ORIGINAL RESEARCH

High Triglycerides Are Associated With Increased Cardiovascular Events, Medical Costs, and Resource Use: A Real-World Administrative Claims Analysis of Statin-Treated Patients With High Residual Cardiovascular Risk

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***Background*—**The American Heart Association recognizes high triglycerides as a cardiovascular risk factor.

***Methods and Results*—**This retrospective observational administrative claims analysis (Optum Research Database) included statin-treated patients ≥45 years old with diabetes mellitus and/or atherosclerotic cardiovascular disease, triglycerides 2.26 to 5.64 mmol/L, and a propensity-matched comparator cohort with triglycerides <1.69 mmol/L and high-density lipoprotein cholesterol >1.04 mmol/L. In the high-triglycerides cohort versus comparators (both n=10 990, 49% women), mean age was 61.7 versus 62.2 years and follow-up was 41.3 versus 42.1 months, respectively. Multivariate analysis of composite major cardiovascular events demonstrated significantly increased risk in the high-triglycerides (n=13 411 patients) versus comparator (n=32 506 patients) cohorts (hazard ratio [HR], 1.35; 95% confidence interval [CI], 1.225–1.485; $P<0.001$), with significantly higher risk for nonfatal myocardial infarction (HR, 1.35; 95% CI, 1.19–1.52; $P<0.001$), nonfatal stroke (HR, 1.27; 95% CI, 1.14–1.42; $P<0.001$), and need for coronary revascularization (HR, 1.51; 95% CI, 1.34–1.69; $P<0.001$), but not unstable angina or cardiovascular death. Increased cardiovascular risk in the high-triglycerides versus comparator cohort was maintained, even with addition of non–high-density lipoprotein cholesterol to the multivariate model and when analyzing high and low high-density lipoprotein cholesterol subgroups. Average total healthcare cost per patient per month (cost ratio, 1.15; 95% CI, 1.084–1.210; $P<0.001$) and rate of occurrence of inpatient hospital stay (HR, 1.17; 95% CI, 1.113–1.223; $P<0.001$) were also significantly greater in the high-triglycerides cohort.

***Conclusions*—**In this real-world analysis, patients with high cardiovascular risk and high triglycerides had worse composite cardiovascular and health economic outcomes than patients with well-managed triglycerides and high-density lipoprotein cholesterol >1.04 mmol/L. **(*J Am Heart Assoc*. 2018;7:e008740. DOI: 10.1161/JAHA.118.008740.)**

Key Words: atherosclerosis • cost • health economics • outcome • resource use • statin therapy • triglycerides

Cardiovascular disease remains the leading cause of death in the United States and accounts for an average of 1 in 3 deaths, or >800 000 deaths annually.[1,2] Approximately 92 million American adults are living with some form of cardiovascular disease or aftereffects of stroke.[2] The direct and indirect costs of cardiovascular disease and stroke total >$330 billion/year.[2] Despite the widespread use of statins that substantially reduce cardiovascular events, many patients continue to have residual cardiovascular risk.[3] This residual cardiovascular risk accounts for significant healthcare burden in the statin era.

Interest in triglycerides and triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease (ASCVD) has been renewed on the basis of evidence from epidemiologic, genetic, and clinical studies. Epidemiologic studies have shown that elevated triglycerides correlate with elevated cardiovascular risk,[4,5] and the American Heart Association has long recognized that elevated triglycerides are an important marker of cardiovascular risk.[6] More recently, genetic,[7–13] genome-wide analysis,[14–17] and mendelian randomization[18–22] studies have suggested a causal role for triglycerides as a modifiable risk factor in the development and progression of ASCVD. Analyses from clinical data have demonstrated that lower on-treatment triglycerides correlate with reduced cardiovascular risk.[23,24]

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Clinical Perspective

What Is New?

- In this real-world administrative claims analysis, statin-treated patients with high residual cardiovascular risk and high triglycerides had worse cardiovascular outcomes, greater healthcare use, and overall higher healthcare costs than matched comparators with well-managed triglycerides.
- The increased cardiovascular risk in the high-triglycerides versus comparator cohorts was maintained, even with the addition of non–high-density lipoprotein cholesterol to the multivariate model and when analyzing high and low high-density lipoprotein cholesterol subgroups.

What Are the Clinical Implications?

- This analysis provides strong support for hypertriglyceridemia as an independent risk factor for atherosclerotic cardiovascular disease.
- This group of patients with high triglycerides and a history of diabetes mellitus and/or atherosclerotic cardiovascular disease is relatively large, may be commonly encountered in clinical practice, and warrants further study.
- Prospective cardiovascular outcome trials of similar patient populations are ongoing and should provide important insights to the findings of this analysis and the future of treating patients with atherosclerotic cardiovascular disease.

Statin-treated patients with elevated triglycerides, controlled low-density lipoprotein cholesterol (LDL-C), and residual high cardiovascular risk are commonly encountered in clinical practice and are increasing in number because of the increase in diabetes mellitus. However, this patient population has not been thoroughly studied and, as such, a better understanding of the prevalence, health burden, healthcare costs, and resource use associated with this population is needed to optimize management.

