



## Echocardiographic and Exercise Test Findings in Patients With Dyslipidemia and Coronary Artery Disease Before and After Treatment With Simvastatin With or Without Fenofibrate

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### ABSTRACT

**Background:** Various treatment protocols for dyslipidemia and coronary artery disease have been suggested. In spite of lipid-lowering effects, various effects of statins and fibrates have been reported in the literature.

**Objectives:** The aim of this study was to assess the cardiac efficacy of Simvastatin with or without fenofibrate on cardiac function.

**Patients and Methods:** A cohort study was conducted on 124 patients with dyslipidemia and coronary artery disease. Patients were randomly divided into two groups: the first group (n = 64) received Simvastatin (60 - 20 mg/day) and fenofibrate (200 mg/day), and the second group (n = 60) received Simvastatin (20 - 60 mg/day) alone. Treatment lasted 1 year, and the patients were evaluated after treatment.

**Results:** The mean age was  $54.3 \pm 6.5$  years, and 53.2% of patients were male. Compared to baseline, after 12 months of treatment the lipid profiles of both groups decreased significantly ( $P < 0.05$ ). The change in left-ventricular ejection fraction in the first group was statistically significant ( $P = 0.01$ ). The exercise test time and metabolic equivalent of tasks index significantly increased in the first group ( $P = 0.014$ ,  $P = 0.006$ ), but these changes were not significant in the second group ( $P = 0.289$ ,  $P = 0.744$ ).

**Conclusions:** Lipid-regulating therapies including Simvastatin and fenofibrate improved myocardial function and reduced myocardial ischemia, so combined therapy is recommended for treating dyslipidemia in high-risk patients for cardiovascular problems.

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### ► Implication for health policy/practice/research/medical education:

This is a challenging issue about the effects of lipid-profile-lowering agents (i.e. fibrates) on myocardial structure and function in patients with coronary artery diseases and dyslipidemia although there are many studies which confirmed the efficacy of these medications on lipid profile via laboratory findings. In this study we focused on the cardiac effect of lipid profile lowering agents via echocardiography and exercise test.

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## 1. Background

Cardiac events due to coronary artery disease (CAD) are the major cause of death in many countries, particularly among developed countries. In addition, myocardial ischemia and related cardiac complications are among the common insufficiencies of CAD (1) Recent studies have revealed the notable role of hyperlipidemia as a

prognostic factor in the structure and function of the left ventricle secondary to the myocardial infarction in patients with CAD (2-4). Also, lipid-regulating drugs, particularly those that reduce cholesterol, such as statins, would improve prognosis in patients diagnosed with cardiac ischemia (acute and chronic), and moreover, could be used to treat hypercholesterolemia effectively and safely (5). These studies have confirmed that lipid-lowering agents could ameliorate the clinical status and prognosis of CAD patients. Some studies have approved the efficacy of the lipid-lowering agents to decline the frequency of (lethal and nonlethal) acute coronary syndromes (6).

The effects of other lipid-lowering agents, especially those that are effective on triglycerides, are not thoroughly examined for cardiac function and structure in patients diagnosed with cardiac ischemia. Currently, there is much interest on the therapeutic effects of statins along with other triglyceride-lowering agents on myocardial structure and function. There is some evidence on the preventive effects of statins on the myocardial remodeling in cases with recent myocardial infarction or patients with nonischemic cardiomyopathy (7). However, the effects of statins accompanied by other lipid-profile-lowering medicines (i.e. fibrates) on myocardial structure and function in patients with CAD and dyslipidemia have not been clearly established.

## 2. Objectives

The objective of this study was to evaluate the plausible effects of Simvastatin with or without fenofibrate on myocardial structure and function as well as paraclinical findings in patients with CAD and dyslipidemia.

## 3. Patients and Methods

A prospective cohort study was conducted on patients with CAD and dyslipidemia. After 6 weeks of antihyperlipidemia therapy based on findings from the National Cholesterol Education Program of the American Heart Association, the patients were examined again (8). The inclusion criteria were as follows: patients diagnosed with constant CAD with positive exercise test time, total cholesterol  $\geq 200$  mg/dL, Triglyceride (TG)  $\geq 250$  mg/dL, low density lipoprotein (LDL)  $\geq 100$  mg/dL, and normal liver function test. Also, patients diagnosed with myocardial infarction in the last 6 months, chronic heart failure (New York Heart Association Function Class II and higher), heart-valve disease, systolic blood pressure  $> 170$  mmHg, diastolic blood pressure  $> 100$  mmHg, dysrhythmia (atrial flutter, atrio-ventricular block II, and more), uncontrolled insulin-dependent diabetes, and serious liver, kidney, and neoplastic diseases were excluded from the study.

