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SPECIAL ARTICLE

Hypercholesterolemia and cardiovascular disease: the dilemma of effective treatment for target achievement according to guidelines and national healthcare policies and a call to action

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ABSTRACT

The burden of cardiovascular disease (CVD) remains a worldwide challenge. CVDs, in particular atherosclerotic CVD, are still an important cause of mortality and morbidity. The increase in life expectancy is a further determining factor in the epidemiology of CVDs in some countries, such as Italy, which increases the urgency of intervening on modifiable risk factors. Among these, hypercholesterolemia is present in a significant percentage of CVD patients. A linear relationship between the risk of acute events and the plasma level of low-density lipoproteins cholesterol (LDL-C) is well known. The reduction of LDL-C levels leads to a decrease in mortality and morbidity. The overall recommendation is to treat hypercholesterolemia intensively and as early as possible. Statins, ezetimibe, bempedoic acid, pro-protein convertase subtilisin/kexin 9 inhibitors (*i.e.*, the monoclonal antibodies alirocumab and evolocumab, or the small interfering RNA inclisiran) are all available for reaching LDL-C targets according to risk profile. While the real-world data confirm the safety of currently recommended LDL-C targets, data on their actual achievement are discouraging, less than half of patients on therapy reach the LDL-C targets recommended by the most recent ESC/EAS Guidelines. The causes of this critical discrepancy are multiple, arising from the various components that characterize the complex relationship between patient and physician within the healthcare system. A call to action is needed. Doctors should be continuously updated on the latest evidence, follow recommendations and engage the patient in the therapeutic process. Regular monitoring of the effects of the prescribed therapy, also through e-health and telemedicine tools, is essential, as well as changing therapy when LDL-C is not adequately controlled. Finally, health systems should align with guidelines and promote good clinical practices, overcoming a silo system, to impact outcomes in terms of overall sustainability.

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KEY WORDS: LDL cholesterol; Dyslipidemia; Cardiovascular system; Prevention and control; Treatment adherence and compliance; Delivery of health care.

Atherosclerotic cardiovascular disease (ASCVD) can be considered a chronic process characterized by a persistent inflammatory state capable of progressively worsening its course. It is known that the *primum movens* of this condition, *i.e*. the accumulation of cholesterol in the arterial wall, occurs much earlier than many clinical manifestations. In this sense, ASCVDs, such as acute myocardial infarction, stroke, and peripheral obliterating arterial disease, can be considered as the last manifestation of a process that, if early identified and adequately managed, can be turned into a significant reduction of mortality and morbidity for a large percentage of the general population.[1] Considering also the hospitalization rate related to these acute events, early therapeutic intervention may also allow a reduction in terms of health care costs.

Among modifiable risk factors, hypercholesterolemia is present in a significant percentage of patients with cardiovascular (CV) disease (D), and a linear relationship between the risk of acute events and the plasma level of low-density lipoproteins cholesterol (LDL-C) is now well known.[2] Despite an extensive body of evidence demonstrating the benefits of LDL-C reduction in lowering CV events, the gap between guideline recommendations and real-world LDL-C target achievement remains significant. This paper is a call to action with the aim of urging clinicians, scientific associations, policymakers, and healthcare organizations to put existing evidence into practice through targeted interventions. By emphasizing actionable strategies and identifying key barriers to implementation, we hope to catalyze a coordinated, system-wide response that addresses the current shortfalls in LDL-C management and ultimately contributes to reduce CV morbidity and mortality. The reduction of LDL-C levels leads to a clear decrease in mortality and morbidity, even early in the first weeks of treatment.[3] The most recent version of the 2019 Guidelines of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) on the management of dyslipidaemias[4] has focused attention on various aspects of hypercholesterolemia control, in particular the re-evaluation of the targets. In line with these updated targets, LDL-C management strategies differ by patient risk profile.[3, 4] For primary prevention in patients at low-to-moderate CV risk, treatment may begin with lifestyle interventions and moderate-intensity statins, escalating to additional agents if targets remain unmet. Conversely, for secondary prevention in high-to-very high-risk patients, intensive LDL-C lowering strategies are prioritized, typically involving high-intensity statins with adjunctive available treatments, *i.e.* ezetimibe, bempedoic acid, proprotein convertase subtilisin/kexin 9 inhibitors (PCSK9i), either the monoclonal antibodies alirocumab and evolocumab, or the small interfering RNA (siRNA) inclisiran. This risk-stratified approach aims to maximize clinical outcomes by targeting LDL-C levels that are most appropriate to each patient's CV risk. In fact, the recommended LDL-C value has been further reduced compared to previous recommendations. For very high-risk patients, for example, the recommended target has been reduced from <70 to <55 mg/dL. In each case, a reduction of at least 50% compared to the baseline value is recommended. These are patients who show at least one of the following conditions: documented ASCVD, severe chronic renal failure (eGFR <30 mL/min), diabetes mellitus with evidence of organ damage, or at least three major risk factors, or diabetes mellitus of Type 1 of long duration (>20 years), a calculated SCORE ≥10% for 10-year risk of fatal CVD, familiar hypercholesterolemia with ASCVD or with another major risk factor. Moreover, for patients with ASCVD experiencing a second vascular event within 2 years, an LDL-C goal of <40 mg/dL may be considered (Figure 1). The recommendations are based on the experimental evidence of several interventions and pro-

