Vascular form and function: two mechanisms for cardiovascular prevention

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This editorial refers to ‘Cholesterol lowering is more important than pleiotropic effects of statins for endothelial function in patients with dysglycaemia and coronary artery disease’† by M. Settergren et al., on page 1753

When Louis Sullivan, of the ‘Chicago School’ of architecture stated that form follows function, he liberated the wave of the Modernist Movement. In its wake, other luminaries including Le Corbusier, Gropius, and Mies van der Rohe changed and challenged the urban landscape into the new century.

Is it any wonder that our reductionist approach to disease and health is also divided between mechanisms of form and those of function? They challenge and change our view of atherosclerosis. The discovery that the endothelium is an autocrine and paracrine organ regulating many functions to prevent the forms of atherosclerosis that cause disease pervades our current constructs. Yet, the importance of atherosclerosis form (size and composition) and arterial function are debated in ways that ignore their close association.

Perhaps equally as beguiling are the mechanisms that determine the change in cardiovascular risk from risk factor reduction. Their further elaboration could help design new therapies with incremental benefits. It is this quest that underlies the study of the effects of HMG CoA reductase inhibitors (statins) on vascular biology, which presumably predicates changes in the risk of cardiovascular events.

Statin pleiotropy

Statins are one of the great medical successes of our age. Initially thought to have their effect by reducing the size of atherosclerotic plaque, increasing evidence shows a far greater effect on endothelial function and plaque composition, including less inflammation and more stable fibrous tissue over weaker lipid-rich compositions. Many of these changes are mediated by improvements in the bioavailability of endothelium-derived nitric oxide in the artery wall. However, these pleiotropic effects can result from lowering low-density lipoprotein (LDL), LDL-independent effects of statins, or both.1 There is a lot at stake in this field. If the benefits are largely due to LDL, then therapies that lower LDL to a greater extent offer the hope of incremental benefits. On the other hand, if LDL-independent effects predominate, this justifies the development of novel therapies that alter LDL-independent pathways.

Experimental studies in cell culture and some in animals show LDL-independent effects of statins on nitric oxide synthase activity, isoprenoids that affect the Rho/Rho kinase inflammatory pathways, and other immunomodulatory signalling by leucocytes.1 However, the importance of these effects with the doses used in humans is widely debated, and concealed by the inevitable fall in LDL with statin therapy.

To some extent, studies of groups rather than individuals can separate LDL-dependent from LDL-independent effects. Compared with groups receiving other LDL-lowering therapies, recent meta-analyses fail to show any substantial non-lipid effects of statins on cardiovascular events2 or changes in the archetypal inflammatory marker C-reactive protein.3 The other approach is to compare a statin with a non-statin of equal LDL lowering. Until recently, there were few methods that achieved LDL lowering approaching even the lowest doses of statins. However, one drug, ezetimibe, comes close. Ezetimibe selectively inhibits cholesterol absorption by binding the Niemann–Pick C1-like 1 protein on the intestinal wall.4 As it does not affect the mevalonate pathway, it has no direct effect on cholesterol or isoprenoid synthesis. In clinical studies, ezetimibe lowers LDL by ~12–19%.5 The most important test of this drug awaits the results of clinical outcomes trials. However, it may also provide insights into the mechanisms of statin effects on arterial function and form.

Vascular function

The study by Settergren et al.6 is one of five to use ezetimibe to flush out any LDL-independent effects of statins on vascular function.

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They tested the effects of two regimens with similar LDL-lowering effects, but with different statin intensity on endothelium-dependent flow-mediated dilation (FMD) of the brachial artery, and endothelin-mediated basal vascular tone of the forearm arterioles. FMD is a clinical measure of nitric oxide bioavailability—a potent vasodilator with anti-inflammatory and antithrombotic effects that inhibit atherosclerosis activity and progression. Endothelin is produced by activated endothelial cells and macrophages, and has opposite effects to increase basal vascular tone (constriction), inflammation, and vascular smooth muscle cell proliferation.\(^7\)

