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LDL-cholesterol distance to target: A practical tool for guiding lipid-lowering treatment decisions

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ABSTRACT

Low-density lipoprotein cholesterol (LDL-C) is causal in atherosclerotic cardiovascular disease (ASCVD), still the leading causes of global morbidity and mortality. The 2025 update of the ESC/EAS guidelines for the management of dyslipidemia recommends increasingly stringent, risk-based LDL-C targets. Beyond achieved LDL-C targets, cumulative exposure over time has emerged as a key determinant of ASCVD risk. Accordingly, treatment strategies should evolve from a traditional stepwise approach toward a more proactive, personalized, and target-oriented model; the recognized impact of cumulative LDL-C exposure further reinforces the importance of early, intensive, and sustained lipid lowering therapies (LLT). Despite this awareness and the availability of effective therapies, LDL-C control in clinical practice remains suboptimal. This gap is largely driven by the so called "therapeutic inertia", involving physician-related factors, patient barriers, and healthcare system constraints; accordingly, fewer than one-third of patients in secondary prevention achieve recommended LDL-C goals. A significant improvement in this situation requires structured treatment algorithms, multidisciplinary care, improved patient education, and integration of digital decision-support tools. A pragmatic framework to improve goal attainment is the estimation of "distance to target", which enables selection of LLT based on the required percentage reduction from baseline LDL-C levels. This approach facilitates alignment between the expected efficacy of available treatments and individual patient needs. While statins remain first-line therapy, combination regimens are frequently required—particularly in very high-risk patients—including ezetimibe, bempedoic acid, PCSK9 inhibitors, and inclisiran.

1. Introduction

Low-density lipoprotein cholesterol (LDL-C) is a causal determinant of atherosclerotic cardiovascular disease (ASCVD), which remains the leading cause of morbidity and mortality worldwide [1]. A linear association exists between the magnitude of LDL-C reduction and the absolute yearly cardiovascular event rate [2]. Despite the availability of effective lipid-lowering therapies (LLT) [3], the attainment of guideline-recommended LDL-C targets remains suboptimal in routine clinical practice [4], as also reported in the DA VINCI registry evaluating patients in primary and secondary care across Europe [5]. Closing the gap between evidence-based guideline recommendations and real-world application requires a holistic perspective on the diverse and interacting factors that fuel implementation failure. This narrative review proposes

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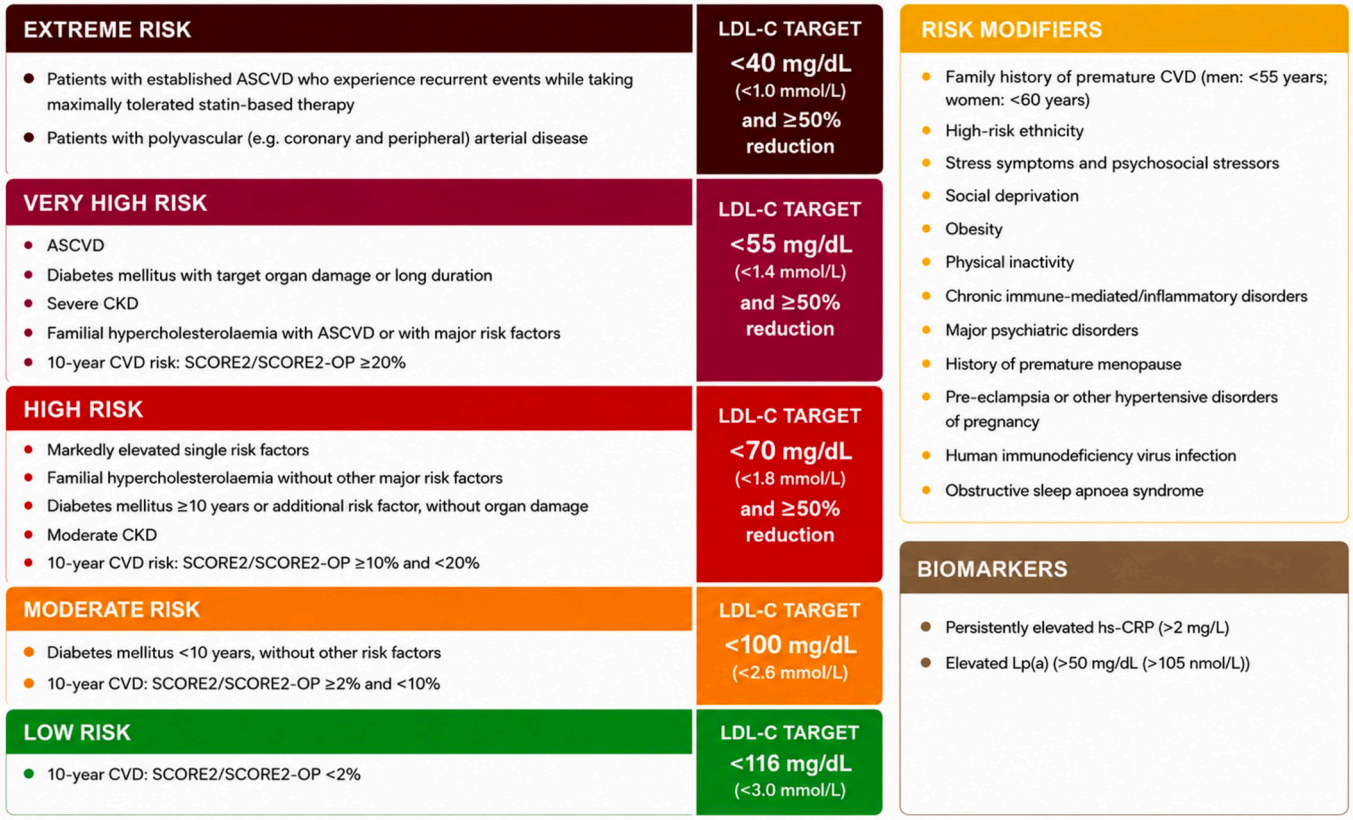

