ORIGINAL ARTICLE

Cumulative non-HDL-cholesterol burden in patients with hypertriglyceridemia receiving long-term fibrate therapy: Real life data from a lipid clinic cohort

Uzun dönem fibrat tedavisi alan hipertrigliseridemi hastalarında kümülatif HDL-dışı kolesterol yükü: Bir lipit klinik kohortunun gerçek hayat verileri

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ABSTRACT

Objective: Though epidemiological data suggest that an elevated triglyceride (TG) level may be a risk factor for coronary artery disease (CAD), there is still insufficient clinical evidence. This study was designed to evaluate the real-life efficacy and side effects of fibrate treatment for hypertriglyceridemia seen in a lipid clinic, as well as cardiovascular and diabetic outcomes.

Methods: This retrospective study evaluated patients who were followed-up for a diagnosis of hypertriglyceridemia at the lipid outpatient clinic of the Ege University Cardiology Department between 1997 and 2018. Data of demographic and clinical characteristics were obtained from hospital records. All patients (n=240) with at least 1 year of follow-up were included in the analysis. During follow-up, patients were treated with fenofibrate, and less frequently, gemfibrozile (14 patients), at different doses according to the TG level and disease severity.

Results: Of the study population, 23% had CAD, 21% were diabetic, and 52% were obese. On admission, 20% were using fibrates and 17% were on statins. The mean admission lipid levels were TG: 281±194 mg/dL, low-density lipoprotein cholesterol: 115±37 mg/dL, high-density lipoprotein (HDL) cholesterol: 43±13 mg/dL, and non-HDL cholesterol: 166±42 mg/dL. The mean length of follow-up was 5.3±4.7 years (range: 1–16 years). A total of 8 (4.3%) patients had adverse effects during follow-up (1 on statin combination and 7 on fibrates alone). The side effects observed were an elevation of liver enzymes in 3, myalgia in 2, insomnia in 1, malaise in 1, and a skin rash in 1 patient. No rhabdomyolysis or myopathy was seen. During follow-up, diabetes developed in 14 and cardiovascular disease (CVD) in 14 patients. The cumulative non-HDL cholesterol level was significantly high in patients who developed diabetes or CVD. Receiver operating curve analysis indicated that a cumulative non-HDL cholesterol value of 1016 mg/dL was predictive of the development of diabetes mellitus or CVD with 85% sensitivity and 70% specificity.

Conclusion: In real life, long-term fibrate use is effective and safe. The cumulative non-HDL cholesterol burden can be used to assess the efficacy of treatment as a simple and easily calculated method. Large studies are needed to further clarify the value of this parameter in predicting the development of both diabetes and CVD.

ÖZET

Amaç: Epidemiyolojik veriler artmış trigliserit (TG) düzeylerini koroner arter hastalığı (KAH) için bir risk faktörü olarak göstermekle birlikte hala yeterli klinik kanıt yoktur. Bu çalışma, bir lipit kliniğinin hipertrigliseridemi hastalarında fibrat tedavisinin etkinliği, güvenirliği ile kardiyovasküler, diyabetik sonlanım noktalarına etkisini gerçek yaşam verilerine dayanarak ortaya koymayı amaçlamıştır.

Yöntemler: Bu geriye dönük çalışmada, 1997 ve 2018 yılları arasında Ege Üniversitesi Lipit polikliniğinde hipertrigliseridemi tanısı ile izlenen tüm hastalar değerlendirildi. Hastaların demografik ve klinik özellikleri ile ilgili veriler hastane kayıtlarından elde edildi. Analize en az 1 yıl takip edilen tüm hastalar (n=240) dahil edildi. Takip sırasında hastalar hem TG düzeylerine hem de hastalık şiddetine göre farklı dozlarda fenofibrat ve daha az sıklıkla gemfibrozil (14 hasta) ile tedavi edilmişti.

Bulgular: Çalışma popülasyonun %23'ünde KAH, %21'inde diyabet ve %52'sinde obezite vardı. Başvuru sırasında %20'si fibrat kullanıyordu ve %17'si statin kullanıyordu. Bazal lipit seviyeleri: TG'ler: 281±194 mg/dL; LDL-kolesterol: 115±37 mg/dL, HDL-kolesterol: 43±13 mg/dL; ve HDL-dışı kolesterol 166±42 mg/dL idi. Ortalama takip süresi 5.3±4.7 (1–16) yıldı. Toplam 8 (%4.3) hastanın takip sırasında adres olay gelişmişti (1 statinle kombinasyonunda ve 7 sadece fibratlarda). Yan etkiler, 3 hastada yükselen karaciğer enzimleri, 2 hastada miyalji, 1 hastada uykusuzluk, 1 hastada halsizlik ve 1 hastada deri döküntüsü idi. Hiçbir rabdomiyoliz veya miyopati gözlenmedi. Takip sırasında 14 hastada diyabet, 14 hastada kardiyovasküler hastalık (KVH) gelişti. Lipit polikliniğine izleme dahil olmalarından itibaren hesaplanan kümülatif HDL-dışı kolesterol değeri diyabet veya KVH gelişen hastalarda indeks olay gelişimi sırasında anlamlı olarak yüksekti. ROC analizinde, 1016 mg/dL'lik kümülatif HDL-dışı kolesterol değeri, %85 duyarlılık ve %70 özgüllük ile diabetes mellitus ve KVH gelişimini öngörmüştür.

