European Journal of Therapeutics

DOI: 10.5152/eurjther.2020.19018

Original Research

Effect of Statin Therapy in Tpe-Interval and Tpe/Qtc Ratio in Patients with Familial Hypercholesterolemia

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ABSTRACT

Objective: Studies have shown that hypercholesterolemia can induce ventricular vulnerability to fibrillation, and statin therapy exerts antiarrhythmic effects.

In the present study, we investigated the relationship between arrhythmogenic substrate and familial hypercholesterolemia (FH) with regard to statin therapy.

Methods: We evaluated 46 statin-naive patients (41±12 years) with FH, and 46 healthy subjects (40±8 years) prospectively. Electrocardiography (ECG) of patients were compared before and after 6 months of intensive statin therapy and with control groups. The ECG parameters were calculated by two experienced cardiologists who blinded to each other's findings.

Results: There were no significant differences found between groups' baseline characteristics. Total cholesterol (343±49 mg/dL vs. 161±12 mg/dL; p<0.001) and low-density lipoprotein-cholesterol (LDL-C) (260±42 vs. 95±13; p<0.001) levels were significantly higher in FH group. Both total cholesterol (343±49 vs. 206±45; p<0.001) and LDL-C (260±42 vs. 138±40; p<0.001) levels were decreased after statin therapy. Both mean baseline Tpe-interval (90.7±9.3 ms vs. 77.6±7.3 ms; p<0.001) and Tpe/QTc ratio (0.219±0.02 vs. 0.193±0.01; p<0.001) were found to be significantly higher in FH group than control subjects. After statin therapy, Tpe-interval (90.7±9.3 ms vs. 81.3±8.3 ms; p<0.001) and Tpe/QTc ratio (0.219±0.02 vs. 0.201±0.02; p<0.001) were significantly decreased. Compared to the control group, Tpe-interval (81.3±8.3 ms vs. 77.6±7.3 ms; p=0.027) and Tpe/QTc (0.206±0.02 vs. 0.193±0.01; p=0.021) ratio remained higher in FH patients after statin therapy. There was a strong and positive correlation between basal LDL-C and Tpe-interval (r=0.740; p<0.001) and Tpe/QTc ratio (r=0.597; p<0.001)

Conclusion: This study showed that Tpe-interval and Tpe/QTc ratio on ECG were significantly prolonged in FH patients and improved with intense statin therapy by lowering LDL-C.

Keywords: Electrocardiography, familial hypercholesterolemia, Tpe/QTc ratio, Tpe-interval, ventricular arrhythmias

INTRODUCTION

Previous experimental studies have shown that hypercholesterolemia can induce proarrhythmic electrophysiological remodeling (1). Both clinical and experimental evidence have shown that the statin therapy provides antiarrhythmic effects. Statins reduce ventricular arrhythmias with their direct antiarrhythmic effects and through pleiotropic properties. This beneficial effect has been shown in nonischemic patients (2, 3). Various surface electrocardiogram (ECG) markers of dispersion of ventricular repolarization (DVR) including QT, QT_c, QT dispersion, QTc dispersion, and T_{peak}–T_{end} (Tpe-interval) have been proposed as predictors of risk for ventricular arrhythmia. The Tpe-interval and Tpe/QTc (QT interval corrected for heart rate) ratio are markers of DVR (4, 5).

Prolonged Tpe-interval reflects abnormal DVR and is related to increased risk of ventricular arrhythmogenesis (6-8). Moreover, previous studies have shown that the Tpe/QTc ratio, which is in-

How to cite: Küçükosmanoğlu M, Kılıç S, Saraçoğlu E, Çekici Y, Vuruşkan E, Kayıkcıoğlu M. Effect of Statin Therapy in Tpe-Interval and Tpe/Qtc Ratio in Patients with Familial Hypercholesterolemia. Eur J Ther 2020; 26(3): 165–71.

