Original Article

Comparison of the Efficacy of Atorvastatin and Rosuvastatin in Preventing Atrial Fibrillation after Coronary Artery Bypass Grafting: A Double-blind Randomized Comparative Trial

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Abstract

Background: *Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by disorganized atrial activity and subsequent mechanical atrial failure. Postoperative AF is a frequent complication of coronary artery bypass grafting (CABG). Although there is evidence of decreased AF after CABG with statin usage, information is scarce regarding a direct comparison between atorvastatin and rosuvastatin. The present study was conducted to compare the efficacy of rosuvastatin and atorvastatin in preventing post-CABG AF.*

Methods: *The present double-blind randomized comparative clinical trial selected CABG candidates with stable ischemic heart disease or acute coronary syndromes. Atorvastatin (40 mg per day) or rosuvastatin (20 mg per day) was prescribed 1 week before surgery, and the outcomes were compared.*

Results: *Two-hundred patients, 100 cases in each group, completed the study. Twenty-five patients in each group were female, and the mean age was 59.30±8.42 years in the rosuvastatin group and 60.13±9.40 years in the atorvastatin group (P=0.513). The frequency of AF was 31% in the atorvastatin group and 27% in the rosuvastatin group (P=0.534). No significant differences existed between the groups concerning the length of hospital and ICU stay (P=0.333 and P=0.161) and in-hospital and 3-month mortality (P=0.315 and P=0.648). A subgroup analysis of only patients with stable ischemic heart disease could not detect a significant difference between the study groups in any of the investigated outcomes. Our logistic regression analysis showed an association only between age and the incidence of AF after CABG (OR, 1.12; 95% CI, 1.05 to 1.20; P<0.01).*

Conclusion: *Rosuvastatin and atorvastatin are similar concerning the prevention of post-CABG AF, but there is a need for future well-designed multicenter studies on this topic.*

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Introduction

Atrial fibrillation (AF) is defined as a supraventricular tachyarrhythmia characterized by disorganized atrial activity and subsequent mechanical atrial failure. AF is the most common cardiac arrhythmia in developed countries.[1, 2] Based on a recent systematic review, the pooled global incidence of AF is 8.1 per 100 patients per year,[3] which has increased in recent years because of population aging, increased prevalence of chronic heart diseases, and improved diagnostic capacity due to equipment advancement.[4] Postoperative AF is a common complication of coronary artery bypass grafting (CABG), which is the most common cardiac surgery.[5, 6] Based on current evidence,[7] the American Heart Association/ American College of Cardiology guidelines recommended the use of β-blockers or amiodarone in the event of β-blocker contraindications for the prevention of post-CABG AF.[8] The other candidate drugs for the prevention of AF after CABG are still under investigation, and there is not enough evidence supporting their routine usage.[9]

Statins, as lipid-lowering agents with anti-inflammatory and antioxidant effects, are a class of drugs with growing usage.[10, 11] Evidence indicates a decreasing frequency of AF after CABG with statin use. A meta-analysis of randomized controlled trials (RCTs) in 2014 found that atorvastatin was significantly associated with reduced risks of AF development in patients undergoing CABG.[12] Further, a meta-analysis of 4 RCTs found a 30% reduction in post-CABG AF and high-sensitivity C-reactive protein in rosuvastatin users.[13] Elgendy et al[14] found that atorvastatin was an effective drug in reducing the risk of postoperative AF. Nonetheless, based on the findings of 2 RCTs, the use of rosuvastatin before CABG is not effective in the prevention of AF.

Head-to-head comparisons found that both atorvastatin and rosuvastatin were effective in decreasing C-reactive protein.[15] Scant information is available regarding the direct comparison of the efficacy of atorvastatin and rosuvastatin in preventing postoperative AF. In a retrospective study, a direct comparison of the efficacy of rosuvastatin and atorvastatin in AF prevention could not detect a meaningful difference between these drugs.[16]

Accordingly, we conducted the current clinical trial to compare the efficacy of rosuvastatin and atorvastatin in preventing AF in patients undergoing CABG as the primary outcome. As secondary outcomes of the study, we also compared the duration of hospital and intensive care unit (ICU) stay and in-hospital and 3-month mortality.

Methods

The present study is a double-blind randomized comparative clinical trial, conducted at Shahid Madani Medical and Training Hospital, affiliated with Tabriz University of Medical Sciences (TUOMS), from September 2018 through March 2020. The Ethics Committee of TOUSM reviewed and approved the study design according to the Declaration of Helsinki. The study did not impose any financial burden on patients. Informed consent was taken before the involvement in the study, and patients' personal information was kept confidential. The study protocol is registered in the Iranian Registry of Clinical Trials (IRCTs).

