

ORIGINAL RESEARCH



Comparison of atorvastatin and rosuvastatin on preventing contrast-induced-nephropathy in patients undergoing primary percutaneous coronary intervention: A multi-centric randomized triple-blind clinical trial

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Abstract

Background: Patients with Contrast-Induced-Nephropathy (CIN) are at a greater risk of in-hospital complications, longer hospitalization, and long-term mortality in comparison with those without CIN. Despite many studies on the helpful effects of statins in preventing contrast-nephropathy, there is not enough evidence comparing different statins in inhibiting CIN. So, we planned this study to compare the efficacy of rosuvastatin and atorvastatin in prevention of contrast-induced nephropathy. **Methods:** This was a randomized clinical trial. The efficacy of two known statins, atorvastatin and rosuvastatin were compared in prevention of CIN in patients with ST-Elevation Myocardial Infarction (STEMI) who underwent Primary Percutaneous Intervention (PPCI) between May 2015 and April 2016 in Qaem and Imam Reza hospital, Mashhad, Iran. Subjects were divided randomly to 80-mg atorvastatin or 40-mg rosuvastatin group before PPCI. Participants' characteristics including echocardiographic, laboratory and demographic data were recorded and incidence of CIN was assessed. **Results:** Two hundred cases with STEMI undergoing PPCI were recruited in the study and randomized to 80-mg atorvastatin (n = 98) or 40-mg rosuvastatin (n = 102) group before PPCI. The incidence of CIN was 5.67% (n = 13) in all participants; 6.3% (n = 7) in the rosuvastatin group and 5.1% (n = 6) in the atorvastatin group. There was a significant difference between creatinine and Glomerular Filtration Rate (GFR) after 48 hours of PPCI. Creatinine was lower and GFR was higher in the rosuvastatin group ($P = 0.029$, $P = 0.005$). **Conclusion:** There was a little trend for prevention of CIN in patients after PPCI in rosuvastatin group compared to atorvastatin group, in full dose. However, this preference was not clinically relevant.

Keywords

Rosuvastatin; Atorvastatin; Primary percutaneous coronary intervention; ST elevation myocardial infarction

1. Background

Contrast Induced Nephropathy (CIN) or Contrast-Induced Related Acute Kidney Injury (CI-AKI) is an acute decrease in renal activity occurring 48 to 72 hours after systemic using contrast media. It is usually defined by pure increase of 0.5 mg/dL in serum creatinine or by a relative raising at least 25% over the base-line level [1]. Another accepted definition is a decrease in estimated Glomerular Filtration Rate (eGFR) to 30 to 60 mL/minute [2]. CIN is a substantial adverse event of iodinated Contrast Medium (CM), responsible for one third of hospital-obtained AKI subjects [3]. It is responsible for 10% to 12% of all cases with in-hospital acute renal failure [2]. In patients with renal failure at baseline, the occurrence

of CIN has been estimated as 42% [4]. This could make temporary or persistent need for hemo-dialysis, especially high risk subjects [5]. Some prognosticator factors of CIN in patients undergoing coronary intervention, include chronic kidney disease, diabetes, anemia, and hemodynamic instability [6], volume and type of contrast agent [7] used during the procedure. It has been shown that high-osmolarity contrast media carry a greater risk, however both low osmolarity and iso-osmolarity ones might trigger CIN [8].

Patients with CIN are at a greater risk of in-hospital complications, longer hospitalization, and long-term mortality in comparison with those without it [9]. Contrast Induced Nephropathy is demonstrated to be more frequent among

