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Original article

Comparison of the preventive efficacy of rosuvastatin versus atorvastatin in post-contrast acute kidney injury in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention

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ABSTRACT

Statins have been shown to reduce the risk of post-contrast acute kidney injury (PC-AKI) in patients undergoing percutaneous coronary intervention (PCI). However, the preventive effect of rosuvastatin versus atorvastatin on PC-AKI in patients with ST-segment elevation myocardial infarction (STEMI) undergoing PCI remains unclear. Patients with STEMI undergoing PCI between January 2010 and May 2016 were consecutively enrolled. A total of 1300 included patients were divided into two groups according to the statin type (atorvastatin: n = 1040; rosuvastatin: n = 260). The primary endpoint was PC-AKI defined as an absolute increase of ≥ 0.5 mg/dL in the level of serum creatinine or an increase of ≥ 25 % over baseline within 48 − 72 h after contrast media exposure. In total, 245 (18.8 %) patients developed PC-AKI. The atorvastatin and rosuvastatin groups had similar rates of PC-AKI (19.1 % vs. 17.7 %, p = 0.595), in-hospital mortality (4.1 % vs. 3.8 %, p = 0.833), and major adverse clinical events (MACE). Multivariate logistic regression analysis revealed that rosuvastatin treatment had an effect similar to atorvastatin regarding PC-AKI (odds ratio [OR] = 0.97, 95 % confidence interval [CI], 0.66 − 1.43, p = 0.874). Propensity score analyses and subgroup analysis demonstrated similar results for PC-AKI. Kaplan-Meier survival curves and Cox proportional regression showed that the atorvastatin and rosuvastatin groups had no differences regarding follow-up mortality. Rosuvastatin exerted a similar preventive effect against PC-AKI and showed similar levels of in-hospital and follow-up all-cause mortality and in-hospital MACE compared with atorvastatin in patients with STEMI undergoing PCI.

1. Introduction

Owing to the widespread use of angiography, post-contrast acute kidney injury (PC-AKI) is an important cause of hospital-acquired acute renal injury. The reported overall incidence of PC-AKI is 3.3–19 % for patients undergoing percutaneous coronary intervention (PCI), and PC-AKI is associated with a prolonged hospital stay and increased mortality [1–3]. PC-AKI cannot be treated effectively after it occurs; thus, avoiding this condition is particularly important. Currently, statins are applied to provide such protective effects [4]. Statins are divided into subtypes based on their structural differences that give rise to variations in their pharmacokinetic effects and efficacy, including their anti-inflammatory effects [5].

The majority of previous studies in this area have focused on comparing statins and placebo or on the dose effects of statins in an effort to evaluate the protective value against PC-AKI. Owing to limited studies, it remains unclear whether such variations between different statin subtypes can result in inconsistent impacts on preventing PC-AKI [6–8]. Therefore, we aimed to compare the preventive effect of atorvastatin and rosuvastatin against PC-AKI in patients with ST-segment

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elevation myocardial infarction (STEMI) undergoing PCI.

2. Material and methods

2.1. Study design and population

This observational cohort study consecutively enrolled STEMI patients undergoing PCI at a cardiac care unit between January 2010 and May 2016. Patients who met the following criteria were excluded: (1) did not use statins; (2) used statins other than atorvastatin and rosuvastatin; (3) had crossover usage of statins; (4) without serum creatinine. Patients who were on hemodialysis at admission, those without PCI or undergoing cardiac surgery, and those who died within 24 h after admission were also excluded. The ethics committee of Guangdong Provincial People's Hospital approved the study protocol, and written informed consent from each patient was obtained. The study followed the principles outlined in the Declaration of Helsinki for all human and animal experimental investigations.

2.2. Laboratory investigations

Serum creatinine (SCr) concentration was measured at admission and daily for 3 days after contrast media exposure. Cardiac biomarker and other standard clinical parameters were measured in the morning after the procedure. Left ventricular ejection fraction (LVEF) was evaluated in all patients using echocardiography within 24–48 h of admission.

