Association Between Triglycerides and Residual Cardiovascular Risk in Patients With Type 2 Diabetes Mellitus and Established Cardiovascular Disease (From the Bypass Angioplasty Revascularization Investigation 2 Diabetes [BARI 2D] Trial)

Adam J. Nelson, MBBS, PhD[a], Ann Marie Navar, MD, PhD[a], Hillary Mulder, MS[a], Daniel Wojdyla, MS[a], Sephy Philip, RPh, PharmD[b], Craig Granowitz, MD, PhD[b], Eric D. Peterson, MD, MPH[a], and Neha J. Pagidipati, MD, MPH[a,*]

Triglyceride (TG) levels encompass several lipoproteins that have been implicated in atherogenic pathways. Whether TG levels independently associate with cardiovascular disease both overall and, in particular among patients with established coronary artery disease (CAD) and type 2 diabetes (T2DM), remains controversial. Data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial was used to evaluate patients with T2DM and CAD. Cox proportional hazards models were used to determine the association between TG levels and outcomes. Stepwise adjustment was performed for demographics, clinical factors, lipid profile and statin treatment. The primary composite outcome was time to CV death, myocardial infarction (MI), or stroke and secondary outcome was CV death. Among 2,307 patients with T2DM and CAD, the mean (±SD) TG levels were 181 (±136) with a median (Q1−Q3) 148mg/dL (104−219). Overall, 51% of patients had TG <150 mg/dL, 18% 150 −199 mg/dL, 28% 200−499 mg/dL and 3% ≥500 mg/dL. Participants with elevated TG levels (≥150 mg/dL) were younger (61 vs 63 years, p <0.001), had higher BMI (32 vs 30 kg/m^2, p <0.001), more likely to have had prior MI (34.2 vs 30.1%, p = 0.033) and revascularization (25.8 vs 21.4%, p = 0.013), had lower HDL-C (34 vs 39 mg/dL, p <0.001) and higher HbA1c (8 vs 7%, p <0.001). In unadjusted analyses, baseline TG levels were linearly associated with both the primary composite and secondary outcomes. In fully adjusted analyses, every 50 mg/dL increase in TG level was associated with a 3.8% (HR 1.038, 95%CI 1.004−1.072, p <0.001) increase in the primary composite outcome and a 6.4% (HR 1.064 95%CI 1.018 −1.113, p <0.001) increase in the secondary outcome. There was no interaction between TG and outcomes within key subgroups including female sex, additional non-coronary atherosclerotic disease, CKD or low LDL (<100 mg/dL). In conclusion, among patients with T2DM and CAD, elevated TG were independently associated with adverse cardiovascular outcomes, even after adjustment for clinical and simple biochemical covariates. **(Am J Cardiol 2020;132:36−43)**

Patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) are at high risk for future cardiovascular (CV) events. Among other factors, hypertriglyceridemia has been implicated as a potential contributor to the observed residual risk in patients with T2DM despite statin therapy. Mechanistically, triglycerides (TG), and more specifically triglyceride-rich lipoprotein remnants, have links with a proatherosclerotic milieu through their ability to, (1) enter the subendothelial vascular space and promote atherogenesis,[1,2] (2) impair the anti-atherogenic efficiency of high-density lipoprotein (HDL) reverse cholesterol transport[3] and (3) increase the susceptibility for low-density lipoprotein to become oxidized.[4] Hypertriglyceridemia has been shown to generally associate with increased risk of incident cardiovascular disease,[5−8] however whether a similar relationship holds for patients with established CAD is less clear. Specifically, whether elevated TG levels are independently associated with CV events or simply serve as a marker for other risk factors is controversial.[9] While post hoc analyses of trials have shown elevated TG levels to confer increased risk for CV events in patients with established CAD,[10−12] these studies have

[a]Duke Clinical Research Institute, Duke University, Durham, North Carolina; and [b]Amarin Pharma Inc., Bridgewater, New Jersey. Manuscript received April 26, 2020; revised manuscript received and accepted July 3, 2020.

This analysis was funded by Amarin Pharma, Inc. BARI-2D was funded by the National Heart, Lung and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases; as well as multiple other private sources of funding (GlaxoSmithKline, Lantheus Medical Imaging, Astellas Pharma, Merck, Abbott Laboratories, Pfizer, MediSense, Bayer, Becton Dickinson, J.R. Carlson Labs, Centocor, Eli Lilly, LipoScience, Novartis, and Novo Nordisk).

See page 42 for disclosure information.

*Corresponding author: Tel: (919) 668-7070; Fax (919) 668-7070
E-mail address: Neha.pagidipati@duke.edu (N.J. Pagidipati).

0002-9149/

https://doi.org/10.1016/j.amjcard.2020.07.005

either relegated T2DM to a binary variable in subgroup analysis, or been performed in a pre-statin era. Using data from BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes), the aims of this study were to; (1) determine the prevalence and distribution of hypertriglyceridemia; (2) examine the association between baseline TG levels and CV events overall and; (3) evaluate these relationships in key subgroups with either disparate or residual risk.