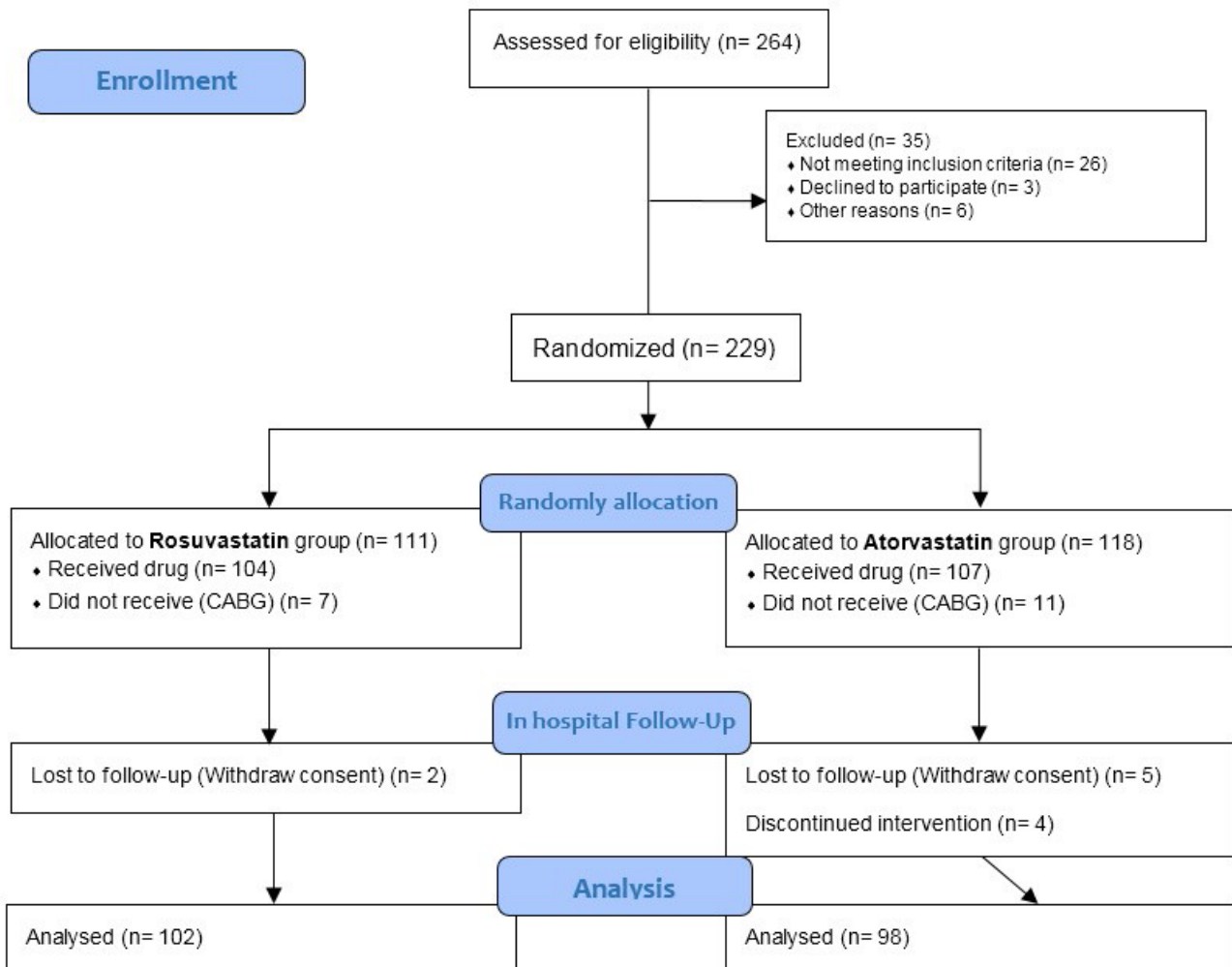


FIGURE 1. Flowchart of the study.

subjects undergoing Primary Percutaneous Intervention (PPCI) rather than elective PCI, due to hemo-dynamic instability within acute cardiac event and the more complex nature of the procedure [10]. Therefore, finding preventive strategies for CIN are seriously required. There are several studies that confirmed the cholesterol lowering effects of statins by their pleiotropic effects, which leads to renal protection [11–13]. Many studies also have indicated that pre-treatment with statins before CM exposure markedly lowered the incidence of CIN [14]; adversely, other studies reported controversial outcomes [15]. In a systematic review, it was mentioned that prescription of statin may not lower CIN in subjects with chronic kidney disease (CKD) [16]. Another important factor that contributes to this disagreement is variation in pleiotropic effects of various statins. Structural characteristics are different in various statins, including solubility, drug delivery, bioavailability and pleiotropic effects [17].