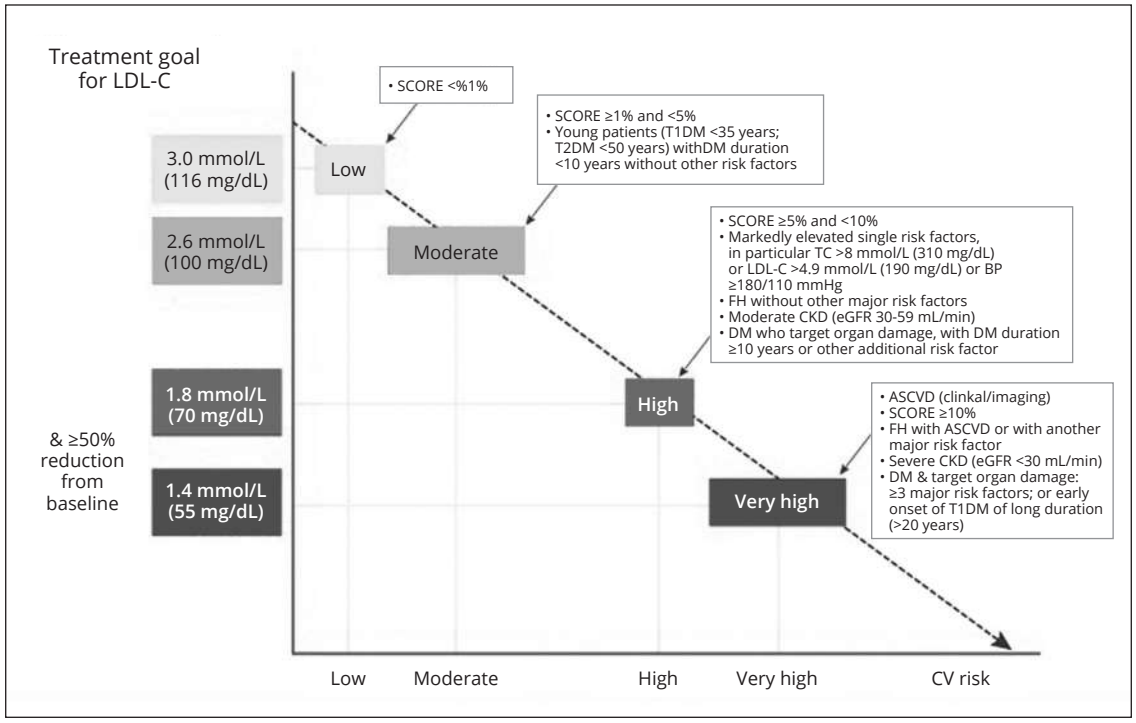

Figure 1.—New targets of low-density lipoprotein cholesterol (LDL-C) based on cardiovascular risk profile (modified from Mach *et al.*).[4]

