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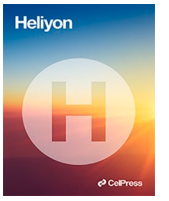

Association of triglyceride levels with adverse cardiovascular events in patients with ST-segment elevation myocardial infarction

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ABSTRACT

Although there is an established association between elevated triglyceride (eTG, ≥175 mg/dl) levels and adverse cardiovascular events, some studies have suggested that eTG levels may be linked to neutral or even improved clinical outcomes, particularly among patients with acute myocardial infarction. However, these studies had certain limitations, including small sample sizes, heterogeneous study populations, and inadequate statistical adjustments. To address these limitations, we conducted an analysis of 5347 patients with ST-segment elevation myocardial infarction (STEMI) between March 2003 and December 2020, using a prospective registry-based cohort from two large, regional STEMI centers. We used a triglyceride level of 175 mg/dl as the cutoff point for eTG levels. Of the study participants, 24.5% (n = 1312) had eTG levels. These patients were more likely to be younger, male, and have a higher number of cardiovascular risk factors compared to those with low TG levels. Despite these unfavorable cardiovascular risk profiles, patients with eTG levels had lower unadjusted risks of 1-year major adverse cardiac events (MACE) -a composite of myocardial infarction, stroke, and death- than those with low TG levels (8.8% vs. 11%, p = 0.034). However, after adjusting for certain clinical factors and lipid profile, eTG levels were not associated with a lower 1-year MACE (aHR: 1.10 (0.71–1.70), p = 0.7). In conclusion, a quarter of STEMI patients had eTG levels and these patients had comparable long-term cardiovascular outcomes compared to those with low TG levels after controlling for clinical factors and lipid profile.

1. Introduction

While a link between high levels of low-density lipoprotein cholesterol (LDL-C) levels and poor outcomes after acute myocardial infarction (AMI) is well established [1], there is sparse data pertaining to the prognostic value of serum triglyceride (TG) levels

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following AMI. Previous epidemiologic, genetic, and mendelian randomization studies reported causal relationships between serum TG levels and atherosclerotic cardiovascular disease (ASCVD) [2–4]. However, the extent of this relationship differed between studies and often became statistically insignificant after adjusting for other lipid parameters [5]. Also, most of these studies were conducted in non-AMI settings.

On the contrary, some observational studies conducted in the setting of AMI have observed a null or inverse relationship between serum TG levels and subsequent post-infarction adverse cardiovascular events [6–11]. However, these studies have been limited by study design (e.g., single-center), statistical under-adjustment, and inclusion of heterogenous populations of patients presenting with AMI. These observations have become of increasingly important clinical relevance in the light of recent emphasis on triglyceride-lowering agents for ASCVD risk reduction [12,13]. We therefore, sought to assess the relationship between serum TG levels and post-infarction clinical outcomes among ST-segment elevation myocardial infarction (STEMI) patients, analyzed from prospective, registry-based cohorts.

2. Methods

This study is a retrospective analysis of a bi-center, prospective, registry-based cohort study involving patients at Minneapolis Heart Institute in Minneapolis and The Christ Hospital in Cincinnati, which are tertiary regional STEMI centers and part of the Midwest STEMI Consortium [14]. The study included 6930 consecutive STEMI patients between March 2003 and December 2020. TG values were typically acquired within 24–48 h following hospitalization for the index STEMI event, regardless of fasting status. Patients with missing serum TG levels (n = 1583; 22.8%) were excluded from analysis, yielding a final study cohort of 5347 (Fig. 1). The study protocol and data-sharing agreement between centers have been approved by each center's Institutional Review Board (IRB).

STEMI was defined as ST-elevation ≥1 mm in at least two contiguous ECG leads or new (or presumably new) left-bundle-branch block with elevated cardiac troponin with at least one value above the 99th percentile upper reference limit. The cohort was divided into two groups based on serum TG levels, with a threshold level of 175 mg/dl [12]. As part of the Midwest STEMI Consortium registry, detailed demographics, comorbidities, medications, lipid panels, and angiographic features were collected by reviewing electronic medical records. The data collection form and definitions, along with their specific details, were previously described [14].

