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Commentary

Low-Density Lipoprotein Cholesterol Treatment Rates in High Risk Patients: More Disappointment Despite Ever More Refined Evidence-Based Guidelines.



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American physicians are now treating dyslipidemia according to a fifth iteration of national guidelines for the use of lipid-lowering therapies [1]. These guidelines are developed with considerable care and deliberation and are, by design, as evidence-based as possible. Specific recommendations are made in order to safely and optimally use pharmacologic interventions to maximize clinical benefit. Since publication of the first Adult Treatment Panel for the Management of Blood Cholesterol, over three decades have elapsed. The association of serum low-density lipoprotein cholesterol (LDL-C) with atherosclerotic cardiovascular disease is one of the most extensively studied and highly established issues in all of medicine [2].

There is unequivocal evidence that the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) significantly reduce ASCVD events (myocardial infarction [MI], stroke, need for revascularization, and mortality) in both primary and secondary prevention settings [3,4]. Moreover, statin therapy is just as beneficial in the elderly with established vascular disease as it is in younger groups of patients [5]. Higher dose statin therapy with greater LDL-C reduction provides additional ASCVD event rate reduction compared to lower dose statin therapy [6]. Other LDL-C lowering agents such as ezetimibe [7] and the proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies [8,9] provide incremental risk reduction when used as adjuvant therapies to background statin use in high risk patients. Despite the great specificity and clarity of guidelines both in the US and in other regions of the world, the appropriate use of lipid-lowering therapies (LLT) is disappointingly and frustratingly low.

Given the incontrovertible strength of evidence, why has this become such a perennial, lasting observation?

1. Impact of adherence and statin titration

There is longstanding evidence that the majority of our patients at highest risk for ASCVD events (i.e., those with established coronary disease and those who have already sustained one or more acute events) are inadequately treated for dyslipidemia. In one recent analysis, only 20% of high risk patients started on a statin are adherent to one after 5 years [10]. An analysis by Rodriguez et al. also showed a 19% adherence rate to statin therapy after 5 years, with less statin persistence among women compared to men [11]. Female sex, identifying as belonging to a non-white ethnic group, older and younger age, and low socioeconomic position are among the most important predictors for low statin adherence [12]. This may explain at least partly why there continues to be disparities in cardiovascular care for women and those identifying as belong to a non-white ethnic group [13,14]. Not surprisingly, reduced adherence to statin therapy correlates with increased risk for ASCVD events and higher healthcare costs in proportion to the lack of adherence [15].

Clinical inertia toward statin titration and an inclination to down titrate are significant problems. In an early study, time to up-titration to maximum statin dose in high risk patients was significantly longer in patients who sustained ASCVD events compared to those who did not [16]. Among very high risk patients initiated on a moderate intensity statin therapy, early up-titration to high intensity is associated with a significantly lower risk of major acute coronary events (MACE) during 2

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years of follow-up compared to no up-titration (Hazard Ratio [HR] 0.76, $P < 0.01$), while delayed up-titration is associated with a smaller non-significant reduction in MACE (HR 0.88, $P = 0.08$); unfortunately, the majority of patients were not up-titrated [17]. When comparing patients with ASCVD adherent to statin $\geq 80\%$ compared to $< 80\%$ of the time, higher adherence correlates with a lower risk of MACE during five years of follow-up (HR 0.51) [18]. Among Asian patients with established ASCVD, statin adherence tertiles track negatively and significantly with risk for recurrent MI and mortality [19]. In both men and women, as well as patients above or below the age of 75 years, tertiles of statin adherence correlate significantly with rising mortality as adherence decreases [20]. Compared to high risk patients with high statin adherence, statin intolerance is associated with a 36% higher rate of recurrent MI and a 43% higher rate of coronary heart disease related events. In patients with a history of carotid revascularization via either endarterectomy or stenting, long-term (5 years) statin adherence is associated with a 25% lower risk for MI, stroke, and mortality [21]. Clearly, for high and very high risk patients, long-term adherence to statin therapy has distinct, measurable benefits for reducing recurrent MI and mortality.

Multiple studies reveal that adoption and application of recommendations by new guidelines is slow and less impactful than one would hope. Although the 2013 American Heart Association/American College of Cardiology (AHA/ACC) blood cholesterol guideline greatly expanded statin eligibility and strongly recommended the use of high dose, high intensity statin therapy for high risk patients, [1] the average serum cholesterol level increased for both men and women in the US between 2012 and 2017 [22]. During this time we also observed an increase in cardiovascular mortality for both men and women. Astonishingly, when comparing data before and after release of the 2013 guideline, statin initiation decreased by 14% and the odds of statin titration decreased by 13%, changes that are opposite to one what would have expected [23]. Some of these changes may at least partly be due to movement away from LDL-C targets and basing treatment more on risk-stratified dosing of statins designed to reduce LDL-C by specific percentages. In another analysis, less than 42% of patients with ASCVD in one health system were treated with high intensity statin therapy as recommended by the 2013 guideline [24]. Finally, in a large practice of cardiologists, only 40% of patients were receiving guideline-specified optimal doses of statins; even the use of prompts in the electronic health record did not stimulate a clinically significant increase in use of optimal statin dosing, even among patients with ASCVD [25].

2. Current view of appropriate use of LLT in high risk patients

In this issue of the *American Journal of Preventive Cardiology*, Baum et al. provide a much more granular analysis of statin usage and attained low-density lipoprotein cholesterol (LDL-C) among patients defined according to the most recent lipid guidelines as high and very-high risk for ASCVD related events in the US. Unfortunately, the findings reveal little to be encouraged about.

