Increased Cardiovascular Risk in Hypertriglyceridemic Patients With Statin-Controlled LDL Cholesterol

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Context: Real-world evidence of the relationship between high triglyceride (TG) levels and cardiovascular (CV) disease (CVD) risk among statin-treated patients with low-density lipoprotein cholesterol (LDL-C) control is lacking.

Objective: We aimed to compare CVD and mortality risk between patients with high vs normal TGs.

Design: Longitudinal observational cohort study.

Setting: Integrated delivery system.

Patients: Patients aged ≥45 years whose TG level was either <150 mg/dL (normal) or between 200 and 499 mg/dL (high) in 2010, were taking only statins, had LDL-C values 40 to 100 mg/dL, and had diagnosed CVD.

Outcome Measures: Patients were followed through December 2016. Our primary outcomes were a composite of nonfatal myocardial infarction (MI), nonfatal stroke, unstable angina, coronary revascularization, and all-cause mortality and a second composite adding peripheral revascularization and aneurysm repair. We compared multivariable-adjusted incidence rates and rate ratios (RRs) of the outcomes and their components.

Results: A total of 14,481 patients comprised the normal TG group, and 2702 patients were in the high TG group. Multivariable-adjusted incidence of the second composite was 10% greater in the high TG group [50.9/1000 person-years, 95% CI 47.0 to 55.2 vs 46.5, 44.8 to 48.2, RR 1.10, 95% CI 1.00 to 1.20, $P = 0.041$]. The difference was driven by nonfatal MI (RR 1.20, 95% CI 1.00 to 1.45, $P = 0.045$), coronary revascularization (RR 1.18, 95% CI 1.00 to 1.40, $P = 0.045$), and peripheral revascularization (RR 1.56, 95% CI 1.14 to 2.13, $P = 0.006$).

Conclusions: CVD risk in high-risk statin-treated patients with atherosclerotic CVD was associated with high TG levels. (***J Clin Endocrinol Metab*** **103: 3019–3027, 2018)**

The large reductions in cardiovascular (CV) disease (CVD) event and mortality rates that have occurred during the last 50+ years (1–4) are, at least in part, attributable to the clear-cut benefits of increasingly aggressive management of low-density lipoprotein cholesterol (LDL-C) levels (5). Nevertheless, substantial CV risk remains among the estimated 92 million US adults with CVD in one of its many forms (6), and CVD continues to be the leading cause of mortality in the United States (7). Elevated triglyceride (TG) levels, which

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Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; EHR, electronic health record; HDL-C, high-density lipoprotein cholesterol; KPNW, Kaiser Permanente Northwest; KPSC, Kaiser Permanente Southern California; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; REDUCE-IT, Reduction of Cardiovascular Events with EPA-Intervention Trial; RR, rate ratio; TG, triglyceride.

is a common finding in clinics, may identify individuals at increased CVD risk and represent an attractive target for additional CVD risk reduction, especially among patients with well-controlled LDL-C on statin therapy (8). *Post hoc* analyses of clinical trials of LDL-C lowering have suggested that TG levels are associated with CVD and mortality in the context of statin treatment (9–12), and a recent report shows a causal relationship between TG levels and CVD (13). However, real-world evidence of the relationship between elevated TG levels and CVD among statin-treated patients who have succeeded in attaining LDL-C control is lacking. Therefore, we conducted an observational longitudinal cohort study using the electronic health records (EHRs) of patients in an integrated delivery system who were at high risk for CVD events and who had statin-controlled LDL-C to determine whether the presence of high TG levels influences CV risk in real-world clinical practice.

Materials and Methods

Kaiser Permanente is an integrated delivery system that provides medical care to individuals in eight semiautonomous regions around the country. For this study, we combined the EHR data of the Kaiser Permanente Northwest (KPNW) and Southern California (KPSC) regions that collectively serve ~4.5 million members. Both organizations use an EPIC®-based EHR that combines seamlessly with enrollment, laboratory, and pharmacy information systems to develop a comprehensive dataset that is standardized into a common data model (14). The KPNW Institutional Review Board approved the study with a waiver of informed consent; the KPSC Institutional Review Board ceded review to KPNW.

The sample for the current study was selected to simulate the inclusion and exclusion criteria of patients with atherosclerotic CVD (ASCVD) participating in the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT), a Phase 3b trial evaluating the safety and efficacy of 4 g daily of pure eicosapentaenoic acid, a prescription omega-3 fatty acid, as an adjunct to statin therapy in reducing CV events in a high-risk patient population with persistent hypertriglyceridemia; details of the study design have been previously published (15).

