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Normal Triglyceride Levels and Coronary Artery Disease Events: The Baltimore Coronary Observational Long-Term Study

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Objectives. **This study sought to evaluate long-term predictors of coronary events in men and women with arteriographically defined coronary artery disease (CAD).**

Background. **There is conflicting evidence of the role of triglycerides (TGs) as a prognosticator of CAD, and no studies have examined the long-term outcome of "normal" levels in predicting new coronary events.**

Methods. **This was a retrospective cohort study that evaluated 740 consecutive patients presenting for diagnostic coronary arteriography between 1977 and 1978. Beginning in 1988, patients with arteriographic CAD (n = 350) were recontacted and asked to complete detailed medical questionnaires. Case and control patients were stratified by development of new coronary events, including death from ischemic heart disease, nonfatal myocardial infarction and revascularization.**

Results. **There were 199 events during the 18-year follow-up period. The mean high density lipoprotein cholesterol (HDL-C) was significantly lower (35 vs. 39 mg/dl; p = 0.002) and TGs higher (160 vs. 137 mg/dl; p = 0.03) in case patients than in control patients; After adjusting for age, gender and beta-adrenergic blocking agent use, multiple logistic regression analysis revealed the following independent predictors of CAD events: diabetes mellitus (relative risk [RR] 2.1, 95% confidence interval [CI] 1.4% to 3.1%), HDL-C <35 mg/dl (RR 1.5, 95% CI 1.1% to 2.0%) and TGs >100 mg/dl (RR 1.5, 95% CI 1.1% to 2.1%). A Kaplan-Meier analysis revealed significantly reduced survival from CAD events in patients with baseline TG levels ≥100 mg/dl compared with TG levels <100 mg/dl (p = 0.008).**

Conclusions. **TG levels previously considered "normal" are predictive of new CAD events. The cutpoints established by the National Cholesterol Education Program for elevated TGs (>200 mg/dl) may need to be refined.**

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The importance of triglycerides (TGs) as a risk factor for coronary artery disease (CAD) has long been controversial. The earliest study demonstrating this association nearly four decades ago (1) was disputed several years later (2). Subsequently, epidemiologic and observational studies disclosed that TG levels predicted CAD in univariate analysis but this effect was often attenuated when other more powerful covariates (e.g., high density lipoprotein cholesterol [HDL-C]) were entered into the analysis (3). Recently, however, a large body of data has revived interest in TGs. They have included the discovery of TG-rich lipoproteins in atherosclerotic plaques (4). In addition, TGs or hydrolyzed TG-rich lipoproteins (e.g., remnant particles) have been shown to predict the extent of CAD (5) and progression of mild to moderate lesions (6,7), the lesions most vulnerable to plaque fissuring and rupture (8).

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The National Cholesterol Education Program (NCEP) have established a cutpoint of 200 mg/dl, below which both total cholesterol and TG levels are considered desirable (9). For total cholesterol, this cutpoint was in part derived from the Multiple Risk Factor Intervention Trial, owing to the marked increase in CAD rates coinciding with a total cholesterol level >200 mg/dl (10). Similar data are not available for TGs; the cutpoint of 200 mg/dl appears to have arisen from modifications of a National Institutes of Health Consensus Development Conference (11). Furthermore, the disparity between median total cholesterol (199.8 mg/dl) and TGs (100 mg/dl) in adult U.S. men and women (12), suggests that the level of TGs presently viewed as "normal" or desirable, may in fact be too high. Therefore, the purpose of the Baltimore Coronary Observational Long-Term Study (COLTS) was to determine whether TG levels in the desirable range may pose an additional risk of new CAD events in patients with arteriographically defined CAD.