The objective of this retrospective observational study analysis of a large real-world administratively derived claims database was to evaluate cardiovascular outcomes, healthcare use, and medical costs in statin-treated patients with high triglycerides and high residual cardiovascular risk compared with patients with well-managed triglycerides and high-density lipoprotein cholesterol (HDL-C).

Methods

The analytic methods included in this section may be used by other researchers for reproducing the results or replicating the procedure herein. Data and study materials will not be made available; the data contained in our database contain proprietary elements owned by Optum and, therefore, cannot be broadly disclosed or made publicly available at this time.

Study Design

This was an observational retrospective analysis of administratively derived data from the Optum Research Database, which includes electronic claims for >160 million individuals and electronic health records for >80 million individuals. Eligible patients had at least 1 claim for statin therapy between January 1, 2010, and December 31, 2010, and had at least 6 months of baseline data before the index date. The date of the first claim for statin therapy during the identification period was defined as the index date, and the baseline period was defined as the 6 months before the index date. The follow-up period began on the index date and ended on the earliest of any of the following: the date of disenrollment from the plan, date of death, or the end of the study on March 31, 2016.

Statin use was based on fills in the first 30 days. Statin medications were summarized according to the number of patients with prescription fills for low-intensity statins (simvastatin, 5 and 10 mg; fluvastatin, 20 and 40 mg; lovastatin, 10 and 20 mg; pravastatin, 10 and 20 mg; pitavastatin, 1 and 2 mg); moderate-intensity statins (simvastatin, 20 and 40 mg; atorvastatin, 10 and 20 mg; rosuvastatin, 5 mg; fluvastatin, 80 mg; lovastatin, 40 and 80 mg; pravastatin, 40 and 80 mg; pitavastatin, 4 mg); and high-intensity statins (simvastatin, 80 mg; atorvastatin, 40 and 80 mg; rosuvastatin, 10, 20, and 40 mg).[25] Statin medications include ezetimibe; ezetimibe alone is categorized as a low-intensity statin. If patients had multiple strengths of statins present, use was assigned hierarchically as high, moderate, or low intensity.

No patient identities or medical records were disclosed for the purposes of this study. This study is fully compliant with the Health Insurance Portability Act (1996).

Study Populations

Patients included were men or women ≥45 years of age on the index date with documented diabetes mellitus and/or ASCVD who were prescribed statins and had at least 6 months of data preindex and for follow-up or had follow-up until death if it occurred in <6 months. Patients in the high-triglycerides analysis cohort were required to have triglycerides 2.26 to 5.64 mmol/L (200–499 mg/dL), and those in the comparator cohort were required to have triglycerides <1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (>40 mg/dL). Other inclusion and exclusion criteria are summarized in Table 1. ASCVD included acute coronary syndrome, myocardial infarction, angina, coronary or other arterial revascularization, stroke, transient ischemic

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Aged ≥45 y • ≥1 prescription claim for a statin medication in 2010 • ≥1 medical claim with a diagnosis procedure code representing ASCVD and/or diabetes mellitus • Known demographics (sex, insurance type, and geographic region) • Continuous enrollment with medical and pharmacy benefits during the baseline period and ≥6 mo starting on the index date, or death within 6 mo of the index date • *High-triglycerides cohort:* triglycerides 2.26 to 5.64 mmol/L (200–499 mg/dL) at most recent laboratory test before index date • *Comparator cohort:* triglycerides <1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (>40 mg/dL)	• Niacin on hand at index date • *ICD-9* codes indicating the presence of any of the following conditions during the 6-mo baseline period: pregnancy; severe liver disease; acute or chronic pancreatitis; malabsorption syndrome or gastric/intestinal bypass surgery; HIV/AIDS; end-stage renal disease, hemodialysis, or peritoneal dialysis; myositis, polymyositis, or rhabdomyolysis; or drug or alcohol abuse

ASCVD indicates atherosclerotic cardiovascular disease (which included acute coronary syndrome, myocardial infarction, angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease); HDL-C, high-density lipoprotein cholesterol; *ICD-9*, *International Classification of Diseases, Ninth Revision*.

attack, or peripheral arterial disease. Use of ezetimibe, fibrates, and prescription omega-3 products was allowed. Data on fish oil dietary supplements were not captured in the claims database because they are not prescription products.

A propensity score analysis was used to create a study population similar to the analysis population with high triglycerides by controlling for possible confounding relationships. The final list of variables included in the propensity score model was determined after review of the prematching descriptive analyses of patient characteristics and other preindex measures and included the following: age; sex; insurance type; region; baseline medical cost; LDL-C relative to the median, if available; baseline use of statin, fibrate, or omega-3 fatty acids; and the following diagnoses (ASCVD, diabetes mellitus, stroke, hypertension, renal disease, and peripheral artery disease). Patients in the high-triglycerides cohort were matched in a 1:1 ratio to the comparator cohort. Patients who were not matched were not included in the descriptive analyses. Non–HDL-C and HDL-C were added to the model in a separate analysis to evaluate their potential impact.

