

Eligibility for Icosapent ethyl in patients undergoing cardiac rehabilitation: A real-world cohort study

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ABSTRACT

Introduction: Despite optimal lipid-lowering therapy, many patients with established cardiovascular disease (CVD) maintain elevated triglyceride (TG) levels, contributing to residual risk. Icosapent ethyl (IPE) has shown clinical benefit in patients with moderate hypertriglyceridemia. This study aimed to evaluate eligibility for IPE treatment based on REDUCE-IT and Italian Drugs Administration (AIFA) eligibility criteria.

Methods: We retrospectively analyzed 1129 patients referred to a cardiac rehabilitation program for a recent acute coronary syndromes or with a chronic coronary syndromes between 2012 and 2025. Fasting TG and LDL were assessed at admission and discharge. We identified patients eligible for IPE treatment based on REDUCE-IT (TG 135–499 mg/dL, LDL 40–100 mg/dL, statin therapy) and AIFA eligibility criteria (TG \geq 200 mg/dL, LDL $<$ 70 mg/dL, BMI \geq 27 kg/m², statin + ezetimibe therapies, age 18–80).

Results: Median TG values significantly decreased from 117 (IQR 86–159) mg/dL at admission to 99 (79–132) mg/dL at discharge ($p < 0.001$). LDL also decreased from 106.7 \pm 40.1 to 62.8 \pm 24.8 mg/dL ($p < 0.001$). Based on REDUCE-IT criteria, 117 patients (10.4 %) were eligible for IPE while only 6 patients (0.53 %) met all AIFA eligibility criteria.

Conclusions: In a large real-world cohort of acute and chronic coronary syndrome undergoing cardiac rehabilitation, over 10 % of patients were theoretically eligible for IPE based on clinical trial criteria. However, less than 1 % met current AIFA eligibility conditions due to added restrictions, highlighting a significant barrier to implementation in clinical practice.

1. Introduction

Despite advances in lipid-lowering therapies, a substantial proportion of patients with established atherosclerotic cardiovascular (CV) disease exhibit residual risk due to persistent elevations in triglycerides (TG), even after achieving target LDL-cholesterol (LDL-C) levels [1]. Hypertriglyceridemia is increasingly recognized as an independent contributor to residual CV risk [2,3] and current dyslipidemia guidelines recommend specific therapy when TG levels exceed 150 mg/dL, as this

threshold is considered clinically relevant for CV risk management [4].

Icosapent ethyl (IPE) is a highly purified formulation of eicosapentaenoic acid with anti-inflammatory and antithrombotic properties that has demonstrated significant efficacy in reducing major CV events in REDUCE-IT [5–7].

REDUCE-IT provided compelling evidence supporting the use of IPE in patients with controlled LDL-C levels who still had moderately elevated TG, particularly when associated with high-risk profiles such as diabetes or recent CV events.

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However, translating these findings into routine practice faces notable challenges. In Italy, the regulatory framework established by the nation drug regulatory agency (Agenzia Italiana del Farmaco – AIFA) imposes stricter eligibility requirements compared to those used in the clinical trials, potentially limiting patient access to this therapy.

Cardiac rehabilitation (CR) programs represent a crucial phase in secondary prevention. These programs offer a unique setting to perform comprehensive risk factor management, CV risk definition and therapeutic optimization [8].

To date, little is known about the proportion of patients undergoing rehabilitation who could qualify for IPE treatment based on available criteria. Our study was aimed at answering this question evaluating proportion of IPE eligible patients in the Niguarda Hospital CR program.

2. Methods

2.1. Study population

We conducted a retrospective observational analysis of 1129 consecutive patients admitted to the cardiac rehabilitation unit at ASST Grande Ospedale Metropolitano Niguarda (Milan, Italy) from January 2012 to June 2025.

Inclusion criteria for the present analysis were: (i) acute or chronic coronary syndrome (ACS and CCS respectively); (ii) complete the full CR course; (iii) availability of biochemical data at both admission and discharge.

ACS was diagnosed accordingly to the fourth universal definition of myocardial infarction characterized by the presence of acute myocardial injury with clinical evidence of acute myocardial ischemia [9]. 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 2024 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 coronary artery disease; (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 [10]. Regarding criteria number ii), only patients that had a following confirmed diagnosis of coronary artery disease were included. Finally, patients respecting criteria number v) were not included in the present analysis because they don’t present a coronary artery disease.

