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Commentary

Lifelong prevention of atherosclerotic cardiovascular disease (ASCVD) through LDL-C control - Means and cost/benefit of sustained very low lifetime LDL-C targets

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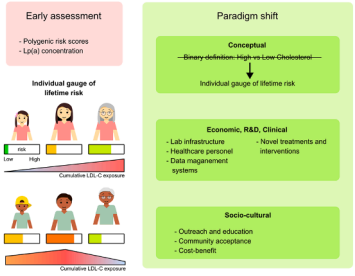
GRAPHICAL ABSTRACT

Central illustration. Coloured bars in the left panel show the impact of age and ethnicity on an individual's lifetime ASCVD risk mediated by cumulative exposure to LDL-C. Even younger individuals with a greater cumulative exposure to LDL-C, despite their age, may have a higher overall risk compared to older individuals with a lower cumulative exposure to LDL-C.



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Atherosclerotic cardiovascular disease (ASCVD) remains a significant global health challenge, contributing substantially to morbidity and mortality rates. Current solutions to global CVD prevention have had modest success, and more radical approaches may be required to slow the tidal wave of CVD.

Central to the pathogenesis of ASCVD is the role of low-density

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lipoprotein cholesterol (LDL-C). The concept of potent lipid lowering therapies with aggressive lipid targets, especially in secondary prevention of cardiovascular disease, is now ingrained in most cardiologists. In the life-course approach, a reduced lifetime cumulative exposure to LDL-C would be anticipated to improve ASCVD outcomes to a greater extent than later lipid control as suggested by those with inherited LDL-C deficiencies [1].

The concept of "LDL-C eradication" [2] is an aspirational idea that conveys the notion of "as low LDL-C as possible, for as long as possible". Central to this is the concept of primordial prevention of suboptimal lipid levels early in life through education and lifestyle, as well as primary prevention to lower lipid levels to a more optimal target, thereby preventing ASCVD [3]. Such an approach may allow regression of established atherosclerosis or prevention of its progression. With potent lipid lowering therapies now widely available, as well as prognostic markers with the potential to identify high-risk individuals in early life, we may finally be ready to attempt more stringent LDL-C control to improve lifelong prevention of ASCVD.

This article examines the feasibility of achieving sustained LDL-C reduction in the era of powerful lipid lowering therapies, and the challenges associated with this pursuit.

In the analysis of the FOURIER-OLE study, long-term use of the PCSK9 inhibitor evolocumab up to 8 years in patients with prior history of ASCVD, appeared to be safe with no apparent increase in the risk of adverse events such as new-onset diabetes, hemorrhagic stroke or neurocognitive events. Earlier initiation of evolocumab led to sustained reduction in LDL-C, with 63.2 % reaching LDL-C <0.4 mmol/L leading to a 15 % relative risk reduction in the primary outcome of cardiovascular death, myocardial infarction, stroke or hospitalisation for unstable angina or coronary revascularisation as compared with those with delayed initiation of a PCSK9 inhibitor [4]. Further post-hoc data from the ODYSSEY trial also suggests the safety of achieving very low LDL-C. Schwartz et al. published promising results of transient very low LDL < 0.39 mmol/L on improvement in cardiovascular outcomes in a non-randomised analysis of ODYSSEY Outcomes trial [5]. Gaba et al. further corroborated the safety and efficacy of very low LDL-C levels in an analysis of FOURIER-OLE [6]. Although long-term data appears promising, it must be interpreted within its limitations as a non-randomised comparison.

Central to the benefit of lipid-lowering treatments is patient adherence. In a study from UK primary care patients, Khunti et al. showed that adherent patients receiving high-intensity lipid-lowering therapy achieved the largest reductions in LDL-C and CVD risk [7]. Adherence to statin therapy is also complicated by statin-associated side effects. Injectable therapies offer potential opportunities in the challenge of adherence to long-term lipid-lowering therapy. Further supporting the feasibility of LDL-C reduction through PCSK9 inhibition, real-world evidence for PCSK9 inhibitors shows a higher degree of adherence when compared to statins [8]. Small-interfering RNA inhibitors offer the potential for even higher adherence, with infrequent injections administered in a clinic setting.