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Received: 27.06.2019 • **Accepted:** 18.11.2019

dependent of heart rate alteration, is a more accurate measurement of ventricular repolarization (6-8). Familial hypercholesterolemia (FH) is associated with elevated levels of low-density lipoprotein-cholesterol (LDL-C) (9). In FH patients, high cholesterol exposure begins in childhood and causes premature atherosclerosis. Most cases of sudden cardiac deaths occur because of ischemic heart disease that causes ventricular arrhythmia (10, 11). To our best knowledge, no study has evaluated the Tpe-interval and Tpe/QTc ratio as markers of ventricular arrhythmogenesis in patients with FH. Therefore, in the present study, we investigated the effect of intensive statin therapy on the Tpe-interval and Tpe/QTc ratio in patients with FH.

METHODS

Study Design and Population

A total of 49 newly diagnosed statin-naive FH patients were evaluated prospectively from January 2016 to October 2017. The diagnosis of FH was based on genetic analysis (pathogenic mutation in the LDL receptor, proprotein convertase subtilisin/kexin 9 [PCSK9] or apolipoprotein B-100 genes) in patients with LDL-C >190 mg/dL (5 mmol/L).

Forty-six age–gender-matched normolipidemic individuals without any medication were included in the study as the control group. All patients were followed-up for 6 months. Patients with coronary artery disease (CAD), history of myocardial infarction, moderate-to-severe valvular heart disease, hypertrophic or dilated cardiomyopathies, thyroid dysfunction, electrolyte disturbances, pulmonary, malignancy, renal dysfunction, hepatic disease, or connective tissue disease were all excluded from the study.

All patients had to undergone treadmill stress test with ECG according to the Bruce protocol or single-photon emission computed tomography to exclude subclinical CAD. Coronary angiography was performed in patients with positive or suspicious result in noninvasive stress testing. Thus, 3 patients were excluded with the diagnosis of CAD, and finally, 46 patients with FH constituted the study population.

The local institutional ethics committee of Gaziantep University Faculty of Medicine has approved the study protocol (2016/104). The study was in compliance with the principles of the Declaration of Helsinki. Informed consent was obtained from the patients included in the study.

Main Points:

- Previous studies have shown that hypercholesterolemia can induce ventricular vulnerability to fibrillation, and statin therapy exerts antiarrhythmic effects.
- In this study, we showed that Tpe-interval and Tpe/QTc ratios were increased in treatment-naive FH patients.
- These parameters were significantly decreased after an intensive statin therapy.
- These results support the possible effects of hypercholesterolemia and statin therapy on Tpe-interval and Tpe/QTc ratio.

Demographic characteristics, medical history, and medication and anthropometric measurements were recorded. Transthoracic echocardiography was performed with EPIQ (Philips Medical Systems, Bothell, WA, USA) in all patients.

Routine blood parameters included were total cholesterol, LDL-C, high-density lipoprotein-cholesterol, triglyceride, fasting blood glucose, and serum creatinine were assessed for all patients. However, for FH patients, these biochemical parameters were evaluated in the third and sixth month of statin therapy. Intensive statin therapy (atorvastatin 80 mg/day or rosuvastatin 40 mg/day) was prescribed at the time of diagnosis of FH and was kept constant throughout the study. Patients did not receive any non-statin lipid-lowering drug during the study period. All patients were followed-up for the side effects of statins, and no significant side effects were noticed during the study period.

Electrocardiography

The ECGs were evaluated both at the time of diagnosis of FH before statin treatment and 6 months after statin treatment. Baseline ECGs were compared between the FH population and control subjects, and also after intensive statin therapy in the FH group. Twelve-lead ECGs were obtained with 10 mm/mV amplitude, and 25 mm/s (Nihon Kohden Corp., Tokyo, Japan) in the supine position. All ECGs obtained in the first and last examination of patients were recorded in the computer. Adobe Photoshop software (400% magnification) was used to measure ECG parameters. Each ECG was evaluated by two experienced cardiologists who were blinded to each other's findings and status of each patient and control subject.

Patients presented with U waves, bundle branch block or evidence of any intraventricular conduction defect, left ventricular hypertrophy, left ventricular dysfunction, and atrial fibrillation in their ECG were excluded from the study. Also, patients who were taking medications, such as antiarrhythmics, antihistamines, digitalis, tricyclic antidepressants, diuretics, and antipsychotics were all excluded from this study.

