



# High versus low doses of rosuvastatin on postoperative outcomes of coronary artery bypass grafting; a double-blind clinical trial

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## Abstract

**Introduction:** Statins are beneficial treatments for patients with cardiovascular disease; however the relation between dose and clinical outcomes has not been evaluated.

**Objectives:** We compared the effects of high versus low-dose of rosuvastatin on postoperative outcomes in patients undergoing coronary artery bypass graft (CABG).

**Patients and Methods:** In this randomized clinical trial study, patients undergoing open heart surgery were randomly divided into two groups of 76 (received 5 mg dose) and 84 (received 20 mg dose) in Heshmat hospital, in Rasht. The study was started during the hospitalization period and after discharge until one month. Data were obtained by demographic questionnaire, clinical and changes in laboratory tests based on pre- and post-surgery. To analyze the variables, paired sample *t* test was applied. *P* value  $\leq 0.05$  was taken as significant.

**Results:** The ages of the participants were  $58.36 \pm 7$  and  $59.5 \pm 9$  years for the treatment with high and low dosages of rosuvastatin (20 mg and 5 mg) respectively ( $P = 0.28$ ). AKI (acute kidney injury) as a primary outcome was not significantly different between the two groups ( $P > 0.05$ ). Secondary outcomes (changes in lipid profiles, new atrial fibrillation (AF), postoperative infection) were not significantly different between the two groups ( $P > 0.05$ ). However, the increased values of CK-MB were significantly more in high-dose rosuvastatin than in low-dose rosuvastatin treated group ( $P < 0.05$ ).

**Conclusion:** In this study, we compared the effects of high versus low doses of rosuvastatin on postoperative outcomes such as AKI, new AF, infection and myocardial infarction (MI) in CABG surgery. We found rosuvastatin can associate with decreased occurrence of postoperative outcomes of CABG in which no significant differences between high versus low dose of this drug.

**Trial Registration:** The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20180113038329N1; <https://irct.ir/trial/29938>; ethical code# IR.GUMS.REC.1396.368).

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## Introduction

Mortality due to cardiovascular surgeries is one of the major clinical and socioeconomic issues worldwide at present (1,2). It has been shown that preoperative statin therapy may reduce the risk of primary mortality after coronary artery bypass grafting (CABG) (3). Several previous clinical trials have investigated the effect of statin therapy on mortality and morbidity related to postoperative CABG complications including atrial fibrillation (AF), myocardial infarction (MI), cerebrovascular accidents, acute renal injury and the length of stay (4). It has been shown that statin therapy has beneficial effects on postoperative ventricular function and its shaping after MI (5). According to the available evidence, statins can be useful in the prevention and treatment

## Key point

In a double-blind clinical trial study on 188 patients, we compared the effect of high versus low doses of rosuvastatin on postoperative outcome of CABG surgery. We found, rosuvastatin can associate with decreased occurrence of postoperative outcomes such as AKI (primary outcome), changes in lipid profiles, new AF, postoperative infections and MI (secondary outcomes) in CABG surgery. In this study no significant differences between two dose effects on outcome were seen. However, the increased values of creatine kinase-MB (CK-MB) was significantly more in high-dose rosuvastatin than in low-dose rosuvastatin treated group ( $P < 0.05$ ).

of heart failure (6). Additionally, statins such as rosuvastatin and atorvastatin are very effective in the reduction of the risk of cerebrovascular accidents (7). Recent studies have shown that statins can protect the heart against ischemic injury. Endothelial nitric



oxide synthase (Enos) mRNA fixation and its expression is one of the important mechanisms associated with anti-apoptotic, anti-inflammatory, antioxidant and stabilizing of atherosclerotic plaques effects of statins (8, 9). Although the protective effects of statins have been reported in hypertrophic and apoptotic conditions, the beneficial effects of strong statins are still debatable, especially with high-dose and long-term administration (10). However, increased survival rates and reduced hospitalization and also the complications which have been observed with the high dose of statins (11,12). Rosuvastatin is a new generation of statins with a dramatic lipid-lowering effect and an anti-atherosclerotic activity (13). In contrast to other common statins, the pharmacological effects of rosuvastatin have not been studied in low-doses (14). Low-dose statin therapy seems to reduce AF after CABG. Accordingly, the routine administration of statins is considered to be helpful in patients who are electively subjected to CABG (15).

