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Effect of statins on atherosclerotic plaque☆

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A B S T R A C T

Lipid lowering therapy has been the mainstay of cardiovascular risk reduction and prevention. Statin drugs have been shown to reduce serum cholesterol along with significant reduction in morbidity and mortality of cardiovascular disease. Whether these benefits are purely through lipid lowering or pleiotropic (cholesterol independent) effects has yet to be fully understood. Advances in cardiac imaging, from intravascular ultrasound to multi-detector coronary computed tomography angiography, have furthered our understanding of statin's effect on atherosclerotic plaque. Notably, statins play a role in plaque regression with reduction in lipid content. These drugs further stabilize atherosclerotic plaque with thickened fibrous caps and macrocalcification that serves to stabilize atheromas.

Introduction

Cardiovascular disease (CVD) continues to remain the leading cause of death in the United States with over 900,000 deaths in 2016 [1]. Atherosclerosis forms the cornerstone of CVD, serving as the pathophysiologic mechanism for ischemic heart disease, stroke, peripheral arterial disease and aneurysm formation. Tremendous advances in the management of cardiovascular (CV) disease over the last several decades, from improved public health awareness and increased focus on prevention to advances in percutaneous coronary intervention and stent development, have reduced the morbidity and mortality of this disease. Statin therapy has had much to do with this with reduction in plasma cholesterol and reduction in frequency of myocardial infarctions (MI). In the early 1970s, Dr. Akira Endo first discovered metabolites in molds like fungi and mushrooms that inhibited *3–hydroxy-3-methylglutaryl-coenzyme A reductase* (HMG-CoA), a key regulatory enzyme in cholesterol biosynthesis. The success of HMG-CoA inhibitors (statins) were first demonstrated in patients with familial hypercholesterolemia, resulting in marked reduction in cholesterol levels though not without significant adverse effects in the early years of the drug, notably elevation in transaminases and muscular dystrophy. The 1994 Scandinavian Simvastatin Survival Study, one of the first large-scale, randomized statin trials, demonstrated that treatment with simvastatin in patients with known coronary heart disease or prior myocardial infarction produced 25% reduction in total plasma cholesterol and 35% reduction in low density lipoprotein (LDL). More importantly, it was one of the first trials to demonstrate a mortality benefit with a relative risk of death in the simvastatin group of 0.70 (95% confidence interval (CI) 0.58–0.85, $p = 0.0003$) and a reduction in frequency of major coronary events with a relative risk of 0.66 (95% Cl 0.59–0.75, $p < 0.00001$) [2]. Statins were similarly shown to reduce the incidence of MI and death from CV causes in almost 6600 men with moderate hypercholesterolemia and no known coronary disease in the West of Scotland Prevention Study [3]. The authors demonstrated that treatment with pravastatin resulted in 20% reduction in total cholesterol and 26% reduction in LDL. They further contributed to the growing body of evidence demonstrating a reduction in cardiovascular events with statins, showing a 31% relative risk reduction in the pravastatin arm (95% CI 17–43%, $p < 0.001$).

Mechanisms underlying atherogenesis

Atherosclerosis affects several key vascular beds, notably coronary, cerebrovascular and peripheral arteries. The pathophysiology underlying atherogenesis is a complex interplay of lipid deposition, endothelial dysfunction, inflammation and smooth muscle cell (SMC) proliferation [4]. Subendothelial retention of lipoproteins triggers a low grade inflammatory response and endothelial dysfunction. The resultant chemokine and cytokine secretion recruits macrophages and other inflammatory cells, which together with lipids, forms the core of the atherosclerotic plaque. These lesions often undergo a partial resolution process, creating a fibrous cap that overlies the atheroma. The fibrous cap arises from migration of SMCs and matrix deposition. The composition and thickness of the fibrous cap has been shown to determine the likelihood of plaque rupture.