Sonuç: Gerçek yaşamda uzun süreli fibrat kullanımı etkili ve güvenlidir. Kümülatif HDL-dışı kolesterol yükü, tedavinin etkinliğini değerlendirmek için basit ve kolay hesaplanan bir yöntem olarak kullanılabilir. Hem diyabet hem de KVH'nin gelişimini öngörmede bu parametrenin değerini netleştirmek için daha fazla sayıda ve büyük çalışmalara gereksinim vardır.

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Both epidemiological and genetic studies have suggested that an elevated triglyceride (TG) level increases the risk of cardiovascular (CV) disease.[1–7] A high TG level contributes to an increased CV risk even in patients who have met low-density lipoprotein (LDL) cholesterol goals with statin treatment.[8,9] An elevated TG level, in the fasting and postprandial states, contributes to structural, functional, and metabolic changes in TG-rich lipoproteins, especially in HDL and LDL cholesterol, which leads to more atherogenic LDL and less protective HDL.[10]

Hypertriglyceridemia plays an important role in the development of diabetes mellitus and pancreatitis by causing lipo-apoptosis.[11–14] However, the available clinical trials are not qualitatively or quantitatively sufficient to assess the effects of TG-lowering treatments, such as fibrates, on the development of CV events and/or diabetes.[13,15] The objective of this study was to contribute to filling this gap by evaluating the efficacy, adverse effects, and CV and diabetic outcomes of patients on fibrate treatment for hypertriglyceridemia by examining the non-HDL cholesterol burden observed on a real-life basis in a lipid clinic that has served patients for more than 20 years.

METHODS

This study was conducted using a retrospective evaluation of patients who were followed up with the diagnosis of hypertriglyceridemia in the lipid outpatient clinic of the Ege University Faculty of Medicine between 1997 and 2018. Data of demographic and clinical characteristics, CV risk factors, family history, CV events, pre- and post-treatment lipid profiles, biochemical analyses, concomitant statin use, and adverse effects were obtained from hospital records. During this 20-year period, fibrate therapy was prescribed to more than 500 patients for hypertriglyceridemia. Of these, all patients with at least 1 year of follow-up on fibrate therapy were included in the study. Patients were treated with fenofibrate, and less frequently, gemfibrozil (14 patients), at different doses, according to both the TG levels and disease severity. Patients were grouped according to the time elapsed since the initiation of fibrate therapy: at least 1 year, 3 years, 5 years, 10 years, and 15 years.

The lipid clinic uses a diagnostic work-up and treatment algorithm. A lipid profile (total cholesterol, LDL cholesterol, and TG); measurement of fasting blood glucose (FBG), glycated hemoglobin, and hemoglobin; and liver function and renal function tests are performed at baseline (first admission) for all patients. During follow-up, patient lipid profiles and biochemical parameters are evaluated every 3–6 months according to clinical need. All patients are also routinely screened for atherosclerosis. In addition, patients with hypertriglyceridemia are screened for diabetes and acute pancreatitis when clinically indicated. Lifestyle changes (incresed physcial activity, weight reduction, less/no alcohol comsumption) are recommended to patients with a high TG level for 6 weeks, and if triglyceride goals are not met, drug therapy is initiated.

Abbreviations:

ALT	*Alanine aminotransferase*
AST	*Aspartate aminotransferase*
CAD	*Coronary artery disease*
CI	*Confidence interval*
CV	*Cardiovascular*
CVD	*Cardiovascular disease*
FBG	*Fasting blood glucose*
HDL	*High-density lipoprotein*
LDL	*Low-density lipoprotein*
MS	*Metabolic syndrome*
NCEP ATP III	*National Cholesterol Education Program Adult Treatment Panel III*
ROC	*Receiver operating characteristic*
TG	*Triglyceride*

Efficacy and safety assessment

The lipid clinic records were used to assess the efficacy of lipid treatment. Since there are many measurements in such a long follow-up period, the annual mean level for each lipid parameter was calculated and the percentage change rate was obtained according to the baseline values. The safety profile was assessed based on changes in laboratory parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, uric acid, and creatinine. Patients with clinically significant abnormal laboratory results (ALT or AST >3 x UNL; urea, creatinine, or uric acid >1.5 x UNL) were followed until recovery was achieved. Symptoms such as myalgia, insomnia, fatigue, etc. that may have been related to the treatment were also recorded from the patient charts.

