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Scientific Update™

Looking beyond Lipid-lowering
New Horizons of Treatment

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Atherosclerosis is a multifactorial disease; its progression is a function of genetic and environmental factors and involves a complex interaction between blood elements, disturbed flow, and vessel wall abnormality. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (collectively termed statins) have been shown to reduce adverse clinical events in patients with documented or at risk of vascular events. There is increasing experimental and clinical evidence to support the concept that statins exert their beneficial effects by mechanisms beyond their lipid-lowering effect. In this *Cardiology Scientific Update*, several thought-provoking approaches will be discussed, including the pleiotropic effects of statins, the emerging role of statins in reducing C-reactive protein (an inflammatory marker), and the possible protective effect of statins against dementia.

Pleiotropic effects of long-term statin therapy

The statins significantly reduce cardiovascular (CV) mortality associated with hypercholesterolemia.[1-3] Although these beneficial effects have been attributed to the statin-mediated lowering of plasma cholesterol, mevalonic acid (the product of the enzyme reaction that is inhibited by statins) can act as a precursor to numerous isoprenoid metabolites.[4] This may lead to pleiotropic effects that may include, but are not limited to, endothelial function, inflammation, coagulation, and plaque vulnerability.[2,5] Experimental and clinical evidence for such possible pleiotropic effects are discussed below.

Endothelial function and oxidative stress

There is increasing evidence that the statins exert their beneficial effects, in part, by directly acting on the walls of blood vessels. This was recently examined in detail in a study in spontaneous hypertensive rats (SHR) with normal blood cholesterol treated for 30 days with atorvastatin.[6] Statin therapy significantly improved endothelial function (as measured by carbachol-induced vasorelaxation in the aortic segments [Figure 1]), and reduced angiotensin II (ANG-II)-induced vasoconstriction. Moreover, mRNA expression of the ANG II type 1 (AT_1) receptor and the NAD(P)H oxidase subunit of p22phox were down-regulated and vascular production of reactive oxygen species (ROS), as measured by lucigen chemiluminescence assays, was reduced. On the other hand, endothelial cell nitric oxide synthase (ecNOS) mRNA and activity in the vessel wall was increased; this was associated with a decline in systolic blood pressure. These data therefore suggest that statins (ie, atorvastatin) reduce mRNA expression of the AT_1 receptor and NAD(P)H oxidase subunit p22phox, which in turn, leads to reduced ROS generation, improved endothelial function, and normalization of blood pressure in SHRs.

In human saphenous vein endothelial cells, treatment with oxidized LDL (ox-LDL) decreased mRNA and protein expression of ecNOS.[7] The statins simvastatin and lovastatin up-regulated ecNOS expression and prevented the down-regulation by ox-LDL. Actinomycin D studies revealed that simvastatin stabilized ecNOS mRNA. Nuclear run-on assays and transient transfection studies with a –1.6 kb ecNOS construct showed that simvastatin did not affect ecNOS gene transcription. Post-transcriptional up-

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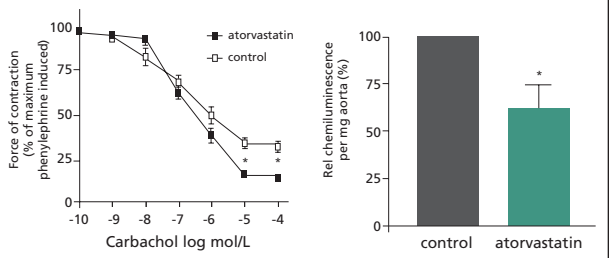
Figure 1: Effect of atorvastatin on endothelial function and oxidative stress in the aortic segments of spontaneous hypertensive rats



regulation of ecNOS expression may therefore be another mechanism for the beneficial effects of the statins on atherosclerosis.

In patients with coronary artery disease (CAD), endothelial dysfunction and oxidative stress (as detected by forearm blood flow response to the co-administration of acetylcholine and vitamin C, respectively) predict the risk of CV events.[8] In patients with acute coronary syndromes (ACS), those who developed myocardial infarction (MI) had significantly higher circulating levels of ox-LDL than patients with unstable angina, stable angina, or controls.[9] Furthermore, in the atherectomy specimens, the surface area containing ox-LDL positive macrophages was significantly greater in patients with unstable angina as opposed to those with stable angina. These data therefore provide clinical evidence that is supportive of a relationship between oxidative stress, endothelial dysfunction, and CV events in patients with CAD.