Patients with stable ischemic heart disease or acute coronary syndromes who were candidates for elective CABG in the event of sinus rhythm before surgery and on-pump cardiac surgery were selected for participation in this study. The exclusion criteria were emergency CABG, a history of previous heart surgery, a left ventricular ejection fraction of 25% or less, size of the left atrium in echocardiography below 6 cm, need for postoperative inotropes, need for a pacemaker after surgery, hyperthyroidism, valvular heart diseases more than average in the aortic or mitral valves, and creatinine levels above 1.5.

The sample size for the current study was calculated considering the 5% to 40% prevalence of post-CABG AF, 90% power of the study, and a significance level of 0.05. Totally, 100 patients were assigned to each group. The patients were randomly divided into 2 groups of 100 with a computer program and assigned to each group one by one. In the week leading up to the CABG, atorvastatin (40 mg per day) for the first group and rosuvastatin (20 mg per day) for the second group were prescribed (both manufactured by Atiyeh Pharmaceutical Company). As the potency of rosuvastatin is approximately twice that of atorvastatin,[17] a double dose of atorvastatin was selected for this study. For appropriate blinding, the drug was given to the 2 groups without any labels, and both drugs were completely similar in color and form, so the patients were not aware of the drug that they received. During the hospitalization period, the medical staff and the colleague that recorded the details of AF via Holter monitoring were not aware of the medication received by the patients.

The patients were admitted to the ICU 72 hours after CABG and underwent Holter monitoring for 48 hours. Electrocardiography was obtained daily until the time of admission to the ward. The minimum duration to determine the presence of AF was 5 minutes. After discharge from the hospital, information about the incidence of complications was obtained by telephone.

An attempt was made to compare the frequency of AF between the 2 groups under the same condition. All the statistical analyses were conducted using SPSS, version 26, with a 95% confidence interval (CI) and a P value of 0.05 as the level of significance. The independent samples t and χ^2 tests were used to assess the data. Binary logistic regression analysis based on standard regression was also used to remove the effects of possible confounders.

Results

Two-hundred patients, including 100 cases in each group, completed the study. Figure 1 presents the CONSORT flow diagram of the study, and Table 1 is a summary of the demographic characteristics of the participants. Fifty patients, 25 in each group, were female. The mean age was 59.30±8.42 years in the rosuvastatin group and 60.13±9.40 years in the atorvastatin group (*P*=0.513). The rate of post-CABG AF in our sample was 29%.

Table 2 is a summary of the outcomes. Thirty-one patients in the atorvastatin group and 27 patients in the rosuvastatin group developed AF after CABG; however, the difference was not statistically significant (*P*=0.534). Additionally, no significant differences were observed between the 2 groups of the study vis-à-vis the CABG-to-AF interval (*P*=0.879), duration of hospitalization (*P*=0.333), and duration of ICU stay (*P*=0.161). In-hospital mortality in the atorvastatin group was 3-fold that in the rosuvastatin group. The rate of in-hospital mortality was 1% in the rosuvastatin group and 3% in the atorvastatin group (*P*=0.315). Regarding 3-month mortality, 3% of the patients in the rosuvastatin group and 2% of the patients in the atorvastatin group lost their lives in our sample (*P*=0.648).

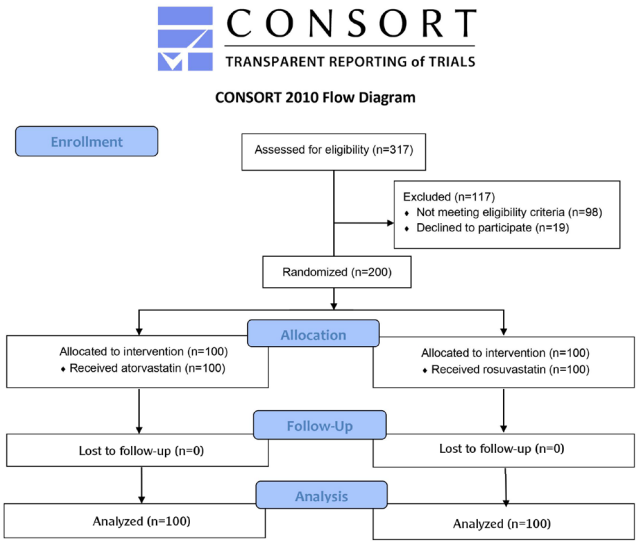

Figure 1. The image depicts the CONSORT flow diagram.