Lipid measurements

All of the laboratory measurements examined were evaluated within the routine procedural work-up of the lipid clinic. Total cholesterol, TG, and HDL cholesterol levels were measured using a Technicon Dax 48 (Bayer AG, Leverkusen, Germany) automated analyzer with blood samples taken follow-

ing 12 hours of fasting. LDL cholesterol levels were calculated using the Friedwald formula. In patients with a TG level >400 mg/dL, the LDL cholesterol level was measured using the enzymatic colorimetric method. The non-HDL cholesterol value was obtained by subtracting the HDL cholesterol value from the total cholesterol value. The decrease in TG and non-HDL cholesterol was calculated using the formula [(final value - pre-treatment value / pre-treatment value) x 100].

Definitions

Hypertension was defined as a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg and/or any antihypertensive treatment. The diagnosis of diabetes was based on a documented FBG level of >126 mg/dL on more than 1 occasion, a postprandial glucose level of >200 mg/dL or a glycated hemoglobin level of >6.5%. Coronary artery disease (CAD) was defined as the presence of past myocardial infarction, coronary angioplasty, and/or coronary artery bypass graft surgery in the patient's personal history. Patients without a previous CV event but with documented ≥50% stenosis in 1 coronary artery based on imaging methods were also accepted to have CAD. The criteria recommended by the International Diabetes Federation were used for the diagnosis of metabolic syndrome (MS) (waist circumference >94 cm for men and >80 cm for women).[16]

Diabetes developing during follow-up was diagnosed based on an FBG level of >126 mg/dL on more than 1 occasion, a postprandial glucose level of >200 mg/dL, or a glycated hemoglobin level of >6.5%. Clinical and angiographic findings of newly developed CAD were also recorded during follow-up. CV events were defined as any cerebrovascular event, proven acute coronary syndrome, and death.

TG levels were classified as normal (<150 mg/dL), high normal (150–199 mg/dL), high (200–499 mg/dL), and very high (>500 mg/dL) according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines during follow-up.[17] The annual mean non-HDL cholesterol value was also obtained (most of the patients had at least 4 measurements per year) and were summed to calculate the total non-HDL cholesterol burden after fibrate treatment through the last recorded visit of the individual patient.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to test normality. All lipid parameters showed skewed distribution except HDL cholesterol. The efficacy measures were analyzed with a paired samples t-test (baseline and post-treatment follow-up values) if normally distributed, and the Wilcoxon rank-sum test was applied for skewed variables. Subgroup analyses were performed for gender, triglyceride level (<150 mg/dL, <200 mg/dL, and <500 mg/dL in follow-up), diabetes, use of fibrate and fibrate-statin combination. A p value of <0.05 (2-sided) was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was used to determine the relationship between the cumulative non-HDL cholesterol burden and the development of diabetes and/or a CV event (disease) during follow-up.

RESULTS

A total of 187 patients (mean age: 49±9.2 years; 37.4% female) who were patients of the lipid outpatient clinic between 1997 and 2018 with a follow-up period of at least 12 months and who were prescribed fibrates due to hypertriglyceyridemia were enrolled in the study. Table 1 shows the clinical and demographic characteristics of the study population. CAD was present in 23.1% of the patients, 44.6% had hypertension, 21.1% had diabetes mellitus, and 74.2% had MS. Half of the study population (52.7%) was obese and 62.4% had a family history of hyperlipidemia. At the time of admission, 20% of the patients were taking a fibrate and 17% were on statin treatment. None of the patients was on a combined therapy of statin and fibrate at admission. By the end of the first year of follow-up, more than half of the patients were on a combined treatment of a statin and a fibrate. The types of statins used were atorvastatin in 78 cases, pravastatin in 5, and rosuvastatin in 14. Only 5 patients were receiving intensive doses.

