The Expanding Role of HMG-CoA Reductase Inhibitors (Statins) in the Prevention and Treatment of Ischemic Heart Disease

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In this month’s issue of Current Problems in Cardiology, Dr Robert Chilton, Associate Professor of Medicine and Director of the Cardiac Catheterization Laboratory at Audie L. Murphy Veterans Affairs Hospital, and Dr Robert A. O’Rourke, the Charles Conrad Brown Distinguished Professor in Cardiovascular Disease at the University of Texas Health Sciences Center at San Antonio, provide a superb up-to-date discussion on an extremely important and common clinical cardiology problem: atherosclerosis and coronary artery disease. This well-referenced and very well-reviewed article discusses the multiple beneficial effect of HMG-Co-reductase (statin) therapy.

The editorial board of Current Problems in Cardiology is greatly obliged to Drs Chilton and O’Rourke for this excellent and extremely useful monograph of statins.

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Introduction

The introduction of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), which are powerful low-density lipoprotein (LDL) cholesterol-lowering drugs, made it possible to confirm the hypothesis that cholesterol reduction decreases total mortality rates. Since 1993 five major trials with statins have been published: three secondary prevention (Scandinavian Simvastatin Survival Study [4S], Cholesterol and Recurrent Events [CARE] Trial, Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID]) and two primary prevention (West of Scotland Coronary Prevention Study [WOSCOPS] and Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/Tex-CAPS]) trials. All trials showed a marked reduction in major coronary artery events, and three found a reduction in total mortality rates; no increases in noncardiovascular-related deaths occurred in any of the trials. These trials documented convincingly that cholesterol-lowering therapy is both safe and effective for reducing the risk of heart disease.

More recently, many important basic mechanistic studies in vascular biology and several innovative clinical studies indicate that the salutary effects of statins in the prevention and treatment of coronary heart disease are not due solely to a reduction in LDL cholesterol. The effectiveness of statin therapy is also related to the direct and indirect effects of the HMG-CoA reductase inhibitors on inflammation, endothelial function, myocardial perfusion, coagulation, and stabilizing the vulnerable atheromatous plaque.

Effects of Statins on Hypercholesteremia

The relationship between elevated serum lipid concentrations and cardiovascular events dates back many centuries. The 1993 report from Klag et al., in which 1117 medical students from the John Hopkins medical
school were monitored from a mean age of 23 for more than 2 decades, demonstrated a positive correlation between serum cholesterol levels and the incidence of cardiovascular disease (Fig 1). Cholesterol levels greater than 200 mg/dL were associated with a marked increase in the incidence of cardiovascular disease. The separation between events and no events in those with total serum cholesterol levels became more marked with the passage of time and when cholesterol levels exceeded 172 mg/dL.

In the Framingham Heart Study, men aged 31 to 39 were evaluated during 30 years of follow-up (Fig 2). Those who had serum cholesterol levels that were greater than 260 mg/dL had a marked increase in the likelihood for development of cardiovascular disease compared with subjects who had cholesterol levels that were less than 180 mg/dL.

In the Multiple Risk Factor Intervention Trial (MRFIT) study, Stamler et al evaluated 361,662 men, aged 35 to 57 years, during a 6-year follow-up to define the mortality rate of coronary artery disease per 1000 patients (Fig 3). Again, there was a strong association between a serum cholesterol level of 150 mg/dL or greater and the incidence of coronary artery disease–related death. In 1998, Grundy described an apparent curvilinear risk ratio between the incidence of coronary artery disease and the serum cholesterol level in his analysis of the Framingham Heart Study and the MRFIT study (Fig 4). Whether this relationship between decreasing cardiac events and lower serum cholesterol levels is curvilinear or long linear and at what level a threshold is reached remains controversial. The CARE and WOSCOPS results, like the Framingham Heart Study,
suggested a threshold at 120 to 125 mg/dL, but the S4 results, like MRFIT, did not (Fig 4).

