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Review Article

Statin Update: Intolerance, Benefit, and Beyond

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Abstract

Statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors) comprise a class of lipid-lowering therapy (LLT) with demonstrated effects on reducing cholesterol synthesis so that less very low-density lipoprotein cholesterol (LDL-C) are secreted into plasma by the liver, ultimately reducing the concentration of plasma LDL-C. An additional effect of statins is upregulation of sterol regulatory element-binding protein 2, upregulation of this protein increases the density of LDL-receptors on the cell surface of hepatocytes and causes greater clearance of LDL-C. Therefore, because statins reduce the creation and increase the clearance of a family of atherogenic particles (particularly LDL-C), there is a clear biologic rationale for the reduction in atherosclerotic cardiovascular disease (ASCVD) events shown in multiple large-scale clinical trials. This makes statins well-suited as the base of therapy in the prevention and treatment of ASCVD. Real and perceived intolerance is the greatest detractor of statins from the potential public health benefits of broad-scale use. Up to one-third of patients who are prescribed statins fail to take them over the long-term and thus derive no benefit. About half of these patients have "perceived statin intolerance," in which they believe they have stain intolerance due to conflated chronic symptoms or concern for adverse effects. Randomized, placebo-controlled blinded trials including such patients demonstrate that approximately 85% can, in fact, tolerate a statin during the blinded period. The other half of the statin-intolerant population is believed to have "real statin-intolerance" due to reproducible legitimate adverse effects such as myalgias, increases in hepatic transaminases, and malaise; there is a pharmacoepidemiologic explanation for this 15% of the patient population. The full public health benefit of statins can only be accomplished through improved patient education and public awareness. This paper will provide an update on statins and their position in clinical lipidology, especially given advances in other forms of LLT.

Key words: Cardiovascular death, intolerance, lipids, low-density lipoprotein cholesterol, myalgia, myocardial infarction, statin, stroke

Introduction

Statins, also known as 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are a class of lipid-lowering therapy (LLT) that has proven effects in reducing the synthesis of cholesterol and as a result, less very low-density lipoprotein cholesterol (VLDL-C) is secreted by the liver into plasma.[1] With less VLDL, there is less conversion to intermediate density lipoprotein (IDL) cholesterol and ultimately LDL-C. Thus, on average, administration of moderate intensity statins can result in a 30–50% reduction in LDL-C; similarly, high-intensity statins can result in a >50% reduction.[2] In addition, statins upregulate sterol-regulatory element binding protein-2 transcription factors, increasing the density of LDL receptors (LDL-R) on the cell surface of hepatocytes allowing for greater clearance of LDL-C.[3]

There are several explanations for why some patients may have a lower than expected reduction in LDL-C. First and foremost, high intake of dietary saturated fat, which stimulates the production of VLDL can partially negate the statin effect on LDL-C.[4] There are known gain-of-function mutations of HMG-CoA-reductase which render statins less effective.[5-8] Patients with normal alleles for LDL-R stand to have the greatest LDL-C reduction and conversely, those with polymorphisms for this complex 839 amino acid protein receptor are likely to have less LDL-C clearance and less of a statin

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benefit. This form of familial hypercholesterolemia (FH) is an important clinical condition to consider when the treated LDL-C remains >145 mg/dl. Other forms of heterozygous FH (HeFH) can result in defects in the production of apoprotein B-100 (apoB), the signal protein on VLDL, IDL, and LDL.[9] Rarely, HeFH can result from a gain-of-function mutation for proprotein convertase subtilisin kexin-9 (PCSK-9), which regulates the density of LDL-R on the hepatocyte surface.

Thus, by reducing the production of a family of atherogenic particles – particularly LDL-C – and increasing its clearance, statins have a strong biologic rationale for the reduction in atherosclerotic cardiovascular disease (ASCVD) events demonstrated in a multitude of large-scale clinical trials. This supports statins as the base of therapy in the prevention and treatment of ASCVD as well as additional therapy as indicated.