In-hospital clinical outcomes including: recurrent MI, stroke, and death were assessed. Major adverse cardiovascular events (MACE) were defined as the composite of the individual outcome components. One-year events were prospectively recorded by educated research assistants in each study site through review of electronic medical records and phone calls. Only 14 subjects were missed to follow-up in the entire dataset.

Continuous variables were presented as mean ± standard deviation or median (interquartile range), depending on the distribution. Discrete variables were reported as counts and percentages and compared using the Chi-square or Fisher's exact test, where appropriate. The analysis of continuous variables was performed using the student's t-test or Wilcoxon rank-sum test, depending on the distribution. Hazard ratios (HR) and 95% confidence intervals for 1-year MACE were estimated using a Cox proportional hazards model which adjusted for age, sex, hypertension, diabetes, dyslipidemia, current smoking status, BMI, previous MI, LDL-C, HDL-C, LAD

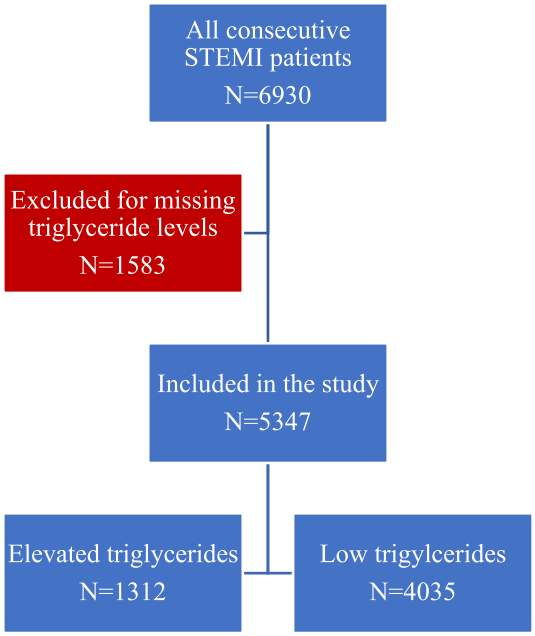

Fig. 1. Patient Flow Diagram. The flow diagram represents the number of patients at enrollment. STEMI = ST-segment elevation myocardial infarction.

culprit artery, whether the left ventricular ejection fraction (LVEF) was less than 45%, and whether pre-PCI TIMI flow was 0/1, as well as the interactions between eTGs and LVEF <45% and pre-PCI TIMI flow 0/1. Scaled Schoenfeld residuals were visually inspected to evaluate the proportional hazards assumption. Complete cases were used in the models, resulting in the exclusion of 3.2% of cases from the analyses. All analyses were performed using R version 4.2.3 and RStudio (R Core Team 2021).

3. Results

A total of 5347 consecutive STEMI patients with available serum TG levels were included in the analysis (Fig. 1). The distribution of TG levels in the analyzed cohort was right-skewed (Fig. 2). Approximately 1/4 of patients (n = 1312; 24.5%) had an eTG levels (≥175 mg/dl). Patients with eTG levels were more likely to be young, males, and have a higher prevalence of hypertension, dyslipidemia, diabetes, current smoking, premature coronary artery disease, and family history of coronary artery disease compared to those with low TG levels (<175 mg/dl). The incidences of cardiogenic shock and cardiac arrest were similar between the two groups. However, the proportion of patients with an impaired left ventricle ejection fraction (<45%) was lower in patients with eTG. In addition, patients with eTG were less likely to have anterior MI and LAD as the culprit infarct-related vessel. Door-to-balloon time and pre- and post-TIMI flow grades were similar between the two groups but patients with eTG were more likely to receive percutaneous coronary intervention **(Table 1).**

Lipid profiles for the TG groups are listed in Table 1. Patients with eTG had higher levels of total cholesterol and LDL-C and lower levels of HDL-C. The median (25th, 75th percentiles) non-HDL cholesterol values were 152 mg/dl (125, 179) and 115 mg/dl (91, 142) in two groups, respectively. Finally, patients with eTG were more likely to receive statin and optimal cardiovascular medical therapy at discharge than those with low TG.