An evaluation of the pathobiologic condition of atherosclerosis also provides important information. In an autopsy study of young men and women who died of natural causes between ages 15 to 34 years, the incidence of fatty streaks and raised lesions were evaluated. Surprisingly, raised plaques in the right coronary artery were found in some women as early as 20 years of age, despite no significant risk factors being identified.
In an evaluation of heart transplant donors at the Cleveland Clinic Foundation, Tuzcu et al. determined the prevalence of disease in the coronary arteries by intravascular ultrasound scanning in transplant donors. The incidence was 17% in 20-year-old patients and 85% in patients older than 50 years of age (Fig 5). Approximately 30% of patients who were transplant donors had evidence of coronary artery disease by intravascular ultrasonography.
A summary of the primary and secondary prevention trials with statins that have been reported at the time of this writing is shown in Fig 6.1-4 The LDL cholesterol (first column) and cardiac event risk (second column) were reduced in each of the statin trials, including those for primary and secondary prevention. In the primary prevention trial, WOSCOP, pravastatin was used at a maximum dose of 40 mg, and in the AFCAPS/TexCAPS study a maximum dose of lovastatin of 40 mg a day was used. In the 4S trial, 20 to 40 mg of simvastatin produced a significant reduction in cardiovascular events, including stroke and peripheral vascular disease. The CARE trial (40 mg of pravastatin) also demonstrated an impressive 30% reduction ($P < .04$) in the development of diabetes in patients receiving statin therapy.23 Whether the reduction in LDL cholesterol is the major factor in decreasing cardiac events is still unclear considering the multiple effects of statin drugs in addition to the reduction in oxidized LDL cholesterol.

In the CARE secondary prevention trial, there appears to be a curvilinear relationship between the rate of major cardiovascular events (MCE) at 75 mg/dL, 125 mg/dL, and 174 mg/dL, with a relatively flat response at 125 mg/dL (Fig 7). When the baseline cholesterol levels were greater than 150 mg/dL, pravastatin at a dose of 40 mg resulted in a 35% decrease in MCE, and when the baseline cholesterol levels were between 125 and 150 mg/dL, pravastatin at a dose of 40 mg resulted in an approximately 26% decrease in MCE. However, if the baseline serum cholesterol on admission was less than 125 mg/dL, the decrease in MCE was only 3% and not significant.
Additional information from prospective epidemiologic studies (eg, MRFIT) are consistent with the data in the CARE trial, suggesting a curvilinear relation between LDL cholesterol reduction and a decrease in heart-related events. A meta-analysis performed in 18 patient populations totaling 172,760 men demonstrated little or no relationship between coronary artery–related death and serum cholesterol in patients with the lowest 20% to 25% of cholesterol levels (up to 170 to 180 mg/dL). In another analysis of the CARE trial (Fig 8), the percent change in coronary artery disease–related risks was related to the percent reduction in LDL cholesterol. A 41% reduction in the risk of coronary artery disease is associated with a 10% to 19% reduction in LDL cholesterol but no further decreases with a reduction of percent LDL of 20% to 35%.
in cholesterol.\(^{26}\) The data indicate that a 10% to 19% reduction in LDL cholesterol will result in a 41% reduction in risk for coronary artery disease and that below this range, any further reduction of the LDL cholesterol will not significantly change the risk.

By contrast, a subanalysis from the 4S secondary prevention trial at 1-year follow-up indicates that potentially reducing the LDL cholesterol to a lower level might lead to fewer coronary artery events\(^{27}\) (Fig 9). There was a continuous decrease in the coronary artery event rate in relation to the LDL cholesterol level. Patients with an LDL cholesterol of 77 mg/dL had a lower percent of coronary events during follow-up than those who had an LDL cholesterol of 174 mg/dL of the cholesterol. Fig 10 displays the same information in a different way. An assessment of the percent reduction in LDL cholesterol in the 4S trial determined that a 1% drop in LDL resulted in an actual decrease in cardiac events of 1.7%. This is highly significant, even though the confidence intervals range from 1.0 to 2.4. Further information from the 4S trial was published in abstract form in 1997\(^ {28}\) (Fig 11). These data show decreasing coronary artery–related events in 3 different groups of patients with LDLs ranging from 58 to 266 mg/dL. The diminution in coronary artery–related events occurred within the group that had the largest reduction in LDL cholesterol. These data are contrary to a curvilinear relationship and suggest more of long linear response to reducing LDL cholesterol with statins.

