

Update on Statins: 2003

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The number of significant developments in the years since the first version of this review has made necessary an update about the evolving role of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, in the management and prevention of cardiovascular disease.¹ Two contrasting events have dominated the statin field in the last 3 years. First, the withdrawal of cerivastatin in 2001 reignited the issue of statin safety. Second, the efficacy and safety of statins in both the primary and secondary prevention of cardiovascular disease in diverse patient populations have helped shape the most recent set of guidelines from the National Cholesterol Education Program (NCEP).² The NCEP's Third Adult Treatment Panel (ATP III) forms the basis for contemporary lipid management. However, very recent trials suggest that even lower LDL cholesterol (LDL-C) targets may be indicated in high-risk patients. Improved understanding of the metabolism, safety, and clinical effects of this class of drugs has placed the statins at the forefront of drug strategies to treat dyslipidemia.

Mechanism of Action, Comparative Pharmacology, and Safety of Statins

HMG-CoA reductase is the rate-limiting enzyme for cholesterol formation in the liver and other tissues. By inhibiting HMG-CoA reductase, statins reduce the hepatocyte cholesterol content, stimulate expression of LDL receptors, and ultimately enhance removal of LDL-C from the circulation. X-ray crystallographic studies have determined the structures of the catalytic portions of HMG-CoA reductase in complex with statins.³ These studies show that the HMG-like moiety of statins occupies the HMG binding site of the reductase enzyme, thus sterically inhibiting the substrate from binding. Additional structural differences among the statins have been elucidated through such crystallographic studies that may account for some differences in the potency of statins. However, atorvastatin, fluvastatin, and rosuvastatin exhibit additional binding via their fluorophenyl groups and the HMG-CoA reductase Arg590 residue, but they differ widely in their relative LDL-C lowering.³

The statins differ in their absorption, plasma protein binding, excretion, and solubility (Table 1) and exhibit variable dose-related efficacy in reducing LDL-C.⁴ In general, LDL-C is reduced by an additional 7% with each

doubling of the statin dose.⁵ In addition, in patients with hypertriglyceridemia, statins achieve a 22% to 45% reduction in triglyceride levels because of decreased hepatic secretion of VLDL. Statins cause relatively minor increases (5% to 10%) in HDL cholesterol (HDL-C).

Statins may be combined with a number of other lipid-modifying drugs, including bile acid-binding resins, niacin, and fibrates. Patients receiving combination therapy should be monitored carefully for evidence of side effects, especially muscle-related symptoms with either niacin or fibrates (Table 2). Statins may also be combined with the novel cholesterol absorption inhibitor ezetimibe.⁶ Approved by the Food and Drug Administration in October 2002, ezetimibe is indicated for use alone or with a statin to reduce elevated total cholesterol and LDL-C. The addition of ezetimibe to a statin provides an additional 14% to 17% reduction in LDL-C. Some studies have reported an increased incidence of hepatic transaminase elevation (>3 times the upper limit of normal) with this combination.⁷ To date, there is no evidence that combination therapy with statins and ezetimibe increases muscle-related side effects beyond the risk associated with statin monotherapy.⁷⁻¹¹

Statin Safety

The American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute has issued a clinical advisory on statin therapy.¹² This document addresses the issue of muscle toxicity with statins and provides recommendations for the appropriate use of statins, including cautions, contraindications, and safety monitoring for patients taking statins. A number of important drug interactions with statins have been described that may increase the risk of muscle-related side effects (Table 2). The cytochrome P450 (CYP) isoform CYP3A4 serves as the major pathway for metabolism of lovastatin, simvastatin, atorvastatin, and cerivastatin (Figure).¹³ Inhibition of the activity of CYP3A4 can increase serum levels of these statins, which raises the potential for side effects. Pravastatin does not undergo metabolism through the CYP450 system but is metabolized by sulfation and conjugation. Fluvastatin is metabolized mainly by CYP2C9 and to a lesser extent by CYP3A4 and CYP2D6. Rosuvastatin is metabolized mainly by CYP2C9 and CYP2C19.¹⁴ Although a potential drug interaction be-