End Points

The primary objective of this analysis was to measure the occurrence of major cardiovascular events, defined as a composite of cardiovascular-related death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the follow-up period. Secondary objectives included quantification of healthcare costs and resource use. Medication compliance was determined using the proportion of days covered, which was calculated by dividing the number of days on which medication was available (on the basis of filled prescriptions) by the number of days between the earliest prescription claim in the observation period through the end of the observation period.

Statistical Analyses

All study variables were analyzed descriptively and reported for the overall study sample as well as stratified and statistically compared by cohort. Mean and SD were provided for all continuous variables. Descriptive techniques that account for the length of observation time, such as per patient per month, were used for analyses of healthcare cost and resource use. Statistical comparison tests included Rao-Scott test and χ^2 tests for categorical measures and *t* tests and analysis of variance for continuous measures. Multivariate prematch analyses used a Cox proportional hazard model to calculate hazard ratios (HRs) for time-to-event analyses and generalized linear models with a γ distribution and log link to calculate cost ratios. Healthcare costs and resource use were assessed on a per-patient–per-month basis. Kaplan-Meier analyses were used to calculate time-to-event probabilities. Clustered *P* values were calculated using a Cox proportional hazard model with cohort as the independent variable. $P<0.05$ was considered statistically significant.

Results

Approximately 1.6 million patients with at least 1 prescription claim for a statin were identified from the Optum Research Database. The Figure shows the disposition of these patients in the high-triglycerides and comparator cohorts after application of inclusion and exclusion criteria. After propensity

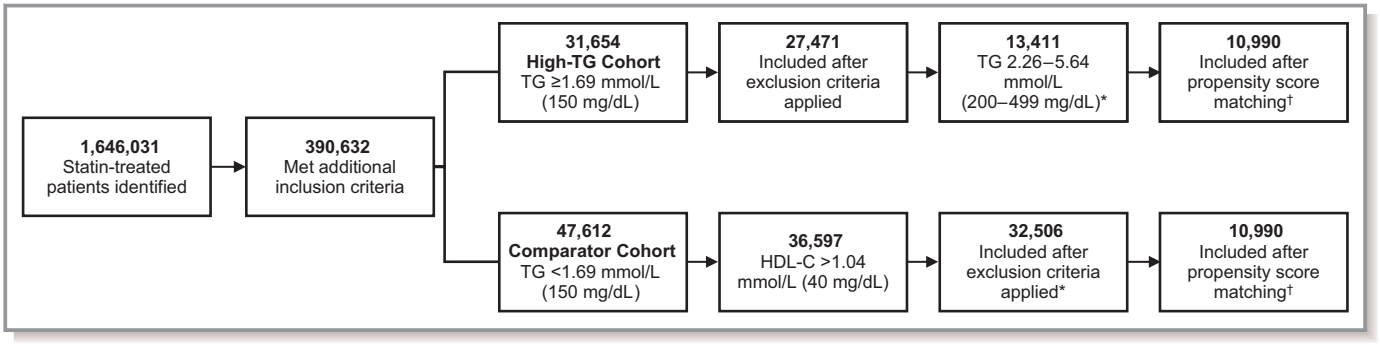

Figure. Patient disposition. *Population used for multivariate analyses. †Population used for patient characteristics and other analyses. HDL-C indicates high-density lipoprotein cholesterol; TG, triglycerides.

score matching, 10 990 patients were included in each cohort.

Because of the propensity score design of this analysis, there were few clinically important differences between the high-triglycerides cohort and the comparator cohort (Table 2). However, as expected, there was a substantial difference in mean triglycerides at baseline (P<0.001). Other lipid parameters were also significantly different, including HDL-C, non–HDL-C, and total cholesterol (all P<0.001). There was also a small, but significant, difference in mean LDL-C (P<0.001). Consistent with the study entry criteria requiring a diagnosis of diabetes mellitus or ASCVD, ≈85% of patients had diabetes mellitus and 29% of patients had ASCVD in both cohorts (Table 3). In addition, 79% of patients had hypertension, and with the exception of peripheral artery disease (14%) and renal disease (12%), all other diagnoses were present in <10% of patients in both cohorts. In the high-triglycerides cohort, 13% of patients were receiving fibrates, 8% were receiving ezetimibe, and 3% were receiving prescription omega-3 fatty acids versus 8% receiving fibrates, 9% receiving ezetimibe, and 2% receiving prescription omega-3 fatty acids in the comparator cohort.

Multivariate analysis of composite major cardiovascular events (controlled for patient characteristics and comorbidities) revealed a 34.9% higher rate of occurrence of a major cardiovascular event per unit time in the high-triglycerides cohort (n=13 411 patients) versus the comparator cohort (n=32 506 patients), with an HR of 1.35 and a 95% confidence interval (CI) of 1.225 to 1.485 (P<0.001; Table 4). Male sex (HR, 1.36; 95% CI, 1.23–1.50; P<0.001), diabetes mellitus (HR, 1.46; 95% CI, 1.26–1.69; P<0.001), and ASCVD (HR, 2.30; 95% CI, 2.05–2.59; P<0.001) were also significant predictors of a major cardiovascular event in this model, as was younger age, which had a protective effect. Significantly higher risk was also found for individual outcomes of nonfatal myocardial infarction (HR, 1.35; 95% CI, 1.19–1.52; P<0.001), nonfatal stroke (HR, 1.27; 95% CI, 1.14–1.42; P<0.001), and need for coronary revascularization (HR, 1.51; 95% CI, 1.34–1.69; P<0.001), but not unstable angina or cardiovascular death (Table 5).

