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Brief Communication

Characteristics and prognosis of patients with elevated triglycerides in acute myocardial infarction: observational data from a large database over a 17-year period



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KEY WORDS

Triglycerides;
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event

Abstract: From a large regional registry, we aimed to address the characteristics and prognosis of patients with elevated triglycerides (TG) among patients hospitalized for an acute myocardial infarction (MI). From the multicenter database of the RICO survey, all consecutive patients hospitalized for an acute MI (2001-2017) and alive at discharge were included. Among the 10,667 patients included, 17.7% had elevated TG. When compared with patients with TG \leq 200 mg/dL, patients with high TG ($>$ 200 mg/dL) were 10 years younger, had a higher BMI, were more frequently men, diabetic, and smokers. At 1-year follow-up, recurrent ischemic events were more frequent in elevated TG patients. In multivariate logistic regression analysis, high TG (OR (95%CI): 1.356 (1.095-1.679)) remained an independent estimate for recurrent ischemic events, even after adjustment for confounding factors. In our large population-based cohort, elevated TG are common in acute MI, and associated with residual risk of recurrent ischemic events, beyond traditional prognostic markers.

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Introduction

Epidemiological, meta-analysis and genetic studies support the hypothesis that high blood triglycerides (TG) levels, whatever the fasting state, are independently associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD) and acute myocardial infarction (MI). The atherogenic effect of TG could be mainly driven by cholesterol-

enriched remnants. Other underlying mechanisms for the increased risk include excessive release of free fatty acids, production of proinflammatory cytokines, clotting factors, and thrombus formation.^{1,2} Real-world studies, such as the large National Health and Nutrition Examination Survey (NHANES), have suggested that hypertriglyceridaemia is common among US adults (26%), even among statin users, meaning that a substantial number of people have residual CV risk despite LDL-C control.³ Moreover, elevated TG were associated with worse CV outcomes when compared to similar patients with normal TG. Among adults from a large database of Ontario population with lipid panels and prevalent ASCVD, increasing TG was associated with pro-

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gressively higher hazard of ASCVD events at approximately 3 years of follow-up.⁴ However, in patients hospitalized for an acute MI, the identification of patients with elevated TGs and characterization of their risk of recurrence of ischemic events remain poorly described. The present study aimed, based on a large observational cohort collected over a 17-year period, to determine the prevalence, characteristics and prognostic impact of high TG levels in patients who experience an acute MI.

Patients and methods

The Côte d'Or MI observatory (RICO) is collecting data on patients hospitalized for an AMI in Côte d'Or.⁵ We retrospectively analyzed all consecutive patients included between January 1st, 2001, and June 30th, 2017, with lipids values and follow-up at 1 year. Patients without TG assay, under fibrates treatment, who died in-hospital or were lost to follow-up were excluded from the study (Figure 1 suppl file).

Data collection and statistical analysis are reported as supplemental files

Results

Among the 10,667 patients included, 17.7% had elevated TG (>200 mg/dL), with a median (IQR) TG of 120 (85-173) mg/dL (Figure 2 suppl file). Baseline characteristics are reported in Table 1.

When compared with patients whose TG \leq 200 mg/dL, patients with elevated TG were 10 years younger, with higher rates of metabolic disorders (such as obesity and diabetes), and more likely to smoke. The rate of men with elevated TG was high, in almost one in five (19.6%), while the rate of women with HTG was lower (13.4%). The rate of prior CVD and long-term lipid lowering therapy including statins and ezetimibe were similar for the two groups. Blood lipids including LDL-Cholesterol and non-HDL cholesterol were higher, but HDL cholesterol was lower. Severity indices of MI, such as rate of STEMI, troponin Ic peak, anterior wall location were more favorable and the rate of subjects with altered LVEF (<40%) were lower in the high TG group. Although patients with high TG were much younger, coronary artery disease (CAD) burden, as assessed by SYNTAX score, and multivessel disease were similar in both groups.

At 1-year follow-up, the rate of unplanned reperfusion was more elevated in the high TG group (10.9 and 5.9%, vs 9.4 and 4.7%, $p=0.047$ and $p=0.028$, respectively). Combined ischemic events, including PCI, CABG, recurrent ischemic events (UA, angina, recurrent MI) and stroke were higher (11.2 vs 9.1%, $p\leq 0.004$) (Figure 1). In order to better understand the relationship between TG and the 1-Y risk, we split the study population into 3 TG tertiles (i.e Triglycerides \leq 95 mg/dL (N=3513), 95 mg/dL < Triglycerides \leq 150 mg/dL (N=3551), and Triglycerides > 150 mg/dL (N=3603)). There was no graded relationship for the is-

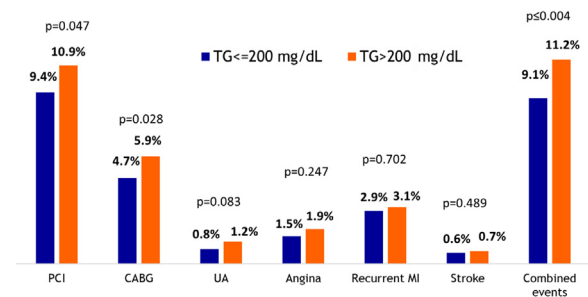


Figure 1 Rate of recurrent ischemic events at one-year follow-up according to triglyceride levels.

