The Achievement of Non-high-density Lipoprotein Cholesterol Target in Patients with Very High Atherosclerotic Cardiovascular Disease Risk Stratified by Triglyceride Levels Despite Statin-controlled Low-density Lipoprotein Cholesterol

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ABSTRACT

Objectives: We sought to estimate the percentage achievements of non-high-density lipoprotein cholesterol (non-HDL-C) target in patients with very high atherosclerotic cardiovascular diseases (ASCVD) risk stratified by triglyceride (TG) levels despite statin-controlled low-density lipoprotein cholesterol (LDL-C) in the Centralized Pan-Middle East Survey on the under treatment of hypercholesterolemia. *Methods*: The non-HDL-C target achievement in patients with diabetes mellites (DM) and patients with established ASCVD was defined according to European Society of Cardiology and European Atherosclerosis Society 2019 guidelines for managing dyslipidemia. Patients were stratified to controlled LDL-C defined as < 70 mg/dL (< 1.8 mmol/L) with normal TG < 150 mg/dL (< 1.7 mmol/L) and high TG between 150–400 mg/dL (1.7–4.5 mmol/L). *Results:* The mean age of our cohort was 58.0±11.0 years, 6.8% (n = 717) were male, 9.7% (104) were smokers, and 48.4% (n = 518) had body mass index of ≥ 30 kg/m². Those with high TG levels male (76.5% vs. 63.8%; $p < 0.001$), smokers (16.1% vs. 7.7%; $p < 0.001$), have metabolic syndrome (77.6% vs. 17.1%; $p < 0.001$), and low HDL-C levels (79.2% vs. 49.4%; $p < 0.001$). The majority (93.9%, n = 1008) were on statins (atorvastatin and rosuvastatin) with only 2.2% (n = 24) on the combined statins plus fenofibrate/gemfibrozil. Only 27.4% (n = 294) of patients had non-HDL-C goal attainment. Goal attainment rates in patients with diabetes (3.1%

vs. 34,4%; $p < 0.001$), coronary artery disease (CAD) (2.4% vs. 37.9%; $p < 0.001$), diabetes plus CAD (0% vs. 40.0%; $p < 0.001$), and CVD (0% vs. 30.0%; $p = 0.048$) were significantly lower in those with higher TG levels. *Conclusions:* A large proportion of statin-controlled LDL-C diabetic patients and patients with established ASCVD with high TGs did not achieve the non-HDL-C target. Our study did not demonstrate an association between ASCVD and high TG levels; and therefore, a follow-up study is highly required to assess long-term ASCVD outcomes in this cohort.

Despite the wide spread of statin use in Arabian Gulf countries, patients with very high risk for atherosclerotic cardiovascular diseases (ASCVD), like diabetic patients with multiple risk factors, patients with severe familial hypercholesterolemia, and patients with established ASCVD remain at very high risk of residual cardiovascular and recurrent cardiovascular events.[1–5]

Several studies have demonstrated a strong association between high triglycerides (TG) and high triglyceride-rich lipoproteins (TRLs) and cardiovascular events.[6–8] Non-high-density lipoprotein cholesterol (non-HDL-C) is a good measure of all atherogenic lipoproteins and defined as:

$$\text{non-HDL-C} = \text{total cholesterol (TC)} - \text{HDL-C.}$$

Hence, regional Middle East consensus papers highly recommend the use of low-density lipoprotein cholesterol (LDL-C) in combination with non-HDL-C as primary therapeutic targets to reduce the risk of future and recurrent cardiovascular events, especially in patients with diabetes mellites (DM) and established ASCVD.[9,10]

We sought to estimate the achievement of the non-HDL-C target in patients with very high ASCVD risk stratified by TG levels despite statin-controlled LDL-C in the Centralized Pan-Middle East Survey on the Undertreatment of Hypercholesterolemia (CEPHEUS).