spective studies which, unlike the management of other risk factors such as arterial hypertension, have not demonstrated an LDL-C level below which benefits are no longer observed in terms of protection from acute CV events, mortality and morbidity.[4] Similarly, the concern about the occurrence of neurodegenerative diseases due to chronically reduced LDL-C values, based on the fact that cholesterol is a key component of cell membranes and myelin sheaths, has been greatly reduced by prospective data of large studies.[5] Therefore, the new point of view on LDL-C control can be summarized with the leitmotif: "lower is better." While achieving LDL-C targets according to established guidelines remains a primary goal, considerable variability exists in patient responses to lipid-lowering therapies. Factors such as genetic background, comorbidities, medication tolerance, and lifestyle differences can influence both the efficacy and tolerability of treatment options. Personalized medicine approaches, which tailor therapy to individual patient profiles, are becoming increasingly relevant in LDL-C management.[6] The overall recommendation is to treat hypercholesterolemia intensively. Furthermore, the best clinical outcomes are more consistent when the treatment is started as early as possible. In fact, experimental studies on PCSK9i have recently confirmed that their administration during an acute coronary syndrome improves medium and long-term prognosis.[7, 8] All scientific evidence currently available recommends early and intensive therapeutic intervention to reduce of LDL-C as quickly as possible.[9] In recent years, in addition to statins and ezetimibe, it is possible to use new classes of cholesterol-lowering drugs, in association with or in replacement of the previous ones, to achieve the LDL-C target according to the individual patient's CV risk profile. For low-to-moderate risk patients in primary prevention, statins and ezetimibe remain first-line options with dose adjustments as needed to reach LDL-C targets.[3, 4] For patients in secondary prevention or those with high-to-very high CV risk, where intensive LDL-C lowering is paramount, combinations such as high-intensity statins with PCSK9i are often more effective.[3, 4] This layered approach ensures

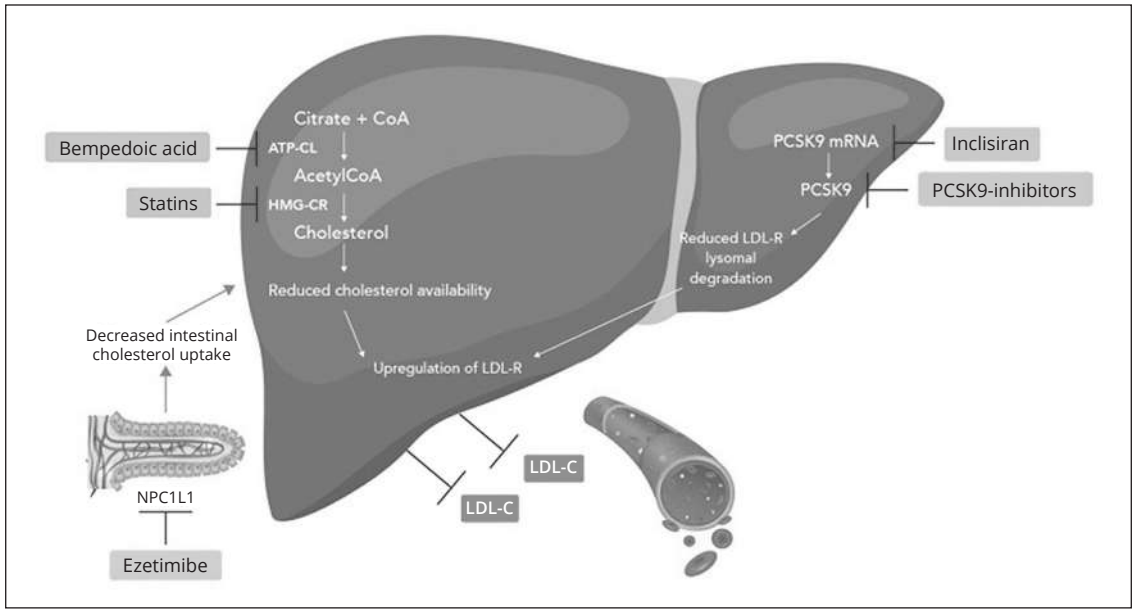

Figure 2.—Overview of cholesterol-lowering drugs currently available in clinical practice (modified from Bardolia *et al*.).[10]