In hypercholesterolemic patients, lovastatin and fluvastatin therapy reduced the platelet cholesterol/phospholipid ratio, platelet aggregation, and LDL susceptibility to oxidation induced by the copper ion.[10] Atorvastatin and gemfibrozil metabolites, but not the parent drug, appeared to be potent antioxidants against lipoprotein oxidation.[11] Thus, LDL oxidation (induced by copper ions and the free radical generating system AAPH) was inhibited in a dose-dependent manner by the O-hydroxy and the p-hydroxy metabolites of atorvastatin and gemfibrozil. Similar inhibition was demonstrated on very low-density lipoprotein (VLDL) and high-density lipoprotein (HDL). The inhibitory effects of atorvastatin metabolites may be related to their free radical scavenger activity. On the other hand, in patients with heterozygous familial hypercholesterolemia, simvastatin therapy for 6 months significantly reduced the possible cytotoxic electronegative LDL portion, even though LDL susceptibility to oxidation was not altered in this study.[12]

Vascular permeability is believed to be a key variable in the atherogenic process. In patients with hypercholesterolemia, simvastatin (administered at 40 mg/day for 1 month) normalized transcapillary albumin escape rate and acetylcholine-induced forearm vasodilatation.[13] These changes did not correlate with a reduction in serum LDL level, indicating that the effects of the statins on vascular permeability and endothelial function are independent of their cholesterol-lowering effects.

Hemostatic mechanisms and inflammatory response

Statins may also reduce the incidence of CV events by minimizing thrombogenic and inflammatory mechanisms. In post-MI patients, pravastatin (administered at 20 mg/day for 8 weeks and 40 mg/day for another 8 weeks) significantly reduced circulating levels of fibrinogen, factor VII, prothrombin fragments 1 and 2, thrombin-antithrombin complexes, and inhibitor of plasminogen activator activity. As above, these changes did not correlate with a reduction in LDL cholesterol.

In another study, patients with symptomatic carotid stenosis who were scheduled for carotid endarectomy were randomized to 3 months of treatment with pravastatin (40 mg/day) or no therapy before the scheduled operation.[14] Carotid plaque composition was subsequently assessed with special stains and immunocytochemistry. When compared with the plaques of the untreated patients, plaques from pravastatin-treated patients had significantly less lipid, less oxidized LDL immunoreactivity, fewer macrophages and T-cells, and less metalloproteinase 2 (MMP-2); however, they had greater inhibition of metalloproteinase 1 (TIMP-1) immunoreactivity, less apoptosis, but a higher collagen content. These observations were interpreted as demonstrating the plaque-stabilizing effects of pravastatin.

The pleiotropic effects of the statins possibly explain the recent observation of increased event rates in ACS patients when statin therapy is withdrawn.[15] In the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study, 1249 patients were not on statin therapy, 379 were taking statins and continued with statin therapy, and 86 discontinued statin therapy after hospitalization. Statin therapy was associated with a reduced rate of death and non-fatal MI at 30-day follow-up. If statins were withdrawn after hospitalization, the event rate increased when compared to patients who continued to receive them. This was related to an increased event rate during the first week after onset of symptoms and was independent of cholesterol levels.

A partial list of the pleiotropic effects of statins is shown in Table 1. They likely account for the beneficial effects of these agents beyond that of lipid lowering. However, clinical evidence for how these mechanisms operate is just emerging. This may lead to the development of new statins with an even wider spectrum of "desirable effects".

The emerging role of statins in reducing CRP: The anti-inflammatory connection

Over the past decade, a great deal of attention has focused on the role of inflammation in the pathophysiology of atherosclerosis and ACS.[16] The sudden conversion from stable CAD to life-threatening ACS usually involves coronary plaque rupture with superimposed thrombosis.[17] Local inflammatory cells release biologically active molecules that lead to plaque

Table 1: The pleiotropic effects of statins

Improve myocardial perfusion
- Improve vascular endothelial function
- Antioxidant effect
- Reduce erythrocyte rigidity and blood viscosity
- Reduce endothelial permeability
- Decrease endothelin production

Atherosclerotic plaque stabilization
- Anti-inflammatory effects
- Reduce plaque content of lipid and ox-LDL
- Reduce macrophage and foam cells
- Reduce MMP activity and apoptosis
- Increase TIMP activity and collagen content
- Anticoagulant and pro-fibrinolytic activity

destabilization. These plaques ultimately rupture, leading to thrombus formation and precipitating arterial occlusion and the ACS. A list of potential inflammatory biochemical markers is shown in Table 2.