Statin Intolerance

The single greatest detractor to statin use and its observed benefit is statin-intolerance. A unified definition of statin intolerance has been proposed: The inability to tolerate at least two different statins – one statin at the lowest starting average daily dose and the other statin at any dose.[10,11] In addition, this statin intolerance should meet these additional conditions: (1) Characterized by inability to use statins due to significant symptoms and/or biomarker abnormalities which can be temporally attributed to the initiation or dose escalation of statins, supported with appropriate drug withdrawal and rechallenge; (2) either "complete" (intolerant to any statin at any dose) or "partial" (intolerant to some statins at some doses); and (3) not attributable to established predispositions such as drug-drug interactions and untreated chronic disease (hypothyroidism, fibromyalgia, and osteoarthritis). Up to one-third of patients who are prescribed statins do not take them over the long-term and hence derive no benefit. Approximately half of such individuals have "perceived statin intolerance" in which conflated chronic symptoms or concern for adverse effects cause them to believe they have statin intolerance. When these individuals participate in randomized, placebo-controlled blinded trials, approximately 85% can tolerate a statin during the blinded period. The other half of the statin-intolerant population is believed to have "real statin intolerance" due to reproducible bona fide adverse effects; most commonly myalgias, increases in hepatic transaminases, and malaise. Data from the Statin Response Examined by Genetic Haplotype Markers study and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine study found that polymorphisms for the organic anion transporter 1, which is responsible for clearance of statins and stain alcohols by the liver, were associated with statin intolerance as defined by a composite adverse event of discontinuation for any side effect, myalgia, or a creatine phosphokinase >3× upper limit of normal during follow-up (occurred in 19%).[12] The SLCO1B1*5 mutation was associated with intolerance of pravastatin and more so with simvastatin, which requires cytochrome P450 3A4 detoxification before the OATP1 step. Furthermore, there was evidence supporting a gene-dose effect (rates of statin intolerance in those with 0, 1, or 2 alleles were 19%, 27%, and 50%, respectively, $P = 0.01$). When these data are considered together with what is known about statin clearance with glucuronidation, cytochrome P450, and now OATP1 systems, it is reasonable to infer that impaired drug clearance and high drug levels (genetically and/or due to drug-drug interactions) play a role in the pathogenesis of statin intolerance in at least half of those who are unwilling to take this class of agents.[13] Importantly, Vitamin D deficiency, ubiquinone depletion, coenzyme Q10, and low lipid levels are unlikely to play pathogenic roles in statin toxicity.[14] In summary, there is a pharmacoepidemiologic explanation for this 15% of the population and only through improved patient education and public awareness can the maximal public health benefit of statins be realized.[15,16]

Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) Trial as a Working Example of CV Benefit

There have been many analyses of the CV benefits of statins. In general, the higher the LDL-C and greater risk, the greater the benefit of statins on coronary heart disease (CHD) events. The most striking example is the JUPITER trial [Table 1].[17] This trial recruited $n = 18{,}702$ statin-naïve men >50 years and women >60 years without diabetes, LDL-C <130 mg/dl, and high sensitivity C-reactive protein (hs-CRP) >2.0 mg/L (present in 2/3 who were screened) and randomized them to rosuvastatin 20 mg daily versus placebo. Rosuvastatin reduced LDL-C from 108 to 55 mg/dl (48% reduction), and this was associated with a 44% reduction in the primary endpoint of myocardial infarction, stroke, revascularization, hospitalization for unstable angina, and cardiac death, $P < 0.00001$. There was a 47% risk reduction in the traditional tripartite endpoint of nonfatal myocardial infarction, stroke, or CV death, $P < 0.00001$. Finally, there was a 20% reduction in all-cause death, $P = 0.02$. From a relative risk reduction standpoint, the JUPITER trial stands as the most successful primary prevention study of statins. The success of this trial is partly ascribed to the use of a high-potency statin and recruiting statin-naïve patients, with the results of patients with hs-CRP > 2.0 mg/dl implying that multiple confounding risk factors that raise hs-CRP were present (adiposity, metabolic syndrome, hypertension, smoking, etc.).