This is a very large retrospective cohort study that included just over 4.5 million patients with ASCVD. Approximately 1.5 million patients had ≥ 1 major ASCVD event. Patients included in the study were also retrospectively assessed for whether or not they met criteria for very high risk (VHR) status per the 2018 lipid guideline. The study included data gathered between 2011-2019 and hence is contemporary. Within the US, only 48.8% (\geq major ASCVD event) and 50.2% (VHR ASCVD) of patients were receiving LLT, which is remarkable and leaves one speechless. Among patients with a history of ASCVD, ≥ 1 major ASCVD event, or VHR ASCVD, only 29.8%, 34.9%, and 35.2% of patients had LDL-C < 70 mg/dL, respectively. Approximately one third of patients in each of the risk groups had LDL-C 70-99 mg/dL. Distressingly, approximately 1 in 5 patients had LDL-C values in the range of 100-129 and 1 in 10 had LDL-C values in 130-189 mg/dL range for each of the three risk categories. Approximately 1 in 5 patients had persistently elevated LDL-C

≥ 100 mg/dL despite being treated with maximally tolerated statin and ezetimibe.

Statin were also under-dosed given that these were all high and very high risk patients. Among patients with a history of ASCVD, ≥ 1 major ASCVD event, or VHR ASCVD, only 34.7%, 42.8%, and 42.6% of patients were receiving a high intensity statin, respectively. Combination therapy usage was low, with statin/ezetimibe combination therapy at approximately 4.5% in each of the three risk groups, and statin/PCSK9 combination therapy at 0.8-0.9% in each group. LDL-C goal attainment rates vary widely by state. Low LDL-C goal attainment rates continue to predominate in the upper Midwestern states (rust belt) and those in the South.

3. Opting for another approach

The statistics provided by Baum et al. are stark and puzzling. All of us recognize the importance of statin intolerance. But these numbers reach well beyond any credible estimate of intolerance to statins and others forms of LLT. Clinical inertia appears to be pervasive, not only in terms of statin titration, but also statin initiation, institution of adjuvant therapy with ezetimibe or PCSK9 monoclonal antibodies, and trying other statins when a patient is intolerant of one. Generations of physicians and patients would have given a king's ransom for these drugs before they were introduced. Now they are taken for granted and even discredited. This is tragic as LLT is life saving and reduces suffering, disability, and premature death. Guidelines are also clearly not being followed by a substantial percentage of healthcare providers. The utilization of nonstatin drugs is distressingly low despite the fact that ezetimibe and the PCSK9s have outcomes data. These are issues that do not simply encompass cost or tolerability; failure to treat appropriately has become pervasive with no signs of improvement over time. Failure to lower LDL-C appropriately unnecessarily leaves significant residual risk on the table, risk that can make the difference between having another MI or requiring yet another stent to sustain myocardial viability.

Perhaps it is time to change the view of LDL-C. LDL-C is the end product of lipoprotein metabolism. Its precursors, very low-density lipoprotein and intermediate density lipoprotein, are reservoirs of oxidizable substrate (triglycerides, fatty acids). LDL is highly concentrated with cholesterol. The histologic components of arterial walls cannot catabolize cholesterol. The assumption is that LDL distributes this cholesterol as a vital regulator of cell membrane fluidity or is an important donor of cholesterol to steroidogenic tissues. All somatic cells have the capacity to produce their own cholesterol. When thinking about LDL-C reduction, the question is rarely about whether we lower it too much, since as made abundantly clear above, the tendency is to lower it too little, leaving patients vulnerable to the progression of disease and acute ASCVD related events. Among statin users, the relationship between attained LDL-C and risk for a CHD event is linear from 25-200 mg/dL [26]. There does not appear to be a lower limit, as even going below 10 mg/dL shows incremental risk reduction without evidence of hazard over a median of 2.2 years of follow-up [8].

LDL particles are a waste product of metabolism and a vascular toxin. On an evolutionary time scale, we were never meant to have the LDL-C levels we currently harbor. Given the global epidemic of ASCVD, LDL-C levels in the average person are most certainly too high. A truly physiologic, nonpathogenic LDL-C level is likely around 40 mg/dL, given that this is the point on the y-axis of a log-linear plot where the hazard ratio for an acute coronary syndrome equals 1, meaning no excess hazard [27]. Based on the principles of toxicology, the more efficiently and completely you remove a toxin from a biological system, the lower the toxicity and the higher the survival. This is precisely what we observe with LDL-reduction studies. This is also echoed by genome-wide association and mendelian inheritance studies: any genetic polymorphism that lowers LDL-C correlates with reduced risk for ASCVD; on the contrary, any genetic polymorphism that induces an elevation in LDL-C correlates with heightened risk for ASCVD [28,29]. It makes a great deal sense to

think of LDL-C toxicity in terms of exposure to x units over y periods of time, giving one a sense of relative risk [29]. The higher the product of x and y , the greater the risk. It thereby makes sense to reduce exposure by as much and as early as possible to reduce the hazard of progressive and inexorable vascular injury and keep patients below their clinical event horizon [30].

By undertreating patients with inadequate doses of statins and underutilizing adjuvant LLTs, physicians are leaving high risk patients susceptible to atherosclerotic plaque progression, plaque inflammation and instability, and acute cardiovascular events. LDL-C levels ≥ 70 mg/dL leads to both vulnerable plaques and vulnerable patients. In the world of cardiovascular disease prevention, it is vital that we rid the system of its most potent toxin: LDL-C, a metabolite responsible for the death and disability of more people than any other known product of human physiology.

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