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# An Observational Longitudinal Multicenter Prospective Study to Evaluate Treatment Patterns in High, Very High, and Extreme Cardiovascular Risk Patients with Hypercholesterolemia, Including Familial Hypercholesterolemia, Over a 1-Year Follow-Up: Protocol of the TRAP-HC Study

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**Keywords**
Hypercholesterolemia; LDL cholesterol; Cardiovascular risk; LDL-C goal attainment; Real-world evidence



## ABSTRACT

*Background: Elevated low-density lipoprotein cholesterol (LDL-C) is a causal driver of atherosclerotic cardiovascular disease (ASCVD). Although current European guidelines recommend intensive LDL-C lowering strategies in high, very high, and extreme cardiovascular risk patients, real-world data consistently show suboptimal goal achievement.*
*Aim and Methods: The TRAP-HC study aims to evaluate real-world treatment patterns, LDL-C goal attainment, and adherence to lipid-lowering therapies (LLTs) in patients with hypercholesterolemia, including familial hypercholesterolemia (FH), at high, very high, and extreme cardiovascular risk over a 1-year follow-up.*
*TRAP-HC is a multicenter, prospective, longitudinal, observational study conducted across up to 15 lipid clinics within the Italian LIPIGEN network. Approximately 2,500 adult patients will be enrolled and followed for one year. The primary endpoint will be the change in LDL-C levels and achievement of guideline-recommended LDL-C goals. Secondary endpoints will include adherence, treatment intensification patterns, and patient-reported attitudes toward therapy.*
*Conclusion: TRAP-HC will provide contemporary real-world evidence on lipid management in high-risk populations and identify gaps between guideline recommendations and clinical practice.*

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## Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, with ischemic heart disease representing the principal contributor to global cardiovascular burden. Data from the Global Burden of Disease study have consistently demonstrated the magnitude of this challenge and its persistent impact on healthcare systems and populations [1]. Among modifiable cardiovascular risk factors, elevated low-density lipoprotein cholesterol (LDL-C) plays a central causal role in the initiation and progression of atherosclerotic cardiovascular disease (ASCVD).

Robust genetic, epidemiological, and interventional evidence supports the concept that LDL-C reduction translates into proportional reductions in cardiovascular events [2, 3]. Consequently, contemporary European guidelines from the European Society of Cardiology and the European Atherosclerosis Society advocate intensive

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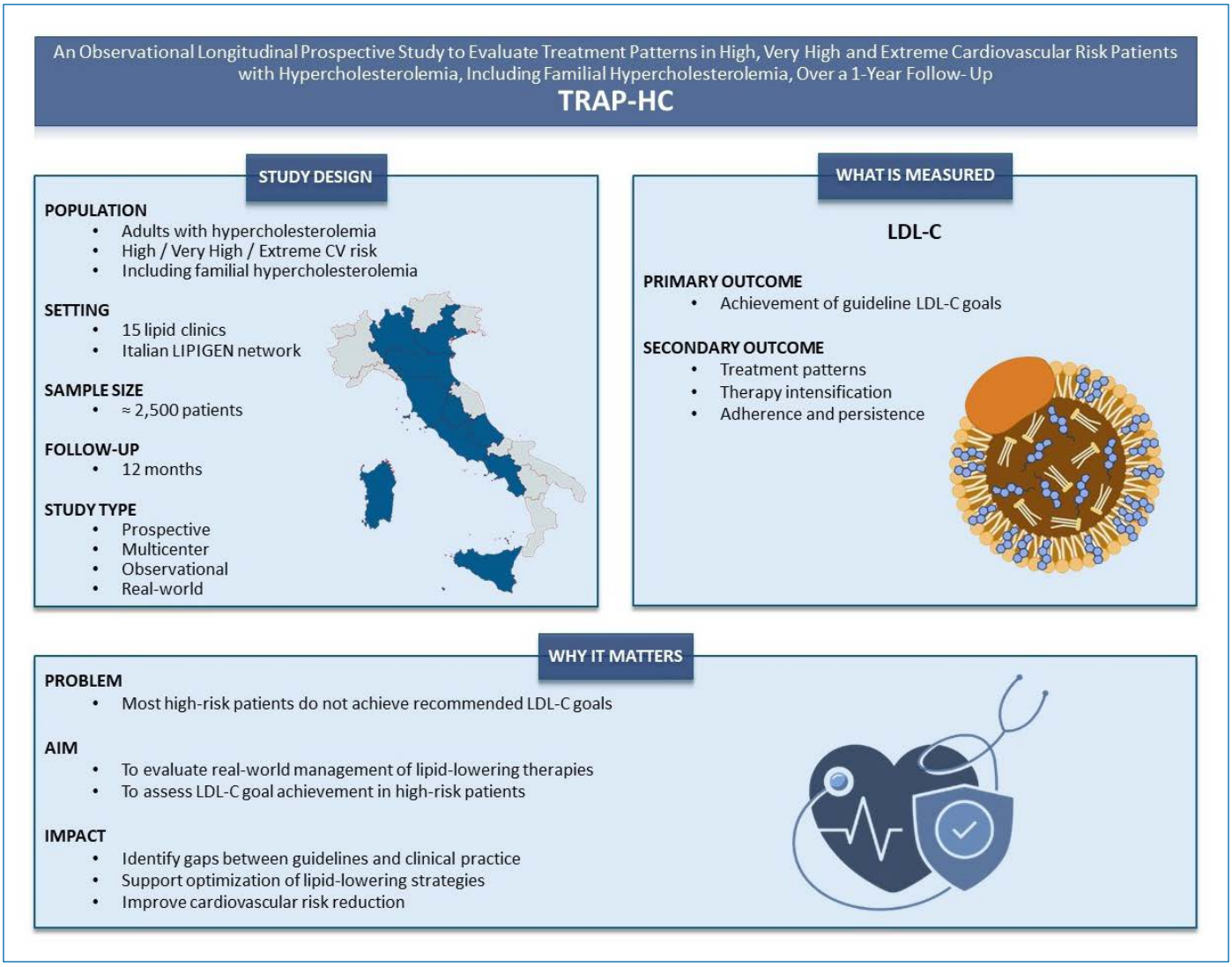