The subgroup analysis of patients with ischemic heart disease is presented in Table 3. The rate of post-CABG AF in the patients with ischemic heart disease was 27.77% in the atorvastatin group and 19.40% in the rosuvastatin group (*P*=0.244). The duration of hospitalization (*P*=0.219) and

Table 1. Demographic characteristics of the patients involved in this study*

Characteristic	Atorvastatin Group (n=100)	Rosuvastatin Group (n=100)	P
Age	60.13±9.40	59.30±8.42	0.513
Heart rate (beat/min)	75.82±7.98	77.14±9.84	0.292
Systolic blood pressure (mmHg)	123.50±13.35	129.13±17.64	<0.01*
Diastolic blood pressure (mmHg)	77.01±8.09	79.40±10.71	0.071
BMI (kg/m^2)	27.82±4.16	27.29±4.61	0.388
Creatinine (mg/dL)	1.09±0.23	1.26±0.87	0.055
Left atrium diameter (cm)	3.62±0.67	3.65±0.71	0.746
CABG duration (h)	5.02±1.04	5.16±1.22	0.384
LVEF (%)	43.77±9.40	43.68±9.49	0.945
Number of grafts	2.44±0.81	2.58±0.75	0.201
Female sex	25 (25.0)	25 (25.0)	1.000
Smoking	38 (38.0)	36 (36.0)	0.770
Diabetes mellitus	30 (30.0)	24 (24.0)	0.342
Hypertension	53 (53.0)	52 (52.0)	0.881
Hyperlipidemia	44 (44.0)	41 (41.0)	0.662
RCA stenosis	65 (65.0)	70 (70.0)	0.448
LAD stenosis	95 (95.0)	97 (97.0)	0.466
LCX stenosis	68 (68.0)	66 (66.0)	0.756
LIMA	96 (96.0)	93 (93.0)	0.353
SVG	94 (94.0)	93 (93.0)	0.772
Beta-blocker	84 (84.0)	80 (80.0)	0.461
Non-dihydropyridine CCB	11 (11.0)	9 (9.0)	0.634
ACEi/ARB	66 (66.0)	68 (68.0)	0.761
Statins	78 (78.0)	73 (73.0)	0.412

*Data are presented as mean±SD or n (%).

BMI, Body mass index; CABG, Coronary artery bypass grafting; LVEF, Left ventricular ejection fraction; RCA, Right coronary artery; LAD, Left anterior descending artery; LCX, Left circumflex artery; LIMA, Left internal mammary artery; SVG, Saphenous vein graft; CCB, Calcium channel blocker; ACE1/ ARB, Angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers

the duration of ICU stay (*P*=0.060) were not statistically different. One patient in each group died in hospital (*P*=0.946), and the rate of 3-month mortality was 1.38% in the atorvastatin group and 2.98% in the rosuvastatin group (*P*=0.514).

The results of the comparison between the AF and non-AF groups are presented in Table 4. The mean age was 64.52±8.07 years in the AF group and 58.02±8.59 years in the non-AF group. A significant difference was noted in this regard (*P*<0.01). In addition, patients with AF had a longer period of hospitalization (*P*<0.01) and a higher rate of in-hospital mortality (5.17% vs 0.70%; *P*=0.042). Moreover, β-blocker

Table 2. Outcomes of the study

Outcomes	Atorvastatin Group (n=100)	Rosuvastatin Group (n=100)	P
AF incidence	31 (31.0%)	27 (27.0%)	0.534
CABG to AF interval (h)	25.43±12.35	25.93±13.37	0.879
Duration of hospital stay (d)	11.21±3.06	11.67±3.62	0.333
Duration of ICU stay (d)	5.07±4.54	4.41±1.27	0.161
Hospital mortality	3 (3.0%)	1 (1.0%)	0.315
Three-month mortality	2 (2.0%)	3 (3.0%)	0.648

AF, Atrial fibrillation; ICU, Intensive care unit

Table 3. Outcomes of the study in the stable ischemic heart disease subgroup

Outcomes	Atorvastatin Group (n=100)	Rosuvastatin Group (n=100)	P
AF incidence	20 (27.7%)	13 (19.4%)	0.244
Duration of hospital stay (d)	11.00±3.18	11.61±3.81	0.219
Duration of ICU stay (d)	5.44±5.52	4.38±1.26	0.060
Hospital mortality	1 (1.4%)	1 (1.5%)	0.946
Three-month mortality	1 (1.4%)	2 (3.0%)	0.514