Settergren’s study found no additional effects of simvastatin 80 mg/day vs combined simvastatin 10 mg and ezetimibe 10 mg/day.\(^6\) As the authors discuss, this conclusion is similar to that of another non-randomized study of FMD that added ezetimibe to atorvastatin 40 mg/day.\(^8\) However, the results differ from two earlier studies in patients with heart failure\(^9\) and coronary disease.\(^10\) The Landmesser study compared simvastatin 10 mg/day with ezetimibe 10 mg/day over 4 weeks in patients with chronic heart failure.\(^9\) LDL cholesterol fell by 15% in both groups, a result similar to that of other studies of ezetimibe,\(^5\) but about half that expected for simvastatin 10 mg.\(^5\) Did the greater improvement in FMD with simvastatin reflect non-LDL effects or greater LDL effects that were measured imperfectly? In the Fichtlscherer study, ezetimibe dropped LDL by 21% compared with 49% with atorvastatin 40 mg/day, and there was greater improvement in FMD in the statin group. Although another two groups had similar LDL lowering with different FMD responses, their lack of random allocation limits the confidence in the results.\(^10\) More recently, another study randomized patients with rheumatoid arthritis to ezetimibe vs simvastatin 20 mg/day using a double-blind crossover design.\(^11\) Simvastatin lowered LDL cholesterol more (39 vs 18%), but the increase in FMD and decrease in pulse wave velocity (improved arterial elasticity) were similar between the two groups.

These studies of vascular function fail to show convincing effects of statins beyond those related to LDL, and are consistent with the conclusions of statin effects on inflammation.\(^3\)

### Vascular form

Statins, and LDL lowering in general, have far greater effects on atherosclerosis composition than the size of atherosclerosis plaque. Studies of atherosclerotic plaque in animals and humans show that statins reduce oxidized LDL and inflammatory cell density and activity by 40–60%, and increase collagen content by 60–70%.\(^12,13\) In contrast, the changes in the size of plaque with intensive statin therapy in humans measured by ultrasound in the coronary or carotid arteries is \(\sim 1–2\%\).\(^14,15\) Our inability to measure plaque composition reliably, arguably a better reflector of plaque stability, creates a vacuum filled by studies of plaque size.

The most widely used tool to assess plaque size is non-invasive ultrasound of carotid intimal medial thickness.\(^16\) This measures the thickness of plaque in relatively normal carotid arteries (average wall thickness \(\sim 0.1\) mm or \(10–15\%\) of lumen diameter). Although the pixel size (axial resolution) is also \(\sim 0.1\) mm,\(^16\) changes of one-tenth of this size are estimated by averaging readings over many sites and hundreds of patients.

In the ENHANCE study, combined simvastatin 80 mg plus ezetimibe 10 mg/day was no better at preventing progression in carotid intimal medial thickness than simvastatin 80 mg/day over 24 months.\(^17\) By this measure, either ezetimibe offers no incremental benefits in preventing plaque progression (hinting that non-LDL effects of statins are important), or this ultrasound technique cannot measure important changes beyond that achieved by intensive LDL lowering with simvastatin 80 mg/day.\(^17\) The hysteria surrounding the ENHANCE study failed to recognize that it studied one facet of vascular biology and not the clinical benefit of ezetimibe. The key limitation is that very small changes in plaque size

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**Figure 1** Lowering LDL cholesterol changes vascular biology to improve endothelial function by increasing bioavailability of nitric oxide (NO) and decreasing endothelin (ET). These lead to much larger changes in plaque composition compared with plaque size. Clinical studies using ezetimibe and statins suggest most of the changes in vasomotor function and inflammation are related to the magnitude of change in LDL, but our ability to measure plaque composition in vivo is limited. (VSMCs = vascular smooth muscle cells).
occur with LDL lowering, in contrast to the very large changes in plaque composition and clinical risk. Clinical studies of vascular form await the development of techniques that reliably measure changes in plaque composition, as these are closely regulated by arterial function, and intimately related to plaque instability that heralds cardiovascular events.

Lowering cardiovascular risk

Settergren’s study provides important data that refute the importance of non-LDL effects of statins, but only randomized controlled trials can test the clinical efficacy and safety of ezetimibe. Until then, statins remain the primary method to lower LDL for cardiovascular risk reduction. New statins and novel therapies need to be tested against proven statin regimens, rather than placebo, to assess their marginal benefits.

The alternative or additional approach beyond statin therapy is to intensify the treatment of other conventional risk factors such as systolic blood pressure, overweight, and smoking, and to encourage physical activity. Targeting multiple risk factors simultaneously compounds risk reduction and, to paraphrase Mies van der Rohe, less is more.

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References


The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.