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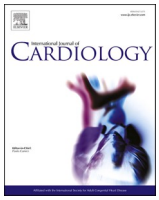

Prevalence of hypertriglyceridemia and its association with extreme cardiovascular risk in patients with acute and chronic coronary syndrome enrolled in a cardiac rehabilitation program

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ABSTRACT

Background: Prevalence of hypertriglyceridemia in patients with Acute and Chronic Coronary Syndrome (ACS and CCS, respectively) in the current era of Low-Density Lipoprotein Cholesterol (LDL-C) targets remains unknown. This study aimed to evaluate the prevalence of triglyceride (TG) levels above 150 mg/dL in ACS and CCS patients enrolled in a Cardiac Rehabilitation (CR) program and to explore its association with extreme cardiovascular (CV) risk.

Methods: We included 905 ACS/CCS patients who participated in the CR program at Niguarda Hospital (Milan) between January 1, 2012, and March 28, 2024. Data on demographic, clinical, and laboratory variables were collected. Extreme CV risk was defined as the occurrence of a CV event within two years or the presence of peripheral artery disease or multivessel coronary involvement.

Results: TG levels significantly decreased during the CR period (median 116.5, I-III quartiles 87–115 vs. 100, 80–133 mg/dL, $p < 0.001$), as did LDL-C levels (106.8 ± 39.3 vs. 64.4 ± 24.9 mg/dL, $p < 0.001$). At the end of CR, 17.6 % of patients had TG levels ≥150 mg/dL (15.0 % among those who reached the LDL-C target). In multivariable analysis, each 10 mg/dL increase in TG was associated with a 4.6 % increased risk of extreme CV risk (OR 1.046; 95 %CI 1.007–1.085; $p = 0.019$). Additionally, hypertriglyceridemia (TG >150 mg/dL) increased the risk of extreme CV risk by 81.5 % (OR 1.815; 95 %CI 1.096–3.007; $p = 0.021$).

Conclusions: Despite high-intensity statin therapy and low LDL-C targets, a significant proportion of patients in CR still exhibited elevated TG levels. Both TG levels and hypertriglyceridemia were strongly associated with the presence of extreme CV risk.

1. Introduction

Triglycerides (TG) and Hypertriglyceridemia (defined as TG levels ≥150 mg/dL) have been strongly associated with CardioVascular (CV) events both in primary and secondary prevention [1–4]. However, none of the drug aimed at reducing TG levels had been successful in improving CV outcomes [5–8] until the advent of icosapent ethyl (IPE), a highly purified form of the ethyl ester of eicosapentaenoic acid (EPA) [9–11].

Even when Low Density Lipoprotein Cholesterol (LDL-C) targets are reached, some patients continue to experience recurrent CV events. Patients who experience a second CV event within two years, or those with peripheral artery disease or multivessel coronary involvement, are categorized as being at extreme CV risk [12].

Hypertriglyceridemia may be a contributing factor to recurrent CV risk. Its prevalence in patients with Acute and Chronic Coronary

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Syndrome (ACS and CCS, respectively) has previously been reported to be around 25 % [13]. However, these reports precede the latest LDL-C target guidelines [2]. Lipid Lowering Therapies (LLT) not only reduce LDL-C but also TG levels (−15–30 % with high intensity statins, −8-10 % with ezetimibe [14], −3-5 % with bempedoic acid and − 15-20 % with PCSK9-inhibitors [15]. While the greater the baseline TG levels, the greater their reduction with an appropriate agent, the wide use of the previously cited LLT for an intensive LDL-C reduction also reduce TG levels, resulting in a lower prevalence of hypertriglyceridemia.

Although Cardiac Rehabilitation (CR) is recommended in all ACS patients or those who have recently undergone revascularization for CCS, fewer than 50 % of these patients participate in CR, especially those at higher CV risk and with poorer control of CV risk factors [16].

Thus, the aim of our study was to assess the prevalence of hypertriglyceridemia in ACS and CCS patients enrolled in a CR program, both in patients who achieved their LDL-C targets and those who did not. Additionally, we evaluated the association between hypertriglyceridemia and the presence of extreme CV risk.

2. Methods

2.1. Study population

This longitudinal study enrolled patients attending the CR program at Niguarda Hospital, Milan, between January 1, 2012, and March 28, 2024. Only patients admitted to CR for ACS or revascularization for CCS were included.

