Statins: effectiveness, safety, and common myths on their role in ASCVD prevention

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Atherosclerotic cardiovascular disease (ASCVD) is one of the few chronic diseases for which we have a clear, causative factor that can be targeted therapeutically to reduce long-term risk. The strength of evidence from genetic, randomized, and observational data all points in the same direction: ASCVD is caused by circulating, cholesterol-carrying, apolipoprotein B (apoB)-containing lipoprotein particles, which above certain threshold concentrations have the ability to leave plasma, pass through the arterial endothelial lining and enter the underlying intima layer, where atherogenesis occurs. Reducing apoB particle numbers can thus drastically slow disease progression. Of the various pharmacological treatments now available for reducing circulating apoB particles, one of the earliest classes of drugs to be developed remains one of the most effective (and affordable) options – statins.

Cholesterol, lipoproteins, and the genesis of ASCVD

High cholesterol is often implicated in the cause of ASCVD, but this explanation is oversimplified and not entirely correct. Cholesterol is a necessary lipid for cells to maintain fluid cell membranes. Even though every cell in the body, with the exception of red blood cells, can synthesize cholesterol, most of the circulating cholesterol in the body is produced by the liver and intestinal cells and is transported via the circulatory system from these organs to the rest of the body. However, like all lipids (fats), cholesterol is *insoluble* in water-based plasma and needs a hydrophilic peptide (a so-called apoprotein) to enwrap and transport the lipids in particles called lipoproteins. Though various classes of lipoproteins exist, only those containing

apoB, short for apolipoprotein B, can enter, aggregate, and be oxidized within an arterial wall, which in turn promotes an inflammatory response, the development of plaques, and thus, ASCVD.

Low-density lipoproteins (LDLs), each of which has a single apoB molecule, make up 90-95% of all apoB-containing lipoprotein particles due to their prolonged plasma residence time relative to other apoB particles, and therefore, LDL cholesterol (LDL-C) is frequently used to estimate apoB. Of note, chylomicron remnants, very low-density lipoprotein, intermediate-density lipoprotein, and lipoprotein (a) particles also each contain a single molecule of apoB, and as such, LDL-C is an underestimation of the total atherosclerotic burden, and plasma apoB concentration is a more direct measure of the number of circulating atherogenic lipoproteins. However, as most standard lipid panels and clinical trials for ASCVD therapies report LDL-C rather than apoB concentration, we will refer mainly to the LDL-C metric through this newsletter.

How do statins help?

In the U.S., 90% of people (the 5th to 95th percentiles) have an LDL-C between 54 and 177 mg/dL, but by standard medical practice, an LDL-C concentration of <100 mg/dL is considered "optimal" in the absence of other risk factors. Without other comorbidities, pharmacological interventions, including statins, are not usually prescribed until LDL-C levels are classified as "high" – that is, when concentrations persistently exceed 160 mg/dL in a patient who is at least 40 years old. However, *all* of these benchmark values and reference ranges exceed the amount of LDL-C that is *necessary* for the body to function optimally, as LDL-C concentrations of just 20-30 mg/dL have been shown to be sufficient for good health. In other words, LDL-C concentration in most humans vastly exceeds the biological need, which is one of the reasons the development of ASCVD is inevitable if you live long enough. Even LDL-C levels in the "optimal" range of up to 100 mg/dL, can be associated with subclinical ASCVD, which is part of why I tend to be relatively aggressive in reducing LDL-C, which sometimes includes statins as part of the treatment.

Statins reduce the amount of circulating apoB through the inhibition of hepatic (liver) cholesterol synthesis. The reduction of intracellular hepatic cholesterol upregulates the expression of the LDL receptor (LDL-R), the receptor by which LDL particles are removed from circulation. Thus, increasing LDL-R expression increases LDL clearance from plasma, thereby reducing the concentration of circulating apoB particles. In other words, statins exert their effect indirectly on LDL clearance by "tricking" the liver into thinking more cholesterol is needed, such that the liver pulls in more LDL from the plasma.

