VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
E-ISSN 2450–8187

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Efficacy and Safety of Atorvastatin 40 mg versus Rosuvastatin 20 mg in Patients with Type 2 Diabetes Mellitus and Previous Acute Coronary Syndrome: A Randomized Clinical Trial

ABSTRACT

Background: The purpose of this study was to compare the efficacy and safety of high-dose atorvastatin (40 mg) versus high-dose rosuvastatin (20 mg) in Egyptian patients with type 2 diabetes and previous acute coronary syndrome history.

Materials and methods: This open-labeled prospective, randomized clinical trial compared once daily atorvastatin 40 mg (Ator®) versus once daily rosuvastatin 20 mg (Crestor®). The primary outcome was the 50% reduction in low-density lipoprotein cholesterol levels at 12 weeks. The secondary outcome was the achievement of low-density lipoprotein cholesterol level < 55 mg/dL.

Results: A total number of 108 patients had a significant percentage of improvement in atorvastatin arm (n = 59) and rosuvastatin arm (n = 49) in low-density lipoprotein cholesterol, total cholesterol, triglycerides, and high-density lipoprotein-cholesterol achieved ($p \leq 0.05$). In atorvastatin arm, 32.2% of patients achieved fifty percent reduction in low-density lipoprotein cholesterol while 34.7% of patients in rosuvastatin arm ($p > 0.05$). Twenty percent of patients achieved low-density lipoprotein cholesterol < 55 mg/dL in atorvastatin group compared to eighteen percent only in rosuvastatin group ($p > 0.05$). Regarding safety, the mean difference in liver transaminases was non-significant between the two groups ($p > 0.05$). Muscular symptoms were experienced by 1.7% patients receiving atorvastatin 40 mg and 10.2% of those receiving rosuvastatin 20 mg ($p > 0.05$).

Conclusions: In Egyptian context, both high doses statin therapy were comparable regarding efficacy and safety in patients with type 2 diabetes and previous history of acute coronary syndrome.

The Clinicaltrial.gov registration ID is: NCT05306990.

(Clin Diabetol 2022, 11; 3: 165–174)

Keywords: Acute coronary syndrome, diabetes mellitus, high-intensity statin therapy, atorvastatin, rosuvastatin

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Clinical Diabetology 2022, 11; 3: 165–174
DOI: 10.5603/DK.a2022.0021
Received: 21.02.2022 Accepted: 19.05.2022

Introduction

Acute coronary syndrome (ACS) is one of the atherosclerotic cardiovascular diseases (ASCVD) that is the leading cause of death worldwide, accounting for

37% of all deaths in people under the age of 70 [1]. ACS is the first clinical manifestation of coronary artery disease (CAD) and defined as the partial or complete occlusion of one of the coronary arteries, which results in partial or complete deficiency in blood supply to the myocardium [2].

ACS is common in patients with diabetes because of the coexisting conditions such as dyslipidemia and hypertension [3]. Diabetes mellitus and dyslipidemia commonly occur together, with lipid abnormalities affecting 60% to 70% of type 2 diabetes mellitus (T2DM) patients [4], because insulin has a direct inhibitory effect on hepatic very low density lipoprotein (VLDL) production; thus, in patients with diabetes where insulin level is low, VLDL levels are increased [5]. This initiates a sequence of events that generates atherogenic remnants, small dense low-density lipoprotein (LDL) and small dense high-density lipoprotein (HDL) particles. Together these components comprise the atherogenic lipid triad [6]. Therefore, those patients' lipid profile is characterized by elevated LDL-C, VLDL-C levels and low HDL-C levels [7].

Owing to their low cost and acceptable efficacy, statins are the cornerstone of cardiovascular risk reduction in patients with T2DM [8]. In a meta-analysis of 14 randomized clinical trials (RCTs) which involved 18,686 patients with T2DM, statin monotherapy resulted in a 9% reduction in all-cause mortality and a 21% reduction in the incidence of major cardiovascular incidents per millimole per liter of LDL lowered [1]. Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors that lower LDL-C levels by inhibiting the rate-limiting step in cholesterol biosynthesis (conversion of HMG-CoA to mevalonate), which, by reducing hepatic cholesterol concentrations, leads to up-regulation of hepatic LDL receptors and increased LDL particle clearance [1, 9].

The most recent American College of Cardiology/American Heart Association guidelines recognize patients with diabetes mellitus between the ages of 40 and 75 years as one of the four main groups that benefit from high-intensity statin therapy with the target of achieving a ≥ 50% reduction in LDL-C levels (level of evidence: A) [10]. The target LDL-C level in diabetic patients with previous history of ACS is < 55 mg/dL [11, 12]. If the patient is intolerant to high-intensity statin therapy and experienced adverse effects, moderate-intensity statin therapy should be initiated with the aim of achieving a 30% to 49% reduction in LDL-C levels (level of evidence: A) [10].

Over the last 25 years, statins have been proved as well-tolerated and safe drugs. However, high doses of statins were sometimes associated with an increased rate of adverse drug reactions such as elevations of liver transaminases, especially alanine transaminase (ALT) [13]. Also, statins associated with muscular symptoms range from myalgia to clinical rhabdomyolysis [14].

We have different study conclusions among different populations regarding efficacy and safety of statins, such as in Chinese population [15] and Korean population [16], and till now there is no preferred treatment for treating dyslipidemia in diabetic patients with ACS history in Egypt. Thus, the current study aims to build on this growing awareness of atherosclerosis specific care of diabetes patients, by examining efficacy and safety of the two most commonly prescribed high-intensity statin therapy among Egyptian population; atorvastatin 40 mg (Ator®) and rosuvastatin 20 mg (Crestor®). The results of this study emphasize that both atorvastatin 40 mg and rosuvastatin 20 mg can be used in patients with type 2 diabetes and normal kidney function. However, aspartate aminotransferase (AST) has been elevated for a while in some rosuvastatin users.