Methods

The design[13] and primary outcome results[14] of the BARI 2D trial have been previously published. In brief, BARI-2D was an international, multicenter trial which enrolled 2,368 participants with T2DM and angiographically documented stable ischemic heart disease between January 2001 and March 2005. Participants were randomized using a 2×2 factorial design; one level dictating cardiovascular treatment, the other dictating T2DM treatment. The randomized cardiac treatment strategies included intensive medical therapy with prompt revascularization (within 4 weeks) or intensive medical therapy with revascularization only when clinically indicated. The randomized glycemic control strategies compared primarily insulin-sensitizing (i.e., thiazolidinediones and/or metformin) versus primarily insulin-providing (i.e. insulin and/or sulphonylurea). The results of the primary analysis showed no significant benefit of prompt revascularization over initial medical therapy, nor was there any notable difference in outcomes between the glycemic strategies.

Beyond the investigational components, the protocol included guideline-mandated concomitant risk factor control for hypertension, dyslipidemia and obesity, in addition to a goal HbA1c of <7.0% regardless of randomization assignment. Major exclusion criteria included definite need for prompt invasive intervention as determined by the treating cardiologist, prior coronary revascularization within the past 12 months, class III or IV congestive heart failure, creatinine >2.0 mg/dL, TG >1000 mg/dL or HbA1c >13%. Institutional review boards at each participating site approved the protocol and all patients provided written informed consent.

The BARI 2D trial data were obtained on request from the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung, and Blood Institute under a data use agreement. The protocol for this analysis was approved by the Duke University Institutional Review Board. Data from participants in the BARI-2D trial with baseline fasting lipids were considered for this analysis.

As per trial protocol, lipid measures were obtained from fasting blood acquired prior to randomization, frozen locally and measured at the core laboratory. HDL-C was quantified using standard enzymatic techniques after the removal of Apolipoprotein-B (Apo-B) containing particles; total cholesterol and TG were quantified with direct enzymatic techniques, and LDL-C was determined through the Friedewald equation. Systolic and diastolic BP were obtained in the seated position using an appropriately sized cuff following 5 minutes of rest; the mean of three BP readings was used and reported to the nearest 2mmHg.

The primary endpoint of this analysis mirrored that of the primary trial, namely a composite of time to CV death, myocardial infarction (MI) or stroke. The secondary outcomes were the individual components of the primary endpoint in addition to coronary revascularization and all-cause death. The diagnosis of spontaneous myocardial infarction was based on a doubling of cardiac biomarkers (creatine kinase-MB or troponin) and evidence of ischemia on the basis of symptoms, electrocardiography, or imaging. Myocardial infarction was classified by a core laboratory; stroke and cause of death were adjudicated by an independent clinical events committee. The average follow-up was 5.3 years for death and 4.6 years for other outcomes.

Participants were grouped by baseline TG levels. This was performed initially by dichotomizing the cohort at a TG value of 150mg/dL which is acknowledged as being 'elevated' in most consensus documents.[15] Participants in the ≥150 mg/dL group were further stratified: (1) 150 −199 mg/dL, (2) 200−499 mg/dL, (3) >500 mg/dL. Continuous variables are summarized as mean (±SD) or median (Q1, Q3). Categorical variables are summarized as counts (%). Comparison between elevated and normal TG groups was performed using the Wilcoxon rank sum test or t-test. Categorical variables were compared using chi-square tests or Fisher's exact test.

To assess the association between TG levels and clinical outcomes, Cox proportional hazards models were fitted. In order to determine how and which factors mediate any triglyceride-outcome relationship, a series of models were fitted with stepwise, cumulative inclusion of covariates as follows: Model 1 - unadjusted; Model 2 - Add age, sex, region, race and ethnicity; Model 3 - Add systolic BP and smoking status; Model 4 - Add BMI, T2DM duration, HbA1c; Model 5 - Add HDL-C, LDL-C and statin use. As the Friedewald equation can inaccurately estimate LDL-C in the setting of elevated TG, a sensitivity analysis was performed by repeating model 5 after adjusting LDL-C values in those patients with TG >300 mg/dL.[16]

To use the same participant sample for all models, chained equations multiple imputation was performed to create 25 data sets with no missing data. Models 1 and 2 included variables with complete information, whereas models 3-5 required the imputed data sets. For those models, the parameter estimates and corresponding chi-square statistics were averaged over the 25 imputed data sets. The linearity assumption was tested for continuous variables using natural cubic splines, and the proportional hazards assumption for all variables using weighted Schoenfeld residuals. No major violations were found. Finally, as a post hoc analysis, we adjusted for non-HDL-C rather than LDL-C. Non-HDL-C provides a coarse assessment of total atherogenic particle burden, including VLDL-C as well as LDL-C. Given their biological and somewhat arithmetic interrelation, non-HDL-C and TG are expected to be correlated. This correlation was assessed graphically and statistically using Spearman's correlation coefficient.