Markers of inflammation

C-reactive protein (CRP) is a prototypic and sensitive marker of inflammation and CV events in patients with stable and unstable angina.[18] Prospective data from apparently healthy men suggest that baseline levels predict the risk of a first MI.[19] This predictive value of baseline CRP in an apparently healthy population appears to be in addition to that of total and HDL cholesterol.[20]

In a nested case-controlled substudy of the Cholesterol and Recurrent Events (CARE) study comparing CRP and serum amyloid A (SAA), both CRP and SAA were higher in patients with recurrent events and the highest risk was observed in those with elevation of both CRP and SAA assigned to placebo therapy.[21] By stratified analyses, the association between inflammation and risk was much attenuated in patients randomized to pravastatin therapy.

World Health Organization standards have been set for high-sensitivity assessment of CRP, and testing for high-sensitivity CRP (hs-CRP) appears to produce consistent results.[22] The assay detects levels of CRP that are usually considered normal, but could be indicative of low-grade inflammation that may be present in the early stages of atherosclerosis.

Another circulating inflammatory marker that has recently been shown to predict the risk of future MI is the intercellular adhesion molecule ICAM-1.[23]

The role of statins in reducing inflammation

Although improvements in the lumen of atherosclerotic arteries with statin therapy was once thought to be an important mechanism for reducing adverse clinical events, there is now

Table 2: Potential inflammatory biochemical markers

General
- C-reactive protein
- Serum amyloid A

Cytokines
- Tumor necrosis factor-α
- Interleukins

Adhesion molecules
- Vascular and cellular adhesion molecules
- E-selectin, P-selectin

Lesion lytic enzymes
- MMP-1, 2, and 3

increasing evidence to suggest that lipid-lowering is an anti-inflammatory intervention that helps to stabilize atherosclerotic plaques.[5,16] Thus, in a classic model of inflammation[24] – carrageenan-induced footpad edema – simvastatin administered orally to mice 1 hour prior to carrageenan injection reduced edema. When administered for 6 weeks to apoE-deficient mice, simvastatin reduced the extent of atherosclerosis in the aorta, even though plasma lipid levels were not altered.

Thermal heterogeneity within atherosclerotic arteries is an *in vivo* measurement of the heat released by activated inflammatory cells in plaques. This has been shown in rabbits fed a high cholesterol diet[25] and in patients to predict the severity of ACS.[26] The statins can also inhibit leukocyte function. The $ß_2$ integrin leukocyte function antigen-1 (LFA-1) plays an important role in inflammation. Some statins have been shown to *selectively* block LFA-1-mediated adhesion and co-stimulation of lymphocytes, an effect that was unrelated to HMG-CoA inhibition.[27] Finally, in human monocyte-derived macrophages, simvastatin produced a dose-dependent decrease in superoxide formation in response to activation by phorbol myristate acetate, thereby reducing the oxidation of LDL.[28] LOX-1 is a lectin-like receptor on endothelial cells that facilitates uptake of ox-LDL.[29] Increased expression of LOX-1 promotes some of the known detrimental effects of ox-LDL, namely increased apoptosis, reduced ecNOS, and increased cell adhesion.[30] Protein kinase B (PKB) has been shown to be important for the expression of ecNOS.

Li et al recently demonstrated ox-LDL up-regulation of LOX-1 protein and mRNA in human coronary artery endothelial cells; this enhanced ox-LDL uptake and decreased phosphorylation of PKB without affecting PKB protein levels.[31] Importantly, atorvastatin and simvastatin decreased the ox-LDL-mediated increase in LOX-1 expression and uptake of ox-LDL. The statins also increase PKB activity in the presence of ox-LDL. Since the PKB pathway is involved with inflammation, the effects of statins on PKB could provide a potential common mechanism for anti-inflammatory effects.

