# The Past, Present, and Future of Statin Therapy

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*Statins are a remarkably safe and efficacious class of medications that have proved to be invaluable in the fight against heart disease. Statins have been prescribed to millions of patients for nearly 20 years; thus there have been hundreds of millions of patient-years of use, with relatively few adverse effects and incalculable benefits. Results from large-scale clinical trials have shown that statins are associated with dramatic decreases in cardiovascular risk. It seems certain that statins will remain a valuable and essential part of the lipid-lowering landscape, but combinations of statins with other lipid-lowering agents are increasingly important. Even with the most potent statins, the desired low-density lipoprotein cholesterol goal might not be attained with statin monotherapy. Furthermore, because of the increasing prevalence of diabetes and the metabolic syndrome, along with their attendant multiple lipid abnormalities, combinations of statins with medications targeted toward multiple lipoprotein particles will emerge.*

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Coronary heart disease (CHD) remains a major cause of death in the United States, and despite continued improvements in cardiovascular care CHD rates remain unacceptably high.[1,2] Elevated levels of low-density lipoprotein cholesterol (LDL-C) are an important contributor to the development of CHD; therefore LDL-C reduction has been a mainstay of CHD prevention and treatment for some time. Dietary advice should always be part of an LDL-C lowering strategy; however, the average LDL-C reduction from diet

alone is approximately 5% to 10%,[3-5] and many individuals require drug therapy along with dietary therapy. The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are associated with considerable reductions in LDL-C and have revolutionized the treatment of hypercholesterolemia. Furthermore, results from large-scale clinical trials (discussed below) have shown that statins are associated with dramatic decreases in cardiovascular risk. The history and discovery of these cardiovascular protective and life-saving medications, data on their current clinical utility and safety, as well as future directions for statin therapy, will be explored in this review.

## History of Statins

In the 1950s and 1960s, the benefits of cholesterol reduction were becoming apparent, and cholesterol-lowering agents were introduced into clinical use. These agents were modestly effective in cholesterol reduction but had several unpleasant side effects, such as gastrointestinal upset, flushing, and unpalatability. In 1971, a Japanese biochemist named Akiro Endo and his colleagues were searching for new antibiotics. Because many micro-organisms require cholesterol for growth, the group was hoping to identify novel factors that would inhibit the rate-limiting enzyme in cholesterol biosynthesis—HMG-CoA-reductase—with the aim of developing these compounds as antibiotics. Ultimately, Endo isolated several inhibitors of HMG-CoA reductase, including one, mevastatin, from the mold *Penicillium citrinum*. This compound was found to be a potent agent for the reduction of serum cholesterol.[6] The pharmaceutical company Merck began similar research in 1976 and isolated lovastatin from the mold *Aspergillus terreus*. By 1990, several statin drugs, such as lovastatin, pravastatin, and simvastatin, were derived and marketed in the United States and across the world. The initial agents in the class—lovastatin, pravastatin, and simvastatin—are all derivatives of a fungal compound. More recently, synthetic statins have been developed. They include atorvastatin, fluvastatin, rosuvastatin, and the statin that was withdrawn from clinical use, cerivastatin (Table 1). The chemical structure of fungally derived statins is quite similar, whereas the structures of the synthetic statins differ somewhat (Figure 1).

Table 1
Chemical and Brand Names of Statins and Their Methods of Production

| Chemical Name | Brand Name | Production Method |
|---|---|---|
| Pravastatin | Pravachol | Fermentation—modified |
| Simvastatin | Zocor | Fermentation—modified |
| Lovastatin | Mevacor | Fermentation |
| Fluvastatin | Lescol | Synthetic |
| Atorvastatin | Lipitor | Synthetic |
| Rosuvastatin | Crestor | Synthetic |
| Cerivastatin | Baycol | Synthetic—no longer available |

## Statin Efficacy

*Lipoprotein Effects*

Statins have generally similar effects on plasma lipids (Table 2). The main effect of statins is the decrease of serum levels of LDL-C, due to the inhibition of intracellular cholesterol biosynthesis, which brings about an upregulation of LDL receptors. Two separate studies have directly compared statin efficacy on lipoprotein parameters and have found rosuvastatin and atorvastatin to be the most potent statins for total cholesterol and LDL-C reduction at currently available doses.[7,8] These are followed (in order of LDL-C lowering potency) by simvastatin, lovastatin, pravastatin, and fluvastatin. The more effective a statin is in decreasing LDL-C, the more effective it also is in decreasing serum triglycerides. As such, the most potent triglyceride-lowering statins are rosuvastatin and atorvastatin, followed, in order, by simvastatin, lovastatin, pravastatin, and fluvastatin.[9] Statins typically afford only a modest increase in levels of high-density lipoprotein cholesterol (HDL-C), and this increase seems to be independent of LDL-C-lowering efficacy. Simvastatin, rosuvastatin, and pravastatin are the most potent HDL-C-raising agents. Simvastatin raises HDL-C 8% to 16%, rosuvastatin 8% to 14%, and pravastatin 2% to 12%.[10] Atorvastatin, fluvastatin, and lovastatin offer up to 9% HDL-C increases. None of the statins decreases lipoprotein(a); in fact, statin therapy is typically associated with an approximately 30% increase in lipoprotein(a).[11]