ACS was diagnosed accordingly to the fourth universal definition of myocardial infarction [17] characterized by the presence of acute myocardial injury with clinical evidence of acute myocardial ischemia. This was defined as a rise and/or fall in Troponin C values, with at least one value above the 99th percentile upper reference limit (> 14 ng/L), and at least one of the following: (i) symptoms of myocardial ischemia; (ii) new ischemic ElectroCardioGraphic (ECG) changes; (iii) development of pathological Q waves; (iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality consistent with ischemic etiology; and (v) identification of a coronary thrombus via angiography.

CCS was defined based on the 2019 European Society of Cardiology (ESC) guidelines and included: (i) patients with suspected coronary artery disease (CAD) and 'stable' angina symptoms and/or dyspnea; (ii) patients with new-onset heart failure (HF) or left ventricular (LV) dysfunction and suspected CAD; (iii) asymptomatic and symptomatic patients with stabilized symptoms within one year of an ACS or recent revascularization; (iv) asymptomatic and symptomatic patients more than one year after the initial diagnosis or revascularization; (v) patients with angina and suspected vasospastic or microvascular disease; and (vi) asymptomatic individuals in whom CAD was detected during screening [18].

Exclusion criteria were: (i) patients with non-ischemic heart diseases (e.g., heart failure, valvular heart disease, or post-cardiac surgery); (ii) patients on therapies that substantially modified triglyceride levels (e.g., omega-3 fatty acid supplements and fibrates). No specific TG exclusion criteria was used but none of the patients had extreme levels (i.e. higher than 500 mg/dL).

For each patient, data were collected at the start of the CR program, including medical history, physical examination, age, sex, Body Mass Index (BMI), and CV risk factors (e.g., family history, arterial hypertension, diabetes mellitus, smoking habits, and dyslipidemia). Baseline laboratory data were collected after an overnight fast and included creatinine, LDL-C, total cholesterol, HDL, triglycerides, and glycemia. Baseline biochemical data refer to the recent hospitalization that led to rehabilitation and were therefore collected before any modification of lipid-lowering therapy. Pharmacotherapy data included the use of beta-blockers, LLT, and antihypertensive medications.

Additionally, we recorded blood pressure (BP) and heart rate on the first day of CR. Glomerular Filtration Rate (GFR) was calculated using the CKD-EPI formula, and chronic kidney disease was defined as GFR < 60 mL/min. For patients with TG levels above 400 mg/dL, direct LDL-C measurement was used; otherwise, Friedewald's formula was applied to calculate cLDL: Total cholesterol - [HDL cholesterol + (TG/5)].

Hypertriglyceridemia was defined as TG ≥ 150 mg/dL, while overweight/obesity was defined as BMI > 25 kg/m^2. The LDL-C target was set at <70 mg/dL for patients enrolled before August 2019, and < 55 mg/dL for those enrolled after that date, in accordance with the ESC dyslipidemia guidelines [2].

All data were extracted from hospital electronic records and the CR database. The study protocol adhered to the Declaration of Helsinki and was approved by the Ethics Committee of the institution.

2.2. Identification of patients at extreme cardiovascular risk

Extreme CV risk was defined according to the 2022 ESC criteria as follow [12]: (i) a SCORE > 20 % in primary prevention; (ii) patients with a history of ACS and other vascular events within the last two years; (iii) patients with a history of ACS and peripheral vascular disease or polyvascular disease; (iv) patients with a history of ACS and concomitant multivessel coronary artery disease; (v) patients with a history of ACS and familial hypercholesterolaemia and (vi) patients with history of ACS and diabetes and at least one additional risk factor between elevated lipoprotein(a) or C-Reactive Protein or the presence chronic kidney disease.

Only criteria 2, 3, and 4 were used, as criterion 1 pertains solely to primary prevention, while criteria 5 and 6 required data that were unavailable (familial dyslipidemia, lipoprotein(a), and C-reactive protein).