QT was calculated from the beginning of the QRS to the end of T wave, which comes back to the isoelectric line. For each QT, two consecutive calculations were done, and the average value of two readings was recorded. Bazett's formula: $QTc=QT/\sqrt{R-R}$ interval was performed to calculate QTc. RR interval was measured as the average of three complexes. Tpe-interval was determined as the interval from the peak of T wave to the end of T wave, where the wave reached the isoelectric line. Tpe-interval was measured mostly in V5. However, if V5 is not suitable for calculation, V4 or V6 leads were used (8, 12, 13).

The calculation was done only in leads with T wave amplitude >1.5 mm. The Tpe/QTc ratio was calculated from these measurements.

Statistical Analysis

Continuous parameters with normal distribution were presented as means and standard deviation, and non-normally distributed parameters were presented as median and interquartile range. Normal distribution was evaluated by Kolmogorov–Smirnov test.

Continuous parameters with normal distribution were compared with Student's t-test and non-normally distributed parameters were compared with Mann–Whitney U test between groups.

Categorical parameters were presented as percentages and compared between groups with the Chi-square test or Fisher's exact test.

Paired Student's t-test was used to compare repeated measurements (at baseline and 6 months) for ECG and laboratory parameters. The correlation coefficients and significance between LDL-C and ECG parameters were calculated by Pearson's or Spearman's test. Changes in LDL-C and ECG parameters before and after statin therapy were represented as Δ, and correlation between ΔLDL-C and ECG parameters were analyzed.

A p-value<0.05 was statistically significant. Statistical analyses were conducted using the Statistical Package for the Social Sciences 115 (SPSS 20.0) for Windows (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

Our study enrolled 46 consecutive patients with newly diagnosed FH (21 females; mean age 41±12 years) and 46 healthy controls (19 females; mean age 40±8 years). Baseline characteristics include gender, age, body mass index, smoking, hypertension, and diabetes mellitus. Table 1 shows similarity between groups with respect to these baseline characteristics. Left ventricular ejection fraction and mean systolic and diastolic blood pressure were also found similar between the two groups.

Total cholesterol, LDL-C, and triglyceride levels were found significantly higher in the FH patients than in the control subjects (Table 1). Levels of both total cholesterol (343±49 mg/dL vs. 206±45 mg/dL; p<0.001) and LDL-C (260±42 mg/dL vs. 138±40 mg/dL; p<0.001) were shown to decrease significantly at the sixth month of the intensive statin treatment. Although, effective reduction was detected in total cholesterol (39.4%±13.1%) and LDL-C (49.2%±16.2%) levels with statin therapy, posttreatment levels of both remained significantly higher than control subjects (for both; p<0.001). ECG evaluation revealed normal sinus rhythm for both FH and control groups. The mean baseline Tpe-interval was found significantly prolonged in the FH patients compared to the control group (90.7±9.3 ms vs. 77.6±7.3 ms; p<0.001) (Table 2). Tpe/QTc ratio was shown to be significantly higher in the FH patients than control subjects (0.219±0.02 vs. 0.193±0.01; p<0.001) (Figure 1). Although QT (399±10.5 ms vs. 389±8.5 ms; p=0.608) and QTc (414±19.5 ms vs. 402±16.9 ms; p=0.094) intervals were prolonged in FH group, it was not statistically significant (Table 2). In FH patients, the Tpe-interval (90.7±9.3 ms vs. 81.3±8.3 ms; p<0.001) and Tpe/QTc ratio (0.219±0.02 vs. 0.201±0.02; p<0.001) were significantly reduced after intensive statin therapy compared to baseline. The QT and QTc intervals did not show any significant change after the statin therapy (for both; p>0.05) (Table 3). Compared to the control group, the Tpe-interval (81.3±8.3 ms vs. 77.6±7.3 ms; p=0.027) and Tpe/QTc ratio (0.201±0.02 vs. 0.193±0.01; p=0.021) were still significantly higher in the FH patients after the statin therapy.