Disturbed (non-laminar) blood flow patterns, shear stress, mechanical perturbations of the vascular wall in addition to lipoprotein deposition all contribute to atherosclerotic plaque formation. Composition of atherosclerotic plaque can vary in lipid core, smooth muscle cell content and fibrous cap thickness. Multidetector coronary computed tomography angiography (CTA) has the capacity to characterize both plaque burden and composition,

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identifying features of so-termed vulnerable plaque [5]. On histological analysis, vulnerable plaque is characterized by a large necrotic core, thin fibrous cap and high content of macrophages and other inflammatory cells [6].

CT based plaque morphology can classify lesions as low-attenuating, fibrofatty, fibrocalcified and densely calcified [7]. This classification is primarily based upon differential attenuation and utilizes differences in Hounsfield Units to identify 'at-risk' plaque. Using intravascular ultrasound (IVUS) as the gold-standard, CT has shown excellent sensitivity and specificity for characterizing plaque morphology [7]. Findings of vulnerable plaque has been shown to translate into clinical outcomes, where Motoyama et al. demonstrated that the presence of low attenuating plaque with positive outward remodeling of the vessel wall was an independent predictor of coronary events with acute coronary syndrome (ACS) occurring in 22% of patients with both high risk features [8]. Conversely, without either of these high risk morphological features, ACS occurred in only 0.5% of the study population. The authors concluded that ACS was independently predicted by either low attenuating plaque and/or positive remodeling with a hazard ratio of 22.8 (95% CI 6.9–75.2, $p < 0.001$).

A key component of atherosclerotic plaque is the fibrous cap which separates thrombogenic material in the necrotic lipid core from the blood compartment. Rupture of the fibrous cap and subsequent thrombus formation accounts for the majority of acute coronary syndromes. However, with the introduction of widespread statin therapy, there is a growing trend in superficial erosion rather than plaque rupture as the cause of ACS [6]. Animal studies have shown that statin therapy reinforces the fibrous cap, decreases the lipid pool and reduces inflammation, all of which increase resistance to rupture. In a study of 126 patients with ACS, Jia et al. demonstrated through optical coherence tomography (OCT) that 31% of patents had erosion as the mechanism of the acute event and 43.7% with true plaque rupture [9]. Superficial erosion was more likely to be associated with a non-ST segment elevation MI compared with patients who had plaque rupture (61.5% vs. 29.1%, $p = 0.008$). OCT analysis confirmed findings in prior animal work that plaque morphological features that favor erosion over rupture include thicker fibrous caps (169.3 ± 99.1 µm vs. 60.4 ± 16.6 µm, $p < 0.001$) and lower frequency of lipid-rich plaque (43.6% vs. 100%, $p < 0.001$).

Statins

The discovery of statins by Akira Endo in the 1970s has dramatically altered the management of cardiovascular disease. Statins have consistently been shown to be of benefit in both primary and secondary prevention of heart disease. Since the Scandinavian Simvastatin Survival Study first demonstrated that cholesterol lowering therapies yield reductions in mortality in patients with prior MI, a myriad studies have shown a reduction in major adverse cardiac events (MACE) and mortality [10–12]. The PROVE IT–TIMI 22 (Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes) study demonstrated that intensive therapy with high dose atorvastatin compared with standard dose pravastatin resulted in much greater reduction in serum LDL (51% vs. 22%, respectively) and lower risk of death from any cause and MI (relative risk reduction of 16%; 95% CI, 5%–26%; $p = 0.005$), and in fact this benefit was seen as early as 30 days after the start of therapy [10]. Several of these early studies also demonstrated slowed plaque progression and even angiographic regression with lipid lowering therapy, providing an important foundation for future work in this arena [12,13].

All statins reduce serum LDL in a non-linear, dose-dependent fashion, but differ in their absorption, excretion and solubility (Table 1) [14,15]. Statins target hepatocytes through inhibition of HMG-CoA reductase, a key regulator of cholesterol biosynthesis [14]. This reduction in intracellular cholesterol production results in upregulation of hepatic LDL receptors which in turn reduces levels of circulating LDL. The downstream effect is reduced accumulation of oxidized LDL within the arterial intima and thwarted inflammatory cascade which promotes monocyte recruitment and foam cell formation, the initial and key step in atherogenesis. This overview of statin mechanism and pharmacology is the result of decades of research that has led to present day guideline-altering management of CVD.