Materials and methods

Study design

A prospective, open-labeled, randomized clinical study was conducted on 108 patients with type 2 diabetes admitted to the National Heart Institute with ACS from April 20, 2017, to January 31, 2021, and were followed up for a period of 12 weeks. The study protocol was approved by both the Institutional Review Board (IRB) of the National Heart Institute, Cairo, Egypt and the ethical committee at the Faculty of Pharmacy, Helwan University, Cairo, Egypt (ethical committee approval number: 02H2019). A written informed consent was obtained from each patient before participation in the study.

Study population

Patients with previous history of ACS (unstable angina, ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction within 6 months prior to conducting this study) were recruited and evaluated for the following inclusion criteria; age ≥ 18 years, diagnosed with type 2 diabetes mellitus and abnormal baseline lipid profile (total cholesterol ≥ 155 mg/dL ± LDL-C ≥ 130 mg/dL ± triglyceride ≥ 200 mg/dL). The exclusion criteria were: patients taking concurrent lipid lowering agents such as bile acid sequestrants (cholestyramine, colesevelam), niacin, ezetimibe, fenofibrate and/or omega-3; patients taking concurrent interacting medications such as ciclosporin, gemfibrozil, clarithromycin and/or itraconazole [17]; patients with active liver disease, bile duct problems, or ALT > 3 × upper limit of normal (ULN); patients with

serum creatinine > 2 mg/dL; patients having incidence or history of hypersensitivity reaction to any of the statin used; women who were pregnant, breast-feeding or of child-bearing potential and not using a reliable form of contraception at the time of recruitment [18] and patients who failed to be followed up.

Methods

Eligible patients after evaluation for inclusion and exclusion criteria were randomly allocated into 2 groups, atorvastatin 40mg treatment or rosuvastatin 20 mg treatment. A computer-generated randomization technique using simple randomization approach was obtained by a statistical consultant who is not involved in the study. The randomization assignment for each patient was kept in a sealed envelope, which was opened by the principal investigator just before the patient enrollment. Patients were randomized to receiving either once daily atorvastatin 40 mg (Ator®) or rosuvastatin 20 mg (crestor®). Patients were educated about their therapies, diet, lifestyle habits and the importance of adherence to their therapies during their visits and interviews. All patients were then followed up for 12 weeks.

Data collection

Patient' demographics such as gender, age, smoking status, body mass index (BMI) were recorded at the start of the study. In addition, detailed medical history, comorbidities and concurrent use of medications were collected. Routine laboratory investigations which include: complete blood picture (hemoglobin, RBCs count, hematocrit value, total leucocytic count and platelets count), kidney function tests (blood urea nitrogen, serum uric acid and serum creatinine), and HbA1c were measured at baseline. Liver function tests (AST and ALT) and lipid profile (total cholesterol, LDL-C, VLDL-C, HDL-C, triglycerides and non HDL-C) were measured at baseline and after 12 weeks.

Patients' adherence

Self-reported measure of medication adherence (Morisky Scale) was used to assess the probability that patients take their medication as prescribed [19]. Morisky scale consists of four questions with a scoring scheme of "Yes" = 0 and "No" = 1; Do you ever forget to take your statin medication? Do you ever have problems remembering to take your statin medication? When you feel better, do you sometimes stop taking your statin medication? And sometimes if you feel worse when you take your statin medication, do you stop taking it? The items are summed to give a range of scores from 0 to 4, the higher scores indicating higher levels of adherence to the prescribed medications [19].

Study objectives and assessments

The primary outcome was achieving ≥ 50% LDL-C reduction, while the secondary outcome was the attainment of LDL-C level < 55 mg/dL. Safety was assessed during the follow-up period by recording the incidence and details of adverse events and laboratory abnormalities. Liver function tests were measured at baseline and after 12 weeks. Any muscular symptoms were recorded at the baseline and during visits of the 4^{th} and the 12^{th} weeks.

Statistical analysis

All statistical tests and graphs were performed using SPSS vs. 25. (IBM, Armonk, New York, United states). Dispersion of the data was given by mean ± SD (standard deviation) for continuous variables, while discrete variables were described as counts and percentages. Normal distribution was assessed by Kolmogorov–Smirnov test. Unpaired Student's t test was used to assay significant differences between mean values of the studied continuous variables among different statin users. For non-normally distributed data, Mann-Whitney test was used. Categorical data was compared according to statin users using Chi-square test. Significance was set at two-sided p-value of ≤ 0.05.

Sample size calculation

Based on findings from Qu et al. [15], the sample size was then calculated assuming 80% power and a priori alpha rate alpha level of 5%. Considering additional 5% of the calculated sample size added to compensate for the loss of follow-up in our study, the final sample size was calculated at 50 patients in each group. Power analysis was done using G*Power 3.1 software.

Results

Patient demographics and distribution

A total of 124 patients were screened for eligibility of the study, of which 8 patients were excluded. Two patients were receiving another lipid lowering therapy, one patient had active liver disease, ALT > 3 × ULN, one patient was receiving concurrent interacting medication, two pregnant women and two patients had serum creatinine > 2 mg/dL. One hundred and sixteen patients (116) were randomized to receive statin treatment where 64 patients received atorvastatin 40 mg and 52 patients received rosuvastatin 20 mg. Over 12 weeks of follow-up period, further 8 patients discontinued the study. Seven patients failed to be followed up and one patient had hypersensitivity reaction. Only 108 patients completed the study (atorvastatin 40 mg (n = 59), rosuvastatin 20 mg (n = 49)) (Fig. 1).