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TABLE 1. Comparative Efficacy and Pharmacology of the 6 Currently Available Statins

Drug	Reduction in TC, %	Reduction in LDL-C, %	Increase in HDL-C, %	Reduction in TG, %	Dosage Form Tablets, mg	Metabolism	Protein Binding, %	T1/2, h	Hydrophilic
Atorvastatin	25–45	26–60	5–13	17–53	10, 20, 40, 80	CYP3A4	98	13–30	No
Fluvastatin	16–27	22–36	3–11	12–25	20, 40, 80	CYP2C9	98	0.5–3.0	No
Lovastatin	16–34	21–42	2–10	6–27	10, 20, 40	CYP3A4	>95	2–4	No
Pravastatin	16–25	22–34	2–12	15–24	10, 20, 40, 80	Sulfation	43–67	2–3	Yes
Rosuvastatin	33–46	45–63	8–14	10–35	5, 10, 20, 40	CYP2C9	88	19	Yes
Simvastatin	19–36	26–47	8–16	12–34	5, 10, 20, 40, 80	CYP3A4	95–98	1–3	No

TC indicates total cholesterol; TG, triglycerides; and T1/2, half-life.

tween clopidogrel and atorvastatin was suspected on the basis of the inhibition of clopidogrel activation by atorvastatin via its effects on CYP3A4,^{15,16} more recent data question the clinical significance of this interaction.^{17,18} Atorvastatin and fluvastatin have minimal renal excretion, and dose adjustment of these statins in patients with renal insufficiency is therefore unnecessary.¹⁹

Although it was initially suspected that gemfibrozil increased statin levels by inhibiting CYP450 enzymes, it is now thought that its inhibition of glucuronidation of statins may be a likely culprit.²⁰ Gemfibrozil undergoes extensive glucuronidation by the UDP-glucuronosyltransferase (UGT) isoforms UGT1A1 and UGT1A3, which also mediate glucuronidation of statins (Figure). Glucuronidation is now recognized as a major pathway for elimination of the active hydroxy acid metabolites of statins. Fenofibrate does not appear to interfere with the UGT1A1 and UGT1A3 enzymes that mediate statin glucuronidation (fenofibrate is glucuronidated by UGT1A9 and UGT2B7).²¹ Perhaps statin-fenofibrate combinations may have less risk for interactions than therapy with statins and gemfibrozil. Other variables that may increase the likelihood of side effects with statins

include advanced age, small body size, female gender, renal and hepatic dysfunction, perioperative periods, hypothyroidism, multisystem disease (especially diabetes), and alcohol abuse.¹²

Although physicians should keep these cautions in mind, they should also remember that myopathy is an extremely uncommon side effect that has long been recognized as a potential risk of these drugs. In the Prospective Pravastatin Pooling Project, which studied more than 112 000 patient-years of drug therapy, pravastatin was withdrawn from only 3 patients because of elevated creatine kinase (CK) levels.²² Given available US data, muscle pain and weakness may affect 1% to 5% of statin-treated patients, and fatal rhabdomyolysis has an estimated incidence of 0.15 deaths per 1 million prescriptions.²³