Pre-specified interaction analyses were performed for the composite and CV death endpoints using the imputed data sets. Unadjusted Cox models were fit with TG, the covariate

of interest, and their interaction. The following covariate interactions with TGs were tested: sex, T2DM duration (in years, defined as time from historical diagnosis to trial entry), CKD (presence or absence, defined by eGFR <60mL/min/m^2), non-coronary vascular disease including peripheral arterial disease (PAD) and/or cerebrovascular disease (CeVD), low LDL (≤100mg/dL), and statin use. For categorical covariates, hazard ratios are presented per 50 mg/dL increase in TG by covariate level. For the interaction with T2DM duration, hazard ratios are presented per 50 mg/dL increase in TG at the following values: 1, 5, 10 and 20 years.

Results

The study population consisted of 2,307 patients (97% of the overall study population) with non-missing fasting TG levels at baseline. Table 1 shows the baseline characteristics overall and by baseline TG level. Similar to the overall trial, the median age of the study cohort was 62 years with the majority being male and of white race. Most of the cohort had obesity with an overall median T2DM duration of just under 10 years. The majority were on a statin. Triglyceride levels were positively skewed with a mean value of 181 (±136) and a median value of 148 mg/dL (104−219). Overall, 51% of patients had TG <150 mg/dL, 18% 150−199 mg/dL, 28% 200−499mg/dL, and 3% 500−1000 mg/dL.

Compared with those with levels below 150 mg/dL, patients with TG levels at or above 150 mg/dL were younger and more likely to be of white race. Sex proportions were similar between the groups, as was Hispanic ethnicity. Although those with elevated TG were more likely to be current smokers, have a history of MI or revascularization, the rates of heart failure, prior stroke and non-coronary vascular disease were similar between the two groups. Statistical differences in T2DM duration, insulin levels, eGFR and albumin-creatinine ratio were observed between groups, however these were numerically small and not clinically meaningful. Patients with elevated TG had higher overall total cholesterol and were more likely to have lower HDL-C. Medication profile was similar with the exception of

Table 1
Baseline characteristics

Characteristics	Total (N=2,307)	Triglycerides (mg/dl)		
		<150 (N=1,167)	≥150 (N=1,140)	p value
Age (years)	62, 56-68	63, 57-69	61, 54-68	<0.001
Women	683 (29.6%)	356 (30.5%)	327 (28.7%)	0.338
Non-White	683 (29.6%)	415 (35.6%)	268 (23.5%)	<0.001
Hispanic	288 (12.5%)	130 (11.1%)	158 (13.9%)	0.048
Current Smoker	287 (12.5%)	129 (11.1%)	158 (13.9%)	0.043
Hypertension requiring Tx	1882 (82.5%)	954 (82.7%)	928 (82.3%)	0.802
Hypercholesterolemia requiring Tx	1869 (82.1%)	928 (80.6%)	941 (83.6%)	0.055
Diabetes duration (years)	9, 4-15	9, 4-16	8, 4-14	0.002
History of MI	730 (32.1%)	346 (30.1%)	384 (34.3%)	0.033
History of CHF	149 (6.5%)	78 (6.7%)	71 (6.3%)	0.645
History of stroke/TIA	225 (9.8%)	117 (10.1%)	108 (9.5%)	0.646
PAD and/or CeVD	549 (23.8%)	267 (22.9%)	282 (24.7%)	0.295
Prior Revascularization	544 (23.6%)	250 (21.4%)	294 (25.8%)	0.013
BMI (kg/m^2)	31, 28-35	30, 27-34	32, 28-35	<0.001
Systolic BP (mmHg)	130, 118-142	130, 118-144	129, 118-140	0.131
Diastolic BP (mmHg)	74, 67-81	73, 67-80	75, 69-81	0.011
Total Cholesterol (mg/dL)	164, 141-192	153, 132-176	177, 152-204	<0.001
LDL-C (mg/dL)	92, 73-115	91, 74-113	93, 72-117	0.390
HDL-C (mg/dL)	37, 31-43	39, 34-46	34, 29-39	<0.001
eGFR (mL/min/1.73m^2)	74, 60-88	75, 61-89	72, 59-87	0.010
HbA1c (%)	7, 6-9	7, 6-8	8, 7-9	<0.001
Insulin (IU/mL)	10, 6-17	9, 5-14	12, 7-19	<0.001
Albumin Creatinine Ratio	12, 5-47	11, 5-41	14, 6-56	0.001
Medications at Baseline				
Statins	1720 (74.7%)	890 (76.4%)	830 (73.0%)	0.061
Beta Blockers	1684 (73.2%)	823 (70.6%)	861 (75.7%)	0.006
ACEi or ARB	1780 (77.3%)	896 (76.8%)	884 (77.7%)	0.604
Non-sublingual Nitrates	730 (31.7%)	341 (29.3%)	389 (34.2%)	0.011
Aspirin	2026 (88.2%)	1029 (88.5%)	997 (87.8%)	0.637
P2Y12 inhibitor	454 (19.7%)	230 (19.7%)	224 (19.7%)	0.972
Thiazolidinedione	440 (19.1%)	232 (19.9%)	208 (18.3%)	0.328
Sulfonylurea	1232 (53.4%)	610 (52.3%)	622 (54.7%)	0.251
Insulin	641 (27.8%)	343 (29.4%)	298 (26.2%)	0.081

