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Invited Commentary | Cardiology

Statins and LDL-C in Secondary Prevention—So Much Progress, So Far to Go

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Elevated circulating concentrations of low-density lipoproteins have been definitively demonstrated to be a cause of atherosclerotic cardiovascular disease (ASCVD). Increasing recognition is given to the importance of reducing lifetime exposure to low-density lipoprotein cholesterol (LDL-C)[1] according to the rule of "the lower the better," but also "the earlier the better" and "the longer the better." Statin therapy reduces the risk of cardiovascular events by approximately a quarter for each reduction in low-density lipoprotein level of 38.6 mg/dL (1 mmol), and long-term LDL-C reduction (40 years) might even be associated with a reduction of cardiovascular mortality by 50% to 55%. The largest absolute benefits of statin therapy occur in individuals at the greatest risk, such as those who have already experienced an ASCVD event.[2] Taken together, these facts might lead us to expect near-universal coverage of statin therapy in the secondary prevention of ASCVD. However, Yao and colleagues[3] shed light on how and why this is not the case in an actual setting. Their 10-year retrospective cohort study using administrative data from 2007-2016 in the US demonstrated increases in the proportion of secondary prevention patients receiving statins (50.3% to 59.9%) and high-intensity statins (25.0% to 49.2%) during the study period. The proportion of patients adherent to statin therapy also increased, from 58.7% to 70.5%.

It is clear that these trends are all in the right direction, but there is still a very long way to go to obtain the maximum possible health benefits from lipid-lowering therapy. It is especially true after the publication of the European Society of Cardiology/European Atherosclerosis Society 2019 lipid guidelines, which decreased the LDL-C target to less than 55 mg/dL (1.4 mmol/L) for very high-risk patients, and which defined patients with extremely high cardiovascular disease risk as those with a second vascular event within 2 years while receiving maximally tolerated statin therapy, and recommended an LDL-C goal of less than 40 mg/dL (1 mmol/L).[4] This target is unlikely to be achieved without good adherence to maximally tolerated statin therapy, and recent data suggest that the goal of less than 55 mg/dL (1.4 mmol/L) is achieved in only 18% of patients.[5] Thus, to meet these targets, experts have recently proposed initial combination therapy with statins and ezetimibe, or triple therapy with proprotein convertase subtilisin/kexin type 9 inhibitors, especially for patients with high baseline LDL-C levels (in which the predicted extent of LDL-C reduction with statins is unlikely to reach the target) and for those at extreme cardiovascular disease risk with the precise definition of this risk group.[4,6,7]

Of particular concern was the finding by Yao and colleagues[3] that women and ethnic minorities were less likely to receive and adhere to statins. The reasons for these discrepancies need to be explored and addressed as a matter of priority. Cost is probably not a major contributor to these differences. The study included only privately insured and Medicare Advantage patients, which limits the eternal validity of the work but reduces the potential for confounding by expense.[3] In any event, the availability of generic statins led to reductions in the cost of statin therapy during the course of the study, which were far more significant than the corresponding increase in statin use. The same phenomenon has been noted with generic ezetimibe; despite that the cost decreased substantially 3 years ago, it is used by only 15% to 20% of patients with indications for combination therapy.

Could different susceptibilities to statin nonadherence/intolerance explain the differences in the extent of statin use? This question cannot easily be answered from an administrative data set; however, it is clear that further research is needed to determine the risk factors for statin intolerance and how these can be addressed. Yao and colleagues[3] used an algorithm that identified statin intolerance from down-titration or discontinuation of therapy, use of multiple statins, or a diagnosis of adverse effects.

This approach is the most rigorous possible in a retrospective study, but it cannot precisely match clinical definitions of statin intolerance,[8] nor can it be certain to distinguish true intolerance from the "drucebo" effect (whereby symptoms are attributed to statin therapy even when the link is not causal, such as muscle pain resulting from musculoskeletal injury).[9] Identification and careful management of these patients will enable them to benefit from statin therapy, especially because it has been confirmed that as many as 95% of patients reporting muscle pain after statin therapy can still receive statins, and complete statin intolerance is observed in no more than 3 to 5 patients per 100.