Table 1. Baseline characteristic and laboratory parameters of FH patients and control group

Parameter	FH (n=46)	Control (n=46)	p
Age, years	41±12	40±8	0.379
Female, n (%)	21 (45.7)	19 (41.3)	0.674
Smoking, n (%)	10 (21.7)	9 (19.6)	0.797
Hypertension, n (%)	8 (17.4)	6 (13.0)	0.562
Diabetes mellitus, n (%)	3 (6.5)	2 (4.3)	1.000
Body mass index (kg/m^2)	27.3±4.2	24.9±3.6	0.324
Systolic BP (mmHg)	128±11	125±8	0.191
Diastolic BP (mmHg)	74±10	71±9	0.171
LVEF (%)	65.3±2.5	66.2±3.1	0.878
Total cholesterol, (mg/dL) Median (IQR)	338 (60)	157 (46)	<0.001
LDL–C (mg/dL) Median (IQR)	253 (16)	91 (11)	<0.001
HDL–C (mg/dL)	42 (17)	47 (6)	0.228
Triglyceride (mg/dL)	139±31	83±22	<0.001
eGFR	94±22	89±13	0.652

BP: blood pressure; eGFR: estimated glomerular filtration rate; HDL–C: high–density lipoprotein–cholesterol; FH: familial hypercholesterolemia; LDL–C: low–density lipoprotein–cholesterol; LVEF: left ventricular ejection fraction

Table 2. Comparison of electrocardiographic findings of the patients with FH and control subjects

Variables	Pretreatment (n=46)	Control (n=46)	p
HR, beats/min	65±6.3	65±4.5	0.374
PR, ms	137±21	141±19	0.477
QRS, ms	89±8	91±6	0.731
QT, ms	399±10.5	389±8.5	0.211
QTc, ms	414±19.5	402±16.9	0.087
Tpe–interval, ms	90.7±9.3	77.6±7.3	<0.001
Tpe/QT	0.227±0.02	0.199±0.01	<0.001
Tpe/QTc	0.219±0.02	0.193±0.01	<0.001

The number of patients with 50%≥LDL-C reduction after intensive statin therapy was 20 (43.5%). No significant difference was found between patients with 50%≥LDL-C reduction and without after statin therapy in terms of Tpe-interval (82.3±8.4 vs. 80.6±8.3; p=0.493) and Tpe/QTc ratio (0.204±0.01 vs. 0.200±0.02; p=0.462). A strong and positive correlation was found between basal LDL-C

Figure 1. Comparison of Tpe-interval and Tpe/QTc ratio between FH (pre and post statin therapy) and control group