### Objectives

We aimed to investigate the effects of low versus high-doses of rosuvastatin on postoperative outcomes in patients undergoing CABG.

### Patients and Methods

#### Patients and settings

This double-blind clinical trial was carried out on 188 patients with age over 18 years old, who had completed the informed consent and then underwent CABG between May 2017 and June 2018 in Heshmat hospital, Rasht in north of Iran.

After the admission, the departments of surgery and anesthesiology independently investigated current medications. Perioperative medications, laboratory findings and echocardiographic data were extracted automatically from the electronic medical records with the aid of the hospital's medical information department. After surgery, all patients were immediately transferred to the intensive care unit and were closely monitored. Postoperative outcome data were collected through manual review of each case by two independent researchers who were blind than the preoperative statin therapy.

#### Randomization and sampling

Of 206 patients enrolled in the trial, five patients did not meet inclusion criteria, 13 patients did not want to participate and 188 patients were randomly allocated to treatment. Then patients were divided into two groups of 94 persons. Of them, 28 were excluded and 160 remained. The remaining patients were divided into two groups of 76 (received 5 mg/daily), 84 (received 20 mg/daily). Of 28 patients excluded from the study, one person died the second day after the surgery. Two patients had arrhythmias, one person was admitted for re-surgical sternotomy due to surgical site infection. Thirteen people had increased drug

withdrawal after discharge, 11 cases did not cooperate and did not come. The flowchart of the patients included in the study is shown in [Figure 1](#).

Enrolled patients were randomized into two groups for 4 weeks. In addition to medication, they were also received dietary restriction and exercise. Randomization was conducted by random table method. Group A received rosuvastatin 5 mg orally once a day, while group B received rosuvastatin 20 mg orally once a day.

The treatment of study groups continued during the hospitalization period and after discharge until one month. The researcher was blind to the patient's classification. Furthermore, a blinded cardiologist received the patient's follow-up. All patients received the same preparation protocol for CABG. Para-clinical evaluations were conducted in our hospital laboratory. The nurses who were responsible for the study patients and laboratory technicians were completely blind to the group's assignment.

Blood samples collection were carried out before surgery and continued during the hospitalization period and after discharge until one month.

#### Inclusion and exclusion criteria

All patients who underwent elective CABG surgery were enrolled to the study since patients with the following criteria were excluded; patients with AF, any liver disease (liver cirrhosis, increases of serum levels of transaminases or serum bilirubin concentration greater than 3 mg/dL), recent administration of antifungal medications (azoles as the CYP3A4 inhibitors), recent administration of medications which included protease inhibitor, macrolides and cyclosporine, history of MI and renal transplantation, renal insufficiency (serum creatinine greater than 2.5 mg/dL), cardiogenic shock, pregnancy and patients who underwent CABG and subsequent complications such as the re-surgical need for any cause, hemodynamic disorders, long incubation period, shock-induced rhythm disturbances, need for pericardiocentesis or chest tubing.

#### Assessing outcomes

The primary outcome was the incidence of postoperative acute kidney injury (AKI), as defined by the recent "Kidney Disease; Improving Global Outcomes criteria (KDIGO)", using serum creatinine level. In brief, the occurrence of AKI was defined as either an increase in serum creatinine  $\geq 0.3$  mg/dL within 48 hours post-operation or an increase to  $\geq 1.5$  mg/dL times baseline within 7 days (16). Secondary outcomes were newly appearing AF and infection was also compared. In addition, MI was investigated through analysis of electrocardiography data and increased levels of cardiac enzymes (CK-MB).

