The American Journal of Cardiology 240 (2025) 71–75

Contents lists available at ScienceDirect

The American Journal of Cardiology

journal homepage: www.elsevier.com/locate/ajc

The Integrated Multidisciplinary Pathway for Large-Scale Management of Dyslipidemia in High-Risk Patients (ENNA) Project: Rationale and Project Design

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ARTICLE INFO

Article History:
Received 3 December 2024
Accepted 20 December 2024

Keywords:
atherosclerotic cardiovascular disease
hypercholesterolemia
high cardiovascular risk
PCSK9i
siRNA
bempedoic acid
lipid-lowering therapy
coronary artery disease

Atherosclerotic cardiovascular disease is a leading cause of morbidity and mortality globally, significantly influenced by modifiable risk factors, particularly hypercholesterolemia. Despite the availability of effective lipid-reducing drugs, achieving the low-density lipoprotein cholesterol (LDL-C) target levels remains a significant challenge in clinical practice, contributing to persistently high rates of cardiovascular events. The intEgrated multidiscipliNary pathway for large-scale maNagement of dyslipidemiA in high-risk patients (ENNA) Project was designed to address the alarming rates of suboptimal lipid management in patients at high and very-high risk in the province of Enna, Sicily. This program aims to optimize LDL-C control through an integrated care model that fosters collaboration among pharmacists, general practitioners, and cardiologists, ultimately promoting a patient-centered approach to therapy. The patients who are eligible are identified using data-driven methods through prescription claims, laboratory results, and hospital discharge data, facilitated by local pharmacies. General practitioners play a crucial role as the primary care providers for initiating or optimizing lipid-reducing therapy, whereas cardiologists are involved in managing more complex cases requiring specialized intervention. The primary objective of the ENNA Project is to increase the percentage of patients at great risk in whom LDL-C targets are achieved, improving overall lipid management and therapeutic adherence.

Atherosclerotic cardiovascular disease (ASCVD) is a chronic inflammatory disease of blood vessels, causing many pathological conditions.[1] The prevention of ASCVD complications requires the control of every modifiable risk factor, among which hypercholesterolemia stands out. A large body of literature has shown a linear correlation between absolute low-density lipoprotein cholesterol (LDL-C) reduction and the risk of major adverse cardiovascular events.[2–5] This evidence has been translated into the recommendation of stringent LDL-C levels, culminating with the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines, which outlined an LDL-C goal <70mg/dL for patients at high risk, <55 mg/dL for patients at very high risk, and a stricter LDL-C target<40 mg/dL for subjects who had >1 ASCVD event within 2 years.[6]

Nowadays, a wide array of lipid-reducing medications is available, yet a large proportion of patients exceed the recommended LDL-C level, contributing to ASCVD morbidity and mortality.[7–10] Hence, the promotion of strategies to address this clinical gap becomes urgent. The intEgrated multidiscipliNary pathway for large-scale maNagement of dyslipidemiA in high-risk patients (ENNA) Project is the result of a close collaboration between the Provincial Health Authority of Enna and CliCon S.r.l. Società Benefit, Health, Economics and Outcomes Research, which propose an innovative system of care with the aim of optimizing the management of lipid-lowering therapy (LLT).

Authors would like to thank Novartis Farma Italy for providing economical funding with this analysis.

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https://doi.org/10.1016/j.amjcard.2024.12.027

This article provides a comprehensive description of the rationale and design of the project.

Despite the well-known efficacy of antiplatelets, antihypertensive, and lipid-reducing drugs to prevent ASCVD, it remains a leading cause of mortality in Europe, responsible for >4 million deaths per year, with an economic burden of approximately €282 billion.[6,11–14]

Although cardiovascular research has made significant strides in facing the so-called residual cardiovascular risk, clinical practice still lags far behind this progress.[15–18] In particular, in Italy, annual cardiovascular mortality accounts for 224,000 deaths, 47,000 of which can be attributable to suboptimal dyslipidemia management.[9]

The reasons for this therapeutic failure include both patient- and physician-related factors. Contributing factors on the physician level are underprescription, heavy workload, and delay in follow-up visits. In contrast, the challenges at patient level include medication nonadherence, mismatch between perceived and real cardiovascular risk, refusal of treatment, fear of tolerability, and adverse reactions.