Graphical Abstract

LDL-C lowering strategies, particularly in patients at high, very high, and extreme cardiovascular risk [4]. Current recommendations include a ≥50% reduction in LDL-C from baseline and absolute LDL-C goals of <70 mg/dL in high-risk patients, <55 mg/dL in very high-risk patients, and <40 mg/dL in individuals categorized as extreme risk [5].

Several lipid-lowering therapies (LLTs) are currently available for the management of hypercholesterolemia. Contemporary strategies rely on a stepwise approach, with statins as first-line treatment, followed by the addition of non-statin agents when needed to achieve LDL-C targets. These include cholesterol absorption inhibitors (e.g., ezetimibe), PCSK9-targeting therapies, ATP-citrate lyase inhibitors, and other agents with complementary mechanisms of action [6-8].

Despite the availability of effective combination therapies, their use in clinical practice remains suboptimal. Several large real-world European studies have revealed substantial gaps between guideline recommendations and clinical practice. The EUROASPIRE V survey highlighted that a significant proportion of patients with established coronary disease fail to achieve LDL-C goals, even in specialized care settings [9]. Similarly, the DA VINCI study demonstrated that LDL-C goal attainment remains unsatisfactory across Europe, particularly among very high-risk individuals [10]. More recently, the SANTORINI study showed that approximately 80% of high and very high cardiovascular risk patients do not reach recommended LDL-C levels, with monotherapy still frequently employed despite the availability of effective combinations and advanced LLTs [11].

The gap between real-world practice and optimal cholesterol management is also evident in patients with familial hypercholesterolaemia (FH), a group characterized by markedly elevated LDL-C levels and particularly high cardiovascular risk. Even in specialized lipid clinics, achieving guideline-recommended LDL-C thresholds in FH patients remains challenging, underscoring the need for better understanding of real-world management strategies [10-13].

Despite the availability of effective therapies and well-defined guideline recommendations, LDL-C goal attainment remains suboptimal in real-world practice. However, there is still limited understanding of how LLTs are actually prescribed, combined, and intensified in routine clinical care, and how these patterns translate into LDL-C outcomes. This lack of granular real-world data is particularly evident in the Italian context.

In this scenario, comprehensive evaluation of treatment patterns, therapeutic intensification, adherence behaviors, and LDL-C outcomes in contemporary clinical practice is critically needed. The TRAP-HC (TReatment pAtterns in Patients with HyperCholesterolemia at high, very high and extreme cardiovascular risk) study has been designed to provide real-world evidence on LLT patterns and LDL-C goal attainment in Italy, with the aim of better characterizing and understanding the extent of the gap between guideline recommendations and routine clinical practice.