#### Ethical issues

The research followed the tenets of the Declaration of Helsinki. This paper was extracted from the residential

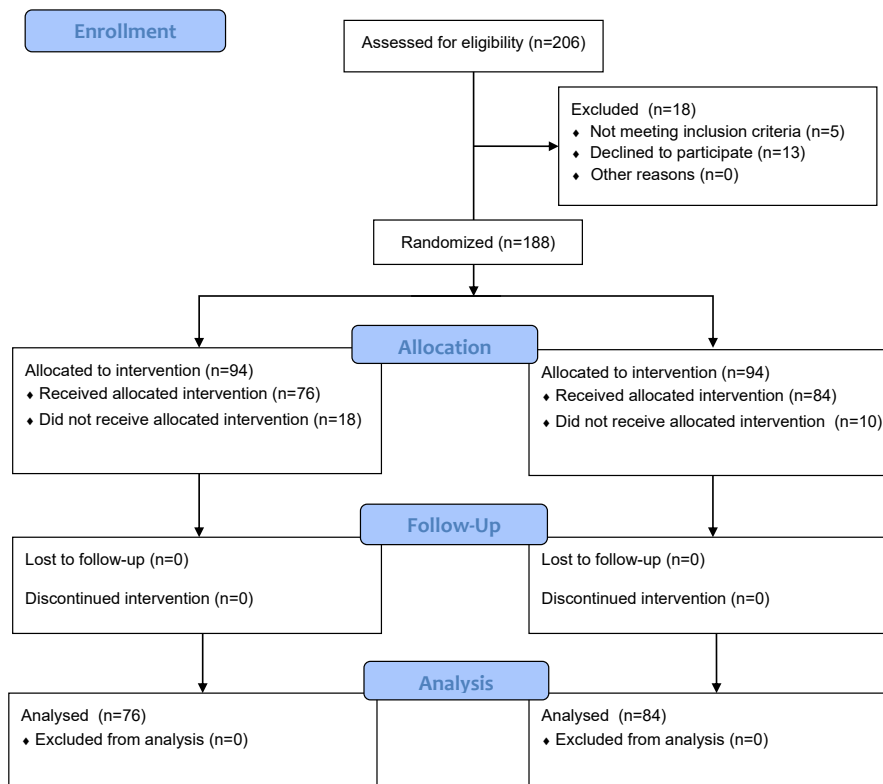


Figure 1. Consort flow diagram.

thesis of Mahdiah Sheikhi, in the department of cardiology, Heshmat hospital, School of Medicine, Guilan University of Medical Sciences. The study was approved by the ethics committee of the Guilan University of Medical Sciences (#IR.GUMS.REC.1396.368). Registration of trial protocol has been approved by the Iranian Registry of Clinical Trial (identifier: IRCT20180113038329N1; <https://irct.ir/trial/29938>). Additionally, informed consent was obtained from all the patients.

### Statistical analysis

Collected data were analyzed using SPSS version 16.0 software (SPSS Inc., Chicago, IL). To compare the qualitative results of the study, the chi-square test was used, while independent *t* test was used to compare the quantitative results. Additionally, pre- and post-interventions results for both groups were compared using the paired *t*-test or Wilcoxon test where appropriate. However, the activity of the enzymes during the study period was compared to their initial level for attenuating the effects of confounder variables. The study patients were classified by age (>40 years and <40 years), gender, and the number of coronary arteries ( $\geq 2$  and <2) and then statistical analysis was applied based on the new classification.  $P < 0.05$  was considered statistically significant.

### Results

The baseline characteristics of the 2 groups according to

statin dose are presented in Table 1.

The ages of the participants were  $58.36 \pm 7$  years and  $59.5 \pm 9$  years for the treatment with high and low-dosages of rosuvastatin (20 mg and 5 mg) respectively. No significant difference was seen between two groups of patients undergoing CABG receiving high and low-dose rosuvastatin in terms of age, gender, body mass index, smoking, alcohol and opium, drug history and angiography data ( $P > 0.05$ ). These findings provide support for homogeneity to the groups (Table 1).