Outcomes of major statin trials

Seven statin medications currently have approval from the Food and Drug Administration for LDL reduction: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

Many landmark randomized controlled trials (a selection of which are summarized in the table below) have shown statins to be effective in reducing the risk of all-cause mortality (ACM) and major adverse cardiovascular events or MACE (i.e., heart attack, stroke, and cardiovascular death). The earliest of these clinical trials used statins for secondary prevention – that is, preventing a second major cardiac event in patients with a history of coronary artery disease. Studies in these populations (e.g., 4S, CARE, LIPID trials) are done in part because they are more expeditious – those who have already had MACE are likely to have a second event faster than a general population without a history of CVD, so trials can be shorter because a difference between test groups is likely to become apparent sooner. But this doesn't mean that results from secondary prevention trials are only relevant for those who have already had heart attacks or strokes. Results from these trials are meant to be extrapolated to provide clues about efficacy in a general population. Indeed, primary prevention studies (the first being WOSCOPS and AFCAPS-TexCAPS) have demonstrated that statin use also reduces the risk of MACE in study populations *without* a history of CVD.

Table: Summary of Results from Landmark Statin Outcome Trials

Prevention	Trial	Statin (Dose)	Follow-Up (years)	Risk Reduction for CV & Mortality Outcomes (ARR)
Secondary	4S	Simvastatin (20-40 mg/day)	5.4	ACM: 3.3% MACE: 6.7%
	CARE	Pravastatin (40 mg/day)	5	ACM: 3.1%Nonfatal MI & fatal CAD: 3.0%
	LIPID	Pravastatin(40 mg/day)	6.1	ACM: 3.1%
Primary & Secondary	HPS	Simvastatin (40 mg/day)	5	ACM: 1.8% MACE*: 5.4%
Primary	WOSCOPS	Pravastatin (40 mg/day)	4.9	ACM: 0.9% Nonfatal MI & fatal CAD: 2.4% CV mortality: 0.7%
	AFCAPS	Lovastatin (20-40 mg/day)	5.2	MACE: 4.1%
	ASCOT-LLA	Atorvastatin (10 mg/day)	3.3	Nonfatal MI & fatal CAD: 1.1% Total coronary events: 1.4%
	JUPITER	Rosuvastatin(20 mg/day)	1.9	MACE: 0.6%

Abbreviations: ARR (Absolute Risk Reduction); ACM (All-Cause Mortality); MACE (Major Adverse Cardiac Events); MI (Myocardial Infarction); CAD (Coronary Artery Disease)
*Includes revascularizations

Of note, first-time MACE tend to have lower mortality than subsequent events thanks to remarkable advances in cardiac life support (e.g., clot-targeting medications, stents, AEDs), so, in contrast to secondary prevention trials, primary prevention trials don't tend to show large magnitudes of improved mortality. However, the benefit of reduced mortality demonstrated in the secondary prevention trials is by extension also granted to those who prevent or postpone a first MACE in primary prevention.

To those who are unfamiliar with clinical literature, the numbers reported in the studies listed above might not seem all that impressive. What does it actually mean to have a 3% absolute risk reduction for ACM over a 5-year trial? It means that for every 33 patients treated with statins for 5 years, there is one fewer death. In other words, the "number needed to treat" (NNT) is remarkably low. But even this estimate simply reflects the risk reduction on a *population* level for a particular statin at a particular dose, which will have varying degrees of efficacy in different individuals. An *individual* can further reduce their risk by optimizing the treatment protocol for their own circumstances, perhaps by using more aggressive dosages.

Similarly, while these large clinical trials are generally conducted in older adults, individuals in non-trial settings have the option to start lowering their LDL-C earlier in life – further enhancing the benefits of these medications.

The benefits of starting statin therapy early

Though it is the current standard medical practice to prescribe statins only when an otherwise healthy patient already has high LDL cholesterol (LDL-C >160 mg/dL), there are substantial benefits to using lipid-lowering therapies before this threshold is reached. An individual who achieves an LDL-C of 75 mg/dL after decades of creeping up to a peak of 160 mg/dL is still at far greater ASCVD risk than an individual who has *always* been at 75 mg/dL. Why? Because the progression of ASCVD is a function of *both* apoB concentration *and* duration of exposure. It's not unlike smoking, where we determine risk by both the number of packs smoked per day and the duration of smoking, reported as pack-years.

The lipid-lowering effect of statins is a slow but steady wane with time, with a decrease in reduction by approximately 8 mg/dL by year six of treatment. (This may be explained by the upward drift of LDL-C we see in aging.) In clinical trials, statin-treated patients achieve the greatest reductions in LDL-C during the first year of statin therapy, after which point the difference between statin-treated groups and placebo groups starts to mildly degrade. If cardiovascular risk were dependent only on absolute apoB particle concentrations at any single point in time, we would expect that CV risk would likewise be lowest during the first year of statin treatment and would increase thereafter in parallel with LDL-C levels.