Previous CV events within two years of the index ACS/CCS were defined as: (i) a prior ACS; (ii) prior coronary revascularization (either percutaneous intervention or coronary artery bypass grafting), whether elective or emergency; (iii) stroke or transient ischemic attack; (iv) prior peripheral artery disease revascularization (thromboendarterectomy or stenting) at the lower limbs and/or carotid arteries; and (v) prior acute lower limb events (ischemia, arterial occlusion, or artery-to-artery embolization). Lacunar infarction or positive imaging for cerebrovascular events (e.g., identification of ischemic areas on CT or MRI) were not considered CV events, as their timing could not be determined without concurrent clinical neurological symptoms.

Peripheral vascular disease was assessed based on a history of peripheral (cerebral or lower limb) events (criteria 3, 4, and 5 of the previous definition) or the presence of an atherosclerotic plaque ≥50 % in non-coronary vessels (e.g., supra-aortic trunks or lower limb arteries) on echography, or an Ankle-Brachial Index <0.9. Polyvascular disease was defined as the involvement of two or more vascular territories by atherosclerosis (including coronary artery disease).

Multivessel coronary artery disease (involving more than three vessels) was determined by analyzing the number of coronary vessels affected by atherosclerotic plaque during coronary angiography.

2.3. Cardiac rehabilitation program

The CR program consisted of 25 sessions over five weeks, conducted in an outpatient setting. The core activity was daily aerobic exercise, which included 45 min of endurance training on a stationary bike, followed by 15 min of rest, and 45 min of bodyweight exercises. The intensity of the physical activity was tailored to each patient's functional capacity and tolerance and was progressively increased throughout the program.

The CR program was delivered by a multidisciplinary team comprising cardiologists (serving as the coordinating figures), nurses, and physiotherapists. In addition, participants received psychological support to help manage emotional well-being and a dietary consultation to encourage lifestyle and nutritional changes.

2.4. Statistical analysis

Results for continuous normally distributed variables are presented as mean ± standard deviation and median (I quartiles, III quartile) for continuous skewed variables (TG and glucose), while categorical variables are reported as counts and percentages.

Patients were divided into two groups based on TG levels (< 150 mg/dL or ≥ 150 mg/dL). Comparisons of continuous variables between groups were performed using Student's *t*-test, while categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. To compare continuous variables at two time points (start and end of CR) within the same group, a paired t-test was used.

A logistic regression model was employed to assess the association between extreme CV risk and TG levels/hypertriglyceridemia, adjusting for covariates such as age, sex, baseline BMI, ACS/CCS, glomerular filtration rate (GFR), discharge LDL-C and diabetes mellitus.

Restricted cubic splines were used to investigate the functional form of continuous covariates. Statistical analyses were conducted using R software (version 4.3.2), and a significance level of 0.05 was applied.

3. Results

3.1. Population characteristics

Table 1 presents the clinical characteristics of the study population, consisting of 905 subjects, the majority of whom were male (82.7 %), with a mean age of 67.0 ± 10.6 years and a mean BMI of 27.0 ± 4.1 kg/m^2.

Regarding CV risk factors, 45.2 % of subjects had a family history of early CV events, 57.0 % were overweight or obese, 20.3 % had diabetes mellitus, 75.1 % had dyslipidemia, 67.9 % had arterial hypertension, and 63.0 % were either current or former smokers.

The patients' cardiological history revealed that 14.9 % had recurrent ACS, 34.1 % had undergone previous coronary revascularization, 8.8 % had peripheral artery disease in the lower limbs, 9.4 % had cerebrovascular disease, 92.7 % were in sinus rhythm, and 18.8 % had chronic kidney disease.

Of the total population, 82.5 % had ACS, while the remaining were undergoing CR for CCS. The mean number of coronary vessels involved was 1.6 ± 0.9, and 17.5 % of patients had three-vessel coronary disease. Overall, 30.6 % of the enrolled patients were diagnosed with extreme CV risk.

LDL-C levels significantly decreased from baseline to discharge (106.8 ± 39.3 vs. 64.4 ± 24.9 mg/dL, $p < 0.001$), primarily due to high intensity statins +/− ezetimibe, with 56.0 % of patients reaching the target LDL-C levels at discharge. Similarly, TG levels decreased significantly (median 116.5, I-III quartiles 87–115 vs. 100, 80–133 mg/dL, p < 0.001). The prevalence of patients with TG levels ≥150 mg/dL at the end of CR was 17.6 %, dropping to 15.0 % among those who achieved the LDL-C target, as shown in Fig. 1, Panel A.