One hundred forty-nine patients meeting the inclusion criteria were randomly divided into 2 groups: the first group received Simvastatin (20 mg/day) and fenofibrate (200 mg/day) with lipid-restricted diet and exercise, and

the second group received Simvastatin (20 mg/day) with the same diet and exercise. The treatment was given for 12 months. Twenty-five patients failed during the follow up. The starting dose of Simvastatin was 20 mg/day. The main objective of this study was to help patients improve their blood-lipid profiles. So, if an LDL level of under 100 was not achieved during the first week, the dose of Simvastatin was increased to 40 mg/day, and if the patient did not respond to this dosage, it was increased to 60 mg/day after 6 weeks (based on recommendations from the National Cholesterol Education Program (9). A lipid profile and a liver-function test were taken at 1.5, 3, and 12 months.

During the study, all patients received a standard therapeutic regiment consisting of 80 mg/day of aspirin, beta blocker, nitrate, and calcium-channel blocker daily. The therapeutic cardiovascular regiment was not adjusted during the study. Before and after the study (12 months), the same specialist took a lipid profile (LDL, TG, high-density lipoprotein [HDL], and cholesterol), liver-function test, electrocardiography, exercise test time, and Doppler echocardiography from the patients. The study was approved by Baqiyatallah University's Scientific and Ethical committee. The study was funded by the Scientific Research committee of the Medicine Department, and no extra expenses were imposed on the patients. Study participation was voluntary, and patients were free to quit the study at any time. After collecting the data, all the statistical analyses were carried out using SPSS version 17 via paired and independent *t* tests, and ANOVA and *P* values of  $< 0.05$  were considered statistically significant.

## 4. Results

Overall, 124 patients completed the study (age range = 42-56; mean and standard deviation =  $54.3 \pm 5.6$ ). The mean age in the first group (treated with a combination of Simvastatin and fenofibrate) was  $52.8 \pm 4.7$  and 53.1% were male; the mean age in the second group (Simvastatin without fenofibrate) was  $53.1 \pm 7.3$  and 53.3% were male. No significant statistical differences were found for the demographic variables between both groups (Table 1).

The lipid profiles from both groups before and after treatment are listed in Table 2. After 6 weeks of treatment, a desirable lipid profile was achieved in only 25 cases (20.16%) in both groups, which in these cases Simvastatin was continued 20 mg/day; while in other cases the dose of Simvastatin was increased to 40 mg/kg. After 6 weeks, LDL did not decrease to 100 mg/dL in 19 cases (15.32%). At the end of 12 weeks treatment, 4.5% of all the patients had an LDL measurement of  $> 100$  mg/dL; for these cases, the Simvastatin dose was increased to 60 mg/day and continued up to 12 months. The 12-month therapeutic protocol in the first and second group decreased their total cholesterol by 25.3% and 12.93%, LDL by 38.97% and 33.91%, HDL by 23.41% and 3.80%, and triglycerides by 44.93% and 3.09%, respectively. Also, the changes from baseline in total cholesterol and LDL in the first group were statisti-

**Table 1.** Demographic and Clinical Findings

Items	First Group (n = 64)			Second Group (n = 60)			P Value Between Groups
	Base Line	12th mo	P Value	Base Line	12th mo	P Value	
Mean age $\pm$ SD	52.8 $\pm$ 4.7	-	-	53.1 $\pm$ 7.3	-	-	0.544
Male	34	-	-	32	-	-	0.659
Female	30	-	-	28	-	-	0.741
Systolic blood pressure, mmHg	134.1 $\pm$ 10.1	133.8 $\pm$ 9.3	0.154	131.2 $\pm$ 10	131.9 $\pm$ 8.5	0.325	0.201
Diastolic blood pressure, mmHg	84.4 $\pm$ 4.3	84.3 $\pm$ 3.1	0.847	83.9 $\pm$ 4.2	84.2 $\pm$ 5.1	0.265	0.754
Smoker	18.1%	18.1%	-	17.9%	17.9%	-	0.841
BMI, Kg/M2	28.1 $\pm$ 2.8	28.6 $\pm$ 3.4	0.369	27.4 $\pm$ 2.6	27.9 $\pm$ 4.1	0.657	0.632
Diabetes mellitus	13.6%	13.6%	-	12.8%	12.8%	-	0.489
Previous MI	18.2%	18.2%	-	10.3%	10.3%	-	0.063
Beta blocker user	52.3%	52.3%	-	53.8%	53.8%	-	0.497
Calcium channel blocker user	29.5%	29.5%	-	30.8%	30.8%	-	0.369
Nitrates user	15.9%	15.9%	-	15.4%	15.4%	-	0.581
ACE inhibitor user	31.8%	31.8%	-	30.8%	30.8%	-	0.807