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; CeVD = cerebrovascular disease; CHF = chronic heart failure; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; MI = myocardial infarction; LDL-C = low-density lipoprotein cholesterol; TIA = transient ischemic attack.

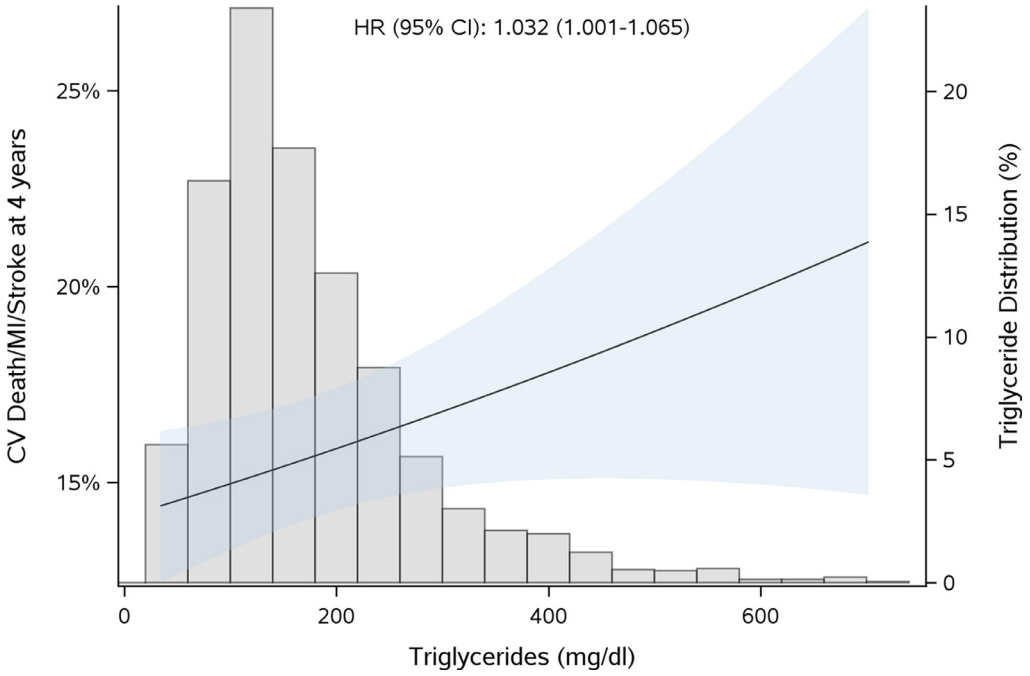

Figure 1. Unadjusted linear association (Model 1) of baseline triglyceride levels with the primary composite cardiovascular outcome (CV death, MI and stroke). Shaded region represents the upper and lower bounds of the 95% confidence intervals. Histogram of triglyceride levels correspond to right Y-axis.

higher rates of beta blocker and non-sublingual nitrate use in patients with elevated TG levels.

The characteristics of patients with elevated TG are presented by strata in Supplementary Table 1. In summary, monotonic relationships were generally observed with the highest TG level stratum more likely to be younger, smoking, have lower HDL-C cholesterol and higher insulin levels (more insulin resistance). Small numbers in the highest stratum limit meaningful conclusions on infrequently prescribed medications, however most notably those with highest TG levels were least likely to be on statins.

Baseline TG levels were linearly associated with the primary composite outcome of CV death, MI and stroke (Figure 1). In the unadjusted model, every 50 mg/dL increase in TG level was associated with a 3.2% (HR 1.032 95%CI 1.001−1.065) increase in CV death/MI/stroke and a 5.8% (HR 1.058 95%CI 1.014−1.105) increase in CV death.