Multivariate analyses of these populations also revealed that total healthcare costs and inpatient hospital visits were

Table 2. Patient Demographics and Baseline Characteristics

Variable	High-Triglycerides Cohort (n=10 990)*	Comparator Cohort (n=10 990)†	P Value
Age, mean (SD), y	61.7 (9.6)	62.2 (9.9)	<0.001
Female sex, n (%)	5433 (49.4)	5424 (49.4)	0.769
Insurance type, n (%)			
Commercial	7589 (69.1)	7571 (68.9)	0.556
Medicare	3401 (30.9)	3419 (31.1)	0.556
Duration of follow-up, mean (SD), mo	41.3 (23.8)	42.1 (23.9)	0.018
Statin intensity, n (%)‡			
Low	937 (8.5)	1084 (9.9)	<0.001
Moderate	6395 (58.2)	6621 (60.3)	0.002
High	3658 (33.3)	3285 (29.9)	<0.001
Baseline§ lipid profile, mean (SD), mmol/L‖			
Triglycerides	2.981 (0.68)	1.110 (0.33)	<0.001
LDL-C	2.748 (1.12)	2.634 (0.90)	<0.001
HDL-C	1.046 (0.24)	1.425 (0.32)	<0.001
Total cholesterol	5.133 (1.24)	4.566 (1.00)	<0.001
Non-HDL-C¶	4.090 (1.17)	3.139 (0.94)	<0.001

Rao-Scott test was used for binary measures; robust SEs were used for continuous measures. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*Triglycerides 2.26 to 5.64 mmol/L (200–499 mg/dL).
†Triglycerides <1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (>40 mg/dL).
‡See Methods for definitions of statin intensity. Z test using robust SEs was used for continuous measures.
§Baseline period excludes index date.
‖To convert from the International System Unit of mmol/L to mg/dL, divide triglycerides by 0.0113 and divide cholesterol by 0.0259.
¶Calculated by subtracting HDL-C result from total cholesterol.

Table 3. Baseline Comorbidities

Comorbidity	High-Triglycerides Cohort (n=10 990)*	Comparator Cohort (n=10 990)†	*P* Value
Diabetes mellitus	9326 (84.86)	9375 (85.30)	0.048
ASCVD	3185 (28.98)	3141 (28.58)	0.156
Myocardial infarction	235 (2.14)	189 (1.72)	0.020
Stroke	349 (3.18)	323 (2.94)	0.177
Angina	571 (5.20)	554 (5.04)	0.562
Coronary revascularization	299 (2.72)	213 (1.94)	<0.001
Peripheral artery disease	1561 (14.20)	1550 (14.10)	0.704
Heart failure	626 (5.70)	519 (4.72)	<0.001
Atrial fibrillation	527 (4.80)	472 (4.29)	0.070
Hypertension	8678 (78.96)	8723 (79.37)	0.106
Transient ischemic attack	403 (3.67)	410 (3.73)	0.788
Renal disease	1322 (12.03)	1314 (11.96)	0.767

Data are given as number (percentage) of each group. Rao-Scott test was used for binary measures; robust SEs were used for continuous measures. ASCVD indicates atherosclerotic cardiovascular disease.
*Triglycerides 2.26 to 5.64 mmol/L (200–499 mg/dL).
†Triglycerides <1.69 mmol/L (<150 mg/dL) and high-density lipoprotein cholesterol >1.04 mmol/L (>40 mg/dL).

significantly higher in the high-triglycerides cohort than the comparator cohort (Table 4). The cost ratio was 1.15 (95% CI, 1.08–1.21; *P*<0.001), indicating an ≈15% higher average total healthcare cost in the high-triglycerides cohort versus the comparator cohort. The mean (SD) total monthly healthcare cost was $1462 ($3354) in the high-triglycerides cohort versus $1279 ($2628) in the matched comparator cohort (*P*<0.001; n=10 990 for both cohorts). On the basis of the per-patient–per-month average total healthcare costs across the variable follow-up time in this study, this extrapolates to an approximate average difference of $24 million/year between these study populations and $220 million/year per 100 000 patients. Baseline diabetes mellitus had a cost ratio of 1.470 (95% CI, 1.32–1.64; *P*<0.001), and baseline ASCVD had a cost ratio of 1.71 (95% CI, 1.56–1.87; *P*<0.001). Younger age, particularly in the range of 45 to 54 years, had a protective effect on cost. A greater proportion of patients in the high-triglycerides cohort had an inpatient visit than the matched comparator cohort (34.0% versus 30.4%; *P*<0.001; n=10 990 for both cohorts). Controlling for patient characteristics, the high-triglycerides cohort had a 16.7% higher rate of occurrence of an inpatient stay in per-unit time than the comparator cohort (HR, 1.17; 95% CI, 1.11–1.22; *P*<0.001). Diabetes mellitus (HR, 1.45; 95% CI, 1.34–1.58; *P*<0.001) and ASCVD (HR, 1.85; 95% CI, 1.74–1.97; *P*<0.001) were also significant predictors of an inpatient stay in this model, as was lower age, which had a protective effect. There was no significant difference in the proportion of patients with an ambulatory visit, and although there was a significant difference in the proportion of patients with an emergency department visit, this was relatively similar between the matched cohorts (55.7% in the high-triglycerides cohort versus 53.9% in the matched comparator cohort; *P*=0.007; n=10 990 for both cohorts).