But a 2022 meta-analysis of statin trials demonstrated quite the opposite, reporting a reduction in MACE risk by 12% for every 38.7 mg/dL reduction of LDL-C at one year of follow-up and a *29%* risk reduction at seven years of follow-up, despite an average 15 mg/dL higher LDL-C levels at year seven than at year one. The most logical explanation for this reduction in risk with longer durations of statin use – despite increasing LDL-C – is that the effects of high apoB (or LDL) levels on ASCVD risk *compound over time*. This conclusion is further supported by Mendelian randomization studies, which have shown that those with a genetic predisposition to lower LDL levels over a lifetime have a significantly reduced risk of ASCVD. Some data suggest that a 38.7 mg/dL reduction in LDL-C over 40 years is associated with a reduction in CV mortality of up to 50%.

The myth of statin inefficacy

Despite evidence to the contrary, some persist in promoting the myth that statins aren't effective in reducing ASCVD risk. These critics generally don't deny that this class of medication effectively reduces circulating LDL levels – rather, they argue that LDL reduction is *itself* not an effective means of lowering cardiovascular risk. The studies we summarized above represent only a small fraction of the evidence supporting statin efficacy and the importance of lowering apoB concentration for reducing ASCVD risk, so on what basis do these critics make their arguments?

Statin naysayers often point to a handful of randomized studies and meta-analyses that report, at best, modest effects of statins on ASCVD risk. But a closer look at these analyses typically reveals significant flaws. As we've seen, ASCVD risk is related to the *interaction of exposure to apoB particles and time*, so differences in clinical outcomes between a statin group and a placebo group are more likely to reach significance in studies employing aggressive statin protocols (i.e., inducing large LDL-C reductions) over a long duration and in a large pool of subjects. Randomized trials are costly to conduct, so their durations are generally kept relatively short (<5 years) – too little time to see significant changes in CV risk if reductions in LDL-C are small, as they often are in the studies cited by statin critics.

Additionally, many studies and meta-analyses rely on LDL-C to estimate ASCVD risk in place of more accurate metrics. Although LDL-C is commonly included in standard lipid panels, the true determinant of atherosclerosis progression is the *number* of atherogenic particles, not their cholesterol content, which varies across particles. Further, LDL-C levels do not consider other classes of atherogenic apoB-containing lipoproteins – very low-density lipoproteins (VLDLs) and chylomicron remnants. Thus, LDL-C may be expeditious as the metric of interest but does not reflect ASCVD risk as accurately as measuring apoB concentration directly. Although the two metrics have a high correlation, they can in some cases be widely discordant, potentially resulting in misleading findings when relying solely on LDL-C.

In denying the harmful effects of apoB, statin critics also point to epidemiological data to argue that any apparent relationship between ASCVD incidence and statin is instead attributable to other covariates, including poor diet, lack of exercise, stress, socioeconomic status, and limited access to healthcare. And it's true – the risk of ASCVD is an accumulation of all of these factors, and the risk of ASCVD can be additionally reduced through other preventative measures such as diet and exercise, but, for most of the population, statins are a far more potent tool to reduce LDL-C, and anti-statin proponents often cherry-pick data to support their position that lifestyle changes are more important.

For instance, critics point to a study of hospitalizations of nearly 137,000 patients who happened to have existing coronary artery disease. The average LDL-C level upon admission was 104.9 mg/dL, well below the threshold of "high" LDL-C concentrations that would indicate statin initiation and only 21.1% of these patients were on lipid-lowering therapy. Since these patients were hospitalized with coexisting CAD despite having an average LDL-C just barely above the "optimal" range, you might conclude prematurely LDL does not play a large role in driving heart disease and that LDL-lowering therapies would therefore not have been helpful in these patients. However, as noted earlier, the "optimal" range is only for those without comorbidities. When it comes to high-risk patients, the target LDL-C level is <70 mg/dL – significantly lower than the average LDL-C measured in this study's patients. The majority of these participants would indeed be considered very high risk – 45.6% had documented prior CAD, other atherosclerotic vascular diseases, or diabetes; 35.5% had a history of hyperlipidemia; and 54.2% had hypertension. So while this population likely would greatly benefit from concurrent lifestyle changes, they also would have likely benefited from a pharmacological lowering of their LDL-C to a target range more appropriate for high-risk patients.