MI: myocardial infarction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; UA: unstable angina

chemic events across the 3 groups, either for revascularization or combined ischemic events, further supporting the prognostic relevance of the threshold at 200 mg/dL.

By multivariate analysis, high TG (OR (95%CI): 1.356 (1.095-1.679), $p=0.005$) was one of the stronger predictors of combined ischemic events, beyond GRACE score (OR (95%CI):1.006 (1.004-1.008), $p<0.001$), diabetes (OR (95%CI) 1.420 (1.182-1.705), $p<0.001$), and obesity (OR (95%CI) 1.242 (1.042-1.479), $p=0.015$). Quality indices of the model were good ($-2\text{Likelihood}=5668.862$; $pHL=0.207$; % classification=90.5) and the interactions between TG and metabolic disorders (TG*diabetes or TG*obesity) were not significant ($p>0.05$). Although crude 1-year CV mortality was lower in patients with elevated TG (3.3% vs 5.7%, $p<0.001$), the rate of death was similar for the 2 groups after adjustment for GRACE risk score ($p=0.410$).

Discussion

This large real-life study reveal the high prevalence of elevated TG (>200 mg/dL), almost 1 in 5, among survivors of acute MI. Patients with high TG were characterized by their younger age and elevated burden of metabolic disorders including diabetes and obesity. Moreover, the risk of recurrent ischemic events at 1-year of follow-up was more elevated in patients with high TG, even when adjusted for cardio-metabolic parameters.

Hypertriglyceridemia prevalence and characteristics

Hypertriglyceridemia is usually multifactorial, through a combination of genetic factors, with monogenic or polygenic determinants, associated with impaired clearance of triglyceride-rich lipoproteins. Secondary causes includes high fat diet, excessive alcohol intake, certain medications, and metabolic conditions (eg, diabetes mellitus, metabolic syndrome, obesity).⁶ The elevated prevalence of TG (18%) in the RICO survey is within the range of major contemporary MI or CAD registries, most addressing the generalizability of the Reduction of Cardiovascular Events with

Table 1 Characteristics of patients according to triglycerides levels.

n (%) or median (IQR)	Triglycerides ≤ 200 mg/dL (n=8781)	Triglycerides > 200 mg/dL (n=1886)	P value
Demographics and CV risk factors			
Age (y)	69 (58-79)	59 (50-71)	< 0.001
Female	2775 (32%)	430 (23%)	< 0.001
BMI (kg/m ²)	26 (24-29) (n=8163)	28 (25-31) (n=1775)	< 0.001
Diabetes	1806/8769 (21%)	512 (27%)	< 0.001
Hypertension	4832 (55%)	1001(53%)	0.122
Current smoking	2460 (28%)	798 (42%)	< 0.001
CV history			
CAD	1513 (17%)	310 (16%)	0.406
MI	1027 (12%)	209 (11%)	0.450
CABG	324 (4%)	61 (3%)	0.336
Stroke	592 (7%)	95 (5%)	0.006
PAD	721 (8%)	125 (7%)	0.021
Family history of CAD	2438 (28%)	614 (33%)	< 0.001
Chronic lipid-lowering medications			
Statins	2383 (27%)	502 (27%)	0.644
Ezetimibe	186 (2%)	41 (2%)	0.879
Biological data			
Total cholesterol (mg/dL)	190 (160-220) (n=8759)	218 (187-250) (n=1878)	< 0.001
LDL-cholesterol (mg/dL)	120 (92-147) (n=8715)	130 (100-159) (n=1816)	< 0.001
HDL-cholesterol (mg/dL)	46 (38-55) (n=8730)	37 (31-44) (n=1864)	< 0.001
Non HDL-cholesterol (mg/dL)	142 (113-171) (n=8714)	180 (150-211) (n=1861)	< 0.001
Triglycerides (mg/dL)	106 (80-141)	254 (222-312)	< 0.001
Troponin Ic peak (μg/L)	14.0 (2.9-41.0) (n=8593)	11.0 (2.3-41.0) (n=1845)	0.001
Clinical data			
LVEF (%)	55 (45-60) (n=8163)	55 (48-62) (n=1775)	< 0.001
LVEF <40%	1179/8163 (14%)	154/1775 (9%)	<0.001
STEMI	4716 (54%)	953 (51%)	0.012
Anterior wall location	3350 (38%)	642 (34%)	0.001
GRACE risk score	146 (122-172) (n=7918)	126 (106-153) (n=1707)	< 0.001
Medications at discharge			
Statin	6796 (77%)	1481 (79%)	0.285
Ezetimibe	135 (2%)	32 (2%)	0.613
Fibrate	8 (0.1%)	12 (1%)	<0.001
Antiplatelet	5714 (65%)	1295 (69%)	0.003
Aspirin	6924 (79%)	1544 (82%)	0.003
Beta blocker	6397 (73%)	1433 (76%)	0.005
CAD burden and reperfusion			
SYNTAX score	9 (5-17) (n=3418)	9 (5-17) (n=774)	0.368
Multivessel disease	4345 (51%) (n=8568)	947 (51%) (n=1855)	0.791
PCI	5961 (68%)	1333 (71%)	0.014
CABG	493 (6%)	129 (7%)	0.039