The mean (SD) 6-month proportion of days covered for statins was 0.76 (0.26), with a median of 0.87 in both matched

Table 4. Effects of High-Triglycerides Cohort Variable in Multivariate Analyses of Major Cardiovascular Events, Total Healthcare Costs, and Initial Inpatient Hospital Stay

Variable	Hazard or Cost Ratio for Cohort Variable	95% CI	*P* Value
Initial major cardiovascular event*	1.349	1.225–1.485	<0.001
Total healthcare costs†	1.145	1.084–1.210	<0.001
Initial inpatient hospital stay*	1.167	1.113–1.223	<0.001

High-triglycerides prematch cohort: triglycerides 2.26 to 5.64 mmol/L (200–499 mg/dL) (n=13 411 patients); comparator prematch cohort: triglycerides <1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (>40 mg/dL) (n=32 506 patients). Separate multivariate analyses of major cardiovascular events, total healthcare costs, and initial inpatient stay were performed. Covariates included triglycerides cohort, as represented herein, along with age (45–54, 55–64, and ≥65 years), sex, insurance coverage type, geographic region of enrollment, baseline clinical characteristics (diabetes mellitus, atherosclerotic cardiovascular disease, and low-density lipoprotein cholesterol laboratory result in relation to median), and baseline medication use (fibrate, prescription omega-3, both, and neither). CI indicates confidence interval; HDL-C, high-density lipoprotein cholesterol.
*Cox proportional hazard model.
†Generalized linear model (γ distribution, log link).

Table 5. Effects of High-Triglycerides Cohort Variable in Multivariate Analyses of Individual Major Cardiovascular Events

Variable	Hazard Ratio for Cohort Variable	95% CI	*P* Value
Nonfatal MI	1.345	1.191–1.517	<0.001
Nonfatal stroke	1.273	1.141–1.420	<0.001
Coronary revascularization	1.506	1.341–1.691	<0.001
Unstable angina	1.208	0.645–2.262	0.555
Cardiovascular-related death (MACE)*	1.332	0.970–1.830	0.076

High-triglycerides prematch cohort: triglycerides 2.26 to 5.64 mmol/L (200–499 mg/dL) (n=13 411 patients); comparator prematch cohort: triglycerides <1.69 mmol/L (<150 mg/dL) and high-density lipoprotein cholesterol >1.04 mmol/L (>40 mg/dL) (n=32 506 patients). Cox proportional hazard model. Covariates included triglycerides cohort, as represented herein, along with age (45–54, 55–64, and ≥65 years), sex, insurance coverage type, geographic region of enrollment, baseline clinical characteristics (diabetes mellitus, atherosclerotic cardiovascular disease, and low-density lipoprotein cholesterol laboratory result in relation to median), and baseline medication use (fibrate, prescription omega-3, both, and neither). It was necessary for statistical modeling to combine some of these covariate categories in certain models because of low event counts. CI indicates confidence interval; MACE, major cardiac adverse event; MI, myocardial infarction.

*Event occurred in an inpatient setting, with visit discharge status indicating a nonfatal event (absence of cardiovascular-related death; cardiovascular-related death was defined as a death in follow-up period [as identified with discharge status or the Death Master File]), based on diagnosis code for MACE event (MI, stroke, or revascularization) in the first or second position, that occurred in the emergency department setting within 1 day of a death date, or in an inpatient stay with a discharge date within 7 days of a death date.

Table 6. Effects of High-Triglycerides Cohort Variable in Multivariate Analyses of Composite and Individual Major Cardiovascular Events: Addition of Non–HDL-C to the Model

Variable	Hazard Ratio	95% CI	*P* Value
Initial major cardiovascular event	1.278	1.176–1.389	<0.001
Nonfatal MI	1.258	1.098–1.440	<0.001
Nonfatal stroke	1.176	1.039–1.331	0.010
Coronary revascularization	1.407	1.235–1.602	<0.001
Unstable angina	1.312	0.657–2.619	0.442
Cardiovascular-related death (MACE)*	1.390	0.974–1.983	0.069

High-triglycerides prematch cohort: triglycerides 2.26 to 5.64 mmol/L (200–499 mg/dL) (n=13 411 patients); comparator prematch cohort: triglycerides <1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (>40 mg/dL) (n=32 506 patients). Non–HDL-C was calculated for patients with both a total cholesterol and HDL-C laboratory result present at baseline. Cox proportional hazard model was used. CI indicates confidence interval; HDL-C, high-density lipoprotein cholesterol; MACE, major cardiac adverse event; MI, myocardial infarction.