Regarding pharmacotherapy, 85.3 % of patients were on beta-blockers, 88.2 % were on statins, 56.7 % were taking ezetimibe, 81.5 % were on antihypertensive therapies, 5.2 % were on PCSK9 inhibitors, and 0.9 % were taking bempedoic acid.

3.2. Hypertriglyceridemia vs no hypertriglyceridemia patients

Supplementary table 1 presents the characteristics of patients categorized by TG levels, using the standard cut-off of 150 mg/dL. Patients with TG levels ≥150 mg/dL had a higher mean BMI (28.7 ± 4.3 vs. 27.6 ± 4.1 Kg/m^2, $p < 0.001$) and a lower rate of reaching LDL-C targets (48.2 vs. 58.5 %, $p = 0.029$). In contrast, age, BP and glucose levels were similar between the two groups.

The hypertriglyceridemia group had a higher prevalence of dyslipidemia (85.4 vs. 71.4 %, $p = 0.001$), smoking (72.3 vs. 62.1 %, $p = 0.048$), previous revascularization (41.6 vs. 28.8 %, $p = 0.002$), peripheral artery disease (13.5 vs. 7.4 %, $p = 0.039$), and chronic kidney disease (27.3 vs. 15.8 %, $p = 0.006$). Moreover, extreme CV risk was more common in the hypertriglyceridemia group (37.6 vs. 27.3 %, p = 0.039), as shown in Fig. 1, Panel B.

Table 1
whole population characteristics at admission and at discharge.

	CR admission	CR discharge	*p*-value
Number	905	905	–
Age, years (mean ± SD)	67.0 ± 10.6	–	–
Male sex, number (%)	748 (82.7)	–	–
Cardiovascular risk factors and previous diseases			
Active or previous smoking, number (%)	570 (63.0)	–	–
Familial history, number (%)	408 (45.2)	–	–
Body mass index, kg/m^2 (mean ± SD)	27.0 ± 4.1	–	–
Overweight/obesity, number (%)	514 (57.0)	–	–
Diabetes mellitus, number (%)	183 (20.3)	–	–
Dyslipidaemia, number (%)	679 (75.1)	–	–
Arterial hypertension, number (%)	614 (67.9)	–	–
Extreme cardiovascular risk, number (%)	271 (30.6)	–	–
Peripheral artery disease, number (%)	78 (8.8)	–	–
Cerebral vasculopathy, number (%)	83 (9.4)	–	–
Previous coronary revascularization, number (%)	309 (34.1)	–	–
Number of coronary vessel involved, number	1.6 ± 0.9	–	–
Three-vessel coronary disease, number (%)	155 (17.5)	–	–
ACS as index event, number (%)	747 (82.5)	–	–
Recurrent ACS, number (%)	132 (14.9)	–	–
Sinus Rythm, number (%)	839 (92.7)	–	–
Chronic kidney disease, number (%)	138 (18.8)	–	–
Cardiovascular drug therapies			
Beta-blockers, number (%)	745 (85.3)	–	–
Statins, number (%)	798 (88.2)	–	–
Ezetimibe, number (%)	366 (56.7)	–	–
Anti-hypertensive, number (%)	667 (81.5)	–	–
PCSK9-inhibitors, number (%)	47 (5.2)	–	–
Bempedoic acid, number (%)	8 (0.9)	–	–
Clinical parameter			
Systolic blood pressure, mmHg (mean ± SD)	124.6 ± 16.2	115.4 ± 11.4	<0.001
Diastolic blood pressure, mmHg (mean ± SD)	74.2 ± 3	66.8 ± 8.8	<0.001
Heart rate, bpm (mean ± SD)	65.8 ± 8.1	–	–
Biochemical data			
Glucose, mg/dl (median, I-III quartiles)	98 (87–115)*	101 (93–118)	0.142
Creatinine, mg/dl (mean ± SD)	1.0 ± 0.3*	–	–
eGFR, ml/min (mean ± SD)	76.9 ± 18.4*	–	–
Total cholesterol, mg/dl (mean ± SD)	175.7 ± 43.2*	132.2 ± 30.7	<0.001
HDL cholesterol, mg/dl (mean ± SD)	42.8 ± 11.1*	44.3 ± 11.6	<0.001
LDL cholesterol, mg/dl (mean ± SD)	106.8 ± 39.3*	64.4 ± 24.9	<0.001
LDL target reached (<55 mg/dl), number (%)	–	505 (56.0)	–
Tryglycerids, mg/dl (median, I-III quartiles)	116.5 (87–159)*	100 (80–133)	<0.001
Hypertrygliceridemia, number (%)	–	137 (17.6)	–
Hypertrygliceridemia (in patients with LDL target <55 mg/dl reached), number (%)	–	66 (15.0)	–