Fig. 1. 2025 ESC Update on Dyslipidemias: cardiovascular-risk categories and LDL-C targets.
Summary of cardiovascular risk categories, corresponding low-density lipoprotein cholesterol (LDL-C) targets, major risk modifiers and biomarkers according to current EAS/ESC guidelines for the management of dyslipidemia[7]. ASCVD, Atherosclerotic Cardiovascular Disease; CVD, cardiovascular disease; CKD, Chronic Kidney Disease; hs-CRP, High-Sensitivity C-Reactive Protein; LDL, Low-Density Lipoprotein Cholesterol; Lp(a), Lipoprotein(a); SCORE2, Systematic Coronary Risk Evaluation 2; SCORE2-OP, SCORE2-Older Persons. Reproduced with permission of Elsevier [7].

a pragmatic framework based on the estimation of distance to target (DtT), highlighting its potential role as a simple and practical precision medicine tool to guide therapeutic decision-making and improve goal attainment in LLT.

2. Risk-Stratification according to low-density lipoprotein cholesterol

The evolution of risk-stratified LDL-C targets reflects the progressive recognition that the causal role of LDL-C in atherosclerosis extends to a much broader range of this parameter than initially assumed. European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines have consistently maintained a target-based approach, recommending progressively lower LDL-C levels with increasing cardiovascular risk, supported by the 10-year risk assessment model of SCORE2 which extended the age range for primary prevention up to age 89 [6]. Overall, this evolution has established the central concept that LDL-C targets should be tailored according to the patient's global cardiovascular risk profile. Within this framework, Fig. 1 summarizes the most recent 2025 ESC Update on dyslipidemias, highlighting contemporary LDL-C targets across different risk categories [7].

The concept of "extreme cardiovascular risk" warrants specific consideration. In the 2019 ESC Guidelines for the Management of Dyslipidaemias [8], an LDL-C target of 40 mg/dL was proposed for patients with documented cardiovascular disease who experienced a second cardiovascular event within two years (not necessarily of the same type) despite maximally tolerated LLT. In the subsequent 2025 ESC update, the two-year temporal criterion was removed [7]. The definition was broadened to include patients with ASCVD who experience recurrent cardiovascular events despite maximally tolerated LLT, as well as patients with multivascular disease.

2.1. *Is a range of target LDL-C values acceptable?*

Current EAS/ESC LDL-C targets are expressed as upper threshold values not to be exceeded. For example, in patients at moderate cardiovascular risk, the recommended LDL-C target is $<$ 100 mg/dL. This raises a practical question: can the therapeutic target be considered achieved in patients with LDL-C values slightly above the recommended threshold (e.g. 105 mg/dL)? In other words, does a clinically acceptable range exist around the guideline-defined LDL-C target within which treatment goals may still be considered fulfilled? Addressing this question is methodologically challenging, and currently only limited evidence is available. The difference in cardiovascular risk associated with such small variations in LDL-C levels is likely minimal in absolute terms, but demonstrating equivalence between values such as 105 mg/dL and 98–100 mg/dL would require very large study populations and prolonged follow-up.

Another key factor is the biological and analytical variability of LDL-C measurements [9]: plasma levels may fluctuate within the same individual and are influenced by pre-analytical and methodological factors, so small differences may fall within normal variability rather than reflecting true clinical differences.

Ethical considerations also limit the available evidence. A formal evaluation of values above guideline-recommended thresholds would require randomized studies intentionally maintaining patients above target, which may be unacceptable with current standards of care. In addition, the relationship between LDL-C and cardiovascular risk is

continuous [10], without a clear biological threshold, meaning that guideline targets function as practical decision-making tools rather than pathophysiological cut-offs. This inherently complicates the definition of a clinically meaningful "tolerance interval."

