Cholesterol and Atherosclerotic Cardiovascular Disease: A Lifelong Problem

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The observational evidence supporting the importance of lifelong exposure to elevated low-density lipoprotein (LDL) cholesterol levels as a cause of atherosclerotic cardiovascular disease (ASCVD) has become overwhelming. The original observation of the relationship of elevated blood cholesterol to future ASCVD came from epidemiological studies such as the Framingham Heart Study. Subsequent research, using epidemiological, genetic, basic science, and subclinical atherosclerosis imaging methodology, consistently show relationships of cholesterol levels to both atherosclerosis development and regression.[1,2] Most compelling are studies that (1) directly link observed atherosclerosis postmortem in young people, to cholesterol levels measured either premortem or postmortem, (2) genetic studies using Mendelian randomization techniques and showing a linear relationship between lifelong exposure to differences in cholesterol levels to ASCVD risk, and (3) longitudinal epidemiological studies that link early-life exposures to subclinical atherosclerosis later in life independent of later-life risk-factor levels.[3–5]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Duncan et al apply the technique of trajectory analysis to a more-contemporary cohort of the Framingham Heart Study, followed for 35 years to determine the relationship of lifelong exposure to elevated LDL cholesterol and low high-density lipoprotein cholesterol to ASCVD and total mortality.[6] For LDL cholesterol, they identified 5 different trajectory groups: consistently low or optimal, consistently borderline, and 3 groups with increasingly elevated cholesterol early in the observation period and declining values over time, attributed to statin treatment. ASCVD event rates were 5 times as high and all-cause mortality 4 times as high in the highest LDL cholesterol trajectory group compared with the optimal LDL cholesterol exposure group. The 2 largest groups, ≈70% of the total cohort, were those with lifelong borderline LDL cholesterol values and those with slightly elevated values that declined over time. Their ASCVD rates were 3 to 4 times that of those with lifelong low LDL cholesterol. Statin use was 7% in the optimal group, 24% in the borderline group, 46% in the elevated and decreasing group, and 91% in the highest group. Consistent with many other Framingham analyses, high-density lipoprotein cholesterol strongly predicted outcomes.

The methods used by Duncan et al take advantage of a unique modeling method, trajectory analyses, paired with a detailed investigation of how statistical differences in the modeling strategy may impact their findings.[6] Their findings were robust to methodology and consistently demonstrated that higher long-term LDL cholesterol and non-high-density lipoprotein cholesterol concentrations are associated with increased ASCVD risk. Interestingly, the decrease in lipid levels in older ages almost entirely reflects increased use of lipid-lowering medications, given that trajectories among untreated participants remained stable. Trajectories in this cohort started at a mean age of around 45 years. However, future studies are needed among younger individuals given that trajectories of lipid levels at younger ages may reflect a more-variable pattern of development and may also provide greater guidance in identifying high-risk individuals. Although no relationships were found for triglycerides with ASCVD, the high intrinsic variability of this measure may limit its use in this type of analysis. Although trajectories were at least as predictive of ASCVD events as other methods of lipid measurement, earlier life trajectories may have greater predictive ability than single measures of lipids given the changes in lipid levels in adolescence and early in adulthood.

These and other advanced statistical modeling techniques, using imputation and trajectory modeling to integrate findings from observational cohorts that span the life course, have produced similar results. Zhang et al have shown that

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early-life exposure to elevated LDL cholesterol predicts future ASCVD independent of later-life exposures.[7] In the CARDIA (Coronary Artery Risk Development in Young Adults) study, risk factors measured 15 to 25 years preceding coronary artery calcium measurement are better predictors of coronary artery calcium score, suggesting that the ability of coronary artery calcium to reclassify ASCVD risk may be, in part, related to it being a measure of chronic risk exposure.[8]