In past decades, the increasing recognition of medication nonadherence as a hidden cardiovascular risk factor has revitalized interest in exploring different modalities to enhance therapeutic adherence, including educational interventions, social support, telemonitoring systems, mobile health applications, and polypill.[19,20]

In the specific case of hypercholesterolemia, given the multifactorial challenges and the magnitude of the related morbidity, mortality, and costs, the implementation of effective solutions to address the previously mentioned gaps becomes imperative. The ENNA Project has been designed to create a dedicated pathway for the treatment of dyslipidemia, supported by a multidisciplinary team that focuses on the patient's needs and establishes a tailored therapy for lipid goal achievement.

Methods

The ENNA Project is a preventive program that proposes a novel model for lipid control in high cardiovascular risk categories, involving several professional specialists: territorial pharmacists, general practitioners (GPs) and cardiologists.

The organizational structure is presented in the Figure 1. The territorial pharmacy acts as "coordinator of the flows, data transmission and distribution unit." It sends prescription claims and medical records in coded form to a company specialized in processing and analysis of data sources (CliCon S.r.l). CliCon S.r.l unifies and cross-references these data, identifying the target patients. Next, the pharmacy receives this report and communicate it to the GPs. The GP serves as a "primary level optimization unit" who can optimize LLT or refer to the specialist as needed. The cardiologist is the "specialist assessment and prescription unit" involved in examining patients who can benefit from the prescription of high-intensity drugs and selection of more appropriate therapy.

The ENNA Project is a prevention program conducted in the provincial territory of Enna, in Sicily (Italy), including 20 cities, with a population of 170,868 (data from the Data Processing Center of the provincial healthcare system of Enna), having the Umberto I as reference hospital.