In the crude analysis, the risks of in-hospital death and MACE were similar between the two groups. However, the 1-year death and MACE risks were significantly lower in patients with eTG compared to those with low TG **(Table 2).** After multivariable analysis, accounting for differences in baseline characteristics, eTG levels was no longer associated with lower 1-year MACE risks (aHR: 1.10 (0.71–1.70), p = 0.7) **(Table 3).**

4. Discussion

Previous studies involving patients with AMI have observed a paradoxical relationship between admission serum TG levels and outcomes after AMI. The recent guidelines and scientific statements [12,13] highlight the use of triglyceride-lowering strategies to reduce cardiovascular events -based on studies in non-AMI settings [15]-; however, the presence of contradictory inverse relationships in AMI settings may result in an underuse of effective post-AMI therapies. In this large, registry-based cohort study, we reported that approximately one-quarter of STEMI patients had eTG levels. These patients had a higher cardiovascular risk profile and were more inclined to receive optimal cardiovascular medical therapy than those with low TG levels. Despite exhibiting unfavorable clinic features, patients with eTG levels had lower 1-year death and MACE risks. However, this trend was no longer apparent after adjusting for clinical and biochemical confounders.

Previous research has questioned the predictive value of TG levels following AMI (STEMI and non-STEMI) and suggested an inverse

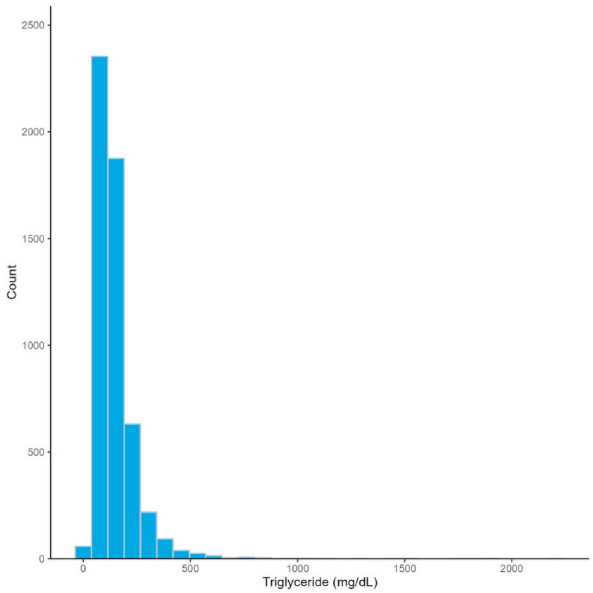

Fig. 2. Triglyceride Levels Distribution. The histogram represents a distribution of triglyceride levels in the study population (R-skewed).

Table 1
Baseline characteristics of STEMI patients with elevated and low triglyceride levels.