2.3. Procedure and treatment

Intravenous isotonic saline was given routinely 3–12 h before or during procedure, and 6–12 h after contrast media exposure, at a rate of 1 mL/kg/h (0.5 mL/kg/h for patients who LVEF < 40 %). PCI was performed by experienced interventional cardiologists according to standard clinical practice. According to the type of statin used, patients were divided into a rosuvastatin group and an atorvastatin group. All patients were administrated with statins at admission. Patients in the two groups received statin therapy (rosuvastatin: 10 mg daily; atorvastatin: 20 mg daily) before contrast agent exposure. Antiplatelet agents (aspirin, clopidogrel, or ticagrelor), diuretics, and angiotensin-converting enzyme inhibitors were used at the attending cardiologist's discretion, according to clinical protocols. The decision to use glycoprotein IIb/IIIa antagonists and the selection of stent type was decided by the operators.

2.4. Clinical outcomes

The primary endpoint was PC-AKI, defined as an absolute increase in the SCr level of ≥ 0.5 mg/dL or an increase of ≥ 25 % over baseline within 48 − 72 h after contrast media exposure (PC-AKI_1). The other PC-AKI definitions included: an absolute increase in SCr of ≥ 0.5 mg/dL within 72 h (PC-AKI_2); an absolute increase ≥ 0.3 mg/dL within 48 h (PC-AKI_3); and an increase of ≥ 50 % (1.5-fold over baseline) within 48 h (PC-AKI_4) after contrast media exposure [9]. The secondary outcomes were in-hospital and long-term all-cause mortality, and in-hospital major adverse clinical events (MACE), defined as composite endpoints including all-cause mortality, stroke, recurrent myocardial infarction, target vessel revascularization, or renal replacement therapy.

2.5. Statistical analysis

The data are presented as the mean ± standard deviation for continuous variables, or absolute values (percentage) for categorical variables. Continuous data were compared using Student's t-tests or the Wilcoxon rank-sum test (if not normally distributed), while categorical data were analyzed using the chi-squared test. Multivariate regression analysis was performed to compare endpoints between the two groups, and odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated. Potential confounders that were significant in the univariate analysis or clinically important were included in the multivariable models. In addition, propensity score analysis was conducted for reducing the selective bias. The propensity score was calculated, and the patients were matched with a ratio of 3: 1 (atorvastatin versus rosuvastatin = 3:1). For survival analyses, the Kaplan–Meier survival method was used to draw cumulative event curves and the log–rank test was used for statistical assessment. Multivariate cox regression analyses for all-cause mortality were also performed. Subgroup analyses were performed according to the age, gender, estimated glomerular filtration rate (eGFR), diabetes mellitus and Killip class III/IV to assess the effects of statins on PC-AKI_1. All probability values were two-tailed, and statistical significance was defined as $p < 0.05$. SAS version 9.2 (SAS Institute, Cary, NC, USA) was used for the statistical analysis.

3. Results

3.1. Baseline characteristics

The study flow was shown in Fig. S1. Finally, a total of 1300 patients (81.9 % male) were finally included, 80 % of whom (n = 1040) used atorvastatin and 20 % (n = 260) used rosuvastatin. Baseline demographics, clinical and procedural characteristics, and biochemical characteristics were similar between the two groups (Table 1). There were no statistically significant differences in hypertension, diabetes mellitus, hyperlipidemia, smoking status, or prior myocardial infarction between the atorvastatin group and the rosuvastatin group, and the eGFR values were 82.58 ± 31.49 mL/min/ 1.73 m^2 and 85.63 ± 30.05 mL/min/1.73 m^2 (p = 0.158), respectively. The contrast media volume, the mean stent length, and the number of stents were not significantly different between the two groups.

3.2. Clinical outcomes

The incidence of PC-AKI_1 during hospitalization showed no significant differences (19.1 % vs. 17.7 %, p = 0.595) between the rosuvastatin and atorvastatin groups, respectively. Approaches using the alternate PC-AKI definitions yielded similar results. In addition, in-hospital mortality (4.1 % vs. 3.8 %, p = 0.833) and MACE (7.8 % vs. 6.9 %, p = 0.638) showed no significant differences between the rosuvastatin and atorvastatin groups, respectively (Fig. 1). Multivariate logistic regression analysis revealed that pretreatment with rosuvastatin or atorvastatin demonstrated a similar effect on PC-AKI_1 (OR = 0.97, 95 % CI, 0.66 − 1.43, p = 0.874) (Table 2). Similar results were also obtained in the context of other PC-AKI definitions (Table S1) and for the in-hospital mortality and MACE (Table S2).

