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The Pleiotropic Effects of Statins: Fact or Fantasy?

By SCOTT KINLAY, MBBS, PhD

Statins have powerful effects on low-density lipoprotein (LDL) cholesterol and total cholesterol and reduce the risk of coronary artery disease and stroke.[1-6] Recent evidence points to the possibility that they have beneficial effects on vascular function beyond cholesterol reduction. These extra effects are often called "pleiotropic," a word originally used to describe the multiple effects of some genes and derived from the Greek roots of *pleio* (more/most) and *tropy* (response to stimuli). The terminology is somewhat confusing since LDL-lowering has many effects on vascular function beyond removing cholesterol from artery walls. Potentially, statins could exert multiple effects on vascular biology, not only by reducing LDL cholesterol, but also by modifying non-LDL lipids, and exerting non-lipid (or lipid-independent) effects.

Atherosclerosis and pleiotropy

Earlier views of the mechanisms of benefit from cholesterol reduction seem rather primitive today (as today's views will no doubt be in the future). Autopsies of patients who died of cardiovascular disease (CVD) revealed arteries clogged with cholesterol in a manner reminiscent of calcium salts accumulating in the water pipes of old houses. Presumably, this cholesterol accumulated over years and eventually narrowed the coronary artery lumen until blood cells, like rush hour traffic on the Mass Pike, ground to a halt to fatally occlude the artery.

Drugs that lowered plasma cholesterol were thought to reduce cholesterol build-up and even remove it from the artery wall. However, angiographic regression trials revealed that statins and other lipid-lowering agents had a disappointing effect on the size ("plumbing effect") of artery lumens.[7] In these studies, changes in lumen diameter attributable to treatment were in the range of 2%-3%. Even in the recent Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, where intravascular ultrasound measured coronary atherosclerosis before and after treatment with 2 statins, similar changes in plaque volume occurred.[8] In spite of these small changes in plaque size, the cardiovascular event rates in these patients – as in other statin trials – were reduced by an impressive 20% or more.

If "size" did not matter in atherosclerosis, we soon learned that "function" did. Atherosclerosis and conventional risk factors (eg, blood lipids, hypertension, smoking, physical activity, and obesity) were related to many functional derangements in the artery wall, including endothelial dysfunction, increased oxidant stress, inflammation, and thrombosis.[9,10] For example, LDL cholesterol entering the artery wall is modified by oxidation. This oxidized LDL activates many pro-inflammatory pathways, including NF-κB that promotes the expression of cellular adhesion molecules on the surface of the endothelium and stimulates the production of cytokines.[9] These

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steps are crucial for the recruitment and activation of inflammatory cells into the atherosclerotic wall. Activated lymphocytes and macrophages in plaque contribute to the degradation of collagen, the production of tissue factor, and the development of the necrotic lipid pool. These factors weaken plaques, predisposing them to rupture and precipitating clinical events such as myocardial infarction (MI). It is now generally recognized that inflamed plaques, not tight stenoses, are the culprits most often responsible for MI and cardiac death.[11-13]

These discoveries changed the paradigm of atherosclerosis from a blocked "water pipe" to an active and dysfunctional disease. As a result, our therapeutic attention focused on the functional changes resulting from risk factor modification and, specifically, statin therapy.

Pleiotropy and risk factor modification

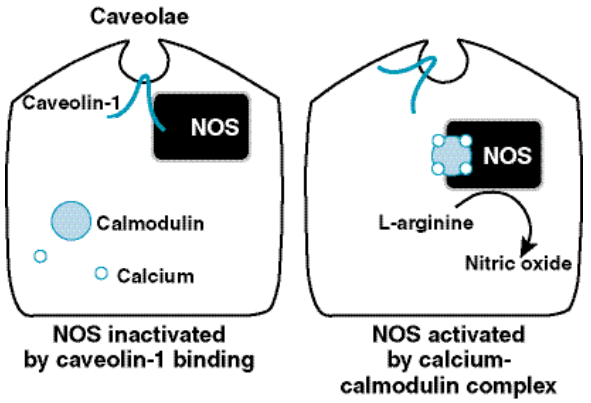
Seminal studies in animals with atherosclerosis induced by arterial injury and high cholesterol diets revealed that dietary manipulation to dramatically reduce blood cholesterol had pleiotropic effects on the artery wall.[14,15] This intervention reversed many of the changes seen in atherosclerosis, including lowering the content of oxidized LDL in the artery wall and reducing the expression of cellular adhesion molecules, pro-thrombotic substances such as tissue factor, and the density of inflammatory cells. At the same time, the expression of collagenase enzymes was reduced and the concentration of plaque-stabilizing collagen increased.[14] These changes occurred with little reduction in the size of plaques, but in humans, similar changes would tend to prevent plaque rupture.