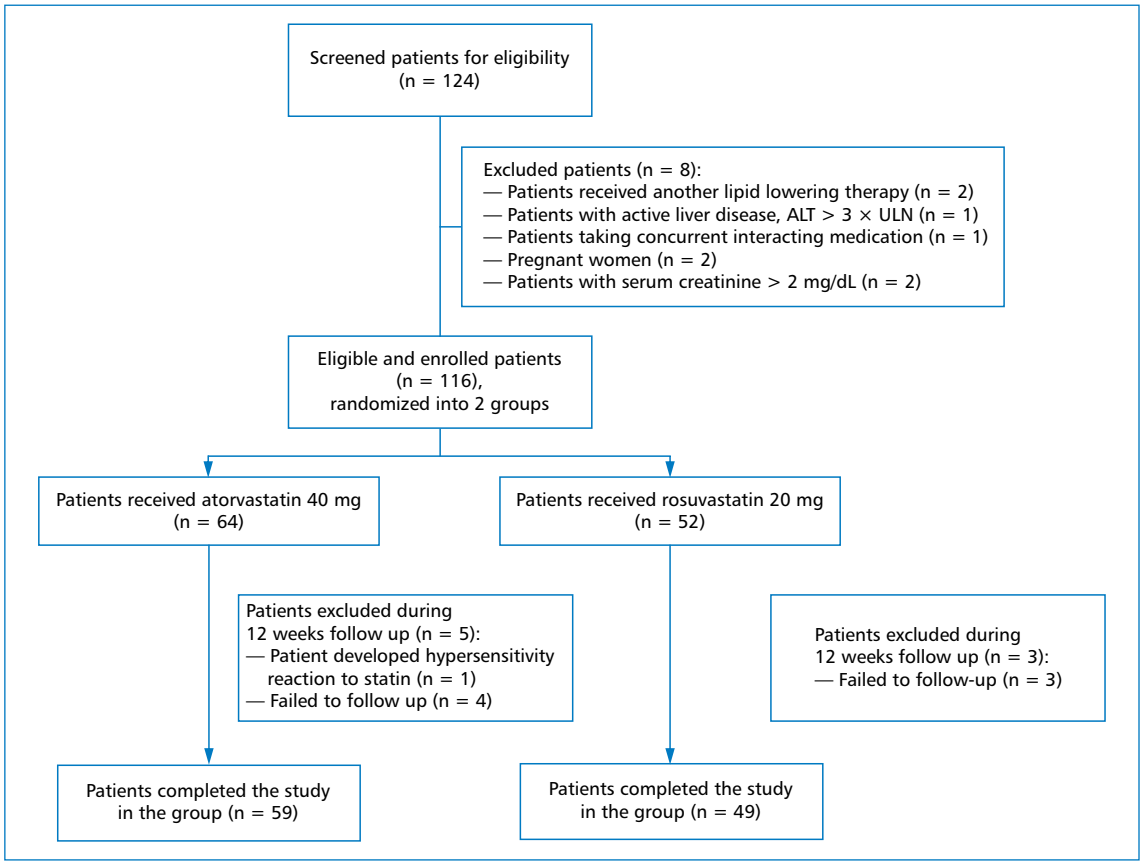

Figure 1. Flowchart of Patients' Enrollment and Follow-up. ALT — alanine transaminase; ULN — upper limit of normal

Baseline demographic characteristics were similar in both statin treatment groups; there was no significant difference in age, sex, concurrent diseases, smoking status and BMI ($p > 0.05$). Almost all of the patients were found to be hypertensive with already known diagnosis (n = 104, 96.3%). Interestingly, more than two-third patients regardless to their response to the therapy were found to have high BMI and were considered obese (n = 83, 76.9%). Among the 108 patients, 78 patients (72.2%) were controlled diabetic patients. Regarding concurrent medications, all patients were on Aspirin 100 mg and clopidogrel 75 mg. 53 patients were on dapagliflozin (49%), 41 patients were on gliclazide (38%), 34 patients were on liraglutide (31.5%), 43 patients were on febuxostat (39.8%) (Tab. 1).

Statin treatment

Efficacy

There was significant improvement in all lipid parameters before and after treatment in both treatment arms ($p \leq 0.05$), as shown in (Tab. 2). Comparison of lipid profile mean difference and percentage improvement after 12 weeks treatment with atorvastatin 40 mg versus rosuvastatin 20 mg is shown in (Tab. 3, Fig. 2), the mean changes in all lipid parameters were non-significant between them ($p > 0.05$). This means that atorvastatin 40 mg and rosuvastatin 20 mg are equivalent regarding efficacy. We further analyzed percentage changes among atorvastatin and rosuvastatin groups and similarly found that these statins are equivalent in efficacy (Tab. 3).

The goal in those patients taking high-intensity statin therapy is to reduce LDL-C by 50% [10]. However, only 32.2% of patients in the atorvastatin arm achieved this goal, and 34.7% of patients in the rosuvastatin arm (Fig. 3A). This difference is not significant between the two statins ($p > 0.05$). The second goal was to achieve LDL-C level < 55 mg/dL [11, 12]. This goal was achieved by 20.3% of patients in the atorvastatin arm and 18.4% in rosuvastatin group, $p > 0.05$ (Fig. 3B).