The criteria for determining causality in medicine is almost prohibitively high, so it should not be taken lightly that consistent, reproducible, high-grade evidence has demonstrated that LDL *causes* ASCVD. While any single randomized trial would be insufficient evidence to determine causality, a pooled analysis of 26 trials with more than 170,000 patients demonstrated that for every 38.7 mg/dL reduction in LDL-C, there was a log-linear 22% proportional reduction in the risk of MACE. The randomized trial data are concordant with the data reported by meta-analyses that include more than 800,000 participants from large, prospective, epidemiologic studies.

The strongest supportive evidence comes from Mendelian randomization (MR) studies on the 50+ genes associated with LDL-C. These studies consistently demonstrate that individuals who have the variants associated with lower LDL-C also have correspondingly lower rates of MACE. Some MR studies have observed up to a 54% risk reduction for every 1 mmol/L (38.7 mg/dL) reduction in LDL-C, suggesting that a lifetime of lower exposure has compounding effects on risk. The evidence from the randomized trials and genetic studies together indicate the absolute magnitude of exposure to plasma LDL-C determines the risk of ASCVD *and* the reduction in risk is independent of *how* LDL is lowered.

Despite the consensus that LDL is a *causative* factor in the development of ASCVD, there are still voices who insist that the role of cholesterol in cardiovascular disease is exaggerated and that the utility of statins is likewise falsely inflated in reducing the risk of ASCVD.

Critics of statins and other apoB lowering therapies conveniently never mention other evidence of apoB as a causative factor in the development of ASCVD, such as the insights gained from cases of familial hypercholesterolemia (FH), a heritable condition of markedly elevated levels of LDL-C and premature atherosclerosis, especially coronary artery disease. Compared to the general population, patients with untreated FH have a 20 times higher risk of developing CAD and approximately a 25-fold increase in the risk of having a heart attack before the age of 60. When FH is recognized and treated, usually with aggressive statin (and now PCSK9 inhibitor) therapy, the relative risk of heart attack has been shown to drop by 76% – not significantly different from the level of the general population, and FH patients on statins show significantly better event-free survival than FH patients without treatment. In untreated men and women with heterozygous FH, it is estimated that 50% will develop ASCVD before the ages of 50 and 60, respectively. Those without FH can still have risk factors such as hypertension, diabetes, smoking, and high apoB, but non-FH men with two or more of these major risk factors had a lifetime risk of 37.5% of fatal CAD or nonfatal MI (even lower in women at 18.3%). Similarly to secondary prevention trials, we can extrapolate what we know about high LDL-C in the general population from those who are genetically predisposed to a lifetime of high apoB.

Statin safety and side effects

Though evidence indicates the positive effects of statins compound over time, some are understandably hesitant to use these medications over long time periods due to concerns over side effects and safety. But contrary to these fears, the side effect profiles of statins are

generally mild, and randomized controlled trials have demonstrated that these medications are safe as a lipid-lowering therapy, though we must rely instead on observational studies for evidence of long-term safety.

Like any medication, statins are not completely without possible adverse effects, including gastrointestinal distress, brain fog, and dose-related muscle pain. The most common side effect, muscle pain, has a variety of causes, and in a meta-analysis of randomized controlled trials, there was around a 7% relative increase in this symptom between the control and intervention groups during the first year, corresponding to an absolute additional rate of muscle pain or weakness of 11 events per 1000 person-years. After the first year, the statin groups showed no increase in muscle-related symptoms compared to the control groups. More potent statins, such as atorvastatin or rosuvastatin, had slightly higher rates compared to more moderate or less potent statins. Depending on the severity of symptoms, switching to a nonstatin therapy, a statin with lower rates of adverse effects, or a lower dose statin (with a combination of other LDL-lowering medications) may be an option. Several alternative therapeutic options to statins – such as PCSK-9 inhibitors or bempedoic acid – are also effective in combatting high LDL.

Other more serious side effects include rhabdomyolysis, elevated liver enzymes, and the development of type 2 diabetes. Rhabdomyolysis is a severe condition that causes skeletal muscle breakdown, and in such cases, statin use should be discontinued. Less than 0.05% of patients on statins develop rhabdomyolysis, but concurrent use of certain antibiotics or other drugs such as fibrates increases this risk. Statin therapy is associated with elevated hepatic transaminases in anywhere from 1-3% of patients. Most of these cases are asymptomatic and do not require discontinuation of therapy; however, statin use in patients with acute liver disease is contraindicated for this reason.