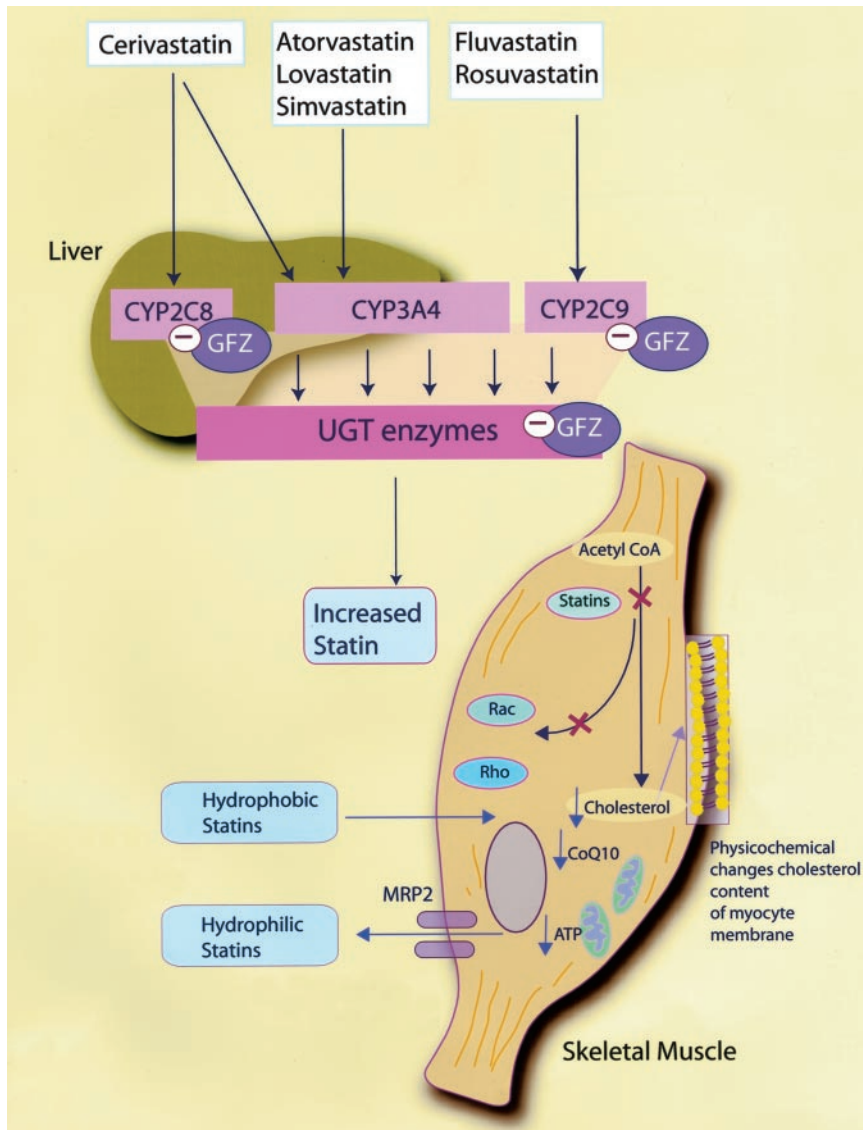
Mechanism of Muscle Toxicity With Statins

Depletion of cholesterol in myocyte cell membranes may affect membrane stability and predispose to myopathy (Figure).^{23,24} Several theories have proposed that the effects on skeletal muscle are due to depletion of intermediates in the cholesterol biosynthetic pathway. Farnesyl pyrophosphate is an intermediate in the synthesis of ubiquinone (coenzyme Q10). Ubiquinone is a steroid isoprenoid that functions in the electron transport chain and participates in oxidative phosphorylation in mitochondria. Although serum ubiquinone levels have been shown to decrease with statin therapy, the observation that intramuscular levels of ubiquinone are not reduced by statins makes ubiquinone depletion a less likely cause of myopathy with statins.²⁵ Prenylation of small GTP-binding proteins such as Rho, Ras, and Rac by farnesyl pyrophosphate and geranylgeranyl pyrophosphate has also been implicated in statin-associated myopathy.²⁶ These GTP-binding proteins play integral roles in cell proliferation and growth.²⁷ Another mechanism recently proposed that may explain myopathy is through interruption of isopentenylation of selenocysteine-tRNA by statins.²⁸