Adjusted associations between baseline TG level and both primary and secondary outcomes are presented in Figure 2. In stepwise adjustment, inclusion of age, sex, region, race, ethnicity, systolic BP and smoking status covariates in the model modestly increased the impact of TG

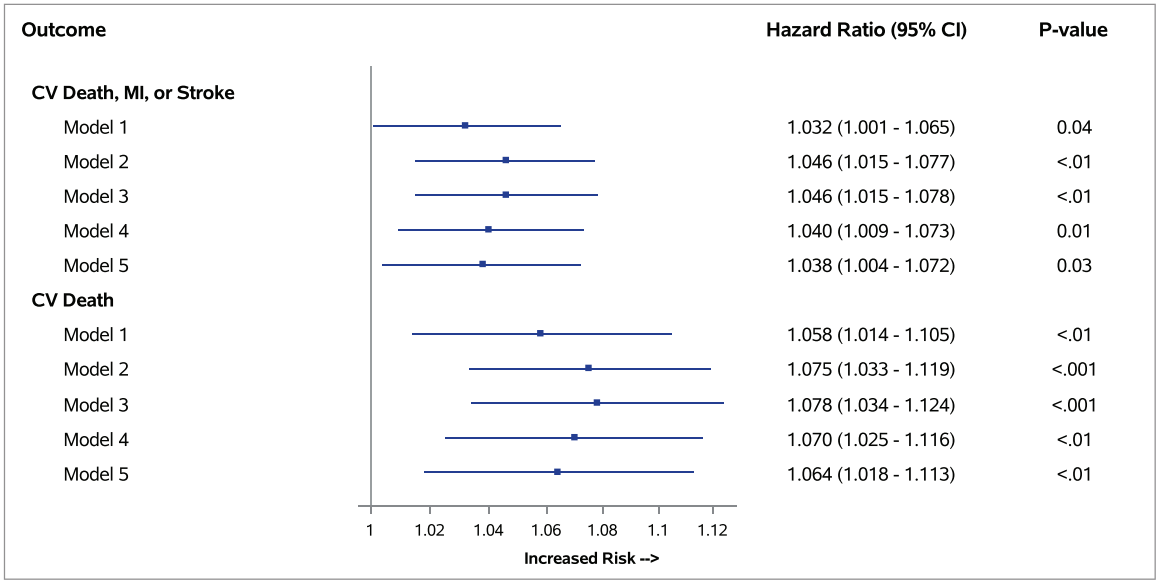

Figure 2. Stepwise adjustment for covariates in models evaluating relationship between baseline triglycerides and cardiovascular outcomes. HR for every 50 mg/dL increase in TG.

levels on risk for adverse CV outcomes. In contrast, the subsequent addition of BMI, T2DM duration, HbA1c, HDL-C, LDL-C and statin use all modestly attenuated the impact of TG levels on risk for both outcomes. Despite this, TG levels retained statistical significance in each model building step. In the fully adjusted model, each 50mg/dL increase in TG was associated with a 3.8% (HR 1.038, 95%CI 1.004−1.072) increase in the risk of CV death/MI/stroke and a 6.4% (HR 1.064, 95%CI 1.018−1.113) increase in the risk of CV death. A sensitivity analysis using adjusted LDL-C levels for patients with TG > 300 mg/dL (11.2% of cohort), did not significantly change these relationships (Supplementary Table 2).

In an exploratory analysis, baseline non-HDL-C was monotonically correlated with TG levels ($\rho = 0.50$, $p < 0.0001$) (Supplementary Figure 1). Substituting non-HDL-C for LDL-C in the fully adjusted model, TG levels were no longer predictive of the composite (HR 1.016, 95%CI 0.977−1.057, p = 0.413) but remained predictive of CV death (HR 1.073 [1.016−1.134], p = 0.012).

Interactions between TG levels and key covariates were evaluated for the primary composite endpoint and CV death. As listed in Table 2, there were no significant interactions for either of the endpoints between TG levels and covariates of interest: sex, T2DM duration, non-coronary atherosclerotic disease, CKD, LDL-C ≤100 mg/dL or statin use.

Discussion

This study, performed in a large population of patients with T2DM and established CAD, has several notable findings; first, a large number of patients with T2DM and CAD had elevated TG. Second, baseline fasting triglyceride levels were linearly associated with subsequent cardiovascular events. Third, the relationship between baseline TG levels and cardiovascular events remained significant despite adjustment for multiple clinical and biochemical covariates. Fourth, the triglyceride-outcome relationship was constant in multiple subgroups including those with low LDL-C.

The finding of a linear relationship between TG levels and subsequent CV events in a dedicated population of statin-treated patients with T2DM and established CAD extends prior studies that have evaluated related populations. In a cohort of 1,917 outpatients with T2DM from Italy, most of whom did not have CAD, the highest tertile