Abbreviations: ACS = Acute Coronary Syndrome; CR = Cardiac Rehabilitation; eGFR = Estimated Glomerular Filtration Rate; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; PCSK9 = Proprotein Convertase Subtilisin/Kexin type 9.

* Biochemical data collected at discharge from hospitalization that led to rehabilitation.

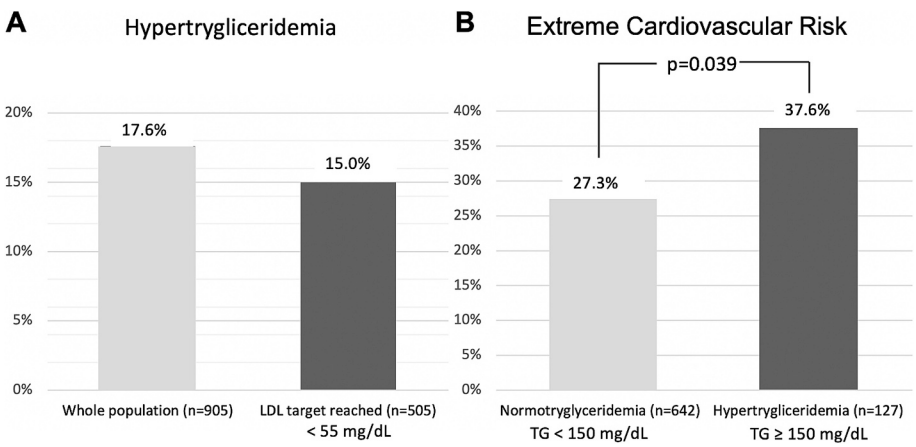

Fig. 1. Hypertriglyceridemia prevalence in the whole population and only in subjects with LDL-Cholesterol target reached (panel A) and prevalence of extreme CV risk in patients with and without hypertriglyceridemia (panel B).

3.3. Multivariable analysis

In a logistic multivariable analysis (Table 2), with extreme CV risk as the dependent variable and covariates including age, sex, baseline BMI, ACS/CCS status, GFR, discharge LDL-C and diabetes mellitus; each 10 mg/dL increase in TG was associated with a 4.6 % increase in the risk of extreme CV risk (OR 1.046; 95 %CI 1.007–1.085; $p = 0.019$). Restricted cubic splines were used to flexibly model the relationship between TG levels and the log-odds of extreme CV risk, supporting the assumption of linearity (Fig. 2). Similarly, having hypertriglyceridemia (TG >150 mg/dL) increased the risk of extreme CV risk by 81.5 % (OR 1.815; 95 %CI 1.096–3.007; $p = 0.021$).

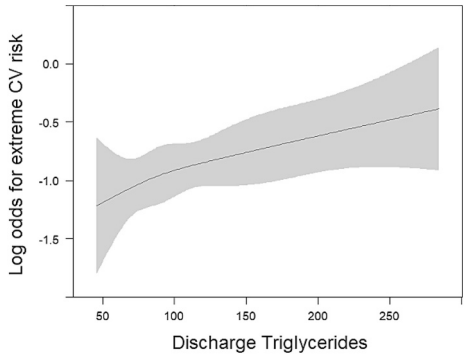

Fig. 2. Association between triglycerides as a continuous variable and extreme CV risk (logit scale) evaluated using restricted cubic splines with 4 knots.