The statins may also have anti-thrombotic effects. Tissue factor (TF) plays a pivotal role in thrombus formation in ACS. In human macrophages, fluvastatin and simvastatin (but not pravastatin) decreased TF activity, protein, and mRNA, effects that were prevented by mevalonate.[32] In a model of porcine aortic media, exposure to venous blood of patients with CAD[33] resulted in quantitative morphometric platelet thrombus formation that was higher in hypercholesterolemic than in normocholesterolemic patients. In hypercholesterolemic patients, treatment with pravastatin decreased platelet thrombus formation in aortic tissue exposed to the blood of these patients.

There is growing body of clinical data suggesting that inflammatory markers may predict response to statin therapy and that statins reduce circulating levels of markers of inflammation in patients with CAD. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), baseline levels of CRP that were higher than the median value (but not homocysteine) predicted an improvement in outcome with lovastatin in patients with *low* lipid levels.[34,35] Lovastatin reduced the CRP level by 14.8% ($p < 0.001$), an effect not associated with the changes in lipid levels. In the CARE study, the hs-CRP level of pravastatin-treated patients decreased over the 5-year follow-up, whereas the level in placebo-treated patients tended to increase over time.[36] There were no relationships between changes in hs-CRP and lipid levels.

The anti-inflammatory effects of statins may partially explain the recent observation of an early reduction in recurrent symptomatic myocardial ischemia in patients with ACS in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study.[37] The reduction of CRP by the statins appears to be a class-effect. In a randomized, double blind, crossover trial of 22 patients with combined hyperlipidemia,[38] simvastatin (20 mg/day), pravastatin (40 mg/day), and atorvastatin (10 mg/day) administered for 6 weeks produced similar reduction in hs-CRP levels.

Recent data have suggested that CRP, aside from being a marker of inflammation, may actually exert detrimental effects, thus contributing to adverse CV events. In human peripheral blood monocytes, purified human CRP in concentrations commonly achieved *in vivo* during inflammation, induced a 75-fold increase in TF procoagulant activity (TCA), with a parallel increase in TF antigen levels.[39] This effect was completely blocked by a monoclonal antibody against human TF. In human monocytes transformed to macrophages, native LDL co-incubated with CRP was taken up by macrophages by macropinocytosis.[40] This uptake of CRP/LDL co-incubate was mediated by the CRP receptor CD32. Thus, CRP-opsonized native LDL may partially mediate foam cell formation in human atherogenesis.

The protective effect of statins on cerebral vascular targets: A clinical epidemiological perspective

Advancing age is one of the strongest risk factors for CV events in the North American population. Accordingly, CV mortality occurs primarily among individuals >65 years of age. Although risk factors for CV disease are more common in the elderly, recent data from CV health surveys have suggested that the elderly are less likely to receive diet or drug therapy for dyslipidemia and hypertension.

In the case of secondary prevention, when CV disease has already been diagnosed, there is little scientific rationale for withholding therapy in older individuals. The situation with primary prevention, however, is a more complex issue, as the predictive power of several risk factors appears to decline with age. The new lipid guidelines published by the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) recognize both total cholesterol and cigarette smoking as strong risk factors in the young, but their importance in the elderly appear less clear.[41] In the Multiple Risk Factor Intervention Trial (MRFIT) study, the relative risk for death from CAD for a given quintile of serum cholesterol level appeared lower in older than in younger patients.[42] Among adult Canadians, the benefits of diet modification is modest in men aged 30 - 59, but is negligible among women and older men.[43] Finally, the coronary risk reduction observed in various statin trials appeared more prominent in younger than in elderly patients (Table 3). Accordingly, the decision to treat blood lipids in elderly patients *without* overt CV disease should probably be individualized.