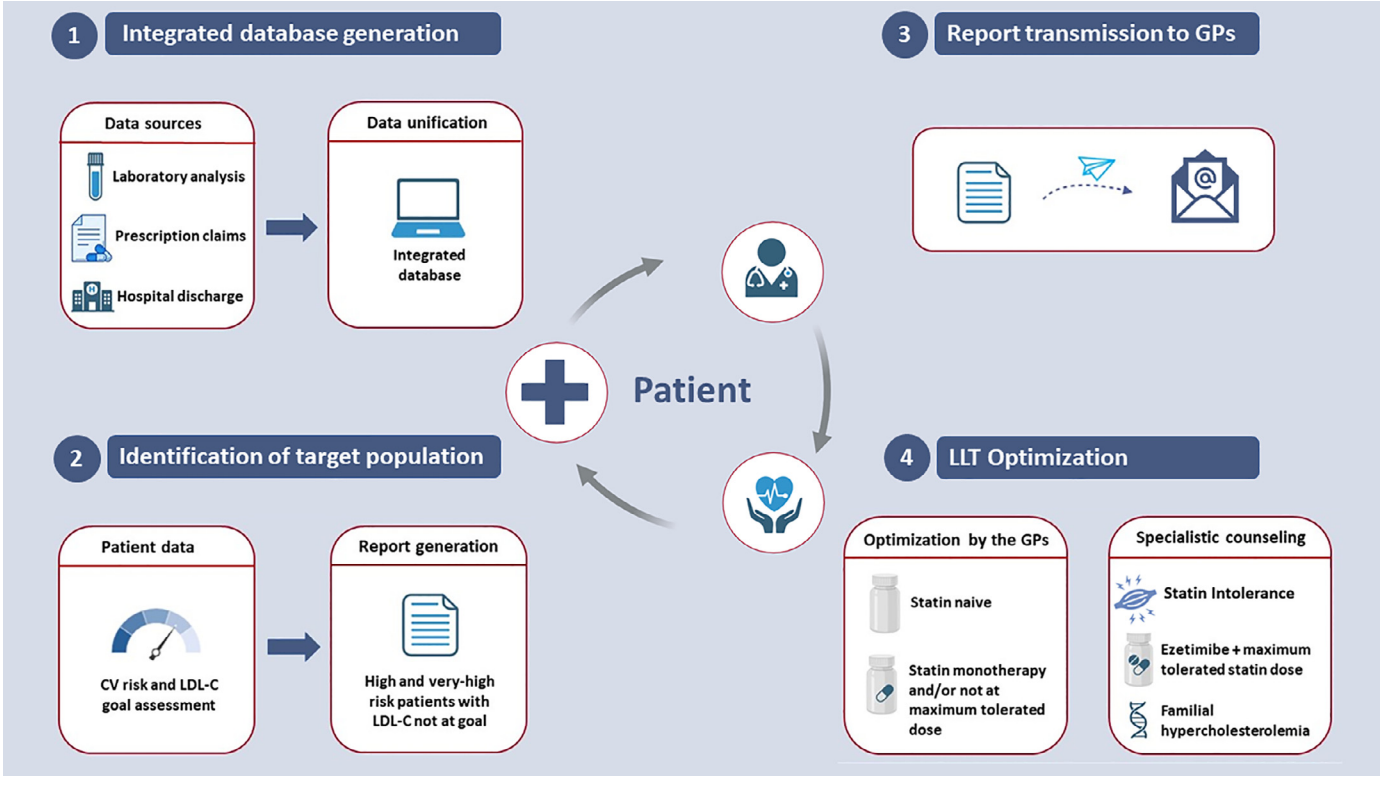

Figure 1. The figure illustrates the network and the steps of ENNA Study. The territorial pharmacists collect medical records and send them to a company specialized in data analysis, receiving back an integrated database of high and very-high risk patients who do not achieve LDL-C goal. The GPs receive the report of the target population who will be included in the study. The LLT will be optimized by the GPs who act as a primary level optimization unit, to start/maximize statin or add combination therapy. Differently, those patients with statin intolerance, combination therapy with maximum tolerated statin dose or suspected familial hypercholesterolemia, will be referred to the cardiology unit, at the dyslipidemia ambulatory of Umberto I hospital. This is a dedicated ambulatory organized for patients who need specialistic counseling to optimize LLT through PCSK9 inhibitors or bempedoic acid.

Abbreviations: CV, cardiovascular; GPs, general practitioners; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9, Proprotein Convertase Subtilisin/Kexin type 9.

The project was launched in October 2023, and it is ongoing. In the first phase, only patients deemed at high and very-high cardiovascular risk according to 2019 European Society of Cardiology/European Atherosclerosis Society guidelines will be included, in both primary and secondary prevention. No explicit exclusion criteria are defined.

The participants are recruited from a primary care setting, through data linkage among a demographic database (data on patients' demographic characteristics), pharmaceutical database (data on prescription of drugs reimbursed by the Italian National Health System, in terms of the related Anatomical-Therapeutic Chemical code, and prescription date), hospitalization database (information on discharge diagnoses classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification and date of diagnoses), diagnostic tests and specialist visits database (date of prescription, type, description activity of diagnostic tests, and procedure), and laboratory test data of lipid profile.

A 3-monthly report in the eligible subjects is sent to the respective GPs, who invite these patients to their office with the purpose of starting LLT in patients who are treatment naive or optimizing it in those on treatment (Figure 2). According to the regional policy, therapeutic optimization by the GP could include: 1) statin dose escalation or 2) adding ezetimibe on maximum tolerated statin therapy. Instead, patients already on LLT with ezetimibe on maximum tolerated statin dose, patients with statin intolerance, and patients with known or suspected familial hypercholesterolemia are referred by the GP to the cardiology unit at the dyslipidemia ambulatory of Umberto I Hospital, for specialist counseling about the opportunity for prescription of high-intensity medications (i.e., bempedoic acid and proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors).

Patient characteristics, medical history, laboratory analysis (lipid profile, diabetes-related parameters, renal function), current LLT, and other medications will be collected at baseline and at 1-year follow-up. LLT details include dose, dose modification, switching, and combination therapy. Moreover, drug intolerance, insufficient responsiveness, adverse reactions, and patients' compliance are documented at baseline and at follow-up.

Clinical outcomes such as death, nonfatal myocardial infarction, stroke, and coronary artery revascularization will also be collected.

Changes in LLT are decided exclusively at the discretion of the physician, in agreement with the patient.

All medications will be prescribed according to the usual standard of care and will not be provided by the project partner.