4. Discussion

The main finding of our study was that 17.6 % of patients with ACS or CCS enrolled in a CR program had hypertriglyceridemia. The prevalence slightly decreased to 15.0 % among patients who achieved their LDL-C target. Some previous analyses reported a higher prevalence of hypertriglyceridemia, ranging from 20 % to 25 % [19,20] while another one found a similar prevalence [21]. However, the majority of these studies were conducted before the introduction of the current, more stringent LDL-C targets in secondary prevention [2]. As mentioned earlier, lower LDL-C targets require more intensive lipid-lowering therapy (LLT), which also results in greater TG reduction. In our study, 56.0 % of patients reached the LDL-C target of 55 mg/dL, which is associated with a significantly lower prevalence of hypertriglyceridemia compared to previous reports. Additionally, when only patients who achieved the LDL-C target were considered, the prevalence of hypertriglyceridemia was further reduced. However, a significant proportion of secondary prevention patients in CR continued to have elevated TG levels, suggesting a potential benefit from further therapeutic intensification.

The second key finding of our study is the correlation between TG levels and extreme CV risk. For every 10 mg/dL increase in TG, the risk of extreme CV risk increased by 4.6 %, reaching a significant 81.5 % increase when the TG threshold of 150 mg/dL was exceeded. In a specific analysis of the ODISSEY trial, when baseline TG levels were examined as a continuous variable, the adjusted risk of Major Adverse CV Events (MACE) was significantly higher by about 1 % for every 10 mg/dL higher triglyceride level (HR 1.008; 95 % CI 1.003–1.013), with similar relationships observed in both treatment groups [4].

These findings are particularly relevant, as despite the reduction in in-hospital events and complications for ACS patients, a substantial number still experience recurrent CV events during the chronic phase of the disease (CCS).

In particular, our analysis has three elements of novelty in comparison to what already published: (i) hypertriglyceridemia has been evaluated in a real-world cohort of patients achieving contemporary

Table 2
Multivariable regression models with extreme CV risk as the dependent variable and discharge triglycerides (model A) and hypertriglyceridemia (model B).

Dependent variable: Extreme CV risk	Model A: Triglycerides		Model B: Hypertriglyceridemia	
Co-variates	OR (95 % CI)	P-value	OR (95 % CI)	P-value
Age, per years	1.015 (0.991–1.039)	0.224	1.015 (0.991–1.039)	0.217
Sex (female vs male)	0.498 (0.273–0.908)	0.023	0.484 (0.266–0.883)	0.018
eGFR (per ml/min)	0.991 (0.979–1.004)	0.192	0.991 (0.979–1.004)	0.177
Discharge LDL cholesterol (per mg/dL)	0.993 (0.985–1.002)	0.120	0.994 (0.985–1.002)	0.130
ACS (yes vs no)	1.247 (0.714–2.178)	0.438	1.200 (0.686–2.099)	0.523
DM (yes vs no)	2.760 (1.721–4.427)	<0.001	2.852 (1.779–4.571)	<0.001
Baseline BMI (per kg/m^2)	0.980 (0.932–1.031)	0.440	0.979 (0.930–1.030)	0.419
Discharge triglycerides (per 10 mg/dL)	1.046 (1.007–1.085)	0.019	–	–
Hypertriglyceridemia (yes vs no)	–	–	1.815 (1.096–3.007)	0.021

Abbreviations: LDL = Low-Density Lipoprotein; ACS = Acute Coronary Syndrome; DM = Diabetes Mellitus; BMI = Body Mass Index.

LDL-C targets in more than 50 % of the cases. Previous works precede the actual targets and/or presents a lower prevalence of LDL-C targets achievements. So, our data are able to isolating the residual risk associated with triglycerides despite optimal LDL-C control; (ii) to the best of our knowledge this is the first study specifically examining the association between hypertriglyceridemia and the concept of extreme cardiovascular risk as defined by recent ESC consensus paper, rather than general CV risk or event recurrence alone; (iii) finally, this association was evaluated within the context of CR, a setting less frequently evaluated and often underrepresented in previous research on residual cardiovascular risk.

Recent scientific efforts have focused on enhancing secondary prevention strategies to reduce the recurrence of CV events and mitigate residual risk in patients with a previous CV event. While traditional CV risk factors, especially LDL-C, play a critical role, it is evident that many patients experience further CV events despite optimal therapy and target LDL-C levels.