Observational studies using trajectory methodology provide new and important insights into our understanding of true prevention of ASCVD, beyond recapitulating the obvious, high LDL cholesterol is bad for you. These methods provide the opportunity to integrate multiple aspects of lifetime patterns—starting levels, slope, and cumulative exposure (area under the curve)—into our understanding of how longitudinal lipid patterns influence risk. Although participants enrolled in these studies likely benefitted from statin treatment, and other secular trends that have led to declining cholesterol levels in the United States over time, event rates remain dramatically higher in all trajectory groups other than the one with lifelong low cholesterol levels, remarkably similar findings to Mendelian randomization studies. Importantly, in this analysis, statins were initiated as primary prevention given that all individuals with prevalent cardiovascular disease preceding exam 8 were excluded from the trajectory analyses. Furthermore, even though statin-use rates are high in the higher LDL cholesterol groups, this usage does not bring event rates down to those observed in the trajectory group with the lowest lifelong cholesterol levels, potentially attributed to pretreatment exposure to elevated cholesterol levels; it is safe to say that statins, as currently used, are not providing maximal impact as preventive treatments.

Although clinical trials provide the highest level of evidence for the value of cholesterol lowering, outcomes of these studies suggest that these interventions may be too little too late. Lipid-lowering trials tend to be conducted in high-risk populations so that differences in event rates can be detected over relatively short time intervals. However, the event rates achieved in these trials with more-intense interventions remain remarkably high compared with those with lifelong low LDL cholesterol.[9] For example, the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trial was "successful" by showing a significant reduction in recurrent coronary events (34–32%) in those receiving both ezetimibe and simvastatin compared with those on simvastatin alone over 6 years of follow-up.[10] For an individual patient, after taking ezetimibe for 6 years, the "benefit" was a 2% lower rate of recurrent cardiovascular disease, hardly clinically meaningful. Guidelines rely on these trials for prevention recommendations regarding lipid lowering, but, in fact, they provide little guidance for younger individuals at high lifetime risk.

Epidemiological studies using trajectory analyses, and Mendelian randomization studies, suggest that the benchmark for event rates for successful ASCVD prevention should not be limited to statistically significant outcomes from randomized trials. Rather, we should start to consider ASCVD rates from low-risk trajectory groups and Mendelian randomization studies as the benchmark. Trials should consider not only statistically significant reductions in event rates, but also determine how close achieved outcomes come to results that are optimal for meaningful control populations.

Meta-analyses of clinical trials provide important information about the value of statins for prevention of ASCVD not reported in the original trials. The greatest benefit from statin treatment occurs in the youngest patients enrolled with the highest lifetime risk and the highest study entry levels of LDL cholesterol.[11,12] Thus, the greatest benefit from initiation of lipid lowering earlier in life would be achieved from the trajectory groups identified by Duncan et al with the highest long-term risk. For these higher-risk groups, familial hypercholesterolemia provides a natural experiment for the importance of earlier introduction of lipid-lowering therapy. Outcomes in familial hypercholesterolemia are directly related to years of exposure to elevated LDL cholesterol exposure.[13] Theoretical models, and outcomes data comparing ASCVD rates in statin treated children with their parents suggest the optimal timing of lipid-lowering therapy for this condition is to begin at around 10 years of age. In The Netherlands, testing of first-degree family members of those with familial hypercholesterolemia resulted in the identification of a large number of untreated affected individuals and a subsequent substantial reduction in ASCVD rates compared with untreated individuals.[14]

The reports of Duncan et al and Zhang et al, in effect, close the loop that began with observational epidemiology studies that began patient recruitment 70 years ago. These studies use contemporary observational epidemiology tools to demonstrate not only the importance of elevated LDL cholesterol as a lifelong risk factor, but also call attention to the fact that the optimal time for intervention to lower LDL cholesterol is not later in life when atherosclerosis is already advanced, but earlier in life, at a time when the atherosclerotic process is less advanced and more likely to be reversed.[1]

Disclosures

Dr Gidding is the Medical Director of the Familial Hypercholesterolemia Foundation. Dr Allen has no disclosures to report.

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