Beyond Statins

In the United States, the entry of generic ezetimibe into the marketplace will allow much greater use of this adjunctive medication. Ezetimibe (when used in addition to a statin) lowers LDL-C by an additional ~18% by impairing enterohepatic reabsorption of cholesterol.[18] This is roughly 3 times greater efficacy than a strategy of doubling the statin dose.[19] The Improved Reduction of Outcomes: Vytorin Efficacy

Table 1: Comparison of three contemporary seminal trials of LLT: The JUPITER, IMPROVE-IT, and further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk (FOURIER) trials

Clinical trial	JUPITER	IMPROVE-IT	FOURIER
Baseline characteristics (averaged between treatment and control groups)	Median age 66.0 years Male sex 61.5% White race 61.8% Diabetes 0% History of MI 0%	Mean age 63.6 years Male sex 75.7% White race 83.8% Diabetes 27.2% History of MI 21.5%	Mean age 62.5 years Male sex 75.5% White race 85.1% Diabetes 36.7% History of MI 80.9%
Study population	17,802 patients, assigned in a 1:1 ratio to rosuvastatin (20 mg daily) (*n*=8901) or placebo (*n*=8901)	18,114 patients, assigned in a 1:1 ratio to simvastatin (40 mg) + ezetimibe (10 mg) (*n*=9067) or simvastatin monotherapy (40 mg) (n=9077) daily	27,564 patients, assigned in a 1:1 ratio to evolocumab (either 140 mg every 2 weeks or 420 mg monthly) (*n*=13,784) or placebo (*n*=13,780)
Primary and composite secondary end points	Primary: MACE (nonfatal MI, nonfatal stroke, unstable angina, revascularization, CV death) Secondary: MI, stroke, CV death	Primary: MACE (CV death, major coronary event [MI, unstable angina, revascularization], stroke) Secondary: (1) Death, major coronary event, stroke. (2) Death (coronary heart disease), MI, urgent revascularization. (3) CV death, MI, unstable angina, revascularization, stroke	Primary: MACE (CV death, MI, stroke, unstable angina, revascularization) Secondary: CV death, MI, stroke
Baseline LDL-C	Median level 108 mg/dl (2.8 mmol/L)	Mean level 93.8 mg/dl (2.4 mmol/L)	Median level 92 mg/dl (2.4 mmol/L)
LDL-C reduction in the treatment group	50%	24%	59%
Primary and composite secondary endpoint RRR	MACE−0.44 (HR 0.56, 95% CI 0.46–0.69, *P*<0.0001) MI, stroke, CV death−0.47 (HR 0.53, 95% CI 0.40–0.69, *P*<0.00001)	MACE−0.064 (HR 0.936, 95% CI 0.89-0.99, *P*=0.016) Death, major coronary event, stroke−0.05 (HR 0.95, 95% CI 0.90–1.0, *P*=0.03) Death (coronary heart disease), urgent revascularization -0.09 (HR 0.91, 95% CI 0.85–0.98, *P*=0.02) CV death, MI, unstable angina, revascularization, stroke−0.05 (HR 0.95, 95% CI 0.90–1.0, *P*=0.04)	MACE−0.15 (HR 0.85, 95% CI 0.79–0.92, *P*<0.001) CV death, MI, stroke−0.20 (HR 0.80, 95% CI 0.73–0.88, *P*<0.001)
All-cause mortality RRR	−0.20 (HR 0.80, 95% CI 0.67–0.97, *P*=0.02)	−0.01 (HR 0.99, 95% CI 0.91–1.07, *P*=0.78)	N/A (HR 1.04, 95% CI 0.91–1.19, *P*=0.54)
Efficacy and safety of LLT	Rosuvastatin significantly reduced the incidence of major cardiovascular events, without significant increase of myopathy, hepatic injury or cancer but with a high incidence of physician-reported diabetes	Ezetimibe added to simvastatin lowered LDL-C levels and improved cardiovascular events. No significant differences in adverse effects were found between statin and placebo groups	Evolocumab lowered LDL-C levels and reduced the risk of cardiovascular events. No significant differences in adverse effects were found between evolocumab and placebo groups.