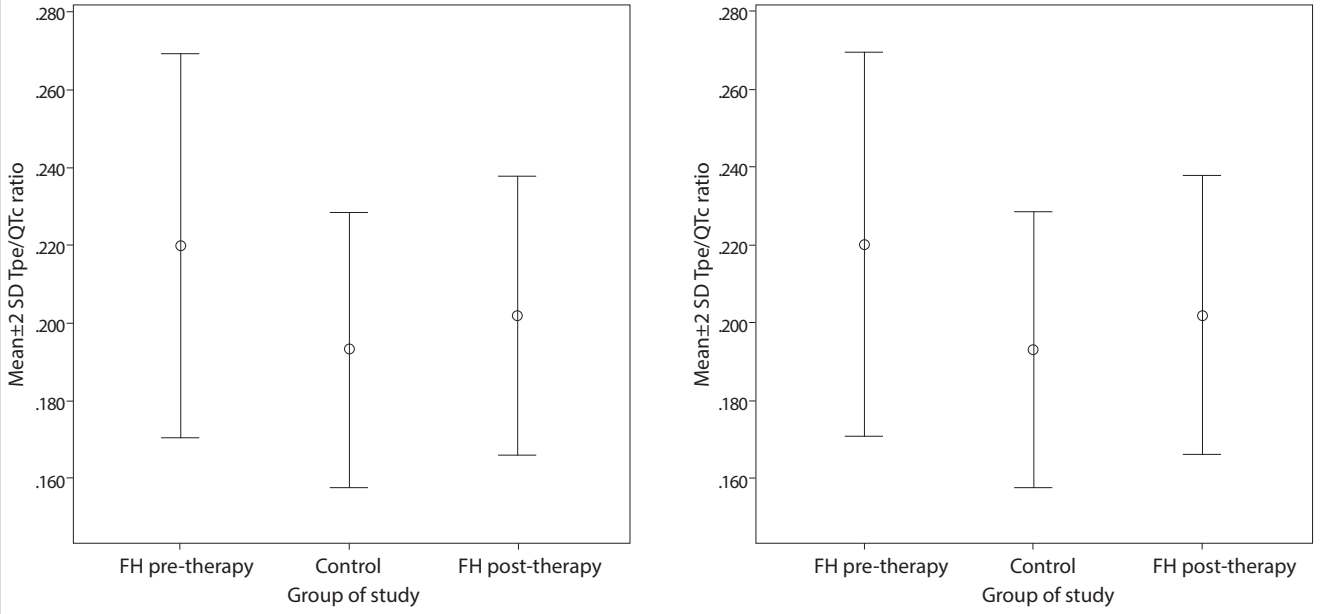
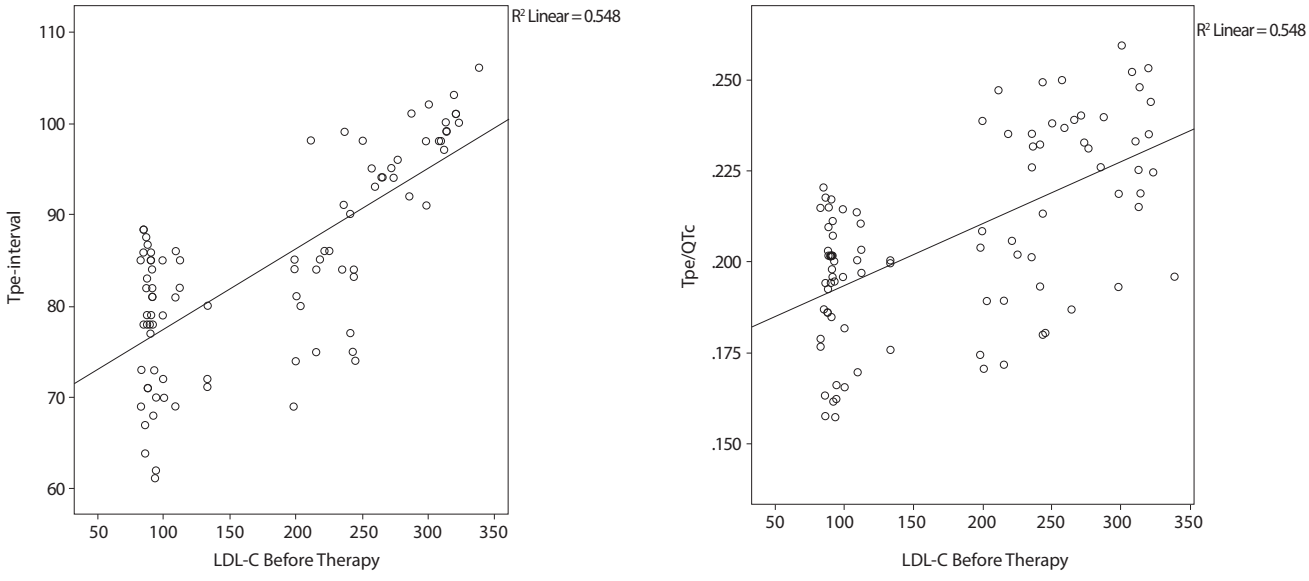


Figure 2. Correlation between TPe-inteval and Tpe/QTc ratio and LDL-C level before therapy



and Tpe-interval (r=0.740, 95% CI: 0.639–0.820; p<0.001) and Tpe/QTc ratio (r=0.597, 95% CI: 0.549–0.706; p<0.001) (Figure 2). However, a significant but weak association was found between LDL-C and Tpe-interval (r=0.349, 95% CI: 0.170–0.512; p<0.001) and Tpe/QTc ratio (r=0.217, 95% CI: 0.001–0.424; p=0.038) after therapy. No significant correlation was found between ΔLDL-C and ΔTpe-interval (r=0.215; 95% CI: −0.356 to −0.561 p=0.172) and ΔTpe/QTc (r=248; 95% CI: −0.50 to −0.566; p=0.113) after statin therapy.