Importantly, the clinical relevance of small deviations depends on baseline cardiovascular risk: the higher the risk, the more important it is to achieve the lowest possible LDL-C levels [11]. This makes the issue less relevant in very high-risk patients, where aggressive LLT is clearly indicated, and more difficult to interpret in low-to moderate-risk populations.

In clinical practice, the debate mainly concerns patients at very high cardiovascular risk, particularly in secondary prevention. The LODESTAR trial (*LOw-Density lipoprotein cholesterol target vs high-intensity statin therapy in coronary ARtery disease*) [12] and the study by Hong S.J. [13]. compared a treat-to-target strategy (LDL-C 50–70 mg/dL) with high-intensity statin therapy, showing non-inferiority in major cardiovascular outcomes, with potential advantages in safety and adherence.

According to the recent AHA/ACC 2026 Guidelines for the management of dyslipidemia in secondary prevention (i.e. with clinical ASCVD), a goal of LDL-C <55 mg/dL is recommended. Although a smaller number of patients with ASCVD, not at very high risk, have an LDL-C goal of at least <70 mg/dL, the majority of those with a history of ASCVD events will likely qualify for an LDL-C goal of <55 mg/dL [14].

Conversely, regarding the lower boundary of LDL-C values, extensive evidence supports the concept that "the lower, the better," with progressively lower LDL-C levels associated with incremental cardiovascular risk reduction. Importantly, no clear lower safety threshold has been identified. The hypothesis of a J-shaped relationship (in which risk begins to rise again, after a progressive reduction, when LDL-C values fall below a threshold value, as occurs in the case of blood pressure and BMI) does not appear to apply to LDL-C, as even very low levels achieved with modern LLT have not been associated with an increased risk of adverse events [15]. LDL-C levels <40 mg/dL - and even <20–30 mg/dL - are associated with further reductions in cardiovascular events without significant safety concerns [10]. This evidence was confirmed by the results of the FOURIER-OLE showing that in patients with ASCVD, long-term achievement of lower LDL-C levels, down to <20 mg/dL, was associated with a lower risk of cardiovascular outcomes with no significant safety concerns [16]. These findings support the safety of intensive LLT and reinforce current guideline strategies advocating increasingly stringent targets based on cardiovascular risk [17,18].

3. The importance of achieving LDL-C targets

Contemporary evidence converges on a physiopathological and clinical principle that is now difficult to dispute: LDL-C reduction should be early, intensive, and sustained over time, as cardiovascular risk depends not only on the instantaneous LDL-C level but also on cumulative lifetime exposure [19,20].

Table 1
On average LDL-C reduction by daily statin dose.

Statin	High Intensity >50%	Moderate Intensity 30–50%	Low Intensity <30%
Atorvastatin	40–80 mg	10–20 mg	—
Rosuvastatin	20–40 mg	5–10 mg	—
Simvastatin	—	20–40 mg	10 mg
Pravastatin	—	40–80 mg	10–20 mg
Lovastatin	—	40 mg	20 mg
Fluvastatin	—	XL 80 mg 40 mg twice daily	20–40 mg
Pitavastatin	—	2–4 mg	1 mg

Classification of statin therapies according to their expected reduction in low-density lipoprotein cholesterol (LDL-C), categorized as high-, moderate-, or low-intensity treatment based on the percentage decrease in LDL-C achieved with different statins and dosages.

3.1. Why is early achievement of LDL-C targets crucial?

The proposed "LDL cumulative exposure hypothesis" clarifies that the biological impact of LDL-C on atherosclerosis depends on both the magnitude and duration of exposure, leading to progressive plaque accumulation and eventually exceeding a critical threshold beyond which acute events become more likely. In this framework, the concept of "plaque–years" represents an integrated biomarker of atherosclerotic risk and provides a strong biological basis for the principle "lower is better and earlier is better" [2,21]. This concept is supported by evidence indicating that the total atherosclerotic plaque burden is approximately proportional to cumulative exposure to circulating apoB-containing lipoproteins, which can be estimated as the product of LDL-C concentration and duration of exposure. From a quantitative perspective, cumulative LDL-C exposure can be expressed as: Plaque-years ≈ age (years) × mean LDL-C (mg/dL). This metric corresponds to the integral of LDL-C over time (i.e., the area under the curve) and provides a clinically intuitive estimate of lifetime atherogenic burden. For example, an individual with a sustained LDL-C of 125 mg/dL will reach approximately 5000 mg-years by age 40, a threshold that corresponds to the level of cumulative exposure at which myocardial infarction risk begins to increase measurably [2]. Beyond this point, plaque burden continues to grow approximately linearly with ongoing exposure, while event risk rises in a log-linear fashion, reflecting the transition from subclinical atherosclerosis to clinically manifest disease.