To mimic the REDUCE-IT population, we identified all KPNW and KPSC patients, aged 45 and older with ASCVD who had a TG level <500 mg/dL in 2010, were receiving statin therapy but no other anti-hyperlipidemic agent, had LDL-C values between 40 and 100 mg/dL, and had a charted diagnosis of myocardial infarction (MI; ICD-9-CM 410.x or 412), stroke (434.x), acute coronary syndrome (411.1), or peripheral artery disease (443.8x, 443.9x). From the 48,141 who met these criteria, we identified high (200 to 499 mg/dL, n = 6737) and normal (<150 mg/dL, n = 34,095) TG groups. Again following REDUCE-IT, we excluded individuals with a life-threatening illness [AIDS/HIV (ICD-9-CM 042.x, 043.x, 044.x), malignant cancer (140.xx–239.xx), or end-stage renal disease (585.6)], planned surgery (defined for this study as any surgery within 6 months of the date of TG testing), liver disease (cirrhosis, hepatitis, alanine transaminase or aspartate transaminase >3× upper limit of normal, or bilirubin >2× upper limit of normal), kidney dysfunction (albumin level <3.4 g/dL, blood urea nitrogen level >20 mg/dL, or a serum creatinine >1.3 mg/dL in men or 1.1 mg/dL in women), or thyroid function abnormalities (thyroid stimulating hormone values <0.4 or >4.2 mU/L, with or without treatment). Although REDUCE-IT excluded New York Heart Association Class IV heart failure only, our data did not contain a heart-failure class. Therefore, we excluded all individuals with a charted heart-failure diagnosis (ICD-9-CM 428.x). These criteria resulted in the exclusion of 4035 patients from the high TG group and 19,614 from the normal TG group for final sample sizes of 2702 and 14,481 patients in the high and normal TG group, respectively. A complete consort diagram of the inclusion and exclusion criteria is provided in Fig. 1.

Index date and follow-up period

If multiple TG results were available in 2010, all had to be <150 mg/dL for a patient to qualify for the normal TG group, and all had to be 200 to 499 mg/dL for a patient to qualify for the high TG group. We used the first available TG level in 2010 as the index value. We defined the baseline period (for baseline data collection) as 6 months before and 6 months after the index TG. To avoid immortal time bias that would result from including the 6-month post-index TG level as follow-up time, we defined the index date for beginning follow-up as the date of the index TG plus 182 days. Patients were followed from the index date through December 2016 for a maximum follow-up period of 6.5 years. Data were censored on 31 December 2016 or when a patient died or left the health plan.

Study outcomes and covariates

We prespecified two composite outcomes. The first included all-cause mortality and first occurrence of a nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. The second added peripheral revascularization and aneurysm repair to the first. In secondary analyses, we evaluated each of the individual components of the composite outcomes separately.

We assessed baseline demographics (age, sex, race), clinical characteristics [smoking status, body mass index (BMI), systolic and diastolic blood pressure, lipid fractions, and comorbidities] as potential covariates and compared them between the high and normal TG groups using t tests for continuous variables and χ^2 tests for dichotomous and categorical variables. We also compared the number of outcomes and the proportion of each group with each outcome that occurred any time during follow-up using χ^2 tests.

We compared multivariable-adjusted incidence rates and rate ratios (RRs) of the outcomes between the TG groups using generalized linear models with Poisson errors (log-link) with follow-up time as an offset variable (to account for differential follow-up). We conducted univariate Cox regression analyses of the association among all candidate variables (see Table 1) and the primary composite outcome. Variables that were significant at $P < 0.05$ were included as potential covariates in multivariable models. From these, we used forward selection to define our multivariable analyses; final incidence models were adjusted for age, sex, race/ethnicity, BMI, smoking status, blood pressure, diabetes, use of insulin, history of MI, stroke or other ischemic heart disease, serum creatinine, and study site. To explore the robustness of our results, we re-estimated the final models for prespecified dichotomous stratifications of age (<65 vs ≥65 years), sex, race (white vs black), Hispanic ethnicity, smoking status, blood pressure (<140/90 vs ≥140/90 mmHg), high-density lipoprotein cholesterol (HDL-C; <40

