49.86 0.997 (0.989-1.004) 0.3839 MEDICATION \$	L na mg/l		273.94 ± 290.34	301.20 ± 331.66	1.000 (0.999–1.001)	0.6253		
Medic Attion 110.1 ± 00.21 (10.0 ± 4.9.26) 0.097 (0.989=1.004) 0.3839 MEDICATION 9-blockers No 81 (13.39) 5 (16.67) 0.773 (0.288=2.076) 0.6091 Yes 524 (86.61) 25 (83.33) 1.656 (0.762=3.596) 0.2028 ACEIs No 274 (45.29) 10 (33.33) 1.656 (0.762=3.596) 0.2028 Yes 331 (54.71) 20 (66.67) CCBs No 432 (71.4) 23 (76.67) 0.760 (0.320=1.804) 0.5339 PPIs Yes 173 (28.6) 7 (23.33) 1.458 (0.682=3.117) 0.3301 PPIs No 277 (45.79) 11 (36.67) 1.458 (0.682=3.117) 0.3301 PLASMA CONCENTRATION RST, ng/mL 3.04 ± 3.26 8.28 ± 5.49 3.139 (1.879=5.245) <0.0001 2.281 (1.441=3.612) 0.0004 RST, ng/mL 0.40 ± 0.54 1.06 ± 1.08 2.610 (1.768=3.853) <0.001 2.281 (1.441=3.612) 0.0004	APOA a/l		1.06 ± 0.28	1.02 ± 0.21	0.501 (0.109–2.308)	0.3752		
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β-blockers No 81 (13.39) 5 (16.67) 0.773 (0.288–2.076) 0.6091 Yes 524 (86.61) 25 (83.33) .	MEDICATION		112120 2 00120	101100 ± 10100		010000		
Yes 524 (86.61) 25 (83.33) ACEIs No 274 (45.29) 10 (33.33) 1.656 (0.762–3.596) 0.2028 Yes 331 (54.71) 20 (66.67)	β-blockers	No	81 (13.39)	5 (16.67)	0.773 (0.288–2.076)	0.6091		
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PLASMA CONCENTRATION RST, ng/mL 3.04 ± 3.26 8.28 ± 5.49 3.139 (1.879–5.245) <0.0001		Yes	328 (54.21)	19 (63.33)	. ,			
RST, ng/mL 3.04 ± 3.26 8.28 ± 5.49 3.139 (1.879–5.245) <0.0001 2.281 (1.441–3.612) 0.0004 RSTL, ng/mL 0.44 ± 0.53 0.73 ± 0.67 1.498 (1.091–2.058) 0.0125 0.0001 2.281 (1.441–3.612) 0.0004 DM-RST, ng/mL 0.40 ± 0.54 1.06 ± 1.08 2.610 (1.768–3.853) <0.0001	PLASMA CONCENTRA	TION						
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DM-RST, ng/mL 0.40 ± 0.54 1.06 ± 1.08 2.610 (1.768–3.853) <0.0001	RSTL, ng/mL		0.44 ± 0.53	0.73 ± 0.67	1.498 (1.091–2.058)	0.0125		
	DM-RST, ng/mL		0.40 ± 0.54	1.06 ± 1.08	2.610 (1.768–3.853)	< 0.0001		

Variables with P < 0.05 were entered into the multivariate model, and only variables with P < 0.05 were retained in the model. Abbreviations as in **Tables 1–3**.



FIGURE 3 | Comparison of plasma RST concentration between control group and CI-AKI group in patients without CKD (A), in patients with CKD (B), and in all patients (C) in stage II. ROC analyses of variables for predicting CI-AKI in patients without CKD (D), in patients with CKD (E), and in all patients (F) in stage II. DM-RST: N-desmethyl rosuvastatin, RST: rosuvastatin; other abbreviations as in Figures 1, 2.

AUC for predicting CI-AKI was calculated in an additional independent cohort that receiving RST treatment (stage II study, **Figures 3D,E**). As shown in **Figure 3F**, plasma RST exposure was validated in predicting CI-AKI in the stage II cohort (AUC = 0.82). Moreover, the best cutoff of plasma RST exposure was 2.88 ng/mL, and the predictive performance of plasma RST exposure in the validation set yielded high true positive rate (93%) and low false positive rate (39%). After integrating all variable, AUC for the CI-AKI classifier was 0.85.

DISCUSSION

Statins are one of the most commonly prescribed medications all over the world, rendering it important to determine their potentially effects in CI-AKI. To the best of our knowledge, this is the first study to investigate the risk of CI-AKI in relation to high plasma statin exposure in a prospective study of patients with CAD. Our study provided solid evidence that high plasma statins exposure independently increased the risk of CI-AKI, after adjusting for several potential confounding variables, including demographics, severity of CAD, clinical measurements, prevalent comorbidities, and concomitant use of medications. These findings have important implications for the management of statins therapy in patients undergoing CAG.