MI: Myocardial infarction, MACE: Major adverse cardiovascular event, CV: Cardiovascular, LDL-C: Low-density lipoprotein cholesterol, RRR: Relative risk reduction, HR: Hazard ratio, CI: Confidence interval, N/A: Not available. LLT: Lipid-lowering therapies, JUPITER: Justification for the use of statins in prevention: An intervention trial evaluating rosuvastatin, IMPROVE-IT: Improved reduction of outcomes: Vytorin efficacy international trial

International (IMPROVE-IT) Trial [Table 1] randomized 18,144 participants with acute coronary syndromes to ezetimibe 10 mg daily in addition to simvastatin 40 mg p.o. q.d. or simvastatin alone. The combination therapy produced an achieved LDL-C of 53.7 mg/dl as compared to 69.5 mg/dl in the simvastatin-only group.[20] This additional 22.7% reduction in LDL-C attributable to ezetimibe was associated with a 2.0% absolute risk reduction in the primary endpoint of a major coronary event (nonfatal myocardial infarction, hospitalization for unstable angina, or coronary revascularization), stroke, or CV death, P = 0.016. IMPROVE-IT – considering JUPITER – suggests that (1) the larger relative benefit is due to the statin and (2) the addition of ezetimibe to statin is associated with further LDL-C lowering. The modest relative benefit in the reduction of events in IMPROVE-IT may be partly due to the limited percent LDL-C lowering and the patient population post-acute coronary syndromes where other factors including prothrombotic and procedural may have introduced variation in the natural occurrence of CHD events.[21]

The advent of PCSK-9 inhibitors has raised an entirely new set of issues with respect to lipid management and reduction in CHD events. These monoclonal antibodies to PCSK-9 allow LDL-R to recycle to the cell surface and clear LDL-C with greater efficiency and have been associated with an additional 60% reduction in LDL-C. The further CV Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial [Table 1] randomized 27,564 patients with stable coronary disease on maximally tolerated statin therapy and LDL-C of 92 mg/dl to evolocumab in standard doses or placebo and the resultant LDL-C values were 30 mg/dl (59% reduction).[22] This was associated with a 15% relative risk reduction in the primary endpoint of nonfatal myocardial infarction, ischemic stroke, coronary revascularization, hospitalization for unstable angina, or CV death, P < 0.001.

Thus, when a statin is used at baseline, the addition of ezetimibe (22.7% additional lowering LDL-C and 2.0% absolute risk reduction in CHD) and monoclonal antibodies against PCSK-9 (59% additional LDL-C lowering and 15% relative risk in CHD) improve outcomes significantly. The largest relative benefit appears to be with the statin positioned as the foundation of therapy (up to ~50% reduction in CHD risk), likely due to its mechanism of action in reducing the production of all the atherogenic particles while upregulating LDL-R at the same time. It is entirely possible that whichever drug is positioned as the first form of LLT may have the largest role in reducing CHD events; however, given the mechanism of action and the results of recent clinical trials, it is unlikely there will be a departure from statins as first-line LLT in patients at risk for and with CHD.

Mechanism of Action for Statins, Ezetimibe, and Monoclonal Antibodies Against PCSK-9

While statins, ezetimibe, and monoclonal antibodies against PCSK9 all contribute to the reduction of LDL-C levels, the mechanism of action for each LLT is different [Figure 1].[17,19,20] Thus, the use of these agents is complementary to one another and is attractive both mechanistically and clinically.

Statins reduce cholesterol biosynthesis in the liver; this is associated with a reduction in LDL cholesterol and decreasing the incidence of CV events. These beneficial effects make it possible for statins to act as primary and secondary prevention of CV events.[1] The mechanism of action for statins is dependent on the inhibition of HMG-CoA reductase, an enzyme that converts HMG-CoA into mevalonic acid, a cholesterol precursor that catalyzes the rate-limiting step in cholesterol production.[1,23,24] Statins reduce serum cholesterol by reducing the synthesis of cholesterol in the liver through HMG-CoA inhibition.[24] The reduction of cholesterol in hepatocytes leads to the increase of hepatic LDL-R (these determine the reduction of circulating LDL and its precursors, IDL, and VLDL), leading to LDL-C being taken from the blood into the liver.[1,24] Interestingly, cholesterol reduction by statins leads to a significant increase in endothelial function.[1] In addition, statins inhibit transendothelial migration and chemotaxis of neutrophils, producing an anti-inflammatory effect.[1]