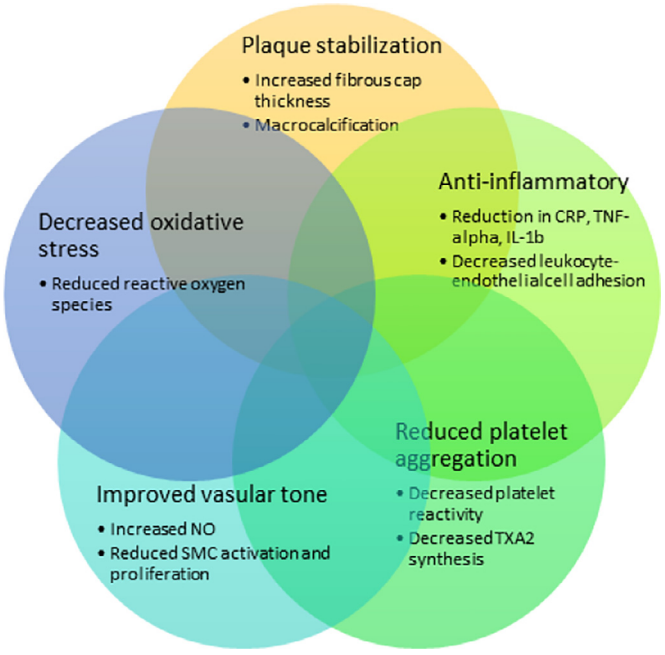

Fig. 1. Pleiotropic effects of statins.
Abbreviations: C-Reactive Protein (CRP); Nitric Oxide (NO); Smooth Muscle Cell (SMC); Tumor Necrosis Factor (TNF); Interleukin (IL); Thromboxane A2 (TXA2).

However even more fascinating are statin's pleiotropic effects, cholesterol-independent CV protective benefits as a result of inhibiting the production of intermediates in the cholesterol biosynthetic pathway (Fig. 1). This topic remains controversial however, and the true contribution of the reduction in these intermediates has not been fully elucidated as it often correlates with concurrent reduction in cholesterol. There is considerable evidence in support of cholesterol-independent effects, mechanistically thought related to inhibition of isoprenoid intermediates in the cholesterol biosynthesis pathway [11,16]. This leads to impaired post-translational modifications of intracellular proteins with downstream effects on endothelial, inflammatory and smooth muscle cells. Several prior statin trials, namely JUPITER (Rosuvastatin to Prevent Vascular Events in Men and Women With Elevated C-Reactive Protein), MIRACL (Effects of Atorvastatin On Early Recurrent Ischemic Events in Acute Coronary Syndromes) and most recently the HOPE-3 (Heart Outcomes Prevention Evaluation) study all showed marked reduction in C-reactive protein (CRP) as high as 83%, in addition to reduction in LDL cholesterol. However it remains unclear if this reduction results from LDL reduction itself or pleiotropic effects of the drug [11,16].

Statins have been shown to have a beneficial effect on vascular tone. In cell studies, HMG-CoA reductase inhibition resulted in upregulation of endothelial nitric oxide (NO) synthase activity, resulting in increased bioavailability of NO, an important regulator of vascular tone, platelet aggregation and vascular SMC proliferation [17]. The latter is a key driver of atherosclerotic plaque

Table 1
Statin pharmacokinetics.

