Journal of Medical Research and Health Sciences
Received 16 July 2021 | Revised 5 Aug 2021 | Accepted 30 Aug 2021 | Published Online 28 Sep 2021

DOI: https://doi.org/10.52845/JMRHS/2021-4-9-7
JMRHS 4 (9), 1476–1481 (2021)

ISSN (O) 2589-9031 | (P) 2589-9023

RESEARCH ARTICLE

Title "Plasma Triglyceride levels Increase the Risk for Recurrent Cardiovascular Disease Independent of High-Density Lipoprotein Cholesterol Level"

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Abstract

Background: Plasma triglyceride (TG) levels are known to confer an increased risk of vascular disease in healthy populations, but data in high-risk patients are scarce. In this study we evaluated the risk on recurrent vascular events conferred by increased plasma TG levels in patients with various clinical manifestations of vascular disease. **Objective:** To assess the Plasma triglyceride levels increase the risk for recurrent Cardiovascular Disease Independent of High-Density Lipoprotein Cholesterol Level.

Methods: This study was done in the Department of Cardiology, Community Based Medical College & Hospital, Bangladesh during July 2017 to June 2020. A Meta-analysis of Population Based prospective Studies of 5731 patients with clinically manifest vascular disease. **Results:** First new vascular events (myocardial infarction, ischemic stroke, vascular death) occurred in 782 subjects during a median follow-up of 4.9 years (interquartile range 2.5–8.1 years). Patients in the highest plasma TG quintile (> 2.24 mmol/L) had a higher risk for recurrent vascular events (HR 1.45; 95%CI 1.13–1.86) compared with the lowest plasma TG quintile (b0.97 mmol/L) after adjustments for age, gender, body mass index, smoking, lipid-lowering medication and low-density lipoprotein-cholesterol. The increased risk associated with increasing plasma TG levels was irrespective of the presence of type 2 diabetes (T2DM), but only present in patients without the metabolic syndrome. Furthermore, the increased risk was particular-ly present in patients with coronary artery disease (CAD) (HR 1.45; 95%CI 1.02–2.08) and was not modified by other lipid levels (p-value for interaction >0.05). Plasma TG still contributed to vascular risk when other lipid levels were at target level.

Conclusions: Higher plasma TG levels are associated with increased risk for recurrent vascular events, in par-ticular in CAD patients. This increased risk is independent of the presence of T2DM and the use of lipid-lowering medication and is not modified by other lipid levels.

Keywords: Triglycerides, Lipoproteins, Vascular disease, Secondary prevention.

1 | INTRODUCTION

Patients with clinical manifestations of vascular diseases are at high risk for new vascular events, and due to improved medical treatment and an aging population, their number is increasing. Although these patients are treated intensively for cardiovascular risk factors, they are still at considerable risk for a recurrent vascular event. Due to an increasing prevalence of obesity and obesity-related insulin resistance, the number of individuals with hypertriglyceridemia is rising (1) (2) . Elevated plasma triglyceride (TG) levels lead to an atherogenic lipoprotein phenotype consisting of high plasma TG levels, low high-density lipoprotein cholesterol (HDL-C) levels and small dense low-density lipoprotein (HDL) particles (3). Therefore, hypertriglyceridemia could contribute to the re-sidual risk and it would be important to assess the risk associated with plasma TG levels on recurrent vascular events in these high-risk patients against a background of well treated risk factors, including widespread use of statin therapy. Plasma TG level has been shown to be an independent risk factor for vascular events in healthy populations (4) (5) and in trials with pa-tients with coronary artery disease (6) (7) . However, drugs lowering plasma TG levels have not clearly proven to be effective in preventing vascular events (8) (9) . Therefore TG levels are not defined as a treatment target in current guidelines, although a TG level of b1.7 mmol/L is propagated as desirable (10) (11). Instead, high density lipoprotein-cholesterol is advocated as a treatment target in patients with hypertriglyceridemia, as also includes TG-rich VHDL-particles (10) (11) . However, it is unclear whether plasma TG levels by itself still add to the risk associated with higher HDL-C levels. In the present study the risk of plasma TG levels for recurrent vascu-lar events in patients with different manifestations of arterial vascular disease was determined. Furthermore, it was evaluated whether this as-sociation was present irrespective of the presence of type 2 diabetes (T2DM) or the metabolic syndrome, the use of lipid-lowering medica-tion, and the location of vascular disease. Finally, modification of the ef-fect of plasma TG levels on vascular events by the level of several other lipoproteins HDL-C and total cholesterol (TC)/HDL-C ratio) was investigated. (12) (13)