In human subjects, lowering LDL cholesterol with resins or by plasma apheresis improved coronary and peripheral endothelial function.[16,17] A number of studies related other risk factors and lipid fractions (triglycerides and high-density lipoprotein [HDL] cholesterol) to endothelial function.[18-22] Together, these studies supported the importance of risk factor modification in the functional improvement of vascular disease that would subsequently prevent clinical events. Conceivably, improvements in endothelial function with statin therapy are due to their potent effects on lowering LDL cholesterol and their smaller effects on lowering triglycerides and raising HDL cholesterol.

Non-lipid effects of statins

The popularity of statins was driven by their relative ease of use and because they have more potent effects on LDL cholesterol than alternative drugs. However, more recent evidence points to additional effects on vascular function and atherosclerosis beyond the lipid changes. Cell culture and intact animal studies have elucidated important cellular mechanisms that are modulated by a variety of statins, while holding cholesterol levels constant. These effects include the increased bioavailability of nitric oxide (NO) in endothelial cells, isoprenoid-mediated effects on vascular function, and other more specific anti-inflammatory effects.

Figure 1: Nitric oxide (NO) is held in an inactive state by caveolin, a protein on the surface of invaginations in the endothelial cell membrane called caveoli. Phosphorylation of NO synthase (NOS) by the heat-shock protein/Akt complex, and subsequent binding of the calcium-calmodulin complex to NOS, increases its activity and the production of NO from L-arginine.[23]



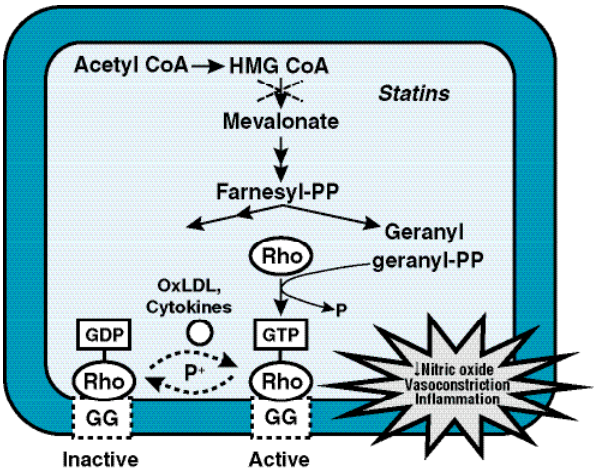
Increased bioavailability of NO

Endothelium-dependent NO promotes vasodilation, suppresses inflammatory pathways, and prevents platelet activation. NO is produced by NO synthase that exists close to invaginations in the endothelial cell surface called caveolae.[23] NO synthase is held in an inactive state by caveolin, a protein on the surface of caveolae, and is activated by phosphorylation from the heat-shock protein/Akt complex and, subsequently, by binding to the calcium-calmodulin complex (Figure 1).[24] In cell culture, statins increase the activity of Akt and phosphorylation of NO synthase.[24] In other experiments, statins promote NO synthase activity by decreasing caveolin in endothelial cells.[25] However, this effect is reversed by adding LDL cholesterol to the supernatant, which points to complex interactions between LDL-independent and LDL-dependent effects of statins on vascular function.

Isoprenoid-mediated effects

Isoprenoids are proteins that are part of the mevalonate pathway, but diverge from the cholesterol pathway (Figure 2). The isoprenoid geranylgeranylpyrophosphate activates a

Figure 2: Isoprenoids, including geranylgeranylpyrophosphate are products of the mevalonate pathway that diverge from the cholesterol pathway. These isoprenoids activate Rho and related proteins, which are lipid-independent pathways that activate many cells and cause inflammation. Isoprenoid production is inhibited by statins.[23]



group of Rho, Rac, and cdc42 proteins that have a number of pro-atherogenic effects, eg, decreasing NO, promoting inflammation and proliferation of cells, and increasing oxidant stress.[23,26] By inhibiting HMG-CoA reductase, statins in cell culture decrease the production of isoprenoids and potentially reverse these effects by cholesterol-independent means. However, oxidized LDL also increases Rho activity[27] so that, in humans, statins could affect Rho activation by both lipid and non-lipid mechanisms.

More specific anti-inflammatory effects

Statins also have effects on other key inflammatory pathways; they decrease CD40 ligand activation of lymphocytes, major histocompatability-II expression important in T-cell activation and, potentially, lymphocyte integrin binding to cellular adhesion molecules on endothelial cells.[28-30] Although the potentially important lipid-independent effects of statins are demonstrable in cell culture, their relevance to clinical practice is unknown since the concentrations of statins required for these effects are usually several orders of magnitude higher than the serum concentrations of statins used therapeutically.