Importantly, this framework explains the heterogeneity in the timing of cardiovascular events: individuals with lifelong lower LDL-C levels accumulate plaque more slowly and reach the critical exposure threshold later in life, whereas those with higher LDL-C levels exceed this threshold earlier and may experience premature events. Accordingly, the concept of plaque–years integrates both intensity and duration of exposure into a single biologically meaningful metric, reinforcing the rationale for early and sustained LLT to delay plaque progression and reduce lifetime risk of atherosclerotic cardiovascular disease [22,23]. The risk is not a snapshot, it is a slope and the steeper the slope, the harder it becomes to reverse [24].

Consistently, analyses from the CARDIA study (*Coronary Artery Risk Development in Young Adults*) demonstrate that cardiovascular risk is determined not only by cumulative LDL-C exposure but also by its timing, with earlier-life exposure conferring a disproportionately greater increase in risk despite similar overall burden, suggesting a persistent "arterial memory" effect [25]; thus, late intervention may not fully offset the consequences of prolonged prior exposure. In parallel, findings from the ARIC study show that the consistency of LDL-C control is a key determinant of outcomes, as a higher time in target range is associated with a significantly lower risk of major cardiovascular events, independent of baseline LDL-C levels [26]. Together, these data support the concept that both early initiation and sustained maintenance of LDL-C reduction are essential [27], whereas intermittent target achievement and prolonged exposure above recommended thresholds contribute to cumulative LDL-C burden and accelerate atherosclerotic progression.

3.2. Distance to target (DtT)

Once the individualized LDL-C goal has been defined according to the patient's cardiovascular risk category, the next practical question is how to translate this information into an effective treatment strategy. A useful and intuitive approach is to estimate first of all the distance to the LDL-C target expressed as the required percentage reduction of basal values to reach the desired target, and then select a LLT capable of achieving at least that magnitude of reduction. This concept allows clinicians to move beyond empirical or stepwise "trial-and-error" intensification and instead tailor therapy according to the degree of LDL-C lowering required to reach the recommended target [28].

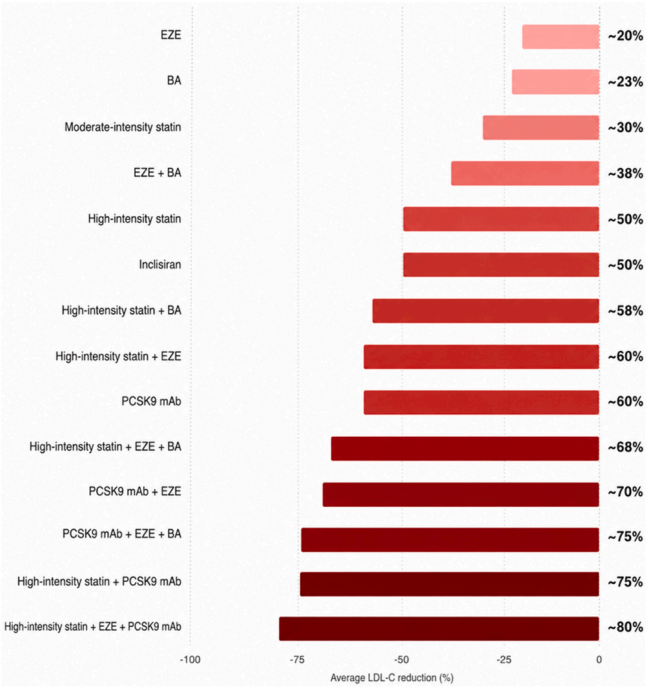

Fig. 2. Average reduction in LDL-C levels with different pharmacological therapies with proven cardiovascular benefits.
Estimated average LDL-C reduction achieved with different lipid-lowering therapies and combination regimens. The figure illustrates the progressive efficacy of monotherapy and combined pharmacological strategies, supporting treatment selection according to the magnitude of LDL-C reduction required. BA, bempedoic acid; EZE, ezetimibe; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9 inhibitor; PCSK9 mAb, monoclonal antibody against PCSK9. Reproduced with permission of Elsevier [7].

The percentage distance from goal can be calculated by subtracting the LDL-C target from the current LDL-C value and dividing this difference by the current level. For instance, if a patient has an LDL-C concentration of 70 mg/dL, in absence of LLT, and the recommended target is 55 mg/dL, the absolute gap is 15 mg/dL, corresponding to approximately a 21% DtT. In such a situation, treatment should aim for an LDL-C reduction of at least 21%, which might be achieved through introduction of a moderate or high-intensity statin. Similarly, if a patient presents with an LDL-C level of 110 mg/dL, with low-dose low-intensity statin, and the therapeutic goal is 70 mg/dL, the difference of 40 mg/dL corresponds to a 36% DdT, suggesting that upfront combination therapy with moderate or high intensity statin plus ezetimibe or bempedoic acid may be more appropriate to go to target.