BMI: Body Mass Index; CABG: Coronary Artery By-pass Graft; CAD: Coronary Artery Disease; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; STEMI: ST Elevation Myocardial Infarction; PAD: Peripheral Artery Disease; PCI: Percutaneous Coronary Intervention.

Icosapent Ethyl–Intervention Trial (REDUCE-IT) trial (TG 150-500 mg/dL and LDL-C 40-100 mg/dL in addition to statin therapy). By strictly applying the eligibility criteria to patients from a nationwide registry, 12.5% of the French MI population had elevated TG.⁷ In a multinational registry, almost 15% of patients with established CAD had high TG.⁸ Moreover, in the Ontario cohort, the largest real world

database to date, almost 24% of participants had elevated TG (≥177mg/dL).⁴ Although CVD risk is increased for lower TGs levels (> 150 mg/dL), 2019 European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) guidelines reported that the use of drugs to lower TG levels should only be considered in high-risk patients when TG are > 200 mg/dL.⁹ Moreover, TG were obtained on non-fasting

samples, further reinforcing the choice of a threshold not too low. Therefore, our aim was to address this population. Although patients with elevated TG were younger, CAD history and burden at coronary angiography were similar for the two groups, strongly suggesting the aggressive atherogenicity of the metabolic environment related to high TG-rich lipoproteins.² Also, the rate of smokers was higher among subjects with TG ≥ 200 mg/dL, in agreement with recent meta-analysis showing that mean TG level of smokers was approximately 38% higher than in non-smokers.¹⁰ Patients from the high TG group were also characterized by their higher rate of elevated BMI, in addition to current smoking, suggestive of differential health behaviors that could influence the prognosis. In particular, poor medications adherence, including statin therapy, has been shown to significantly impact post MI prognosis, even when adjusted for sociodemographic factors.¹¹ However, these data were not collected in our real-world study. Therefore, unmeasured factors such as medications adherence may have influence the results. Furthermore, genetic factors such as TGRL- metabolism related variants (i.e. modulating LPL function) associated with ASCVD could also impact the prognosis.¹

Among optimally statin-treated MI patients included in randomized clinical trials testing lipid-lowering strategies, fasting TG predicted outcomes, including recurrent ischemic events.¹² In the atorvastatin-arm of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, short-term risk for a primary composite endpoint (death, non-fatal MI, stroke, cardiac arrest, UA) was at 15%, and gradually increased across TG tertiles, with 1st tertile as reference (> 135 mg/dL). Median TG levels (160 mg/dL) were higher than in the present study. Analysis from 15,817 subjects in Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome (dal-OUTCOMES) (median TG at 115 mg/dL), showed that the highest quintiles of TG, starting above 80 mg/dL, were associated with elevated risk of events combining CV death, non-fatal MI, ischemic stroke, UA or resuscitated cardiac arrest, at long-term follow-up. Observational cohort studies also found a stepwise-elevated ASCVD risk according to TG levels. In the large database of 196 717 subjects with prevalent ASCVD from the Ontario population, median TG was similar to our study (115 (80-159) mg/dL) and the prevalence of diabetes was progressively higher with higher TG levels.⁴ At 3-years of follow-up, elevated TG were associated with increasing rate of the primary composite outcome, such that individuals with the highest TG (> 354 mg/dL) had 52% higher risk than those in the lowest TG category (< 88 mg/dL). The risk was mainly driven by the rate of recurrent ischemic events, i.e. non-fatal MI/UA or revascularization and were similar among men and women, diabetics and non-diabetics, and among those with controlled vs. elevated LDL-C. In a nationwide cohort from Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) study on 1st-ever MI survivors, TG measured at early re-visit post MI

had the strongest predictive value for CV outcomes at 4-Y follow-up, above other blood lipids (i.e. HDL and LDL cholesterol).¹³ However, only top quintiles were associated with all-cause mortality. Moreover, in a recent small retrospective study in patients undergoing PCI with low baseline LDL-C (< 55 mg/dL), higher TG (≥ 103.5 mg/dL) predict ischemia-driven coronary revascularization events, but not CV death.¹⁴

Remnant lipoproteins generated during the intravascular remodeling of TRL has emerged as major driver of ASCVD risk.² As small remnant particles enriched in cholesterol, they may contain up to four-fold greater cholesterol per particle than LDL and enter into the intima, thus contributing substantially to the atherosclerosis risk through formation of macrophage foam cells and inflammation promotion.