The mean follow-up period of the study population was 5.3±4.7 years (range: 1–16 years). Table 1 illustrates the clinical characterization of the study population grouped according to the time elapsed since the initiation of fibrate therapy of at least 1 year, 3 years, 5 years, 10 years, and 15 years. The biochemical lab-

Table 1. Baseline demographic and clinical characteristics of the study population by follow-up period

Follow-up	1 year	3 years	5 years	10 years	15 years
N	187	109	80	45	12
Age, years±SD (min-max)	49±9 (17–75)	49±8 (22–66)	49±8 (22–65)	50±7 (22–65)	50±5 (39–58)
Female, n (%)	70 (37.6)	46 (41.5)	45 (51.7)	20 (43.2)	7 (58.3)
Coronary artery disease, n (%)	43 (23.1)	23 (19.8)	19 (24.1)	13 (29.5)	4 (33.3)
Cardiovascular risk factors					
Smoking, n (%)					
Yes	74 (39.2)	52 (48.1)	24 (29.1)	14 (29.5)	4 (33.3)
Quit	27 (14.5)	18 (15.1)	16 (20.3)	11 (25.0)	4 (33.3)
Never	86 (46.2)	39 (36.8)	40 (50.6)	20 (45.5)	4 (33.3)
High blood pressure	83 (44.6)	48 (44.3)	36 (45.6)	22 (48.8)	6 (50)
Type II diabetes mellitus	39 (21)	18 (15.1)	11 (13.9)	3 (5)	1 (8.3)
Obesity	98 (52.7)	57 (49.1)	40 (50.0)	26 (59.1)	9 (75)
Body mass index ≥30 kg/m	50 (26.9)	25 (23.6)	15 (19)	10 (22.7)	2 (16.7)
Metabolic syndrome	138 (74.2)	75 (70.8)	55 (69.6)	32 (72.7)	10 (83.3)
Family history, n (%)					
Coronary artery disease	106 (56.5)	68 (62.3)	50 (63.3)	29 (65.9)	8 (66.7)
Type II diabetes mellitus	88 (47.3)	48 (43.4)	35 (44.3)	21 (47.7)	5 (41.7)
High blood pressure	111 (59.7)	70 (64.2)	44 (55.7)	21 (47.7)	7 (58.3)
Hyperlipidemia	116 (62.4)	66 (60.4)	47 (59.5)	30 (66.6)	9 (75)
Medication use, n (%)					
Statin+ fibrate combination	97 (51.9)	68 (62.3)	55 (68)	33 (73)	9 (75)

SD: Standard deviation; Min: Minimum; Max: Maximum

oratory data are summarized according to the annual follow-up periods in Tables 2A and B.

Efficacy

Baseline and follow-up TG levels are shown in Figure 1. At baseline, the TG level was normal in 1.6% of the cases, high normal in 1.1%, high in 48.1%, and very high in 49.2%. At the end of the first year, the values were 10.7%, 16.6%, 58.3%, and 14.4%, respectively. After the third year, the values were 12.5%, 19.3%, 60.5%, and 7.3% respectively. There were no very high TG values in the groups with 10 and 15 years of treatment, as seen in Figure 1. Evaluation of the percent change in lipid level revealed that there was a statistically significant decrease of 88.2% (95% confidence interval [CI]: 268.5–434.7) in the TG level, 61.4% (95% CI: 11.6–29) in LDL cholesterol level, and 73.2% (95% CI: 33.1–62.9) in the non-HDL cholesterol level after treatment. The HDL cholesterol was significantly greater in 51.3% (95% CI: 2.1–1.1). Figure 2 shows the percent decline in TG and non-HDL cholesterol levels in subsequent years.

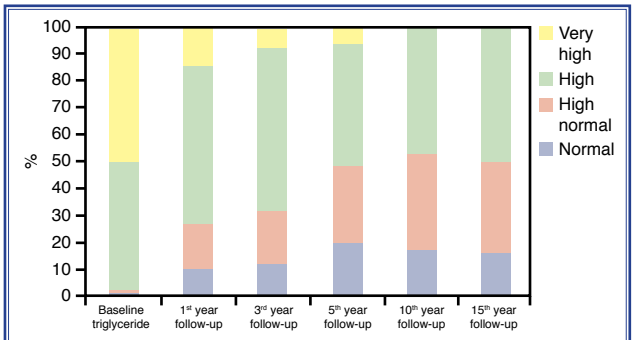


Figure 1. Triglyceride level according to length of follow-up.

Adverse effects

There was no significant change in the level of uric acid, creatinine, urea, or liver enzymes indicative of adverse events in the first year of treatment (Table 2a). A total of 8 (4.3%) patients had adverse effects during follow-up: 1 patient was on a statin combination