A recent study of 4 patients who reported muscle symptoms while taking statins that resolved during placebo use suggests that statin-mediated muscle damage can occur in the absence of CK elevation.²⁹ Muscle biopsies were performed in 3 patients during statin therapy and then again during placebo use. While the subjects were taking statins, muscle biopsies showed increased lipid content in mitochondria, fibers that did not stain for cytochrome oxidase activity, and

TABLE 2. Important Drug Interactions With Statins

Fibrates (especially gemfibrozil)
Niacin
Warfarin
Digoxin
Verapamil
Amiodarone
Cyclosporine
Tacrolimus
Fluconazole, itraconazole, ketoconazole
Erythromycin, azithromycin, clarithromycin
HIV protease inhibitors
Nefazodone
Venlafaxine
Fluoxetine
Sertraline
Antihistamines
Benzodiazepines
Grapefruit juice



Putative mechanisms of statin myotoxicity. Increased serum concentrations of statins can occur when drug interactions arise at the level of CYP enzyme and/or UGT enzyme systems. Predominant CYP isoforms that participate in statin metabolism are shown. Most prevalent metabolizing isoform is CYP3A4, which serves as major pathway for metabolism of lovastatin, simvastatin, atorvastatin, and cerivastatin. Major effect of gemfibrozil (GFZ) is inhibition of glucuronidation of statins. Gemfibrozil itself undergoes extensive glucuronidation by specific UGT isoforms that also mediate glucuronidation of statins. Gemfibrozil also inhibits CYP2C8 and CYP2C9. Putative myotoxic effects of statins include physicochemical actions accompanying cholesterol depletion on myocyte cell membranes, depletion of intermediates in cholesterol biosynthetic pathway that modulate activity of small GTP-binding proteins such as Rho and Rac, reductions in ubiquinone or coenzyme Q10 (CoQ10), and depletion of ATP. Other proposed mechanisms include putative effects on multidrug resistance protein 2 (MRP2), which is expressed in muscle and which may play a role in egress of statins from muscle.

ragged red fibers. These findings were not seen on repeat biopsy while subjects were not receiving statins. Interestingly, these patients did not have elevated CK levels while taking statins. The molecular mechanism responsible for myopathy with normal CK levels was not elucidated in this study, and the significance of these findings requires further evaluation.³⁰ Confirmation of this report is necessary before one can reach a meaningful conclusion.

Recent Clinical Trials

The classic statin trials completed in the 1990s have shaped the rationale for contemporary lipid-lowering practice.¹ Since then, a number of additional trials have been published that extend the observations of the classic statin trials and widen the population of patients who may benefit from lipid-lowering therapy. During this time, an important blurring of the boundary between the traditional concepts of primary and secondary prevention has also taken place. It is now clear that many patients, such as diabetics, who do not have an overt history of a vascular event may nevertheless have high risk

for myocardial infarction (MI) and stroke. "High-risk prevention" has been a theme of recent studies.

The Heart Protection Study

The Medical Research Council/British Heart Foundation Heart Protection Study (HPS) of cholesterol lowering with simvastatin in 20 536 high-risk individuals is the largest statin trial performed to date.³¹ Patients aged 40 to 80 years with coronary heart disease (CHD), other occlusive arterial disease, or diabetes were included in the study. All patients were randomly allocated to receive 40 mg of simvastatin daily or placebo. The mean baseline LDL-C was 132 mg/dL (3.41 mmol/L). Treatment with simvastatin significantly reduced all-cause mortality by 13% ($P=0.0003$). There were also significant reductions of $\approx 25\%$ in the relative risks for nonfatal MI or CHD death ($P<0.0001$) and for coronary or noncoronary revascularization ($P<0.0001$). There was no heterogeneity of benefit in any of the subgroups compared with the overall study cohort, including the diabetic patients, women, and the elderly (>70 years). Benefit was consistent across all tertiles of baseline LDL-C. Moreover, it is note-

worthy in HPS that the benefit of statin therapy may have been greater if the crossover rate to active treatment in the trial had not been so high: 17% of the placebo-allocated group were receiving nonstudy statin therapy during follow-up, usually because of CHD diagnosed at entry or higher pretreatment total cholesterol and LDL-C. There was no difference between the simvastatin group and the placebo group in the incidence of muscle pain or weakness. On the basis of the HPS data, the Food and Drug Administration approved in 2003 a revised indication for simvastatin that expanded its application beyond patients with elevated cholesterol to include patients with high coronary risk (eg, noncoronary vascular disease or diabetes).