A particular strength of this research is the wide-ranging definition of ASCVD used. Use of such a large data set (284 949 patients) allows a broader approach to inclusion criteria than is often achievable in randomized controlled trials.[3] The study included patients with myocardial infarction, angina, revascularization, ischemic stroke, and transient ischemic attack. However, the largest group of participants (composing > 40% of the study population) was patients with peripheral artery disease.[3] This inclusion is important because of observations that patients with peripheral artery disease (PAD) (and polyvascular disease) have a high risk of cardiovascular and all-cause mortality, and that the risk of stroke or myocardial infarction in patients with PAD is equivalent to that of those with coronary disease. Statin use, high-intensity statin use, and statin adherence were all lower in patients with stroke, transient ischemic attack, and PAD than in those with coronary artery disease. This is of particular interest because, according to the recent definition, patients with early acute coronary syndrome with PAD/ or polyvascular disease and not reaching the LDL-C goal despite optimal lipid-lowering therapy are classified as having extremely high cardiovascular risk.[7] Yao et al[3] discussed the possibility that this finding may result from a misperception that patients without coronary heart disease are at lower risk of subsequent ASCVD events, and the fact that most large statin trials recruited a population of coronary heart disease patients. Whatever the reason, this finding illustrates a key area in which statin use might be improved by patient education and clear guidelines for physicians.

The period during which this study was conducted is interesting and might represent the end of the era in which the burden of lipid-lowering therapy in ASCVD was largely on statins alone. Ezetimibe was available during the course of the study (and it would have been interesting to have more data on add-on therapies such as ezetimibe and nutraceuticals) and newer lipid-lowering agents are increasingly available. As such, were this study to be repeated in a further 10 years, the focus on statins without consideration of other drugs would give an incomplete representation of ASCVD risk reduction. Meanwhile, this study demonstrates the enormous potential benefit of more widespread use of statins—and the challenge in achieving that benefit. This study might also convince physicians that in the case of statin nonadherence, intolerance, or both, we should not wait weeks or even months in trying to achieve maximally tolerated statin doses. Instead, we should immediately start combination therapy with ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, and even nutraceuticals to avoid visit-to-visit variability in LDL-C levels and the consequent increased risk of recurrent cardiovascular disease, especially in patients at very high and extreme risk of cardiovascular disease.

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REFERENCES

1. Penson PE, Pirro M, Banach M. LDL-C: lower is better for longer—even at low risk. *BMC Med*. 2020;18(1):320. doi:10.1186/s12916-020-01792-7

2. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388(10059):2532-2561. doi:10.1016/S0140-6736(16)31357-5

3. Yao X, Shah ND, Gersh BJ, Lopez-Jimenez F, Noseworthy PA. Assessment of trends in statin therapy for secondary prevention of atherosclerotic cardiovascular disease in US adults from 2007 to 2016. *JAMA Netw Open*. 2020;3(11):e2025505. doi:10.1001/jamanetworkopen.2020.25505

4. Mach F, Baigent C, Catapano AL, et al; ESC Scientific Document Group. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455

5. Ray KK, Molemans B, Schoonen, WM, et al EU-Wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study. *Eur J Prev Cardiol*. Published online August 28, 2020. doi:10.1093/eurjpc/zwaa047

6. Banach M, Penson PE. What have we learned about lipids and cardiovascular risk from PCSK9 inhibitor outcome trials: ODYSSEY and FOURIER? *Cardiovasc Res*. 2019;115(3):e26-e31. doi:10.1093/cvr/cvy301

7. Solnica B, Sygitowicz G, Sitkiewicz D, et al. 2020 Guidelines of the Polish Society of Laboratory Diagnostics (PSLD) and the Polish Lipid Association (PoLA) on laboratory diagnostics of lipid metabolism disorders. *Arch Med Sci*. 2020;16(2):237-252. doi:10.5114/aoms.2020.93253

8. Banach M, Rizzo M, Toth PP, et al. Statin intolerance: an attempt at a unified definition: position paper from an international lipid expert panel. *Expert Opin Drug Saf*. 2015;14(6):935-955. doi:10.1517/14740338.2015.1039980

9. Penson PE, Mancini GBJ, Toth PP, et al; Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group and International Lipid Expert Panel (ILEP). Introducing the "drucebo" effect in statin therapy: a systematic review of studies comparing reported rates of statin-associated muscle symptoms, under blinded and open-label conditions. *J Cachexia Sarcopenia Muscle*. 2018;9(6):1023-1033. doi:10.1002/jcsm.12344