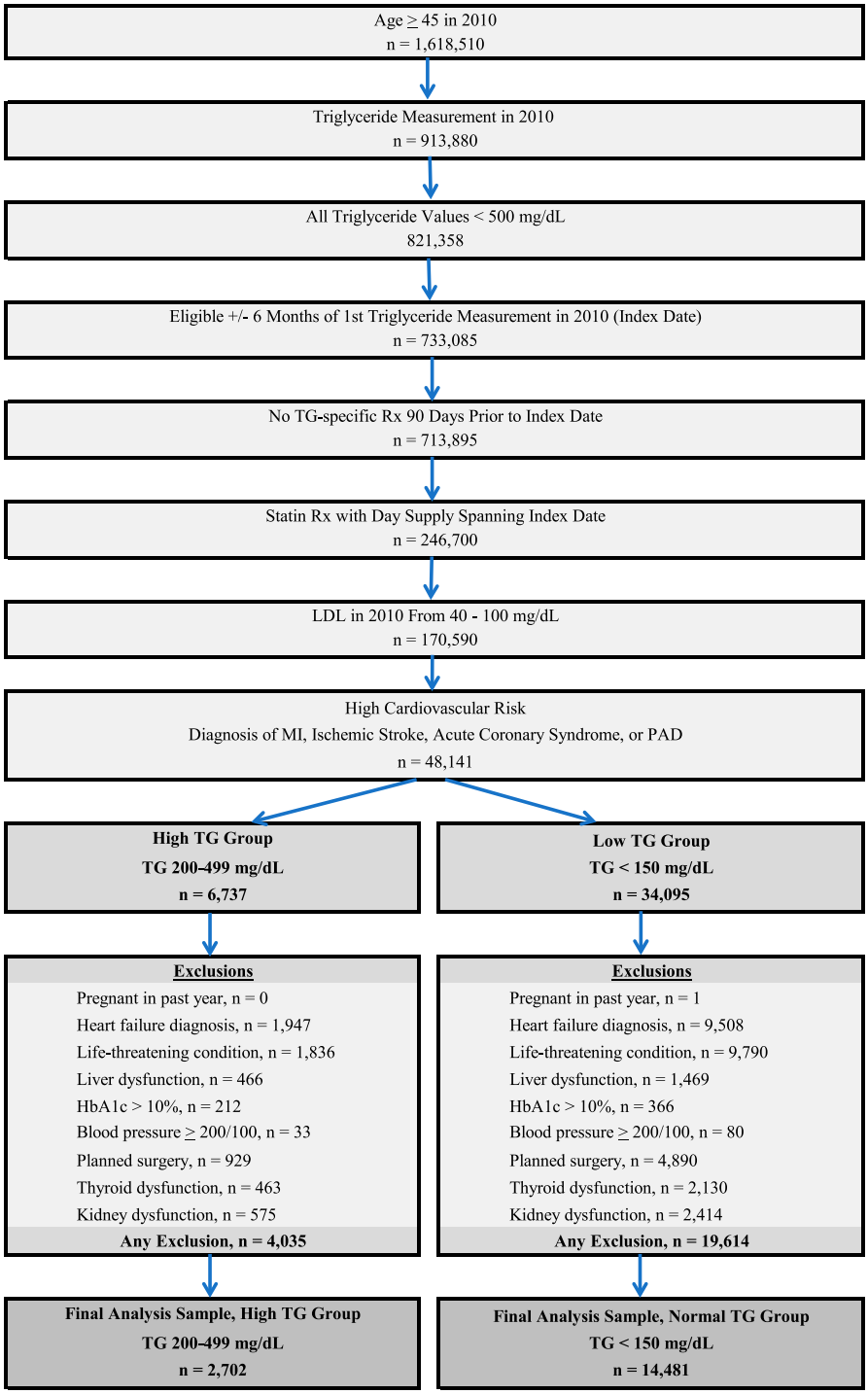

Figure 1. Consort diagram of the application of REDUCE-IT-like inclusion and exclusion criteria. PAD, peripheral artery disease; Rx, prescription.

vs ≥40 mg/dL), diabetes, and chronic kidney disease [CKD; estimated glomerular filtration rate (eGFR) <60 vs ≥60 mL/min/1.73 m^2]. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patients in the high TG group (n = 2702) were significantly different from patients in the normal TG group (n = 14,481); they were younger and more likely to be white or Hispanic, to smoke, to have lower HDL-C levels, and to have a higher prevalence of diabetes and CKD (Table 1). The crude prevalence of the composite outcomes at any time during follow-up did not differ between groups (Table 2; 24.4% vs 25.4%, $P = 0.272$ for the first composite; 26.3% vs 27.0%, $P = 0.478$ for the second composite). However, patients in the high TG group were more likely to experience a nonfatal MI (6.3% vs 5.2%, $P = 0.023$) and either coronary (7.7% vs