AF, Atrial fibrillation; ICU, Intensive care unit

Table 4. Comparison of demographic characteristics based on the incidence of AF*

Characteristic	AF (n =58)	Non-AF (n =142)	P
Age	64.52±8.07	58.02±8.59	<0.01*
Heart rate (beat/min)	76.16±9.50	76.59±8.79	0.742
Systolic blood pressure (mmHg)	125.63±13.99	126.55±16.49	0.673
Diastolic blood pressure (mmHg)	76.86±10.36	78.67±9.24	0.191
BMI (kg/m^2)	27.30±4.45	27.64±4.37	0.582
Creatinine (mg/dL)	1.07±0.24	1.19±0.73	0.122
Left atrium diameter (cm)	3.81±0.54	3.68±0.73	0.153
CABG duration (h)	5.35±0.92	5.10±1.19	0.094
LVEF (%)	43.56±8.91	43.78±9.62	0.864
Number of grafts	2.52±0.73	2.50±0.80	0.855
Female sex	10 (17.2)	40 (28.2)	0.102
Smoking	20 (34.5)	54 (38.0)	0.628
Diabetes mellitus	21 (36.2)	33 (23.2)	0.057
Hypertension	31 (53.3)	74 (52.1)	0.859
Hyperlipidemia	19 (32.7)	66 (46.5)	0.071
RCA stenosis	34 (58.6)	101 (71.1)	0.082
LAD stenosis	42 (72.4)	120 (84.5)	0.042*
LCX stenosis	30 (51.7)	104 (73.2)	<0.01*
LIMA	54 (93.1)	135 (95.1)	0.567
SVG	55 (94.8)	132 (92.9)	0.622
Beta-blocker	40 (69.0)	119 (83.8)	0.010*
Non-dihydropyridine CCB	6 (10.3)	14 (9.8)	0.911
ACEi/ARB	44 (75.9)	118 (83.1)	0.232
Statins	41 (70.7)	110 (77.5)	0.310
Outcomes			
Duration of hospital stay (days)	12.88±3.13	10.94±3.29	<0.01*
Duration of ICU stay (days)	4.83±1.20	4.71±3.82	0.760
Hospital Mortality	3 (5.2%)	1 (0.7%)	0.042*
3 Months mortality	3 (5.2%)	2 (1.4%)	0.120

*Data are presented as mean±SD or n (%).

AF, Atrial fibrillation; BMI, Body mass index; CABG, Coronary artery bypass grafting; LVEF, Left ventricular ejection fraction; RCA, Right coronary artery; LAD, Left anterior descending artery; LCX, Left circumflex artery; LIMA, Left internal mammary artery; SVG, Saphenous vein graft; CCB, Calcium channel blocker; ACEi/ARB, Angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers; ICU, Intensive care unit

Table 5. Univariate and multivariate analyses of all the participants of the study

Characteristic	Univariate			Multivariate		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P
Rosuvastatin	0.74	0.34 - 1.58	0.435			
Female sex	1.61	0.67 - 3.88	0.285			
Age	1.09	1.04 - 1.15	<0.01*	1.12	1.05 - 1.20	<0.01*
RCA stenosis	0.88	0.39 - 1.99	0.773			
LAD stenosis	1.76	0.19 - 15.65	0.602			
LCX stenosis	0.59	0.27 - 1.30	0.191			
Hypertension	1.64	0.74 - 3.64	0.209			
Heart rate	0.99	0.95 - 1.03	0.802			
Beta-blocker	1.90	0.83 - 4.35	0.118			
Creatinine	0.54	0.15 - 1.94	0.347			
Non-dihydropyridine CCB	1.31	0.38 - 4.57	0.654			
ACE1 ARB	1.62	0.75 - 3.49	0.211			
Smoking	0.94	0.41 - 2.15	0.890			
Diabetes mellitus	1.28	0.54 - 3.03	0.561			
Hyperlipidemia	0.73	0.33 - 1.63	0.452			
LVEF (%)	0.99	0.95 - 1.03	0.999			
Left atrium diameter (cm)	1.79	0.90 - 3.55	0.091			
CABG duration (h)	1.38	0.92 - 2.07	0.115			
Number of grafts	1.03	0.63 - 1.67	0.904			
BMI (kg/m^2)	0.98	0.89 - 1.07	0.684			

CI, Confidence interval; RCA, Right coronary artery; LAD, Left anterior descending artery; LCX, Left circumflex artery; CCB, Calcium channel blocker; ACE1/ARB, Angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers; BMI, Body mass index

users were less likely to develop post-CABG AF (P=0.010).