In the first report of the Post-Coronary Artery Bypass Grafting Trial after 4.3 years of treatment with lovastatin in patients whose LDL cholesterol level was between 93 to 97 mg/dL had significantly less progres-

![Fig 9. Data from 4S Trial analyzed at 1 year indicate LDL and cholesterol lesser percent of coronary events at average level of 77 mg/dL than at higher levels up to 174 mg/dL.](image-url)
The percent of cardiac events that were present in each of the major primary and secondary trials, including myocardial infarction and cardio-

\[\text{FIG 10. Further analysis of 4S trial shows percent reduction in LDL of 1% to be associated with 1.7% decrease in cardiac events.}\]

\[\text{FIG 11. Reduction in LDL levels in relationship to major coronary events is shown for 4S trial with decrease in coronary events occurring in patients in 3 different ranges of LDL cholesterol. There was a reduction in major coronary event rates in the 58 to 104 mg/dL group, as well as in those with much higher levels of LDL cholesterol after therapy with simvastatin at 1 year.}\]
vascular deaths is depicted in Fig 13. Included in this illustration are the results of the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial, in which gemfibrozil was used in the treatment arm. The beneficial effect of using statins in patients with high lipid levels is obvious. The highest incidence of control subjects who had myocardial infarction or cardiovascular death occurred in the 4S trial, followed by the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial, LIPID, CARE, WOSCOP, and AFCAPS trials. Thus, in the 4S trial it
would be necessary to treat only 13 patients for a period of 4 to 5 years to prevent one myocardial infarction or cardiovascular-related death. By contrast, in the AFCAPS trial, 71 people would need to be treated over a period of many years to prevent one myocardial infarction or cardiovascular-related death.

The Reversal of Atherusclerosis with Lipitor RheothRex for Acute Myscardial Infarction (REVERSAL) trial is an ongoing study assessing the effects of high-dose versus low-dose statin therapy on plaque volume with intravascular ultrasonography used in 600 patients. The objective is to determine whether it is possible to decrease plaque volume with high-dose statin by use of atorvastatin (80 mg) and to compare the results with 40 mg of pravastatin. Two other important ongoing trials include the Treating to New Target trial and the Incremental Decrease in Endpoints through Aggressive Lipid lowering trial. The Treating to New Target is a 5-year trial with 8600 patients with prior coronary events enrolled. The primary endpoint is heart-related death or nonfatal infarction. Events in patients receiving atorvastatin 80 mg, which should reduce LDL levels to around 75 mg/dL, and in patients receiving atorvastatin 10 mg, which should decrease the LDL cholesterol to about 100 mg/dL, will be compared. It is hoped that this trial will answer the question of whether a lower LDL cholesterol is better for preventing heart-related events. The Incremental Decrease in Endpoints through Aggressive Lipid lowering study will be completed in approximately 2005. In this secondary prevention trial, 7600 patients will be treated with atorvastatin 80 mg or simvastatin 40 mg/d. This 5-year trial will also address the question of whether an LDL cholesterol level less than 100 mg/dL is more efficacious than a level of 100 or greater. Another important concern is whether deleterious effects result from very low serum LDL levels, which has thus far not been proven to be the case.

The relationship between treatment of coronary artery disease with pravastatin and the onset of diabetes was evaluated in a subgroup of the WOSCOPS primary prevention trial (Fig 14). In this subanalysis, there was a reduction in new-onset diabetes, which was 30% less than in the group who did not receive pravastatin therapy. The Heart Outcomes Prevention Evaluation trial comparing the angiotensin-converting enzyme inhibitor ramipril with placebo also found approximately a 30% reduction of new-onset diabetes in patients in a secondary prevention trial that was published earlier. These trials suggest that both statins and angiotensin-converting enzyme inhibitors are important in treating the diabetic population.

Many physicians believe that serum cholesterol concentrations should be kept low to lessen the risk of cardiovascular disease. However, defini-
tive studies of the relation between serum cholesterol and all-cause death are still pending. In the elderly patient it is even more uncertain. A cohort study of cholesterol levels and all-cause death in the elderly was recently reported from the Honolulu Heart program. To the investigators’ surprise, the patients in the lowest cholesterol quartile had the highest all-cause mortality rate over 20 years.³³ By contrast, in a subgroup from the LIPID trial of 3514 patients, 65 to 75 years of age, pravastatin reduced the risk for all cardiovascular disease events, and similar relative effects were observed in older and younger people. Because older patients are at a greater risk than younger patients for major cardiovascular events, the absolute benefit of treatment was significantly greater in the older patients.³⁴ In the ongoing Study Assessing Goals in the Elderly (SAGE) trial, ambulatory patients, age 65 to 85, with a history of coronary artery disease are being treated with atorvastatin 80 mg or pravastatin 40 mg in a double-blind comparative parallel arm study assessing the relative reduction in duration of myocardial ischemia.

