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Impact of Triglyceride Levels Beyond Low-Density Lipoprotein Cholesterol After Acute Coronary Syndrome in the PROVE IT-TIMI 22 Trial

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Objectives The purpose of this study was to assess the impact of on-treatment triglycerides (TG) on coronary heart disease (CHD) risk after an acute coronary syndrome (ACS).

Background The PROVE IT-TIMI (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) 22 trial demonstrated that low-density lipoprotein cholesterol (LDL-C) <70 mg/dl was associated with greater CHD event reduction than LDL-C <100 mg/dl after ACS. However, the impact of low on-treatment TG on CHD risk beyond LDL-C <70 mg/dl has not been explored.

Methods The PROVE IT-TIMI 22 trial evaluated 4,162 patients hospitalized for ACS and randomized to atorvastatin 80 mg or pravastatin 40 mg daily. The relationship between on-treatment levels of TG and LDL-C and the composite end point of death, myocardial infarction (MI), and recurrent ACS were assessed 30 days after initial presentation.

Results Low on-treatment TG (<150 mg/dl) was associated with reduced CHD risk compared with higher TG in univariate analysis (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.62 to 0.87; $p < 0.001$) and in adjusted analysis (HR 0.80, 95% CI 0.66 to 0.97; $p = 0.025$). For each 10-mg/dl decrement in on-treatment TG, the incidence of death, MI, and recurrent ACS was lower by 1.6% or 1.4% after adjustment for LDL-C or non–high-density lipoprotein cholesterol and other covariates ($p < 0.001$ and $p = 0.01$, respectively). Lower CHD risk was also observed with TG <150 mg/dl and LDL-C <70 mg/dl (HR 0.72, 95% CI 0.54 to 0.94; $p = 0.017$) or low on-treatment TG, LDL-C, and C-reactive protein (<2 mg/l) (HR 0.59, 95% CI 0.41 to 0.83; $p = 0.002$) compared with higher levels of each variable in adjusted analysis.

Conclusions On-treatment TG <150 mg/dl was independently associated with a lower risk of recurrent CHD events, lending support to the concept that achieving low TG may be an additional consideration beyond low LDL-C in patients after ACS. (The PROVE IT-TIMI 22 trial; NCT00382460) (J Am Coll Cardiol 2008;51:724–30) © 2008 by the American College of Cardiology Foundation

Epidemiologic surveys have observed that elevated levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) are associated with increased risk of coronary heart disease (CHD) (1), and therapeutic strategies that lead to a statistically significant reduction in LDL-C lower CHD event rates (2). The magnitude of CHD risk reduction as a consequence of LDL-C lowering often ranges between 25% and 35% (3). One potential impediment limiting further reduction in CHD events despite low on-treatment LDL-C is residual elevation in serum triglyceride (TG) levels (4). Historically, elevated TG has predicted CHD events in univariate analysis, only to weaken after adjustment for other covariates, including plasma glucose and high-density lipoprotein cholesterol (HDL-C), to which it is strongly and inversely correlated

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(5). Yet, even after adjustment for HDL-C, detailed evaluation of population-based prospective studies has disclosed an independent effect of TG on CHD events (6). Coupled with the knowledge that combined hyperlipidemia (i.e., elevated LDL-C and TG) promotes CHD to a significantly greater extent than either high LDL-C or TG alone (7), the present analysis was undertaken to test the hypothesis that low on-treatment levels of TG when added to low LDL-C would be superior to low LDL-C alone in reducing subsequent CHD events after an acute coronary syndrome (ACS).