Table 2A. Baseline and 1-year follow-up laboratory characteristics

Follow-up	N	All patients	N	1-year follow-up	*p*
Total cholesterol (mg/dL)	187	274±89	187	226±83	0.001
Triglycerides (mg/dL)	187	722±619	187	373±397	0.001
Low-density lipoprotein cholesterol (mg/dL)	182	141±61	185	118±44	0.001
High-density lipoprotein cholesterol (mg/dL)	187	41±10	187	41±11	0.54
Non-high-density lipoprotein cholesterol (mg/dL)	187	233±88	187	185±83	0.001
Uric acid (mg/dL)	187	5.0±1.5	187	4.9±1.4	0.22
Urea (mg/dL)	187	34±10	187	36±10	0.02
Creatinine (mg/dL)	187	0.9±0.6	187	0.9±0.2	0.05
Glycated hemoglobin (%)	187	6.2±3.5	187	5.7±0.9	0.010
Fasting blood glucose (mg/dL)	187	110±39	187	105±29	0.008
Alanine aminotransferase (U/L)	187	22±8	187	22±9	0.15
Aspartate aminotransferase (U/L)	187	27±17	187	27±15	0.55

Paired samples t-test used for normally distributed and Wilcoxon rank-sum test for skewed distributed variables.

Table 2B. Laboratory characteristics during follow-up

Follow-up	3 years	5 years	10 years	15 years
N	109	80	45	12
Total cholesterol (mg/dL)	209±45	200±41	189±37	193±31
Triglycerides (mg/dL)	281±194	253±158	200±61	196±52
Low-density lipoprotein cholesterol (mg/dL)	115±37	110±27	108±31	105±28
High-density lipoprotein cholesterol (mg/dL)	43±13	42±9	42±8	46±9
Non-High-density lipoprotein cholesterol (mg/dL)	166±42	158±43	146±37	148±34
Fasting blood glucose (mg/dL)	103±24	103+17	105±19	105±12
Alanine aminotransferase (U/L)	22±7	24±6	21±5	25±10
Aspartate aminotransferase (U/L)	27±16	29±13	25±13	22±7

and 7 were on fibrates alone. Table 3 is a summary of patient adverse effects. The side effects recorded were an elevation liver enzymes in 3 patients (elevation >3x the upper limit of normal in AST and/or ALT), myalgia in 2 patients, insomnia in 1 patient, weakness in 1 patient, and a skin rash in 1 patient. No rhabdomyolysis or myopathy was observed in any of the patients. In 5 patients with side effects, the drug was discontinued, and the dose was reduced in the other 3 patients.

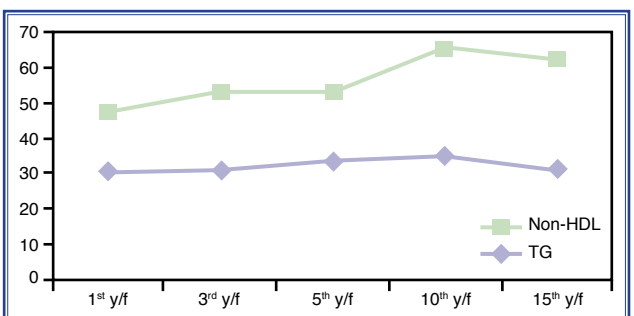


Figure 2. Percent change of triglyceride and non-HDL cholesterol values over time. HDL: High-density lipoprotein; TG Triglycerides; y/f: Year of follow-up.

Clinical follow-up

At baseline, 23.5% of the patients studied had CAD. Of these, 20 (10.7%) had previously undergone percutaneous coronary intervention and 13 (7%) coronary surgery. During follow-up, 14 patients (7.4%) had a new CV event, 9 had CAD, 4 patients had cerebrovascular disease and 1 patient had both CAD and cerebrovascular disease. Only 2 of these events were new. The non-HDL cholesterol level was higher in all cases with CV events; however, the difference was

Table 3. Clinical features of patients with adverse effects during follow-up

	Age	Gender	CAD	DM	Adverse effect	Timing	Statin and dose	Fibrate dose (mg/day)	Result
1	42	F	None	None	Weakness	2nd year	None	250	Dose reduced
2	51	F	None	None	Skin rash	1st year	None	250	Dose reduced
3	52	F	None	None	Insomnia	2nd year	A – 40 mg	250	Started again
4	49	F	None	None	Elevated LFT*	2nd year	None	250	Dose reduced
5	59	F	None	None	Myalgia	1st year	None	250	Medication stopped
6	55	F	None	None	Myalgia	2nd year	None	267	Medication stopped
7	39	M	None	None	Elevated LFT*	2nd year	None	267	Medication stopped
8	39	M	None	None	Elevated LFT*	2nd year	None	267	Medication stopped

A: Atorvastatin; CAD: Coronary artery disease; DM: Type II diabetes mellitus; F: Female; LFT: Liver function test; M: Male *: Alanine aminotransferase or aspartate aminotransferase ≥3 x ULN.

not statistically significant. The cumulative non-HDL cholesterol level was significantly higher in patients with a new CV event compared to those without a new CV event (851 mg/dL vs. 1221 mg/dL, respectively; p=0.025).