2 | METHODS

This study was done in the Department of Cardiology, Community Based Medical College & Hospital, Bangladesh during July 2017 to June 2020. A Meta-analysis of Population Based prospective Studies of 5731 patients with clinically manifest vascular disease. For the present study, data were used from the Second Manifestations of ARTerial disease (SMART) cohort. This is a Meta-analysis of Population Based prospective Studies, designed to establish the presence of concomitant arterial diseases and risk factors for atherosclerosis in patients with known arterial disease or a cardiovascular risk factor, who were newly referred to the Department of Cardiology, Community Based Medical College & Hospital, Bangladesh. All patients gave written informed consent hospital approved the study. After informed consent, patients underwent a vascular screening protocol including a health questionnaire, laboratory measurements and physical ex-amination. For these analyses, TG was log transformed to have a normal distribution and used as a continuous variable. In order to test for interaction, i.e. whether the relation between plasma TG levels and vascular events was modified by HDL-C category, we included these interaction terms in the Cox model. If the p-value of the interaction term was b0.05, effect-modification was considered present. Analyses were performed using the statistical package Predictive Analytics Soft-Ware (PASW) Statistics 19. For all analyses, P-Value <0.05 was considered significant.

Supplementary information The online version of this article (https://doi.org/10.52845/JMRHS/2021-4-9-7) contains supplementary material, which is available to authorized users.

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3 | RESULTS

Baseline characteristics of the study population according to quin-tiles of plasma TG are presented in (Table 1). The prevalence of the met-abolic syndrome increases from 14% in quintile 1 to 80% in quintile 5. With increasing quintiles of plasma TG, the proportion of current smokers increased, paralleled by an increase in the incidence of peripheral artery disease. During a median follow-up of 4.9 years (interquartile range 2.5–8.1 years), 782 first new vascular events occurred. Overall, 193 (non-)fatal ischemic strokes, 451 (non-)fatal myocardial infarctions and 473 vascular deaths occurred. As shown in (Table 2), the risk of vascular events increased across quintiles of plasma TG and was 45% higher in the highest quintile (HR 1.45; 95%CI 1.13–1.86) compared to the lowest quintile (model 2 for the combined endpoint. P for trend across quintiles was 0.002. The risk for ischemic stroke was 47% higher in the highest TG quintile (HR 1.47; 95%CI 0.89–2.42) compared to the lowest TG quin-tile, the risk for myocardial infarction 56% higher (HR 1.56; 95%CI 1.11–2.18) and the risk for vascular death 48% higher (HR 1.48; 95%CI 1.07–2.05). Additional adjustment for HDL-C (model 3), considerably weakened the effect of plasma TG on all vascular endpoints (HR for all vascular events: 1.22; 95%CI 0.93–1.60, highest quintile compared to lowest quintile). Additional adjustment for HDL-C instead of HDL-C in model 2 only slightly attenuated the effect of plas-ma TG on vascular events (data not shown). In patients without T2DM (n = 4774), plasma TG in the highest quintile increased the risk (HR 1.47; 95%CI 1.11–1.96) for all vascular events compared plasma TG in the lowest quintile. In patients with T2DM (n = 957), the risk for all vascular events was only slightly higher in quintile 5 compared to quintile 1 (HR 1.11; 95%CI 0.65–1.91), and the association between plasma TG and vascular events seemed slightly u-shaped. When analyzed continuously, the HR for all vascular events was similar for both groups (HR1.17; 95%CI 0.86–1.58 in T2DM vs. HR 1.23; 95%CI 1.04–1.46) and p for interaction was 0.894. Plasma TG did increase the risk for all vascular events in patients without the metabolic syndrome (HR 1.29; 95%CI 1.00–1.66, p = 0.047 for log-TG), but not in patients with the meta-bolic syndrome (HR 0.94; 95%CI 0.74–1.18, p = 0.584 for log-TG); p for interaction by the metabolic syndrome was 0.051. Plasma TG levels and risk of new vascular events according to the localization of vascular disease In patients with coronary artery disease, increasing levels of TG were most clearly associated with increased risk of new vascular events (Table 3).

