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# Lipid-Lowering Therapy Seen Through the Lens of Experts: Expectations Thwarted by Reality

**EDITORIAL COMMENT**
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Low-density lipoprotein cholesterol (LDLc) is a key determinant of atherosclerotic cardiovascular disease (ASCVD) worldwide.[1,2] Statins reduce mortality and morbidity regardless of LDLc baseline levels, either in primary or secondary prevention.[3,4] Non-statin LDLc lowering therapies are equally effective in reducing the risk of several outcomes and follow statins along the same linear relationship: For every 39 mg/dL reduction in LDLc levels, the relative risk of cardiovascular events decreases by 22%-24%.[5]

Patients with previous ischemic events, diabetic individuals with either target organ lesions or 3 or more risk factors, and those with familial hypercholesterolemia and 1 additional risk factor, comprise a cohort exposed to a very high risk of events and need persistent and aggressive LDLc lowering.[3,6] Such patients, provided that goals be achieved and maintained in the long run, derive the highest absolute risk reduction from LDLc-lowering therapy.[4] Furthermore, statins—the backbone of lipid-lowering therapy (LLT)—show a very favorable safety profile.[4,7,8]

Notwithstanding the radical change in the natural history of atherosclerotic disease promoted by statins, their long-term adherence all across the globe, as well as the compliance to LDLc goals set by various guidelines, seems way too far from ideal, which in turn, frustrates much of the expectations toward their benefits.[7,9-14] Although Turkey has the highest prevalence of premature coronary artery disease among European countries,[15] rates of statin discontinuation continuously mount along a period of 6 months past the first prescription, and only 18% of patients in secondary prevention achieve LDLc goals <70 mg/dL: Surprising data, given the countrywide reimbursement of statins by the Turkish health system. Reasons for the low adherence and high discontinuation rate may vary among countries or regions in the same country, and the most commonly reported causes are fear of side effects by patients, coupled with low awareness of benefits, dissemination of negative or fake news, and therapeutic inertia.

Worthy of mention is the inertia to associate ezetimibe as an add-on to statins when goals are not achieved: Despite its proven value to further reduce LDLc levels and cardiovascular outcomes,[6,16] data from registries have shown that its addition to statins in patients with ASCVD remains very low[9,13,17,18] and does not progress during a 2-year follow-up.[19]

PCSK9 inhibitors (PCSK9i) are the most efficacious non-statin LDLc-lowering agents[20] and were proven capable of reducing cardiovascular outcomes when added to maximally tolerated statin doses (MTD) in very high-risk patients.[21,22]

Recently, important contributions were added to the body of data demonstrating the usefulness of PCSK9i in the secondary prevention of ASCVD. In a randomized double-blind trial of 300 patients who underwent percutaneous coronary intervention for acute myocardial infarction, the non-culprit arteries were assessed serially by intravascular ultrasonography (IVUS), near-infrared spectroscopy, and optical coherence tomography (OCT). Alirocumab added to high-intensity statin therapy, compared with placebo, resulted in a significantly greater reduction of atheroma volume in non-infarcted arteries after 52 weeks of treatment.[23] In a similar study, patients with a non-ST elevation acute myocardial infarction, treated with MTD statins and randomized to evolocumab 420 mg monthly or placebo, were followed serially for 52 weeks with IVUS and OCT. Evolocumab treatment resulted in a greater increase in minimal fibrous cap thickness and a decrease in maximum lipid arc, translating regression and stabilization

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of atherosclerotic lesions.[24] In addition, the recently published Fourier open-label extension study reported a statistically significant reduction in cardiovascular mortality in the cohort treated with evolocumab, after an extended 5-year follow-up (hazard ratio 0.77 [95% CI, 0.60-0.99]; $P=.04$).[25] A further 15% decrease in cardiovascular events was documented in the group originally allocated to evolocumab, while, on the other hand, the total 7-year mean exposure time to the active compound did not promote any increment in the low adverse event rate reported in the parent trial.