that therapy intensity is matched to the individual's risk level, balancing efficacy with long-term adherence considerations. These drugs and their mechanisms of action are summarized in Figure 2.[10] Statins remain the first-line treatment for LDL-C reduction due to their proven efficacy, favorable safety profile, and low-cost. Common side effects include mild muscle pain and gastrointestinal symptoms, generally manageable and reversible. Severe muscle-related side effects, such as myopathy, are rare and typically occur with high dosages. Monitoring of liver enzymes and creatine kinase (CK) can help detect any adverse effects (AE) early, enabling safe, long-term use. Bempedoic acid is an inhibitor of an enzymatic step in cholesterol synthesis, further upstream than that inhibited by statins, and is able to reduce LDL-C by approximately 25% when used as monotherapy, by 18% in association with moderate or high intensity statins, by 38-40% in a fixed-dose combination regimen with ezetimibe, and by 30% when associated with PCSK9i. It is orally administered once a day.[10] Common AE include hyperuricemia, which may lead to gout in predisposed patients, and mild increases in hepatic enzyme levels. The favorable safety profile makes it particularly useful in patients with statin intolerance or those who are at risk of muscular side effects. Alirocumab and evolocumab are fully human monoclonal antibodies that inhibit PCSK9 increasing the expression of the low-density lipoprotein receptor (LDLR) on the surface membrane of hepatocytes, and the elimination of LDL-C from the bloodstream. These drugs, administered subcutaneously biweekly or monthly, have a low incidence of side effects. Patients may complain of mild, self-limiting injection site reactions, which have shown to improve with counseling and alternative administration techniques. Of importance, observational studies indicate no significant increase in neurocognitive or muscular adverse events, further supporting their safe use.[8, 9] They can reduce LDL-C levels by approximately 60% when used as monotherapy, and by approximately 85% when combined with high intensity statins and ezetimibe. As already mentioned, the earlier they are administered, for example after an acute event such as an acute coronary syndrome, the better the prognosis. The intense reduction in LDL-C is confirmed even several years after the start of therapy, as well as the reduction of CV events.[5, 7, 8, 11, 12] Lastly, inclisiran, a siRNA that inhibits the hepatic synthesis of the protein PCSK9, has also been shown to increase the expression of LDLR on the surface membrane of

hepatocytes thus significantly reducing LDL-C. The drug is administered subcutaneously, with the peculiar scheme of one injection at the start of therapy, a second one after 3 months, and then every 6 months.[13] In addition to the innovative mechanism of action, being the first siRNA approved for the treatment of hypercholesterolemia, it is able to reduce the LDL-C value by at least 50%, and to maintain this effect for up to 18 months of therapy, as evaluated in the registration randomized control trial and in the subsequent pooled analysis.[14, 15]

Hypercholesterolemia is a chronic condition that needs a life-long therapy, then concerns may arise about safety and cost-effectiveness of the different drugs available. Several studies have demonstrated that safety profiles for statins and ezetimibe, even in association, are favorable because the AE present with low incidence and low impact on the overall patient's health. Moreover, AE usually resolve with therapy suspension. Safety is confirmed when analyzing real world and older populations, and all the benefits obtained with the therapy, *i.e*. reducing major adverse cardiac events (MACE), overcome the risks related to the AE. All PCSK9i also proved to be safe in the long term.[16, 17]

From an economical point of view, statins and ezetimibe have been proved to be cost-effective, especially after generic pricing of statins and even when administered in primary prevention.[18] Controversy is still present about PCSK9i. In fact, because of the still high cost of the biologic synthesis of both drugs, currently a favorable cost-effectiveness can be observed only in patients at very high CV risk and in secondary prevention.[19-21] However, cost-effectiveness analyses predict that the break-even point will be exceeded in the near future.