New diabetes mellitus was detected in 14 patients (7.5%) during the 1st, 2nd, 3rd, 5th, 6th, 7th, 8th, and 11th years of follow-up. Figure 3 summarizes the evaluation of the TG level according to the NCEP ATP III guidelines in patients with newly developed diabetes mellitus. Only 6 of these patients had diabetes in their family history. The mean baseline TG level of the new diabetes group was 744.1±886.2 mg/dL and the mean baseline non-HDL cholesterol level was 228±44 mg/dL. The cumulative non-HDL cholesterol burden was significantly higher in patients with newly developed diabetes than in those without (822 mg/dL and 1575 mg/dL, respectively; p=0.001). ROC analysis revealed that the cumulative non-HDL cholesterol value of 1016 mg/dL was predictive of the development of diabetes mellitus and CV disease with 85% sensitivity and 70% specificity (Fig. 4).

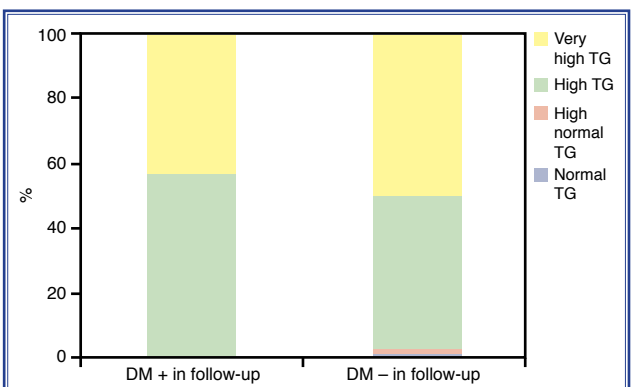
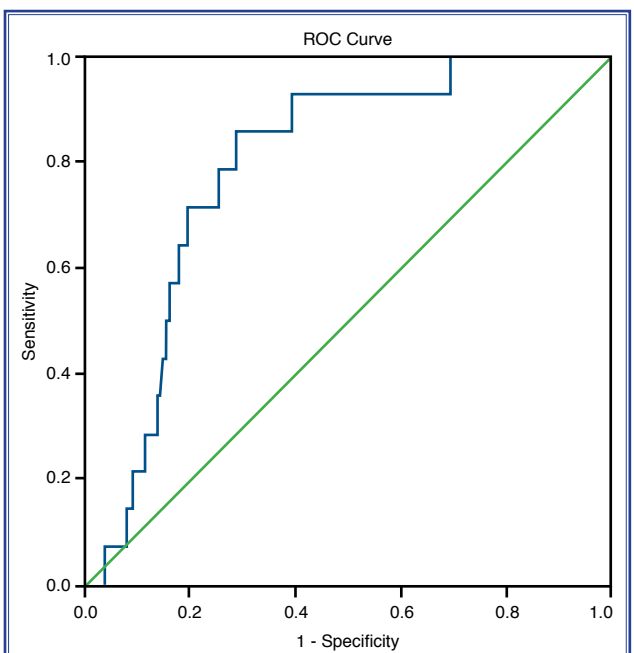


Figure 3. Triglyceride level in patients who developed diabetes during follow-up. National Cholesterol Education Program Adult Treatment Panel III classification used. DM: Diabetes mellitus; TG: Triglyceride.



Area	Std. Errora	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
0.752	0.041	0.0001	0.671	0.833

Figure 4. The receiver operating characteristic (ROC) curve and area under the curve for the total non-high-density lipoprotein cholesterol burden.

DISCUSSION

Fredrickson's classification of dyslipidemia, which was defined more than 50 years ago, emphasizes the contribution of a high TG level to the development of atherosclerosis.[18–20] However, it is still debated whether the TG level is an independent predictor of CVD.[13–21] The NCEP ATP III guidelines identified the TG level as a predictor of CV risk following a meta-analysis.[22] A linear relationship was also found between the TG level and the development of CAD in the Prospective Cardiovascular Munster study, and a TG level of >200 mg/dL was reported to particularly increase the risk.[2] Although the data remain limited, meta-analyses indicate that an elevated TG level, especially in the presence of atherogenic dyslipidemia, is predictive of CVD.[13,23] Moreover, new analysis of the Copenhagen General Population Study has shown that individuals not eligible for statin treatment but with a TG level >264 mg/dL have a greater CVD risk compared with those eligible for statin treatment.[24]