*Pleiotropic Effects of Statins*

Statins have been reported to exhibit a broad array of pleiotropic activities that may contribute to their ability to decrease cardiovascular risk.[12] Some of these properties include

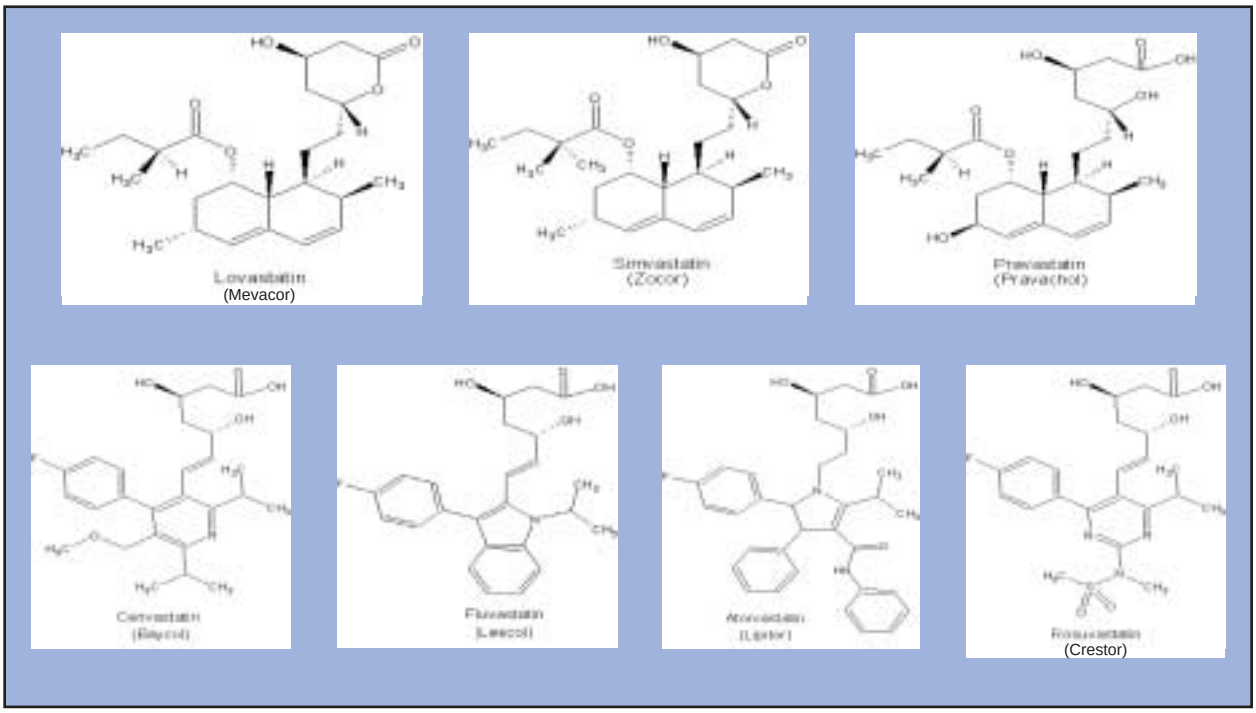


**Figure 1.** *Molecular structures of the statin family of drugs.* www.medreviews.com

reduction in inflammation, plaque stabilization, improvement of endothelial function, inhibition of smooth muscle proliferation, reduction in adhesion molecules, prevention of cholesterol esterification, reduction in proteinases, inhibition of platelet aggregation, and reduction in thrombogenic factors. Although these pleiotropic effects are intriguing, they have not yet definitively been proven to contribute to the clinical benefits of statins, though evidence is accumulating. Furthermore, the extent to which such

Table 2
Lipoprotein Effects of Currently Available Statins

| | | Lipoprotein Effects | | | |
|---|---|---|---|---|---|
| **Drug** | **Daily Dose** | **TC** | **LDL** | **HDL** | **TG** |
| Atorvastatin (Lipitor) | 10–80 mg | ↓ 25%–45% | ↓ 35%–60% | ↑ 5%–9% | ↓ 19%–37% |
| Fluvastatin (Lescol) | 20–80 mg | ↓ 17%–27% | ↓ 22%–36% | ↑ 3%–9% | ↓ 12%–23% |
| Lovastatin (Mevacor) | 10–80 mg | ↓ 16%–34% | ↓ 21%–42% | ↑ 2%–9% | ↓ 6%–27% |
| Pravastatin (Pravachol) | 10–80 mg | ↓ 16%–27% | ↓ 22%–37% | ↑ 2%–12% | ↓ 11%–24% |
| Rosuvastatin (Crestor) | 5–40 mg | ↓ 33%–46% | ↓ 45%–63% | ↑ 8%–14% | ↓ 10%–35% |
| Simvastatin (Zocor) | 5–80 mg | ↓ 19%–36% | ↓ 26%–47% | ↑ 8%–16% | ↓ 12%–33% |

TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.