The changes in lipid values are listed according to statin dose in Table 2. We found no statistically significant difference between high-density lipoprotein cholesterol (HDL-C) values in the preoperative and one month postoperative periods in the groups received high and low-doses of rosuvastatin ( $P > 0.05$ ).

However, there was a significant difference between low-density lipoprotein cholesterol (LDL-C) value at bedtime and one month after surgery in the group received high-dose of rosuvastatin. Additionally, LDL-C was reduced by 5.55 mg/dL with rosuvastatin 5 mg/d and 10.5 mg/dL with rosuvastatin 20 mg/d. Moreover, the reductions with high-dose of rosuvastatin were statistically significantly greater than the reduction associated with low-dose of rosuvastatin ( $P = 0.021$ ).

Likewise, cholesterol values in the preoperative and postoperative periods were significantly different in the groups received high and low-doses of rosuvastatin ( $P =$

**Table 1.** Baseline characteristics of propensity-matched population according to statin dose

Variable	Group		P value
	Low-dose	High -dose	
Male (gender)	47 (61.8)	57 (67.9)	0.426
Age, years	58.36±7	59.5±9	0.28
BMI, kg/m <sup>2</sup>	27.3±4.67	26.3±38.73	0.103
Previous conditions			
Hypertension	50 (65.8)	54 (68.3)	0.824
Diabetes	49 (64.5)	30 (35.7)	0.001
Chronic kidney disease	1 (1.3)	2 (2.4)	0.62
Hyperlipidemia	30 (39.5)	27 (32.1)	0.33
Respiratory disease	3 (3.9)	1 (1.2)	0.34
Smoking	21 (27.6)	30 (35.7)	0.27
Alcohol abuse	2 (2.6)	1 (1.2)	0.6
Opium abuse	5 (6.6)	11 (13.1)	0.17
Medication			
β-Blocker	59 (77.6)	74 (88.1)	0.078
ARB	60 (78.9)	64 (76.2)	0.677
ACEI	9 (11.8)	6 (7.1)	0.309
CCB	8 (10.5)	6 (7.1)	0.449
Nitroclonidine	48 (93.2)	52 (61.9)	0.87
Diuretic	13 (17.1)	24 (28.6)	0.086
Atorvastatin	21 (27.6)	26 (31)	0.64
Angiography data			
3VD	61 (80.3)	73 (86.9)	0.255
2VD	13 (17.1)	10 (11.9)	0.349
SVD	2 (2.6)	0(0)	0.22

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; MI, myocardial infarction; RBC, red blood cell; 3VD, three-vessel disease; 2VD, two-vessel disease; SVD, single-vessel disease.

Values are shown as n (%) or mean±SD. For categorical variables, Fisher's exact test, chi-square, and Mann-Whitney U were used.  $P < 0.05$  was considered statistically significant.

0.028 and  $P = 0.0001$ , respectively).

Accordingly, plasma triglyceride was reduced by 41.5 mg/dL with rosuvastatin 5 mg/d and 41.35 mg/dL with rosuvastatin 20 mg/d, since the reductions with rosuvastatin 20 mg/d were significantly greater than the reduction associated with rosuvastatin 5 mg/d ( $P = 0.028$  and  $P = 0.001$  respectively). On the other hand, the t-test

found no statistically significant difference between HDL-C, LDL-C, cholesterol, triglyceride changes in the preoperative and postoperative periods between the two groups who received high and low-dose of rosuvastatin ( $P > 0.05$ ).

Table 3 shows a statistically significant difference between CK-MB values before surgery and 12 and 24 hours after surgery in the groups received low and high-dose of rosuvastatin ( $P = 0.001$ ). Besides, a significant difference between CK-MB changes over time between the two groups of patients received high and low-dose of rosuvastatin was detected ( $P = 0.023$ ).