Table 1. Baseline Characteristics of Patients With High vs Normal TGs

	TG, 200–499 mg/dL	TG, <150 mg/dL	*P* Value[a]
n	2702	14,481	–
Age, y	66.0 (60.0, 74.0)	70.0 (62.0, 77.0)	<0.001
Men, %	1698 (62.8)	9302 (64.2)	0.166
Race/ethnicity, %			<0.001
Hispanic—all races	551 (20.4)	2562 (17.7)	
Non-Hispanic white	1759 (65.1)	8306 (57.4)	
Non-Hispanic black	84 (3.1)	2154 (14.9)	
Non-Hispanic Asian	261 (9.7)	1249 (8.6)	
Other non-Hispanic	47 (1.7)	210 (1.5)	
Current smoker, %	268 (9.9)	1048 (7.2)	<0.001
BMI, kg/m^2	30.4 (27.1, 34.3)	27.9 (24.9, 31.6)	<0.001
Systolic blood pressure, mm Hg	130 (121, 138)	129 (120, 137)	<0.001
Diastolic blood pressure, mm Hg	71 (65, 76)	69 (64, 75)	<0.001
TG, mg/dL	243 (216, 282)	97 (77, 118)	<0.001
LDL-C, mg/dL	76 (64, 87)	77 (66, 87)	0.007
HDL-C, mg/dL	40 (35, 46)	48 (41, 58)	<0.001
MI, %	801 (29.6)	4413 (30.5)	0.389
Stroke, %	364 (13.5)	2200 (15.2)	0.021
Unstable angina, %	60 (2.2)	365 (2.5)	0.357
Other ischemic heart disease, %	1225 (45.3)	6833 (47.2)	0.077
CKD, % (eGFR, <60 mL/min/1.73 m^2)	917 (33.9)	4255 (29.4)	<0.001
Type 2 diabetes, %	1351 (50.0)	5418 (37.4)	<0.001
Insulin, %	342 (12.7)	1477 (10.2)	<0.001
ACEi or ARB, %	2109 (78.1)	10,879 (75.1)	0.001
Diuretic, %	934 (34.6)	4323 (29.9)	<0.001
β-Blocker, %	1922 (71.1)	9338 (64.5)	<0.001
Any antihypertensive, %	2572 (95.2)	13,588 (93.8)	0.006

Data are medians (interquartile ranges) or n (%).

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

[a] *P* values are from Wilcoxon Sign tests for continuous measures and χ^2 tests for dichotomous and categorical variables.

5.9%, $P < 0.001$) or peripheral (2.1% vs 1.6%, $P = 0.026$) revascularization, whereas more patients in the normal TG group died (13.4% vs 16.0%, $P < 0.001$). All of these significant findings were similarly significant for men, but only the prevalence of coronary revascularization was significantly different among women.

After multivariable statistical adjustment and accounting for time to event (Table 3), the RR indicated that the high TG group was 10% more likely to experience the second composite outcome compared with the normal TG group [RR 1.10, 95% confidence interval (CI) 1.00 to 1.20, $P = 0.041$]. The difference was driven by the rates of nonfatal MI (RR 1.20, 95% CI 1.00 to 1.45, $P = 0.045$), coronary revascularization (RR 1.18, 95% CI 1.00 to 1.40, $P = 0.045$), and peripheral (RR 1.56, 95% CI 1.14 to 2.13, $P = 0.006$) revascularization. The incidence rate (per 1000 person-years) of the second composite was greater among the high vs normal TG group, but the CIs overlapped (50.9, 95% CI 47.0 to 55.2 vs 46.5, 95% CI 44.8 to 48.2). Incidence of the first composite outcome was not significantly different between groups, with rates of 45.9 per 1000 person-years (95% CI 42.2 to 49.9) in the high TG group and 42.8 per 1000 person-years (95% CI 41.1 to 44.5) in the normal TG group and a RR of 1.07 (95% CI 0.98 to 1.18, $P = 0.127$). Rates of all-cause mortality, nonfatal stroke, unstable angina, and aneurysm repair were elevated among the high TG group but were not significantly different from patients with normal TG levels.