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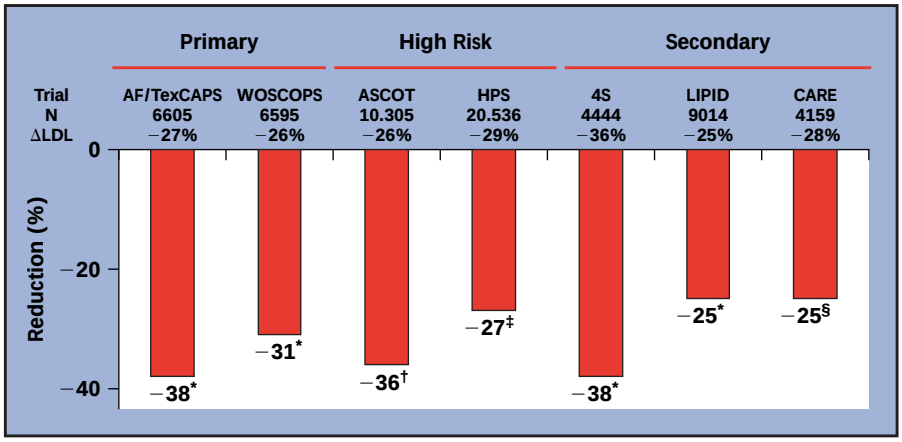


**Figure 2.** *Reduction in major cardiovascular events in the statin clinical trials. AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; WOSCOPS, West of Scotland Coronary Prevention Study; ASCOT, Anglo-Scandinavian Outcomes Trial–Lipid-Lowering Arm; HPS, Heart Protection Study; 4S, Scandinavian Simvastatin Survival Study; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease Trial; CARE, Cholesterol and Recurrent Events Trial; *P < .001; †P = .0005; ‡P < .0001; §P < .002.*

properties are independent of the lipid effects of statins is uncertain.

## Landmark Statin Clinical Trials

In 1994, the Scandinavian Simvastatin Survival Study (4S trial)[13] was published. This trial demonstrated, for the first time, the remarkable efficacy of the statins against hard cardiovascular outcomes (cardiovascular events and death) in dyslipidemic patients. Since that time, there have been numerous additional clinical trials of statin therapy, which can broadly be classified into 3 groups: (1) placebo-controlled statin trials, (2) comparison trials between 2 different statins, and (3) comparison trials between 2 different doses of the same statin. This section will summarize some of the landmark statin clinical trials and clarify how they affected the goals of lipid-lowering therapy in current medical practice.

### *Placebo-Controlled Statin Trials*

The cardiovascular risk reductions with statins compared with placebo in the landmark clinical trials are summarized in Figure 2.

**4S Trial.** The 4S trial was designed to evaluate the effect of cholesterol lowering with simvastatin on mortality and morbidity in patients with CHD.[13] A total of 4444 patients with angina pectoris or previous myocardial infarction and elevated serum cholesterol levels were randomized to double-blind treatment with simvastatin or placebo. Over a median follow-up period of 5.4 years, simvastatin was associated with a relative risk (RR) of death of 0.70 (95% confidence interval [CI] 0.58-0.85, $P = .0003$), a 30% relative mortality reduction. The RR of having one or more major coronary events with simvastatin therapy was 0.66 (95% CI 0.59-0.75, $P < .00001$), a 34% RR reduction. There was also a 37% reduction ($P < .00001$) in the risk of undergoing myocardial revascularization procedures in the simvastatin group. This study showed for the first time that a statin could reduce not only coronary events but also total mortality.

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**WOSCOPS.** The next large placebo-controlled statin trial published was the West of Scotland Coronary Prevention Study (WOSCOPS).[14] This double-blind study was designed to determine whether pravastatin therapy could reduce the incidence of nonfatal myocardial infarction and death from CHD in men with hypercholesterolemia and no history of myocardial infarction. In the study 6595 men, aged 45 to 64 years, with a mean (± SD) plasma cholesterol level of 272 ± 23 mg/dL, were randomized to receive pravastatin (40 mg/d) or placebo. The average follow-up period was 4.9 years. Pravastatin reduced the risk of nonfatal myocardial infarction or death from CHD by 31% (95% CI 17%-43%, $P < .001$). There were similar reductions in the risk of definite nonfatal myocardial infarctions (31% reduction, $P < .001$), death from CHD (definite cases alone: 28% reduction, $P = .13$; definite plus suspected cases: 33% reduction, $P = .042$), and death from all cardiovascular causes (32% reduction, $P = .033$). There was no excess of deaths from noncardiovascular causes in the pravastatin group.