METHODS

The details of this study have already been described.[11] Briefly, the CEPHEUS study was a multi-center non-interventional survey of patients on lipid-lowering drugs (LLDs) in six Arabian Gulf countries (Saudi Arabia, UAE, Oman, Qatar, Bahrain, and Kuwait). A total of 5276 patients were enrolled in this survey from outpatient clinics by 177 specialists and primary care physicians. The study was conducted between 22 November 2009 and 7 July 2010. The inclusion criteria were: patients ≥ 18 years old taking LLDs for ≥ 3 months, with no dose change for a minimum of six weeks.

A fasting blood sample was taken from each subject to measure TC, HDL-C, TG, apolipoprotein A1 (apo A1), apo B, glucose, and glycated hemoglobin. LDL-C was calculated using Friedewald's formula. Non-HDL-C was calculated using the following formula:

$$\text{non-HDL-C} = \text{TC} - \text{HDL-C.}$$

Blood samples were collected in three tubes (5 mL in a gel tube, 2 mL in a fluoride tube, and 2 mL in an EDTA tube). All blood samples were shipped by air courier, and the tests were performed at the King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia). All the laboratory tests underwent internal and external quality control checks. In this study, we only included patients with very high ASCVD risk status (DM with major risk factors and patients with established ASCVD) defined by the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) 2019 guidelines for the management of dyslipidemia.[12] These patients were further stratified into controlled LDL-C defined as < 70 mg/dL (< 1.8 mmol/L) with normal TG < 150 mg/dL (< 1.7 mmol/L) and high TG between 150–400 mg/dL (1.7–4.5 mmol/L).[13] The non-HDL-C target was defined as < 100 mg/dL (< 2.6 mmol/L).[13] Low HDL-C was defined < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women.[13]

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between
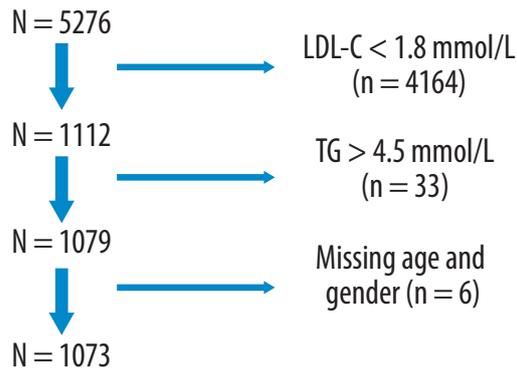
Figure 1: Schematic diagram of the patient flow of theCentralized Pan-Middle East Survey on the Undertreatment of Hypercholesterolemia study.

groups were analyzed using Pearson's chi-squared tests (or Fisher's exact tests for cells < 5). For continuous variables, mean and standard deviation were used to summarize the data. Analyses were performed using Student's *t*-test. An a *priori* two-tailed level of significance was set at 0.05. Statistical analyses were conducted using STATA version 16.1 (STATA Corporation, College Station, TX, USA).

This study complied with the Declaration of Helsinki. The study had approval from the internal review bodies/ethics committees of each participating institution in the Arabian Gulf countries. Informed written consent was also obtained from all patients enrolled in the study.

RESULTS

The full CEPHEUS cohort consisted of 5276 patients. However, this study included only 1112 patients who had controlled LDL-C (< 1.8 mmol/L). Furthermore, we only recruited those with TG levels of ≤ 4.5 mmol/L (n = 1079). Six patients with missing age and gender were excluded from the analysis with the final working sample of 1073 patients [Figure 1]. The overall mean age was 58.0±11.0 years, 66.8% (n = 717) were male, 9.7% (518/1070) were smokers, and 48.4% (n = 518) had BMI ≥ 30 kg/m². The proportion of patients that had metabolic syndrome (MetS), DM, and CAD were 31.8% (338/1064), 73.0% (n = 780), and 48.7% (n = 523), respectively. The proportion of patients with high TG levels (≥ 1.7–4.5 mmol/L) was 23.8% (n = 255).