*Event occurred in an inpatient setting with visit discharge status indicating a nonfatal event (absence of cardiovascular-related death; cardiovascular-related death was defined as a death in follow-up period [as identified with discharge status or the Death Master File]) based on diagnosis code for MACE event (MI, stroke, or revascularization) in the first or second position, that occurred in the emergency department setting within 1 day of a death date, or in an inpatient stay with a discharge date within 7 days of a death date.

cohorts (n=10 990). The overall mean (SD) proportion of days covered for statins was 0.67 (0.30) and 0.68 (0.29) for the high-triglycerides and matched comparator cohorts, respectively, with a median of 0.76 for both (n=10 990).

Because cholesterol in triglyceride-rich lipoproteins is captured in non–HDL-C, non–HDL-C was added to the multivariate analyses to determine if the increase in cardiovascular risk in the high-triglycerides cohort would be attenuated. We found that, although there was some attenuation in cardiovascular risk in the high-triglycerides cohort when adjusting for non–HDL-C, the risk of major cardiovascular events remained statistically significant in the high-triglycerides versus the comparator cohort in the model (Table 6). In addition, because HDL-C is inversely associated with triglycerides, the cardiovascular risk associated with high and low HDL-C in the high-triglycerides cohort was compared with the comparator cohort in a Kaplan-Meier analysis over a 5-year time period. In the high and low HDL-C subgroups within the high-triglycerides cohort, the risk of major cardiovascular events remained statistically significant versus the comparators (Table 7).

Discussion

This real-world analysis of administratively derived data from >20 000 patients in the Optum Research Database identified statin-treated patients with high triglycerides and a diagnosis of diabetes mellitus and/or ASCVD to be at a 34.9% higher risk of major cardiovascular events than a comparator cohort of patients with triglycerides <1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (>40 mg/dL) while controlling for other comorbidities. Reflective of the higher risk of major cardiovascular events, high triglycerides (2.26–5.64 mmol/L [200–499 mg/dL]) were also associated with significantly higher medical costs and resource use. This is consistent with a prior observational analysis that found triglycerides in the range 2.26 to 5.64 mmol/L (200–499 mg/dL) to be associated with significantly higher total medical costs than in patients with triglycerides <1.69 mmol/L (<150 mg/dL) (P<0.001).[26]

The population under investigation in this analysis represents a notably large group. In a separate analysis of the Optum Research Database of 4 867 300 patients with at least 1 prescription fill for a statin, 1 418 866 had at least 1 LDL-C measurement ≤2.59 mmol/L (≤100 mg/dL); of these patients, 693 308 (48.9%) had at least 1 triglycerides measurement ≥1.69 mmol/L (≥150 mg/dL), and 421 974 (29.7%) had at least 1 triglycerides measurement ≥2.26 mmol/L (≥200 mg/dL). This is supported by large cardiovascular outcomes trials, including or limited to patients with type 2 diabetes mellitus, wherein ≈15% to 20% of

Table 7. Kaplan-Meier Analysis of Initial Composite and Individual Major Cardiovascular Events in Patients With Triglycerides 200 to 499 mg/dL and HDL-C <40 mg/dL Versus HDL-C ≥40 mg/dL Compared With the Comparator Cohort