**CARE.** Although the 4S and WOSCOPS studies had confirmed that lowering the cholesterol level in patients with hypercholesterolemia reduces the risk of coronary events, the effect of lowering cholesterol levels in the majority of patients with coronary disease, who have average levels, had not been determined. The

Cholesterol and Recurrent Events (CARE)[15] trial studied this population. In this trial, 4159 patients with myocardial infarction who had plasma total cholesterol levels below 240 mg/dL (mean, 209 mg/dL) and LDL-C levels of 115 to 174 mg/dL (mean, 139 mg/dL) were randomized to receive either pravastatin (40 mg/d) or placebo. The primary endpoint was a fatal coronary event or a nonfatal myocardial infarction. Pravastatin therapy was associated with a 24% RR reduction (95% CI 9%-36%, $P = .003$) in the primary endpoint. The need for coronary bypass surgery was reduced by 26% ($P = .005$), and the need for coronary angioplasty was reduced by 23% ($P = .01$). The frequency of stroke was reduced by 31% ($P = .03$). These results demonstrate that the benefit of cholesterol lowering extends to the majority of patients who have coronary disease and average cholesterol levels.

*Results of the CARE trial demonstrate that the benefit of cholesterol lowering extends to the majority of patients who have coronary disease and average cholesterol levels.*

**AFCAPS/TexCAPS.** The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[16] was designed to determine whether patients without CHD and with only average serum cholesterol levels would benefit from statin therapy. In this trial, 6605 individuals without clinically evident atherosclerotic cardiovascular disease with average total cholesterol and LDL-C levels and below-average HDL-C levels were randomized to receive either lovastatin (20-40 mg/d) or placebo. The main outcome measures were appearance of a first acute major coronary event, defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death. Lovastatin reduced the incidence of first acute major coronary events by 37% (RR 0.64, 95% CI 0.50-0.79, $P < .001$), myocardial infarction was reduced by 40% (RR 0.60, 95% CI 0.43-0.83, $P = .002$), unstable angina was reduced by 32% (RR 0.68, 95% CI 0.49-0.95, $P = .02$), coronary revascularization procedures were reduced by 33% (RR 0.67, 95% CI 0.52-0.85, $P = .001$), coronary events were reduced by 25% (RR 0.75, 95% CI 0.61-0.92, $P = .006$), and cardiovascular events were reduced by 25% (RR 0.75, 95% CI 0.62-0.91, $P = .003$). This trial supported the use of statin therapy in individuals without CHD, with average total cholesterol and LDL-C levels and below-average HDL-C levels.

**PROSPER.** The above-mentioned trials definitively demonstrated that statin therapy reduces coronary and cerebrovascular morbidity and mortality in middle-aged individuals; however, many individuals questioned these agents efficacy and safety in the elderly. The aim of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial[17] was to test the benefits of pravastatin treatment in an elderly cohort of men and women with, or at high risk of developing, cardiovascular disease and stroke. In this study, 5804 individuals aged 70 to 82 years with a history of, or risk factors for, vascular disease were randomized to receive either pravastatin (40 mg/d) or placebo. Follow-up was 3.2 years on average, and the primary endpoint was a composite of coronary death, nonfatal myocardial infarction, and fatal or nonfatal stroke. Pravastatin reduced the incidence of the primary endpoint by 15% (hazard ratio [HR] 0.85, 95% CI 0.74-0.97, $P = .014$). Coronary heart disease death and nonfatal myocardial infarction risk was reduced by 19% (HR 0.81, 95% CI 0.69-0.94, $P = .006$). Stroke risk was not affected (HR 1.03, 95% CI 0.81-1.31, $P = .8$). New cancer diagnoses were more frequent in the pravastatin group than in the placebo group (HR 1.25, 95% CI 1.04-1.51, $P = .020$). However, incorporation of this finding in a meta-analysis of all pravastatin and all statin trials showed no overall increase in risk.

**HPS.** Unlike prior statin trials, which required at least average cholesterol levels for entry into the study, the Heart Protection Study (HPS)[18] evaluated a wide range of high-risk patients, irrespective of their initial cholesterol levels. A total of 20,536 adults (aged 40–80 years) with coronary disease, other occlusive arterial disease, or diabetes were randomized to receive simvastatin (40 mg/d) or placebo during a 5-year treatment period. Primary outcomes were mortality and fatal or nonfatal vascular events. All-cause mortality was significantly reduced (1328 deaths [12.9%] among 10,269 randomized to simvastatin vs 1507 [14.7%] among 10,267 randomized to placebo; $P = .0003$), owing to a highly significant 18% reduction in coronary deaths (587 [5.7%] vs 707 [6.9%]; $P = .0005$). There was a 24% reduction in the first event rate for nonfatal myocardial infarction or coronary death (898 [8.7%] vs 1212 [11.8%]; $P < .0001$), for nonfatal or fatal stroke (444 [4.3%] vs 585 [5.7%]; $P < .0001$), and for coronary or noncoronary revascularization (939 [9.1%] vs 1205 [11.7%];

$P < .0001$). The RR reductions were similar (and significant) in each subgroup of participants studied, even those who presented with LDL-C levels below 116 mg/dL.