Despite many studies on positive consequences of statins in CIN, there is no adequate evidence regarding any discrepancy between statins in inhibiting CIN. Kaya *et al.* showed the same efficacy of atorvastatin and rosuvastatin in preventing CIN in patients with STEMI undergoing PPCI [18]. Kim *et al.* [19] illustrated similar efficacies of rosuvastatin and

atorvastatin as well. According to limited studies in this field, we evaluated the efficacy of full-dose rosuvastatin and atorvastatin in prevention of CIN.

2. Methods

This was a multi-centric triple-blind randomized clinical trial, to compare the efficacy of two known statins, atorvastatin and rosuvastatin in prevention of CIN in STEMI patients who underwent PPCI.

2.1 Sample size

The sample size was calculated according to below formula and the study of Kaya *et al.* [18]:

$$2n = \frac{\left((Z_{1-\frac{\alpha}{2}} - 1)^2 + (Z_{1-\beta})^2 \right) \times (P_0(1 - P_1) + P_0(1 - P_2))}{(P_1 - P_0)^2}$$

2.2 Inclusion and exclusion criteria

The study subjects included a total of 264 patients referred to the hospital with the diagnosis of STEMI between May 2015 and April 2016, who underwent PPCI at Qaem and Imam Reza

TABLE 1. Demographic and basic laboratory and clinical data of patients in the two groups.

Variable	Rosuvastatin group (n = 102)	Atorvastatin group (n = 98)
Gender (n, %)	Male (61, 54.5) Female (41, 46.6)	Male (51, 45.5) Female (47, 53.4)
Age (Mean \pm SD), years	60.93 \pm 11.84	61.72 \pm 10.28
BMI (Mean \pm SD) kg/m ²	26.31 \pm 2.21	25.91 \pm 3.23
Diabetes (n, %)	13, 12.7	16, 16.3
HTN (n, %)	70, 68.6	82, 83.7
HLP (n, %)	33, 32.4	32, 32.7
Smoking (n, %)	29, 28.4	22, 22.4
Addiction (n, %)	13, 12.7	16, 16.3
Total Cholesterol (Mean \pm SD) mg/dL	239.52 \pm 52.18	254.64 \pm 73.46
LDL (Mean \pm SD) mg/dL	173.44 \pm 9.87	186.54 \pm 58.07
HDL (Mean \pm SD) mg/dL	45.20 \pm 17.31	39.13 \pm 7.14
TG (Mean \pm SD) mg/dL	135.80 \pm 59.36	131.17 \pm 51.30
TIMI	20.42 \pm 4.02	20.87 \pm 3.74
Contrast (Mean \pm SD), mL	213.92 \pm 63.21	226.02 \pm 55.71
LVEF (Mean \pm SD) %	40.44 \pm 7.77	40.35 \pm 7.93

hospitals, Mashhad, Iran. The patients were randomized to 80 mg atorvastatin or 40 mg Rosuvastatin group before PPCI. Due to incomplete data, 35 patients were excluded (Fig. 1). All patients were naive to statins.

Patients under hemodialysis, or those with renal failure before angiography, cardiogenic shock, drug consumption, such as N-Acetyl-Cysteine and vitamin C, contrast media use for other reasons, use of mannitol, diuretics, theophylline and dopamine in the recent two weeks before PPCI (ruling out patients for bias), intra-aortic balloon pump, history of Coronary artery bypass grafting (CABG) (because of higher risk for CIN), history of cardiac surgery and patients using G2b3a drugs during PPCI were excluded.

2.3 Randomization

Finally, 229 patients were randomized into 2 groups; 118 patients to 80-mg atorvastatin group and 111 in the 40-mg rosuvastatin group. Blood samples were obtained to evaluate whole blood count and biochemistry parameters at presentation and 24 and 48 hours later. Primary endpoint was incidence of CIN.

2.4 Routine treatment considerations

STEMI was determined as the existence of ST-segment elevation at-least one millimeter in two or more tandem leads (two millimeters for V1 to V3) or new-onset left bundle-branch block. All subjects underwent PPCI during the first twelve-hours after the starting chest pain. They administered 300-mg chewable aspirin, a 600-mg loading dose of clopidogrel on admission and standard heparin and 10,000 Unit intravenously prior to the procedure.