Methods

Patient selection and baseline data. Seven hundred forty consecutive patients were admitted for diagnostic cardiac catheterization at The Johns Hopkins Hospital between February 1977 and April 1978. They comprised a group of patients

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Abbreviations and Acronyms

BMI = body mass index
CAD = coronary artery disease
CI = confidence interval
COLTS = Baltimore Coronary Observational Long-Term Study
HDL-C = high density lipoprotein cholesterol
LDL-C = low density lipoprotein cholesterol
NCEP = National Cholesterol Education Program
RR = relative risk
TG = triglyceride

evaluated for coronary risk factors associated with arteriographically defined CAD (13). All patients completed a detailed self-administered risk factor questionnaire and fasting blood was sampled on the morning before catheterization. Plasma cholesterol and TG levels were determined in a Technicon Auto Analyzer II (Technicon Instruments Corp.). Preparative ultracentrifugation (18 h × 105,000 *g*) allowed for separation of very low density lipoprotein cholesterol from HDL-C and low density lipoprotein cholesterol (LDL-C). HDL-C was measured following heparin-manganese precipitation of apolipoprotein B-containing lipoproteins. LDL-C was estimated by the Friedewald equation (14). Coronary arteriograms were graded by three cardiologists after qualitatively analyzing the degree of stenosis in 15 segments of the coronary tree (15). Ventriculography was performed to evaluate left ventricular function.

Data collection and end points. In 1988, the follow-up study was designed. Patients were excluded if they had had a myocardial infarction within 3 months of the baseline coronary angiogram (16) or had received heparin before lipid or lipoprotein measurements (17) (n = 205). Rigorous attempts were made to recontact the remaining 535 patients through a variety of sources, including referring physicians, medical records, the Motor Vehicle Agency and the Social Security Administration. Once a patient was located, each was asked to complete medical questionnaires detailing new cardiovascular events and diagnostic and therapeutic interventions occurring subsequent to the baseline (1977 to 1978) coronary arteriogram. End points included cardiovascular death, based on the International Classification of Diseases, Clinical Modification (ICD-9-CM Codes 410-411) (18); nonfatal myocardial infarction, defined by electrocardiographic and enzymatic criteria (19); surgical revascularization (unless scheduled in concert with the baseline coronary angiogram); percutaneous transluminal coronary angioplasty; and nonsurgical coronary vessel occlusion. End points were confirmed by medical records, death certificates (obtained through the National Death Index) and autopsy records (where applicable). As data collection was completed in November, 1996, a total of 18 years of follow-up information was obtained.

Statistical analysis. Data collected at baseline were stored in the SAS data base system and used for subsequent analysis. Patients were grouped into those with and without new cardiovascular events. Continuous and categorical variables were analyzed by the Student *t* test and chi-square analysis, respectively. The designated level of significance was $p < 0.05$. Categoric variables for lipoproteins included low HDL-C (<35 mg/dl) and elevated LDL-C (>130 mg/dl) as outlined by the NCEP (9). The TG cutpoint of 100 mg/dl was selected because it approximates the median level in adult men (112 mg/dl) and women (88 mg/dl) in the United States and Canada (12). Other categorical variables were the number of "diseased" vessels, defined as 50% or greater stenosis in an epicardial coronary artery segment, left ventricular ejection fraction <35%, presence or absence of hypertension, beta-blocker use, diabetes mellitus, cigarette smoking, obesity (body mass index [BMI] >27), and sedentary lifestyle.

An age- and gender-adjusted Cox proportional hazards regression model was employed to estimate the effect of specific covariates as independent predictors of new CAD events. Relative risk and the corresponding 95% confidence interval were designated for each statistically significant covariate. A Kaplan-Meier survival analysis (20) assessed the time to event rate stratified by a TG cutpoint of 100 mg/dl.

Table 1. Cardiovascular Events in the Baltimore Coronary Observational Long-Term Study

	No. of Patients
Death from ischemic heart disease (ICD-9 410–411)	136
Nonfatal myocardial infarction	20
Coronary revascularization	38
Nonsurgical vessel occlusion	5
Total	199

ICD-9 = International Classification of Disease, Ninth Revision.

Results

Patient follow-up. Of the 535 patients meeting the initial eligibility criteria, follow-up information was attained for 492 (92%). This report focuses on patients with arteriographic CAD defined at baseline (n = 350). Sixty-three percent of women (n = 72) and 56% of men (n = 278) (p = 0.3) had new events during the 18-year follow-up period; most patients (64%) succumbed to ischemic heart disease (Table 1).