**ALLHAT.** The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[19] was a large National Institutes of Health–funded study. The objective of the ALLHAT lipid-lowering trial was to determine whether pravastatin compared with usual care reduced all-cause mortality in older, moderately hypercholesterolemic, hypertensive participants with at least one additional CHD risk factor. In this trial, a subset (n = 10,355) of participants from the parent trial were randomized to receive pravastatin (40 mg/d) or to usual care, with a mean follow-up period of 4.8 years. Mean baseline cholesterol and triglyceride levels were as follows: total cholesterol, 224 mg/dL; LDL-C, 146 mg/dL; HDL-C, 48 mg/dL; and triglycerides, 152 mg/dL. The primary outcome was all-cause mortality. During the trial, 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, compared with 8% with usual care; among the random sample who had LDL-C levels assessed, levels were reduced by 28% with pravastatin, compared with 11% with usual care. All-cause mortality was similar for the 2 groups (RR 0.99, 95% CI 0.89-1.11, $P = .88$). CHD event rates were not significantly different between the groups (RR 0.91, 95% CI 0.79-1.04, $P = .16$). Although in this study pravastatin did not reduce either all-cause mortality or CHD significantly, the results might be due to the modest differential in total cholesterol (9.6%) and LDL-C (16.7%) between the pravastatin and usual-care groups compared with prior statin trials and the high rate of non-study statin usage in the usual-care group.

**ASCOT-LLA.** Similar to the ALLHAT lipid-lowering trial, the Anglo-Scandinavian Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA)[20] studied the potential benefits of cholesterol lowering with statins in the primary prevention of CHD in hypertensive patients who were not conventionally thought to be dyslipidemic. In this trial, a subset (n = 10,305) of participants from ASCOT, with nonfasting total cholesterol levels of 240 mg/dL or less, were randomized to receive either atorvastatin (10 mg/d) or placebo, with the primary outcome measure being nonfatal myocardial infarction and fatal CHD. The study was planned to last for 5 years; however, treatment was stopped after a median follow-up of 3.3 years owing to a highly significant 36% reduction in the primary endpoint (HR 0.64, 95% CI 0.50-0.83, $P = .0005$). This benefit emerged in the first year of follow-up. Fatal and nonfatal stroke was reduced by 27% (HR 0.73, 95% CI 0.56-0.96, $P = .024$).

*The ASCOT-LLA study was planned to last for 5 years; however, treatment was stopped after a median follow-up of 3.3 years owing to a highly significant 36% reduction in the primary endpoint.*

**CARDS.** Although it is known that type 2 diabetes is associated with a substantially increased risk of cardiovascular disease, the role that lipid lowering plays in reducing events in this population had not been fully explored, particularly in those without elevated LDL-C. The Collaborative Atorvastatin Diabetes Study (CARDS)[21] therefore aimed to assess the effectiveness of atorvastatin (10 mg/d) for primary prevention of major cardiovascular events in patients with type 2 diabetes without high concentrations of LDL-C. A total of 2838 patients aged 40 to 75 years were randomized to receive either atorvastatin (10 mg/d) or placebo. Study participants had no documented previous history of cardiovascular disease, an LDL-C concentration of less than 160 mg/dL, and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension. The primary endpoint was time to first occurrence of acute CHD events, coronary revascularization, or stroke. Analysis was by intention to treat. The trial was terminated 2 years earlier than expected (median follow-up, 3.9 years) because the prespecified early stopping rule for efficacy had been met. There was a 37% risk reduction with atorvastatin use (95% CI −52% to −17%, $P = .001$). Acute CHD events were reduced by 36% (95% CI −55% to −9%), coronary revascularizations by 31% (95% CI −59% to 16%), and stroke by 48% (95% CI −69% to −11%). Atorvastatin reduced the death rate by 27% (95% CI −48% to 1%, $P = .059$).

**MIRACL.** Although all of the above trials studied patients with chronic atherosclerotic disease or risks, the role of lipid-lowering therapy in acute ischemic events was studied in the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial.[22] We know, however, that patients experience the highest rate of death and