Table 2
Primary and secondary outcomes, according to prespecified subgroup

Variable	Events/N (%)	Hazard Ratioper 50 mg/dL increase in TG (95% CI)	Interactionp value
CV death/MI/Stroke			
Sex			0.369
Female	132/683 (19.33%)	1.008 (0.944 − 1.075)	
Male	263/1624 (16.19%)	1.042 (1.007 − 1.079)	
History of Non-Coronary Artery Disease	275/1758 (15.64%)	0.985 (0.909 − 1.067)	0.198
Diabetes Duration (years)			0.690
1		1.025 (0.971 − 1.083)	
5		1.028 (0.986 − 1.073)	
10		1.033 (1.000 − 1.066)	
20		1.041 (0.998 − 1.086)	
CKD	265/1731 (15.31%)	1.033 (0.983 − 1.085)	0.915
LDL-C			0.164
LDL-C ≤100 mg/dL	143/857 (16.69%)	1.021 (0.985 − 1.060)	
LDL-C >100 mg/dL	230/1323 (17.38%)	1.002 (1.000 − 1.003)	
Statin use	294/1720 (17.09%)	1.037 (1.004 − 1.071)	0.474
CV death			
Sex			0.318
Female	42/683 (6.15%)	1.003 (0.890 − 1.131)	
Male	99/1624 (6.10%)	1.071 (1.025 − 1.119)	
History of Non-Coronary Artery Disease	88/1758 (5.01%)	1.040 (0.933 − 1.159)	0.675
Diabetes Duration (years)			0.333
1		1.024 (0.941 − 1.115)	
5		1.036 (0.971 − 1.106)	
10		1.051 (1.003 − 1.102)	
20		1.082 (1.023 − 1.144)	
CKD	84/1731 (4.85%)	1.056 (0.995 − 1.122)	0.964
LDL			0.262
LDL-C ≤100 mg/dL	44/857 (5.13%)	1.045 (0.994 − 1.099)	
LDL-C >100 mg/dL	87/1323 (6.58%)	1.002 (1.000 − 1.004)	
Statin use	106/1720 (6.16%)	1.067 (1.023 − 1.113)	0.335

CKD = chronic kidney disease; LDL-C = low-density lipoprotein cholesterol.

For CKD, low LDL and statins, the HR was derived using 25 imputation data sets. Rates were computed using the original data and so do not reflect the imputed values that were used in the Cox models.

of TG levels was independently associated with all-cause mortality after adjustment for other lipid parameters.[17] Similar findings by Toth et al. were reported from a propensity matched analysis of 21,980 patients in an administrative setting which included patients with either T2DM (~85%) and/or CAD (~30%).[18] In the study by Toth et al., those with TG >200 mg/dL were at 34.9% higher risk of MI, stroke or revascularization when compared with a matched cohort with TG <150 mg/dL. In studies of patients with a recent ACS, baseline TG levels in both the MIRACL and dal-OUTCOMES trials were associated with both short term (16 weeks) and longer term (31 months) cardiovascular events (coronary death, non-fatal MI, stroke, angina).[12] Similarly, an earlier analysis of the PROVE-IT TIMI 22 trial which also enrolled early post-ACS patients, showed lower TG levels (<150 mg/dL) to be independently associated with a 20% relative risk reduction of CV events (death, MI, and recurrent ACS).[11]

Our study extends this prior work in several ways. Ours was a focused evaluation of a large group of patients with both T2DM and angiographically proven CAD; a population hitherto relegated to subgroup status in prior work. Further, unlike the epidemiologic studies our results leveraged high veracity trial data which included granular covariate information and robust, adjudicated outcome events. These factors are likely to have increased our precision in determining the presence of a triglyceride-outcome relationship and allowed us to demonstrate linearity.

Our analysis suggests TG levels continue to be associated with future risk of cardiovascular events in patients with established CAD despite achieving low levels of LDL-C (≤100 mg/dL). This is consistent with prior literature on the subject,[19] and implicates TG levels as an important component of residual risk observed in patients with T2DM who continue to sustain recurrent events despite low LDL-C levels. With as many as 50% of patients exhibiting a similar lipid phenotype on statin therapy, there exists a large population with potentially unmet treatment needs.[20–22]

Consistent with other work,[23,24] our results suggest that TG levels are associated with increased risk for CV events in patients with established ASCVD, however whether triglycerides are directly in the causal pathway or simply a surrogate marker of risk remains unclear. Our analysis found that even after adjusting for factors associated with both TG levels and CV risk such as T2DM duration, LDL-C, and BMI, triglyceride levels remained associated with CV events. A recent Mendelian randomization study demonstrated that the risk reduction achieved through either LDL-C or TG lowering was related to the proportional change in Apo-B,[25] which may be the primary mediator of the triglyceride-outcomes relationship. While adjustment for Apo-B would have allowed us to uncouple a relationship between triglyceride levels and particle number, this was not measured in BARI-2D. Instead, we performed an exploratory adjustment for non-HDL-C, which is considered a coarse marker for Apo-B particle number (i.e., LDL, IDL, VLDL) and showed a weakening of the association between outcomes and TG levels. This attenuation is likely a result of both the correlation between TG levels and non-HDL-C, as well as the potential for independent atherogenicity of VLDL-C. Nevertheless, because TG levels and LDL-C continue to be measured routinely in clinical practice, our findings of independent increases in CV risk related to increases in TG levels remain clinically relevant.