Event	Cohort		Time, y						Clustered *P* Value*
			0.5	1	2	3	4	5	
Initial major cardiovascular event	Triglycerides test population, HDL-C <40 mg/dL	Survival	0.9829	0.9703	0.9448	0.9178	0.8900	0.8646	<0.001
		At risk	7412	6242	4736	3731	2486	1889	
	Triglycerides test population, HDL-C ≥40 mg/dL	Survival	0.9844	0.9717	0.9470	0.9255	0.9098	0.8880	
		At risk	3029	2544	1893	1515	1048	791	
	Comparator	Survival	0.9866	0.9757	0.9602	0.9381	0.9214	0.9059	
		At risk	10 479	8898	6836	5494	3753	2911	
Nonfatal MI	Triglycerides test population, HDL-C <40 mg/dL	Survival	0.9944	0.9902	0.9807	0.9679	0.9586	0.9466	<0.001
		At risk	7496	6355	4892	3892	2634	2031	
	Triglycerides test population, HDL-C ≥40 mg/dL	Survival	0.9951	0.9907	0.9837	0.9737	0.9674	0.9585	
		At risk	3061	2588	1958	1578	1103	842	
	Comparator	Survival	0.9953	0.9914	0.9857	0.9780	0.9708	0.9648	
		At risk	10 567	9028	6982	5678	3910	3054	
Nonfatal stroke	Triglycerides test population, HDL-C <40 mg/dL	Survival	0.9947	0.9898	0.9776	0.9644	0.9499	0.9381	<0.001
		At risk	7497	6351	4882	3889	2627	2022	
	Triglycerides test population, HDL-C ≥40 mg/dL	Survival	0.9932	0.9876	0.9753	0.9652	0.9548	0.9442	
		At risk	3056	2582	1941	1569	1086	833	
	Comparator	Survival	0.9949	0.9901	0.9839	0.9733	0.9653	0.9546	
		At risk	10 563	9018	6976	5664	3908	3051	
Coronary revascularization	Triglycerides test population, HDL-C <40 mg/dL	Survival	0.9906	0.9836	0.9723	0.9628	0.9511	0.9391	<0.001
		At risk	7465	6307	4846	3863	2609	2003	
	Triglycerides test population, HDL-C ≥40 mg/dL	Survival	0.9942	0.9894	0.9804	0.9692	0.9672	0.9555	
		At risk	3058	2583	1942	1562	1094	831	
	Comparator	Survival	0.9938	0.9892	0.9830	0.9751	0.9684	0.9646	
		At risk	10 551	9002	6954	5654	3894	3039	
Unstable angina	Triglycerides test population, HDL-C <40 mg/dL	Survival	1.0000	0.9998	0.9995	0.9995	0.9995	0.9991	0.520
		At risk	7536	6406	4972	3994	2730	2117	
	Triglycerides test population, HDL-C ≥40 mg/dL	Survival	0.9997	0.9997	0.9992	0.9992	0.9992	0.9992	
		At risk	3075	2609	1980	1610	1129	867	
	Comparator	Survival	0.9997	0.9996	0.9993	0.9991	0.9991	0.9991	
		At risk	10 612	9099	7065	5786	4016	3151	
Cardiovascular-related death (MACE)†	Triglycerides test population, HDL-C <40 mg/dL	Survival	0.9997	0.9990	0.9973	0.9960	0.9937	0.9917	0.037
		At risk	7536	6407	4975	3997	2733	2119	
	Triglycerides test population, HDL-C ≥40 mg/dL	Survival	0.9997	0.9990	0.9981	0.9964	0.9951	0.9951	
		At risk	3076	2610	1982	1611	1129	867	
	Comparator	Survival	0.9994	0.9988	0.9980	0.9975	0.9968	0.9954	
		At risk	10 615	9102	7070	5790	4017	3152	

HDL-C indicates high-density lipoprotein cholesterol; MACE, major cardiac adverse event; MI, myocardial infarction.

*Clustered *P* values were calculated using Cox proportional hazard model with cohort as independent variable.

†Event occurred in an inpatient setting with visit discharge status indicating a nonfatal event (absence of cardiovascular-related death; cardiovascular-related death was defined as a death in follow-up period [as identified with discharge status or the Death Master File]) based on diagnosis code for MACE event (MI, stroke, or revascularization) in the first or second position, that occurred in the emergency department setting within 1 day of a death date, or in an inpatient stay with a discharge date within 7 days of a death date.

patients had triglycerides ≥2.26 mmol/L (≥200 mg/dL) and LDL-C <2.59 mmol/L (<100 mg/dL) and ≈25% to 40% had triglycerides ≥1.69 mmol/L (≥150 mg/dL) and LDL-C <2.59 mmol/L (<100 mg/dL).[23,27–32] Despite this relatively high prevalence, there is a lack of prospective data designed specifically to investigate such patient populations with high triglycerides despite statin therapy.

This lack of prospective data will begin to be addressed by several ongoing clinical trials investigating the impact of various triglyceride-lowering therapies on cardiovascular outcomes in high-risk statin-treated patients. REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial; URL: http://www.clinicaltrials.gov. Unique identifier: NCT01492361) is expected to be the first of these trials to present results, which are expected in the second half of 2018. This phase 3b, international, multicenter, prospective, double-blind, placebo-controlled, parallel-group trial randomized ≈8000 high-risk patients receiving stable statin therapy with triglycerides 1.69 to 5.64 mmol/L (150–499 mg/dL) to the highly purified omega-3 fatty acid icosapent ethyl (ethyl ester of eicosapentaenoic acid) 4 g/d or matching placebo.[33] Patients in this trial are required to have a history of cardiovascular disease or diabetes mellitus plus an additional cardiovascular risk factor. A protocol amendment early in the trial changed the allowed lower limit for triglycerides from 1.69 mmol/L (150 mg/dL) to 2.26 mmol/L (200 mg/dL). Similar to the analysis reported herein, the primary efficacy end point is a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia. The STRENGTH (Study to Assess Statin Residual Risk Reduction With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia) trial (URL: http://www.clinicaltrials.gov. Unique identifier: NCT02104817) is a phase 3, randomized, placebo-controlled cardiovascular outcomes trial enrolling ≈13 000 patients receiving stable statin therapy with triglycerides 2.03 to 5.64 mmol/L (180–499 mg/dL) and HDL-C <1.09 mmol/L (<42 mg/dL) in men and <1.22 mmol/L (<47 mg/dL) in women to omega-3 carboxylic acids (mixture of eicosapentaenoic and docosahexaenoic acids) or placebo.[34] Finally, PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes; URL: http://www.clinicaltrials.gov. Unique identifier: NCT03071692) is a phase 3, randomized, placebo-controlled cardiovascular outcomes trial of the investigative triglyceride-lowering agent pemafibrate enrolling ≈10 000 patients; the population for this study includes statin-treated patients with diabetes mellitus, triglycerides 2.26 to 5.64 mmol/L (200–499 mg/dL), and HDL-C ≤1.04 mmol/L (≤40 mg/dL).[35]