While experts and health authorities grapple with the challenges of low adherence to foundational lipid-lowering drugs, updated guidelines now strongly recommend upfront combination therapy with statins and ezetimibe in patients deemed as high cardiovascular risk, or triple upfront therapy with the addition of PCSK9i in those regarded as extremely high risk.[26-28] By moving away from the sluggish stepwise approach, experts agree that rapid and intense LDLc lowering right from the start in highly vulnerable patients may offer survival advantages and better long-term adherence to medical therapy.

The above preamble summarizes some key concepts and a few recent studies that constitute the backdrop against which the execution and results of the investigation led by Kızılırmak et al[29] should be discussed.

The authors elaborated a structured questionnaire that addressed cardiovascular risk categories, current treatment practices with an emphasis on LLT, attainment of recommended LDLc goals, and requirement for PCSK9i. The core idea consisted in capturing experts' perceptions on the real-world management of patients at high and very high cardiovascular risk. In the present study, the meaning of "perception" must not be regarded as a simple review of information provided by clinical trials, large-scale registries, guidelines, and modeling of patient eligibility to different classes of lipid-lowering drugs. Albeit based on published data, perceptions are strongly influenced by regional imbalances in the quality of medical care and patient education across a single country, drug reimbursement availability, level of social inequality, gender bias, and spread of misinformation.

In order to establish common ground on a set of perceptions related to secondary prevention of ASCVD, the authors assembled a group of 12 experienced opinion leaders in preventive cardiology and lipidology and used the Delphi panel method to elaborate a structured questionnaire consisting of 6 main questions. Importantly, the study aimed not at assessing the experts' experience but rather their perceptions on the general practice in Turkey.

The Delphi panel method is a validated research tool designed to gather consensus on issues where there is paucity of solid evidence-based data or when the outcome of interest is influenced by subjectivity. It is also widely used to develop health quality indicators.[30] Basically, the process begins with the definition of a problem upon which, structured questions are developed for experts to resolve in an individual and anonymous fashion. Information is collected, feedback is provided to each participant, and reassessment may involve new questions. After a short sequence of rounds, a consensus is expected to emerge.[31]

In the present study, hypothetical patient populations with ASCVD were constructed by the panel participants, and specific issues were addressed with a focus on LDLc goals, recurrent events, responses to treatment, and the use of PCSK9i. Worthy of note, the first author declared an employment tie with the manufacturer of 1 of the 2 commercially available PCSK9i. These monoclonal antibodies are very potent LDLc-lowering agents, and it is a matter of interest to identify unmet needs for this class of compounds, barriers to a wider access by patients and, ideally, to formulate possible solutions in partnership with health authorities and pharmaceutical industries in attempts to overcome some of those hurdles.

The main findings of this study can be summarized as follows:

- The proportion of patients with recurrent vascular events was estimated to reach 18.4%, meaning that almost 1 out of 5 patients missed a chance to avert a second event, had appropriate therapy been adopted timely.
- In patients with recurrent vascular events treated appropriately, LDLc levels<100 mg/dL should be reached in 72% of those treated with MTD statins. Corresponding percentages would yield similar values for MTD statins plus ezetimibe, while about 93% would reach LDLc<100 mg/dL with a PCSK9i added to combination therapy. Those proportions did not seem to differ significantly among subjects without recurrent vascular events. Of note, the overall percentage of patients not reaching LDLc levels <100 mg/dL despite MTD plus ezetimibe would range between 20.2% and 21.5% and would increase as a function of pretreatment baseline LDLc.
- Among patients with insufficient response to MTD statins, 77.5% would receive add-on ezetimibe. There is a sharp contrast with the estimated approach for patients who would not respond to MTD statin plus ezetimibe: Among the 20.2% of patients on dual LLT without adequate response, only 10.9% would be expected to receive a prescription for a PCSK9i, with no further action taken over the remaining 89.1%. It is worth mentioning that the panelists do not project an ideal scenario, but rather, they envision a very conservative approach based on current estimates. Nonetheless, in the "ideal" world, free of reimbursement restrictions, the PCK9i prescription rate in case of inadequate response to dual LLT could escalate up to 50% depending on the magnitude of the residual LDLc level.