Arguments to support LDL-independent effects of statins in clinical practice

Part of the difficulty in assessing the LDL-independent effects of statins in clinical practice is the near impossibility of using statins without lowering LDL cholesterol. Some of the arguments in support of LDL-independent effects include:

- Statins improve stroke risk when, epidemiologically, LDL cholesterol is not considered to be related to, or only a minor risk factor for, stroke.
- The separation of cardiovascular event curves in recent statin trials appears earlier than would be anticipated from lipid-lowering.
- Statin effects on C-reactive protein (CRP), a marker of inflammation, are related to improved clinical outcomes and unrelated to statin effects on LDL cholesterol.
- Statins improve vascular function better than non-statin interventions that achieve similar LDL reductions.

Stroke, LDL cholesterol, and statins

Unlike coronary heart disease, large epidemiological studies have shown equivocal relationships between LDL or total cholesterol and all stroke risk.[31] Yet, statins clearly reduce the risk of stroke by about 20%-30% in most large clinical trials,[1-6] leading some researchers to suggest that the benefits of statins on stroke risk must be related to lipid-independent effects. However, the pathology of carotid atherosclerosis (a risk factor for stroke) suggests a different conclusion. There is a close correlation between plasma cholesterol and the extent of carotid atherosclerosis measured by non-invasive ultrasound.[32] Autopsy studies of patients who have died of stroke reveal complex disease in the carotid arteries that is similar to that seen in the coronary arteries: plaque with thin fibrous caps, necrotic lipid cores, inflammatory cells, and overlying thrombus.[33]

Of course, stroke is a diverse group of conditions that includes causes other than carotid disease. In our society, as in most developed countries, ischemic stroke predominates, with fewer cases due to intracranial and subarachnoid hemorrhage. Ischemic stroke may be related to lacunar infarcts that are typically associated with small artery disease related to hypertension; embolic stroke due to thrombus or atherosclerosis originating in the heart, aortic arch, or great vessels; or potentially disrupted plaque in the large intracranial arteries. In the Multiple Risk Factor Intervention Trial (MRFIT), cholesterol levels were related to the future development of ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage.[34] In this study, there was no relationship between plasma cholesterol and hemorrhagic strokes, but there was a clear increasing risk of non-hemorrhagic stroke with higher plasma cholesterol. Thus, the poor relationship between cholesterol and stroke in other studies may reflect a dilution of the relationship caused by lumping strokes due to different etiologies together.

Comparisons of the reduction in stroke risk to on-treatment cholesterol levels from statin and non-statin trials reveal a similar relationship on the same regression

line. These data suggest that lipid reduction is an important mechanism for stroke benefits related to statin therapy.

More rapid benefits in statin versus non-statin trials

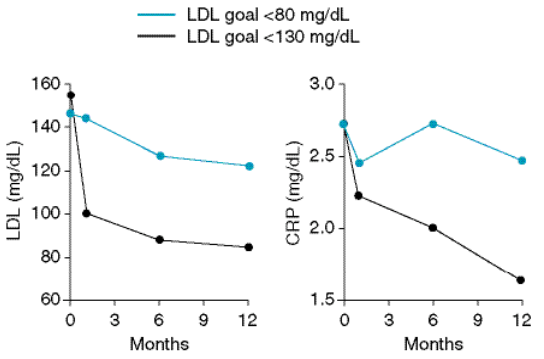
In several recent statin trials, the curves of event rates between the statin and placebo groups, or between the intensive statin and modest statin groups, started to separate within weeks or months of enrollment.[1-6,35] In contrast, in the first lipid-lowering trials, it generally took several years for differences to appear between the cholesterol-lowering and comparator arms.[1-4] Some investigators have suggested this early separation of event curves is evidence of the lipid-independent effects of statins. However, the relationship between the reduction in coronary event rates and on-treatment cholesterol levels is surprisingly tight and there is no suggestion of a different relationship between statin and non-statin interventions.[36] Meta-regression analysis also reveals that the relationship between the differences in total cholesterol between the two arms of lipid-lowering trials is closely related to differences in cardiovascular event rates. Furthermore, the differences in cholesterol and event rates in the most recent statin studies, with early separations of event curves, fall exactly on the regression line established for the older studies with later separation in event rates.[37] The separation in event curves is highly dependent on the size of the effect, the number of patients in the study, and the underlying level of risk. Although it is attractive to look at a graph and marvel over the "separation of curves," this retrospective analysis has little validity.