Safety

Regarding safety, both treatments were well tolerated and the overall frequency and type of adverse events were similar between treatment groups. Liver transaminases were measured at baseline and at 12 weeks; there was no significant increase in liver

Table 1. Patients' Demographics

	Atorvastatin 40 mg (n = 59)	Rosuvastatin 20 mg (n = 49)	P
Age [years] (Mean ± SD)	58.5 ± 8.7	60.9 ± 7.7	0.069*
Gender, n (%)			0.414**
Female	17 (28.8)	18 (36.7)	
Male	42 (71.2)	31 (63.3)	
Smoking, n (%)			> 0.99**
No	45 (76.3)	38 (77.6)	
Yes	14 (23.7)	11 (22.4)	
Body mass index [kg/m^{2}], n (%)			0.172**
Normal weight (18.5 < 25)	0 (0)	3 (6.1)	
Overweight (25 < 30)	15 (25.4)	7 (14.3)	
Obesity class I (30 < 35)	26 (44.1)	25 (51)	
Obesity class II (35 < 40)	13 (22)	12 (24.5)	
Obesity class III (≥ 40)	5 (8.5)	2 (4.1)	
Diabetes control, n (%)			> 0.99**
Controlled DM (HbA1c < 7%)	43 (72.9)	35 (71.4)	
Uncontrolled DM (HbA1c ≥ 7%)	16 (27.1)	14 (28.6)	
Concurrent diseases, n (%)			0.515**
Hypertension	57 (96.6)	47 (95.9)	
Acute decompensated heart failure	0 (0)	1 (2)	
Atrial fibrillation	3 (5.1)	1 (2)	
Hyperuricemia	27 (45.8)	24 (49)	
Concurrent medications, n (%)			0.425**
Dapagliflozin (Farxiga®)	28 (47.5)	25 (51)	
Gliclazide (Diamicron®)	21(35.6)	20 (40.8)	
Liraglutide (Victoza®)	18 (30.5)	16 (32.7)	
Vildagliptin (Galvus®)	10 (16.9)	4 (8.2)	
Bisoprolol (Concor®)	9 (15.3)	7 (14.3)	
Valsartan (Tareg®)	6 (10.2)	7 (14.3)	
Febuxostat (Feburic®)	25 (42.4)	18 (36.7)	

*Mann-Whitney test; **Chi-square test
DM — diabetes mellitus; SD — standard deviation

Table 2. Lipid Parameters Measured Before and After Treatment

	Atorvastatin 40 mg (n = 59)			Rosuvastatin 20 mg (n = 49)		
	Baseline values mg/dL (Mean ± SD)	After 12 weeks treatment values mg/dL (Mean ± SD)	P	Baseline values mg/dL (Mean ± SD)	After 12 weeks treatment values mg/dL (Mean ± SD)	P
TC	191.5 ± 42.1	137.3 ± 32.6	< 0.001*	197.2 ± 43.2	142.5 ± 29.0	< 0.001*
LDL-C	115.8 ± 35.0	69.1 ± 28.3	< 0.001*	122.7 ± 35.8	73.8 ± 25.5	< 0.001*
HDL-C	36.3 ± 9.1	39.6 ± 8.9	< 0.001*	37.9 ± 10.7	40.4 ± 8.6	0.032*
TG	216.1 ± 148	161.4 ± 133.0	< 0.001*	183.2 ± 76.1	141.5 ± 50.8	< 0.001*
VLDL-C	39.4 ± 19.3	28.7 ± 13.7	< 0.001*	36.6 ± 15.1	28.3 ± 10.2	< 0.001*
Non-HDL-C	155.2 ± 42.3	97.7 ± 33.1	< 0.001*	159.3 ± 42.7	101.8 ± 29.3	< 0.001*

*Paired t-test. Statistically significant at p ≤ 0.05 level
HDL-C — high-density lipoprotein-cholesterol, LDL-C — low-density lipoprotein-cholesterol, TC — total cholesterol, TG — triglycerides, VLDL-C — very low density lipoprotein-cholesterol

Table 3. Lipid Profile Mean Difference and Percentage of Improvement After 12 Weeks of Treatment with Atorvastatin 40 mg versus Rosuvastatin 20 mg

	Mean difference		P	% of improvement after treatment		P
	Atorvastatin 40 mg mg/dL (Mean ± SD)	Rosuvastatin 20 mg mg/dL (Mean ± SD)		Atorvastatin 40 mg % (Mean ± SD)	Rosuvastatin 20 mg % (Mean ± SD)	
Total cholesterol	-54.2 ± 35.3	-54.7 ± 37	0.942*	27 ± 14.7	25.8 ± 16.1	0.836**
LDL-C	- 46.7 ± 31.9	-48.9 ± 30.9	0.725*	37.7 ± 22.5	37.5 ± 21.3	0.659**
HDL-C	3.3 ± 6.8	2.6 ± 8.1	0.667**	6.3 ± 22.3	5.6 ± 21.9	0.688**
TG	-54.7 ± 68.5	-41.6 ± 54.3	0.26**	20.8 ± 28	17.5 ± 24.3	0.323**
VLDL-C	-10.7 ± 13.9	-8.4 ± 10.9	0.34**	21.0 ± 28.4	17.6 ± 24.4	0.264**
Non-HDL-C	-57.5 ± 37.3	-57.4 ± 34.6	0.995*	35.3 ± 18.6	33.8 ± 19.1	0.899**

*Unpaired t-test, **Mann-Whitney test.
HDL-C — high-density lipoprotein-cholesterol; LDL-C — low-density lipoprotein-cholesterol; TG — triglycerides; VLDL-C — very low density lipoprotein-cholesterol

transaminases in both groups, except for AST in rosuvastatin group. The mean difference was calculated in both arms (as shown in Tab. 4) and we found non-significant difference between them ($p > 0.05$). As concerns muscular symptoms, myalgia was experienced by 1.7% patients receiving atorvastatin 40 mg and 8.2% of those receiving rosuvastatin 20 mg. Two percent (2%) of patients in rosuvastatin arm experienced lower back pain, as clarified by Figure 4.

Discussion

This study showed randomized comparison between atorvastatin 40 mg and rosuvastatin 20 mg in patients with type 2 diabetes and ACS history. To the best of our knowledge, the safety and efficacy of high-intensity statin therapy were not investigated in the Egyptian population previously. High-intensity statin therapy is used commonly in Egyptian patients with diabetes and ACS. This is what lead us to work on this point to find out which statin is preferable than the other regarding the safety and efficacy.