Kaplan-Meier survival analysis showed that patient pretreatment with rosuvastatin had a similar effect as with atorvastatin regarding all-cause mortality with median follow up time of 2.3 years (p = 0.683) (Fig. 2). Cox proportional regression demonstrated that the two groups showed similar rates for all-cause mortality (adjusted hazard ratio = 1.11, 95 % CI 0.75–1.65; p = 0.597) (Fig. S2).

3.3. Propensity score analyses

After propensity score matching, 585 patients were administered with atorvastatin and 195 patients with rosuvastatin in a 3:1 ratio. The baseline characteristics between the two groups were well-balanced (Table 1). The results showed that the effect of atorvastatin and rosuvastatin on PC-AKI_1 were not significant (OR = 1.11, 95 % CI, 0.66 − 1.85, p = 0.696). Similar results were found in the outcomes of in-hospital mortality (OR = 1.75, 95 % CI, 0.51 − 5.98, p = 0.372) and in-hospital MACE (OR = 2.17, 95 % CI, 0.82 − 5.70, p = 0.117) (Table 3). Other propensity score analyses demonstrated similar results.

Table 1
Baseline Characteristics of Study Patients.

Variables	All patients		P value	Propensity-matched patients		P value	Standard difference (%)
	Atorvastatin (n = 1040)	Rosuvastatin (n = 260)		Atorvastatin (n = 585)	Rosuvastatin (n = 195)		
Age	62.07 ± 12.34	62.83 ± 12.55	0.375	62.92 ± 12.27	62.74 ± 12.69	0.860	1.45
Age ≥ 65, year	456 (43.8 %)	127 (48.8 %)	0.147	265 (45.3 %)	94 (48.2 %)	0.481	NA
Male, n (%)	853 (82.0 %)	212 (81.5 %)	0.857	472 (80.7 %)	161 (82.6 %)	0.561	−4.86
Previous medical history, n (%)							
Hypertension	555 (53.4 %)	127 (48.8 %)	0.192	303 (51.8 %)	103 (52.8 %)	0.804	−2.05
Diabetes	264 (25.4 %)	73 (28.1 %)	0.376	156 (26.7 %)	49 (25.1 %)	0.673	3.51
Hyperlipidemia	110 (10.6 %)	25 (9.6 %)	0.649	64 (10.9 %)	21 (10.8 %)	0.947	0.55
Smoke	453 (43.6 %)	118 (45.4 %)	0.595	255 (43.6 %)	87 (44.6 %)	0.803	−2.07
Previous MI	51 (4.9 %)	17 (6.5 %)	0.290	35 (6.0 %)	10 (5.1 %)	0.658	3.73
SBP, mmHg	122.28 ± 22.17	122.17 ± 23.01	0.943	122.47 ± 21.77	123.84 ± 23.20	0.455	6.08
DBP, mmHg	73.65 ± 13.52	74.29 ± 13.46	0.497	74.31 ± 13.70	74.33 ± 13.64	0.987	−0.14
Triglycerides, mg/dL	1.59 ± 1.18	1.51 ± 1.10	0.358	1.53 ± 1.02	1.52 ± 1.02	0.937	0.65
Total cholesterol, mg/dL	4.84 ± 1.16	4.88 ± 1.32	0.624	4.88 ± 1.16	4.88 ± 1.30	0.997	−0.03
LDL, mg/dL	3.06 ± 1.00	3.16 ± 1.13	0.195	3.13 ± 1.01	3.16 ± 1.09	0.759	−2.48
HbA1C, %	6.71 ± 1.80	6.78 ± 1.67	0.621	6.73 ± 1.86	6.68 ± 1.57	0.715	NA
Albumin, g/L	33.42 ± 4.16	33.75 ± 4.34	0.270	33.81 ± 4.09	33.82 ± 4.29	0.977	−0.24
Hemoglobin, g/L	136.31 ± 18.67	136.46 ± 17.13	0.927	137.30 ± 18.53	137.50 ± 16.11	0.916	NA
eGFR, mL/min/1.73 m^2	82.58 ± 31.49	85.63 ± 30.05	0.158	84.11 ± 31.62	84.28 ± 29.88	0.945	−0.58
Killip class			0.762			0.980	
I	741(71.3 %)	183 (70.4 %)		423 (72.3 %)	141 (72.3 %)		0.00
II	211(20.3 %)	53 (20.4 %)		113 (19.3 %)	37 (19.0 %)		0.87
III	42 (4.0 %)	13 (5.0 %)		26 (4.4 %)	9 (4.6 %)		−0.82
IV	46 (4.4 %)	11 (4.2 %)		23 (3.9 %)	8 (4.1 %)		−0.87
LVEF, %	51.97 ± 11.48	52.67 ± 11.06	0.390	52.58 ± 11.44	52.55 ± 11.00	0.970	0.31
Previous medications, n(%)							
Aspirin	1026 (98.7 %)	254 (97.7 %)	0.260	585 (100.0 %)	195 (100.0 %)	1.000	0.00
Clopidogrel	1030 (99.0 %)	254 (97.7 %)	0.078	585 (100.0 %)	195 (100.0 %)	1.000	0.00
ACEI	840 (80.8 %)	204 (78.5 %)	0.403	486 (83.1 %)	162 (83.1 %)	1.000	0.00
CCB	105 (10.1 %)	23 (8.8 %)	0.545	57 (9.7 %)	19 (9.7 %)	1.000	0.00
Diuretics	268(25.8 %)	65(25.0 %)	0.799	147 (25.1 %)	52 (26.7 %)	0.670	−3.51
PPI	723 (69.5 %)	174 (66.9 %)	0.418	401 (68.5 %)	134 (68.7 %)	0.964	−0.37
Stent number, n	1 (1−2)	1(1−2)	0.752	1 (1−2)	1 (1−2)	0.533	1.65
Stent length, mm	33 (20−54)	33 (18−54)	0.931	33 (18−54)	33 (21−54)	0.630	0.35
CM > 100, ml	732 (78.4 %)	197 (81.1 %)	0.358	457 (78.1 %)	161 (82.6 %)	0.185	NA
CM volume, ml	100 (100−150)	100 (100−130)	0.428	100 (100−150)	100 (100−150)	0.640	−2.04
Hospitalization, days	7 (5−9)	7 (5−9)	0.853	7 (5−8.50)	7 (5−9)	0.538	NA

MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HbA1C, glycated hemoglobin; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitors; CCB, calcium-channel blockers; PPI, proton pump inhibitor; CM, contrast medium.

3.4. Subgroup analyses

Subgroup analyses for age ≥ 65 years, gender, eGFR ≤ 60 mL/min/1.73m^2, diabetes mellitus and Killip class III/IV were performed and showed similar results that rosuvastatin had a similar effect as atorvastatin on PC-AKI_1 (Fig. 3).

4. Discussion

The present study demonstrated that rosuvastatin and atorvastatin had similar efficacy in preventing PC-AKI, in-hospital mortality, follow-up all-cause mortality, and in-hospital MACE in patients with STEMI undergoing PCI. These findings support the notion that it is a statin class-effect, rather that a specific statin effect, as also suggested in previous reports [10].

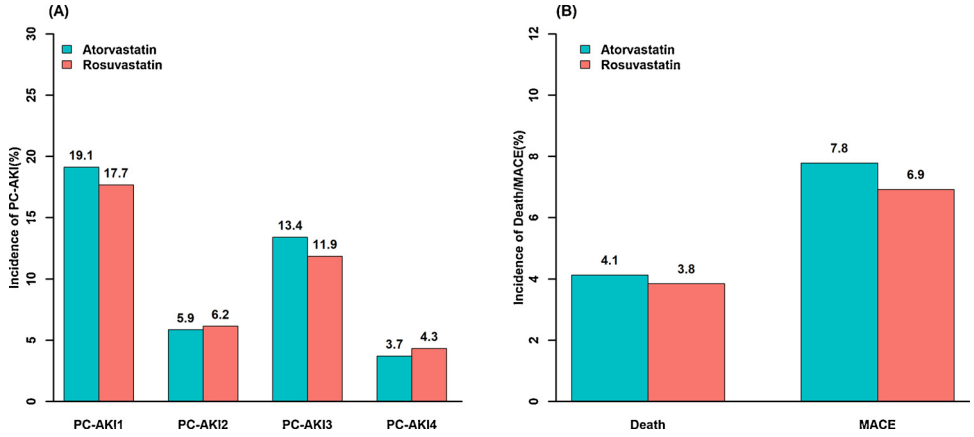

Fig. 1. In hospital clinical outcomes between patients with rosuvastatin and atorvastatin.