Additionally, this study identified that the use of PPIs was significantly and independently associated with increased risk of CI-AKI, and should be administered carefully. These findings are also in agreement with studies reporting (Arora et al., 2016; Lazarus et al., 2016; Moledina and Perazella, 2016) that PPIs are emerging as an important contributing cause to CKD. Clinicians should closely monitor patients taking PPIs by urinalysis and renal function tests to recognize any renal insufficiency in time.

With the increasing role of contrast media in diagnostic and interventional procedures, especially in the field of cardiology, the prevalence of CI-AKI is expected to rise. Pathophysiology of CI-AKI is not exactly understood, and multiple causes, including acute tubular necrosis from poor perfusion, nephrotoxicity from contrast media, use of nephrotoxic medications, cholesterol embolization, procedure-related factors, or a combination of these, may be involved (Kooiman et al., 2015). The prevention of CI-AKI can decrease mortality, morbidity, therapeutic costs and hospital stays. The role of various drugs in prevention of CI-AKI (such as statins) is still controversial and warrants future studies. Some researchers have reported no association between statin use and CI-AKI, whereas others have found that statin use is protective against the incidence of CI-AKI, or that it is associated with an increased risk of CI-AKI. In 2012, Li et al. (2012) performed a meta-analysis including 7 studies and 1,399 patients that investigated the potential benefit of short-term highdose statins in the prevention of CI-AKI. The results of this study demonstrated that a significant improvement in the incidence of CI-AKI. On the contrary, it has been reported that a shortterm administration of high doses of atorvastatin before and after contrast exposure does not decrease the incidence of contrastinduced nephropathy in patients with pre-existing CKD (Toso et al., 2010). One potential factor contributing to this discrepancy is the presence of marked clinical and statistical heterogeneity between studies.

Our results confirm the findings from previous retrospective observational analysis (Dormuth et al., 2013) and retrospective cohort study (Chung et al., 2013). The former discovered that in patients with non-chronic kidney disease, current users of highpotency statins were 34% more likely to be hospitalized with AKI within 120 days after starting treatment (Dormuth et al., 2013). The latter found that statins with high cholesterol-lowering efficacy might increase the risk for developing severe renal failure (Chung et al., 2013). The biological mechanism of statins on kidney injury remained not fully investigated. The higher risk of CI-AKI in patients with high potency statins treatment may be related to an increased risk of proteinuria or rhabdomyolysis. Our results was also supported by an experimental study that AT with a dose of 150 mg/kg/day for 7 days was nephrotoxic for rats, whereas lower doses at 10 or 50 mg/kg/day for 7 days were not accompanied by renal injury (Nasri et al., 2016), suggesting that administration of statins in high doses may itself be directed to renal tubular cell injury.

CI-AKI is likely to remain a significant challenge for cardiologists in the future because the prevalence of comorbid conditions with aging among patients with CKD. It is more frequent in elderly patients with renal insufficiency. Some authors agreed that when renal function is normal, there is no risk of CI-AKI (Andreucci et al., 2017). Therefore, we further divided patients into two subgroups according to baseline renal function, and discovered that patients with CKD had higher incidence than that in patients without CKD. The association between high plasma statin exposure and CI-AKI still remained highly significant in both subgroups.

Several limitations of this study need to be mentioned. Firstly, it was a single-center study and the sample size

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was relatively small. To address this defect, we used other patient populations that receiving other statin treatment to validate and confirm the predictive value of plasma statin and its metabolites concentrations for CI-AKI. Secondly, we detected the statin concentration at 10–12 h after dose instead of whole profile. However, in the clinical setting, it is easier to monitor steady statin concentration. Additional large-scale, multicenter clinical trial of statin efficacy in CAD patients is thus warranted.

CONCLUSION

Our study demonstrated that high plasma exposure of AT and its metabolites could significantly increase the risk of CI-AKI, which was further validated and confirmed in patients receiving RST treatment. Thus, statins should be used with greater caution in patients with CAD undergoing CAG, and plasma levels of statin and metabolites should be monitored to reduce the occurrence of CI-AKI.

AUTHOR CONTRIBUTIONS

LC, XB, HL and HW performed experiment, performed data analysis, and wrote the manuscript; QZ, ShaZ and YiL participated in data analysis; YoL, GH participated in patient recruitment; QL, JC and BZ revised manuscript; ShiZ, MH and QG designed the study and revised manuscript. All authors reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar. 2018.00427/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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