## Methods

### *Study design and objectives*

TRAP-HC is a multicenter, prospective, observational, longitudinal cohort study designed to evaluate real-world lipid management in patients at high, very high, and extreme cardiovascular risk.

The observational design reflects routine clinical practice. No investigational medicinal products will be administered and no therapeutic decisions will be dictated by the protocol. Patients will continue to receive LLTs according to the judgment of their treating physicians and current standards of care.

The primary objective of the TRAP-HC study is to assess real-world LDL-C control in patients with hypercholesterolemia at high, very high, and extreme cardiovascular risk over a 1-year follow-up. Secondary objectives include the characterization of LLT patterns over time, including treatment intensification, combination strategies, switching, and discontinuation. The study also examines adherence and persistence to LLTs and explores their association with LDL-C goal attainment.

### *Study population*

The study will be conducted in 15 lipid clinics in Italy participating in the LIPIGEN network, a nationwide collaborative network of lipid clinics coordinated by the Italian Society for the Study of Atherosclerosis [14].

The participating centres will competitively enrol 2,500 adult subjects (≥18 years) with hypercholesterolemia, including individuals classified as high, very high, or extreme cardiovascular risk, according to curent European guidelines. Subjects with clinically or genetically diagnosed FH will also be included Patients with secondary dyslipidemia, as well as subjects with hypertriglyceridemia (HTG), will be excluded. . The study population is expected to consist predominantly of non-FH patients (approximately 85%), reflecting the real-world distribution within lipid clinics.

The sample size of 2,500 subjects was determined to ensure high precision in estimating LDL-C variations across the entire cohort and within key clinical subgroups. Based on an expected standard deviation of 25 mg/dL, this sample size provides 80% power to detect even minor mean longitudinal changes in LDL-C (down to 1.5 mg/dL) at a two-sided significance level of 0.05. Furthermore, this robust sample size guarantees adequate statistical power for analysis within the FH subpopulation (n≈375), allowing for the detection of clinically relevant differences of 4 mg/dL. The final target also accounts for potential data attrition, ensuring the study remains powered for all secondary and exploratory endpoints.

### *Study procedures and follow-up*

All study procedures are conducted within the framework of routine clinical practice, without protocol-mandated therapeutic interventions. After verification of eligibility criteria, patients who provide written informed consent will be enrolled during a six-month recruitment window and followed for 1 year. Upon enrolment, each participant will be assigned a unique, centrally generated identification code to ensure pseudonymization and prevent duplication across participating centers. Only the treating physician will retain the link between the identification code and patient identity, in compliance with data protection regulations, including the European General Data Protection Regulation (GDPR; Regulation (EU) 2016/679).

Baseline period

At the baseline visit (T0), comprehensive clinical biochemical and therapeutic data will be collected. Demographic information includes age, sex, ethnicity, body weight, height, and body mass index (BMI). A detailed medical history will be obtained, with specific attention to prior major adverse cardiovascular events (MACE), including myocardial infarction, stroke, coronary, or peripheral revascularization procedures, and documented atherosclerotic cardiovascular disease. Relevant comorbidities such as diabetes mellitus, hypertension, and chronic kidney disease will be recorded.

The diagnosis of FH, whether clinical or genetically confirmed, will be documented. For newly referred patients without a prior confirmed diagnosis, the diagnosis will be documented during the follow-up, according to standard clinical practice.

A complete lipid profile will be collected at baseline, including total cholesterol, LDL-C, High-Density Lipoprotein Cholesterol (HDL-C), triglycerides, apolipoprotein B, and lipoprotein(a). When available, historical lipid data, particularly pre-treatment LDL-C levels, will be retrieved to allow estimation of baseline untreated cholesterol exposure. Laboratory assessments will also include liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase), renal function parameters (serum creatinine and estimated glomerular filtration rate), and creatine kinase levels.

Data regarding physical examination and assessment of vital signs, performed as part of routine care, will be also collected.

All prior and concomitant medications will be documented, with detailed recording of LLTs, including statins, ezetimibe, PCSK9 inhibitors, bempedoic acid, fibrates, lomitapide, evinacumab, and siRNA-based therapies, when applicable. Dosage and duration of therapy will be recorded.