The major finding is that both atorvastatin 40 mg and rosuvastatin 20 mg have a significant improving effect on the lipid profile of all patients ($p \leq 0.05$). These results are consistent with LUNAR study [20] which compared rosuvastatin 20 mg, rosuvastatin 40 mg and atorvastatin 80 mg for 12 weeks. However, in a Chinese study in hypercholesterolemic patients [15], there was a significant decrease in total cholesterol, LDL-C and non-HDL-C in both treatment arms. But only rosuvastatin group had significant increased levels of HDL-C but not atorvastatin group. Genetic variations among different populations may influence statin efficacy. It was proved that ATP-binding cassette (ABC) and solute carrier (SLC) membrane transporters are capable of regulating statin pharmacokinetics parameters as absorption; thus, impacting statin efficacy and safety [21, 22].

Comparing the two statin treatment groups (atorvastatin 40 mg versus rosuvastatin 20 mg) with each other, the mean difference changes in all lipid parameters were non-significant between them ($p > 0.05$). We further analyzed the percentage of change and similarly found that percentages are non-significant among the two treatment arms ($p > 0.05$). This suggests that atorvastatin 40 mg and rosuvastatin 20 mg are equivalent regarding efficacy. Our results were consistent with a study that showed no differences in percentage changes in total cholesterol, LDL-C and triglycerides among atorvastatin and rosuvastatin groups [23]. Also, our findings were comparable with PATROL trial [24], which compared atorvastatin (10 mg), rosuvastatin (2.5 mg) and pitavastatin (2 mg) and confirmed no significant differences in LDL-C and triglycerides lowering effects. However, HDL-C increased in the rosuvastatin group only. On the other hand, LUNAR study [20] showed that rosuvastatin was more effective than atorvastatin in reducing LDL-C, increasing HDL-C and improving other blood lipid parameters. This may be due to different doses of both medications (atorvastatin 80 mg and rosuvastatin 40 mg). Another study showed that rosuvastatin 10 mg is more effective than atorvastatin 10 mg [16]; this may be due to incompatible equivalent doses of both drugs and also different non-diabetic Korean population. Genetic variation among populations plays an important role in affecting efficacy of statin, as mentioned before. As shown in the results previously, statin monotherapy does not achieve the LDL-C goal in most patients; that's why new guidelines recommend the addition of ezetimibe and proprotein convertase subtilisin/Kexin (PCSK-9) inhibitors in those patients who do not achieve their LDL-C goal by statin monotherapy [12]. Patients' demographics may af-

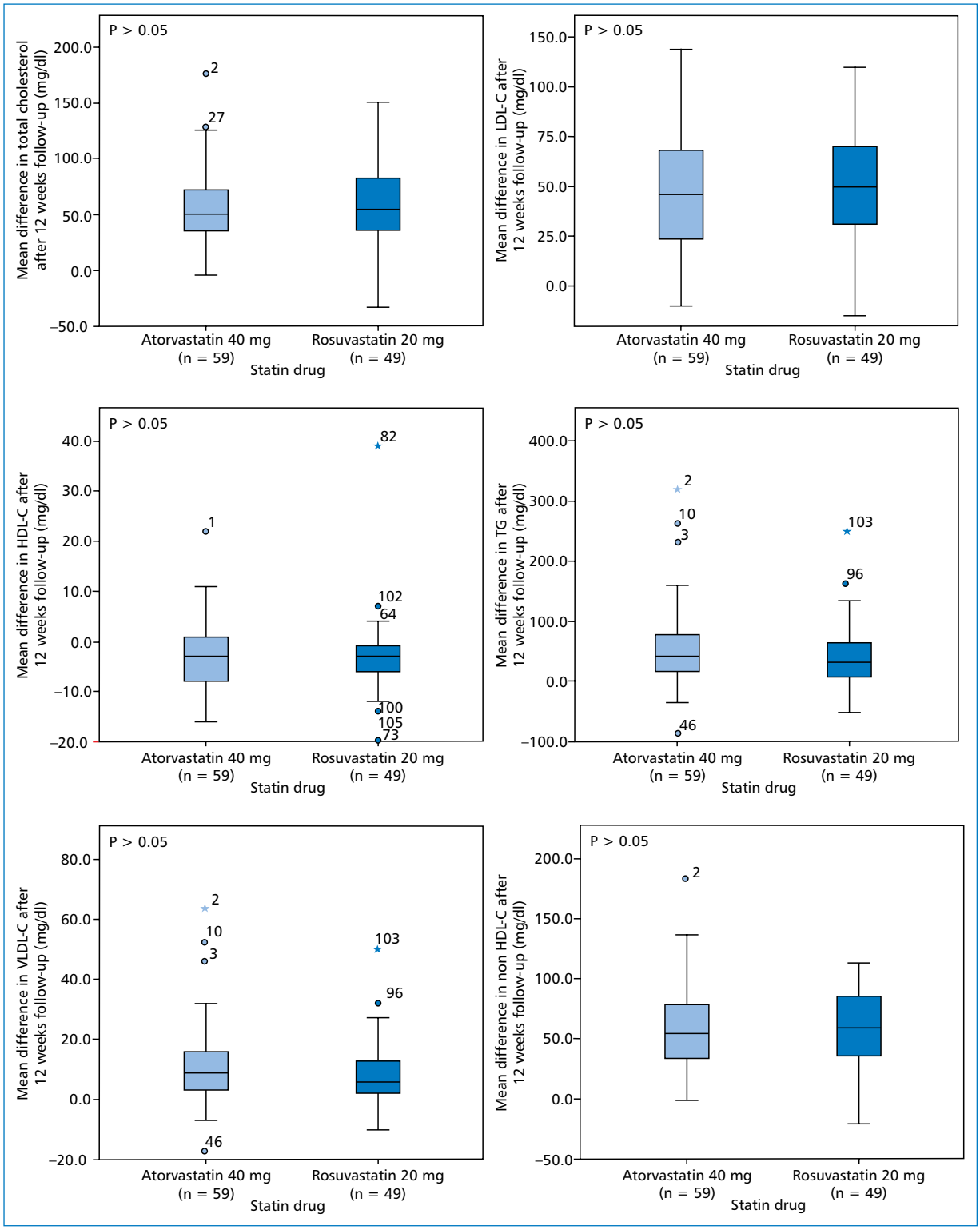

Figure 2. Lipid Profile Mean Difference After 12 Weeks Treatment with Atorvastatin 40 mg versus Rosuvastatin 20 mg

fect LDL-C goal achievement; age (men ≥ 45 years, women ≥ 55 years) and cigarette smoking are major risk factors that modify LDL-C goals [25].