Finally, the density of the lipoprotein particle size may be important. In 52 postmenopausal women with type II hyperlipidemia, the results of a 12-week trial of 40 mg of fluvastatin administered once a day was assessed.³⁵ Importantly, measuring the total LDL cholesterol did not show a significant reduction with the use of fluvastatin. However, when the small dense particles LDL-4, LDL-5, and LDL-6 were specifically measured along with apolipoprotein B, they were reduced by treatment with fluvastatin (Fig 15).³⁵ This may represent a whole new area that needs assessment relative to the effects of statin drugs. Most statin trials

![FIG 14. In WOSCOPS study 5.5 years of treatment with pravastatin resulted in 30% reduction versus placebo in development of diabetes mellitus. Only pravastatin of the indicators shown in this figure was associated with the reduction in the incidence of developing diabetes mellitus during follow-up. BMI, Body mass index; TRIG, triglycerides.](image.png)
have assessed total LDL cholesterol and not LDL-1 to LDL-6 as subtypes.

**Statins and the Vulnerable Atherosclerotic Plaque**

The atherosclerotic plaque that is vulnerable to spontaneous rupture through its fibrous cap or to erosion of the fibrous cap with secondary vasoconstriction and accumulation of platelets have been well studied by use of coronary angioscopy and intravascular coronary ultrasonography, as well as magnetic resonance imaging.36-39

On coronary angioscopy, areas appearing yellow indicate the presence of fat along the blood vessel lining and tend to be associated with thrombus 5 times as often as occurs with the white plaque. The yellow plaque appears to have a larger lipid core within the cap and frequently has an irregular surface that is somewhat eccentric; it often represents a 30% to 50% coronary artery obstruction.36-39 In addition, the temperature of the plaque has been noted to be approximately 0.5°C hotter than the surrounding tissue, suggesting inflammation of the plaque area, which may influence its likelihood to rupture.39

High-risk lesions for plaque rupture or erosion tend to be soft plaques, to be eccentric, to have less calcium than nonvulnerable plaques, and to have a thin fibrous cap.41,43 These are depicted by angioscopy and also by intravascular ultrasonography and tissue characterization techniques. There tends to be an increased concentration of angiotensin-converting enzyme in the lipid core, as well as an increase in metalloproteinases.6,43

In autopsy studies performed by Burke et al,44 differentiation was made...
between vulnerable atherosclerotic plaques and atherosclerotic plaques not likely to rupture. The major difference is a marked increase in the amount of lipid found in the plaque area when it is unstable or vulnerable (Fig 16). There was no difference between the percent of calcium found in the stable or ruptured plaque; it occurred in less than 5% in each. However, the lipid concentration of 23.8% in the ruptured plaque is much greater than the 14.1% of the nonruptured plaque. This indicates the potential benefits of reducing the lipid core to a minimum with antilipid therapy. Scanning for calcium would not be expected to help identify which patients are likely to have a vulnerable atherosclerotic plaque.44,45

In another study of 33 patients undergoing direct coronary atherectomy for unstable angina, the atherectomy tissue was available for assessment of the angiotensin II content and the interleukin-6 content, as well as the histologic study.46 High concentrations of angiotensin II were found at the shoulder regions of the plaque, along with interleukin-6 and angiotensin receptor activation.

In an important basic molecular biologic study, the effect of statin drugs on the macrophages, metalloproteinases, and the smooth muscle cells of atheroma in rabbits with hypercholesterolemia were evaluated.43 Macrophages play an important role in acute coronary artery syndromes and have the ability to produce connective tissue–degrading enzymes that subsequently can break down the fibrous cap itself. Moreover, the rapid regression of atherosclerosis can be produced by a low-fat diet that
decreases the macrophage expression and also reduces the matrix metalloproteinases and tissue factors. In this study by Fukumoto et al, statin drugs (pravastatin and fluvastatin) reduced the matrix metalloproteinases, which are secreted by macrophages present at the corner of the plaques. Also, an increase in interstitial collagen was especially prominent in the pravastatin-treated animals.