Since the reduction of plasma LDL-C which can be obtained by dietary therapy alone is on average around 5% and considering the well-established dose-dependent potency of different statins (Table 1), this approach also allows clinicians to select the most appropriate statin type and dosage capable of achieving the required LDL-C reduction. By matching the expected lipid-lowering efficacy of each treatment with the calculated distance from goal clinicians can rationally select the most appropriate therapy from the outset, minimizing delays in achieving LDL-C targets (Fig. 2). Consistent with guideline recommendations, LDL-C levels should then be reassessed 4–6 weeks after initiation or intensification of therapy, allowing further optimization if the desired target has not yet been achieved, always through the same method.

3.3. LDL-C target achievement in clinical practice

To translate these principles into clinical practice, several representative clinical scenarios can be considered. The following examples illustrate how LDL-C targets and lipid-lowering strategies may be applied across different cardiovascular risk profiles, from untreated very-high-risk patients to individuals already receiving therapy and those with extreme risk (Fig. 3).

Importantly, treatment intensification must consider the pharmacodynamic characteristics of statins [29]. The relationship between statin dose and LDL-C reduction follows a logarithmic dose–response curve, commonly referred to as the “rule of six” [30]. Doubling the statin dose provides only a modest additional LDL-C reduction—about 6% of the baseline level—beyond what has already been achieved. This occurs because inhibition of HMG-CoA reductase and the consequent upregulation of hepatic LDL receptors approach a plateau at moderate statin doses [31]. Further dose escalation therefore yields only limited additional increases in LDL receptor expression and LDL clearance. As a result, intensifying statin therapy beyond moderate doses provides small incremental reductions in LDL-C, which explains why combination therapy with agents such as ezetimibe or PCSK9 inhibitors is often required to achieve substantial further lipid lowering. This aspect becomes crucial considering that the use of combination LLTs has increased in Europe, rising from 10% in the DA VINCI registry (2017–2018) to approximately 39% in the SANTORINI registry (2020–2022). However, among patients at highest risk, LDL-C goal attainment improved only modestly, from 20% in DA VINCI to 30% in SANTORINI [32].

3.4. Lipid lowering therapies in clinical practice

Beyond healthy lifestyle modifications, a robust pharmacological armamentarium is available to mitigate LDL-C-mediated cardiovascular risk. While statins remain the cornerstone of therapy, several non-statin agents have emerged. The following section delineates the main lipid lowering agents. Recent advances in LLT have expanded beyond traditional inhibition of cholesterol synthesis, with novel agents targeting alternative pathways to address residual cardiovascular risk in patients inadequately controlled by conventional treatments [33]. Pharmacological inhibition of cholesteryl ester transfer protein is also being revisited [34]. A new highly selective CETP inhibitor, Obicetrapib shows favorable effects on atherogenic lipids and lipoproteins, i.e. reduction of LDL-C, apolipoprotein B, and Lp(a), while increasing HDL-C [35]. Therapies including monoclonal antibodies, antisense oligonucleotides, and siRNA are now able to reduce not only LDL-C but also triglycerides, and remnant cholesterol, making them particularly relevant in severe dyslipidemias such as familial hypercholesterolemia [33,36]. Gene-editing approaches based on CRISPR technology are also under investigation, with the potential to achieve durable lipid lowering through permanent inactivation of targets such as PCSK9 [37]. In parallel, oral small-molecule PCSK9 inhibitors are under development, aiming to improve both efficacy and treatment adherence [38,39].

4. Therapeutic inertia

Despite robust scientific evidence and increasingly stringent targets, fewer than one-third of patients in secondary prevention achieve recommended LDL-C levels, highlighting a persistent gap between guidelines and real-world practice [40]. A primary contributor to the suboptimal attainment of LDL-C targets in contemporary practice is therapeutic inertia, the failure to intensify treatment despite unmet evidence-based goals.

Large registries consistently confirm this gap: target attainment was only 33% in the DAVINCI study, while SANTORINI reported that nearly 80% of ASCVD patients failed to reach goals, with many receiving no LLT at all [5,41]. Similarly, the INTERASPIRE registry (*INTErnational Action on Secondary and PRImary prevention by intErvention to Reduce Events*) showed that only 16.6% of ASCVD patients achieved LDL-C <55 mg/dL one year after hospitalization. Even within structured

EXTREME HIGH-RISK PATIENT

LDL BASELINE	TARGET	CURRENT THERAPY	Absolute distance (mg/dl)	Percentage distance (%)	INTENSIFICATION PROPOSED
48 mg/dL	≤ 40	Moderate Statin + EZE	8	17%	Add BA
68 mg/dL	≤ 40	Moderate Statin + EZE	28	41%	Consider add PCSK9 mAb or Inclisiran
78 mg/dL	≤ 40	Moderate Statin + EZE	38	49%	Consider add PCSK9 mAb or Inclisiran
105 mg/dL	≤ 40	High intensity Statin + EZE	65	62%	Consider add BA + PCSK9i or Inclisiran