Risk factor assessment and lipoprotein measurements. The prevalence of selected risk factors in men and women is shown in Table 2. There was a significantly higher prevalence of diabetes mellitus in women and cigarette smoking in men. Most men and women had TG levels ≥100 mg/dl and were sedentary. The mean baseline levels of lipids and lipoproteins in patients with and without new CAD events is listed in Table 3. There were significantly higher levels of TGs and lower levels of HDL-C among patients with new events. Similarly, we found a higher rate of diabetes mellitus and obesity (BMI >27 kg/m^2) at baseline in patients having new CAD events (Table 4). The high overall rate of sedentary lifestyle and cigarette smoking may have precluded significant differences between the groups.

Table 2. Prevalence of Selected Risk Factors in Men and Women With Coronary Artery Disease at Baseline

	Men (n = 278)	Women (n = 72)	p Value
BMI >27 kg/m^2	33%	36%	NS
Cigarette smoker	80%	63%	0.003
Diabetes mellitus	12%	22%	0.024
Hypertension	36%	44%	NS
Low HDL	51%	71%	0.003
Sedentary lifestyle	76%	75%	NS
TGs ≥100 mg/dl	69%	63%	NS

BMI = body mass index; HDL = high density lipoprotein; TGs = triglycerides.

The baseline prevalence of selected risk factors in CAD patients with new CAD events is shown in Table 4. There was a significantly higher prevalence of obesity and diabetes mellitus compared with other variables tested. We also assessed the impact of beta-blockers, agents that commonly elevate TGs (21). A higher prevalence of beta-blocker use was observed with a TG level ≥100 mg/dl than with a TG level <100 mg/dl (53% vs. 49%, p = 0.013), although beta-blocker use was not an independent predictor of new events (see later).

Figure 1 illustrates the baseline TG quartiles in CAD patients with new events. There was a significantly higher prevalence of low TGs (first quartile mean <101 mg/dl) than high TGs (quartiles 2 to 4) in patients without new CAD events (p = 0.002).

Regression and survival analyses. A univariate analysis assessed the effect of various covariates on CAD event rate. The variables tested included beta-blocker use, BMI >27, cigarette smoking, diabetes mellitus, HDL-C <35 mg/dl, hypertension, LDL-C >130 mg/dl, sedentary lifestyle and TG level ≥100 mg/dl. Only diabetes mellitus, TG level ≥100 mg/dl and HDL-C <35 mg/dl were statistically important predictors of new events. A Cox regression analysis adjusted for age, gender and beta-blocker use demonstrated that diabetes mellitus (relative risk [RR] 2.1, 95% confidence interval [CI] 1.4% to 3.1%), HDL-C <35 mg/dl (RR 1.5, 95% CI 1.1% to 2.0%) and TG level ≥100 mg/dl (RR 1.5, 95% CI 1.1% to 2.1%) were independent predictors of new CAD events. Even after exclusion of diabetic patients, TGs remained a significant predictor of new CAD events (RR 1.8, 95% CI 1.2% to 2.7%). Kaplan-Meier survival analysis (Fig. 2) demonstrated significantly reduced survival from subsequent CAD events in patients with a baseline TG level ≥100 mg/dl than in those with higher TG levels (p = 0.008).

Table 3. Mean (±SD) Baseline Levels of Selected Variables With and Without New Coronary Artery Disease Events

Variable	CAD	No CAD	p Value
Age	54.3 ± 9.5	54.1 ± 8.9	NS
TC	219.0 ± 41.1	216.6 ± 48.4	NS
LDL-C	152.6 ± 39.0	149.2 ± 45.8	NS
TGs	160 ± 95.6	137.2 ± 101.4	0.03
HDL-C	35.2 ± 8.9	38.7 ± 11.3	0.002

*CAD = coronary artery disease; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TC = total cholesterol; TGs = triglycerides.