Table 2
Multivariate analysis of PC-AKI$_1$.

Variables	Multivariable analysis		
	OR	95 %CI	P value
Atorvastatin to Rosuvastatin	0.97	0.66 − 1.43	0.874
Age (every 1 years)	1.39	1.00 − 1.94	0.054
Diabetes	0.74	0.52 − 1.07	0.113
Hypertension	1.63	1.17 − 2.26	0.004
Smoke	0.84	0.60 − 1.18	0.319
Total cholesterol	1.52	1.10 − 2.10	0.011
LVEF (every 1%)	1.82	1.20 − 2.75	0.005
Killip class	1.28	1.06 − 1.55	0.012
Contrast volume	1.09	0.74 − 1.60	0.663

LVEF, left ventricular ejection fraction; PC-AKI$_1$,post-contrast acute kidney injury, an absolute increase in the serum creatinine level of ≥ 0.5 mg/dL or an increase of ≥ 25 % over baseline within 48 − 72 h after contrast media exposure.

Emerging evidence has proven the close correlation between PC-AKI and in-hospital adverse events; thus, new and improved strategies for preventing the occurrence of PC-AKI are required. Previous studies have shown that statins can protect against PC-AKI in patients undergoing PCI [11,12]. However, most of the previous studies compared statins vs. placebo or investigated various doses of statins. A prospective randomized controlled trial (RCT) by Mario and colleagues [13] reported that patients treated with rosuvastatin had lower rates of PC-AKI than those without rosuvastatin in patients with non-ST-elevation acute coronary syndrome (ACS). High-dose atorvastatin might further reduce PC-AKI in ACS patients according to another RCT performed by Naikuan et al., but this result was in contrast to a previous non-randomized study [14,15].

Few studies were found that explored the differences in PC-AKI risk reduction between rosuvastatin and atorvastatin. Liu et al. [7] enrolled 1078 consecutive patients with chronic kidney disease (CKD) undergoing elective PCI and demonstrated that rosuvastatin and atorvastatin exerted similar efficacy for preventing PC-AKI. This study was restricted to CKD patients. Liyun and colleagues found that the rate of PC-AKI in an atorvastatin group and a rosuvastatin group was similar among coronary artery disease (CAD) patients [16]. STEMI patients experience more systemic inflammation than CAD patients; therefore, the anti-inflammatory differences between statins may be amplified. Thus, it is unsuitable to extrapolate the results from CAD patients to STEMI patients. Kaya et al. [6] performed the first study in this area, which included 192 STEMI patients undergoing primary PCI, and showed that high-dose atorvastatin and rosuvastatin initiated prior to coronary intervention had similar effects in preventing PC-AKI. Subsequently, Firouzi, A et al. performed a similar study and drew similar conclusions [8]. These two studies used the same definition of PC-AKI; however, it was not the current common definition of PC-AKI recommended by the European Society of Urogenital Radiology guidelines [17]. The different definitions of PC-AKI had differing impacts on the clinical outcomes. For the patients with STEMI, the definition of PC-AKI with an increase in serum creatinine of ≥0.5 mg/dL is more sensitive because it recognizes more selectively those patients with a higher risk of mortality and morbidity [18]. However, in the above two studies, the incidence of PC-AKI with this definition was slightly higher in the rosuvastatin group than in the atorvastatin group. Furthermore, the baseline characteristics of creatinine and eGFR, which are the most important risk factors of PC-AKI, were significantly different between the statin groups in the Firouzi study, and the final result did not adjust for these different variables [8]. Therefore, together with these complications and the lack of a pre-calculated sample size for the two RCTs, it is hard to draw the conclusion that atorvastatin and rosuvastatin had a similar effect on PC-AKI. In contrast to these two studies, although the present study was an observational cohort study, the baseline characteristics