Statin	Origin	Elimination half-life (hours)	Excretion	Solubility	Bioavailability (%)
Lovastatin	Natural or fungal-derived	3	Hepatic: >70% Renal: 10%	Lipophilic	5
Simvastatin	Natural or fungal-derived	2	Hepatic: >80% Renal: 13%	Lipophilic	5
Fluvastatin	Synthetic	1.2	Hepatic: >70% Renal: 6%	Lipophilic	24
Atorvastatin	Synthetic	14	Hepatic: >95% Renal: <5%	Lipophilic	12
Pravastatin	Natural or fungal-derived	1.8	Hepatic: >46% Renal: 20%	Hydrophilic	18
Rosuvastatin	Synthetic	19	Hepatic: 90% Renal: 10%	Hydrophilic	20

Adopted from Schachter [15]

progression and statin medications have been shown to reduce proliferation and migration of vascular SMCs. This process is especially evident in the cardiac transplant population where Kobashigawa et al. showed that patients treated with pravastatin compared with patients receiving no HMG-CoA reductase inhibitor had lower rates of coronary artery vasculopathy (3 vs. 10 patients, $p = 0.049$), the pathogenesis of which relates to activation of smooth muscle cells as a result of a chronic immune response in the transplant recipient [18].

Statin medications have also been implicated in reducing platelet aggregation as well having antithrombotic properties that may contribute to the overall reduction in cardiovascular death. Sikora et al. showed a strong positive correlation between hyperlipidemia the degree of ADP-activated platelet adhesion [19]. Treatment with statin medications resulted in 38–57% reduction in platelet adhesion. Potential mechanisms involve altered intraplatelet cholesterol to phospholipid ratios which results in increased expression of thromboxane A2 synthesis and increased pro-adhesion receptor density.

Another important pleiotropic effect of HMG-CoA reductase inhibitors is the anti-inflammatory properties and reduction in oxidative stress. In vitro and in vivo models, as well as evidence from clinical studies, have supported the idea that statins reduce systemic inflammation [20]. Statins reduce CRP levels as well as inhibit mediators of inflammation such as tumor necrosis factor-alpha and interleukin 1b. These anti-inflammatory effects are critical in curbing progression of atherosclerotic plaque. Arterial imaging with fluorodeoxyglucose (FDG) positron-emission tomography (PET) has allowed for identification of inflammation within atherosclerotic plaque and has been shown to correlate with systemic markers of inflammation. Singh et al. demonstrated that patients treated with statins showed reduced FDG uptake in left main coronary artery lesions with high risk plaque features which the authors defined as noncalcified or partially calcified [21]. This becomes important in the clinical realm as it allows for further risk stratification among patients with atherosclerosis, identifying patients at highest risk for future thrombotic events [22]. The pleiotropic effects of statins continue to be debated. Labos et al. reviewed 25 primary and secondary prevention statin trials adapting an Egger regression model to test for pleiotropy, a technique commonly used in Mendelian randomization studies [23]. The authors report that when applying this model to reanalyze available studies, most of the effects of statins are mediated through LDL reduction and not via pleiotropic effects.

Impact of statin therapy on atherosclerotic plaque

The clinical benefit of statin therapy in patients with coronary artery disease is unquestionable. Whether purely through LDL reduction or more likely in concert with pleiotropic effects including reduction in inflammation, improved vascular tone and decreased platelet aggregation, treatment with statins have resulted in significant reduction in mortality and morbidity. Advances in imaging, notably computed tomography and PET, have allowed for in-depth evaluation of changes within atherosclerotic plaque that occur with statin therapy.