They received acetylsalicylic acid 80 mg/twice daily, clopidogrel 75 mg/twice daily, and rosuvastatin 20 mg/day or atorvastatin 80 mg/daily post-procedurally. For all of them, the

Thrombolysis in Myocardial Infarction (TIMI) flow grade was evaluated after stenting. Angiographic no-reflow was determined as a final TIMI flow grade lesser than three. Positive history of hypertension was defined as having at least 2 blood pressure measurements more than 140/90 mmHg or use of anti-hypertensive medications before the current admission. Also, a positive history of diabetes mellitus was characterized as at least 2 fasting blood sugar levels $>$ 126 mg/dL or consuming anti-diabetic agents before the current admission. All participants were hydrated (0.9% sodium-chloride 1 mL/kg/hour) intravenously, for twelve hours after the intervention. Blood specimens were obtained pre and post P-PCI for measuring serum creatinine. The CIN was defined as previously defined [20]. CIN was categorized as grade 0 (serum creatinine increase more than 25% superior to base-line and less than 0.5 mg/dL more than base-line), grade 1 (increase in serum creatinine \geq 25% more than baseline and less than 0.5 mg/dL above baseline) or grade 2 (serum creatinine increase \geq 0.5 mg/dL above baseline) [21].

2.5 Ethics

The study was confirmed by Mashhad University of Medical Sciences ethics committee (code IR.MUMS.fm.REC.1395.90). Before inclusion in the study, the aim of study was described for patients and a written informed-consent was obtained.

2.6 Statistics

Data entered Statistical Package for Social Sciences software (SPSS 21.0, Chicago, IL, The USA). Quantitative variables expressed as mean \pm standard-deviation and categorical variables with count and percent. The Student's *t* test or Mann-Whitney U test was used for continuous variables comparison. Categorical variables were analyzed using Chi-square test or

TABLE 2. Comparison of renal function indicators in the two groups.

Variable		Rosuvastatin (n = 102)	Atorvastatin (n = 98)	P Value
Before PPCI Cr. (mg/dL)		1.36 ± 0.29	1.42 ± 0.23	0.112
24 hours Cr (mg/dL)		1.45 ± 0.35	1.48 ± 0.28	0.515
48 hours Cr (mg/dL)		1.4 ± 0.33	1.51 ± 0.35	0.029
Before PPCI GFR (mL/min/1.73 m ²)		53.76 ± 16.75	47.5 ± 10.87	0.061
24 hours GFR (mL/min/1.73 m ²)		50.84 ± 17.1	47.09 ± 12.13	0.074
48 hours GFR (mL/min/1.73 m ²)		52.48 ± 16.97	46.48 ± 12.24	0.005
Cr difference from baseline to 48 h (mg/dL)		0.03 ± 0.17	0.08 ± 0.18	0.06
CIN Grade (n, %)	Grade 1	4, 30.8	0	0.026
	Grade 2	3, 23.1	6, 46.2	

Fisher’ Exact Test. Multivariable logistic regression analysis was used to determine the independent predictors of CIN. P value lower than 0.05 was considered as statistically significant.

3. Results

Overall, 200 subjects with STEMI undergoing PPCI were recruited in this investigation. They were randomized to 80-mg atorvastatin (n = 98) or 40-mg rosuvastatin (n = 102) group before PPCI. There was no markedly difference regarding baseline variables between the two groups (P > 0.05) except for HDL. Table 1 presents demographic and baseline laboratory data of patients in the two groups.

The incidence of CIN was 5.67% (n = 13) in all participants; 6.3% (n = 7) in the rosuvastatin group and 5.1% (n = 6) in the atorvastatin group. Also, 2% of patients (n = 4) developed a grade 1 CIN versus 4.5% (n = 9) grade 2 CIN. Renal indicators are listed in Table 2. No significant difference was found between the two groups at baseline (P > 0.05). There was a significant difference between creatinine and GFR levels after 48 hours of PPCI. Creatinine was lower and GFR was higher in the rosuvastatin group compared to the atorvastatin group (P = 0.029, P = 0.005). A meaningful difference was seen between the two groups regarding CIN grades.