With regards to safety profile related to statin therapy, muscular symptoms are the most common side effects that vary from mild (myalgia) to severe (rhabdomyolysis) [26]. On interviews during visits, 10.2% in the rosuvastatin group and 1.7% in the atorvastatin group reported adverse events. The most frequent adverse event in the rosuvastatin group was myalgia

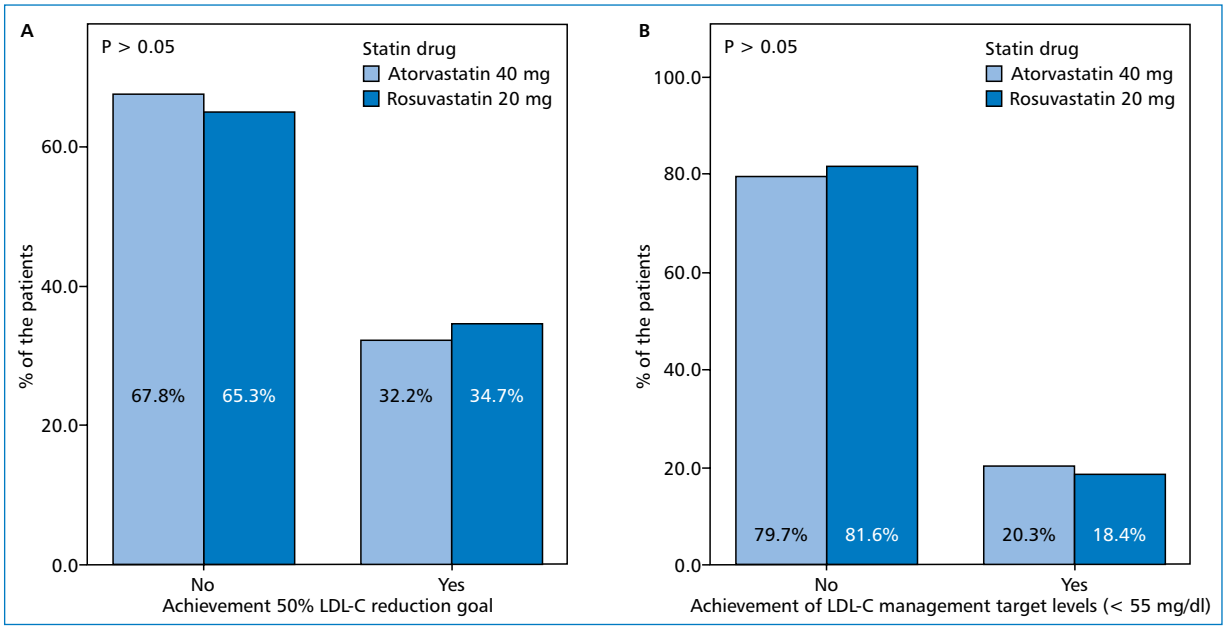

Figure 3. Percentage of Patients Who Achieved (a) 50% LDL-C Reduction and (b) LDL-C < 55 mg/dL in Atorvastatin versus Rosuvastatin Group

Table 4. Mean Difference in Liver Enzymes After Treatment with Atorvastatin versus Rosuvastatin

	Atorvastatin 40 mg U/L (Mean ± SD)	Rosuvastatin 20 mg U/L (Mean ± SD)	P
Mean difference ALT	–0.1 ± 5.5	–1.3 ± 8	0.906*
Mean difference AST	–1.5 ± 9.9	–2.3 ± 7.4	0.546*

*Mann-Whitney test; ALT — alanine transaminase; AST — aspartate transaminase; SD — standard deviation, U/L — unit/liter,

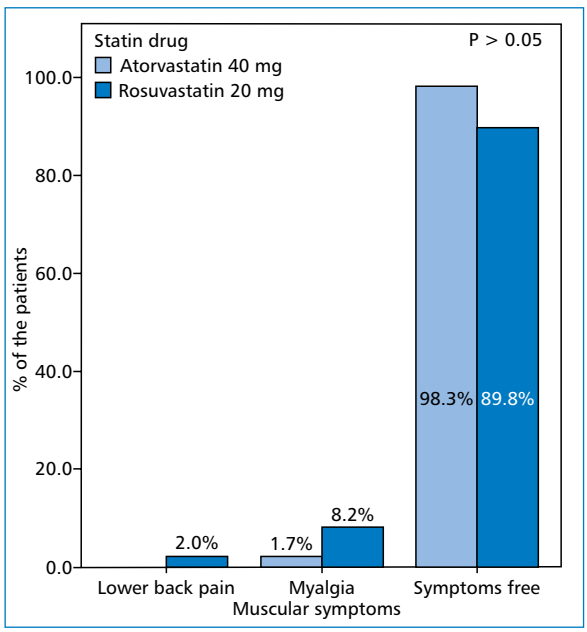

Figure 4. Muscular Symptoms Reported with Statin Use

with incidence of 8.2% and one case suffered from lower back pain. Only one adverse event (myalgia) was reported in the atorvastatin group (1.7%). All adverse events were mild, developed within 2 weeks after starting treatment, had no action taken, and resolved spontaneously. Similarly, the muscular symptoms were reported rarely in the literature [16, 27].