Table 1: Baseline characteristics of the study population according to quintiles of plasma triglycerides (TG).

Total population (n = 5731)	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Range TG (mmol/L)	b0.97	0.97–1.24	1.25–1.60	1.61–2.24	> 2.24
Median TG (mmol/L)	0.80	1.10	1.41	1.88	2.90
N	1163	1133	1158	1131	1146
Age (years)	60.5 ± 11.1	60.8 ± 10.2	61.0 ± 10.3	59.5 ± 10.3	58.3 ± 9.8
Male gender, n (%)	843 (73)	820 (72)	855 (74)	813 (72)	914 (80)
Female gender, n%	532 (53)	320 (52)	355 (54)	412 (42)	523 (60)
BMI (kg/m^2)	25.6 ± 3.7	26.1 ± 3.6	26.9 ± 4.0	27.6 ± 4.0	28.0 ± 4.1
Waist circumference (cm)	91 ± 12	93 ± 11	96 ± 12	98 ± 11	100 ± 11
Systolic blood pressure (mm Hg)	141 ± 21	140 ± 2	142 ± 20	140 ± 20	143 ± 20
Diastolic blood pressure (mm Hg)	79 ± 10	79 ± 10	80 ± 10	79 ± 10	81 ± 10
Total cholesterol (mmol/L)	4.3 ± 1.0	4.7 ± 1.1	4.9 ± 1.1	5.2 ± 1.1	5.6 ± 1.2
HDL-C (mmol/L)	1.4 ± 0.4	1.3 ± 0.4	1.2 ± 0.3	1.1 ± 0.3	1.0 ± 0.3
Creatinine (µmol/L)	89 ± 25	92 ± 42	95 ± 39	95 ± 34	100 ± 55
MDRD-GFR (mL/min/1.73 m^2)	78 ± 17	77 ± 17	74 ± 17	75 ± 18	75 ± 20
Type 2 diabetes mellitus, n (%)	147 (13)	148 (13)	174 (15)	207 (18)	281 (25)
Homa-IR[b]	2.1 ± 1.4	2.6 ± 2.0	3.0 ± 2.0	3.3 ± 2.3	4.0 ± 3.1
Metabolic syndrome NCEP ATP III, n (%)	165 (14)	214 (19)	319 (28)	741 (66)	912 (80)
Current smoking, n (%)	312 (27)	328 (29)	387(33)	399 (35)	475 (41)
Use of alcohol in the last year, n (%)	882 (76)	813 (72)	805(70)	762 (67)	790 (69)
Antiplatelet/anticoagulant agents, n (%)	986 (85)	929 (82)	953(82)	916 (81)	890 (78)
Use of blood pressure lowering agents, n (%)	804 (69)	833 (73)	846(73)	858 (76)	858 (75)
Use of lipid-lowering agents, n (%)	811 (70)	755 (67)	707(61)	711 (63)	657 (57)
Coronary arteries, n (%)	681 (59)	691 (61)	699(60)	688 (61)	689 (60)
Cerebrovascular, n (%)	390 (34)	315 (28)	331(29)	283 (25)	305 (27)
Aneurysm abdominal aorta, n (%)	77 (7)	98 (9)	107(9)	112 (10)	119 (10)
Peripheral arteries, n (%)	164 (14)	208 (18)	233(20)	264 (23)	312 (27)

FIGURE 1:

Continuous variables are shown as mean ± standard deviation.

[a]Calculated with Friedewald formula up to plasma TG 9 mmol/L

[b]Only measured from July 2003 onwards

[c]Patients could be classified in more than 1 vascular disease category

Compared to quintile 1, the risk of new vascular events was increased with 45% in quintile 5 (HR 1.45; 95%CI 1.02–2.08). P for trend across quintiles was 0.027. After adjustment for HDL-C (model 3), higher TG levels the increase in risk did not reach statistical significance anymore (HR 1.34; 95%CI 0.92–1.96). In patients with cerebrovascular disease

the risk in quintile 5 was slightly increased compared to quintile 1, although this was not statistically significant. Moreover, there was no clear trend across quintiles (p for trend 0.315). In peripheral artery disease/AAA there was no relation between TG plasma levels and risk of future vascular events.