With the exception of age, results for the second composite outcome were consistent across stratifications (Table 4). Only the interaction between group and age was statistically significant ($P = 0.001$), with a larger effect observed among those under age 65 compared with 65 and older.

Discussion

In this observational longitudinal cohort study of 17,183 patients with ASCVD and statin-controlled LDL-C, we found that TG levels in the 200- to 499-mg/dL range were significantly associated with CVD events over a mean follow-up of 5 years when compared with otherwise similar patients with TG levels <150 mg/dL. Because we controlled for a number of demographic and clinical risk factors, and both TG groups had LDL-C levels ranging 40 to 100 mg/dL, while on statin therapy, our results reflect differences in CVD risk that can be explained, at least in part, by the difference in TG levels.

Table 2. Crude Prevalence (No. and %) of Study Outcomes Occurring Any Time During Follow-Up

	All Patients			Men			Women		
	TG, 200–499 mg/dL	TG, <150 mg/dL	*P* Value[a]	TG, 200–499 mg/dL (n = 1698)	TG, <150 mg/dL (n = 9302)	*P* Value[a]	TG, 200–499 mg/dL (n = 1004)	TG, <150 mg/dL (n = 5179)	*P* Value[a]
Mean follow-up, y (SD)[b]	4.9 (1.9)	5.0 (1.9)	0.001	4.9 (1.9)	5.0 (1.9)	0.080	4.9 (1.9)	5.1 (1.8)	0.002
Primary composite outcomes									
First composite outcome	660 24.4%	3682 25.4%	0.272	417 24.6%	2408 25.9%	0.249	243 24.2%	1274 24.6%	0.790
Second composite outcome	711 26.3%	3906 27.0%	0.478	452 26.6%	2563 27.6%	0.428	259 1.6%	1343 25.9%	0.929
Secondary outcomes									
Nonfatal MI	169 6.3%	750 5.2%	0.023	116 6.8%	519 5.6%	0.042	53 5.3%	231 4.5%	0.257
Nonfatal stroke	129 4.8%	736 5.1%	0.501	72 4.2%	451 4.8%	0.279	57 5.7%	285 5.5%	0.825
Unstable angina	35 1.3%	154 1.1%	0.289	24 1.4%	115 1.2%	0.548	11 1.1%	39 0.8%	0.267
Coronary revascularization	208 7.7%	857 5.9%	<0.001	153 9.0%	681 7.3%	0.016	55 5.5%	176 3.4%	0.002
Peripheral revascularization	58 2.1%	225 1.6%	0.026	41 2.4%	164 1.8%	0.068	17 1.7%	61 1.2%	0.181
Aneurysm repair	21 0.8%	123 0.8%	0.706	17 1.0%	98 1.1%	0.845	4 0.4%	25 0.5%	0.721
All-cause mortality	363 13.4%	2321 16.0%	<0.001	210 12.4%	1430 15.4%	0.001	153 15.2%	891 17.2%	0.128

[a] *P* values based on χ^2 tests.

[b] Follow-up times vary by outcome but are similar in duration and variance.

Past research spanning several decades has repeatedly identified TG as an important CVD risk factor (16), yet the contribution of TG to CVD and peripheral vascular disease risk after adjustment for other factors has been difficult to pinpoint. The Emerging Risk Factors Collaboration, an analysis of over 300,000 individuals from 68 prospective studies, found that the hazard ratio for coronary heart disease attributed to elevated TG was 1.37 (95% CI 1.31 to 1.42) after adjustment for nonlipid factors and became nonsignificant (0.99, 0.94 to 1.05) following adjustment for HDL-C and non-HDL-C (17). As very LDL particles are the main carrier of TG and are a component of non-HDL-C, this biological correlation may have resulted in statistical overcorrection (18). Moreover, all subjects were free of vascular disease at baseline, a decidedly different study population from ours. In any case, three other large meta-analyses of studies of general populations found that TG levels remained highly, significantly associated with CVD after adjustment for HDL-C, suggesting that TG are indeed acting independently as a CVD risk factor (16, 19, 20). Our results are unique in that we focused on statin-treated patients with controlled LDL-C and established ASCVD, and TG levels may play a larger role in CVD risk in this more selected, high-risk population. Furthermore, in our study, neither HDL-C nor its interaction with TG group was an important predictor of our composite CVD outcome, further demonstrating that elevated TG levels may confer independent CVD risk.