Methods

Study population and protocol. The study population originated from the PROVE IT-TIMI (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) 22 trial, a study prospectively designed to compare the effect of intensive versus standard therapy to reduce LDL-C, as previously reported (8,9). Briefly, 4,162 men and women hospitalized for ACS with total cholesterol <240 mg/dl, or <200 mg/dl if receiving lipid-lowering therapy, were randomly assigned to receive intensive therapy (atorvastatin 80 mg daily) or standard therapy (pravastatin 40 mg daily) for a mean follow-up period of 2 years. In addition, gatifloxacin versus placebo was tested concomitantly in a factorial design. Total cholesterol, TG, and HDL-C were measured using an enzymatic colorimetric assay (Roche Modular system, Roche Diagnostics, Indianapolis, Indiana) after the recommended 12-h overnight fast (10). The LDL-C was estimated using the formula: total cholesterol − (TG/5 + HDL-C) (11), or directly measured if TG exceeded 400 mg/dl. Lipid and lipoprotein levels were obtained at baseline, 1, 4, 8, 16, and 24 months, and the final visit. The composite end point of death, myocardial infarction (MI), or recurrent ACS was used as previously outlined (12).

Abbreviations and Acronyms

ACS = acute coronary syndrome
CHD = coronary heart disease
CRP = C-reactive protein
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
MI = myocardial infarction
TG = triglycerides

Statistical analysis. Kaplan-Meier event rates for the composite end point of interest were determined during follow-up (at 2 years) after censoring patients with events within 30 days of the initial ACS event. Hazard ratios (HRs) and associated 95% confidence intervals (CIs) were calculated using selected cut-points as referents. Cut-points were derived from the National Cholesterol Education Program Adult Treatment Panel III guidelines (13,14) and included: LDL-C <70 mg/dl, the optional target goal in ACS patients; TG <150 mg/dl, the normal designate also used in the metabolic syndrome classification; and HDL-C <40 mg/dl in men and <50 mg/dl women, as similarly classified (14). In addition, other selected cut-points for TG (100 and 200 mg/dl) and non–HDL-C (100 and 130 mg/dl) were evaluated (13–15). The impact of TG <150 mg/dl with achieved dual parameters of low LDL-C (<70 mg/dl) and C-reactive protein (CRP; <2 mg/l) (16) on recurrent CHD events was also examined. A Cox proportional hazards model included clinically important variables (e.g., age, gender, smoking, hypertension, obesity, diabetes), potential confounders or effect modifiers (e.g., low HDL-C, peripheral vascular disease, prior statin therapy, prior ACS), and intervention (atorvastatin 80 mg/day vs. pravastatin 40 mg/day) to estimate the effect of on-treatment LDL-C and

Table 1 Baseline Characteristics by TG Quintile at 30 Days After an ACS

Characteristic	TG Quintile 1 (n = 763)	2 (n = 753)	3 (n = 737)	4 (n = 732)	5 (n = 733)	Total (n = 3,718)
General						Mean
Mean age, yrs	59.7	59.2	58.8	57.5	55.3	58.1
Men, %	81.9	78.9	76.0	74.0	82.0	78.6
Coronary risk factors, %						
Current smoker	30.0	34.0	33.7	41.3	42.4	36.2
Hypertension	46.7	45.3	51.7	51.8	51.6	49.4
Obesity (BMI >30 kg/m^2)	28.4	34.8	39.2	43.8	51.3	39.4
Diabetes	13.8	16.1	16.4	19.1	20.6	17.2
Prior ACS	22.4	23.5	28.1	28.3	34.8	27.4
Prior statin use	20.3	21.9	26.5	27.1	31.8	25.5
Peripheral vascular disease	4.6	6.1	5.4	5.5	6.6	5.6
Lipids and lipoproteins, median (IQR)						
TG, mg/dl	69 (59–77)	97 (90–102)	123 (116–130)	162 (150–177)	254 (218–317)	
Total cholesterol, mg/dl	120 (100–146)	130 (112–153)	138 (118–160)	152 (127–178)	170 (147–193)	
LDL-C, mg/dl	63 (47–82)	68 (53–88)	73 (54–92)	78.5 (57–102)	81 (59–101)	
HDL-C, mg/dl	42 (36–50)	41 (35–47)	40 (34–47)	38 (32–45)	35 (30–42)	
High-sensitivity CRP, mg/l	1.41 (0.66–3.31)	1.90 (0.87–4.26)	1.93 (0.95–4.36)	2.15 (1.02–4.43)	2.36 (1.14–4.43)	

ACS = acute coronary syndrome; BMI = body mass index; CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

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