Independence of changes in LDL and CRP

The effect of statins on CRP and LDL cholesterol is often assessed by correlation coefficients. The lack of a correlation between these 2 variables in any single study is sometimes considered evidence for an LDL-independent effect of statins on inflammation. However, the temporal relationship between CRP and LDL reduction is very similar. In both the Vascular Basis Study (where serial CRP and LDL were measured in patients with stable angina, Figure 3)[38] and the TIMI-22/PROVE-IT trial in acute coronary syndrome patients, the decline in CRP and LDL closely track each other.[35,39]

Correlation analyses are limited by the range of change in CRP and LDL compared to their measurement variability. LDL cholesterol has a well-defined intra-individual variability that is fairly constant across LDL values. CRP, on the other hand, has low variability at low levels (<1 mg/dL), but increasingly greater intra-individual variability at higher values.[40] Since most statin event trials are conducted in patients with elevated CRP (>1 mg/dL), any correlation between change in CRP and LDL is masked by the large intra-individual variability of these measurements. In other words, "the noise may obscure the signal."

Figure 3: In studies where C-reactive protein (CRP) and LDL cholesterol are measured serially, the temporal relationship between the decline in CRP and LDL cholesterol and statin therapy tracks fairly closely.[38]



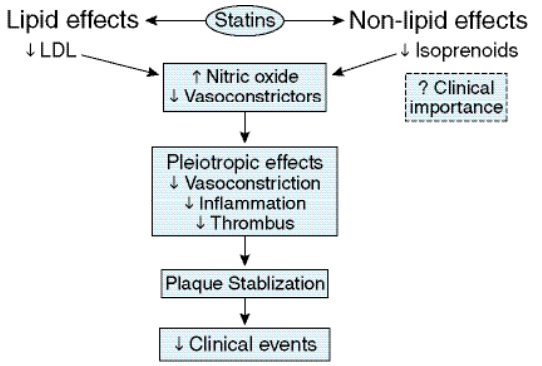
Effects of statin versus non-statin interventions on vascular function

The recent development of ezitimibe, a non-statin LDL-lowering agent, has permitted the short-term comparison of statin versus non-statin interventions on vascular function. In some of the early trials comparing the 2 interventions, statin therapy has improved endothelial function to a greater extent than non-statin agents that lower LDL to a similar degree.[41] More evidence from similar studies may provide greater support for the concept of the lipid-independent effects of statins; however, the magnitude of their importance for clinical event reductions still requires elucidation.

Conclusions

Statins, like other modes of risk factor reduction, have pleiotropic effects on endothelial function, inflammation, and thrombosis. Although plausible mechanisms for their lipid-independent effects have been demonstrated in experimental studies, some lipid-independent pathways are also modified by changes in LDL, suggesting redundancy that precludes firm conclusions about complex organ systems. In

Figure 4: Pleiotropic effects likely lie in a causal pathway that relates lipid changes and possibly lipid-independent effects of statins to plaque stabilization preventing clinical events.



clinical studies, the ability to separate LDL cholesterol lowering from the LDL-independent effects of statins is difficult. Statistical modeling both supports and refutes the lipid-independent effects of statins and, therefore, the magnitude of their lipid-independent effects is far from clear. The pleiotropic effects of the statins likely lie in a causal pathway that links the lipid-mediated changes and, possibly, the lipid-independent effects of statins, to changes in plaque stability that ultimately prevent clinical events (Figure 4). The relative importance of lipid and lipid-independent effects on the clinical benefits of statins is unknown and should be debated only briefly by friends over a good bottle of wine. Whatever side of this scientific controversy you choose, statins remain an important part of our clinical armamentarium. The more important reason for continuing this debate is that it may lead to a better understanding of new mechanisms that could foster the development of novel therapies to augment the therapeutic options for preventing clinical events due to atherosclerotic disease.

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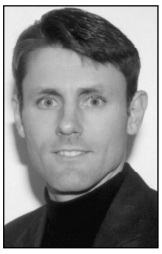

Dr. Scott Kinlay *is Director of Intravascular Ultrasound at the Brigham and Women's Hospital, Boston; Director of Vascular Medicine and Endovascular Therapy at the Veterans Affairs Medical Center West Roxbury; and an Assistant Professor of Medicine at Harvard Medical School. Dr. Kinlay attended medical school at the University of Sydney, Australia. He completed his cardiology and internal medicine training at John Hunter Hospital in Australia and postgraduate training in cardiology, interventional cardiology, and endovascular therapy for peripheral vascular disease at Brigham and Women's Hospital. He is a Fellow of the American College of Cardiology, the Royal Australasian College of Physicians, and the Cardiac Society of Australia and New Zealand. His research interests focus on endothelial function, arterial inflammation, and dyslipidemia. He has outpatient clinics at the Brigham and Women's Hospital and the VA Medical Center for patients with dyslipidemia, and those requiring medical or endovascular therapy for coronary artery and peripheral vascular disease including carotid artery disease.*

Contact information:

Telephone: BWH – 617-732-6896

VA – 617-323-7700 ext. 35064.

Dr. Kinlay has received grants from Pfizer and has served as a speaker or consultant for Bristol-Myers Squibb, Merck, Pfizer, and Schering-Plough.

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