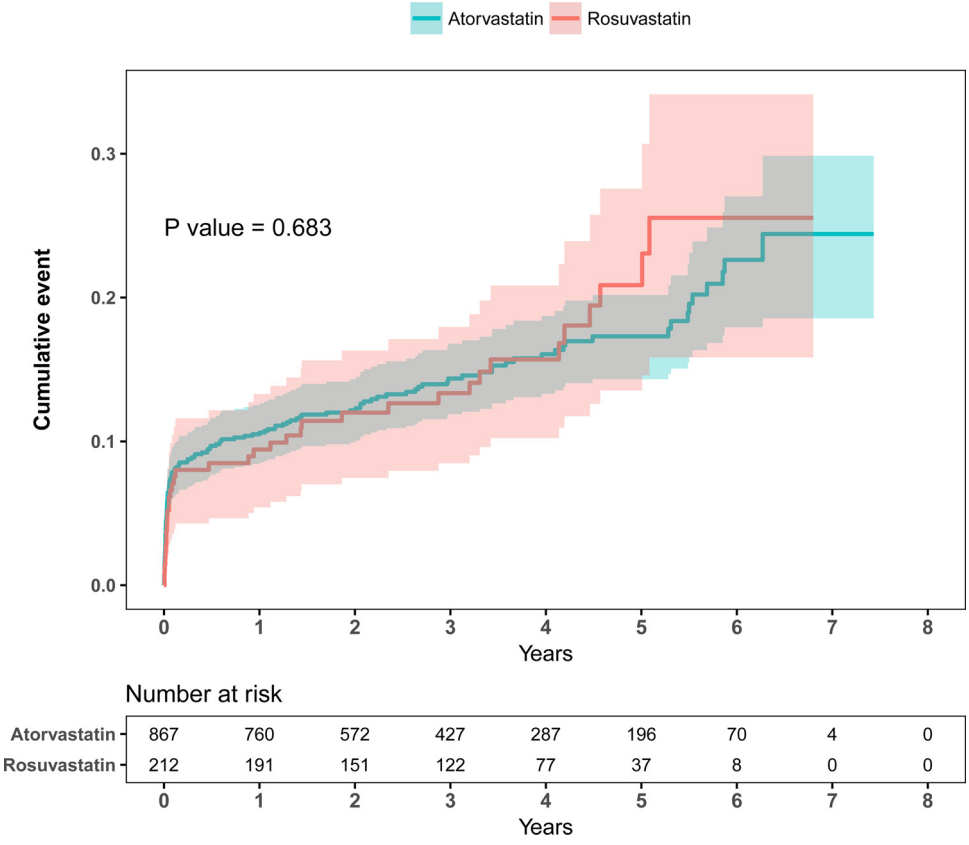

Fig. 2. Cumulative rate of follow-up all-cause mortality between patients with rosuvastatin and atorvastatin.

Table 3
Propensity score analysis of clinical outcomes.

Outcomes	Propensity scores matching analysis (1:3)			Analysis by adjusting the propensity scores			Stratification analysis		
	OR	95 %CI	P	OR	95 %CI	P	OR	95 %CI	P
$PC\text{-}AKI_1$	1.11	0.66 − 1.85	0.696	1.03	0.67 − 1.50	0.900	1.01	0.63 − 1.61	0.962
In-hospital mortality	1.75	0.51 − 5.98	0.372	1.02	0.46 − 2.24	0.971	1.03	0.47 − 2.28	0.942
In-hospital MACE	2.17	0.82 − 5.70	0.117	0.96	0.53 − 1.73	0.898	0.99	0.55 − 1.79	0.981

$PC\text{-}AKI_1$, post-contrast acute kidney injury, an absolute increase in the serum creatinine level of ≥ 0.5 mg/dL or an increase of ≥ 25 % over baseline within 48 − 72 h after contrast media exposure; MACE, major adverse clinical events.

between the two groups were similar, and the result remained the same with different definitions of PC-AKI and across the various subgroups. Our current study filled the gap of the selection between atorvastatin and rosuvastatin for preventing PC-AKI, which is clinically importance, using multivariate analysis and propensity score analysis to control the bias.