Importantly, the present study of a large real-world database helps to more fully and accurately characterize the population of statin-treated patients with residual cardiovascular risk and high triglycerides. This type of real-world data, collected from electronic administrative claims and medical records, is pragmatic in that it examines this patient population in the context of clinical practice.[36,37] It brings novel perspective to the healthcare costs and disease burden of this large population outside of clinical trials and may help to place the results of the ongoing cardiovascular outcomes trials into a real-world perspective. The high prevalence of diabetes mellitus in the general population and the apparent coexistence of diabetes mellitus and high triglycerides in many patients suggest that this population may be at significant cardiovascular risk, and is worthy of further study; patients with diabetes mellitus in the population studied herein will be the subject of a future analysis.

The average total healthcare cost associated with high triglycerides in this study was ≈15% higher than for those with triglycerides in the normal range; this was reflected by an increased total healthcare cost of ≈$183 per month per patient with high triglycerides. In addition, patients with high triglycerides were 16.7% more likely to have an inpatient visit, which would be expected to incur increased costs. Given the prevalence of high triglycerides and the associated residual risk, the potential economic impact of high triglycerides over a lifetime is, therefore, likely substantial. A strength of this type of real-world experience study is that it encompasses a large number of patients and measures all healthcare costs. Cost estimates were conservative because this study did not estimate costs that may have been paid by other payers, and the study did not include nonmedical costs associated with patient or societal expenditures, such as transportation for treatment or missed work days.

In addition to the differences in baseline triglycerides and HDL-C per study inclusion criteria and design, there were differences in baseline levels of other parameters, including non–HDL-C and HDL-C, which represent study limitations. However, when non–HDL-C was added to the model, there was some attenuation of the impact of the cohort variable, although the findings remained statistically significant. With regard to baseline HDL-C, analyses of high and low HDL-C indicated that freedom from cardiovascular events at 5 years was significantly higher in the low-triglycerides comparator group than in the high-triglycerides group, regardless of whether HDL-C was high or low, but was incrementally higher in the group with higher HDL-C.

The real-world nature of this database has limitations. Observational studies often use existing data, rather than prospectively collected data, which can add to the uncertainty about findings and limit the usefulness of such data.[37] Although claims data are valuable for examination of healthcare outcomes, treatment patterns, healthcare resource use, and costs, all claims databases have certain

inherent limitations affecting generalizability because the claims are collected for the purpose of payment and not research. The findings of this study should be considered within the limitations of the data and study design. With regard to the patient population, only patients with continuous eligibility were included, and thus patients who did not maintain membership during the baseline period and the outcome period for at least 6 months starting with the index date were excluded. This study was limited to patients enrolled in managed care plans in the United States and may not be generalizable to other populations. With regard to medication, the claims records of dispensed medications do not indicate whether the medication was consumed or whether it was taken as prescribed, and use of over-the-counter medications, prescription samples provided by physicians, or prescriptions filled outside the health plan was not observable in the pharmacy records. With regard to disease state, the presence of a diagnostic code may not necessarily be conclusive for the presence of any given disease. With regard to statistical analyses, those reported herein should be evaluated in the context of the large sample size, which may indicate statistical significance for some parameters, even when differences are small and not clinically important. Real-world studies may contain inaccurate recording of health events, missing data, and uncertainty about internal validity.[37,38] In the present study, laboratory test results during the follow-up period were only available for a subset of patients. The extent of missing data may not be distinguishable from the lack of an administered test. This analysis was designed to assess health status and burden over time in patients with high triglycerides, despite generally controlled LDL-C, and was not designed to assess the potential effects of any adjunct treatment modality. Furthermore, given the observational nature of the study, and despite robust propensity-matching and multiple sensitivity analyses, a possibility of residual unmeasured confounding cannot be excluded. Despite these standard and study design–specific limitations, these data allow for examination of healthcare burden, use, and expenditure patterns in a real-world setting with a large sample size of patients with diverse medical histories, apart from the highly controlled environment of clinical trials.

Conclusions

Statin-treated patients with high residual cardiovascular risk and high triglycerides (2.26–5.64 mmol/L [200–499 mg/dL]) had worse cardiovascular outcomes, greater healthcare use, and overall higher healthcare costs than comparators who had triglycerides <1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (>40 mg/dL). These patients with high triglycerides had a higher risk for nonfatal myocardial infarction and nonfatal stroke and need for coronary revascularization than those with lower triglycerides and higher HDL-C. The increased cardiovascular risk in the high-triglycerides versus comparator cohorts was maintained even with the addition of non–HDL-C to the multivariate model and when analyzing high and low HDL-C subgroups. This analysis provides strong support for the conclusion that hypertriglyceridemia represents an independent risk factor for ASCVD. This group of patients with high triglycerides and a history of diabetes mellitus and/or ASCVD is relatively large, may be commonly encountered in clinical practice, and warrants further study. Prospective cardiovascular outcome trials of similar patient populations are ongoing.

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