VERY HIGH-RISK PATIENT

LDL BASELINE	TARGET	CURRENT THERAPY	Absolute distance (mg/dl)	Percentage distance (%)	INTENSIFICATION PROPOSED
59 mg/dL	≤ 55	Moderate Statin + EZE	4	6.7%	None / Doubling Statin
68 mg/dL	≤ 55	High intensity statin / Moderate statin + EZE	13	19%	Add EZE / Consider Add Bempedoic
78 mg/dL	≤ 55	Moderate intensity Statin	23	29.5%	Consider High intensity statin + EZE
105 mg/dL	≤ 55	High intensity Statin + EZE	50	47.6%	Add PCSK9i or Inclisiran
140 mg/dL	≤ 55	High intensity Statin + EZE	85	60.7%	Add PCSK9i / Inclisiran + Bempedoic acid

HIGH-RISK PATIENT

LDL BASELINE	TARGET	CURRENT THERAPY	Absolute distance (mg/dl)	Percentage distance (%)	LIPID LOWERING THERAPY
60 mg/dL	≤ 55	–	5	8.3%	Start low intensity Statin / EZE / BA
80 mg/dL	≤ 55	–	25	31.6%	Start moderate intensity Statin / Consider Statin + EZE
140 mg/dL	≤ 55	–	85	60.7%	Start high intensity statin + EZE or + BA

MODERATE RISK PATIENT

LDL BASELINE	TARGET	CURRENT THERAPY	Absolute distance (mg/dl)	Percentage distance (%)	LIPID LOWERING THERAPY
80 mg/dL	≤ 70	–	10	13%	Start low intensity statin / EZE / BA
110 mg/dL	≤ 70	–	40	37%	Start moderate intensity statin / Low intensity statin + EZE or BA / EZE + BA
150 mg/dL	≤ 70	–	80	53%	Start Moderate intensity statin + EZE or BA / PCSK9 mAb / Consider high intensity statin + EZE or BA or PCSK9 mAb

Fig. 3. Proposed Approach to LDL-C Management According to Cardiovascular Risk Level.
Illustrative examples of lipid-lowering treatment intensification strategies based on cardiovascular risk category, baseline LDL-C level, and the gap from recommended LDL-C targets. The figure illustrates how the degree of LDL-C reduction needed may inform the selection and stepwise escalation of pharmacological therapies in routine clinical practice. BA, bempedoic acid; EZE, ezetimibe; LDL, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9 inhibitor; PCSK9 mAb, monoclonal antibody against PCSK9.

cardiac rehabilitation and secondary prevention programs, as in the ITACARE-P registry (*ITAlian CArdiac REhabilitation – Prevention registry*), 43% of very high-risk patients achieved LDL-C <55 mg/dL, yet only 18% of those at extreme risk reached <40 mg/dL. Alarmingly, treatment remained unchanged in about half of patients not at target; and when intensification occurred, only 42% of adjustments were theoretically sufficient to achieve guideline-recommended thresholds [42]. The BRING-UP registry confirmed that only 33% of secondary prevention patients reached LDL-C targets, citing the marked underutilization of PCSK9 inhibitors and inclisiran [43].

The roots of therapeutic inertia are multifactorial, involving physician-, patient-, and system-level determinants.

Cognitive biases are a key factor among physician-related drivers. Cognitive science has demonstrated that most of the clinical reasoning occurs through two systems. One is fast, intuitive and automatic. The other is more deliberate and analytical. The intuitive mode of decision-making is characterized by heuristics, i.e. shortcuts, maxims, 'seen these many times before' and ways of thinking. Stress, fatigue and overload can lead to bias. A lack of insight into personal bias is common, whereby clinicians tend to overestimate the quality of care provided (perception–reality gap) [44]. In the context of therapeutic inertia, there is a tendency to rely on "soft excuses" to justify inaction, and to exaggerate concerns about adverse effects (confirmation bias). The most promising strategies for mitigating bias are those that do not rely on self-checking, such as team-based decision making, the use of appropriate cognitive aids, or the use of clinical decision support systems. Knowledge deficits also persist, as only half of physicians correctly identify targets for high-risk patients [45]. Evidence suggests that structured, algorithm-based care pathways can substantially improve outcomes: in the PENELOPE study, stepwise intensification enabled 87% of very-high-risk patients to reach LDL-C goals [46], while modelling analyses from ITACARE-P indicate that systematic combination therapy could theoretically increase target attainment to 95% [47].