Hepatic function is also known to be affected by statin use [26]. Fluctuations in liver transaminases are a second end-point in the safety of the concerned medications. In the current study despite treatment with high-intensity statin therapy, no patients had elevated ALT or AST > 3 × ULN. Thus, there were no adverse events related to hepatic function reported with the use of any of the statins used in this study. In addition, there was no significant change in liver transaminases (ALT and AST) in both treatment arms ($p > 0.05$). This is not surprising because the literature confirmed that statin use is safe even in liver patients [28]. Our results revealed a significant increase in AST in rosuvastatin

group ($p = 0.035$), but it is important to mention that the increase in AST in rosuvastatin group was not $> 3 \times$ ULN and did not require drug discontinuation or dose adjustment. AST is not a specific parameter for liver injury and elevated AST level is associated with cardiovascular risk factors, particularly, metabolic syndrome, abdominal obesity, insulin resistance and diabetes [29]. Also, it may be related to the incidence of muscular symptoms that might be influenced with increase in AST level [30]. The two studied statins' safety profiles were comparable to each other and consistent with PULSAR study [18], which compared atorvastatin 20 mg and rosuvastatin 10 mg, and PATROL study [24] that showed no significant difference between the statins regarding liver function laboratory tests. In addition, no adverse events related to hepatic function were reported with the use of any of the statins among dyslipidemic patients with diabetes [27].

Conclusions

In conclusion, atorvastatin 40 mg and rosuvastatin 20 mg are equivalent regarding efficacy, in terms of LDL-C lowering effect, LDL-C goal achievement and improving atherogenic lipid profile. In addition, increasing HDL-C levels may provide further reduction in cardiovascular events risk. Both statins equally reduce total cholesterol, triglycerides, VLDL-C and non HDL-C. With regard to safety, both statins are safe and tolerable in Egyptian patients with type 2 diabetes and previous history of ACS.

Strength and limitations

The strengths of this study are the prospective collection of the data and the clinical randomization methodology. Also, a further point of strength is that we used sensitivity analysis to confirm results by doing two different methods while assessing the efficacy of the two drugs: mean difference and percentage of improvement. Also, in spite of short term follow-up period, patients were interviewed 3 times during the study; at baseline, 4^{th} and 12^{th} weeks. Adherence to treatment is a direct cause of good clinical response. Poor patients' compliance and adherence is very common in patients with diabetes and ACS taking statin especially that it is a daily drug [31]. However, in the recruited patients, almost all patients showed good adherence (except for those 7 patients excluded from the study due to their poor adherence) when assessed by Morisky scale. This explored the significance of patient education for good compliance especially in population with diabetes and hypertension where poor adherence is common. On the other hand, the limitations of the study are relatively small sample size of patients enrolled in the study due to single center nature of the study. Also, the relatively short study period (3 months) prevented us from assessing the long-term metabolic adverse effects.

Acknowledgments

This study was supported by cardiology clinics at National Heart Institute, Cairo, Egypt. The authors would like to extend appreciation to National Heart Institute for data arrangement and gratefully acknowledge the patients who participated in this study.

Conflict of interest

None declared.

REFERENCES

1. Khavandi M, Duarte F, Ginsberg HN, et al. Treatment of dyslipidemias to prevent cardiovascular disease in patients with type 2 diabetes. Curr Cardiol Rep. 2017; 19(1): 7, doi: 10.1007/s11886-017-0818-1, indexed in Pubmed: 28132397.
2. Bashandy M, Elgalil HA, Elhassan HA. Epidemiological and clinical profile of acute coronary syndrome of Egyptian patients admitted to the Coronary Care Unit, Al-Azhar University Hospital, New Damietta. The Scientific Journal of Al-Azhar Medical Faculty, Girls. 2019; 3(3): 625, doi: 10.4103/sjamf.sjamf_74_19.
3. American Diabetes Association. 9. Cardiovascular Disease and Risk Management. Diabetes Care. 2017; 40(Suppl 1): S75–S87, doi: 10.2337/dc17-S012, indexed in Pubmed: 27979896.
4. Low Wang CC, Hess CN, Hiatt WR, et al. Clinical update: Cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations. Circulation. 2016; 133(24): 2459–2502, doi: 10.1161/CIRCULATIONAHA.116.022194, indexed in Pubmed: 27297342.
5. Vergès B. Pathophysiology of diabetic dyslipidaemia: where are we? Diabetologia. 2015; 58(5): 886–899, doi: 10.1007/s00125-015-3525-8, indexed in Pubmed: 25725623.
6. Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. Diabetologia. 2003; 46(6): 733–749, doi: 10.1007/s00125-003-1111-y, indexed in Pubmed: 12774165.
7. Schofield JD, Liu Y, Rao-Balakrishna P, et al. Diabetes Dyslipidemia. Diabetes Ther. 2016; 7(2): 203–219, doi: 10.1007/s13300-016-0167-x, indexed in Pubmed: 27056202.
8. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. Circ Res. 2017; 120(1): 229–243, doi: 10.1161/CIRCRESAHA.116.308537, indexed in Pubmed: 28057795.
9. Ginsberg HN. REVIEW: Efficacy and mechanisms of action of statins in the treatment of diabetic dyslipidemia. J Clin Endocrinol Metab. 2006; 91(2): 383–392, doi: 10.1210/jc.2005-2084, indexed in Pubmed: 16291700.
10. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019; 73(24): e285–e350.
11. Mach F, Baigent C, Catapano AL, et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41(1): 111–188, doi: 10.1093/eurheartj/ehz455, indexed in Pubmed: 31504418.
12. Handelsman Y, Jellinger PS, Guerin CK, et al. Consensus Statement by the American Association of Clinical Endocrinologists