	Elevated Triglycerides n = 1312	Low Triglycerides n = 4035	p-value
Demographics			
Age	59 ± 13	65 ± 14	**<0.001**
Male	998 (76)	2817 (70)	**<0.001**
Clinical characteristics			
Hypertension	815 (62)	2352 (59)	**0.020**
Dyslipidemia	797 (62)	2110 (53)	**<0.001**
Diabetes	366 (28)	685 (17)	**<0.001**
Previous MI	283 (22)	811 (20)	0.262
Previous stroke	38 (2.9)	185 (4.6)	**0.008**
Current smoking	536 (62)	1311 (54)	**<0.001**
Body mass index	31.2 ± 6.1	28.6 ± 5.9	**<0.001**
History of CAD	385 (29)	1169 (29)	0.815
Premature CAD	598 (46)	1192 (30)	**<0.001**
Family history of CAD	568 (47)	1562 (42)	**0.004**
At presentation			
Cardiogenic shock (pre-PCI)	77 (5.9)	298 (7.4)	0.062
Cardiac arrest (pre-PCI)	105 (8)	329 (8.2)	0.862
Anterior MI	504 (39)	1749 (44)	**0.001**
LVEF <45%	343 (27)	1364 (35)	**<0.001**
Laboratory			
Total triglycerides	228 (196, 298)	104 (78, 132)	-
Total cholesterol	186 (159, 214)	155 (130, 184)	**<0.001**
LDL-C	103 (79, 131)	94 (72, 120)	**<0.001**
HDL-C	32 (28, 37)	38 (33, 45)	**<0.001**
Non-HDL-C	152 (125, 179)	115 (91, 142)	**<0.001**
Angiographic features			
Culprit vessel			**<0.001**
LM	1 (<0.1)	37 (0.9)	
LAD	375 (29)	1409 (35)	
LCx	217 (17)	497 (12)	
RCA	551 (43)	1465 (37)	
Graft	27 (2.1)	83 (2.1)	
Multiple	13 (1)	39 (1)	
None	109 (8.4)	452 (11)	
TIMI flow (pre-PCI)			0.579
0 or 1	706 (56)	2107 (55)	
2 or 3	546 (44)	1690 (45)	
TIMI flow (post-PCI)			0.064
0 or 1	15 (1.2)	76 (2)	
2 or 3	1235 (99)	3717 (98)	
Door to balloon time, min	94 (71, 120)	94 (69, 124)	0.539
Treatment types			
Medical management	15 (1.6)	116 (4)	**<0.001**
PCI	911 (96)	2667 (93)	**0.001**
CABG	23 (2.4)	81 (2.8)	0.510
Discharge medications			
Aspirin	1238 (97)	3698 (95)	**0.002**
Beta-Blocker	1180 (92)	3517 (90)	**0.023**
P2Y12 Inhibitor	1155 (91)	3363 (87)	**<0.001**
Statin	1181 (93)	3514 (90)	**0.007**

Values are n (%), mean ± SD, and median (IQR). CABG indicates coronary artery bypass graft; CAD coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending; LCx, left circumflex; LDL-C, low-density lipoprotein cholesterol; LM, left main; MI, myocardial infarction; PCI, percutaneous coronary intervention; and RCA, right coronary artery.

relationship between serum TG levels and short- and long-term cardiovascular adverse outcomes, termed the "lipid paradox" [6–8]. However, the role of TG levels in STEMI patients has been poorly studied with conflicting results [9–11]. For example, a small, single-center study of 247 STEMI patients found that serum TG levels (assessed within 24 h) were a negative predictor of short- and long-term MACE after adjusting for clinical and angiographic confounders [9]. However, the study was limited by a small sample size and inadequate statistical adjustment for lipid parameters. In contrast, a recent, large AMI national registry, including over 20000 patients, did not find any significant correlation between serum TG levels (assessed within 72 h) and all-cause mortality in either STEMI or non-STEMI study populations after adjusting for several risk factors [10]. The authors attributed the observed null findings to adjusting for multiple variables [10]. Our study, in line with the later, supported the null relationship with TG levels and MACE risks following STEMI after accounting for multiple clinical and lipid parameters. Finally, the time to lipid panel acquisition following an index myocardial ischemic event could have an impact on values of individual components of the lipid profile. Inconsistency of collection times may partially contribute to the discrepant observations among the various studies.

Although our study cannot establish causality, the underlying mechanisms for the observed null relationship between serum TG

Table 2
In-hospitality and 1-year clinical outcomes in STEMI patients with elevated and low triglyceride levels.

	Elevated Triglycerides n = 1312	Low Triglycerides n = 4035	p-value
In-Hospital			
Myocardial infarction	9 (0.7)	28 (0.7)	0.976
Stroke	7 (0.5)	30 (0.7)	0.425
Death	30 (2.3)	120 (3)	0.191
MACE	46 (3.5)	175 (4.3)	0.190
1-Year			
Myocardial infarction	39 (3)	125 (3.1)	0.778
Stroke	16 (1.2)	73 (1.8)	0.140
Death	66 (5)	274 (6.8)	**0.023**
MACE	115 (8.8)	436 (11)	**0.034**

MACE is a composite of myocardial infarction, stroke, and death.

Table 3
Multivariable analysis for 1-year MACE in STEMI patients.