On the patient side, inertia is driven by low health literacy and poor risk perception of "silent" atherosclerosis, leading to poor adherence and resistance to treatment intensification. Imaging-based communication can dismantle this inertia by providing tangible evidence of disease. In the VIPVIZA trial *(Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention)* [48], carotid ultrasound imaging improved patients' understanding of vascular risk and was associated with better adherence to preventive therapies, while similar benefits have been observed with Coronary Artery Calcium (CAC) scoring [49]. Fixed-dose combinations also enhance persistence compared with multi-pill regimens [50,51]. The nocebo effect further contributes to perceived statin intolerance, with randomized trials demonstrating similar symptom rates during placebo exposure and true intolerance affecting <5% of patients [52,53]. Within this context, targeted educational initiatives and shared decision-making strategies are essential to improve treatment acceptance and strengthen patient engagement.

System-level determinants also play a major role. High-throughput outpatient settings limit opportunities for risk communication and therapy optimization; studies indicate that clinicians devote a median of only 2.02 min to cholesterol discussion during chronic care visits [54] and that even a 1-min increase in visit duration is independently associated with higher statin prescription rates, suggesting inertia is deeply embedded in contemporary workflow constraints [55]. Integrating guideline education and electronic reminders into routine ASCVD workflows, has been shown to improve statin prescribing and LDL-C target attainment, as demonstrated in large cluster randomized trials

and implementation programmes [56].

Gender disparities further compound therapeutic inertia, as women are less likely to receive aggressive LLT or achieve lipid goals. Compared to men, women exhibit lower target attainment, particularly in ASCVD (31% vs. 47% reaching <70 mg/dL). These gaps are driven by lower prescription rates for both overall statins (26% vs. 33%) and high-intensity regimens. Notably, this bias persists regardless of provider gender, highlighting a systemic implementation gap that warrants targeted corrective strategies [57].

In this scenario, DtT represents a promising and pragmatic decision-support metric that may help bridge this persistent implementation gap. Importantly, DtT can be seamlessly integrated into routine clinical workflow through electronic health record–embedded calculators, clinical decision-support tools, or simple point-of-care algorithms. Automated estimation of the required percentage LDL-C reduction may prompt timely therapy optimization, reinforce adherence to guideline pathways, and reduce variability in clinical practice. By transforming guideline targets into an immediately operational metric, the DtT concept may help bridge the gap between evidence and implementation.

5. Peculiar patient groups

Cardiovascular prevention has progressively evolved toward a more individualized strategy that acknowledges the marked heterogeneity of risk across different patient groups.

In individuals with multiple borderline abnormalities, this personalized approach is critical to unmasking what López-Gil et al. described as “Gulliver syndrome” [58]. Much like the fictional character was immobilized by a multitude of tiny threads, these patients suffer from a systemic underestimation of risk because their individual markers—such as marginal hypertension and mild dyslipidemia—appear clinically modest in isolation. However, the synergistic effect of these clustered disturbances substantially accelerates the atherosclerotic process. Imaging-based reclassification may help overcome this inertia. Data from the MESA study (*Multi-Ethnic Study of Atherosclerosis*) demonstrate that CAC scoring effectively refines risk stratification, with higher cardiovascular event rates observed in individuals with CAC >100 despite initially low or intermediate estimated risk [59]. Integrating CAC into clinical decision-making therefore allows more precise identification of patients who may benefit from earlier and more intensive LLT [14].

In contrast, the older population requires a careful individualization of LDL-C targets, balancing the well-established benefits of LLT with the specific challenges of frailty, multimorbidity, polypharmacy, and competing risks [60,61]. The evidence for statin-based LLT consistently demonstrates proportional reductions in major vascular events across age groups, with benefit extending to individuals aged 75 years and above in secondary prevention [62]; however, the evidence for primary prevention in adults over 75–80 years will be addressed in the STAREE trial *(STAtins in Reducing Events in the Elderly)*, a randomised double-blind placebo-controlled trial examining the effects of statins in community dwelling older people without CVD, diabetes or dementia [63,64]. Furthermore, older adults frequently achieve clinically meaningful LDL-C reductions even with low-to-moderate intensity statin regimens [65], supporting a pragmatic approach to therapy selection.

Within this demographic, the DtT framework must be interpreted in light of the expected time-to-benefit of LLT and the patient's projected life expectancy [66]. In older patients presenting with severe frailty,

Fig. 4. From LDL-C distance to the right “club”: the golf analogy for reaching lipid targets.
Graphical illustration of the “distance-to-target” concept using a golf analogy to depictlipid-lowering treatment intensity according to the gap between current and recommended LDL-C levels. The figure emphasizes that a greater distance from LDL-C goals requires earlier and more intensive therapeutic strategies, including combination therapies. LDL,-C, low-density lipoprotein cholesterol.

advanced cognitive impairment, or established dependence in basic and instrumental activities of daily living (BADL/IADL), the strict pursuit of a numerical DtT may be clinically inappropriate. In such scenarios, the therapeutic priority should often shift from target-driven lipid-lowering to preventive deprescribing, minimizing the risk of drug-drug interactions and polypharmacy-related adverse events. Conversely, robust older adults with preserved functional autonomy and a reasonable life expectancy should not be denied intensive therapy based solely on chronological age. In these appropriate candidates, the DtT remains a highly valuable decision-support tool, provided it is thoughtfully integrated into a comprehensive clinical and functional evaluation.