The prevalence of dementia increases with the number of CV risk factors and dyslipidemia appears to be a strong

Table 3: Impact of therapy with statins based according to age groups

Study	Age	Coronary event relative risk reduction (%), active treatment vs. placebo
4S[1,49]	<60	37
	>60	27
CARE[3]	<60	20
	>60	27
LIPID[50]	<55	32
	55-64	20
	65-69	28
	≥70	15
WOSCOP[2]	<55	40
	≥55	27
AFCAPS/ TexCAPS[51]	≤57	46
	>57	30

independent risk factor for the development of dementia (Alzheimer's disease). In the Rotterdam Study,[44] indicators of atherosclerosis – based on carotid ultrasonography and the ratio of ankle-to-brachial systolic pressure – were associated with dementia and its major subtypes, Alzheimer's disease (odds ratios 1.3-1.8) and vascular dementia (odds ratio 1.9-3.2). In a prospective, longitudinal, community-based study of 1111 non-demented subjects over a 7-year period, levels of LDL cholesterol were strongly associated with incident dementia with stroke, after adjusting for vascular factors and demographic variables. Levels of LDL corrected for lipoprotein(a) were an even stronger predictor of dementia with stroke in the multivariate analysis. In another prospective study of 1449 subjects in eastern Finland followed for 21 years, increased systolic blood pressure ≥ 160 mm Hg and total cholesterol ≥ 6.5 mmol/L in midlife had a significantly higher risk of Alzheimer's disease in later life, even after adjustment for age, body mass, education, vascular events, smoking, and alcohol consumption.

There are to date no prospective, randomized, controlled data to suggest that lipid-lowering therapy will reduce the risk of dementia, although the results of several observational studies are interesting and provide the rationale for randomized controlled studies. In a cross-sectional analysis of hospital records,[45] the prevalence of probable Alzheimer's disease was compared among patients who received statin therapy, patients who received other medications used in the treatment of hypertension and CV disease, and the entire study population. In the cohort taking statins during the 2-year study, the prevalence of probable Alzheimer's disease was 60% and 70% lower than in the total patient population and in those who took other medications, respectively.

In a prospective study of 1037 postmenopausal women with CAD in the Heart and Estrogen/progestin Replacement Study,[46] the Modified Mini-Mental State Examination (MMMSE) was administered at the end of the study after 4 years of follow-up. Compared with women in the lower quartiles, women in the highest LDL cholesterol quartile at cognitive testing had worse MMMSE scores and an increased likelihood of cognitive impairment (adjusted odds ratio 0.76; 95% CI, 1.04-2.97). A reduction in the LDL cholesterol level during the 4 years tended to be associated with lower odds of impairment (adjusted odds ratio, 0.61; 95% CI, 0.36-1.03) compared with women whose levels increased. Higher total and LDL cholesterol levels, corrected for lipoprotein(a) levels, were also associated with a worse MMMSE score and a higher likelihood of impairment, whereas high-density lipoprotein cholesterol and triglyceride levels were not associated with cognitive changes. Compared with non-users, statin users had higher mean MMMSE scores and a trend towards a lower likelihood of cognitive impairment (odds ratio 0.67, 95% CI, 0.42-1.05), findings that seem to be independent of lipid levels.

In a recent secondary analysis of the Canadian Study of Health and Aging (CSHA-2),[47] the relationship between use of a lipid-lowering agent (LLA) and incident dementia was examined in 2305 subjects. The key finding was that LLA use was significantly more common in younger (age 65-79 years) than in older (age > 80 years) subjects. The use of LLAs was not associated with other factors indicative of a healthier lifestyle; it was, however, associated with a history of smoking and hypertension. The use of statins and other LLAs reduced the risk of Alzheimer's disease (odds ratio 0.26, 95% CI, 0.08-0.88) and all types of dementia (odds ratio 0.21, 95% CI, 0.08-0.54) in subjects < 80 years, even after adjustment for gender, education, and self-rated health. This study partially eliminated some of the indication bias and therefore provides further support of an association between LAA use and reduced risk of incident dementia.

The only published, placebo-controlled trial that examined the impact of an intervention on dementia was the Systolic Hypertension in Europe (Syst-Eur) study.[48] In this study, patients without dementia, at least 60 years old, who had blood pressure 160-219/< 95 mm Hg, were randomized to active or placebo antihypertensive therapy. Cognitive function was assessed by the MMSE. If the MMSE score was ≤ 23, diagnostic tests for dementia (DSM-III-R criteria) were performed. In the 2-year median follow-up, active antihypertensive treatment (as compared to placebo), reduced the incidence of dementia by 50%, including dementia due to various etiologies.

As alluded to earlier, both hypertension and hypercholesterolemia are risk factors for the development of dementia.[44] Given the results of Syst-Eur and the observational studies discussed earlier, there are strong reasons to believe that randomized controlled trials of lipid lowering on dementia should be forthcoming.

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