Plaque regression

Plaque regression involves removal of lipid and necrotic core, restored endothelial function and cessation of intravascular smooth muscle cell proliferation [24]. Early studies evaluating the impact of lipid lowering therapy on atherosclerotic plaque traditionally relied on IVUS and carotid intima-media thickness (CIMT) as surrogates for plaque quantification. Brown et al., in the late 1990s, showed that men with CAD and high risk for subsequent CV events who were treated with lipid lowering therapy of any variety, ranging from statins to niacin and bile acid binders, experienced a lower incidence of clinical events by 73% (95% CI 23–90%) and reduced progression of coronary lesions [25]. The ASTEROID (Effect of Rosuvastatin Therapy on Coronary Artery Stenoses Assessed by Quantitative Coronary Angiography) trial was the first large study, enrolling nearing 350 patients, to show reduction in atheroma volume by IVUS in statin naïve patients treated with high dose rosuvastatin with nearly 64% showing evidence of plaque regression [26]. As imaging techniques improved, the addition of virtual histology IVUS allowed for differentiation of various plaque phenotypes (i.e. fibrofatty vs. necrotic core) [27]. In a meta-analysis evaluating changes in plaque composition with statin therapy as measured with IVUS virtual histology, statins were found to alter the composition of atherosclerotic plaque, specifically reducing fibrous volume without significant changes in fibrofatty or necrotic core volumes [28]. The authors further noted however, that statins did not have a significant change in lumen diameter.

While all statins lower LDL, the changes in plaque volume and plaque composition are not uniform. Puri and colleagues in the SATURN (Effect of Two Intensive Statin Regimens on Progression of Coronary Disease) trial evaluating high intensity statin therapy (atorvastatin 80 mg or rosuvastatin 40 mg) in ACS versus non-ACS patients, those with ACS had higher rates of plaque regression (-1.46 ± 0.14 versus -0.89 ± 0.13; $p = 0.003$) despite achieving similar reductions in LDL and inflammatory markers [29]. In fact, ACS clinical presentation was found to be independently associated with plaque regression. This may be due to differences in plaque composition in patients with ACS, with prior studies showing greater proportion of lipid-rich plaque and greater necrotic core in the coronary trees of ACS patients [30]. Dose variation, high intensity versus low intensity treatment approach, influences plaque reduction. In a randomized controlled trial comparing the effects of moderate intensity statin regimen with pravastatin 40 mg to high

intensity consisting of atorvastatin 80 mg, Nissen et al. demonstrated that the atorvastatin group had no change in atheroma volume over the 18-month treatment period whereas patients treated with pravastatin showed progression of coronary atherosclerosis [31].

The high temporal and spatial resolution of coronary CTA offers noninvasive, direct visualization of atherosclerotic plaque and the ability to accurately characterize plaque composition as well as identify features associated with vulnerable plaque such as positive remodeling and low attenuating lesions [32]. In a retrospective observational study of patients undergoing consecutive CTAs, Zeb et al. attempted to evaluate the differences in plaque progression among statin and non-statin users [33]. Over a mean follow-up period of 406 days, the authors reported that total plaque volume was reduced in the statin group compared to non-statin users (-33.3 mm^3 $\pm$ 90.5 vs. 31.0 mm^3 $\pm$ 84.5, p = 0.0006). The progression of noncalcified plaque was also significantly reduced compared with non-statin users (-47.7 mm^3 $\pm$ 71.9 vs. 13.8 mm^3 $\pm$ 76.6, $p < 0.001$). Interestingly the study found that statins increased the amount of calcified plaque, though the results were not statistically significant. This early work has been validated in the more contemporary PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) study which enrolled over 1250 patients worldwide and sought to prospectively evaluate the long-term effects of statins on plaque progression [34]. Progression of atherosclerotic plaque volume was slowed in patients taking statins compared with those not on statin medications with interval change in plaque volume of 1.76 $\pm$ 2.40% per year vs. 2.04 $\pm$ 2.37% per year, respectively ($p = 0.002$). This difference was related to slowed progression of noncalcified plaque, specifically fibrous and fibrofatty phenotypes, with no difference in progression of low attenuating plaque. In keeping with prior work, the study also demonstrated that statin therapy increased calcified plaque volume compared with the non-statin group (1.27 $\pm$ 1.54% per year vs. 0.98 $\pm$ 1.27% per year, respectively; $p < 0.001$). Statins' differential effects on plaque composition did not translate into a clinically significant change in luminal narrowing, though some improvement in coronary stenosis was observed.