A composite outcome that includes mortality may overemphasize less serious events, such as revascularization, especially when mortality may not be the direct result of CVD. As we did not have access to specific causes of death, we could not determine whether mortality was CV related. Despite a higher proportion of subjects in the normal TG group dying during follow-up, we did not find a substantial difference between groups in the multivariable-adjusted risk of all-cause mortality that accounted for time to event. Older age and slightly longer follow-up among patients with normal TG levels likely accounts for the difference in the crude and adjusted results. Importantly, all-cause mortality comprised 51% of the second composite outcome in the high TG group and 63% in the normal TG group. Given these findings, it may be more appropriate to consider the individual components of the composite as the better measure of CV events.

Our findings were driven by a significantly increased risk of nonfatal MI and coronary and peripheral revascularization. In unadjusted data, nonfatal MI was significantly different between the TG groups among men but not women. However, a higher (albeit nonsignificant) proportion of women in the high TG group experienced an MI, suggesting that the lack of

Table 3. Adjusted[a] Incidence of Study Outcomes per 1000 Person-Years and RRs

Outcome	TG, 200–499 mg/dL	TG, <150 mg /dL	RR	*P* Value
Primary composite outcomes				
First composite outcome	45.9 (42.2–49.9)	42.8 (41.1–44.5)	1.07 (0.98–1.18)	0.127
Second composite outcome	50.9 (47.0–55.2)	46.5 (44.8–48.2)	**1.10 (1.00–1.20)**	**0.041**
Secondary outcomes				
Nonfatal MI	10.5 (8.9–12.4)	8.7 (8.0–9.5)	**1.20 (1.00–1.45)**	**0.045**
Nonfatal stroke	8.4 (7.0–10.2)	7.8 (7.1–8.5)	1.09 (0.89–1.33)	0.423
Unstable angina	2.3 (1.6–3.3)	1.6 (1.3–2.0)	1.39 (0.94–2.06)	0.101
Coronary revascularization	11.9 (10.2–13.9)	10.0 (9.3–10.9)	**1.18 (1.00–1.40)**	**0.045**
Peripheral revascularization	3.4 (2.5–4.5)	2.2 (1.8–2.6)	**1.56 (1.14–2.13)**	**0.006**
Aneurysm repair	1.3 (0.8–2.0)	1.2 (0.9–1.5)	1.06 (0.64–1.76)	0.817
All-cause mortality	20.7 (18.4–23.2)	19.9 (18.8–21.1)	1.04 (0.92–1.17)	0.533

Boldface indicates statistical significance.

[a]Adjusted for age, sex, race/ethnicity, BMI, smoking status, blood pressure, diabetes, use of insulin, history of MI, stroke or other ischemic heart disease, serum creatinine, and study site.

significance may have been a result of fewer events rather than sex.

It must be noted that 50% of the high TG group had a diagnosis of diabetes at baseline (vs. 38% in the normal TG group), a variable we controlled for in our multivariable analyses. The known, increased risk of CV and peripheral artery disease among patients with diabetes (21, 22), coupled with our findings, suggests that hypertriglyceridemia may be of particular importance in predicting, and perhaps causing, CVD in patients with diabetes (23, 24). In addition, although clinical trials have not established that tight glycemic control reduces CVD and may even increase the risk of death (25, 26), the association between glycemic control and CVD and mortality has been demonstrated in observational studies (27, 28). However, as less than one-half of our study sample had diabetes, only 49% had a baseline measure of HbA1c, and 61% had a baseline fasting glucose recorded. The large amount of missing data precluded us from including measures of glycemia in our analyses.

Our focus was on comparing CVD events and mortality between statin-treated patients with controlled LDL-C and moderately elevated vs normal TG. Prior studies have included patients with the full range of TG levels and measured their effect either continuously, after log transformation, or by comparing dichotomized cut-points or upper and lower tertiles or quintiles of TG (10–12, 16, 19, 20, 29). Whereas these characterizations of TG levels offer important evidence of an association with CVD risk, they are of limited clinical value, as they do not align with guideline-recognized elevated ranges of TG levels (23, 30, 31). In contrast, our study focused on a level of hypertriglyceridemia that represents approximately one-fifth of the US adult population (32).