Moreover, the prescription claims data from the territorial pharmacy are used to assess the appropriateness of prescriptions and medication adherence through the "fail-to-refill" method.[21]

The principal aim of the ENNA Project is to increase the attainment of the LDL-C goal in patients at high and very-high risk, through a novel integrated system of care. The percentage of patients at LDL-C target and the mean LDL-C level after 1 year will provide proof of the efficacy of the proposed clinical pathway.

As a preventive program, the statistical analysis will be performed in a purely exploratory and descriptive way; no primary outcome has been defined for sample size calculation.

Baseline characteristics will be presented as means (SD) or median (interquartile range) of continuous variables and as percentages of categorical variables

LDL-C values at baseline and at 1-year follow-up will be analyzed descriptively as a continuous parameter and as LDL-C categories. Absolute and percentage change from baseline at 1-year follow-up in LDL-C will be analyzed. Results will be reported by cardiovascular risk classification, LLT received, and the proportion of patients attaining LDL-C goals.

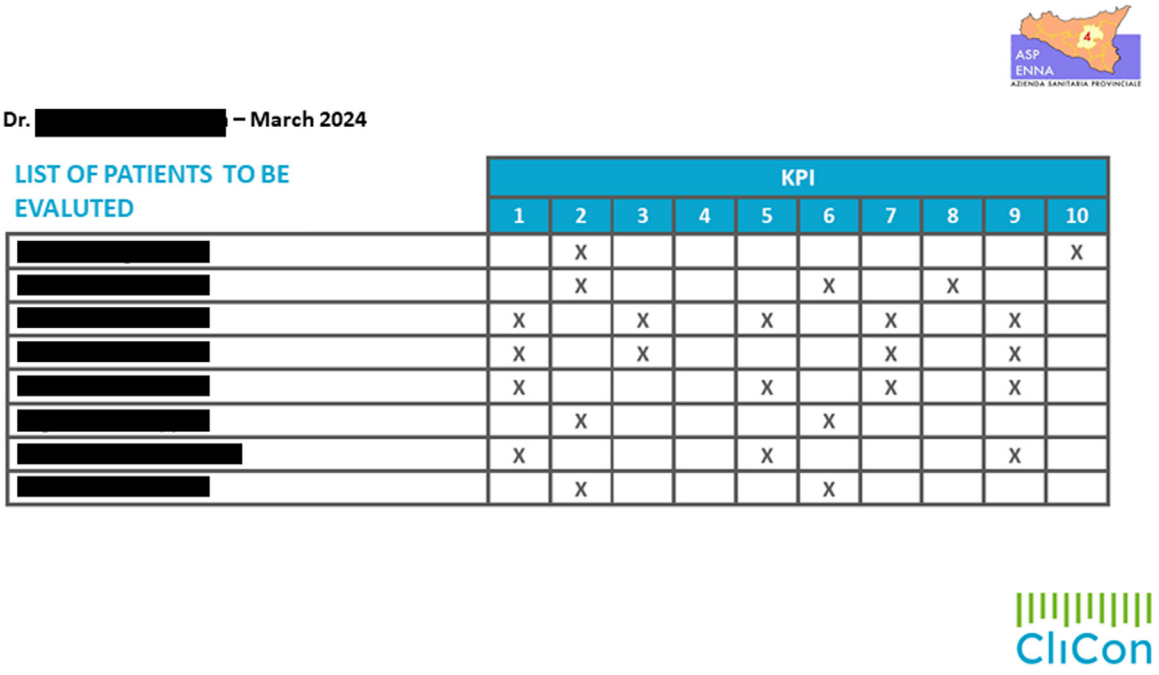

Figure 2. Three-monthly report. The figure illustrates the report received by the GPs. The column on the left contains the patients to be evaluated (the names are redacted for privacy). The columns on the right give additional information. In particular, columns 1 and 2 indicate patients already on LLT (at great and very great risk, respectively). Columns 3 and 4 indicate patients with suboptimal LLT or nonadherence to therapy (at great and very great risk, respectively); columns 5 and 6 indicate patients who have not undergone a cardiologic visit within the last 3 months (at great and very great risk, respectively); columns 7 and 8 indicate patients with LLT prescription ruled according to Italian Medicines Agency note (at great and very great risk, respectively); and columns 9 and 10 indicate patients adherent to LLT (at great and very great risk, respectively). KPI = key performance indicator.