recurrent ischemic events during the early period after an acute coronary syndrome (ACS); therefore, the objective of the MIRACL trial was to determine whether treatment with atorvastatin (80 mg/d), initiated early after an ACS, reduces death and nonfatal ischemic events. In this study, 3086 adults aged 18 years or older with unstable angina or non-Q-wave acute myocardial infarction were randomized to receive either atorvastatin (80 mg/d) or placebo between 24 and 96 hours after hospital admission. The primary endpoint event, defined as death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization, was measured at 16 weeks. There was a 16% reduction in the risk of a primary event with early atorvastatin therapy (RR 0.84, 95% CI 0.70-1.00, $P = .048$). There were no significant differences in risk of death, nonfatal myocardial infarction, or cardiac arrest between the atorvastatin group and the placebo group, although the atorvastatin group had a lower risk of symptomatic ischemia with objective evidence and of requiring emergency rehospitalization (6.2% vs 8.4%; RR 0.74, 95% CI 0.57-0.95, $P = .02$). There were also fewer strokes in the atorvastatin group than in the placebo group (12 vs 24 events; $P = .045$). Abnormal liver transaminase levels (more than three times the upper limit of normal) were more common in the atorvastatin group than in the placebo group (2.5% vs 0.6%; $P < .001$). This study demonstrated that for patients with ACS, lipid-lowering therapy with atorvastatin (80 mg/d) reduces recurrent ischemic events in the first 16 weeks, mostly recurrent symptomatic ischemia requiring rehospitalization.

*The MIRACL study demonstrated that for patients with acute coronary syndromes, lipid-lowering therapy with atorvastatin reduces recurrent ischemic events in the first 16 weeks.*

*Statin Versus Statin Trials*

**PROVE-IT.** The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)—Thrombolysis in Myocardial Infarction 22 trial[23] was designed to determine whether intensive lipid-lowering therapy with atorvastatin (80 mg/d) would improve outcomes in patients hospitalized for an ACS within the preceding 10 days as compared with a more moderate lipid-lowering regimen of pravastatin (40 mg/d). In the study, 4162 patients who had been within 10 days of an ACS were randomized with follow-up between 18 and 36 months (mean, 24 months). The primary endpoint was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. The study was designed to establish the noninferiority of pravastatin as compared with atorvastatin with respect to the time to an endpoint event; however, the study instead demonstrated a 16% reduction in the risk of an event with atorvastatin 80 mg/d ($P = .005$, 95% CI 5%-26%). Therefore, among patients who have recently had an ACS, an intensive lipid-lowering statin regimen provides greater protection than a standard regimen against death or major cardiovascular events.

**REVERSAL.** A trial with a treatment design similar to that of the PROVE-IT study was also performed. In this study, however, patients with stable coronary atherosclerotic disease were tested rather than patients with an ACS. This study, the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial,[24] aimed to compare the effect of regimens designed to produce intensive lipid lowering (atorvastatin 80 mg/d) or moderate lipid lowering (pravastatin 40 mg/d) on coronary artery atheroma burden and progression, as assessed by intravascular ultrasound. A total of 654 patients were randomized and received study drug; 502 had evaluable intravascular ultrasound examinations at baseline and after 18 months of treatment. The primary efficacy parameter was the percentage change in atheroma volume (follow-up minus baseline). The primary endpoint (percentage change in atheroma volume) showed a significantly lower progression rate in the atorvastatin group ($P = .02$). Compared with baseline values, patients treated with atorvastatin had no change in atheroma burden, whereas patients treated with pravastatin showed progression of coronary atherosclerosis. The investigators, furthermore, hypothesized that in this study the differences between the two regimens might have been related to the greater reduction in atherogenic lipoproteins and C-reactive protein in patients treated with atorvastatin.

*Low-Dose Versus High-Dose Statin Trials*

**A to Z.** The Aggrastat to Zocor study, or A to Z study, phase Z,[25] assessed whether early intensive simvastatin treatment had advantages over a delayed conservative simvastatin strategy in ACS patients. Patients with ACS were randomized

to receive either 40 mg/d of simvastatin for 1 month followed by 80 mg/d thereafter or placebo for 4 months followed by 20 mg/d of simvastatin. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke. Follow-up was for at least 6 months and up to 24 months. A total of 343 patients (16.7%) in the placebo-plus-simvastatin group experienced the primary endpoint, compared with 309 (14.4%) in the simvastatin-only group (40 mg/80 mg) (HR 0.89; 95% CI 0.76-1.04, $P = .14$). Cardiovascular death occurred in 109 and 83 patients (5.4% and 4.1%, respectively) in the two groups (HR 0.75, 95% CI 0.57-1.00, $P = .05$), but no differences were observed in other individual components of the primary endpoint. No difference was evident during the first 4 months between the groups for the primary endpoint (HR 1.01, 95% CI 0.83-1.25, $P = .89$), but from 4 months through the end of the study the primary endpoint was significantly reduced in the simvastatin-only group (HR 0.75, 95% CI 0.60-0.95, $P = .02$). Myopathy (creatine kinase >10 times the upper limit of normal, associated with muscle symptoms) occurred in 9 patients (0.4%) receiving simvastatin 80 mg/d, in no patients receiving lower doses of simvastatin, and in 1 patient receiving placebo ($P = .02$). This statin trial showed that among patients with ACS, the early initiation of an aggressive simvastatin regimen resulted in a favorable trend toward reduction of major cardiovascular events, but this reduction did not reach statistical significance.