As shown in Table 1, those with high TG levels were male (76.5% vs. 63.8%; *p* < 0.001), smokers (16.1% vs. 7.7%; *p* < 0.001), have MetS (77.6% vs. 17.1%; *p* < 0.001), and low HDL-C levels (79.2% vs. 49.4%; *p* < 0.001). As outlined in Table 2, 93.9% (n = 1008) were on statins (atorvastatin and rosuvastatin) with only 2.2% (n = 24) on the combined statins plus fenofibrate/gemfibrozil.

Only 27.4% (n = 294) of patients had non-HDL-C goal attainment. Goal attainment rates in DM (3.1% vs. 34.4%; *p* < 0.001), CAD (2.4% vs.37.9%; *p* < 0.001), DM plus CAD (0% vs. 40.0%; *p* < 0.001), and CVD (0% vs. 30.0%; *p* = 0.048)

Table 1: Demographic and clinical characteristics.

Characteristics	All (N = 1073) n (%)	Triglyceride levels		*p*-value
		< 1.7 mmol/L (n = 818) n (%)	≥ 1.7–4.5 mmol/L (n = 255) n (%)	
Age, years, mean±SD	58.0 ± 11.0	59.0 ± 11.0	57.0 ± 10.0	0.017
Gender, male	717 (66.8)	522 (63.8)	195 (76.5)	< 0.001
Smoker	104 (9.7)	63 (7.7)	41 (16.1)	< 0.001
BMI ≥ 30, kg/m² (n = 1070)	518 (48.4)	387 (47.3)	131 (51.4)	0.278
MetS (n = 1064)	338 (31.8)	140 (17.1)	198 (77.6)	< 0.001
Low HDL-C	606 (65.5)	404 (49.4)	202 (79.2)	< 0.001
Family history of CVD	228 (21.2)	164 (20.0)	64 (25.1)	0.085
Diabetes mellitus	780 (73.0)	585 (72.7)	195 (76.5)	0.121
Hypertension	789 (73.5)	595 (72.7)	194 (76.1)	0.291
Coronary artery disease	523 (48.7)	398 (48.7)	125 (49.0)	0.919
Peripheral artery disease	31 (2.9)	23 (2.8)	8 (3.1)	0.786
CVD	51 (4.8)	40 (4.9)	11 (4.3)	0.706

BMI: body mass index; MetS: metabolic syndrome; CVD: cerebrovascular disease; HDL-C: high-density lipoprotein cholesterol.
Low HDL-C < 1.0 mmol/L in males and < 1.3 mmol/L in females.

Table 2: Medication history.

Characteristics	All (N = 1073) n (%)	Triglyceride levels		p-value
		< 1.7 mmol/L (n = 818) n (%)	≥ 1.7–4.5 mmol/L (n = 255) n (%)	
Statin therapy only	1008 (93.9)	774 (94.6)	234 (91.8)	0.095
Ezetimibe-Simvastatin	3 (0.3)	1 (0.1)	2 (0.8)	0.116
Statin+(fenofibrate/gemfibrozil)	24 (2.2)	15 (1.8)	9 (3.5)	0.11

Table 3: Non-high-density lipoprotein cholesterol goal achievements (< 2.6 mmol/L) stratified by diabetes mellitus (DM), coronary artery disease (CAD), and cerebrovascular disease (CVD).

Characteristics	All (N = 1073) n (%)	Triglyceride levels		p-value
		< 1.7 mmol/L (n = 818) n (%)	≥ 1.7–4.5 mmol/L (n = 255) n (%)	
All	294 (27.4)	284 (34.7)	10 (3.9)	< 0.001
DM (n = 780)	207 (26.5)	201 (34.4)	6 (3.1)	< 0.001
CAD (n = 523)	154 (29.4)	151 (37.9)	3 (2.4)	< 0.001
DM+CAD (n = 359)	104 (29.0)	104 (40.0)	0	< 0.001
CVD (n = 51)	12 (24.5)	12 (30.0)	0	0.048

patients were significantly lower in those with higher TG compared to those with lower TG levels [Table 3].