Multivariate analysis showed that within different parameters evaluated in this study, random blood glucose (P = 0.002), ejection fraction (P = 0.044), and volume of contrast media (P = 0.039) could significantly predict CIN. Fig. 2 shows the ROC curve.

Area under the curve were 0.675, 0.725, and 0.601 for random blood glucose (cutoff point: 180.5, specificity: 89.2%, and sensitivity: 84.6%; CI: 0.48 to 0.87), contrast media (cutoff point: 160, specificity: 79.5%, and sensitivity: 84.6%; CI: 0.54 to 0.90), and ejection fraction (cutoff point: 32.5, specificity: 82.7%, and sensitivity: 92.3%; CI: 0.45 to 0.78), respectively.

4. Discussion

Current investigation was designed to compare the effectiveness of high dose rosuvastatin and atorvastatin in prevention of CIN in patients undergoing PPCI. Studies in this field are limited with controversial outcomes [18, 19].

Patients with CIN regularly have high serum creatinine levels 24-48 hours after contrast usage, then would peak at 3-5 days and return to base-line after 7-10 days. Urine analysis might illustrate tubular epithelial cells, granular casts and minimal proteinuria [22]. However, CIN may cause the necessity for dialysis, prolongation of hospital stay, potential non-reversible renal damage and mortality [3].

The incidence of CIN was 5.67% in the current study in the both groups. The authors found a similar efficacy of both statins in prevention of CIN. However, there was a significant decrease in rosuvastatin compared to atorvastatin regarding 48-hour creatinine index, 48-hour GFR index and difference of creatinine from baseline to 48-hour. In addition, the difference of CIN grade was significantly lower in the rosuvastatin group. The results showed superiority of rosuvastatin over atorvastatin to a few extents. However, clinically relevant results were not obtained. Park *et al.* [23] evaluated 334 STEMI patients in a prospective trial in four groups; low dose statin, high dose statin, high dose statin plus NAC, and high dose statin plus NAC plus NaHCO. They showed CIN in 21.6% of subjects, and high-dose statin plus NAC was related to lower occurrence of CIN in STEMI patients who had undergone primary PCI compared to statin only. Moreover, Kaya *et al.* showed comparable efficacy of rosuvastatin and atorvastatin based on creatinine and GFR values at 48 hours following intervention. Liu *et al.* [19] in another study, compared the effect of rosuvastatin and atorvastatin in CIN prevention in patients with CKD undergoing PCI. They included 1078 CKD patients undergoing elective PCI. They divided patients to group 1 (n = 273, 10 mg rosuvastatin) and group 2 (n = 805, 20 mg atorvastatin). Contrast Induced Nephropathy was observed in 58 (5.4%) patients. Their results showed that the occurrence of CIN was the similar with rosuvastatin (5.9%) or atorvastatin (5.2%) (P = 0.684) group. Kandula *et al.* [24] reported an observational investigation on 239 patients who received statins and 114 subjects who received no statins. They demonstrated that statin treatment was not related to CIN prevention (OR = 1.6, 95% CI: 0.86 to 3.22, P = 0.12). Toso and his colleagues [25] did a prospective RCT with 304 patients to evaluate the effect of high-dose atorvastatin on CIN prevention in CKD patients undergoing PCI. The outcomes indicated that short-term high doses of atorvastatin, used periprocedurally, did not lower CIN incidence in patients with