**TNT.** The most recently published large statin trial was the Treat to New Targets trial (TNT),[26] designed to assess the efficacy and safety of lowering LDL-C levels below 100 mg/dL in patients with stable CHD. In the TNT trial, 10,001 patients with clinically evident CHD and LDL-C levels of less than 130 mg/dL were randomized to receive either 10 mg/d or 80 mg/d of atorvastatin. Patients were followed for a median of 4.9 years. The primary endpoint was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke. There was a 22% relative reduction in risk of a first cardiovascular event in individuals randomized to receive 80 mg/d of atorvastatin (HR 0.78, 95% CI 0.69-0.89, $P < .001$). There was no difference between the 2 treatment groups in terms of overall mortality. Therefore, this trial demonstrated that lipid-lowering therapy with 80 mg/d of atorvastatin in patients with stable CHD provides significant clinical benefit beyond that afforded by treatment with 10 mg/d of atorvastatin. This did, however, occur with a greater incidence of elevated aminotransferase levels. The incidence of persistent elevations in liver aminotransferase levels was 0.2% in the group given 10 mg/d of atorvastatin and 1.2% in the group given 80 mg/d of atorvastatin ($P < .001$).

*Overwhelming evidence demonstrates that statin therapy significantly reduces stroke rates in patients with CHD.*

Hypercholesterolemia has not traditionally been considered an important risk factor in the development of stroke; however, overwhelming evidence demonstrates that statin therapy significantly reduces stroke rates in patients with CHD. There are many possible explanations for this finding. Statins might provide cerebrovascular protection by reducing the incidence of embolic stroke from cardiac, aortic, and carotid sites. Statins might also act to stabilize vulnerable carotid atherosclerotic plaques, and recent evidence suggests that statins might improve cerebral blood flow.[27]

## Statin Safety

Statins are generally very well tolerated, and serious adverse effects are rare. Currently, there seems to be no discernible differences between the statins in the range or severity of adverse effects, although experience is more limited with rosuvastatin. The most serious reported adverse effects are skeletal muscle toxicity and hepatotoxicity. Though most patients are aware of statin-associated hepatotoxicity, it is the less worrisome of these two adverse effects. As noted in the American College of Cardiology/American Heart Association/American Heart, Lung, and Blood Institute advisory on the safety of statins,[28] although transaminase elevations with statins might occur, whether this represents true hepatotoxicity has not been determined. This document also notes that progression to liver failure is exceedingly rare with statins, if in fact it ever happens. Skeletal muscle toxicity with statins is better established and was brought to public attention by the withdrawal of the drug cerivastatin. There is a wide spectrum of muscle adverse events with statins, ranging from mild myopathy to frank rhabdomyolysis.[29] The total reported

incidence of statin-associated myotoxicity ranges between 1% and 7%.[29] The risk of myopathy seems to be increased by high doses of statins, certain concomitant medications, or the presence of renal impairment. Myalgia is the most common side effect with statins, whereas rhabdomyolysis and myositis, the most serious of muscle effects, account for less than 0.1% of all statin-related adverse effects.[29]

*The frequency of rhabdomyolysis reported with the currently available statins is less than one in 100,000 and is comparable for all currently available statins.*

Cerivastatin was a unique case, with an incidence of myotoxicity that was more than 10 times that of other statins.[30] The majority of cases of rhabdomyolysis occurred with the highest dose of cerivastatin (0.8 mg), and there was a particularly high incidence associated with the use of cerivastatin in combination with the fibric acid derivative gemfibrozil. The frequency of rhabdomyolysis reported with the currently available statins is less than one in 100,000 and is comparable for all currently available statins.[30] Death due to rhabdomyolysis is even rarer, with a reported incidence of <1:1,000,000. Renal adverse events are a relatively new concern with statin therapy. Mild proteinuria has recently been identified in patients treated with statins, and this has been seen with all of the currently available statins.[31] The proteinuria seen has been described as being generally transient and reversible and has not been associated with any change in renal function; thus the significance of this finding is unknown. In fact, statin therapy has been shown in several trials to improve glomerular filtration rates.[31]

The statins all have distinct pharmacodynamic and pharmacokinetic properties that might result in differences in safety. Approximately 60% of cases of statin-related rhabdomyolysis have been attributed to drug–drug interactions.[32]

Most of the statins are metabolized through the cytochrome P (CYP)450 metabolic pathway. Atorvastatin, simvastatin, and lovastatin use the CYP3A4 isoenzyme, whereas fluvastatin uses the CYP2C9 isoenzyme. Pravastatin and rosuvastatin do not depend on the CYP450 pathway.

CYP3A4 is involved in the metabolism of a large number of medications, leading to the possibility of drug–drug interactions. Any drug whose affinity for the CYP3A4 isoenzyme is greater than the affinity of the statin will inhibit the statin from binding, thereby inhibiting its metabolism.[33] In addition to several medications, grapefruit juice is also known to inhibit the CYP3A4 isoenzyme. Although enzymes of the CYP450 system are clearly important in metabolism of some statins, they are not the only determinants of potential statin toxicities. The pharmacokinetic disposition of drugs, including statins, is known to be influenced by a wide variety of metabolic enzymes, by renal function, and by cellular transporter systems.[34] All of these parameters might influence statin metabolism.