Statins are thought to reduce PC-AKI through anti-inflammation activity, relieving endothelial dysfunction and oxidative stress, reducing contrast accumulation in renal tubular cells, protecting podocytes, and restricting mesangial cell proliferation [4]. Rosuvastatin, a type of hydrophilic statin, elicits a greater reduction in low-density lipoprotein compared with other statins and has a longer plasma half-life, with stronger anti-inflammatory efficacy than atorvastatin [19–21]. Thiago et al. [22] demonstrated that rosuvastatin performed better than atorvastatin in reducing oxidative stress and inflammation in mice. In contrast, de Zeeuw found atorvastatin to be more efficacious for reducing PC-AKI than rosuvastatin in patients with diabetes and progressive kidney disease [23]. These findings indicated that a stronger effect against oxidative stress or inflammation might not always provide better PC-AKI prevention. However, the mechanism difference between rosuvastatin and atorvastatin for preventing PC-AKI remains unclear. Our results indicated that their protective value was similar. The following reasons might be considered. First, the characteristics of the study cohort were quite similar; therefore, differences in the impact on PC-AKI can be attributed to the statins. Second, rosuvastatin may be favorable for PC-AKI prevention through anti-inflammatory and anti-oxidative stress pathways; although the data is limited, atorvastatin is protective for podocytes [24]. In addition, the interaction between the anti-inflammation and anti-oxidative stress pathways is also possible. Additional studies are needed to explore potential reasons for the similarity in the protective value of rosuvastatin and atorvastatin.

Our study has several limitations. Firstly, although we performed the multivariate and propensity score analysis to avoid the inherent limitation of observational study, the residual cofounders may exist. However, the result of the present research should be considered hypothesis-generating. The different role of statins on PC-AKI needs to be determined in further randomized controlled studies. Secondly, our study population was limited to STEMI patients, and it may not be appropriate to extend the results to patients in other ACS sub-categories. Thirdly, due to variations in the timing of measurements, some positive patients may have been left out; thus, the true incidence of PC-AKI may be underestimated. Forth, we did not have the follow-up medical records of statins, thus, the drugs compliance is unknown. Finally, the preventive influence of statins and their different doses on the incidence of PC-AKI lacks further estimation.

5. Conclusions

Compared with atorvastatin, rosuvastatin exerted a similar effect in preventing PC-AKI, in-hospital and follow-up all-cause mortality, and in hospital MACE in STEMI patients undergoing PCI.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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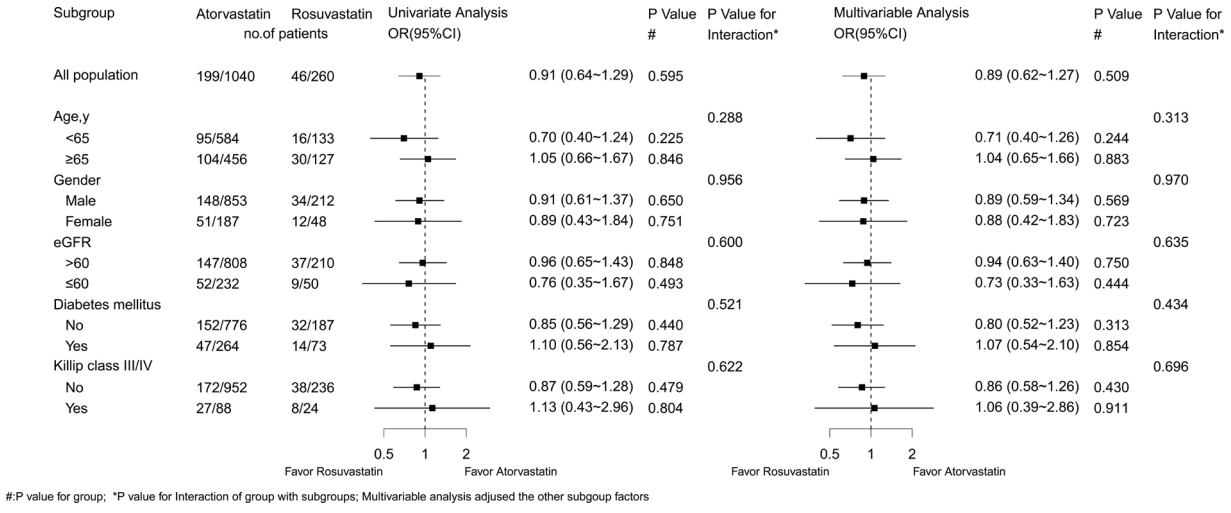

Fig. 3. Subgroup analyses of $PC\text{-}AKI_1$.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biopha.2020.110336.

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