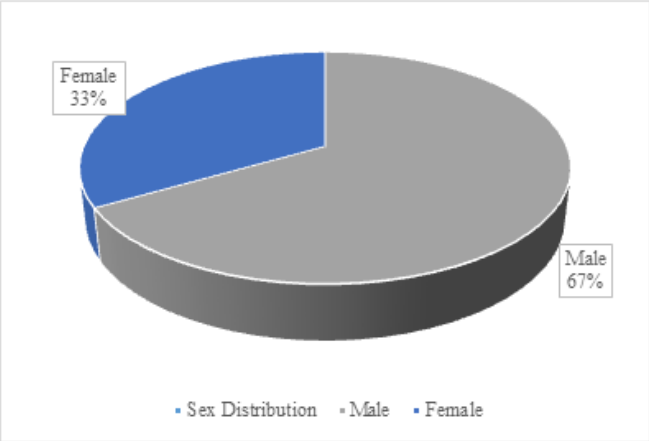

FIGURE 2: Sex distribution of patients.

Table 2 : Risk of new vascular events in quintiles of plasma TG.

Model		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
TG range (mmol/L)		b0.97	0.97–1.24	1.25–1.60	1.61–2.24	>2.24
N = 5731 (male/female)		1163 (775-388)	1133 (755-378)	1158 (772-386)	1131 (754-377)	1146 (764-382)
Ischemic stroke	# events	24	29	39	44	57
	I	Reference	1.04 (0.60–1.78)	1.23 (0.74–2.30)	1.39(0.85–2.30)	1.75(1.08–2.84)
	II	Reference	0.96 (0.56–1.65)	1.06 (0.63–1.79)	1.23(0.74–2.06)	1.47(0.89–2.42)
Myocardial infarction	# events	52	75	99	100	125
	I	Reference	1.22 (0.85–1.73)	1.39 (0.99–1.94)	1.43(1.02–2.00)	1.67(1.20–2.31)
	II	Reference	1.18 (0.83–1.68)	1.31 (0.93–1.84)	1.36(0.96–1.92)	1.56(1.11–2.18)
Vascular death	# events	55	80	112	98	128
	I	Reference	1.18 (0.84–1.67)	1.35 (0.97–1.86)	1.27(0.91–1.77)	1.62(1.18–1.77)
	II	Reference	1.13 (0.80–1.59)	1.24 (0.89–1.72)	1.19(0.85–1.67)	1.48(1.07–2.05)
All vascular events	# events	96	134	170	169	213
	I	Reference	1.17 (0.90–1.52)	1.29 (1.00–1.65)	1.32(1.02–1.69)	1.59(1.25–2.03)
	II	Reference	1.11 (0.86–1.45)	1.18 (0.91–1.52)	1.22 (0.94–1.58)	1.45(1.13–1.86)
Male and female ratio 3:1.						

FIGURE 3:

Table 3: Risk of new vascular events in quintiles of plasma TG according to localization of vascular disease.

TG range (mmol/L)	Model	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Patients with cerebrovascular disease (n = 1624)	# events/N	34/390	41/315	71/331	60/283	70/305
	I	Reference	1.19 (0.76–1.88)	1.47 (0.98–2.23)	1.45(0.95–2.22)	1.38(0.91–2.10)
	II	Reference	1.10 (0.70–1.76)	1.30 (0.85–1.99)	1.27(0.81–1.97)	1.25(0.81–1.92)

FIGURE 4:

Patients could be classified in more than 1 vascular disease category. Abbreviations: AAA, aneurysm of the abdominal aorta. Further as in (Table 1.3.4). Plasma TG levels and risk of new vascular events according to baseline levels of HDL-C ratio. Visualizes the risk of vascular events across plasma TG quintiles according to strata for HDL-C and TC/HDL-C ratio at baseline. The lower risk lipid stratum in the low TG quintile served as a reference category. This figure illustrates the results presented in (Table 4), showing an increased risk with increasing plasma TG-levels irrespective of other lipid levels, and showing a contribution of plasma TG levels to increased vascular risk even when other lipids are at target level (Figure 2).