Exclusion criteria for the present analysis 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).

At the beginning of the CR program, the following information was systematically collected for each patient: demographic details (age, sex), anthropometric data (body mass index - BMI), clinical history, and CV risk factors such as family history, hypertension, diabetes, dyslipidemia, and smoking status.

Laboratory analyses were performed using the Modular Analytics SWA platform (Roche Diagnostics), which applies enzymatic colorimetric techniques: GOD-PAP for glucose, CHOD-PAP for total cholesterol, third-generation methods for HDL-C, and GPO-PAP for

triglycerides. When triglyceride levels exceeded 400 mg/dL, LDL-C was measured directly. In all other cases, LDL-C was estimated using Friedewald’s equation: total cholesterol minus HDL-C and one-fifth of triglyceride concentration. Serum creatinine was assessed through the kinetic Jaffé method, and the estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula. Chronic kidney disease (CKD) was defined by an eGFR below 60 mL/min.

Baseline biochemical data refer to the recent hospitalization that led to rehabilitation and were therefore collected before any modification of lipid-lowering therapy (LLT). CR discharge biochemical data refers to the values evaluated few days before the end of the program. Pharmacotherapy data were collected at the end of CR and included the use of beta-blockers, LLT, and antihypertensive medications.

Blood pressure (BP) and heart rate were measured both at the start and at the end of the CR program. A BMI greater than 25 kg/m² was used to classify individuals as overweight or obese. All relevant data were obtained from the hospital’s electronic medical records and the dedicated CR database.

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and received approval from the local Ethics Committee.

2.2. Cardiac rehabilitation program

The CR program at Niguarda Hospital is conducted on an outpatient basis and includes 25 sessions focused primarily on supervised aerobic training.

The daily training schedule centered on aerobic work: 45 min of cycling endurance, a 15-min recovery period, and then another 45 min devoted to body-weight drills. Exercise load was individualized according to each patient’s capacity and gradually intensified over the course of rehabilitation in order to reach the 75–85 % of the peak heart rate evaluated during a 6-min walking test performed on the first day of CR.

A multidisciplinary staff — cardiologists coordinating, supported by nurses and physiotherapists — oversaw the sessions. Patients also had access to psychological counselling for emotional well-being and dietetic guidance to reinforce healthy lifestyle changes [11].

2.3. IPE eligibility definitions

IPE eligibility was defined both with the REDUCE-IT trial inclusion/exclusion criteria [7] and with the reimbursement criteria defined by AIFA.

Regarding the firsts they were: (i) TG between 135 and 499 mg/dL; (ii) LDL between 40 and 100 mg/dL; (iii) on-going statin therapy.

AIFA eligibility/reimbursement criteria were: (i) TG ≥ 200 mg/dL; (ii) LDL < 70 mg/dL; (iii) BMI ≥ 27 kg/m²; (iv) age 18–80 years; (iv) on-going maximum tolerated combination therapy with statins and ezetimibe.

2.4. Statistical analysis

Continuous variables were summarized using means and standard deviation (when normally distributed) or medians and interquartile ranges (when skewed) while categorical variables were expressed as counts and percentages. Paired student *t*-test was used to

compared continuous normally distributed variables between CR admission and discharge. Same tests were performed with Wilcoxon signed-rank test for continuous skewed variables and with McNemar test for categorical variables. SPSS 13.0 (SPSS, IBM, United States) was used for statistical analysis and two-sided *p*-value < 0.05 was considered statistically significant.

3. Results

A summary of the clinical and biochemical characteristics of the 1129 patients at initiation and conclusion of the CR program is reported in Table 1. Most were referred following an acute coronary syndrome (85 %), while the remaining 15 % had a chronic coronary syndrome. The population was predominantly male (82.8 %) with a mean age of 61.9 ± 10.4 years. Common cardiovascular risk factors included dyslipidemia (72.5 %), hypertension (66.3 %), current or past smoking (63.0 %), diabetes mellitus (19.6 %), and a family history of cardiovascular disease (46.4 %). Furthermore, the average BMI was 26.8 ± 4.5 kg/m², and 53.0 % of patients were classified as overweight or obese.