## Combination Therapy and Future Approaches

The ability to reduce LDL-C beyond that which is achievable with current potent statins will likely not be met by the development of even more potent statins. Instead the combination of statin therapy with other lipid-lowering medications will be required. The selective cholesterol absorption inhibitor ezetimibe, when added to statin therapy, lowers LDL-C by an additional 25%.[35] The addition of ezetimibe to statin therapy is an effective treatment option that might enable more patients to achieve optimal LDL-C levels and reduce their risk for CHD. However, in the quest to further reduce the risk of major coronary events and stroke, other therapeutic strategies beyond LDL-C reduction have been sought, and the field of preventative cardiology has been turning attention to the other lipoproteins that seem to be involved in atherosclerosis, especially HDL.[36] Circulating HDL levels can be increased directly by increasing the synthesis of apolipoprotein A-I and/or by inhibiting the clearance of apolipoprotein A-I. HDL levels have been shown to increase with regular aerobic exercise, modest alcohol consumption, weight loss, a high-fat diet, and smoking cessation.[37] HDL levels decrease with smoking, obesity, menopause, and high-carbohydrate diets.[37] Pharmacologic agents that increase HDL include statins, niacin, fibric acid derivatives, phenytoin, and hormone replacement therapy.[37] However, the magnitude of HDL elevation with clinically available drug therapy is generally small and highly variable.

*The selective cholesterol absorption inhibitor ezetimibe, when added to statin therapy, lowers LDL-C by an additional 25%.*

A number of exciting agents to impact HDL and apolipoprotein A-I are currently in various stages of clinical trials.[36] Direct administration of plasma-derived apolipoprotein A-I, reconstituted HDL containing recombinant apolipoprotein A-$I_{Milano}$ (a mutant form of apolipoprotein A-I), or their synthetic mimetics are being tested.[38] Medications that activate specific subtypes of nuclear hormone receptors, particularly the retinoids, have entered clinical trials. Pharmacologic therapy to enhance the expression and/or activity of hepatic HDL scavenger receptors represents a novel strategy for augmenting reverse cholesterol transport.[38] Cholesterol ester transfer protein (CETP) inhibitors can significantly raise HDL levels. The CETP inhibitor torcetrapib, when used in combination with atorvastatin, has been shown to increase HDL by 40% to 61%.[39] This strategy seems very promising but still requires demonstration of clinical benefits. HDL therapy might also have an acute therapeutic application to treat cardiovascular disease at the site of the vulnerable, unstable atherosclerotic plaque. Single high-dose infusions and repeated injections of lower doses of apolipoprotein A-I variants or mimetics complexed to phospholipids have produced remarkable effects on the progression and regression of atherosclerosis in animal models. The positive results of these studies have led to clinical trials testing the hypothesis and the potential use of synthetic HDL as a new treatment modality for ACS.[40] One or more of these new therapies that substantially raise HDL and enhance function will likely prove to be important therapeutic agents to add to statin therapy to achieve further reductions in cardiovascular risk.

## Conclusions

In summary, the statins remain a remarkably safe and efficacious class of medications that have proven to be invaluable in the fight against heart disease. Statin drugs have been prescribed to millions of patients for nearly 20 years; thus there have been hundreds of millions of patient-years of use, with relatively few adverse effects and untold benefits. Statins were first introduced as a treatment for hypercholesterolemia, but since their introduction they have been shown to provide a remarkable array of clinical benefits. It seems certain that statins will remain a valuable and essential part of the lipid-lowering landscape, but in the future, combinations of other lipid-lowering agents with statins will undoubtedly also emerge. Even with the most potent statins, the desired LDL-C goal might not be attained with statin monotherapy; therefore, combination therapy will become more important. Furthermore, because of the increasing prevalence of diabetes and the metabolic syndrome, along with their attendant multiple lipid abnormalities, combinations of statins with medications targeted toward multiple lipoprotein particles will emerge. ■

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### Main Points

- The main effect of statins is the decrease of serum levels of low-density lipoprotein cholesterol (LDL-C), due to the inhibition of intracellular cholesterol biosynthesis, which brings about an upregulation of LDL receptors.
- Results from large-scale clinical trials have shown that statins are associated with dramatic decreases in cardiovascular risk.
- Currently, there seem to be no discernible differences between the statins in the range or severity of adverse effects; the most serious reported adverse effects are skeletal muscle toxicity and hepatotoxicity.
- The ability to reduce LDL-C beyond that which is achievable with current potent statins will likely not be met by even more potent statins being developed; instead the combination of statin therapy with other lipid-lowering medications will be required.
- The field of preventative cardiology has been turning attention to the other lipoproteins that seem to be involved in atherosclerosis, especially high-density lipoprotein (HDL); a number of exciting agents to impact HDL and apolipoprotein A-I are currently in various stages of clinical trials.

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