In the recent Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial of 654 patients with symptomatic coronary artery disease, a 20% or greater stenosis by angiography, and LDL-C levels between 125 mg/dL (3.23 mmol/L) and 210 mg/dL (5.43 mmol/L), atorvastatin 80 mg/d induced greater improvement in intravascular ultrasound measurements than pravastatin 40 mg/d.³² Final LDL-C values in the pravastatin and atorvastatin groups respectively were 110 mg/dL (2.84 mmol/L) and 79 mg/dL (2.04 mmol/L). After 18 months of treatment, atorvastatin-treated patients were less likely to experience progression ($P=0.02$). No differences were seen in adverse events or liver and muscle enzyme elevations between the 2 regimens, and no patient experienced myopathy.

Some trials are addressing the "lower is better" hypothesis on clinical event end points by evaluating high-dosage statin treatment against moderate-dosage treatment or usual care. The recent Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) trial suggested that open-label atorvastatin, titrated to reach an LDL-C level <80 mg/dL (2.07 mmol/L), was superior to usual care in CHD patients in a managed care setting (public presentation, Donald Hunninghake, MD, March 8, 2004). In the pipeline are the Treat to New Targets (TNT) trial of atorvastatin 10 mg versus 80 mg daily in CHD patients and the Study of Effectiveness of Additional Reduction in Cholesterol and Homocysteine (SEARCH) of simvastatin 20 mg versus 80 mg daily.³³

The Prospective Study of Pravastatin in the Elderly at Risk

Although 24% of individuals in HPS were over age 70 years, it and earlier statin trials focused almost exclusively on middle-aged subjects. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) was the first randomized controlled trial of 2804 men and 3000 women aged 70 to 80 years with a history of or risk factors for vascular disease.³⁴ Subjects were randomly assigned to pravastatin 40 mg per day. The primary end point was a composite of CHD death, nonfatal MI, and fatal or nonfatal stroke. Average follow-up was 3.2 years. Pravastatin lowered LDL-C concentrations by 34% and reduced the relative risk for the primary end point by 15% ($P=0.014$). Mortality due to CHD fell by 24% ($P=0.043$) in the pravastatin group, and nonfatal MI risk was also reduced. New cancer diagnoses were more frequent with pravastatin than with placebo; however, incorporation of this finding in a meta-analysis of all pravastatin and all statin

trials showed no overall increase in cancer risk. Pravastatin had no significant effect on cognitive function or disability.

Earlier secondary-prevention statin studies established a statin benefit on stroke risk. In HPS, stroke was also significantly reduced by 25% ($P<0.0001$).³¹ Although the absolute stroke rates in these clinical trials were small, these studies showed that statin therapy decreased ischemic stroke without increasing hemorrhagic stroke. The PROSPER study, however, failed to show a stroke benefit.³⁵ The null finding may reflect the greater age of its cohort and its shorter duration compared with other studies.

