LDL-cholesterol control in high-risk individuals: an international obstacle and call for earlier combination lipid-lowering therapy

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The global burden of cardiovascular disease (CVD) mortality is projected to increase by 75% over the next 25 years, approaching 35.6 million by 2050 [1]. Eastern European nations, including Slovakia, are among regions with the highest projected age-standardized CVD mortality rates (~305 per 100,000 population) [1]. The large magnitude of CVD is directly attributable to upstream risk factors, and elevated low-density lipoprotein-cholesterol (LDL-C) ranks as the third highest contributor to CVD risk in Eastern European nations, behind only hypertension and poor diet (high sodium, low fiber) [1]. As such, assessment of the adequacy of LDL-C treatment and control, especially among high-risk individuals in the Eastern European region, has important global health implications.

In this issue of *Archives of Medical Science*, Toth *et al.* evaluated attainment of low-density lipoprotein-cholesterol (LDL-C) goals among more than 72,000 individuals with acute coronary syndrome (ACS), stroke, and at very high risk for CVD in Slovakia over a 2-year period (2017–2019) [2]. Very high-risk CVD was defined according to European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines [clinical atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus with target organ damage, presence of three major risk factors, ≥ 20-year duration of type 1 diabetes, severe chronic kidney disease, 10-year calculated SCORE risk ≥ 10%, or familial hypercholesterolemia with clinical ASCVD] [3]. Leveraging an average of three measurements among participants, the mean LDL-C ranged between 3.1 and 4.3 mmol/l (120 to 166 mg/dl), which generally decreased across the study period. However, a very low number of participants met guideline-based LDL-C goals, as less than 10% met the LDL-C < 1.8 mmol/l (< 70 mg/dl) goal and less than 3% had LDL-C < 1.4 mmol/l (< 55 mg/dl). Additionally, at least 6% of participants in each patient group (ACS, stroke, very-high risk for CVD) had severe hypercholesterolemia defined by LDL-C ≥ 4.1 mmol/l (≥ 190 mg/dl) [2].

This provocative study by Toth *et al.* underlines large gaps in LDL-C control among high-risk individuals in Slovakia, and this analysis may serve as a case-study/prototype for future approaches to reducing the

burden of CVD attributable to hypercholesterolemia. Follow-up work in this space may focus on the optimal frequency of lipid panel testing required to attain LDL-C goals and whether there are potential differences in LDL-C control according to demographics or risk factor profile. Additional areas of focus may include clinician awareness, clinic visit time, and the potential value of telehealth to improve the adequacy of risk factor control. Lastly, there are likely disparities in LDL-C control not only on the country/region level, but also according to urban-rural differences and vicinity to academic medical centers.

While there have been fairly consistent improvements to population-wide LDL-C levels across the globe, such progress does not necessarily reflect successful implementation of guideline care and LDL-C control in high-risk individuals. Across both Europe and the United States, between one-half and two-thirds of individuals with clinical ASCVD do not attain LDL-C goals < 1.8 mmol/l (< 70 mg/dl) [4–6]. As such, global health messaging should be appropriately reframed to emphasize the important gaps in preventive cardiology and hypercholesterolemia care.

While there are several barriers to attainment of LDL-C control and real-world implementation of guidelines, a low utilization of combination lipid-lowering therapy is one important contributing factor. Phase 3 CVD outcome trials demonstrating utility of combination lipid lowering therapy when added to statins for ezetimibe (IMPROVE-IT, 2015) [7] and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (FOURIER [8] & ODYSSEY OUTCOMES [9], 2017–2018) were completed 8–10 years ago. However, combination lipid-lowering therapy remains quite underutilized in year 2025 among high and very-high risk individuals. Data from the SANTORINI Study (Treatment of High and Very High Risk Dyslipidemic Patients for the Prevention of Cardiovascular Events in Europe: A Multinational Observational Study) found that only about one-quarter of high and very high-risk adults receive combination lipid-lowering therapy [10]. Utilization of PCSK9 mAb therapy (4%) in SANTORINI was much lower than the generic ezetimibe (17%) and mirrors a similar, very-low rate of PCSK9 mAb prescription in the United States [11].

As our means of LDL-C lowering continues to expand with emerging novel therapies, messaging and focus should remain centered on foundational LDL-C control and delivering such therapies to the appropriate patients. Initial data from the VICTORIAN-INITIATE trial suggests that an "inclisiran first" strategy for combination therapy may help overcome therapeutic inertia. Here, individuals randomized to inclisiran versus usual care had substantially larger reductions in LDL-C (60% vs. 7%) with a much higher corresponding percentage attaining LDL-C < 70 mg/l (82% vs. 22%) and LDL-C < 55 mg/dl (72% vs. 9%) [12]. Phase 3 CVD outcome trials for inclisiran, a small interfering ribonucleic acid inhibiting hepatic transcription of PCSK9, are ongoing.

Given the substantial improvements required for attaining LDL-C control in clinical ASCVD as well as long-term safety and efficacy of non-statin lipid-lowering therapies, we anticipate that future updates of cholesterol guidelines in Europe and the United States will more heavily emphasize the utility of combination lipid-lowering therapy to achieve optimal LDL-C values in high risk individuals. Additionally, earlier combination lipid-lowering therapy may help minimize any potential side effects from high-intensity statin therapy. For asymptomatic individuals without clinical ASCVD and severe hypercholesterolemia with LDL-C ≥ 4.1 mmol/l (≥ 190 mg/dl), further risk stratification with coronary artery calcium testing may help identify individuals who derive the greatest benefit from combination lipid-lowering therapy as opposed to high intensity statin therapy alone. Similar to the management of present-day hypertension, we foresee a future of hypercholesterolemia management consisting of several potential first-line non-statin agents to add to background statin therapy, which may be personalized according to patient preferences and risk factor profile.

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Conflict of interest

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