Plaque stabilization

Coronary artery calcification has come to be recognized as a powerful measure of cardiovascular risk, having added value over traditional Framingham risk scores [35]. Paradoxically however, statin treatment alters atheroma composition by reducing non-calcified plaque and increasing proportion of dense calcified plaque. Differential phenotypes of macrophages play a significant role in vascular calcification. The proinflammatory M1 phenotype of macrophages promotes microcalcification through smooth muscle cell differentiation into osteoblasts. The M1 phenotype is associated with plaque progression [36]. In contrast, the anti-inflammatory M2 macrophage phenotype, associated with plaque regression, facilitates macroscopic calcium deposition. One theory is that statins may facilitate the M2 phenotype of macrophages and thus promote plaque regression and macrocalcification that serves to stabilize atherosclerotic plaque. Work in vascular biology by Libby and others have further demonstrated that the anti-inflammatory M2 macrophage phenotype reduces matrix degradation, contributing to plaque stability.

Another critical aspect to plaque stability is the fibrous cap. Among other factors, thin fibrous caps are markers of vulnerable plaque and increase risk for plaque rupture resulting in ACS. The EASY-FIT (Effect Of Atorvastatin Therapy On Fibrous Cap Thickness In Coronary Atherosclerotic Plaque As Assessed By Optical Coherence Tomography) study used OCT to evaluate the change in fibrous cap thickness in 70 patients with unstable angina using atorvastatin 5 mg/day compared with 20 mg/day [37]. The higher statin dose arm showed a greater increase in fibrous cap thickness and correlated with reduction in serum LDL and high sensitivity CRP. A meta-analysis of similarly designed studies aimed at characterizing fibrous cap thickness with OCT after statin therapy showed increase in fibrous cap thickness with statins however this increase was shown to be independent of reduction in serum LDL [38].

Reduction in inflammation

As alluded to previously, Tawakol et al. demonstrated the presence of inflammation within arterial plaque using FDG PET imaging in adults with established atherosclerosis or risk factors [39]. There was a reduction in FDG uptake in a dose-response fashion after treatment with high intensity atorvastatin, a change seen as early as four weeks after treatment initiation. The molecular mechanisms underlying the anti-inflammatory response with statins is thought to relate to their unique pleiotropic effects. Statins reduce reactive oxygen species production and decrease release of pro-inflammatory cytokines such as interleukins and tumor necrosis factor alpha [40]. This in turn reduces monocyte recruitment and curbs plaque progression. Further, the shift toward a more favorable, anti-inflammatory phenotype of monocyte-derived macrophages promotes plaque stability. While further work is needed to fully elucidate the exact molecular mechanisms of statins' anti-inflammatory effects, trials like CANTOS (Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease) have provided demonstrable evidence that inflammation not only plays a key role in atherosclerosis but may in fact be a novel target for therapies aimed at reducing adverse cardiovascular events [41]. The CIRT (Cardiovascular Inflammation Reduction Trial) trial which is currently in progress aims to directly test the inflammatory hypothesis with low-dose methotrexate in patients with stable CAD with end-points of MI, stroke and cardiovascular death [42].

Future directions

Shifting the focus away from lipid lowering, the unique pleiotropic effects of statins have allowed for a better understanding of atherogenesis and the complex interplay between inflammation and vascular biology. Improved imaging modalities have further aided in this understanding, enabling a deeper appreciation of plaque composition and the detection of inflammation on a lesion specific basis. Technology such as FDG-PET and CTA will also be essential for studying long-term changes in plaque morphology of not only the coronary tree but also carotid and aortic atheromas. Given evidence that statin therapy increases plaque calcification, further work will be needed to determine the prognostic implication of coronary calcium score in serial evaluation of patients with CAD.

The newest agent targeting lipid lowering are proprotein convertase subtilsin-kexin type-9 (PCSK9) inhibitors. Mechanistically unique from statin drugs in that rather than targeting sterol synthesis, these monoclonal antibodies promote LDL clearance from the circulation. What remains unknown is the effect PCSK9 inhibitors will have on plaque composition and its effects, if any, on plaque regression.

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