and American College of Endocrinology on the Management of Dyslipidemia and Prevention of Cardiovascular Disease Algorithm - 2020 Executive Summary. Endocr Pract. 2020; 26(10): 1196–1224, doi: 10.4158/CS-2020-0490, indexed in Pubmed: 33471721.
13. Rosa GM, Carbone F, Parodi A, et al. Update on the efficacy of statin treatment in acute coronary syndromes. Eur J Clin Invest. 2014; 44(5): 501–515, doi: 10.1111/eci.12255, indexed in Pubmed: 24601937.
14. Rosenson RS, Baker SK, Jacobson TA, et al. An assessment by the Statin Muscle Safety Task Force: 2014 update. J Clin Lipidol. 2014; 8(3 Suppl): S58–S71, doi: 10.1016/j.jacl.2014.03.004, indexed in Pubmed: 24793443.
15. Qu HY, Xiao YW, Jiang GH, et al. Effect of atorvastatin versus rosuvastatin on levels of serum lipids, inflammatory markers and adiponectin in patients with hypercholesterolemia. Pharm Res. 2009; 26(4): 958–964, doi: 10.1007/s11095-008-9798-6, indexed in Pubmed: 19082693.
16. Park JS, Kim YJ, Choi JY, et al. Comparative study of low doses of rosuvastatin and atorvastatin on lipid and glycemic control in patients with metabolic syndrome and hypercholesterolemia. Korean J Intern Med. 2010; 25(1): 27–35, doi: 10.3904/kjim.2010.25.1.27, indexed in Pubmed: 20195400.
17. Newman CB, Preiss D, Tobert JA, et al. American Heart Association Clinical Lipidology, Lipoprotein, Metabolism and Thrombosis Committee, a Joint Committee of the Council on Atherosclerosis, Thrombosis and Vascular Biology and Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Stroke Council. Statin safety and associated adverse events: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2019; 39(2): e38–e81, doi: 10.1161/ATV.0000000000000073, indexed in Pubmed: 30580575.
18. Clearfield MB, Amerena J, Bassand JP, et al. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia--Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). Trials. 2006; 7: 35, doi: 10.1186/1745-6215-7-35, indexed in Pubmed: 17184550.
19. Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: response to authors. J Clin Epidemiol. 2011; 64(3): 255–7; discussion 258, doi: 10.1016/j.jclinepi.2010.09.002, indexed in Pubmed: 21144706.
20. Pitt B, Loscalzo J, Monyak J, et al. Comparison of lipid-modifying efficacy of rosuvastatin versus atorvastatin in patients with acute coronary syndrome (from the LUNAR study). Am J Cardiol. 2012; 109(9): 1239–1246, doi: 10.1016/j.amjcard.2011.12.015, indexed in Pubmed: 22360820.
21. Rocha KC, Pereira BM, Rodrigues AC. An update on efflux and uptake transporters as determinants of statin response. Expert Opin Drug Metab Toxicol. 2018; 14(6): 613–624, doi: 10.1080/17425255.2018.1482276, indexed in Pubmed: 29842801.
22. Ruiz-Iruela C, Padró-Miquel A, Pintó-Sala X, et al. KIF6 gene as a pharmacogenetic marker for lipid-lowering effect in statin treatment. PLoS One. 2018; 13(10): e0205430, doi: 10.1371/journal.pone.0205430, indexed in Pubmed: 30304062.
23. Her AY, Kim JY, Kang SM, et al. Effects of atorvastatin 20 mg, rosuvastatin 10 mg, and atorvastatin/ezetimibe 5 mg/5 mg on lipoproteins and glucose metabolism. J Cardiovasc Pharmacol Ther. 2010; 15(2): 167–174, doi: 10.1177/1074248409357922, indexed in Pubmed: 20147603.
24. Saku K, Zhang Bo, Noda K, et al. PATROL Trial Investigators. Randomized head-to-head comparison of pitavastatin, atorvastatin, and rosuvastatin for safety and efficacy (quantity and quality of LDL): the PATROL trial. Circ J. 2011; 75(6): 1493–1505, doi: 10.1253/circj.cj-10-1281, indexed in Pubmed: 21498906.
25. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001; 285(19): 2486–2497, doi: 10.1001/jama.285.19.2486, indexed in Pubmed: 11368702.
26. Ward NC, Watts GF, Eckel RH, et al. Statin Toxicity. Circ Res. 2019; 124(2): 328–350, doi: 10.1161/CIRCRESAHA.118.312782, indexed in Pubmed: 30653440.
27. Barakat L, Jayyousi A, Bener A, et al. Comparison of Efficacy and Safety of Rosuvastatin, Atorvastatin and Pravastatin among Dyslipidemic Diabetic Patients. ISRN Pharmacol. 2013; 2013: 146579, doi: 10.1155/2013/146579, indexed in Pubmed: 23476802.
28. Bader T. Yes! Statins can be given to liver patients. J Hepatol. 2012; 56(2): 305–307, doi: 10.1016/j.jhep.2011.08.016, indexed in Pubmed: 21963520.
29. Ndrepepa G. Aspartate aminotransferase and cardiovascular disease—a narrative review. Journal of Laboratory and Precision Medicine. 2021; 6: 6–6, doi: 10.21037/jlpm-20-93.
30. Armitage J. The safety of statins in clinical practice. Lancet. 2007; 370(9601): 1781–1790, doi: 10.1016/S0140-6736(07)60716-8, indexed in Pubmed: 17559928.
31. Bates TR, Connaughton VM, Watts GF. Non-adherence to statin therapy: a major challenge for preventive cardiology. Expert Opin Pharmacother. 2009; 10(18): 2973–2985, doi: 10.1517/14656560903376186, indexed in Pubmed: 19954271.