DISCUSSION

This study evaluated the achievement of the non-HDL-C target < 100 mg/dL (< 2.6 mmol/L) in patients with very high ASCVD risk (DM with major risk factors and patients with established ASCVD) and high TG 150–400 mg/dL (1.7–4.5 mmol/L) versus normal TG < 150 mg/dL (< 1.7 mmol/L) despite statin-controlled LDL-C < 70 mg/dL (< 1.8 mmol/L). Non-HDL-C was achieved in 3.9% in patients with very high TG compared to 34.7% in patients with normal TG levels ($p < 0.001$).

Patients with high TG levels were younger and had a higher rate of smoking, MetS, and low HDL-C than patients with low TG levels. Even though most patients were on statins, only a small percentage were on combination therapies (2.2%) that specifically target the lowering of TG in both groups. Hence, this could explain the small percentage of patients achieving the non-HDL-C in both groups. Patients with high TG, low HDL-C, and high risk for ASCVD can benefit from the combination therapies of fibrate and omega 3, as shown by many studies.[14–16]

We found no association between ASCVD and high TG levels. This contrasts with the study by Nicholos et al,[17] which demonstrated greater CV events in patients with DM with high TG levels and controlled LDL-C. The small sample size could explain our findings. Our study was not intended to look at the CV events. Several epidemiological, genetic studies, and post-hoc analyses of clinical trials demonstrated strong associations between high TG, TRLs, and ASCVD.[4–6] Moreover, lower on-treatment TG level was associated with lower CV risk.[18,19]

Patients with DM and established ASCVD should be recommended to adhere to lifestyle intervention and evidence-based CV therapies.[20] Statins are still considered the first-line therapeutic option to reduce LDL-C levels to the recommended therapeutic targets in these very high risk patients. Statins can be used as monotherapy or in combination with other treatments like ezetimibe and monoclonal PCSK9 inhibitors.[12] Despite the current best treatments, patients continue to experience residual CV risk, especially in patients with high TG and low HDL-C.[12] In the Fenofibrate Intervention and Event Lowering in Diabetes[12] and The Action to Control Cardiovascular Risk in Diabetes[15] clinical trials in diabetic patients with the

subpopulation with atherogenic dyslipidemia (high TG and low HDL-C), the use of fibrate therapies alone or in combination with a statin, resulted in a significant 27% and 31% risk reduction of CV events, respectively. Moreover, the use of 4 g/d of the highly purified omega-3 fatty acid icosapent ethyl in combination with a statin in the Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial, in patients with elevated TG and DM or established ASCVD, resulted in a significant 25% and 20% risk reduction in CV events and CV mortality, respectively.[16]

Non-HDL-C is a good measure of all atherogenic lipoproteins, including LDL, very LDL, intermediate-density lipoprotein, and lipoprotein a. Several studies have shown non-HDL-C to have a better predication of ASCVD risk than LDL-C.[21–23] Moreover, many international lipid guidelines consider non-HDL-C as a primary or secondary therapeutic target, especially in patients with high TG and TRLs found in high prevalence in patients with DM.[12,20,24,25] Both the Middle East lipid consensus papers (2016 and the updated 2021)[9,10] recommend a 50% reduction and < 70 mg/dL (< 1.8 mmol/L) for LDL-C in addition < 100 mg/dL (< 2.6 mmol/L) for non-HDL-C as primary targets in patients with very high risk including DM and established ASCVD.

Our study has important limitations. This study was an observational cross-sectional trial that did not assess long-term outcomes. We assessed TG levels, other cardiometabolic risk factors, and ASCVD at entry level and did not evaluate the impact of changes during follow-up. Observational real word data does not establish causality but provides important data concerning risk and associations as seen in clinical practice. The population studied is relatively small, and considerable variability in practice patterns across the countries exists, and probably even among study site; therefore, caution should be exercised when extrapolating the results to the general population.

CONCLUSION

A large proportion of statin-controlled LDL-C diabetic patients and patients with established ASCVD with high triglycerides did not achieve the non-HDL-C target. The current study did not demonstrate an association between ASCVD and high TG levels, and a follow-up study is required to assess long-term ASCVD outcomes in this cohort.

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