A history of previous percutaneous coronary intervention (30.3 %), coronary artery bypass grafting (7.3 %), stroke or transient ischemic attack (8.2 %), and peripheral artery disease (5.5 %) was also recorded. The coronary anatomy of the index hospitalization (the one that leads to the CR) showed critical lesions in the LAD (63.5 %), right coronary (37.9 %), circumflex (33.6 %), and left main (5.5 %), with multivessel involvement in 41.5 % of cases. Atrial fibrillation was present in 6.9 %, and 18.1 % of patients had chronic kidney disease (eGFR <60 mL/min).

At baseline, mean systolic and diastolic BP were 124.1 ± 16.0 mmHg and 74.5 ± 9.5 mmHg, respectively, and the average resting heart rate was 62.8 ± 8.6 bpm. The mean peak CK-MB and high-sensitivity troponin T levels were 104.9 ± 238.6 µg/L and 2333.5 ± 3972 ng/L, respectively.

Regarding pharmacologic treatment at discharge, the majority of patients were prescribed statins (77.8 %) and beta-blockers (73.0 %), while 38.1 % received ezetimibe, 60.4 % ACE inhibitors or ARBs, and 6.5 % were on diuretics.

Median TG levels significantly decreased from 117 mg/dL (IQR 86–159) at admission to 99 mg/dL (IQR 79–132) at discharge ($p < 0.001$, Fig. 1, panel A). Similarly, LDL-C levels showed a significant reduction from 98 mg/dL (IQR 61–123) to 59 mg/dL (IQR 47–76, $p < 0.001$, Fig. 1, panel B).

Among the total cohort, 117 patients (10.4 %) fulfilled REDUCE-IT inclusion criteria and were considered theoretically eligible for IPE administration. In contrast, only 6 patients (0.53 %) met the comprehensive AIFA eligibility requirements, primarily due to more stringent thresholds for TG and LDL-C, as well as the prerequisite for combination therapy and BMI criteria (Fig. 1, panel C).

Fig. 2 details the reasons for ineligibility. For REDUCE-IT, the dominant obstacle was triglyceride levels outside 135–400 mg/dL (83.2 %), whereas 15.9 % had LDL-C values outside 40–100 mg/dL and 22.2 % were not receiving statins. Among the patients excluded by the trial criteria, 65.9 % failed a single requirement, 32.8 % failed two, and 1.3 % failed all three. Under the AIFA reimbursement rules, the main limiting factor was triglycerides below 200 mg/dL (68.1 %). Additional frequent exclusions were a BMI under 27 kg/m² (56.1 %), LDL-C ≥ 70 mg/dL (24.6 %), no ezetimibe (26.2 %), no statin treatment (22.0 %), and age outside 18–80 years (2.5 %). Within the AIFA-ineligible group, 10.9 % breached one criterion, 25.8 % two, 33.6 % three, 19.1 % four, 10.3 % five, and 0.3 % all six.

4. Discussion

The main finding of our study was that, in our CR ACS and CCS patients, despite a substantial proportion of patients (10.4 %) that could benefit from IPE therapy following REDUCE-IT inclusion criteria, only 0.53 % (6 over 1129 patients) fully respect the AIFA criteria and could receive the drug with health care system reimbursement.

To the best of our knowledge, only one previous study evaluates the prevalence of patients that could initiate IPE in the Italian setting and so with the same reimbursement criteria of our study. The proportion of patients with ACS who might be eligible for treatment with IPE was assessed in a recent sub-analysis of the JET-LDL observational registry [12]. 15.6 % of the patients met the REDUCE-IT laboratory eligibility

Table 1

Whole population characteristics at cardiac rehabilitation admission and at discharge.