DISCUSSION

In the present study, we showed that Tpe-interval and Tpe/QTc ratio were prolonged in treatment-naive patients with FH as compared to control subjects. Tpe-interval and Tpe/QTc ratio were also shown to be decreased significantly after the statin therapy in patients with FH. To our best knowledge, this is the first report that demonstrated prolonged Tpe-interval and increased Tpe/QTc ratio in FH patients and their improvement after intense LDL-C lowering with statins. Moreover, our results

Table 3. Comparison of electrocardiographic findings of the patients with FH (pre– and posttreatment)

Variables	Pretreatment (n=46)	Posttreatment (n=46)	p
HR, beats/min	65±6.3	63±4.5	0.091
QT, ms	399±10.5	393±9.2	0.608
QTc, ms	414±19.5	404±17.7	0.094
Tpe–interval, ms	90.7±9.3	81.3±8.3	<0.001
Tpe/QT	0.227±0.02	0.206±0.02	<0.001
Tpe/QTc	0.219±0.02	0.201±0.02	<0.001

showed that improvement of ECG parameters might explain effects of intensive statin therapy.

Previous studies have reported that lipid-lowering therapy (LLT) reduces coronary artery events and mortality (14, 15). The beneficial effects of LLT could be attributed to the reduction of ventricular arrhythmias and sudden death (14-16). This hypothesis was first evaluated by De Sutter et al. (17) who reported that in patients with CAD, receiving an implantable cardioverter-defibrillator (ICD), LLT reduction was associated with occurrence of inappropriate shocks. Similarly, Mitchell et al. (18) have shown that LLT was associated with a 40% reduction in relative hazard of recurrence of ventricular tachycardia/fibrillation in patients with an ICD for secondary prevention. In addition, the results of Multicenter Automatic Defibrillator Implantation Trail II (MADIT-II) have shown that use of statin decreases the risk of ventricular fibrillation and sudden cardiac death (19). Vrtovec et al. (20) demonstrated that atorvastatin treatment had shortened the QTc interval and thus might have reduced the risk of arrhythmias in patients with advanced heart failure. These clinical trials supported the evidence of favorable effects of statin on ventricular arrhythmias. Previous experimental studies had also demonstrated that hypercholesterolemia produced significant cardiac proarrhythmic neural and electrical remodeling (1, 21, 22). These neural and electrical remodeling processes may contribute to of the presence of ventricular arrhythmia (1, 21, 23). In their study, Liu et al. (21) showed that hypercholesterolemia-induced significant nerve sprouting and sympathetic hyperintervention, prolonged action potential duration and QTc interval, and increased the repolarization dispersion in a rabbit model. In this study, the researchers had also shown that the neural and electrophysiological remodeling induced by hypercholesterolemia was associated with increased ventricular vulnerability to fibrillation. Simvastatin had shown to significantly reduce the vulnerability of ventricular fibrillation via mechanism of reduction of hypercholesterolemia-induced neural and electrophysiological remodeling in another study conducted by the same researchers (1). Experimental studies provide strong evidence for the hypercholesterolemia-induced life-threatening ventricular arrhythmias. Both experimental and clinical trials support the beneficial effects of statins on life-threatening ventricular arrhythmias.

The T wave is indicative of ventricular repolarization in ECGs. The Tpe-interval is the marker of the total DVR. An increased Tpe-interval is associated with malignant ventricular arrhythmias (24-26). Yayla et al. (27, 28) in their studies, have shown that both Tpe-interval and Tpe/QTc ratio are increased in patients with systemic sclerosis and aortic stenosis that might explain increased frequency of ventricular arrhythmias in these cases.