Ezetimibe is an intestinal and biliary cholesterol absorption inhibitor. Its primary target of action is to inhibit the delivery of intestinal cholesterol to the liver through the transport protein Niemann–pick C1 like 1 protein (NPC1L1). Therefore, the mechanism of action for ezetimibe is dependent on the inhibition of NPC1L1. By binding to the NPC1L1 receptor, ezetimibe prevents uptake of intestinal luminal micelles – which contain cholesterol – into enterocytes.[24,25]

Because cholesterol uptake is reduced and hepatic cholesterol is decreased, ezetimibe causes a depletion of hepatic LDL-C stores, leading to upregulation of hepatic LDL-R, thereby causing LDL-C to be taken up by the liver from the blood.[24,25] In addition to inhibition of intestinal cholesterol absorption, ezetimibe is also able to interact with hepatic NPC1L1, and thus reduces biliary cholesterol absorption. The dual absorption further reduces serum cholesterol levels.[25] As demonstrated in IMPROVE-IT, combining ezetimibe with simvastatin provides greater reductions in LDL-C levels than those achieved with either agent used as monotherapy; this incremental CV benefit is presumably due to reductions of both intestinal and hepatic sources of cholesterol.[17,26,27]

This benefit is consistent with the LDL hypothesis in that lowering LDL acts as a primary target of therapy for the primary and secondary prevention of CV events.[25,28] It is noteworthy that the NPC1L1 receptor (the target of ezetimibe) and HMG-CoA reductase (the target of statins) are roughly the same by polymorphisms, indicating that the efficacy of LDL-C lowering through the NPC1L1 receptor is comparable to that through the HMG-CoA reductase.[28]

PCSK9 plays an important role in LDL-C/LDL-R metabolism.[29] Therefore, anti-PCSK9 monoclonal antibody-induced reduction of LDL-C is dependent on the inhibition of PCSK9, which increases LDL-C metabolism by recycling LDL-R on the surface of hepatocytes. Under conditions of high levels of PCSK9, the degradation of the PCSK9-LDL-R complex in lysosomes is increased. In contrast, when PCSK9 levels are low, hepatic surface LDL-R levels become high because LDL-R

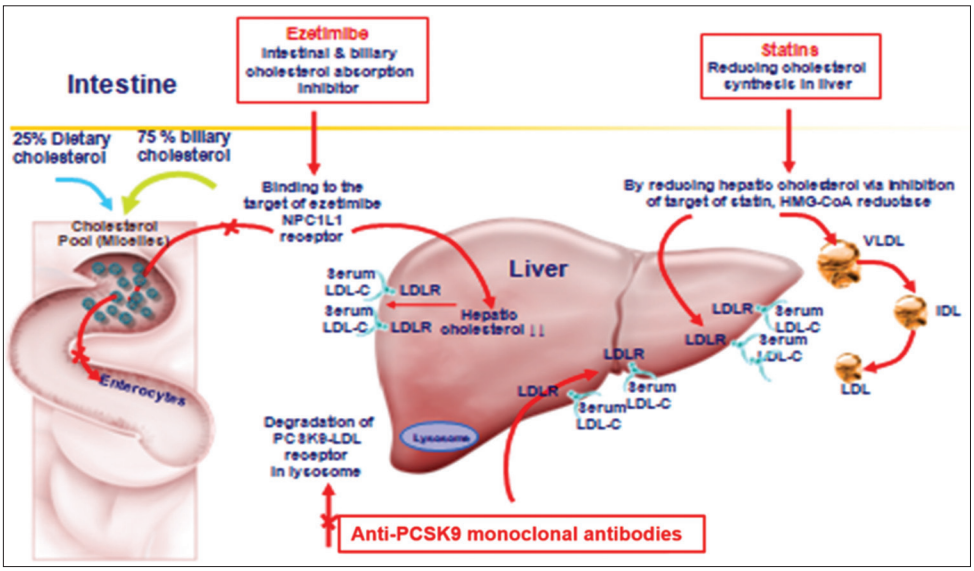

Figure 1: Mechanisms of action for statins, ezetimibe, and monoclonal antibodies against PCSK-9

can be recycled to the hepatic surface after delivery of LDL-C particles to endosomes, thus resulting in lower circulating LDL-C levels.[29] PCSK9 activity can be inhibited by monoclonal antibodies against PCSK9 through the extracellular pathway.[29]