Elevated blood glucose is another possible side effect of statin use, and the onset or progression of type 2 diabetes is another reported effect of statins. The exact mechanism for this development is not currently known, but there are several pathways of glucose metabolism that may be affected. The excess risk of new-onset type 2 diabetes from any statin is estimated to be 9-12% higher when compared to placebo, and in large meta-analyses, this outcome is a moderate effect. However, the risk of new-onset diabetes is statin-specific: atorvastatin, rosuvastatin, and simvastatin have reported dose-dependent excess risks from 10% to upwards of 40% depending on the study. Some of the variability between risks reported is due to heterogeneity in statin dose and duration of treatment, as well as the population itself – one of the strongest risk factors for a new diagnosis was metabolic syndrome or pre-diabetes at baseline. In other words, those most likely to be pushed over the edge already had some degree of metabolic dysfunction.

Understanding the effects of statins on glycemic control is useful guidance for statin selection in individuals with pre-existing T2D or prediabetes, since the degree of change in glycemic control is statin-dependent, with some statins having no association with any risk of new-onset T2D. However, it is important to note that, despite the importance of metabolic health, the risks of statins for glycemia control are still small compared to risks of elevated cholesterol levels, and the cardiovascular benefits of lipid management outweigh the risk of T2D for most patients.

That said, of all the side effects of statins, this one is probably the most difficult to pinpoint because of the many factors that increase insulin resistance and deteriorate glycemic control (e.g., weight gain, reduction in activity, poor sleep, the aging process itself). In our practice, we rely on continuous glucose monitors as a tool to monitor changes in glycemic control as a harbinger of statin-induced insulin resistance. (For more information on statins and diabetes risk, keep an eye out for the upcoming AMA #53, which will cover this topic in greater depth.)

Statins: an effective defense against ASCVD

Heart disease is the leading cause of death for both men and women in the United States, but the irony is that it is also one of the few chronic diseases from which death is almost entirely preventable by managing three things: blood pressure, smoking, and apoB. We have multiple classes of highly effective drugs capable of reducing apoB particle concentration and nearly halting ASCVD progression altogether, and among those classes, statins remain the first line of defense.

So why is cardiovascular disease still a perennial top killer, in both men and women, in the US and globally? One reason is the lack of perceptible symptoms in the early stages of the disease, with warning signs coming only when we have our lipid levels tested, underscoring the importance of doing so early and often. But a second reason is that even when lab tests do reveal elevated LDL-C or better yet apoB concentration, in many cases, we don't respond by using those effective drugs at our disposal. In standard medical practice, the decision for how to treat high levels of apoB rests on short-term, 10-year risk models. These models unsurprisingly can only estimate risk in patients over the age of 40, as a 10-year risk of ASCVD will be immeasurably low in a 35-year-old with elevated apoB. But that same 35-year-old left untreated will be at a higher *lifetime* risk of ASCVD.

Public health recommendations against smoking are a noteworthy example of how we could be better at treating known causative risk factors. Smoking is a known *causative* risk of lung cancer, and as such, large-scale efforts have been made toward discouraging picking up the habit in the first place and toward helping those who do smoke to quit as soon as possible. Even though a 35-year-old smoker is unlikely to get lung cancer in their next decade of life, we don't tell them it's okay to smoke for twenty years and then quit, because even former smokers are at a higher risk for lung cancer than never-smokers. The same idea is true for apoB. Treating elevated apoB earlier in life lowers the cumulative exposure to atherogenic particles, and thus lowering *lifetime* risk of ASCVD.

While the advice to modify diet, stop smoking, reduce blood pressure, increase exercise, and reduce stress can certainly all improve heart health, these measures typically aren't enough to eliminate the risk of ASCVD mortality in those with high apoB. They are equivalent to the idiomatic knife in a gunfight, and with heart disease accounting for nearly 700,000 annual deaths in the U.S., clearly, this opponent comes with considerable firepower, so shouldn't we defend ourselves accordingly? When it comes to avoiding MACE and CVD mortality, statins are one element of armor that we have available – one that is more effective the earlier we use it. Even critics pointing to flawed, cherry-picked studies mostly argue that these medications are

simply less effective than most evidence suggests – *not* that they provide no benefit at all, and after decades of widespread statin use, evidence continues to indicate that they are safe and that side effects are relatively rare.

ASCVD is a powerful enemy with which we must all contend. We are fortunate to have an equally powerful defense in the many approved lipid-lowering medications, of which statins are an effective and affordable class.

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