**Table 2.** Laboratory Findings

Items	First Group			Second Group		
	Baseline	12 <sup>th</sup> mo	P Value	Baseline	12 <sup>th</sup> mo	P Value
Total cholesterol	230.1 $\pm$ 41.3	172.5 $\pm$ 47.9 <sup>b</sup>	< 0.001	231.9 $\pm$ 35.5	201.9 $\pm$ 42.5	0.061
Total triglyceride	295.1 $\pm$ 41.3	162.5 $\pm$ 47.9 <sup>c</sup>	0.003	290.9 $\pm$ 35.5	281.9 $\pm$ 40.5	0.083
HDL <sup>a</sup>	38.9 $\pm$ 7.3	48.01 $\pm$ 8.1 <sup>c</sup>	0.021	39.4 $\pm$ 8.1	40.9 $\pm$ 9.3	0.542
LDL <sup>a</sup>	147.8 $\pm$ 33.6	90.2 $\pm$ 36.3 <sup>b</sup>	< 0.001	150.1 $\pm$ 27.8	99.2 $\pm$ 33.6	0.024
AST <sup>a</sup>	24.8 $\pm$ 5.3	26.2 $\pm$ 4.6 <sup>c</sup>	0.014	23.5 $\pm$ 5.2	24.1 $\pm$ 4.1	0.601
ALT <sup>a</sup>	26 $\pm$ 4.61	26.9 $\pm$ 3.1	0.259	25.7 $\pm$ 3.2	26.2 $\pm$ 4.1	0.365

<sup>a</sup> Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; HDL, High-density lipoprotein; LDL, Low-density lipoprotein

<sup>b</sup>  $P < 0.001$

<sup>c</sup>  $P < 0.01$

**Table 3.** Echocardiographic Findings

Items	First Group		Second Group	
	Baseline	12 <sup>th</sup> mo	Baseline	12 <sup>th</sup> month
LV <sup>a</sup> ejection fraction, %	59.8 $\pm$ 8.04	62.9 $\pm$ 4.43 <sup>b</sup>	61.1 $\pm$ 3.4	60.04 $\pm$ 6.4
LV mass, gr/m <sup>2</sup>	77.5 $\pm$ 9.7	74.6 $\pm$ 10.4	77.4 $\pm$ 12.2	80.6 $\pm$ 13.6 <sup>c</sup>
E <sup>b</sup> /A <sup>c</sup> ratio	0.97 $\pm$ 0.2	1.01 $\pm$ 0.21	0.98 $\pm$ 0.19	0.97 $\pm$ 0.23
Isovolumic relation Time, s	0.088 $\pm$ 0.02	0.089 $\pm$ 0.01	0.090 $\pm$ 0.02	0.092 $\pm$ 0.01

<sup>a</sup> Abbreviation: LV, left ventricular

<sup>b</sup> E, early diastolic transmitral velocity

<sup>c</sup> A, late diastolic transmitral velocity

<sup>d</sup>  $P < 0.001$

<sup>e</sup>  $P < 0.01$

cally significant at  $P = 0.01$ , whereas the triglyceride and HDL changes were significant at  $P = 0.001$ . Nonetheless, no significant changes were detected in the lipid profile of the second group except for LDL amount ( $P = .024$ ).

At the end of the 12-month study period, diastolic-function parameters (early and late diastolic transmitral velocity, isovolumetric relaxation time) had not changed significantly from baseline in either group Table 3, although the change in left ventricular (LV) ejection fraction in the first group was statistically significant ( $P = 0.01$ ). The LV mass index statistically increased in the second group after the 12-month treatment ( $P = 0.039$ ), whereas no statistically significant changes appeared in the first group. The anti-ischemic effect was investigated

with exercise test time, which significantly increased in the Simvastatin-fenofibrate group Table 4. The metabolic equivalent of tasks index increased ( $4.32 \pm 0.5$  to  $5.68 \pm 0.5$ ) in the first group, but the changes were not statistically significant in the second group.