The fact that the results of the few available randomized controlled trials[13,25] with fibrates were not as successful as statins led to the thought that TG-lowering treatment would be ineffective in the prevention of CV events. However, the study subjects were not usually enrolled according to TG level, and most studies were conducted on patients with diabetes and mildly elevated TG levels.[13,26] Moreover, these fibrate studies were not designed to discover the real efficacy of TG-lowering therapy in the prevention of CV events.[13] The recent REDUCE-IT trial (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial), designed to test the effect of TG lowering using omega-3 acids in high-risk patients with a severely elevated TG level, showed a significant reduction in CV events.[27]

The present study is an evaluation of real-life data of a mean 5.3-year use of fibrates in a lipid clinic. This long-term follow-up with fibrate treatment (primarily fenofibrate) showed a significant and sustained reduction of 88.2% in TG levels, 61.4% in LDL cholesterol levels, and 73.2% in non-HDL cholesterol levels, without severe adverse effects. Curiously, the frequency of side effects in such a long follow-up was significantly lower than that reported in large trials. This may be due to frequent and careful monitoring of the patients by a specialized prevention team.

In the present study, diabetes developed in 14 patients and CVD, including cerebrovascular disease, in 14 patients. Analysis also revealed that a subgroup of patients had a sustained high TG level during treatment. Moreover, the cumulative non-HDL cholesterol was significantly high in patients who developed diabetes or CVD. Non-HDL cholesterol is accepted as an indicator of atherogenic dyslipidemia and suggested as a treatment target following LDL cholesterol, especially in hypertriglyceridemic states, in recent guidelines.[15]

To the best of our knowledge, this study is the first to define and assess cumulative non-HDL cholesterol for the development of CV events. In the literature, the cumulative LDL cholesterol was calculated in a limited number of patients with familial hypercholesterolemia to determine the total cholesterol exposure and was reported to be associated with CV event development.[28] The cumulative non-HDL cholesterol level we used may be indicative of exposure to atherogenic dyslipidemia.

A high TG level generates a lipo-toxic effect and impairs insulin secretion of beta cells;[11,12,29] therefore, chronic elevation of the TG level is speculated to cause or accelerate the development of type II diabetes.[30] The significantly high cumulative non-HDL cholesterol level in our newly diabetic patients might substantiate this hypothesis.

The high number of patients lost to follow-up and the lack of a control group are limitations of the present study. The retrospective design may also be a limitation; however, it was the only way to examine long-term, real-world management of these patients. Lifestyle has a significant impact on the TG level, which may affect the ability to measure the long-term efficacy of TG-lowering therapy. However, we only enrolled patients whose TG level had not decreased after 6 weeks of lifestyle changes to lower the TG level. The single-center nature of the study may also be accepted as a limitation. However, this is a first description of cumulative non-HDL-cholesterol and real-life data for a very long (>20 years) period of fibrate treatment. In the literature, there is only 1 other such long-running fibrate study that shared data from a lipid clinic. The analysis of 10 years of fibrate use in 189 patients revealed effective lowering of TG levels with very few adverse events, similar to our results.[31]

The high rate of combination therapy with statins in our study population might be a limitation, as statin usage might also affect the clinical results and non-HDL cholesterol levels. However, since guidelines suggest statins as the first-line therapy for high-risk patients with an elevated TG level, it's impossible to discriminate statin users from fibrate-only patients in a real-life setting of such a high risk population (74.2% with MS and 23.1% with CAD at baseline). This study was not designed to test the effect of fibrate therapy on CV events or diabetes development. Rather, it was designed to evaluate the efficacy, adverse effects, and both CV and diabetic outcomes of patients on fibrate therapy for elevated TG levels in a real-life setting.

In conclusion, our study emphasizes the importance of cumulative non-HDL cholesterol burden, a sign of TG elevation in association with atherogenic dyslipidemia. Real-life data indicated that long-term fibrate use is effective and safe. The cumulative non-HDL cholesterol burden, described for the first time in our study, is a simple and easily calculated method that can be used to assess the efficacy of treatment. Additional large studies are needed to clarify the value of this parameter in predicting the development of both diabetes and CVD.