Statins in Hypertensive Patients

The lipid-modification arm of the larger Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) hypertension trial sought to determine whether pravastatin compared with usual care reduces all-cause mortality in 10 355 older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor.³⁵ Unlike other large-scale statin trials, treatment with pravastatin 40 mg/d produced no clinical benefit compared with usual care.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is a multicenter randomized trial designed to compare 2 antihypertensive strategies for the prevention of CHD in 19 342 hypertensive subjects. ASCOT also included a lipid-lowering arm (ASCOT-LLA), which was a double-blind, randomized comparison of the cardiovascular effects of atorvastatin compared with placebo.³⁶ ASCOT-LLA included 10 305 hypertensive patients (aged 40 to 79 years with at least 3 other cardiovascular risk factors) with nonfasting total cholesterol concentrations <242 mg/dL (6.25 mmol/L) who were randomly assigned atorvastatin 10 mg or placebo. The primary end point was nonfatal MI and fatal CHD. Treatment was stopped after a median follow-up of 3.3 years after interim analysis detected a 36% relative risk reduction ($P=0.0005$) in the primary end point, favoring atorvastatin.

Why were ALLHAT-LLT results at variance with ASCOT-LLA and all other large statin trials published to date? During the ALLHAT-LLT, 32% of usual-care participants with and 29% without CHD started taking lipid-lowering drugs. At year 4, total cholesterol levels were reduced by 17% with pravastatin versus 8% with usual care. The difference in total cholesterol (9%) between the pravastatin and usual-care groups in ALLHAT-LLT is significantly smaller than the difference in cholesterol levels between placebo and treatment groups in other statin trials. This high crossover rate combined with concerns about recruitment and study design may have contributed to the null finding in ALLHAT-LLT. The more rigid design of ASCOT supports the role of statin therapy in hypertensive and high-risk patients.

Statins in Acute Coronary Syndromes

Over the last 3 years, a growing body of literature suggests that statin therapy is beneficial when administered early to patients who present with an acute coronary syndrome (ACS). This is primarily based on observational studies that have exploited preexisting ACS databases to compare outcomes among patients receiving statins with those not taking

lipid-lowering therapy.^{37–39} The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study randomized patients to atorvastatin 80 mg or placebo within 24 to 96 hours of admission with unstable angina or non-ST-elevation MI.⁴⁰ The relative risk for a primary end-point event (defined as death, nonfatal MI, cardiac arrest with resuscitation, or recurrent symptomatic ischemia requiring emergent rehospitalization) was reduced, largely because of a reduction in recurrent ischemia ($P=0.02$). Importantly, at this highest dosage of statin, the rate of serious side effects was similar ($<1\%$) in both groups, although statin users did have an increased rate of liver enzyme elevation (2.5% versus 0.6%).

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study compared the effects of early initiation of pravastatin 40 mg/d versus atorvastatin 80 mg/d on clinical events in 4162 post-ACS patients. After a mean follow-up of 2 years, the more intensive atorvastatin regimen appeared to reduce the risk for the combined incidence of major cardiovascular events and death by 16% ($P<0.005$) compared with pravastatin.⁴¹ The atorvastatin group reached a median on-treatment LDL-C level of 62 mg/dL (1.60 mmol/L) compared with the pravastatin group's 95 mg/dL (2.46 mmol/L). The event curves began to diverge as early as 30 days into the study. In our opinion, the difference was likely due to the greater LDL-C reduction by atorvastatin, although some have hypothesized that a difference in pleiotropic effects between these agents may have contributed to the finding.

Taken together, MIRACL and PROVE-IT make the beginnings of a case for early statin use in ACS management. Initiation of a statin during the acute hospitalization may have the additional benefit of improving long-term compliance with therapy.⁴² Other recent observational data indicate that statins are beneficial in patients undergoing coronary intervention by increasing short- and long-term survival and reducing periprocedural cardiac enzyme elevation.^{43–47}