Tpe/QTc ratio was suggested as a more accurate measure of DVR because Tpe-interval is affected by the variations in body weight and heart rate (8).

Our study showed that both Tpe-interval and Tpe/QTc ratio are markers of ventricular transmural dispersion of repolarization and are significantly longer in FH patients than the control subjects. Our results are in line with previous reports of association between hypercholesterolemia and repolarization dispersion. Our study showed significant decrease in Tpe-interval and Tpe/QTc ratio after LLT with statins. This result is important to provide further evidence for both experimental and clinical studies that evaluated the effects of the statin therapy in ventricular repolarization and life-threatening ventricular arrhythmias.

Our results might be explained by either long-term exposure to high-level LDL-C or beneficial effects of statin therapy. Long-term exposure to elevated LDL-C levels in asymptomatic FH patients might have led to prolonged Tpe-interval and Tpe/QTc ratio because of subclinical atherosclerosis, microvascular dysfunction, and endothelial dysfunction (29-31). Impaired subclinical left ventricular systolic functions had also been shown previously in asymptomatic FH patients compared to control subjects by 2D strain echocardiography (32). Although after intensive statin therapy, Tpe-interval and Tpe/QTc ratio were significantly decreased compared to baseline, but it remained prolonged than control subjects. Additionally, there were no significant differences seen between patients with ≥50% LDL-C reduction attained and without. This result might support the effect of long-term exposure to high levels of LDL-C as a leading cause of prolonged Tpe-interval and Tpe/QTc ratio.

The decrease of Tpe-interval and Tpe/QTc ratio might be explained by possible pleiotropic effects of statin therapy (33). Many studies have shown the effect of statin therapy on regression of atherosclerosis, both in symptomatic and asymptomatic patients (34-36). Kayikcioglu et al. (33) have shown improvement of endothelial functions and normalization of ischemic findings even in normolipidemic patients with cardiac syndrome-x after only 3 months of statin therapy. Therefore, the favorable effect that we observed in the Tpe-interval and Tpe/QTc ratio after such a short statin therapy might be the result of improvement in endothelial functions. Thus, we suggest that with a longer statin therapy it might be possible to normalize the Tpe-interval and Tpe/QTc ratio in FH patients.

Our study has several limitations. It is a single-center study with low number of patients and a short follow-up duration of only 6 months. Therefore, the clinical outcomes such as ventricular

arrhythmic episodes could not be evaluated. Our study population consisted of newly diagnosed treatment-naive FH patients. Moreover, the diagnosis of FH was confirmed genetically in all subjects. Therefore, this population represents a more homogeneous FH population. Another important limitation is that patients received atorvastatin or rosuvastatin, which had different effect on ECG parameters.

CONCLUSION

This prospective observational study presented an evidence that suggested Tpe-interval and Tpe/QTc ratios were increased in treatment-naive FH patients. These parameters were significantly decreased after an intensive statin therapy. These results support the possible effects of hypercholesterolemia and statin therapy on Tpe-interval and Tpe/QTc ratio. All these findings should be confirmed in prospective, multicenter studies. These markers might be better predictor of sudden death and ventricular arrhythmias in FH patients. Therapies such as PCSK9 inhibitors or combination of LLT should be evaluated for their effects on arrhythmogenic substrate in patients with FH.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gaziantep University School of Medicine (2016/104).

Informed Consent: All participants signed informed consent forms before study inclusion.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.K., S.K.; Design - M.K., S.K., E.S.; Supervision E.V., M.K.; Resources - Y.Ç., E.S., E.V.; Materials - M.K., Y.Ç.; Data Collection and/or Processing - M.K., S.K., E.S., Y.Ç.; Analysis and/or Interpretation - E.V., M.K.; Literature Search - M.K., S.K.; Writing Manuscript - S.K, M.K, E.S.; Critical Review - E.V., M.K.; Other - Y.Ç, M.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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