Variable	HR (95% CI)	p-value
Elevated triglycerides	1.10 (0.71–1.70)	0.7
Age	1.03 (1.02–1.04)	<0.001
Female	0.97 (0.78–1.21)	0.8
Hypertension	1.44 (1.14–1.82)	0.002
Diabetes	1.50 (1.20–1.87)	<0.001
Dyslipidemia	0.89 (0.72–1.10)	0.3
Current smoker	0.88 (0.69–1.11)	0.3
BMI	1.00 (0.98–1.02)	>0.9
Previous MI	1.44 (1.16–1.80)	0.001
LDL-C	1.00 (1.0–1.00)	0.10
HDL-C	0.99 (0.98–1.00)	0.022
LAD culprit	1.06 (0.72–1.57)	0.8
Pre-PCI TIMI Flow 0/1	1.16 (0.93–1.44)	0.2
LVEF <45%	0.51 (0.41–0.64)	<0.001

BMI indicates body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending.

levels and the likelihood of adverse cardiovascular events remain unclear. Nonetheless, there are several plausible reasons for the null or inverse correlations between TG levels and the likelihood of adverse cardiovascular events, particularly in the context of AMI. Inflammation significantly influences all stages of atherosclerosis, from the formation of early fatty streaks to plaque rupture and thrombus formation [16]. Pro-inflammatory cytokines, for instance, have been demonstrated to inhibit the activity of plasma lipoprotein lipase (LPL), which is responsible for catalyzing the breakdown of TG [17,18].

Moreover, peripheral tissues utilize TG as a source of energy, particularly during periods of acute stress [19]. The sympathetic activation during the acute phase of STEMI increases the plasma LPL activity, releasing free fatty acids, TG, and lipoproteins for energy supply [20]. Hence, in the setting of an increased burden of inflammation and sympathetic activation during the acute phase of STEMI, the measured TG levels may not accurately reflect the actual levels present.

Besides, not all TG particles contribute to atherosclerosis [21]. Unlike cholesterol, TG's do not accumulate solely in the atherosclerotic plaques and are susceptible to degradation by mast cells. TG particles are carried in lipoproteins in the plasma, such as VLDL, chylomicron, and remnants given its hydrophobic nature [19]. Remnants, compared to other particles, can infiltrate into the vessel wall and induce atherosclerosis [22]. However, remnants are not routinely measured in clinical practice, despite their importance in atherosclerosis [23]. This indicates that the measured TG levels may not accurately reflect the actual atherosclerotic risk. Therefore, the development of diagnostic and therapeutic strategies targeting remnants may represent a new target to modulate the ASCVD risk [16].

The purpose of this observation is not to downplay the importance of TG levels in cardiovascular events. In parallel with the literature, we observed that STEMI patients with high TG levels were more likely to have hypertension, diabetes, high LDL-C, and low HDL-C. Therefore, it's worth noting that statin or non-statin-based therapies are advised to lower the risk of ASCVD in patients with eTG as per recent national guidelines [12,13].

The current study has certain limitations as it is based on a retrospective analysis of prospective cohorts. As such, despite using multivariable regression analysis, there may be unobserved confounding factors that may influence the results. Additionally, the event rates were low in our study, which could limit the predictive value of any lipid perturbation.

5. Conclusion

In conclusion, the present study results demonstrate that serum TG levels ≥175 mg/dl in STEMI patients frequently coexist with

other ASCVD risk factors but appear to have a comparable long-term MACE risk as those with low TG levels after adjusting for clinical and biochemical confounding factors.

Author contribution statement

Mehmet Yildiz: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Michael D. Miedema, Timothy D. Henry and Frank V. Aguirre: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Avinash Murthy, Santiago Garcia and Scott W. Sharkey: Analyzed and interpreted the data; Wrote the paper.

Seth Bergstedt, Brynn K. Okeson and Christian W. Schmidt: Analyzed and interpreted the data.

Lucas Volpenhein: Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

AMI	Acute myocardial infarction
ASCVD	Atherosclerotic cardiovascular disease
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
LPL	Lipoprotein lipase
MACE	Major adverse cardiac event
STEMI	ST-segment elevation myocardial infarction
TG	Triglyceride
eTG	Elevated triglyceride
VLDL	Very-low-density lipoprotein

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