In Italy, the new classes of drugs, *i.e*. bempedoic acid, PCSK9i, inclisiran, alirocumab an evolocumab have obtained approval and reimbursement from AIFA (Agenzia Italiana del Farmaco, Italian Agency for drugs) for the treatment of primary hypercholesterolemia (homozygous or heterozygous) or mixed dyslipidemia, in association with diet and statin therapy and other lipid-lowering therapies in patients who are not able to reach the LDL-C target with the maximum tolerated dose of statin. They can also be used in monotherapy or in combination with other lipid-lowering therapies in patients who are intolerant to statins or who have contraindications to statin therapy.

Given the need for early and intensive control of hypercholesterolemia, the situation that emerges from real-world evidence is however very different. While the real-world data confirm the safety of currently recommended targets of LDL-C levels and the 'lower is better' principle in patients with ASCVD,[15] data on effective achievement of LDL-C targets are discouraging. The multicenter DA VINCI study analyzed approximately 6000 patients from 18 different European populations.[22] The patients were treated with cholesterol-lowering therapy for both primary and secondary prevention. Overall, only 33% of the sample achieved the targets recommended by the 2019 ESC Guidelines, and the higher the risk profile, the more this percentage was low. Post-myocardial infarction patients with a very high CV risk were also undertreated, as also confirmed by the results of two Italian registries according to which less than 40% of patients showed an LDL-C <70 mg/dL at the time of enrollment (even considering as targets those indicated in the 2016 ESC/EAS Guidelines).[23]

A call to action is needed. Scientific societies can play an important role in this regard. SICOA (Società Italiana Cardiologia Ospedalità Accreditata, namely the Italian Society of Accredited Hospital Cardiology) has promoted a scientific board to analyze the issue and suggest possible solutions. This article aims to share such hypotheses. The causes of the critical discrepancy between guidelines on dyslipidemia and real-world practice are multiple and arise from the various components that characterize the complex relationship between patient and physician within the healthcare system. Barriers to the successful implementation of evidence-based medicine can include general challenges, such as therapeutic inertia and patient adherence, and local and specific issues, notably the local healthcare system and prescription policies. Globally, many patients struggle to adhere to cholesterol-lowering therapy due to a lack of symptom relief from LDL-C reduction, a general concern about pos-

sible side effects and complex dosing regimens, all of which may contribute to therapeutic inertia among physicians. Locally, region-specific issues arise from the variability in prescribing rights. For instance, in some regions of Italy CV specialists have the same prescribing authority regardless of the inpatient or outpatient clinic in which they practice, while in others, advanced and innovative therapies are limited to selected centers, resulting in unequal access to care for patients. Instead, the patient who is managed within the health system should receive the same opportunities for care. Similarly, in many other countries, depending on the type of health system, whether public, insurance, hybrid, there are legislative and process issues. The latter are important to personalize therapy, as it is necessary to identify not only the individual clinical history, but also to understand the socio-economic-cultural context in order to propose a correct educational and communication path and improve adherence. The shortage of healthcare personnel in recent years worsens the management system with negative consequences on the quality of care. Addressing all these sets of challenges would help bridge the LDL-C treatment gap and promote better adherence and outcomes. Indeed, undertreatment might depend upon either under-prescription or low adherence, or both. From the physician's point of view, the loss of adequate prescription of a certain drug and/or its higher dosage that would reach the therapeutic target can be related to the so-called "therapeutic inertia" and/or loss at follow-up. A lack of expertise and knowledge of the guidelines can be advocated as main causes, together with organizational problems and local healthcare system policies that hinder or at least do not facilitate drug prescription and supply, in particular for outpatients. When such policies are not homogenous throughout a nation, it leads to inequality of treatment for citizens even within the same country. Furthermore, due to the recent shortage of medical and nursing staff, long outpatient waiting lists increase losses in follow-up and limit up-titration of therapies. Lastly, the physician may fail to communicate to the patience the importance of staying on drugs or irrationally act cautiously using low dosages to avoid side effects and discontinuation of treatments. All these vicious behaviors contribute to the failure to reach the recommended targets.