Established ASCVD will be ascertained if medical history reports any of the following conditions: coronary artery ASCVD (acute or chronic coronary artery syndromes; percutaneous or surgical coronary artery revascularization), cerebral ASCVD (stroke; transient ischemic attack; carotid artery disease), or peripheral ASCVD (peripheral arterial disease; retinal vascular disease; abdominal aortic aneurysm; renovascular disease).

All statistical analyses will be performed by CliCon S.r.l.

Discussion

In the past decade, lipid-reducing pharmacotherapy has experienced a substantial expansion, giving us complete and effective tools to treat dyslipidemia, even in patients with a greater gap to their LDL-C threshold.[6–8,22,23] Notwithstanding, the baseline data of the Treatment of high and very high riSk dyslipidemic pAtients for the preveNTion of cardiOvasculaR events in Europe–a multInatioNal observatIonal (SANTORINI) study revealed unsatisfactory dyslipidemia management in patients at great and very great risk in Europe.[9] In particular, the Italian data showed the LDL-C goal was achieved in only 20.3% of these subjects, with low rates of combination therapy prescriptions.[6,24] Such evidence highlights an alarming problem of public health care, considering the impact of ASCVD complications, morbidity, and mortality. Those findings led the European Union member states to expend more economic resources on preventive measures to face challenges such as medication nonadherence, underprescription, and fear of adverse events, supporting digital tools or novel initiatives.

The development of the ENNA Project stems from this need, seeking to organize new pathways for LLT management in great-risk categories. A key point in the planning of the program has been the recognition as an Achille's heel of the GP's role in recruiting patients at great risk, in the Italian setting.

The project attempts to fill this lack through the innovative use of data assets to identify patients needing LLT optimization and to promptly report them to the physician. Hence, the patient receives adequate measures through the synergy among the territorial pharmacy, the GP, and the cardiologist, which might generate several benefits. Firstly, patients with insufficient lipid control are detected directly from a primary care setting, providing an opportunity for more effective prevention of major adverse cardiovascular events and for cost saving. Moreover, this project should educate the healthcare providers to pay more attention to assessing cardiovascular risk, adhere to guideline-driven approaches, periodically monitor the results of the prescribed LLT, and eventually intensify the therapeutic regimen. Besides, the ENNA Project tries to overcome the barrier of clinical inertia, given some physicians may postpone starting LLT in primary prevention without evaluating the cardiovascular risk or may miss opportunities to intensify the treatment regimen in patients who have already started medications but exceed their lipid goal.

An increased LDL-C level is a major risk of ASCVD, associated with high rates of mortality and relevant economic burden. Therefore, better control of hypercholesterolemia is a public health priority. Current pharmacotherapy, enriched with the advent of the new lipid-reducing drugs, represents a breakthrough in the field of prevention, but effective strategies for correct implementation remain necessary. The ENNA Project lays on a multidisciplinary team including the territorial pharmacy, the GP, and the cardiologist, creating a link between the territory and the hospital that yields a dedicated pathway for patients at high cardiovascular risk. Moreover, the identification of the target population is data-driven, using an innovative system of health technology. The integrated system of care proposed by the ENNA Project has the features of a cost-effective strategy, promising enough to be applied more broadly in the near future.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Federica Agnello: Conceptualization, Investigation, Project administration, Writing – original draft, Writing – review & editing. **Calogero Russo:** Conceptualization, Investigation. **Giulia Laterra:** Visualization. **Salvatore Ingala:** Investigation. **Stefania Saragoni:** Data curation. **Mario Giuffrida:** Methodology. **Paola Maria Greca:** Investigation, Supervision, Writing – review & editing. **Francesco La Tona:** Visualization. **Noemi Rinaldi:** Visualization. **Ilaria Gagliano:** Validation, Visualization. **Carmela Nappi:** Data curation. **Alessandro Ghigi:** Data curation, Validation, Visualization. **Maria Cappuccilli:** Data curation, Methodology. **Luca Degli Esposti:** Investigation, Methodology, Visualization, Writing – original draft. **Lorenzo Scalia:** Investigation, Writing – original draft. **Emanuele Cassarà:** Project administration, Resources, Visualization. **Marco Barbanti:** Supervision, Validation, Visualization, Writing – review & editing.

Data Availability

No new data were generated or analyzed in support of this research.

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