Follow-up assessments

Participants will be followed for 1 year. Data collection at follow-up will include an assessment within 12 months from the baseline visit, in line with routine clinical practice, where at least one annual follow-up visit is recommended for these patients. Additionally, where available, a follow-up assessment within 6 months from baseline will also be collected. No additional visits beyond standard care are mandated by the protocol.

At each follow-up visit, an updated lipid profile will be recorded (if available), including total cholesterol, LDL-C, HDL-C, and triglycerides.

All modifications to LLTs will be systematically recorded, including treatment intensification, dose adjustments, switching between agents, initiation of combination therapy, or discontinuation. Reasons for therapeutic changes, such as inadequate LDL-C response, adverse effects, statin intolerance, patient preference, or reimbursement constraints, will be documented whenever available.

Adverse events (AEs) and serious adverse events (SAEs) occurring during the study period will be documented according to routine clinical practice and local regulatory requirements.

Data management

All collected data will be entered into a dedicated electronic Case Report Form (eCRF). Data entry will follow predefined quality con-

trol procedures to ensure accuracy, completeness and internal consistency. The database will undergo medical and scientific review prior to final analysis. Patient confidentiality will be maintained throughout the study and all analyses will be conducted on pseudonymized data.

*Study endpoints*

As for the primary objective of the TRAP-HC study (to assess real-world LDL-C control in patients with hypercholesterolemia), the primary endpoint is the proportion of patients achieving LDL-C goals at 12 months, according to contemporary recommendations from the European Society of Cardiology and the European Atherosclerosis Society. The secondary endpoints include i) the percentage of subjects who achieve the LDL-C goal at 6 months, and ii) the distance from the goal in subjects who do not achieve it, at 6 and 12 months

For the secondary objective related to the characterization of LLT patterns over time, primary endpoint is the proportion of patients receiving each class of LLT at baseline and at 12 months. Secondary endpoints include

i) proportion of patients undergoing treatment intensification (dose increase or addition of a new LLT) during follow-up;
ii) proportion of patients on combination therapy at each follow-up visit;
iii) rate of therapy switching (from one LLT to another) over 12 months; and
iv) rate of therapy discontinuation over 12 months.

For the secondary objective related to treatment adherence and persistence to LLTs primary endpoint is the proportion of patient's adherent to prescribed LLT at 12 months (based on self-reported patient data). Secondary endpoints include i) proportion of adherent patients at 6 months, ii) proportion of persistent patients with LLT at 6 and 12 months (no treatment discontinuation); iii) association between adherence/persistence and LDL-C goal attainment.

*Statistical Analysis*

All statistical analyses will be performed on the full study population with available data, considering a total observation period of 12 months from baseline.

The primary analysis will focus on the longitudinal change in LDL-C levels and the achievement of ESC/EAS cardiovascular risk-stratified goals within this one-year timeframe. Every enrolled subject is expected to have at least one follow-up assessment by the end of the study period to be included in the primary evaluation. For each patient, the percentage reduction in LDL-C will be calculated as (LDL-C minus pre-treatment LDL-C)/ pre-treatment LDL-C and compared both with the expected reduction of the prescribed lipid-lowering therapy (LLT) and the reduction required to reach individual guidelines targets. Subjects will be classified as 'at goal' or 'not at goal' based on their latest available assessment within the year, with further stratification according to their distance from the target.

A specific secondary analysis will be conducted on the subgroup of patients with a follow-up visit occurring within the first 6 months. Changes in the lipid profile (LDL-C, total cholesterol, HDL-C, and triglycerides) will be analysed using paired t-tests or Wilcoxon signed-rank tests, as appropriate, and further explored through linear mixed-effects models to account for the varying number and timing of follow-up visits while adjusting for baseline covariates. Cumulative lipid exposure, such as "cholesterol years," will be calculated where data allow.

The evolution of LLT regimens, including dose adjustments, treatment switches, or discontinuations, will be monitored and analysed alongside patient-reported adherence and persistence. Adherence will be defined as taking the therapy as directed, while persistence will track the continued use of LLT without interruption. Differences in adherence and goal attainment between subgroups – such as treatment-naïve versus previously treated patients, or different LLT types – will be assessed using Chi-square or Fisher's exact tests, and the association between these factors will be explored via logistic regression.