Table 5 presents the results of univariate and multivariate analyses based on the incidence of post-CABG AF. Our logistic regression analysis revealed a significant association between age and the incidence of post-CABG AF (P<0.01), which was still significant in the multivariate analysis (P<0.01).

Discussion

The present study compared the efficacy of rosuvastatin and atorvastatin in preventing AF in patients undergoing elective CABG. Our results showed that these 2 drugs did not differ significantly in the prevention of post-CABG AF. Moreover, treatment with either atorvastatin or rosuvastatin did not differ significantly concerning the length of hospital and ICU stay and in-hospital and 3-month mortality. We also detected a significant association between age and the risk of post-CABG AF.

AF is one of the most common complications of patients after CABG. The pathophysiology of AF development after CABG depends on several factors; nevertheless, evidence suggests that inflammation and fibrosis play the crucial role.[18] CABG is one of the principal surgeries with the presence of high numbers of intensive inflammatory conditions,[19] which can lead to post-CABG AF. AF after CABG happens in about 5% to 40% of patients. It usually occurs in 2 to 4 days and often during the first 30 days after CABG.[9] In our sample of patients, the prevalence of post-CABG AF was 29%. The interval between CABG and AF in patients who developed AF was 25.65±12.63 hours in our sample.

The benefits of statin therapy in reducing the risk of AF in patients with cardiovascular disease may be due to their anti-inflammatory and antioxidant effects, improving lipid metabolism, preventing atherosclerosis, reducing endothelial dysfunction, and activating the neurohormonal system.[18, 20]

The results of comparing statins in recent systematic reviews were based on a comparison of effects between atorvastatin and rosuvastatin and a placebo, and in this condition, atorvastatin showed higher efficacy than rosuvastatin in the prevention of post-CABG AF.[14] A comprehensive retrospective study in Turkey in 2013 featured data from multiple original articles and directly compared atorvastatin and rosuvastatin but reported no significant difference in terms of the prevention of post-CABG AF.[16] Our prospective study confirmed the results of that investigation insofar as we found no difference between atorvastatin and rosuvastatin concerning the incidence of post-CABG AF. Additionally, the study in Turkey reported a postoperative AF rate of 17.9% in the atorvastatin group and 22.2% in the rosuvastatin group.[16] In our sample, the rate of postoperative AF was 31% in the atorvastatin group and 27% in the rosuvastatin group, which was higher than previous reports at Rajaie Cardiovascular Medical and Research Center in Tehran (15.8%)[21] and Tehran Heart Center (7.2%)[22] and similar to studies by Aranki et al (33%)[23] and Almassi et al (30%)[24] in the United States.[21] Several risk factors play a role in postoperative AF development, such as age, male sex, obesity, a low left ventricular ejection fraction, a history of supraventricular arrhythmias, mitral valve surgery, left atrial enlargement, diabetes mellitus,

chronic obstructive pulmonary disease, chronic renal failure, increased aortic cross-clamp time, postoperative use of digoxin, and postoperative withdrawal of β-blockers or angiotensin-converting enzyme inhibitors.[16] These factors may have caused the observed discrepancies in the rate of post-CABG AF in different studies.

The ultimate goal of all treatment interventions is to prevent the occurrence of dangerous disease outcomes, such as cognitive impairment, decreased quality of life, intolerance to physical activity, hospitalization, stroke, and death. The results of a meta-analysis found that statin therapy (including atorvastatin and rosuvastatin) curtailed the length of stay in the hospital, while it was not effective in shortening the length of stay in the ICU.[25] Based on our assessment, atorvastatin and rosuvastatin were not statistically different in terms of reducing mortality or the duration of hospitalization in CABG candidates.

The adjustment of patients based on the mentioned associated factors and the double-blind study design were the most notable strengths of the current study. Still, the small sample size was the salient limitation of our study.

Conclusion

Despite the usage of statins, about 29% of our patients developed AF within 48 hours after CABG. Rosuvastatin and atorvastatin did not differ significantly in the prevention of post-CABG AF. There is a need for more well-designed multicenter studies with a considerable sample size to confirm the findings of this study.

Acknowledgments

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