The linear and independent relationship with risk does not indicate that reducing serum TG levels by any means would be associated with cardiovascular benefit. Importantly, the majority of agents in clinical trials including fish oil supplements, fibrates, statins and niacin have been underwhelming in their ability to lower CV risk due to either, (1) modest reductions in TG levels or (2) the restriction of benefits to a highly selected population which appeared to occur distinct from observed triglyceride lowering. In contrast to prior studies, the recent REDuction of Cardiovascular Events with Icosapent ethyl Trial (REDUCE-IT) study of icosapent ethyl, a pure, stable, prescription formulation of eicosapentaenoic acid (EPA), demonstrated profound reductions in cardiovascular events in patients with elevated TG levels. However, the benefits were derived independent of TG level changes.[26] Recent findings suggest that achieved high blood levels of EPA from icosapent ethyl dosing were largely associated with the CV benefits observed in REDUCE-IT, as compared to lipid or lipoprotein biomarkers such as TG levels.[27] Adding further complexity to the relationship between omega-3 fatty acids, TG levels and CV outcomes is the recent announcement that the STRENGTH trial (Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia) has been terminated due to futility. While there are differences in the compounds - Epanova in STRENGTH being EPA/DHA, and icosapent ethyl in REDUCE-IT being EPA alone - their early phase data suggested similar expected changes in serum levels of omega-3 fatty acids.

Trials of agents are currently underway with more potent and specific TG level lowering capacity. Pemafibrate, a next generation PPAR-alpha agonist, has been shown to reduce TG levels by 50% and increase HDL-C by 13% and is currently being studied in a phase III trial due to report in 2022.[28] In addition, two RNA interfering agents targeting genes for apolipoprotein C-III (APOC3, NCT03783377) and angiopoietin-like protein 3 (ANGPTL3, NCT03747224) have produced promising phase I/II trials with reductions in TG of 64% and 66%, respectively.[29,30] Whether these TG level-lowering agents will confer benefit independent of their salutary effects on LDL-C/HDL-C remains to be seen.

This study is a post hoc analysis of a clinical trial and thus observational in nature. The effects of residual confounding and reverse causation cannot be quantified. Our data lacked certain potential clinical confounders such as alcohol use and hormone status. The cohort was predominantly white and male and of relatively narrow age range, thus the results may not be generalizable to a broader group of patients with T2DM and CAD. Similarly BARI 2D excluded patients with severe hypertriglyceridemia (>1000mg/dL) and included only a minority >500mg/dL; thus, the degree to which the triglyceride-outcomes relationship retains linearity at very high TG levels cannot be inferred from our data.

In conclusion, this study of largely statin-treated patients with T2DM and CAD from the BARI 2D trial, baseline

triglyceride levels were independently associated with adverse cardiovascular outcomes. Whether lowering TG levels leads to improved cardiovascular outcomes remains to be seen.

Disclosures

AJN - Grants from Diabetes Australia and the Royal Australasian College of Physicians; AMN - Grants from Regeneron and Sanofi during the conduct of the study; additional research grants to her institution from Regeneron, Sanofi, Amgen, Janssen, and Amarin during the conduct of the study outside of the submitted work; and personal fees from Regeneron, Sanofi, Amgen, Astra Zeneca, NovoNordisk, and Amarin outside of the submitted work; SP - Employee of Amarin Pharma, Inc.; CG - Employee of Amarin Pharma, Inc. EDP - Grants and personal fees from Sanofi and grants from Regeneron during conduct of study as well as grants and personal fees from AstraZeneca, Amgen, and Merck outside of the submitted work. NJP - Grants from Amgen, Regeneron Pharmaceuticals, Sanofi-Aventis, and Verily Life Sciences. HM, DW - both have nothing to declare.

Authors' contribution

AJN - Data curation; Visualization, Writing-Original Draft, Project Administration; AMN - Conceptualization, Methodology, Writing-Review and Editing; HM - Formal analysis, Writing-Review and Editing; DW - Formal analysis, Writing-Review and Editing; SP - Conceptualization, Writing-Review and Editing; CG - Conceptualization, Writing-Review and Editing; EDP - Conceptualization, Methodology, Writing-Review and Editing, Funding acquisition, Supervision; NJP - Conceptualization, Methodology, Writing-Review and Editing; Supervision, Project Administration.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.005.