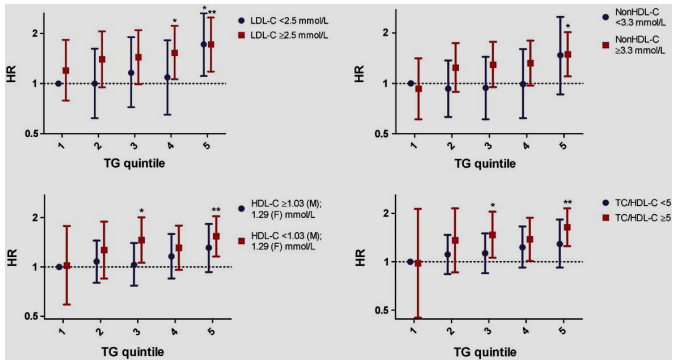

FIGURE 5: Risk for new vascular events for quintiles of TG stratified for other lipoprotein measures at baseline. All HRs were adjusted for age, gender, smoking, lipid-lowering medication and BMI. In Fig. 1c, additional adjustment was made for HDL-C. * pb 0.05; ** pb 0.01.

Table 4: Risk of new vascular events conferred by plasma log-triglyceride levels, stratified for other lipoprotein levels at baseline.

HDL-C	b2.5 mmol/L	=2.5 mmol/L
Events/N	169/2118	613/3613
HR Model I	1.30(1.00–1.69)	1.31(1.10–1.55)
HR Model II	1.27(0.97–1.67)	1.29(1.08–1.53)

FIGURE 6:

Hazard ratio (95% confidence interval), adjusted for: Model I: age and gender. Model I lipid-lowering medication, BMI and HDL-C (adjustment for HDL-C only when stratified for HDL-C). Abbreviations: TC, total cholesterol. Further as in Table 1. P b 0.05. P b 0.01. As displayed in (Table 4), higher plasma log-TG levels were still associated with increased

risk of new vascular events when other lipids are at target level. Although the increase in risk with increasing plasma log-TG was statistically significant in some strata and not in others, the overall effect was not modified by either high or low stra-tum. When stratified for HDL-C ratio, p for interaction was 0.472, 0.247, 0.774 and 0.151 respectively, which implies that the risk conferred by TG is not different regardless of other lipid levels.

4 | DISCUSSION

In patients with clinically manifest vascular diseases, high plasma TG levels increase the risk of recurrent vascular events, particularly in patients with CAD. This risk is independent of the presence of T2DM and the use of lipid-lowering medication. Higher plasma TG levels increase risk in patients with either low (b2.5 mmol/L) or high (≥2.5 mmol/L) HDL-C and either low (b3.3 mmol/L) or high (≥3.3 mmol/L). Previous meta-analyses showed that plasma TG is a risk factor for the development of cardiovascular diseases in healthy populations, independent of HDL-C (4) (5) . In patients with known CAD who were treated with statins, plasma TG levels have been shown a risk factor for recurrent vascular events, even at low HDL-C levels (6) (7) . The pre-sent study expands the results of previous trials to an unselected pop-ulation of patients with CAD who are encountered in everyday clinical practice and treated intensively with lipid-lowering medication. However, plasma TG levels were not associated with an increased risk for recurrent vascular events in patients with CVD, PAD or AAA. Since the different vascular disease categories were not mutually exclusive, presence of interaction by location of vascular disease could not be statistically tested. The difference in vascular risk by plasma TG between these disease categories may be partially explained by the different metabolic profile of patients with CAD compared to patients with vascular disease at other locations. In our study, patients with coronary artery disease had a higher average BMI and waist cir-cumference, but they had a lower blood pressure and were less likely to smoke. Therefore, vascular events in these patients may result from adipose tissue dysfunction and increase in plasma TG and may be 'fat-driven', more than in patients with vascular diseases at different loca-tions. In short, these results show that in the current era of intensive treatment of vascular risk factors, plasma TG levels still contribute to residual risk, in particular in patients with CAD. Higher plasma TG levels may be seen as a marker of insulin resis-tance, as is present in obesity, metabolic syndrome and T2DM, condi-tions known to be associated with an increased cardiovascular risk (14). Still, our results show that the risk associated with plasma TG is not due to its association with BMI, the metabolic syndrome or T2DM. Adjustment for BMI or stratification for T2DM did not essentially affect the vascular risk associated with high plasma TG, indicating that plasma TG is an independent risk factor for vascular events in patients with clinically manifest vascular disease. Also adjustment for HOMA-IR did not change the risk associated with plasma TG, making subclinical insu-lin resistance as an explanation unlikely. Only in patients with the met-abolic syndrome, the risk associated with plasma TG seems to be absent. This may either indicate that plasma TG level on its own does not con-tribute risk in this metabolically unhealthy state; or that patients with metabolic syndrome but still low plasma TG levels have other comorbidities that decrease plasma TG. Also after adjustment for HDL-C or HDL-C, high plasma TG levels were associated with higher risk of recurrent vascular events, in accordance with other studies in healthy populations and statin trials (7) (15). Thus, these results may suggest a beneficial effect of lowering plasma TG in secondary prevention. However, drugs lowering plasma TG levels, such as fibrates, have not clearly proven to be effec-tive in preventing vascular events (8) (9) . Therefore, triglyceride levels are not used as treatment targets in current guidelines (10) (11). In-stead, NCEP ATP III guidelines advise HDL-C as the treatment tar-get in patients with TG >2.3 mmol/L (200 mg/dL). HDL-C includes TG-rich VHDL-particles in contrast to HDL-C (10). Data from the present study show that the risk associated with high TG levels is independent of HDL-C. Fig. 1 shows an increased risk with TG even when the HDL-C target has been reached, although this increased risk pertains only to the highest TG quintile,