Table 4. Baseline Prevalence of Selected Variables With and Without New Coronary Artery Disease Events

Variable	CAD	No CAD	p Value
BMI >27 kg/m^2	38%	25%	0.003
Cigarette smoker	74%	70%	NS
Diabetes mellitus	17%	7%	0.0002
Hypertension	38%	32%	NS
Sedentary lifestyle	74%	76%	NS

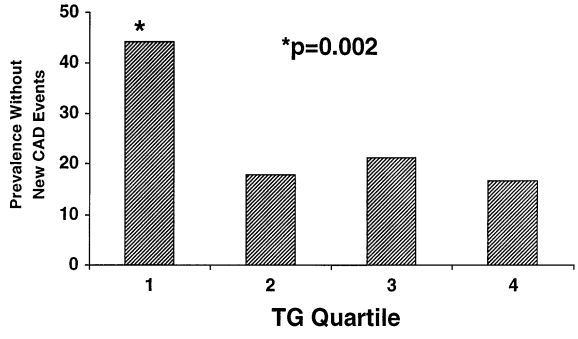
BMI = body mass index; CAD = coronary artery disease.

Discussion

The most novel finding of this 18-year follow-up study is that a TG level previously viewed as "normal" and within the desirable range (100 to 199 mg/dl) predicts new CAD events in patients with arteriographically defined CAD. The study also extends previous observations that diabetes mellitus and low HDL-C are independent predictors of CAD (22,23).

Mechanisms linking TG and TG-rich lipoproteins to CAD. Previous studies may have failed to expose lower TG levels as a potentially important source of CAD events because of the lack of a curvilinear effect as seen with LDL-C (10). Inhibited hydrolysis of TG-rich lipoproteins resulting in very high TG levels (>1,000 mg/dl) has with few exceptions (24) been more commonly associated with pancreatitis rather than CAD (25). By contrast, partial or complete hydrolysis yields particles that are smaller and cholesterol enriched. These remnant particles appear to be avidly incorporated by macrophages in a manner analogous to modified LDL-C (26). Indeed, there is increasing

Figure 1. Baseline TG quartiles in patients with CAD and new events. Quartile 1 = <101 mg/dl; quartile 2 = 101 to 134 mg/dl; quartile 3 = 135 to 186 mg/dl; quartile 4 = >187 mg/dl. Bar graph illustrates the prevalence of each quartile in patients with CAD without new events. Patients without a CAD event evidenced a higher prevalence of low TGs (quartile 1) and a lower prevalence of high TGs (quartiles 2 to 4) than did patients with a new event (p = 0.002).



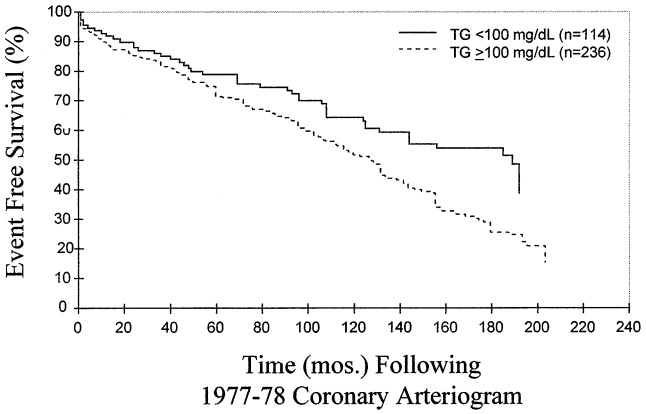


Figure 2. Kaplan-Meier survival analysis comparing patients with CAD stratified by baseline TG level (100 mg/dl) at 1977 to 1978 coronary arteriography. Wilcoxon log-rank test indicates significant differences in event-free survival between the groups ($p = 0.008$).

evidence that lipoprotein lipase genetic polymorphisms or mutations that lead to partial catabolism of TG-rich lipoproteins may be associated with premature CAD even in the absence of overt hypertriglyceridemia (27–29). Enhanced atherogenicity of TG-rich lipoproteins may also result indirectly by means of increased transfer of TG to lipoproteins of higher density (LDL-C and HDL-C) in exchange for cholesteryl esters (30). Both TG-rich LDL-C and HDL-C are avidly hydrolyzed by hepatic lipase; the consequences are a predominant population of small, dense LDL-C particles that are highly susceptible to oxidation (31) and cholesteryl ester poor HDL-C that may bolster apolipoprotein A-I catabolism, thereby attenuating reverse cholesterol transport (32). Postprandial lipemia may also contribute to atherogenesis (33). Delayed clearance of TG-rich lipoproteins has been observed in CAD patients (34) and may occur despite normal fasting TG levels (35). Finally, hypertriglyceridemia may promote thrombogenicity owing to enhanced secretion of factor VII and plasminogen activator inhibitor (36).