Statin drugs have been shown to stabilize plaque in many studies. By inhibiting apoptosis of endothelial cells, statins prevent plaques from developing erosion, which may result in sudden death or other cardiovascular events. Serum tumor necrosis factor–α (TNF-α) has been found to be elevated in both acute myocardial infarction and heart failure. The administration of a statin actually protects the production of nitric oxide synthetase, even when high levels of TNF-α have been placed in a culture of human neutrophils. If the statin is subsequently placed in the media, the actual nitric oxide level returns to an even higher level than baseline in these white blood cells in the presence of TNF-α, again showing a protective and potentially beneficial effect on a molecular level.

In a landmark clinical study, Corti et al studied symptom-free patients with hypercholesterolemia. They performed magnetic resonance imaging before and at 6 and 12 months of simvastatin therapy (Fig 17). At 12 months, significant reductions in vessel wall thickness and vessel wall areas without changes in lumen area were observed in aortic (n = 35) and carotid (n = 25) atherosclerotic lesions in human beings. Thus lipid low-
ering by simvastatin is associated with significant regression of atherosclerotic lesions.

In a randomized, double-blind clinical trial in 325 patients with familial hypercholesterolaemia, treatment was either atorvastatin 80 mg (n = 160) or simvastatin 40 mg (n = 165) administered daily, on an intent-to-treat basis. The primary end point was the change of carotid intima media thickness, as measured by quantitative B-mode ultrasound scanning, over 2 years. The change in thickness differed significantly between the two groups (P = .0001). Atorvastatin showed greater reductions in cholesterol concentrations than did simvastatin. Thus aggressive LDL-cholesterol reduction was accompanied by regression of carotid artery intima media thickness in patients with familial hypercholesterolemia, whereas conventional LDL lowering was not.

**Effects of Statins on Inflammation**

A very important aspect of statin therapy is the ability of HMG-CoA reductase inhibitors to act as antiinflammatory agents. Certainly the hallmark feature of a complex atherosclerotic lesion is its ability to develop inflammation, necrosis, cellular proliferation, and also lipid disposition. All of these interact in concert to produce a very vulnerable plaque that potentially could rupture. The composition of LDL in the

![Composition of LDL](image)

**FIG 18.** Two different processes may start inflammatory response. The first includes oxidation of toxic compounds that are found in the atherosclerotic plaque itself and in the other the precursor of inflammatory prostaglandins is denied from arachidonic acid.
complex lesion is made up of unsaturated fatty acids and phospholipids. Two different processes may start the inflammatory response (Fig 18). The first includes oxidation of toxic compounds that are found in the plaque itself, and the other is the precursor of inflammatory prostaglandins from arachidonic acid. Serum high-sensitivity C-reactive protein (hs-CRP) can certainly be measured in most hospital laboratories and is used in risk stratification of patients with suspected coronary artery disease.53

A recently published study by Ridker et al53 showed that statin therapy was effective in the primary prevention of coronary events among patients with relatively low lipid levels but with elevated levels of hs-CRP. The observation that the reduction of hs-CRP levels and lipid levels induced by statins did not correlate with one another suggests that, in addition to reducing LDL cholesterol, statins may also inhibit the inflammatory or noninflammatory processes that influence acute phase responses.

Figure 19 is from a 5-year prospective study performed with carotid artery ultrasonography in 826 patients comparing the odds ratio for development of carotid atherosclerosis in relationship to chronic infection, lipids, and hypertension.54 At baseline, the participants were free of atherosclerosis by carotid artery echocardiography, whereas after 5 years, there was a marked increase in the odds ratio for carotid artery disease in patients with chronic infection as compared with those with elevated lipids and hypertension.54

An increased relative risk of future myocardial infarction in the Physi-
cians Health Study was related to various factors associated with inflammation (Fig 20). In this study of 15,000 physicians, fibrinogen, intracellular adhesion molecules, interleukin-6, and C-reactive protein were all increased in patients with a greater relative risk of future myocardial infarction.52 The best identifier of a high-risk for future myocardial infarction was the presence of hs-CRP plus a total cholesterol/high-density lipoprotein cholesterol ratio that is elevated.