Final results will be stratified by age, sex, cardiovascular risk category, and FH status. Continuous variables will be summarized as mean ± standard deviation or median (interquartile range) according to their distribution, while categorical variables will be presented as counts and percentages. A two-sided p-value $< 0.05$ will be considered statistically significant, with adjustments for multiple comparisons where appropriate.

*Ethical considerations*

The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent will be obtained from all participants, and the study protocol will be reviewed and approved by an independent ethics committee.

## Discussion

Current recommendations from EAS/ESC guidelines advocate intensive LDL-C reduction, particularly in patients at very high and extreme cardiovascular risk. However, large observational studies such as EUROASPIRE V, DA VINCI, and SANTORINI demonstrate that a substantial proportion of patients fail to achieve these goals, even in specialized settings. These findings suggest that therapeutic inertia, insufficient use of combination therapy, concerns about adverse effects, reimbursement constraints and suboptimal adherence contribute to residual lipid-related risk [16].

TRAP-HC aims at addressing these challenges by adopting a prospective longitudinal design that captures dynamic changes in therapy over time. Unlike cross-sectional registries, this approach allows evaluation of how clinicians respond to inadequate LDL-C control, whether intensification strategies are implemented and how patient adherence evolves during follow-up. By analysing treatment patterns at baseline, six months, and twelve months, the study will provide insight into the timing of therapeutic adjustments and their effectiveness in reducing LDL-C levels.

The inclusion of patients across high, very high, and extreme risk categories allows assessment of risk-stratified management. Patients at extreme risk, who are expected to achieve the most stringent LDL-C thresholds, represent a particularly vulnerable population in whom failure to reach goals may have substantial clinical consequences. The study also incorporates individuals with FH, a condition characterized by lifelong exposure to elevated LDL-C and markedly increased cardiovascular risk. Evaluating real-world LDL-C control in this subgroup is especially relevant given the complexity of their therapeutic management and frequent need for combination or advanced therapies.

Another important aspect of TRAP-HC is the integration of adherence and persistence analyses. Even highly effective lipid-lowering agents cannot reduce cardiovascular risk if not taken consistently [17]. By combining prescription data with patient-reported information, the study seeks to provide a comprehensive assessment of adherence patterns, including use of oral and injectable therapies. Understanding the relationship between adherence and LDL-C goal attainment may inform targeted strategies to improve long-term cardiovascular prevention.

The evaluation of treatment modification patterns is equally relevant. In an era of expanding therapeutic options, including high-intensity statins, ezetimibe, PCSK9 inhibitors, bempedoic acid, and siRNA-based agents, the real-world sequencing and combination of therapies remain heterogeneous. TRAP-HC offers an opportunity to describe contemporary prescribing behaviour within specialized lipid clinics and to determine whether intensification occurs appropriately in response to inadequate lipid control.

From a public health perspective, the findings of TRAP-HC may have implications beyond individual patient management. Identifying systematic barriers to LDL-C goal attainment, whether clinical, behavioural, or organizational, may support the development of structured care pathways and educational interventions. Moreover, the quantification of "distance from goal" provides a nuanced measure of residual risk, highlighting not only whether goals are achieved but also how far patients remain from recommended thresholds.

The observational nature of the study enhances external validity, as it reflects genuine clinical practice without protocol-driven interventions. Nevertheless, this design also entails limitations. Adherence measures based partly on self-report may be subject to reporting bias, as patients may overestimate their adherence or inaccurately recall medication use. Additionally, follow-up duration of one year, while sufficient to assess lipid dynamics and treatment adaptation, does not allow direct evaluation of long-term cardiovascular outcomes. Furthermore, participating centers are specialized clinics, many of which are already involved in studies evaluating LLTs. As a result, patient management and therapeutic optimization may not fully reflect patterns observed in general practice, where a substantial proportion of patients at cardiovascular risk are managed.

Despite these limitations, TRAP-HC is expected to generate clinically meaningful data in a large, characterized cohort managed within specialized centers. By providing detailed longitudinal evidence on LDL-C control, adherence and therapeutic evolution, the study contributes to bridging the gap between evidence-based recommendations and real-world implementation.

In conclusion, TRAP-HC addresses a critical unmet need in contemporary cardiovascular prevention: understanding how lipid-lowering strategies are applied in daily practice and which factors determine successful LDL-C goal achievement. The insights derived from this study may inform future optimization of lipid management strategies and ultimately contribute to reducing the burden of atherosclerotic cardiovascular disease.

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