Table 4 showed a statistically significant difference between blood urea nitrogen (BUN) values in the preoperative and 48 hours after surgery in the groups who received high versus low dose of rosuvastatin ( $P = 0.001$  and  $P = 0.001$  respectively). Moreover, there was a statistically significant difference between serum creatinine levels before and after surgery in the group received low-dose of rosuvastatin ( $P = 0.001$ ), however a statistically significant difference between serum creatinine levels before and after surgery was not seen in the recipient group with high-dose of rosuvastatin ( $P = 0.632$ ).

However, *t* test showed no statistically significant difference between the changes in serum creatinine in preoperative and 48 hours after surgery between the two groups that received 5 mg/d and 20 mg/d doses of rosuvastatin ( $P > 0.05$ ).

We found that AF occurred in the group received low-dose of rosuvastatin more than in the higher dose and postoperative infection was more common in the group receiving high-dose of rosuvastatin (Figure 2).

Fisher's exact test showed that there was no significant difference between these two postoperative events in the two groups receiving high and low-dose of rosuvastatin ( $P > 0.05$ ).

## Discussion

In this study, we compared the effects of high versus low-dose of rosuvastatin on postoperative outcomes of CABG surgery. We found that the administration of rosuvastatin did not increase the incidence of postoperative outcomes

**Table 2.** Comparison of lipid laboratory test according to statin dose

Variable	At bedtime		A month after surgery		P value*
	Low-dose group	High-dose group	Low-dose group	High-dose group	
HDL-C (mg/dL)	40.228 ± 8.07	39.64 ± 7.89	40.83 ± 7.36	40.38 ± 6.44	0.917
P value**	0.53	0.345	0.53	0.345	
LDL-C (mg/dL)	70.51 ± 31.1	79.31 ± 44.77	64.02 ± 22.51	69.97 ± 29.17	0.599
P value**	0.079	0.021	0.079	0.021	
Chol (mg/dL)	148.77 ± 41.04	158.33 ± 58.56	137.39 ± 31	163.22 ± 40.79	0.143
P value**	0.028	0.0001	0.028	0.0001	
TG (mg/dL)	192.2 ± 105.1	181.7 ± 108.3	150.7 ± 67.7	140.4 ± 52.37	0.987
P value**	0.0001	0.002	0.0001	0.002	

HDL, high-density lipoprotein; LDL, low-density lipoprotein; Chol, cholesterol; TG, triglyceride.

Values are shown as mean ±SD. For categorical variables, \**t* test and \*\*paired *t* test was used.  $P < 0.05$  was considered statistically significant.

**Table 3.** Cardiac laboratory test in population according to statin dose

	Time						P value*
	At bedtime		12 hours after surgery		24 hours after surgery		
	Low-dose group	High -dose group	Low-dose group	High -dose group	Low-dose group	High -dose group	
CK-MB (IU/L)	25.33 ± 8.66	27.13 ± 8.7	37.58 ± 17.16	33.76 ± 10.89	34.26 ± 12.12	35.69 ± 12.42	0.023
P value**	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	

CK-MB, creatine kinase-MB.

Values are shown as mean ±SD. For categorical variables, \*t test and \*\*paired t test was used.  $P < 0.05$  was considered statistically significant.

**Table 4.** Renal failure laboratory tests in population according to statin dose

Variable	At bedtime		A month after surgery		P value*
	Low-dose group	High-dose group	Low-dose group	High-dose group	
Serum creatinine (mg/dL)	1.06 ± 0.2	1.13 ± 0.18	1.11 ± 0.26	1.12 ± 0.24	0.068
P value**	0.001	0.632	0.001	0.632	

BUN, Blood urea nitrogen.

Values are shown as mean ±SD. For categorical variables, \*t test and \*\*paired t test was used.  $P < 0.05$  was considered statistically significant.

of CABG regardless of dosage. In addition, the incidence of postoperative infection and newly appearing AF did not differ based on statin therapy. Regardless of their lipid-lowering effects, statins exhibit numerous protective effects on the cardiovascular system including improved endothelial function, enhanced stability of atherosclerotic plaques and decreased oxidative stress and also inflammation. Since according to the guidelines, most patients scheduled for CABG are likely to administer statins preoperatively (16).