The clinical suspicion of familial hypercholesterolaemia (FH) is paramount in patients presenting with pronounced hypercholesterolaemia (typically LDL-C $\geq$190 mg/dL), particularly when accompanied by physical stigmata such as tendon xanthomas or a family history of premature ASCVD. Diagnosis is generally established using validated clinical algorithms, including the Dutch Lipid Clinic Network [67] or Simon Broome criteria [68], all of which fail to sufficiently identify children with FH (for a specific review on this topic the readers can refer to 2026 consensus paper of the EAS [69]). Genetic testing for pathogenic variants in *LDLR*, *APOB*, or *PCSK9* confirm the diagnosis and enable cascade screening among relatives [70,71]. Risk stratification designates asymptomatic FH patients as high risk (target <70 mg/dL), whereas those with documented ASCVD or evidence of structural damage are categorized as very high risk, requiring a stringent target of <55 mg/dL and a minimum 50% reduction from baseline [72]. In this context, management strategies differ between heterozygous (HeFH) and homozygous FH (HoFH) patients. In HeFH, treatment generally follows the standard risk-based lipid-lowering algorithm but is initiated earlier and pursued more aggressively. In contrast, the management of HoFH is particularly challenging, considering that LDL apheresis remains a safe therapeutic approach to reduce their cardiovascular risks [73]. Among pharmacological therapies, particularly useful are those decreasing triglyceride-rich apoB-containing lipoproteins upstream of LDL particle formation [33], i.e. lomitapide (a microsomal triglyceride transfer protein inhibitor) [74] and evinacumab (an ANGPTL3 monoclonal antibody) [75], that lower LDL-C, by reducing the production or enhancing the clearance of triglyceride-rich lipoprotein remnants upstream of LDL particle formation.

FH represents a paradigm of accelerated vascular aging where lifelong lipid exposure necessitates aggressive LDL-C targets far earlier than in the general population. A key limitation of current clinical practice is the reliance on single LDL-C measurements, which fail to capture the concept of “cholesterol-years”—the cumulative lifetime exposure to atherogenic lipoproteins beginning at birth [72]. Consequently, even individuals treated from a young age may develop substantial subclinical atherosclerosis, as treated LDL-C levels often remain above physiological values. Imaging-based approaches, including carotid ultrasound, CAC scoring, and coronary CT angiography, improve detection of subclinical atherosclerosis and support earlier intensification of therapy. Risk stratification may be further refined by incorporating elevated lipoprotein(a) , an important contributor to residual risk [76,77]. According to that, it should be considered that cascade testing for elevated Lp(a) from index cases with FH and elevated Lp(a) is effective in identifying new cases of elevated Lp(a) [78]. This is useful when the proband has both FH and elevated Lp(a) [79].

Across these populations, delayed treatment escalation prolongs cumulative LDL-C exposure and amplifies lifetime atherosclerotic risk, highlighting the need for proactive and individualized therapeutic strategies to reduce the burden of disease [80].

6. Conclusions

Overall, the DtT should be interpreted as a flexible decision-support metric adapted to the patient's biological context and risk trajectory. By tailoring intervention intensity to the patient's phenotypic context, actual atherogenic burden, and life expectancy, the DtT framework provides a scalable decision-support tool to overcome therapeutic inertia and improve long-term ASCVD prevention. Achieving lipid targets in cardiovascular prevention can be compared to the strategic game of golf, where success depends on choosing the right approach for the distance that separates the player from the hole (Fig. 4). In the same way that a golfer carefully evaluates how far they are from the green before selecting a club, clinicians must assess how far a patient's LDL-C level is from the recommended target. When the distance is short, a gentle and precise stroke—analogous to modest therapeutic adjustments—may be sufficient to reach the goal. However, when the LDL-C level is far from target, a more powerful and decisive intervention is required, just as a golfer must select a driver or a long iron to cover a greater distance. This highlights the importance of tailoring therapy intensity to the magnitude of the gap: the larger the deviation from the LDL target, the more aggressive the lipid-lowering strategy should be. Combination therapies, high-intensity statins, or newer agents can be seen as the “long clubs” in the physician's bag, enabling a substantial reduction in cholesterol levels. Conversely, relying on insufficient therapy when the patient is far from target would be like attempting a long shot with a short club—ineffective and unlikely to achieve the desired outcome. Ultimately, both in golf and in lipid management, success lies in accurately judging the distance, selecting the appropriate tool, and executing the plan with precision to reach the final objective: the hole in golf, and optimal cardiovascular risk reduction in clinical practice.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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