Table 4. Adjusted[a] RRs (95% CI) for the High vs Normal TG Groups for Specified Stratifications and Test for Interaction

	RR	95% CI	*P* for Interaction
Overall	1.10	1.00–1.20	–
<65 y	1.24	1.04–1.47	0.001
≥65 y	0.99	0.89–1.09	
Women	1.12	0.97–1.29	0.698
Men	1.07	0.96–1.20	
Non-Hispanic white	1.15	1.04–1.26	0.598
Non-Hispanic black	1.03	0.64–1.66	
Hispanic	1.09	0.89–1.33	0.831
Not Hispanic	1.10	0.99–1.21	
Nonsmoker	1.10	1.01–1.21	0.545
Current smoker	1.01	0.77–1.31	
BP, <140/90 mmHg	1.07	0.97–1.18	0.444
BP, ≥140/90 mmHg	1.18	0.99–1.40	
HDL-C, >40 mg/dL	0.99	0.87–1.13	0.070
HDL-C, ≤40 mg/dL	1.08	0.96–1.23	
No diabetes	1.06	0.93–1.21	0.234
Type 2 diabetes	1.13	1.00–1.27	
eGFR, ≥60 mL/min/1.73 m^2	1.14	1.02–1.28	0.313
eGFR, <60 mL/min/1.73 m^2	1.07	0.94–1.21	

Abbreviation: BP, blood pressure.

[a]Adjusted for age, sex, race/ethnicity, BMI, smoking status, blood pressure, diabetes, use of insulin, history of MI, stroke or other ischemic heart disease, serum creatinine, and study site.

Whether elevated TG levels are a cause of or merely a biomarker for CVD cannot be established from epidemiologic or observational studies. Nevertheless, there is now mounting genetic evidence from mutational analyses, genome-wide association studies, and Mendelian randomization studies that TG abnormalities lie in the causal pathway of ASCVD (33). The elevated risk of CVD events that we observed among the statin-treated high TG group may be amenable to reduction with some TG-lowering interventions. This hypothesis is currently being tested in three large, ongoing CV outcome trials in high CV risk patients on statin therapy with specific agents that lower TG and other biomarkers (15, 34, 35).

Although an early meta-analysis found that the summary estimate of TG-associated CVD risk was greater among women than men (16), two subsequent meta-analyses did not find differences by sex (17, 19). We did not observe meaningful differences between sexes in our data. Indeed, with the exception of age, we did not observe any statistically significant interactions between TG group and the variables we tested. That the results differed by age suggests that the TG levels among older adults are less causative of CV events than among younger adults.

Strengths of our study included adequate sample size and follow-up of up to 6 years that allowed us to capture a sufficient number of events to find important differences between groups. The inclusion of a wide range of covariates allowed us to isolate the effect of the TG grouping on CVD outcomes. Our study also has notable limitations. Despite the large sample size, the detailed selection criteria could raise questions of generalizability. However, within our source population, among statin-treated patients with at least one TG measurement and LDL-C <100 mg/dL, 40% had a TG level ≥150 mg/dL, and 23% had a TG level ≥200 mg/dL. These findings are consistent with large CV outcome trials in which ~25% to 40% of participants had LDL-C <100 mg/dL and TG ≥150 mg/dL, and 15% to 20% had LDL-C <100 mg/dL and TG ≥200 mg/dL (10, 11, 36–38). We used observational laboratory data that do not contain a reliable determination of fasting status at the time of the TG tests. As we limited our data to outpatient TG results, it is likely that a majority of the tests were nonfasting. Although fasting TG may be preferred for diagnosing hypertriglyceridemia (39), nonfasting values have repeatedly been shown to predict CVD risk better (40–42). Moreover, as nonfasting TGs are substantially higher than fasting TGs (39, 43), the resulting misclassification of patients with normal fasting but high postprandial TG levels would have biased our results toward the null. Our estimates of excess CVD risk in the high TG group may therefore be conservative. By design, we assessed CVD risk factors (including TG levels) only in the baseline year. Whether changes in TG or other lipid parameters during follow-up affected our results is not known. Real-world studies may contain inaccurate recording of health events, missing data, and uncertainty about internal validity. Despite these limitations, analysis of real-world data can, by definition, provide important information about patient risk, as seen in clinical practice (44, 45).

Conclusions

Despite statin-controlled LDL-C levels, CV events were greater among ASCVD patients with high compared with normal TG levels, suggesting that persistent hypertriglyceridemia is associated with risk of CV outcomes in high-risk patients.

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