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REFERENCES

1. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA 2007;298:299–308. [CrossRef]
2. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 2007;115:450–8. [CrossRef]
3. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. JAMA 2008;300:2142–52. [CrossRef]
4. Nordestgaard BG. Triglyceride-Rich Lipoproteins and Atherosclerotic Cardiovascular Disease: New Insights From Epidemiology, Genetics, and Biology. Circ Res 2016;118:547–63. [CrossRef]
5. Faergeman O, Holme I, Fayyad R, Bhatia S, Grundy SM, Kastelein JJ, et al. Plasma triglycerides and cardiovascular events in the Treating to New Targets and Incremental Decrease in End-Points through Aggressive Lipid Lowering trials of statins in patients with coronary artery disease. Am J Cardiol 2009;104:459–63. [CrossRef]
6. Ference BA. Using Genetic Variants in the Targets of Lipid Lowering Therapies to Inform Drug Discovery and Development: Current and Future Treatment Options. Clin Pharmacol Ther 2019;105:568–81. [CrossRef]
7. Ference BA. Causal Effect of Lipids and Lipoproteins on Atherosclerosis: Lessons from Genomic Studies. Cardiol Clin 2018;36:203–11. [CrossRef]
8. Cziraky MJ, Watson KE, Talbert RL. Targeting low HDL-cholesterol to decrease residual cardiovascular risk in the managed care setting. J Manag Care Pharm 2008;14:S3–S31.
9. Alagona P Jr. Beyond LDL cholesterol: the role of elevated triglycerides and low HDL cholesterol in residual CVD risk remaining after statin therapy. Am J Manag Care 2009;15:S65–S73.
10. Gotto AN, Pownall HJ. Lipid regulating drugs and LDL apheresis. In: Gotto AN, Pownall HJ, editors. Manual of Lipid Disorders: Reducing the Risk for Coronary Heart Disease. 2nd ed.Baltimore: Lippincott Williams & Wilkins; 1999. p. 292-328.
11. Unger RH, Clark GO, Scherer PE, Orci L. Lipid homeostasis, lipotoxicity and the metabolic syndrome. Biochim Biophys Acta 2010;1801:209–14. [CrossRef]
12. Seghieri M, Tricò D, Natali A. The impact of triglycerides on glucose tolerance: Lipotoxicity revisited. Diabetes Metab 2017;43:314–22. [CrossRef]
13. Ferrari R, Aguiar C, Alegria E, Bonadonna RC, Cosentino F, Elisaf M, et al. Current practice in identifying and treating cardiovascular risk, with a focus on residual risk associated with atherogenic dyslipidaemia. Eur Heart J Suppl 2016;18:C2–C12. [CrossRef]
14. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, et al. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol 2014;2:655–66. [CrossRef]
15. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman

MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. [Article in English, Spanish] Rev Esp Cardiol (Engl Ed) 2017;70:115.
16. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet 2005;366:1059–62. [CrossRef]
17. 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;285:2486–97. [CrossRef]
18. Fredrickson DS, Lees RS. A system for phenotyping hyperlipoproteinemia. Circulation 1965;31:321–7. [CrossRef]
19. Fredrickson DS. An international classification of hyperlipidemias and hyperlipoproteinemias. Ann Intern Med 1971;75:471–2. [CrossRef]
20. McCullough PA, Ahmed AB, Zughaib MT, Glanz ED, Di Loreto MJ. Treatment of hypertriglyceridemia with fibric acid derivatives: impact on lipid subfractions and translation into a reduction in cardiovascular events. Rev Cardiovasc Med 2011;12:173–85.
21. Gotto AM Jr. Triglyceride as a risk factor for coronary artery disease. Am J Cardiol 1998;82:22Q–5Q. [CrossRef]
22. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–39.
23. Maki KC, Guyton JR, Orringer CE, Hamilton-Craig I, Alexander DD, Davidson MH. Triglyceride-lowering therapies reduce cardiovascular disease event risk in subjects with hypertriglyceridemia. J Clin Lipidol 2016;10:905–14. [CrossRef]
24. Madsen CM, Varbo A, Nordestgaard BG. Unmet need for primary prevention in individuals with hypertriglyceridaemia not eligible for statin therapy according to European Society of Cardiology/European Atherosclerosis Society guidelines: a contemporary population-based study. Eur Heart J 2018;39:610–9. [CrossRef]
25. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–61. [CrossRef]
26. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–74. [CrossRef]
27. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med 2019;380:11–22. [CrossRef]
28. Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. J Lipid Res 2009;50:S172–S7.
29. Barbagallo CM, Averna MR, Citarrella R, Rizzo M, Amato M, Noto D, et al. Transient chylomicronemia preceding the onset of insulin-dependent diabetes in a young girl with no humoral markers of islet autoimmunity. Eur J Endocrinol 2004;150:831–6. [CrossRef]
30. Ayvaz G, Balos Törüner F, Karakoç A, Yetkin I, Cakir N, Arslan M. Acute and chronic effects of different concentrations of free fatty acids on the insulin secreting function of islets. Diabetes Metab 2002;28:3S7–3S112.
31. Mombelli G, Banfi F, Falcioni S, Sirtori CR. Persistently increased HDL-cholesterolemia and reduced triglyceridemia in a large lipid clinic population treated with fenofibrate for 15 years or longer. Int J Cardiol 2009;133:412–4. [CrossRef]

Keywords: Cumulative non-high-density lipoprotein cholesterol burden; fibrates; long-term lipid changes; triglycerides.

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