There are many other variables, on the other hand, that can negatively influence patients' adherence to therapy.[24, 25] Many studies on large populations have shown that there are several patient-related factors that influence treatment adherence, such as age, sex, gender variables, low level of education, difficult social contexts, poor economic resources, cognitive and vision/hearing deficits, and lack of caregivers associated to lower adherence. In addition, the presence of both comorbidities and polypharmacy negatively interferes, indeed adherence progressively and significantly reduces as the number of tablets taken daily by the patient increases.[26] All together this results in an increased incidence of negative outcomes, such as recurrent CV events and hospitalizations, which in turn have a negative impact on the quality of life, the survival rate, and cause an increase in healthcare burden and costs.[27] Some aspects are peculiar to cholesterol-lowering therapy. In fact, treating hypercholesterolemia reduces the risk of MACE, but does not modify symptoms, so the patient may not take the therapy regularly because she/he does not immediately perceive advantages of the treatment. A final obstacle is represented by the risk of statin-induced myopathy. We know that the incidence of this side effect (demonstrated by a significant increase in the plasma CK value) is around 1.5-5% in trial populations,[28] but in clinical practice up to 20-25% of patients on statins complain of muscle and/or joint pain/weakness. For this reason, the patient often spontaneously interrupts the treatment, a rare example of a nocebo effect, often linked to poor and superficial information.

Poor adherence to therapy potentially results in a significant (and avoidable) increase in MACE, together with a worsening of patients' quality of life and increased mortality and economic impact for the Health Care Systems.[29] Several interventions can be implemented to try to limit the problem, as summarized in Figure 3.[30]

Clinicians should know clearly the objectives of the therapy, first identifying the risk profile of each patient, that determines the LDL-C target value. During follow-up, there is a need for regular review of therapy and plasma lipid values, as

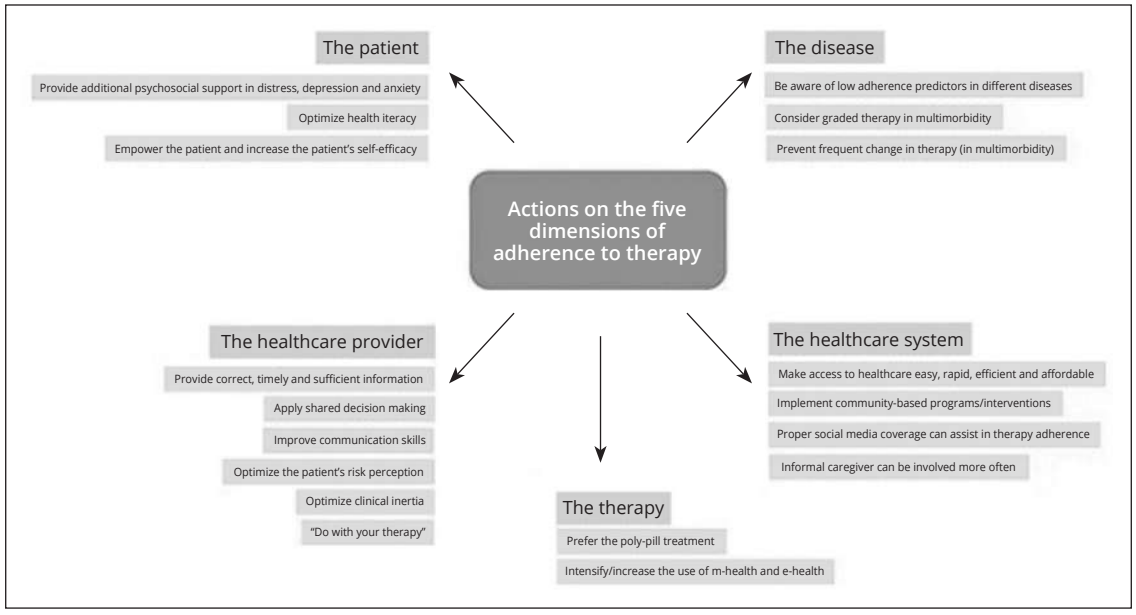

Figure 3.—How to optimize the adherence to drug therapies by acting at several levels (modified from Pedretti *et al.*).[30]

well as monitoring for potential side effects. Regarding the latter, it is important to distinguish the side effects from other symptoms not related to the drugs. In essence, the clinician should identify the pitfalls to avoid therapeutic inertia and to favor patient's adherence.