In a relevant clinical study of 22 patients participating in a double-blind randomized crossover 6-week trial, the effects of different statins at relatively comparable doses on hs-CRP are depicted in Fig 21. There was a significant drop in hs-CRP with pravastatin, simvastatin, and atorvastatin in relation to baseline values.55 There was no effect on interleukin-6 and no relation with lipids, indicating that CRP might be useful in deciding whether to treat patients with borderline criteria by the National Cholesterol Program guidelines.

In a study of postmenopausal women over a period of approximately 3 years, the levels of CRP and of total cholesterol TC/HDL cholesterol ratios were related in 28,263 patients to cardiovascular events53 (Fig 22). The data in women are similar to those in men, showing again that the antiinflammatory markers seem to be very predictive of future cardiovascular events.

It is generally accepted that inflammation measured by a number of different parameters can increase the future risk for myocardial infarction or other cardiovascular events. Fig 23 lists several trials that are now in progress, including Wizard and others, with the actual number of patients...
in each of these trials that are being treated with azithromycin. As indicated in the upper left, inflammation is a precursor of developing atherosclerosis. Also, Pravastation Orator Vastatin Evaluation and Infection Therapy (PROVE IT) is an ongoing study comparing atorvastatin and pravastatin in more than 4000 patients in an attempt to define the differences, the potency of various statins for reducing potential triggers of inflammation.

**Effects of Statins and the Anticoagulation System**

Patients with coronary atherosclerosis intermittently have plaque rupture that permits blood to come in contact with the inside of the
atherothrombotic tissue. The resulting marked increase in tissue factor can accelerate hypercoagulability. The use of statins has been known for some time to actually increase the production of tissue plasminogen activator (tPA), a very useful compound in the fibrinolytic system for preventing thrombosis. A study with aortic cells in rats indicates that the actual increase in tPA is markedly enhanced by lovastatin. Also, the
actual plasminogen activation inhibitor (PAI-1), which tends to increase thrombosis, is decreased with the use of lovastatin.\textsuperscript{58} As indicated by zymography,\textsuperscript{*} the fibrinolytic system is improved by increased tPA and also by decreased PAI-1.

Statins also decrease tissue factor, which is a major atherothrombotic agent.\textsuperscript{59} The effect of fluvastatin on tissue factor on unstimulated cells is shown in Fig 24. There is a significant decrease in tissue factor when fluvastatin is used. The simvastatin and pravastatin are also depicted with a reduction in tissue factor activity (Fig 25). However, pravastatin requires a larger dose in concentration as compared with simvastatin to obtain the same effect.

Bleeding times from wounds were assessed in a study in 17 patients who had hypercholesterolemia (Fig 26). The patients were placed on 20 mg of simvastatin, and after 3 months they were reevaluated with the repeat study of several different blood-clotting factors.\textsuperscript{60} This figure demonstrates that it takes approximately 60 seconds longer from baseline before these clotting factors are reduced after administration of simvastatin. This study shows reduced rates of prothrombin activation, factor 5A generation, fibrinogen cleavage, factor 13 activation, and an increased rate

\textsuperscript{*}Zymography involves electrophoresis of secreted proteases through discontinuous polyacrylamide gels containing enzyme substrates. This may be particularly relevant in the treatment of diabetic patients with coronary artery disease.

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**FIG 25.** Effects of simvastatin (S) and pravastatin (P), 2.5 umol/L, on TF activity in unstimulated (white) and LPS-stimulated (shaded) macrophages. Bars represent percent of control and are mean ± SEM of triplicate determinations from four experiments. Asterisk indicates $P < .05$ compared with preceding bar. S, Simvastatin, P, pravastatin. [Reprinted with permissions]
of factor 5A inactivation. All these lead to depressed clotting, which may be beneficial for patients who are at risk for atherothrombi.