Notably, the recent ODYSSEY outcomes analysis demonstrated that post-ACS patients with TG $\geq$ 150 mg/dL had significantly higher risk of MACE, even after achieving LDL-C < 55 mg/dL, than those with TG < 150 mg/dL (9.0 vs 6.4 %; HR 1.345; 95 % CI 1.010–1.791) [4]. Two other studies on ACS patients need to be cited. In the first one, among the 14,483 patients enrolled in an ACS registry, 6624 (45.7 %) had triglycerides >135 mg/dL and 7945 (54.9 %) had LDL-C < 100 mg/dL; a total of 3028 (20.9 %) patients fulfilled both criteria. A second group of 3391 patients (23.4 % of the population) had an LDL-C < 70 mg/dL and triglycerides 135–500 mg/dL. At multivariable analysis they had higher risk of death (HR 1.14; 95 % CI 1.02–1.27) and MACE (HR 1.11; 95 % CI 1.01–1.21) [22]. Furthermore, in a retrospective cohort of 4884 ACS patients, persistent hypertriglyceridemia (≥150 mg/dL) was associated with recurrent MACE at 6-, 12-, and 24-months post-ACS ($p < 0.05$), and the relative risk ranged between 1.20 and 1.35 at these timepoints [23]. Both these studies confirm that residual risk from hypertriglyceridemia is a frequent issue and is strongly associated with increased probability of CV events recurrences.

In fact, the recently published ESC criteria for extreme CV risk emphasize early identification of high-risk individuals to enable more intensive treatment and reduce the recurrence of CV events [12]. Our results demonstrated a significant association between TG levels and extreme CV risk highlighting the potential importance of intensifying treatment for this risk factor, particularly in the secondary prevention setting.

Notably, not all TG-lowering therapies have demonstrated CV benefit. Omega-3 supplementation with combinations of EPA and docosahexaenoic acid (DHA), trials (of which the latest was the STRENGHT study [5] mainly showed negative results with no reduction in CV events compared to placebo. Similarly, also trial with fibrates supplementation fails to find a reduction in CV events [24] expect for diabetic patients with low HDL-C [25].

Also the latest trial on the topic, PROMINENT with pemafibrete failed to identify a significant reduction in CV events despite effective TG lowering [8]. These findings emphasize that therapeutic efficacy could depends on pleiotropic effects beyond TG reduction alone.

Using IPE, instead of EPA + DHA, formulations findings were completely different. The efficacy of IPE in CV prevention was firstly supported by the JELIS trial. This is an open-label, blinded endpoint, large-scale CV outcomes trial in Japanese involving 18,645 patients with hypercholesterolemia and demonstrating a 19 % relative risk reduction in major coronary events with IPE (1.8 g/day) added to statin therapy, compared with statin alone (HR 0.81, 95 % CI 0.69–0.95, $p = 0.011$) [9]. Although the trial was conducted in a different population and design, it provided early supportive evidence of EPA's cardioprotective potential.

Further evidence comes from a randomized open-label trial by Nosaka et al., which enrolled 238 patients with ACS treated with percutaneous coronary intervention. Patients receiving IPE (1.8 g/day) in addition to statins experienced a 58 % reduction in CV events at 1-year follow-up compared to those receiving statin therapy alone [25].

In the REDUCE-IT trial, patients treated with 4 g/day (higher than the dose used in the two previous studies due to lower baseline EPA plasma concentrations in non-Japanese populations) of IPE experienced a 4.8 % absolute reduction in the primary composite endpoint of CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina over 4.9 years, compared to placebo [26]. Eligible patients had TG levels between 135 and 499 mg/dL and LDL-C levels between 41 and 100 mg/dL, with most participants in secondary prevention (70.7 %). The treatment arm in the REDUCE-IT trial showed a 17.2 % event rate in the primary endpoint, compared with 22 % in the control arm, resulting in a statistically significant difference (HR 0.75, 95 % CI 0.68–0.83, $p < 0.001$). Additionally, IPE provided further benefits in CV death (4.3 % vs. 5.2 %, HR 0.80, 95 % CI 0.66–0.98, $p = 0.03$). However, there was a higher incidence of adjudicate endpoint of hospitalization for atrial fibrillation/flutter in the IPE group (3.1 % vs. 2.1 %, $p = 0.004$) and a slight increase in bleeding events (2.7 % vs. 2.1 %, $p = 0.06$).