	CR admission	CR discharge	p-value
Number	1129	1129	–
ACS [n, %]	960 (85.0)	–	–
CCS [n, %]	169 (15.0)	–	–
Age [years]	61.9 ± 10.4	–	–
Male gender [n, %]	328 (82.8)	–	–
CV risk factors and previous diseases			
Current or former smokers [n, %]	711 (63.0)	–	–
Familiar history of CV disease [n, %]	524 (46.4)	–	–
Body mass index [kg/m ²]	26.8 ± 4.5	–	–
Overweight or obesity [n, %]	598 (53.0)	–	–
Diabetes [n, %]	221 (19.6)	–	–
Dyslipidaemia [n, %]	819 (72.5)	–	–
Hypertension [n, %]	748 (66.3)	–	–
Peripheral artery disease [n, %]	62 (5.5)	–	–
Previous stroke/TIA [n, %]	93 (8.2)	–	–
Previous PCI [n, %]	342 (30.3)	–	–
Previous CABG [n, %]	82 (7.3)	–	–
Critical coronary lesions			
- LAD [n, %]	717 (63.5)	–	–
- RC [n, %]	428 (37.9)	–	–
- CX [n, %]	379 (33.6)	–	–
- LM [n, %]	62 (5.5)	–	–
Number of coronary arteries involved			
- 1 [n, %]	516 (45.7)	–	–
- 2 [n, %]	293 (26)	–	–
- 3 [n, %]	175 (15.5)	–	–
Atrial fibrillation	78 (6.9)	–	–
CKD (eGFR <60 mL/min) [n, %]	204 (18.1)	–	–
CV drug therapies			
Beta-blockers [n, %]	–	824 (73.0)	–
Statins [n, %]	–	878 (77.8)	–
Ezetimibe [n, %]	–	430 (38.1)	–
ACE-inhibitors or ARB [n, %]	–	682 (60.4)	–
Calcium Channel blockers [n, %]	–	96 (8.5)	–
Diuretics [n, %]	–	73 (6.5)	–
Clinical parameter			
SBP [mmHg]	124.1 ± 16.0	114.7 ± 10.9	<0.001
DBP [mmHg]	74.5 ± 9.5	66.7 ± 8.6	<0.001
HR [bpm]	62.8 ± 8.6	61.7 ± 8.0	0.002
Biochemical data			
Peak CK-MB [mcg/L]	104.9 ± 238.6	–	–
Peak hs-TnT [ng/L]	2333.5 ± 3972	–	–
Triglycerides [mg/dL] median (IQR)	117 (86–159)	99 (79–132)	<0.001
LDL cholesterol [mg/dL] median (IQR)	98 (61–123)	59 (47–76)	<0.001
LDL cholesterol [mg/dL] mean	106.7 ± 40.1	62.8 ± 24.8	<0.001
Glucose [mg/dL] median (IQR)	102 (89–120)	101 (92–118)	0.4
eGFR MDRD [ml/min/1.73m ²]	78.87 ± 20.3	–	–
Echocardiography			
LVEF [%]	53.2 ± 8.1	55.5 ± 7.8	<0.001
Eligibility for icosapent ethyl prescription			
REDUCE-IT [n, %]	–	117 (10.4)	–
AIFA [n, %]	–	6 (0.53)	–

Abbreviations: CR = Cardiac Rehabilitation; ACS = Acute coronary syndrome, CCS = Chronic coronary syndrome, CV = Cardiovascular; TIA = Transitory Ischemic Attack; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery By-pass Graft; LAD = Left Anterior Descending; LM = Left Main; RC = Right coronary; CX = Circumflex coronary; CKD = Chronic Kidney Disease; eGFR = estimated Glomerular Filtration Rate; ACE = Angiotensin Converting Enzyme; ARB = Angiotensin Receptor Inhibitors; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; CK-MB = Creatin Kinase MB isoform; hs-TnT = high sensitivity Troponin T; LDL = Low-Density Lipoprotein; HR = Heart Rate;

LVEF = Left Ventricular Ejection Fraction; AIFA: Agenzia Italiana del Farmaco (Italian Drugs Administration).

REDUCE-IT criteria (statin therapy; triglycerides between 135 and 499 mg/dL and low-density lipoprotein cholesterol between 40 and 100 mg/dL) and AIFA reimbursement criteria covered by the National Health Service (age 18–80 years, maximum tolerated dose of statins and ezetimibe, body mass index ≥ 27 kg/m², TG ≥ 200 mg/dL, and LDL-C < 70 mg/dL).

criteria for IPE, whereas only 0.2 % fulfilled the stricter AIFA reimbursement requirements.

This two real-world analyses highlights a critical gap between clinical trial eligibility and actual treatment accessibility for IPE in patients with ACS [7] or undergoing CR for ACS or CCS (the actual study). Despite over 10 % of our population meeting REDUCE-IT criteria, fewer than 1 % were eligible under current AIFA reimbursement policies.