The patient needs to know and understand the reasons to be on therapy, the targets to reach, and its impact on primary or secondary CV prevention. Therefore, the communication should be clear, simple, and complete, in line with the capabilities of the person in front. The decision-making process should be shared with the patient, especially by clarifying doubts/fears related to superficial knowledge or misunderstandings, to achieve the patient's engagement. For example, in case of worry related to possible myopathic effects due to statins, the clinician should reassure the patient that this effect can be monitored (CK levels), the statin can be changed or reduced, or even replaced by other agents. In this sense, in chosen patients a more frequent monitoring program, also using telemedicine, could help in keeping patients' compliance high.[31]

Attention should be paid in simplifying the treatment schedule, utilizing pre-constituted oral combination of drugs, to reduce the number of tablets that the patient must take during the day, not only for cholesterol-lowering therapy (statin + ezetimibe, bempedoic acid + ezetimibe), but also for drugs for associated diseases, such as arterial hypertension and diabetes mellitus. In summary, adequate awareness, motivation for therapy, regular monitoring, and simplification of therapeutic schemes represent effective tools to improve patient adherence.

Ultimately, improving the effectiveness of therapy necessarily involves effective healthcare organization that, in turn, connects doctors and patients. The difficulties caused by the lack of resources, logistics and healthcare personnel undermine the stability and regularity of the doctor-patient relationship. These difficulties can be remedied by implementing telemedicine activities, and by updating progressively the national healthcare or insurance policies. Teleconsultation and remote monitoring could significantly improve the effectiveness of therapeutic programs that should also include lifestyles' changes, such as diet, physical activity, smoking habits, on the other hand they could allow to identify possible side effects and limit self- discontinuation of drugs. Also, those patients with limited access to the outpatient clinic (bedridden patients, older or chronic disabled patients) would also be followed appropriately. This system has

already demonstrated a positive impact on the effectiveness of screening and diagnosis, as well as follow-up of patients with chronic diseases.[30]

The burden of major CVD remains a worldwide challenge, in particular ischemic heart disease and ASCVD are still an important cause of mortality and morbidity.[32] The impact of the increase in life expectancy is a further determining factor in the epidemiology of CVD in many countries, which further increases the urgency of intervening on modifiable risk factors.

In conclusion, although scientific evidence has demonstrated the great benefits of earlier and more intensive treatments to lower LDL-C, in the real-world less than half of patients on therapy achieve the LDL-C targets recommended by the most recent ESC/EAS Guidelines. This is even most evident in the categories of patients at high and very high CV risk, *i.e.* precisely patients who most need to modify this crucial causative factor are those furthest from therapeutic goal.

This happens for multiple reasons depending upon both the doctor and the patient sides. The clinician, also due to lack of time or scarce organization in the outpatient clinic, may be inclined not to change a long-term therapy (therapeutic inertia phenomenon), or is lacking in communicating the benefits of a certain therapy. The patient, on the other hand, is not interested in understanding the benefits of a treatment, for a factor that does not cause evident symptoms, and is more worried about the possible side effects, and the interactions with the other ongoing medications.

Finally, many difficulties arise from a leaking healthcare network, where policies are confined to a silo system rather than an all-encompassing vision of the CV burden that includes pharmaceutical spending, reduction of costs from hospitalization, from disabling diseases, and the quality of life in an aging population.[33] An efficient healthcare organization must include telemedicine and teleconsultation facilities. In countries, like Italy, where each region applies different rules, the different approaches should be overcome, in order to give access to the same therapeutic possibilities for the entire population of the same country.