**Effects of Statins on Endothelium Dysfunction**

There has been considerable recent interest concerning the effects of statins on the endothelial cell and nitric oxide production. In a study recently performed in the porcine model with pigs that had been fed a normal cholesterol level diet, ones that had hypercholesterolemia and ones that were hypercholesteremic receiving simvastatin treatment, the high-density lipoprotein remained very similar when comparing the hypercholesteremic and the hypercholesterolemic-plus-statin animals. The photomicrographs demonstrated a marked increase in the endothelium nitric oxide synthase (eNOS) as being produced in the normal tissue in the endothelial surface. In the hypercholesterolemic animals, there was no nitric oxide production of any significance, but in the hyperglycemic animals on statins, the actual eNOS was increased with statins resulting in the production of nitric oxide.
The commonly used compound pravastatin, which is used by many physicians for lowering LDL cholesterol, also decreases caveolin 1, which is a scaffolding protein that causes decreased expression of eNOS (Fig 27). The eNOS is a compound that helps increase and up-regulate nitric oxide. With increases of circulating LDL cholesterol levels of caveolin-1 would normally be increased. Atorvastatin has the ability to actually shut down the expression of caveolin-1. Thus another advantage of use of statin compounds in patients who have high lipids is the decreased expression of caveolin-1 with the use of these HMG-CoA reductase inhibitors.

New vascular structure tube formation may occur with the use of compounds used to lower lipids. Oxidized LDL cholesterol has the ability to inhibit vascular endothelial growth factor (VEGF), which promotes the growth of blood vessels in patients with ischemic heart disease. In a study with human umbilical vein cells seeded on growth factor, there was no new blood vessel formation in the control population when no statin was administered. However, when simvastatin was added, the formation of new tube formation was observed for the first time. The same observation occurred with pravastatin, and the compound VEGF that is well known to promote blood vessel growth also produces new tube formation. Statins and angiotensin-converting enzyme inhibiting drugs used to decrease ischemia actually promote the growth of blood vessels and form new tubes just like VEGF does.

The effects of high cholesterol levels on patients endothelial function can be demonstrated by the use of acetylcholine, which is dependent on
the normal production of nitric oxide for the patient’s forearm blood vessels to vasodilate and increase flow is shown in Fig 28. Note that there is marked impairment of flow when one compares 19 healthy control subjects versus 35 patients with hypercholesteremia. The patients with hypercholesteremia have a marked reduction in the forearm blood flow response to acetylcholine versus the patients who are healthy (Fig 28, A). The effect of adding cerivastatin, another agent that is commonly used for the control of hypercholesteremia results in improved forearm blood flow (Fig 28, B). There is a marked improvement in the patients that have hypercholesteremia by the addition of a statin again showing improved endothelial function.

In an important clinical study, patients who had average serum cholesterol levels were given pravastatin to assess the effects of lowering cholesterol on the myocardial perfusion single photon emission computed tomography (SPECT) scanning. In a randomized placebo-controlled study with crossover design, 20 patients were given pravastatin 20 mg or placebo for 16 weeks, then crossed over to the opposite medication for an additional 16 weeks. Thallium-201 SPECT images and positron emission tomography (PET) nitrogen 13 ammonia perfusion images were obtained at the end of each period. This study showed a variable but marked improvement in myocardial blood flow in multiple areas on the SPECT images with areas of stress-induced ischemia markedly improved or absent.

In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, a nuclear medicine substudy uses electrocardiography-gated dual isotope myocardial perfusion SPECT imaging with thallium 201 and technetium sestamibi, the latter given after an adenosine pharmacologic stress. An improvement often to normal has been noted in patients with stress-induced ischemia after 6 to 14 months of treatment with aggressive medical therapy including statins and also in those treated with percutaneous coronary intervention, followed by aggressive medical therapy, including statins (Fig 29). This result is also consistent with a study by Schwartz et al showing that pravastatin improves stress-induced radio nuclide myocardial perfusion abnormalities by 6 months.

In another important study, 12 patients with coronary artery disease were evaluated by use of $^{13}$N ammonium PET imaging with adenosine at baseline and 4 months later with baseline measurements made plus the addition of low- and high-dose adenosine. The same measurements

*Cerivastatin has been voluntarily withdrawn from the U.S. market because of increasing reports of rhabdomyolysis with cerivastatin.
repeated 4 months after the treatment of LDL cholesterol, which initially averaged 171 mg/dL and subsequently decreased to an average of 99 mg/dL with statin therapy.\textsuperscript{68} The myocardial blood flow at baseline was not significantly different between a normal segment and an abnormal segment (Fig 30). However, the scan response to adenosine was an increased myocardial blood flow in normal segments but no increase in blood flow in the segments with reduced uptake. After 4 months of statin therapy, the adenosine increase in blood flow is markedly increased. This again indicates that longer treatment with statin improves blood flow in patients with ischemic heart disease.

