

COMMENT

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Aggressive low-density lipoprotein (LDL) lowering for primary prevention: still an elusive goal

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Abstract

Cardiovascular disease (CVD) is the leading cause of mortality globally. Low-density lipoprotein (LDL) plays an important role in CVD pathophysiology. Research has shown the safety and efficacy of keeping LDL at very low levels for CVD prevention. Therefore, experts recommend intense LDL-lowering approaches starting at young ages, promoting the mantras “the lower, the better” and “the earlier, the better.” This commentary discusses the challenges regarding applying aggressive LDL-lowering approaches in the general population, including pharmacological efficacy and side effects, the cost-effectiveness of interventions, and patient adherence to treatment regimens.

Keywords Lipid, Cholesterol, Prevention, Dyslipidemia, Statin

Cardiovascular diseases (CVDs) are considered the most common cause of mortality worldwide, accounting for approximately 19.8 million fatalities in 2022 [1]. High levels of low-density lipoprotein (LDL) play a substantial role in the formation of atherosclerosis. Therefore, LDL has been a target for preventing CVD. The latest prevailing guidelines recommend identifying high-risk individuals using risk assessment calculators and lowering their LDL levels through lipid-lowering drugs and lifestyle modifications [2]. Although this approach has been successful in reducing CVD mortality, the LDL levels in the general population are significantly higher than desirable levels [3]. Despite the remarkable efforts to lower LDL levels,

approximately 70 million adults in the United States have an LDL level of more than 130 mg/dl [4]. Therefore, scientists are still looking for effective approaches to lower LDL levels for primary prevention.

Emerging evidence on the safety and beneficial effects of very low LDL levels has led to a shift in the paradigm of preventive cardiology. Lowering LDL showed promising effects on CVD, even in individuals with low LDL levels [5]. Recently, Michael E. Makover et al. [6] suggested early and aggressive reduction of LDL levels to prevent CVD in the general population. The mentioned study [6] proposed an LDL level below 55–70 mg/dl as the target for primary prevention based on the CVD risk profile, with a stricter LDL control for those with a higher CVD risk from a young age, ideally before the onset of atherosclerosis. While this strategy has the potential to revolutionize preventive cardiology, it has its challenges. In this article, we briefly point out the obstacles associated with early and aggressive LDL-lowering strategies.

Current recommendations from prevailing guidelines have highlighted the promising benefits of

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lifestyle modification in dyslipidemia management, such as healthy dietary habits and regular physical activity [2]. Lifestyle modification and consuming functional foods and nutraceuticals could effectively lower the LDL level and reduce the need for pharmacological interventions [7]. However, relying exclusively on lifestyle modification might not be enough to achieve the intended extremely low goal level of LDL among individuals with high LDL levels. Therefore, ensuring extremely low LDL levels in the general population necessitates a significant number of healthy individuals to use lipid-lowering medications over an extended period. As a result, it is essential to establish safe, efficient, and cost-effective preventive strategies. Despite the development of new generations of lipid-lowering medications, statins continue to be the first-line medication for primary and secondary prevention. High-intensity statins can only reduce LDL levels to 50% of the baseline, which might not be adequate for meeting the desired targets in the general population [8]. Consequently, additional medications like ezetimibe, bempedoic acid, or PCSK9 inhibitors may be required, alongside statins, to reach optimal targets. However, a meta-analysis has indicated that adding ezetimibe or PCSK9 inhibitors to statins did not improve cardiovascular outcomes in low-risk individuals [9]. Based on the International Lipid Expert Panel (ILEP) recommendation, bempedoic acid may be considered for primary prevention in high-risk patients who could not reach the desirable LDL level despite using the maximally tolerated dose of statins and ezetimibe (level B recommendation) [10]. However, evidence on using bempedoic acid for primary prevention in low-risk individuals is still scarce.

However, like all medications, lipid-lowering drugs have some adverse effects. While current evidence supports the idea that the benefits of lipid-lowering drugs outweigh the risks, prolonged use in a large portion of the population could magnify even rare adverse effects into significant public health concerns. Statin-associated muscle symptoms (SAMS) are the most prevalent side effect, affecting up to 29% of individuals taking statins [8]. Moreover, emerging research suggests that statins may increase the risk of new-onset diabetes and insulin resistance, which are fundamental contributors to cardiometabolic diseases [11]. Adverse effects of statins, particularly SAMS, are among the main reasons for statin non-adherence [12]; however, the prevalence of statin intolerance is usually overestimated. A recent meta-analysis showed that the prevalence of statin intolerance was 9.1% [13]. Also, PCSK9 inhibitors have certain limitations, including the need for subcutaneous injections, potential allergic reactions and myalgia at the injection site, and a high cost that may not be cost-effective for primary prevention at present [14, 15]. Inclisiran, a novel small interfering RNA inhibitor of PCSK9, increased the

adherence by increasing the injection intervals to twice a year, but a recent study in the UK showed that Inclisiran is not cost-effective for primary prevention at the current cost [16]. Although bempedoic acid has demonstrated favorable outcomes in reducing major cardiac adverse events, HbA1c, and inflammatory markers, its administration is associated with an elevated risk of gout [17]. It is noteworthy that increased uric acid levels and gout symptoms are reversible upon discontinuation of the medication. The International Lipid Expert Panel holds the consensus that such adverse effects bear minimal clinical significance [10].

Michael E. Makover and colleagues have proposed initiating lipid-lowering treatment at a young age, ideally before the development of atherosclerosis, without relying on risk assessment tools [6]. Firstly, determining the appropriate age for commencing lipid-lowering medication is crucial. Secondly, another obstacle to the implication of the “the earlier, the better” strategy is that treatment adherence tends to be lower among younger individuals, particularly for primary prevention [18]. Thirdly, risk assessment currently serves as the foundation of primary prevention in existing guidelines. It facilitates shared decision-making and enhances lipid-lowering and anti-hypertensive treatments by evaluating overall CVD risk based on multiple risk factors, not solely lipid profiles [19].

Taken together, achieving extremely low LDL levels in the general population is still an elusive goal. Aggressive LDL-lowering treatment strategies should be defined concisely and their cost-effectiveness should be evaluated. Insurance companies must be willing to cover these strategies, and the public should be educated about the benefits of maintaining very low LDL levels to improve treatment adherence.

Abbreviations

CVD	Cardiovascular disease
LDL	Low-density lipoprotein
ILEP	International Lipid Expert Panel
SAMS	Statin-associated muscle symptoms

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Author contributions

MF and RH conceptualized the article and edited the manuscript. MS was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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