1. Mamo JC, Proctor SD, Smith D. Retention of chylomicron remnants by arterial tissue; importance of an efficient clearance mechanism from plasma. *Atherosclerosis* 1998;141(Suppl 1):S63–S69.
2. Zilversmit DB. A proposal linking atherogenesis to the interaction of endothelial lipoprotein lipase with triglyceride-rich lipoproteins. *Circ Res* 1973;33:633–638.
3. Skeggs JW, Morton RE. LDL and HDL enriched in triglyceride promote abnormal cholesterol transport. *J Lipid Res* 2002;43:1264–1274.
4. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med* 1989;320:915–924.
5. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA* 2007;298:309–316.
6. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk* 1996;3:213–219.
7. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet* 2014;384:626–635.
8. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation* 2007;115:450–458.
9. Emerging Risk Factors C, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993–2000.
10. Faergeman O, Holme I, Fayyad R, Bhatia S, Grundy SM, Kastelein JJ, LaRosa JC, Larsen ML, Lindahl C, Olsson AG, Tikkanen MJ, Waters DD, Pedersen TR. Steering Committees of I. Trials TNT. Plasma triglycerides and cardiovascular events in the treating to new targets and incremental decrease in end-points through aggressive lipid lowering trials of statins in patients with coronary artery disease. *Am J Cardiol* 2009;104:459–463.
11. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E, Investigators PI-T. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol* 2008;51:724–730.
12. Schwartz GG, Abt M, Bao W, DeMicco D, Kallend D, Miller M, Mundl H, Olsson AG. Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. *J Am Coll Cardiol* 2015;65:2267–2275.
13. Brooks MM, Frye RL, Genuth S, Detre KM, Nesto R, Sobel BE, Kelsey SF, Orchard TJ, Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial I. Hypotheses, design, and methods for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. *Am J Cardiol* 2006;97:9G–19G.
14. Group BDS, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503–2515.
15. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr., Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol* 2019;73:e285–e350.
16. Martin SS, Blaha MJ, Elshazly MB, Toth PP, Kwiterovich PO, Blumenthal RS, Jones SR. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA* 2013;310:2061–2068.
17. Miselli MA, Nora ED, Passaro A, Tomasi F, Zuliani G. Plasma triglycerides predict ten-years all-cause mortality in outpatients with type 2 diabetes mellitus: a longitudinal observational study. *Cardiovasc Diabetol* 2014;13:135.
18. Toth PP, Granowitz C, Hull M, Liassou D, Anderson A, Philip S. 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. *J Am Heart Assoc* 2018;7:e008740.
19. Nichols GA, Philip S, Reynolds K, Granowitz CB, Fazio S. Increased residual cardiovascular risk in patients with diabetes and high versus normal triglycerides despite statin-controlled LDL cholesterol. *Diabetes Obes Metab* 2019;21:366–371.
20. Fan W, Philip S, Granowitz C, Toth PP, Wong ND. Hypertriglyceridemia in statin-treated US adults: the National Health and Nutrition Examination Survey. *J Clin Lipidol* 2019;13:100–108.
21. Ghandehari H, Kamal-Bahl S, Wong ND. Prevalence and extent of dyslipidemia and recommended lipid levels in US adults with and without cardiovascular comorbidities: the National Health and Nutrition Examination Survey 2003-2004. *Am Heart J* 2008;156:112–119.
22. Rana JS, Liu JY, Moffet HH, Solomon MD, Go AS, Jaffe MG, Karter AJ. Metabolic dyslipidemia and risk of coronary heart disease in 28,318 adults with diabetes mellitus and low-density lipoprotein cholesterol <100 mg/dl. *Am J Cardiol* 2015;116:1700–1704.
23. Marston NA, Giugliano RP, Im K, Silverman MG, O'Donoghue ML, Wiviott SD, Ference BA, Sabatine MS. Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: a systematic review and meta-

regression analysis of randomized controlled trials. *Circulation* 2019;140:1308–1317.
24. Triglyceride Coronary Disease Genetics C, Emerging Risk Factors C, Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, Ouwehand W, Watkins H, Samani NJ, Saleheen D, Lawlor D, Reilly MP, Hingorani AD, Talmud PJ, Danesh J. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* 2010;375:1634–1639.
25. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, Laufs U, Oliver-Williams C, Wood AM, Butterworth AS, Di Angelantonio E, Danesh J, Nicholls SJ, Bhatt DL, Sabatine MS, Catapano AL. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA* 2019;321:364–373.
26. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr., Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM, Investigators R-I. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;380:11–22.
27. Bhatt DL, Miller M, Steg PG, Brinton EA, Jacobson TA, Ketchum SB, Granowitz C, Tardif JC, Ballantyne C. *Achieved eicosapentaenoic acid levels strongly predict cardiovascular benefit in REDUCE-IT*. Chicago (virtual): American College of Cardiology Scientific Sesions; 2020.
28. Pradhan AD, Paynter NP, Everett BM, Glynn RJ, Amarenco P, Elam M, Ginsberg H, Hiatt WR, Ishibashi S, Koenig W, Nordestgaard BG, Fruchart JC, Libby P, Ridker PM. Rationale and design of the pemafibrate to reduce cardiovascular outcomes by reducing triglycerides in patients with diabetes (PROMINENT) study. *Am Heart J* 2018;206:80–93.
29. Watts GF. *RNA interference targeting hepatic angiopoietin-like protein 3 results in prolonged reductions in plasma triglycerides and LDL-C in human subjects*. Philadelphia: American Heart Association: Scientific Sessions; 2019.
30. Schwabe C. *RNA interference targeting apolipoprotein C-III results in deep and prolonged reductions in plasma triglycerides*. Philadelphia: American Heart Association: Scientific Sessions; 2019.