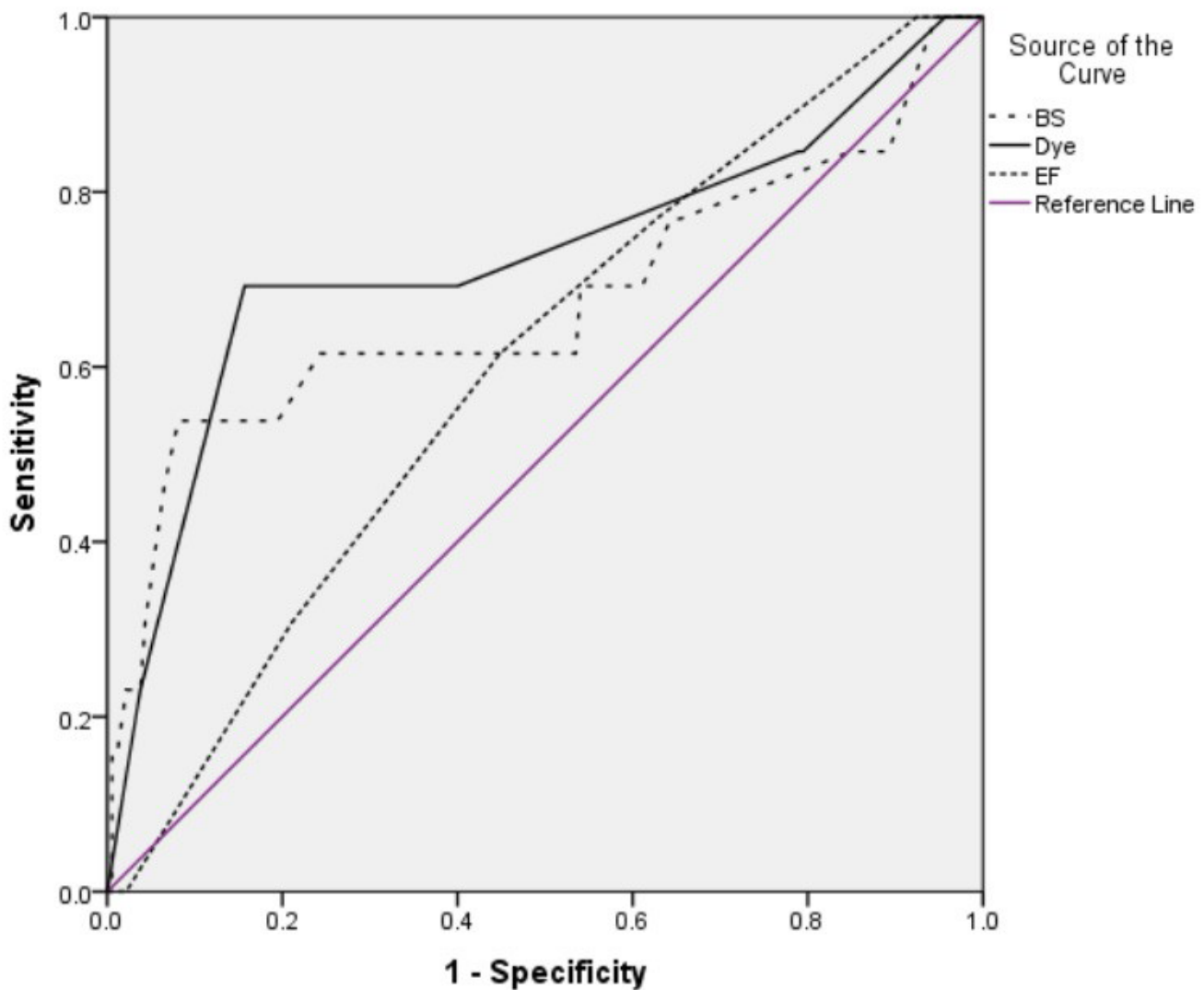


FIGURE 2. ROC curve of parameters predicting contrast induced nephropathy.

preexisting CKD. But, in another RCT [26] on 410 CKD patients, a single high dose of atorvastatin pretreatment 24 hours prior to CM exposure, was effective in reduction of CIN occurrence. The same results have been published from some RCTs [27–29]. Two large-scale clinical trials showed that rosuvastatin in patients undergoing PPCI could lower CIN incidence.

Leoncini *et al.* [30] declared that in patients with ACS without ST-segment elevation, pretreated with rosuvastatin (40 mg on admission, then 20 mg/day) decreased CIN incidence compared to control patients. Another study illustrated that rosuvastatin meaningfully lowered the risk of CIN post-exposure to CM [31]. Despite no recommendation in guidelines for administration of statins to prevent CIN, clinicians are progressively considering them as an effective choice according to the existing evidence [13]. According to our results and comparison with previous studies, there is no definite relationship between statin usage and prevention of CIN. In this study, in contrast to previous investigations, we administered full dose of rosuvastatin and atorvastatin. However, we found a little superiority for rosuvastatin which was not clinically relevant.