Interestingly, our study showed a slightly lower percentage of patients eligible for IPE according to REDUCE-IT criteria (10.4 %) compared to the JET-LDL subanalysis (15.6 %). This discrepancy may be partly attributed to the different periods of data collection and the intensity of lipid-lowering therapy. The JET-LDL registry included patients between 2019 and 2023, a timeframe in which high-intensity statin therapy, often in combination with ezetimibe or PCSK9 inhibitors, had become more widely adopted and aligned with contemporary

guidelines. In contrast, our cohort spans from 2012 to 2025, thus incorporating an earlier period when less aggressive lipid-lowering strategies were more common, particularly before the widespread implementation of high-potency statins and combination therapies. This therapeutic gap may have led to a larger proportion of patients in our cohort being excluded from REDUCE-IT criteria due to suboptimal LDL-C or absence of statin therapy.

Some previous studies evaluate the prevalence of patients reaching the REDUCE-IT criteria all consistently show that, depending on the population examined and the criteria applied, a substantial proportion of very high-risk patients could be considered eligible for IPE therapy. In particular, the prevalence of IPE eligibility ranging from 15 to 20 % in ACS subjects [13–17] reaching the highest value of 30–45 % in diabetic patients [16–21].

To the best of our knowledge, only one studies evaluate the prevalence of IPE eligibility in a primary prevention setting. In a population-based analysis of United States adults aged 45–84 years, approximately 3.6 million individuals (3.1 % of the total population) would meet REDUCE-IT eligibility criteria for IPE, obviously a lower prevalence when compared to studies in the secondary CV prevention settings [22].

Conversely, AIFA eligibility in both populations was significantly lower the 1 % (0.53 % in our population and 0.2 % in the JET-LDL registry). The most common barrier in both studies was failure to

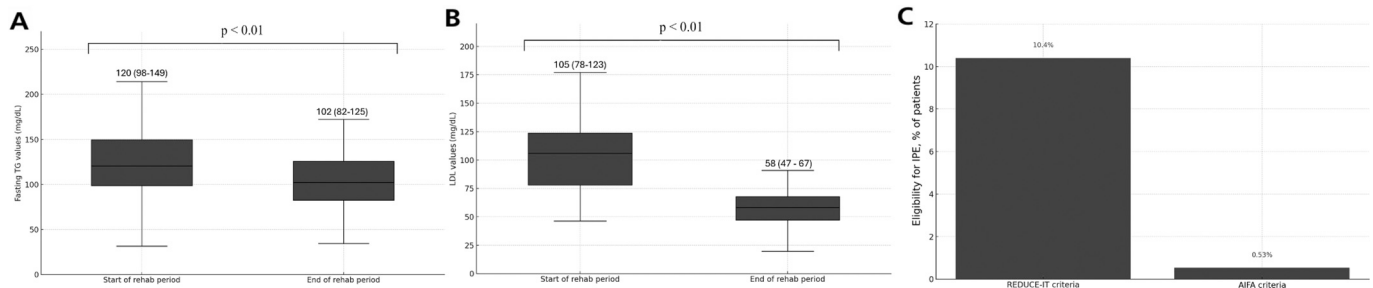


Fig. 1. Boxplot representing fasting TG (panel A) and LDL cholesterol (panel B) values before and after the cardiac rehabilitation period (values reported as median, first and third quartile; whiskers represent the 5th and 95th percentiles). Panel C represent eligibility for IPE prescription according to REDUCE-IT and AIFA criteria. Abbreviations: TG = TriGlycerides; LDL = low-density lipoprotein; IPE = IcosaPent ethyl, AIFA = Agenzia Italiana del FARMACO (Italian drugs administration). REDUCE-IT criteria (statin therapy; triglycerides between 135 and 499 mg/dL and low-density lipoprotein cholesterol between 40 and 100 mg/dL) and AIFA eligibility criteria covered by the National Health Service (age 18–80 years, maximum tolerated dose of statins and ezetimibe, body mass index ≥ 27 kg/m², TG ≥ 200 mg/dL, and LDL < 70 mg/dL).