What is the main take-home message from the paper by Kızılırmak et al?[29] There is a clear unmet need for potent LDLc-lowering agents such as PCSK9i. The invited panelists admitted that at least half of Turkish cardiologists would wish to prescribe these agents in face of the worst scenario: non-attainment of recommended goals despite dual LLT and high residual levels of LDc. A more conservative projection by the panelists accounted for current practice and provided a much less ambitious rate of prescription, estimated in 9%-11% of cases. However, reality is grimmer: According to current practice in Turkey, only 0.6%-1.2% are treated with MTD statins, ezetimibe, and PCSK9i, given the absence of reimbursement and unaffordability for a large proportion of the population at risk.

Other investigators have attempted to project the eligibility for PCSK9i. Applying a goal of 70 mg/dL without requirement for a ≥50% reduction of baseline LDL-C, Cannon et al[32] found a need

for PCSK9i in 16.6% of patients in a mixed ASCVD cohort derived from an administrative database. A recent simulation study found—for the same 70 mg/dL goal—a proportion of 31.9% of patients eligible for PCSK9i, when accounting for an accompanying ≥50% reduction from baseline. If aiming just the absolute 70 mg/dL value, the percentage of eligible patients would decline to 18.3%.[17] The aforementioned studies were based on American College of Cardiology (ACC)/American Heart Association (AHA) guidelines,[33] and more stringent goals have been set by European Society of Cardiology (ESC)/European Society of Atherosclerosis (EAS).[6] According to a Swiss study,[34] eligibility for PCSK9i in order to attain ESC/EAS targets would encompass 51% of the cohort of very high-risk patients, in contrast to only 14% by ACC/AHA guidelines. Regardless of the criteria adopted, the real scenario in Turkey reveals a significant underutilization of PCSK9i.

According to the panelists projections, the proportion of patients attaining LDLc <100 mg/dL at the expense of MTD statins and ezetimibe would be slightly less than that of subjects achieving <100 mg/dL by MTD statins monotherapy. Such projections may have underestimated the real LDLc lowering efficacy of the combination approach. Recently, a randomized open-label non-inferiority trial tested, in patients with ASCVD, the effect of a fixed-dose combination of moderate-intensity rosuvastatin plus ezetimibe, against high-intensity rosuvastatin monotherapy, upon a composite endpoint of stroke, cardiovascular mortality, and myocardial infarction. During a mean 3-year follow-up, there were no significant differences in the primary endpoint between the 2 groups. In contrast, LDLc concentrations <70 mg/dL at 1, 2, and 3 years were observed in 73%, 75%, and 72% of patients in the combination therapy group, and 55%, 60%, and 58% of patients in the high-intensity statin monotherapy group (all $P < .0001$). Moreover, in patients allocated to combination therapy, there was only a 4.8% discontinuation rate, contrasting with the 8.2% discontinuation rate in the monotherapy group ($P < .001$). According to a simulation model spanning a 5-year horizon, approximately 3.7 million and 4.4 million Major Adverse Cardiovascular Events (MACE) were estimated to be averted, across 6 countries over 5 years, by the addition of, respectively, ezetimibe to MTD statin or by the adoption of a fixed-dose combination of statin and ezetimibe, both approaches aimed at the attainment of 2019 ESC/EAS cholesterol-lowering goals.[35] Therefore, efforts must be directed toward favoring, in very high cardiovascular risk cohorts, the upfront combined use of high-potency statins and ezetimibe,[36] ideally in fixed-dose formulations: This yet affordable strategy deserves more attention from physicians and health policymakers.

In conclusion, the authors should be congratulated for their collective brainstorming. Hopefully, their efforts will contribute to improve initiatives aimed at better managing high-risk patients.

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