Our study found a lower CV death rate at 1-year of follow up in subjects with elevated TG, probably related to younger age and less severe MI seeing as the difference was lost after adjustment for confounding, in particular on age. However, we cannot exclude the impact of other unmeasured confounding. In Asian CAD or MI populations, an inverse association was found between TG levels and CV mortality risk, but which also disappeared after adjustment.^{15,16} Ventricular arrhythmias, i.e. ventricular fibrillations, the most frequent cause of CV deaths following an acute MI, are mainly driven by LV remodeling and related to markers of MI severity.¹⁷ Consistent with this finding, our study showed that patients with elevated TG, which were much younger than patients with lower TG, had less LVEF dysfunction, and a reduced infarct size, as assessed by troponin Ic peak. Although the cause of death was not reported, we assumed that a better functional profile might explain the reduced mortality in this group. Death within the few months following an ischemic event mainly results from severity of injury, while recurrent ischemic events are mainly mediated by atherosclerotic plaque instability and CAD progression.

Study limitations

The characteristics of RICO patients are similar to those found in the nationwide French Registry of Acute ST-Elevation or Non-ST-elevation Myocardial Infarction (FAST-MI) registry, suggesting its representativeness on the French scale.¹⁸ However, the representability is limited by the exclusion criteria (hypertriglyceridemia, fibrate therapy, and lost to follow-up). Moreover, patients who died during hospital phase were at high risk, with older age, a higher rate of women, but a lower level of TG than survivors and the exclusion of these subjects could thus represent a survival bias limiting the representativeness of the study. This was an observational retrospective study, therefore causality of the relationship between TG and recurrent ischemic events cannot be conclusively proven and we cannot rule out significant unknown confounding factors associ-

ated with the prognosis. Non-fasting patients might be over-represented among those with higher TG levels. Moreover, non-fasting TG was better able to predict ASCVD risk than fasting TG.^{19,20} Thus, the fasting state might not modify the findings.

Recent alternative methods such as Martin-Hopkins allow a more accurate estimation of cardiovascular risk than Friedwald calculation. The present study covering the 2001-2017 period, used Friedwald formula for LDL-C calculation, which could bias the findings, as Friedwald equation is not reliable when TGs are elevated. Thus, we cannot firmly exclude a role of LDL-C as a contributor to the outcomes.

Conclusion

In this real-world large database of patients who survived an acute MI, elevated TG were common (almost 1 in 5 patients), and associated with increased risk of non-fatal recurrent ischemic events, in particular of revascularization. Our findings suggest that MI patients with elevated TG levels require more careful follow-up and aggressive multiple risk factor interventions.

Disclosure of conflict of interest

MF reports having received grants, consulting fees and/or honoraria and delivering lectures for Abbott, Amarin, Amgen, AstraZeneca, Ajanta, Kowa, Merck and Co, Novartis, Organon, Pfizer, Recordati, Sanofi/Regeneron, Servier, SMB, Ultragenyx and Viatrix. FC reports having received non-financial support and speaking fees for Amgen, MSD, Novartis, Sanofi and Pfizer. YC reports having received consultant or speaking fees for Bayer, BMS/Pfizer, Boehringer Ingelheim, Novartis, Sanofi and Servier. MZ declare research grants from Amarin Corp and speaking fees from Organon and Amgen. No declaration for the other authors.

CRediT authorship contribution statement

Marianne Zeller: Writing – original draft. **Frédéric Chague:** Validation. **Maud Maza:** Data curation, Formal analysis, Methodology. **Florence Bichat:** Data curation, Formal analysis. **Yves Cottin:** Validation. **Michel Farnier:** Conceptualization, Funding acquisition, Supervision.

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Author contribution

MF: conception, design of the study and critical revising for important intellectual content; MM and FB: acquisition of data, analysis and interpretation of data; MZ: drafting the article; YC and FC: final approval.

Use of AI and AI-assisted Technologies Statement

AI has not been used in the writing process of this manuscript.

Ethical statement

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Participants provided consent prior to inclusion, and the ethics committee approved the protocol.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jacl.2023.11.004](https://doi.org/10.1016/j.jacl.2023.11.004).

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