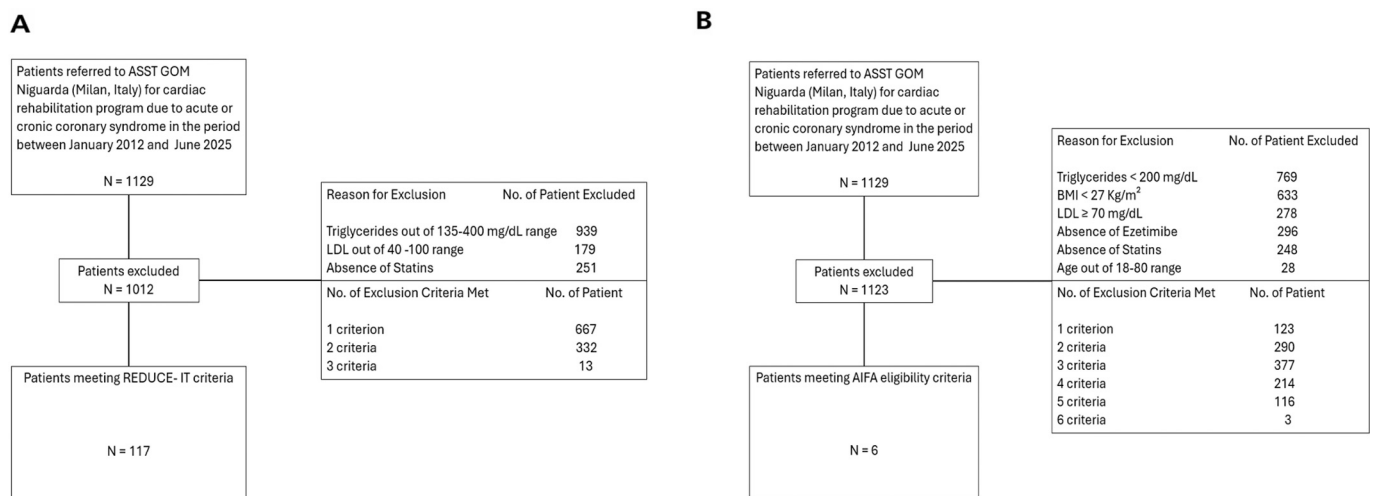


Fig. 2. Flowchart of patient selection for eligibility to IcosaPent Ethyl eligibility based on REDUCE-IT criteria (panel A) and AIFA criteria (panel B). Abbreviations: AIFA = Agenzia Italiana del FARMACO (Italian drugs administration); BMI = body mass index; LDL = low-density lipoprotein. REDUCE-IT criteria (statin therapy; triglycerides between 135 and 499 mg/dL and low-density lipoprotein cholesterol between 40 and 100 mg/dL) and AIFA eligibility criteria covered by the National Health Service (age 18–80 years, maximum tolerated dose of statins and ezetimibe, body mass index ≥ 27 kg/m², TG ≥ 200 mg/dL, and LDL < 70 mg/dL).

reach the minimum triglyceride threshold of 200 mg/dL, despite many patients falling within the REDUCE-IT target range. This suggests that lowering the TG cut-off to reflect trial-based evidence could significantly expand access to effective therapies.

While REDUCE-IT criteria capture a meaningful proportion of patients, the transition to real-world clinical application is hindered by administrative constraints. The AIFA criteria, although designed to ensure appropriate use of public healthcare resources, may inadvertently exclude patients who would otherwise benefit from IPE based on strong evidence.

Regarding REDUCE-IT results, the benefits observed have been attributed not only to triglyceride lowering, but also to pleiotropic effects of IPE, such as plaque stabilization, anti-inflammatory actions, and improved endothelial function [5,6,23,24]. The EVAPORATE trial provided compelling imaging-based insight into these effects using serial coronary computed tomography angiography to assess coronary plaque morphology over 18 months. Compared to placebo, IPE significantly reduced low-attenuation plaque volume, a marker of vulnerable plaque, with a median change of -0.3 mm^3 vs $+0.9 \text{ mm}^3$ ($p = 0.006$). Additionally, IPE was associated with significant regression in multiple plaque components, including total plaque volume (-9% vs $+11\%$, $p = 0.002$), non-calcified plaque (-19% vs $+9\%$, $p = 0.0005$), and fibrofatty plaque (-34% vs $+32\%$, $p = 0.0002$), despite no significant difference in triglyceride reduction between groups ($p = 0.91$). These findings suggest that IPE's cardiovascular benefit may stem largely from non-lipid mechanisms, particularly plaque stabilization and compositional remodeling [25]. Furthermore, the benefit observed in the REDUCE-IT trial was independent of baseline TG levels, reinforcing the concept that pleiotropic effects play a critical role.