New LDL-C Targets

A question raised by HPS³¹ and PROVE-IT⁴¹ is whether an LDL-C goal of <100 mg/dL (2.59 mmol/L) is adequate in high-risk patients who already have low LDL-C levels. In PROVE-IT, aggressive LDL-C lowering with high-dose atorvastatin (to a median of 62 mg/dL [1.60 mmol/L]) reduced major cardiovascular events compared with standard-dose statin therapy (median LDL-C 95 mg/dL [2.46 mmol/L]). Moreover, in HPS, even the subgroup with LDL-C concentrations <100 mg/dL (2.59 mmol/L) exhibited significant risk reduction when statin therapy was introduced. Therefore, HPS and PROVE-IT indicate that additional benefit could be achieved by lowering the LDL-C level substantially below 100 mg/dL (2.59 mmol/L). As we await the results of additional clinical trials, such as TNT and SEARCH, new recommendations from the NCEP have proposed an LDL-C goal of <70 mg/dL (1.81 mmol/L) for very high-risk patients.⁴⁸

Cholesterol-Independent Effects of Statins

There has been considerable debate as to whether statins possess cholesterol-independent effects. The biological basis

for the "statin pleiotropy hypothesis" is the site of action of statins in the cholesterol biosynthetic pathway.^{49,50} In addition to lowering intracellular levels of sterols, statins also reduce levels of isoprenoids, which are derived from intermediates of the cholesterol biosynthetic pathway. These intermediates, such as farnesylpyrophosphate, serve as important lipid-attachment molecules for the posttranslational modification of many proteins, including heterotrimeric G proteins and small GTP-binding proteins such as Ras and Rho. These molecules play fundamental roles both in cell growth and in signal transduction and mitogenic pathways.^{26,27}

Cholesterol-independent effects of statins have been described most extensively in relation to effects of statins in restoring endothelial function via enhanced availability of nitric oxide.⁵¹ A variety of other pharmacological effects of statins have been described that may promote plaque stability through modulation of macrophage activation,⁵² immunological effects,^{53,54} and antiplatelet and antithrombotic actions. Investigators have explored the direct, cholesterol-independent inhibition by statins of leukocyte function-associated antigen-1 as a novel target for the development of agents that may suppress the inflammatory response in several diseases.⁵⁴

Most pleiotropic effects of statins in cell culture studies can be reversed by the addition of mevalonic acid, which restores the antegrade integrity of the cholesterol biosynthetic pathway and its intermediates. The clinical importance of the noncholesterol effects of statins in humans has been notoriously difficult to determine, because in humans, statin treatment is almost always associated with cholesterol lowering, even in patients with initially low cholesterol levels. For now, it would appear that the majority of the clinical benefit of statins is due to LDL-C lowering. Putative cholesterol-independent effects of statins remain a possible therapeutic bonus and an important area for exploration that may highlight novel therapeutic targets for drug development.

Conclusions

Statin treatment forms the basis of contemporary drug therapy for atherosclerotic vascular disease. Clinical evidence clearly supports the use of statins in the majority of patients with vascular disease and elevated, average, or even below-average cholesterol levels. Recent clinical trials have broadened the population of patients who will benefit from statin therapy, and the HPS strongly supports the use of statins to lower LDL-C levels beyond those recommended in current NCEP III guidelines. Even though the safety of statin therapy was called into question after the withdrawal of cerivastatin, contemporary data on statin safety indicate that these drugs are very safe. Although the mechanisms responsible for muscle toxicity with statins are unknown, a number of promising avenues for research have been highlighted in recent years. There is a maturing appreciation of the therapeutic potential of combination therapy with statins and of the need for closer attention and monitoring for adverse effects in patients taking combination lipid-lowering therapy. Moreover, we now have a heightened respect for the potential of drug interactions with statins and a greater understanding of

recently elucidated metabolic pathways for statin metabolism. Ongoing trials will address new therapeutic targets and dictate future guidelines. The issue of adjunctive effects of statins beyond lowering LDL-C remains controversial, but there is substantial evidence to suggest putative cholesterol-independent effects of statins.

Disclosure

Dr Vaughan is a member of the Speakers' Bureau for Pfizer, Inc and Merck & Co, Inc. Dr Gotto is a current consultant with Merck & Co, Inc; AstraZeneca Ltd; Bristol-Myers Squibb; Novartis; Reliant Pharmaceuticals; and Pfizer, Inc.

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