which is a small group of the patients with HDL b3.3 mmol/L and therefore the confidence intervals are large and include 1. However, this may still imply that current lipid targets do not suffice in all patients with high TG and a search for other approaches to reduce plasma TG-associated residual risk may be worthwhile. Apo lipoprotein B (apoB) levels may explain the risk associated with plasma TG when HDL-C levels are low and have been pro-posed to estimate risk in hypertriglyceridemic patients. The Mercury II trial showed that for patients with TG ≥2.3 mmol/L (≥200 mg/dL) only 37% of the patients reaching the HDL-C goal of 3.37 mmol/L (130 mg/dL) during statin therapy also reached the apoB goal of 90 mg/dL (16). In the present study apoB was only available for 2075 patients, and consequently we could not verify this explanation. In the present study, the risk associated with higher plasma TG levels disappeared after adjustment for HDL-C, which is tightly correlated with plasma TG. As HDL-C concentrations are more stable than TG concentrations, the relation of HDL-C with vascular events may be clearer. However, a part of the risk associated with low HDL-C may actually reflect risk associated with increased levels of VHDL remnants and small dense HDL. The present results show a trend towards an increased risk associated with higher TG levels even if HDL-C is high. A clinical implication of these results is the need for increased attention for plasma TG levels, in particular in patients with CAD. To reduce residual risk, lowering plasma HDL-C or even HDL-C to current targets may not be sufficient. As long as there are no TG-lowering drugs proven to be effective in reducing vascular events, focus should be on a strict HDL-C target. In patients with elevated plasma TG levels (≥2.3 mmol/L=≥200 mg/dL or even 1.7 mmol/L =≥150 mg/dL) a strict HDL-C target (2.6 mmol/L = 100 mg/dL) could be defined to lower the risk associated with plasma TG. We acknowledge several limitations of the study. First, apoB levels were only available for a small proportion of patients, disabling the use in additional analyses. Furthermore, only baseline lipid levels were available. The use of lipid-lowering medication at baseline was 64%. It is likely that during follow-up lipid-lowering therapy was started in more patients, influencing plasma lipid levels. (17) However, this will probably have resulted in only small changes in plasma TG levels. Moreover, the effect of starting lipid-lowering therapy will most likely result in a small underestimation of the effect of plasma TG, as the proportion of patients with lipid-lowering therapy at base-line was lowest in patients with high plasma TG.

4.1 | Conclusion

In conclusion, high plasma TG levels confer an increased risk for recurrent vascular events in patients with clinically manifest vascular disease, especially patients with CAD. This relationship was independent of HDL-C and use of lipid-lowering medication and is present is at target level.

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How to cite this article: Ahmed H. Title "Plasma Triglyceride levels Increase the Risk for Recurrent Cardiovascular Disease Independent of High-Density Lipoprotein Cholesterol Level". Journal of Medical Research and Health Sciences. 2021;1476−1481. https://doi.org/10.52845/JMRHS/2021-4-9-7