The main actions to counteract the underuse of hypocholesterolemic therapeutic strategies are summarized in Table I. These actions mainly concern doctors, patients and healthcare systems and answer the question: what should each of them do?

Medical doctors should be continuously updated on the most recent evidence and follow the recommendations to achieve the targets, they should also engage the patient in the therapeutic choice process, explaining in an understandable and direct manner the motivations and aims of the therapy, as well as the possible AE without intimidating the patient, adapt their language to the understanding abilities of the individual patient, regularly monitor the effects of the prescribed therapy, and change it when LDL-C is not adequately controlled. Patients should ask for more information about the benefits of a specific treatment, ask for simple and tailored dosing schedules, alert their doctor in case of undesirable side effects, and understand when these are not related to the cholesterol-lowering drug, ask for clarification of any doubt and fear she/he may have regarding the medicines. Healthcare systems should align with the guidelines and promote good clinical practices, be aware of the impact on outcomes in terms of overall sustainability, overcoming the silo system, be organized and structured with the aim of removing logistical barriers that hinder the doctor/patient relationship, and promoting clear and transparent interaction between them, implement telemedicine services, which have already demonstrated a promising positive effect on screening, early diagnosis and follow-up of patients with chronic diseases on long-term pharmacological therapies.

TABLE I.—*Summary of the decisive actions to overcome the gap between desirable LDL-C therapeutic targets and actual targets in the real-world.*

Medical doctors	Patients	Healthcare systems
Be updated	Ask for more info	Be aligned with guidelines
Engage the patient	Ask for simple programs	Overcome silo logics
Communicate clearly	Report side effects	Facilitate doctor/patient relation
Monitor and follow-up	Address doubts and fears	Implement telemedicine

A further boost to accomplish the guideline goals comes from recent evidence that treatment of inflammation combined with optimal lipid lowering is likely to be crucial for the future ASCVD management.[34]

Furthermore, integrating machine learning with innovative technologies, such as blockchain, as proposed in a previous work,[35] could offer advanced tools for predictive and personalized analysis in the management of dyslipidemia, enhancing clinical effectiveness and data handling.

Although it represents a discussion limited to a small group of cardiologists, this special article aims to encourage the medical-scientific community to maintain a high level of attention on the topic of effective CV prevention and promote awareness among all stakeholders.

Nowadays, thanks to scientific evidence and new therapeutic options, there is the possibility of reducing cardiovascular burden, which is the main cause of death and hospitalization as well as disability and costs in the Western world. This opportunity is often dashed by the difficulties of management systems and health policies. To counter this dichotomy, the integration of the skills of clinicians and health managers could guide the planning, enacting, sustaining and scaling of healthcare improvement.[33] In this perspective, SICOA wishes to urge the need to design studies that take into account all aspects of therapeutic success in the field of cardiovascular prevention and include all healthcare stakeholders with the aim of urgently implementing healthcare management, also through the use of appropriate machine learning systems, to achieve a significant reduction in cardiovascular burden.

Key messages

• While the real-world data confirm the safety of currently recommended LDL-C targets, data on their actual achievement are discouraging, less than half of patients reach the LDL-C targets recommended by the most recent ESC/EAS Guidelines.

• The causes of the gap between guidelines and real-world practice are multiple and arise from the components of the complex relationship between patient and physician within the healthcare system, such as therapeutic inertia, patient adherence, issues related to the local healthcare system and prescription policies.

• A call to action is needed with the aim of urging clinicians, scientific associations, policymakers, and healthcare organizations to promote targeted interventions.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

All authors have participated to the conception of the special article, analysis of the real-world contest, review of the references, discussion of the results and conclusions, and accuracy of the work; Laura A. Dalla Vecchia, Francesco De Stefano, Maurizio Bussotti, Cosmo Godino, Marco Bernardi, Luigi Spadafora, Edvige Palazzo Adriano have participated to drafting the manuscript; Pasquale Guarini, Roberto F. Pedretti revised it critically. All authors read and approved the final version of the manuscript.

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