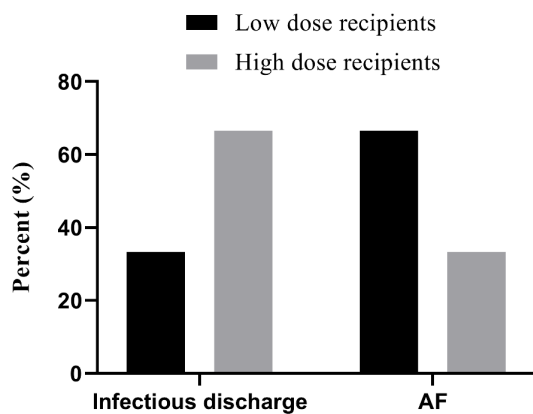
Because the main mechanisms of AKI after cardiac surgery include perioperative inflammatory response and oxidative stress (17,18), the anti-inflammatory, antioxidant and endothelial stabilizing effects of preoperative statins were expected to have a potentially renoprotective role, since these effects have been vigorously investigated in previous clinical studies (19-22). However, the results of our study indicated no statistically significant difference between the changes in BUN, creatinine values in the

preoperative and 48 hours after surgery between the two groups received 5 mg/d and 20 mg/d doses of rosuvastatin which was similar to a meta-analysis conducted by Xiong et al (22). According to the results of the present study, no statistically significant difference between HDL-C, LDL-C, cholesterol, triglyceride changes in the preoperative and postoperative periods between the two groups received high and low-dose of rosuvastatin was seen, while we could not find a superiority over each other. Pitt et al (23) compared the efficacy of 20 mg and 40 mg rosuvastatin with that of 80 mg atorvastatin in decreasing LDL cholesterol in patients with acute coronary syndrome. The results of their study contradicted our results. This difference in results is due to the sample size and kind and duration of statin therapy. On the other hand, Hwang et al (24) compared the efficacy of rosuvastatin mono-therapy 20 mg versus rosuvastatin 5 mg and ezetimibe 10 mg as a combination therapy on lipid parameters in patients with type 2 diabetes mellitus. Their results indicated that both treatments were generally well tolerated while no differences between two groups were detected. Notably, the results of their study were similar to our study.

Our study also showed a significant difference between CK-MB changes over time between the two groups of patients who received high and low-dose of rosuvastatin. This finding suggests that results with rosuvastatin therapy were effective in postoperative myocardial injury. This finding is in concordance with the results of the study by Jiao et al too (25).

## Conclusion

In this study, we compared the effects of high versus low-dose of rosuvastatin on postoperative outcomes of CABG surgery and found rosuvastatin can be helpful in reduced postoperative outcomes of CABG, although there were no significant differences between the high versus low



**Figure 2.** Evaluation of postoperative events in patients undergoing CABG in two groups receiving high and low doses of rosuvastatin. AF; atrial fibrillation.



dose of drug. In addition, the increased values of CK-MB were significantly more in high-dose rosuvastatin than in low-dose rosuvastatin treated group. It is suggested that a study with a larger and uniform sample size be designed and implemented to minimize the impact of confounder variables.

### Limitations of the study

The limitation of our study could be period of follow up in this group of patients. It seems that one month follow up was not adequate for receiving better results. Additionally, another limitation of this study was it had an open label design that could affect the results of the study. It is recommended that a larger, more uniform sample study be designed and implemented to reduce the impact of confounding factors.

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### Authors' contribution

Study concept and design; FM, AS and HDT. Acquisition of data; MSH and MM. Statistical analysis; MSH. Drafting of the manuscript; MGH and MSH. Critical revision of the manuscript for important intellectual content; all authors. All authors read and approved the final version.

### Conflicts of interest

The drug was provided by the Abidi Pharmacy Company freely. The authors declare that Dr.Abidi pharmaceutical Company had no role in the design and conduct of the study; collection of the data, and analysis of the data.

### Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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