TG levels and CAD risk. In the present study, a threshold effect for enhanced CAD risk was observed at TG levels ~100 mg/dl. This is noteworthy because an increased prevalence of dense, more atherogenic LDL-C particles emerge as TG levels exceed 100 mg/dl (31). That earlier studies stratified by TG cutpoints of 200 mg/dl lacked the power to detect significant differences in event rate may have reflected an inordinate number of patients with considerably lower TG levels. Indeed, extrapolation of previous published data have disclosed an elevated risk of CAD when TG exceeds 100 mg/dl. In a 30-year follow-up study of the Framingham Heart Study, the relative risk of CAD was nearly twofold higher in men and women with TG levels >250 mg/dl compared with <100 mg/dl (37). Similarly, in the Prospective Cardiovascular Munster Study of 4,221 patients followed up for 6 years, there was slightly greater than twofold risk of CAD events within the highest tertile of TG (>162 mg/dl) than with the lowest (<105 mg/dl) ($p < 0.001$); the vast majority of patients in the study evidenced TG levels <200 mg/dl (mean TG levels with and without CAD were 163 and 134.5 mg/dl, respectively) (38). Comparable findings extended to patients with fasting hyperglycemia where TG levels above the median (123 mg/dl) had a significant impact on CAD mortality rates (39).

TG reduction and CAD event rate/arteriographic changes. Although recent evidence ascribes a noteworthy role for TG in assessing CAD risk, no studies have examined the impact of selective TG reduction on the CAD event rate. In the Helsinki Heart Study, patients with TG levels >200 mg/dl and a high LDL-C/HDL-C ratio (>5) exhibited the greatest reduction in CAD events with gemfibrozil (40). A trial evaluating bezafibrate on CAD progression in survivors of myocardial infarction found significantly reduced arteriographic progression in association with reduced TG (31%) and fibrinogen (12%) levels, despite only modest HDL-C elevation (9%) and no significant reduction in LDL-C (41). More recently, gemfibrozil reduced TG levels 36% and retarded progression of saphenous vein bypass graft lesions in normolipidemic men (mean TG level ~150 mg/dl) with low HDL-C levels (42). An ongoing secondary prevention study in normocholesterolemic patients will assess the relative contribution of TG reduction (and HDL-C raising) on cardiovascular end points (43).

Study limitations. Limitations of the present study include lack of apolipoprotein B measurements, which were not routinely performed at the study's outset. The measurement of the apolipoprotein B particle number is important because of the association between elevated TG levels and small, dense LDL-C (44). Moreover, lipid and lipoprotein measurements are variable and influenced by postprandial fat and factors affecting rheology (45). Although only one fasting measurement was performed in the present study, TG variability was minimized by measuring levels in the fasting state (14 h) and in the supine position before cardiac catheterization. In addition, patients were eliminated from participation if 1) blood was drawn after heparin was administered (heparin activates lipoprotein lipase and may falsely lower TG) and 2) a myocardial infarction occurred within 3 months of the study owing to artifically elevated TG elevation compared with basal conditions (46). Finally, the study was performed in patients admitted for diagnostic coronary arteriography. As such, the level of TG at which CAD risk was found to increase (100 mg/dl) may not be applicable to the population at large.

Conclusions and potential implications. A recent case-control study (47) supports the meta-analysis by Hokanson and Austin (48) that TG independently predicts initial CAD events even after adjustment for HDL-C. The present study extends these observations to CAD patients with a "normal" TG level. One potential implication would be further encouragement of hygienic measures (e.g., weight loss and exercise) than presently advocated for CAD patients in whom TG levels are well within the desirable range (e.g., 100 to 199 mg/dl). The utility of pharmacologic therapy is presently under evaluation (43). Notwithstanding, until randomized clinical trials demonstrate an independent effect of TG reduction on CAD event rate, it

is unlikely that significant alterations in TG cutpoints and therapeutic strategies will accompany future NCEP revisions.

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