Another group studied the short-term effects of cerivastatin on endothelial function and endothelial-related products in elderly diabetic patients.\textsuperscript{69} Twenty-seven elderly diabetic patients with or without mild hypercholesterolemia were enrolled in the study. Endothelium-dependent flow mediated dilation, endothelium-independent dilation by nitroglycerin in the brachial artery, nitric oxide-related products, and endothelium-related products were evaluated. Flow-mediated dilation was significantly
increased by cerivastatin treatment, as were plasma-nitrate levels and cGMP values within 3 days.

**Recommendations**

The currently available statins are listed in Table 1. The previously mentioned review documents the need for an expanding role of HMG co-A reductase in clinical practice. This raises several important questions:

1. Who should have a lipid profile estimated?
   A. Patients with acute myocardial infarction, acute coronary syndromes, stable angina; those who have had PIC and/or CABG; those with documented coronary, carotid, or peripheral atherosclerosis; and those with an aortic aneurysm.
   B. Patients who are in the high-risk subgroups (e.g., those with diabetes, systemic hypotension, smokers, obesity, and adult children or patients with any of these disease in A and B).
   C. Ideally, all adults.

2. When should they be started on statin therapy?
   Immediately, when identified in a high-risk patient with a
clinical syndrom or who has several risk factors and requires primary prevention.

3. Which statin should be used?
   Any of the currently approved ones.

4. What is the goal(s) of statin therapy?
   A. For secondary prevention LDL of 60 to 85 mg/dL
   B. For primary prevention
      1. Low-risk group 85 to 100 mg/dL
      2. High-risk group 60 to 85 mg/dL

   This is a more aggressive approach than the National Cholesterol Education Program, but appears consistent with the available clinical data.

   The recent lipid-lowering trials that used clinical or angiographic endpoints support the hypothesis that in patients with significant risk for events as determined by the presence of pre-existing atherosclerosis, an aggressive approach to hyperlipidemic therapy is justified and does not appear to be associated with major short-term adverse events.70

**Summary**

There is accumulating published data on a daily basis indicating the favorable effects of the HMG-CoA reductase inhibitors (statins) on patients with atherosclerosis, particularly relative to patients with coronary artery disease. The effects of statins on lowering LDL cholesterol levels has been well documented. In addition, there is information indi-
cating that statins stabilize the vulnerable atherosclerotic plaque, decrease inflammation, and restore normal endothelial function in experimental animals and in human beings. There is increasing data indicating that statins improve coronary artery blood flow reserve and augment blood flow to areas of myocardial ischemia. This has resulted in marked improvement in abnormal myocardial perfusion images during stress as reported from at least 3 institutions. Future studies should indicate the optimal level of LDL cholesterol reduction with the use of these important pharmaceutical agents that appear to cause regression of coronary atherosclerotic plaques and likely have complementary effects when used in combination with angiotensin-converting enzyme inhibitors.

S. H. Rahimtoola: Dr O’Rourke has provided a superb review on the multiple beneficial effects of statins, which leads to his recommendations for the expanded role of such therapy in clinical practice. I want to emphasize that all practicing physicians should read this review carefully and be very aggressive about determining the lipid profile in all their adult patients and in people who are in the high-risk group for coronary artery disease.

The choice of statin drug and its initial starting dose should be determined by the level of LDL-C and desired level of LDL-C with therapy. It does not make much sense to start with a low dose in all patients and gradually increase the dosage over a period of months. The recommendations of Dr Robert A. O’Rourke, who is the cochairman of the COURAGE trial (an extremely important trial), are important for all practicing clinicians.

The approach described above is supported by a press release at the November 2001 AHA Scientific Session by Collins et al for the Heart Prevention Trial of 20,000 volunteers at high risk for coronary artery disease. Cholesterol lowering below 80 mg/dL reduced event rate by one third.

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