Finally, in the RESPECT-EPA study, which enrolled 1225 patients with CCS, 1.8 g/day of IPE showed a reduction in the occurrence of the primary composite endpoint (CV death, non-fatal myocardial infarction, non-fatal ischemic stroke, unstable angina, and coronary revascularization) compared to placebo, though the result was of borderline statistical significance (9.1 % vs. 12.6 %, HR 0.79, 95 % CI 0.62–1.00, $p = 0.055$) [10]. However, the incidence of the secondary composite endpoint of coronary events (sudden cardiac death, myocardial infarction, unstable angina, and coronary revascularization) was significantly lower in the EPA group (6.6 % vs. 9.7 %, HR 0.73, 95 % CI 0.55–0.97, $p = 0.031$).

A meta-analysis found that IPE therapy was associated with a lower rate of coronary revascularization (HR 0.76, 95 % CI 0.65–0.88, $p = 0.0002$) compared to traditional omega-3 therapies (EPA + DHA) [27].

The mechanism by which IPE determine its beneficial effects, and the other TG lowering therapies don't, is probably related to its pleiotropic effects (anti-inflammatory and anti-platelet) [26]. In fact, the benefit observed in the REDUCE-IT trial was independent of baseline TG levels, suggesting that these effects play a critical role. Furthermore, the mechanism by which IPE may reduce coronary revascularization is also to plaque stabilization. In fact, IPE has been shown to significantly reduce coronary plaque volume both in intravascular ultrasound studies and in coronary CT angiography assessment [25,26]. In contrast, EPA + DHA therapies have not demonstrated significant changes in plaque composition in either coronary tomography or cardiac magnetic resonance studies [4,27–29].

Reflecting these findings, the 2019 ESC guidelines on dyslipidemia management recommend the use of IPE in high-risk patients with TG levels between 135 and 499 mg/dL, despite optimal statin therapy, to further reduce residual CV risk [2]. This recommendation is now echoed across contemporary ACS and CCS guidelines. In August 2023, the ESC released updated guidelines for the management of ACS which include a class IIb recommendation for IPE 2 g twice daily that may be used in patients with ACS and TG levels between 135 and 499 mg/dL despite statin treatment [16].

Similarly, the American Heart Association – American College of Cardiology 2023 CCS guideline (published in July 2023) endorses IPE as an adjunct therapy. Specifically, in patients who are already on maximally tolerated statin therapy, with LDL-C < 100 mg/dL and persistent fasting TG levels of 150–499 mg/dL after ruling out secondary causes, IPE should be considered to further reduce the risk of MACE and CV death [30].

Our study had several limitations. First, as mentioned earlier, not all criteria for extreme CV risk assessment could be used due to a lack of available data. Additionally, we lacked data on specific CV drug types and dosages, and we did not assess alcohol intake. Finally, as this was a single-center study, the results may not be fully generalizable, as CR referral criteria may differ across institutions. The multifactorial nature

of the link between TG, hypertriglyceridemia, and extreme CV risk makes it challenging to account for all relevant factors, and it is possible that some variables (such as inflammation, endothelial function and glycated hemoglobin) were not evaluated.

5. Conclusion

Despite high-intensity statin therapy and achieving lower LDL-C targets, a substantial proportion of patients in CR continue to have elevated TG levels. Both TG levels and hypertriglyceridemia were significantly associated with extreme CV risk, highlighting the need for more intensive therapeutic strategies to mitigate residual risk in high-risk patients.

CRediT authorship contribution statement

Chiara Tognola: Writing – original draft, Data curation, Conceptualization. **Davide Bernasconi:** Writing – review & editing, Methodology, Formal analysis. **Rita Cristina Myriam Intravaia:** Writing – review & editing, Validation, Data curation. **Giulia Brioschi:** Writing – review & editing, Validation, Data curation. **Giorgio Toscani:** Writing – review & editing, Validation, Data curation. **Michela Algeri:** Writing – review & editing, Validation, Data curation. **Atea Shkodra:** Writing – review & editing, Validation, Data curation. **Elvira Inglese:** Writing – review & editing, Validation, Investigation, Data curation. **Luciana Sciumè:** Writing – review & editing, Visualization, Methodology. **Romano Danesi:** Writing – review & editing, Visualization, Resources, Investigation. **Giovanna Beretta:** Writing – review & editing, Validation, Resources. **Cristina Giannattasio:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Alessandro Maloberti:** Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

the authors declare they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2025.133608.

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