Data from the JUPITER trial demonstrate that rosuvastatin-treated patients achieved both LDL-C and hs-CRP reduction, thereby leading to a reduction in ASCVD events.[20] The results indicate that the direct linkage between cholesterol and inflammation in the atherosclerotic plaque exists, and the beneficial impact of statins on inflammation is proportional to the reduction of levels of LDL-C.[22] Recently, it has become clear that hs-CRP is not a causal factor for atherosclerosis, but rather a powerful risk biomarker for ASCVD events. In fact, both rosuvastatin and ezetimibe have the ability to decrease CRP and improve CV outcomes.[22] However, the relationship between the reduction of LDL-C and CRP has not been observed in clinical trials of anti-PCSK9 monoclonal antibodies, perhaps due to the exclusion of patients with systemic inflammation.[22] Another postulated mechanism of action by which statins and ezetimibe decrease CV risk is by improving vascular endothelial dysfunction and by reducing pro-inflammatory cytokines, CRP, and damage of the arterial wall.[22] A recent clinical trial comparing simvastatin at a high dose of 80 mg to simvastatin 10 mg/ezetimibe 10 mg found that the decrease in LDL-C and improvement of endothelial function (assessed by flow-mediated vasodilation) were similar between the groups.[30] The results suggest that the improvement in endothelial function with statins is likely dependent on a reduction in LDL-C, independent of the dose of statin administered, without evidence of a pleiotropic action.[30]

Conclusions

There remains a large opportunity to improve CHD event rates across the globe with the use of statins in primary and secondary care. Approximately half of "statin intolerance" is perceived and is amenable to another trial of statin therapy in the well-prepared patient. The other half of statin intolerance has a genetic basis in impaired clearance of statins and their metabolic breakdown products which are toxic to skeletal myocytes when they remain in high concentrations in plasma over time. The use of rosuvastatin in a primary prevention population at risk for CHD resulted in a 48% reduction in LDL-C and a corresponding 44% reduction of CHD, conferring a 20% reduction in mortality. The addition of ezetimibe or PCSK-9 inhibition therapy to maximally tolerated statins further lowers LDL-C by 24% and 50%, respectively. However, this corresponds to a much smaller relative risk reduction of CHD events (6% and 15%, respectively) and neither ezetimibe nor PCSK-9 inhibitors have demonstrated a mortality benefit. Therefore, at this time, statins should remain foundational LLT in the prevention of CHD events.

- The mechanism of action for statins: By reducing the synthesis of cholesterol in the liver through the HMG-CoA inhibition, statin-reduced cholesterol in hepatocytes converts VLDL to IDL to LDL, and results in the increase of hepatic LDL-R, thereby leading to LDL-C being up taken from blood into the liver (upper left corner of figure).
- The mechanism of action for ezetimibe: By binding to the NPC1L1 receptor, ezetimibe prevents uptake of intestinal luminal micelles, which contain cholesterol, into enterocytes. Due to reduced cholesterol uptake and decreased hepatic cholesterol, ezetimibe leads to upregulation of hepatic LDL-R, causing LDL-C to be taken up by the liver from the blood (upper right corner of figure).
- The mechanism of action for anti-PCSK9 monoclonal antibodies: By inhibition of PCSK9 on the surface of hepatocytes, anti-PCSK9 monoclonal antibodies interrupt the degradation of the PCSK9-LDL receptor complex in lysosomes, and recycle LDL-R on the hepatic cell surface,

thus resulting in lower circulating LDL-C levels (bottom of figure).

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