These findings support the rationale for IPE use even in patients with TG levels lower than traditional hypertriglyceridemia thresholds, provided they remain at high residual risk.

Notably, elevated triglyceride levels are often a marker of a broader metabolic derangement, including insulin resistance, low HDL-C, and pro-inflammatory states, which further contribute to cardiovascular risk [5,6]. The presence of triglyceride-rich lipoproteins and their remnants has been implicated in atherogenesis even at borderline TG values, reinforcing the need for comprehensive risk stratification beyond absolute thresholds [26].

Another point of our study deserves to be mentioned, i.e. the significant reduction in LDL cholesterol and TG levels observed in our CR patients within a relatively short timeframe. In fact, CR program represent a valuable opportunity to optimize patients' therapies (and more specifically LLT also for emerging one). Integration of targeted therapeutic evaluation into CR workflows might facilitate earlier identification of candidates for adjunctive LLT.

These findings are consistent with existing literature, which highlights the role of CR in promoting lipid optimization. For instance, a study by Nosaka et al. demonstrated that early initiation of statin plus IPE acid therapy after ACS, within a CR framework, led to superior lipid profile improvements and better clinical outcomes compared to statin monotherapy [27]. Moreover, large cohort analyses such as the RESPIRE registry [28] have shown that patients participating in CR are more likely to reach LDL-C targets recommended by guidelines [2], with greater adherence to therapy and healthier lifestyle adoption.

Similarly, comparative studies have demonstrated that patients not referred to CR after ACS exhibit lower rates of LDL-C target achievement and higher residual risk, even when pharmacologic therapy is similar [29,30]. These differences may reflect both improved adherence and the multifactorial benefits of CR, including supervised exercise, dietary guidance, and structured follow-up.

Our study has several limitations being the most important one its retrospective and monocentric nature. This could limit generalizability together with the fact that all our patients underwent CR. Although it is strongly recommended for all ACS and CCS patients, referral rates remain low, ranging from 20% to 50% [31]. CR patients are often those

with recurrent CV events, extreme CV risk [32], multiple comorbidities, and suboptimal CV risk factor control [33], which may explain the frequent detection of lipid abnormalities such as hypertriglyceridemia in this setting. Due to this, IPE eligibility could be further significantly lower in population that with ACS that doesn't access to a CR program [12] as well as for CCS patients. Secondly, adherence to combination LLT (statins plus ezetimibe) was based on discharge prescriptions and may not reflect long-term compliance. Third, the use of non-fasting TG or post-prandial variations was not considered, although these fluctuations can significantly influence eligibility for IPE administration and CV risk estimation [34]. Additionally, we acknowledge the absence of longitudinal endpoints (e.g., CV events or mortality) to validate the prognostic relevance of eligibility stratification in this population. Finally, lifestyle changes during CR (such as improved diet and physical activity) likely contributed to lipid profile improvement, but their individual contributions were not quantifiable in our study.

5. Conclusions

In this large cohort of patients undergoing CR, a significant proportion met clinical trial-based criteria for IPE use, yet national eligibility policies drastically restricted real-world accessibility. Our findings underscore the importance of revisiting current prescribing frameworks to align evidence-based benefits with patient access. Broadening IPE eligibility may help reduce residual CV risk and optimize outcomes in secondary cardiovascular prevention.

CRedit authorship contribution statement

Filippo Brucato: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Chiara Tognola:** Methodology, Investigation. **Antonella Moreo:** Visualization, Validation, Supervision. **Marco Bellomare:** Project administration, Methodology, Investigation, Conceptualization. **Giovanni Pio Prencipe:** Formal analysis, Data curation, Conceptualization. **Maddalena Lettino:** Formal analysis, Data curation, Conceptualization. **Giuseppe Trocino:** Validation, Project administration. **Viola Dadone:** Visualization, Validation, Data curation. **Simona Pierini:** Methodology, Investigation, Funding acquisition, Formal analysis. **Giovanna Viola:** Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Fabrizio Oliva:** Visualization, Validation, Supervision. **Piera Merlini:** Visualization, Validation. **Cristina Giannattasio:** Formal analysis, Data curation, Conceptualization. **Alessandro Maloberti:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare they have no conflict of interest.

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