Multiple novel lipid lowering therapies such as bempedoic acid, ezetimibe, inclisiran, evinacumab and others that are in development (e.g. obicetrapib), add to the options available now and in the future for clinicians and patients alike. The safety and tolerability of these treatments have made stringent LDL-C control a possible, although still remote, target. Despite these advancements, however, the cumulative effect of LDL-C implies that sustaining low LDL-C levels from as early an age as possible would have the greatest reduction in ASCVD. In a meta-analysis on the impact of lipid lowering therapies on CVD in RCTs by Burger et al., the average relative risk reduction (RRR) in major vascular events observed for primary prevention was 26 % per 1 mmol/L reduction in LDL-C [9]. Conversely, a mendelian randomisation study by Valdes-Marquez et al. showed a 50 % reduction in RRR for coronary heart disease per genetically determined 1 mmol/L reduction in LDL-C, emphasizing the cumulative effect of LDL-C on lifetime ASCVD risk [10]. Furthermore, in the Progression of Early Subclinical Atherosclerosis (PESA) study, Mendieta et al. showed that the impact of LDL-C on subclinical atherosclerosis progression was more pronounced in younger participants [11]. In effect, a comprehensive assessment and target-setting for LDL-C in early life promises to have a big impact on primordial prevention of CVD. This also requires a greater emphasis on the use of exposure time models of ASCVD risk as opposed to 10-year risk in clinical pathways.

Despite early data on safety and tolerability, concerns remain around the real-world application and cost-effectiveness of novel therapies in achieving sustained very low LDL-C levels. Work from Kazi et al. found that PCSK9i use in all eligible patients with ASCVD or heterozygous FH in the US would save $29 billion over 5 years, yet drug costs would increase by $592 billion [12]. The analysis based on 2017 prices recommended a price reduction of 71 % for PCSK9i to be a cost-effective intervention. Conversely, initiating statins on eligible high-risk patients who are not currently on lipid-lowering treatment, would be estimated to save $12 billion. Recent data from the SANTORINI database indicated that only 20 % of high and very high risk ASCVD patients were achieving LDL-C goals as per the ESC/EAS guidelines, and 21.8 % were not on lipid lowering therapies [13]. Further adding to the complexity of the messaging for patients and physicians, it is also known that many patients with CVD events have "normal" cholesterol and many with elevated LDL-C do not develop CVD [14]. Current challenges include poor understanding of the lifetime exposure to LDL-C as cause for atherosclerosis, and reluctance to commence lipid lowering therapy amongst physicians and patients [15].

The broader concept that arises is a lifecourse approach for lipid management. Use of polygenic risk scores and measurement of a person's Lp(a) concentration may offer a chance to assess one's lifetime ASCVD risk early on in life, helping mould behaviours towards lipids, and intensive strategies such as injectables for LDL-C eradication.

Personalized lifetime lipid management with removal of labels for "high" cholesterol

In a theoretical scenario where there is no longer a specific threshold to label patients as having "high cholesterol" and lipid disorders are viewed on a spectrum, the concept of sustained stringent LDL-C control may stand a chance. Such an approach would require a shift from the traditional binary classification of cholesterol levels to a more individualized gauge of estimated lifetime risk. This may help bring about a leftward shift of population LDL-C with significant reduction in ASCVD overall. Yet, this poses several challenges in terms of implementation and economic implications. Healthcare systems would need to adapt to the increased demand for comprehensive cholesterol profiling, including more frequent testing and monitoring. This may require significant investments in laboratory infrastructure, personnel, and data management systems. Additionally, the cost of novel lipid-lowering treatments and interventions aimed at achieving LDL-C eradication would need to be considered. The economic impact of widespread implementation of such strategies would require careful evaluation to ensure their feasibility and cost-effectiveness in the long term. Most importantly, this would require the buy-in of individuals in the community and an open discussion of cost and benefit to the individual and population.

Potential for gene-editing approaches to lifelong LDL-C eradication

There now exist gene-editing strategies that show promise as a "fire and forget'' lifelong treatment for LDL-C control. Early evidence from clustered regularly interspaced short palindromic repeats (CRISPR) gene-editing strategies to induce long-lasting knockdown of PCSK9 have produced LDL-C reduction with few side effects in experimental and preclinical models [16]. With the advancement of such gene-editing therapies soon, this may be a futuristic approach to prevent ASCVD.

In conclusion, this article highlights the potential for intensive lifetime reduction in LDL-C to achieve a major reduction in ASCVD risk. Despite successes of multiple modalities to target lipids, real-world application remains the biggest challenge. Concerns of applicability

and cost-effectiveness demand a paradigm shift to how the health system approaches and engages with the public on the topic of lipids. Incorporation of early-life genetic testing, Lp(a) in the incorporation of a lifetime approach to lipids, as well as reversal of current thinking about "normal" or "high" cholesterol levels offer opportunities to make inroads in the battle against cardiovascular diseases.

CRediT authorship contribution statement

Mayank Dalakoti: Conceptualization, Writing – original draft, Writing – review & editing. **Salim Virani:** Writing – review & editing.

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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