## 5. Discussion

The results showed that the therapeutic effect of a Simvastatin-fenofibrate regimen on the lipid profiles and the ejection fraction of the LV increased, whereas patients who received Simvastatin alone showed an increase in the LV size and mass. Additionally, we conclude that a compound regimen containing Simvastatin and

**Table 4.** Exercise Test Findings

Items	First Group			Second Group		
	Baseline	12 <sup>th</sup> mo	P value	Baseline	12 <sup>th</sup> mo	P value
Exercise test time (Min)	5.21 ± 1.81	6.01 ± 1.08 <sup>b</sup>	< 0.001	5.43 ± 1.26	5.32 ± 1.20	0.089
METS <sup>a</sup>	4.32 ± 0.50	5.68 ± 0.54	< 0.001	4.43 ± 0.92	4.41 ± 1.11	0.121

<sup>a</sup> Abbreviation: METS; metabolic equivalents tasks<sup>b</sup> P < 0.01

fenofibrate could improve cardiac function compared to a regimen consisting of Simvastatin alone. Moreover, regarding the changes in exercise test time, myocardial ischemia could be lessened more by administering Simvastatin and fenofibrate together than by administering Simvastatin alone. Furthermore, echocardiography findings showed an increase in end-diastolic and systolic volumes and LV mass due to Simvastatin without fenofibrate prescription in comparison with Simvastatin and fenofibrate, which can be responsible for remodeling secondary to chronic cardiac ischemia; this finding is compatible with the findings for exercise test time in a study by Mohlenkamp *et al.* (10).

Some studies have investigated the impacts of these medications on the lipid profiles and heart functioning. Zeman *et al.* conducted a clinical trial study on 86 patients who were divided into two groups similar to the present study. They demonstrated that long-term treatment (at least 1 year) by one fibrate and statin could conspicuously rectify lipid profiles without any significant changes in hepatic or muscular enzymes. However, they used Pravastatin and ciprofibrate instead of Simvastatin and fenofibrate, and they did not investigate cardiac-function parameters. Therefore, their findings are not comparable with the findings of the present study (11).

Also, Klosiewicz-Latoszek *et al.* demonstrated that the combination therapy with Simvastatin and fenofibrate would effectively regulate serum-lipid profiles in patients diagnosed with mixed hyperlipidemia rather than a separate prescription of each, and although cardiac outcomes were not investigated, the results correspond to our study's results (12). Other studies have also emphasized and corroborated the effectiveness of combination of one statin and one fibrate (particularly fenofibrate) to regulate hypercholesterolemia and hypertriglyceridemia, although the impact of this protocol on cardiac function as well as its efficacy on lipid profiles has not been cleared (13, 14). In compared to statins, fibrates may increase HDL levels despite a decline in triglycerides. Also, fibrates can increase HDL levels by activating plasmatic lipase lipoproteins (15). Some experimental studies have demonstrated a preventive effect of statins and fibrates on myocardial hypertrophy via reducing atherogenic lipoproteins and inhibiting the synthesis of isoprenoids (16, 17). In addition, 12-month monotherapy with Atorvastatin (20-60 mg/day) had no prominent effect on the decline of the LV mass (18).

Myocardial ischemia during daily activities can induce by dysregulation of the vasomotor activity of the coronary artery. Also, an increase in LDL and TG levels may

disrupt endothelial activity and lead to coronary artery spasms (19). Therefore, declines in LDL and TG levels and increases in HDL could regulate endothelial activity and prevent coronary disease (20). The effects of statin-fibrate protocol on coronary artery blood supply have been affirmed (21). In this study, a significant decrease over 12 months in myocardial ischemia in patients with CAD who underwent fibrate-statin treatment could be a result of establishing endothelium (22).

It seems that some factors are related to the diminution of myocardial ischemia after receiving statin and fibrate more than changes in blood lipids. Recent studies have demonstrated that statins could alleviate endothelial inflammation, atherosclerotic plaque formation, arrhythmias, and increase revascularization (23). Myocardial ischemic is an inflammatory process, and, therefore, the anti-inflammatory effect of statins can be useful for performance and survival of ischemic tissue. However, the effect of fibrates has not yet been approved for controlling inflammations (24, 25). It seems that the 1-year therapy by statin plus fenofibrate could have a positive effect on myocardial structure and function, both in cases with CAD and dyslipidemia and in a thorough improvement on blood-lipid profiles. The limitations of the present study were a lack of angiographic findings and supplemental analysis changes to confirm the anti-ischemic effect of this protocol in these patients. We recommend that future studies investigate the efficacy of this therapeutic protocol on cardiac function and atherosclerotic plaque by using angiography in patients diagnosed with combined dyslipidemia.

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