Probable mechanisms for positive effects in prevention of

CIN by statins are LDL lowering effects, potency, lipophilicity, renal preservation and anti-inflammatory properties [32]. Otherwise, the difference (hydrophilic and lipophilic) between statins regarding their efficacy in lowering risk of CIN is obscure. Rosuvastatin, with a hydrophilic structure, has acute pleiotropic effects, and has been shown to diminish LDL more prominently, without rising side effects, and enhances prognosis more than other statins [33]; it also incurs a positive renoprotective influence in patients with renal failure [34]. Moreover, rosuvastatin has a greater plasma half-life and more powerful anti-inflammatory outcomes than atorvastatin [34]. A late meta-analysis showed that rosuvastatin may enhance apolipoprotein A_I levels at all doses more than atorvastatin [34]. Apolipoprotein A_I could stabilize lipoprotein structure and has antioxidant and anti-inflammatory characteristics [35]. These differences between rosuvastatin and atorvastatin may justify their difference in preventing CIN.

There are some known risk factors in developing CIN, which include diabetes mellitus, old age, features of contrast media, and volume of contrast media [36]. The researchers demonstrated that blood sugar, ejection fraction and volume of contrast media could predict CIN significantly. Park *et al.*

[23] showed that hyperglycemia and the use of intra-aortic balloon pump (IABP) were independent predictors for CIN. Liu et al. showed that, rosuvastatin and atorvastatin had the same effectiveness for inhibition of CIN after adjustment for potential confounding risk factors (OR = 1.17, $P = 0.623$). Also, Kaplan-Meier survival-analysis demonstrated that patients using rosuvastatin or atorvastatin had the same incidences of all-cause mortality (9.4% versus 7.1%, respectively; $P = 0.290$) and major cardiovascular complications (29.32% versus 23.14%, respectively; $P = 0.135$) during follow up [19]. Liu et al. [19] showed that age of more than 75 years, IABP use, and primary PCI were independent risk factors of CIN, yet an eGFR of ≤ 60 mL/min/1.73m² was not related to PCI development. However, Ando et al. [37] expressed that eGFR was a risk factor for CIN in patients with STEMI treated with PPCI.

5. Limitations

The researchers did not have access to urine laboratory results, which could help in the assessment of CIN by different common definitions of CIN. However, long-term follow-ups might yield more reliable outcomes. Moreover, we did not report some other information such as lesions treated, duration of procedure and symptom onset to balloon time, because they were not within the scope of this study.

6. Conclusions

The two studied statins were different in preventing CIN in patients with STEMI. Despite this, the researchers found that CIN grades were significantly lower in the rosuvastatin group, while 48-hour creatinine and GFR were significantly better in the rosuvastatin group. The current results indicated that rosuvastatin may prevent CIN in patients with STEMI patients who underwent PPCI. The authors showed that the volume of contrast media, ejection fraction, and preprocedural blood sugar could significantly predict the incidence of CIN. Performing large-scale and multi-centric studies according to different definitions of CIN could be promising.

ABBREVIATIONS

ACS, Acute Coronary Syndrome; CIN, Contrast Induced Nephropathy, CI-AKI, Contrast-Induced Related Acute Kidney Injury; eGFR, Estimated Glomerular Filtration Rate; CM, Contrast Medium; PPCI, Primary Percutaneous Intervention; CKD, Chronic Kidney Disease; CABG, Coronary Artery Bypass Grafting; STEMI, ST-Elevation Myocardial Infarction ; TIMI, Thrombolysis in Myocardial Infarction; HDL, High-Density Lipoprotein; BMI, Body Mass Index; HTN, Hypertension; HLP, Hyperlipidemia; LDL, Low-Density Lipoprotein; TG, Triglyceride; LVEF, Left Ventricular Ejection Fraction; NAC, N-Acetyl Cysteine; IABP, Intra-Aortic Balloon Pump.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was confirmed by Mashhad University of Medical Sciences ethics committee (code IR.MUMS.fm.REC.1395.90). Registry Accessibility of this article: <http://irct.ir/trial/27377>, Trial registration code: IRCT2017101236737N1. Before inclusion in the study, the aim of study was described for patients and a written informed-consent was obtained.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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