Review Paper

Statins and C-Reactive Protein Levels

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In patients with or at risk for cardiovascular disease (CVD), including hypertensive individuals, lowering levels of low-density lipoprotein cholesterol (LDL-C) reduces CVD risk. Statins are the most effective of available therapies for lowering LDL-C. Extensive clinical trial data have shown that the degree of LDL-C reduction obtained depends on the particular statin used and that intensive LDL-C lowering reduces the incidence of cardiovascular events compared with more moderate LDL-C lowering. More recent data suggest that effects independent of LDL-C lowering may also play a part in the reduction in cardiovascular events. C-reactive protein (CRP), a marker of inflammation, is a potential predictor of CVD risk, and statins reduce CRP levels by up to 60%. CRP reduction is independent of LDL-C lowering, and variation between statins in CRP reduction may play some role in CVD event reduction rates. At present, however, there are few outcome data relating to the cardiovascular benefits of reducing CRP. (J Clin Hypertens. 2007;9:622–628) ©2007 Le Jacq

Patients with hypertension are at increased risk for cardiovascular disease (CVD), and most with stage I hypertension with target organ involvement or stage II disease (blood pressure [BP] >160/100 mm Hg) will require 2 or more antihypertensive medications to control their BP.[1] These medications include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and thiazide-type diuretics. Patients with hypertension and diabetes may require intensive therapy to attenuate their risk factors and have a more stringent BP goal of <130/<80 mm Hg.

Many patients treated for hypertension will also require strict management of lipid abnormalities. According to the Third National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines, patients with hypertension require only 1 other CVD risk factor (smoking, low levels of high-density lipoprotein cholesterol [HDL-C], family history of coronary heart disease [CHD], or age 45 years or older for men or 55 years or older for women) to be classified as at least at moderate risk of CHD, with a correspondingly lower low-density lipoprotein cholesterol (LDL-C) target than those at lower risk.[2] As a consequence, many hypertensive patients will need lipid-lowering medications.[2] A number of lipid-lowering agents are available; it can be difficult to know which to select, since lipid-lowering efficacy differs among agents and not all have outcomes data. Even within drug classes, there are differences; statins, for example, differ in their LDL-C–lowering efficacy, and other possible effects unique to each statin may also influence reductions in cardiovascular events. This review will discuss which criteria may be the more important ones to consider when choosing a lipid-lowering agent.

GREATER LDL-C REDUCTION, GREATER REDUCTION IN CVD RISK

In clinical guidelines for cholesterol management,[2,3] considerable emphasis has been placed on populations for whom it is most important to lower LDL-C. These populations include patients with existing

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Table I. Variable Effects of Lipid-Lowering Drugs[a]

Lipid-Lowering Class	LDL-C Reductions	Triglyceride Reductions	HDL-C Increases
Fibrates, %	5–20	20–50	10–20
Bile acid sequestrants, %	15–30	No effects	3–5
Niacin, %	5–25	20–50	15–35
Ezetimibe, %	18	8[b]	1
Statins, %	18–55	7–30	5–15

Percentages are mean change from baseline except where marked. Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. [a]Modified from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[2] [b]Median percentage change from baseline.

CVD, diabetes, or multiple CVD risk factors (eg, smoking or hypertension). If the 10-year CHD risk is >20%, a particularly stringent LDL-C goal of <100 mg/dL is set. Even when patients' baseline LDL-C levels are already at or below their allocated goal, however, statin therapy to further lower LDL-C may give additional reduction in CVD risk, as demonstrated in a number of clinical trials in higher-risk patients.[4,5]

Consequently, virtually all patients at risk for CVD will benefit from lipid-lowering. First-step therapy for the modification of LDL-C is lifestyle change; however, in many cases this will not lower LDL-C to assigned goals, and pharmacologic lipid-lowering therapy may be necessary. The most commonly used LDL-C–lowering agents are bile acid sequestrants, cholesterol-absorption inhibitors (eg, ezetimibe), fibrates, niacin, and statins.

Lipid-Lowering Ability

Each class of lipid-lowering agents differs in its ability to reduce LDL-C levels; their effects on other serum lipids are similarly variable (Table I).[2,6,7] Statins are the drug class of choice for lowering LDL-C. The degree of LDL-C reduction obtained depends on the particular statin used, however. Comparative studies of the LDL-C–lowering capacity of currently available statins have shown that atorvastatin and rosuvastatin produce greater reductions in LDL-C than fluvastatin, lovastatin, pravastatin, or simvastatin.[8,9]

While statins are the most effective therapy for treating hypercholesterolemia, not all patients achieve, or maintain, recommended LDL-C goals on standard-dose statin monotherapy,[10] particularly if they remain at their initial dose. Consequently, patients may need to be titrated to a higher statin dose to achieve their LDL-C targets. A few patients will be unable to reach their LDL-C goal, even when medication is titrated to the maximum dose. Under these circumstances, one option is to introduce combination therapy, although this may potentially increase the risk of adverse events and noncompliance, as well as the risk of possible drug interactions.[11] Statins can be combined with bile acid sequestrants, fibrates, niacin, or ezetimibe[12–15]; some statin monotherapies, however, may have greater LDL-C–lowering efficacy than combination therapies with other agents.[16] It might be advisable, therefore, to consider switching to a more potent statin or reaching maximum dosages of the original monotherapy before initiating combination therapy.

CVD Risk Reduction

Evidence is not available for all of the currently available lipid-lowering medications to demonstrate that they reduce the risk of CVD, especially in high-risk patients with hypertension and other risk factors. To date, there are no published results from ezetimibe monotherapy trials assessing its effects on the incidence of cardiovascular events. Niacin is an effective agent in correcting dyslipidemia, but data on the benefits of niacin on CVD risk are limited, although a long-term follow-up of the Coronary Drug Project showed a significant 11% reduction (P=.0004) in mortality with niacin compared with placebo.[17] Clinical trials of fibrates have demonstrated that reductions in primary cardiovascular end points were usually associated with reductions in LDL-C levels and/or increases in HDL-C levels[18] in addition to the large reductions in triglyceride levels that are observed with this therapy. In one trial, however, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, fenofibrate 200 mg/d in type 2 diabetics did not significantly reduce the primary end point after 5 years compared with placebo in 9795 patients.[19] A meta-analysis has indicated that fibrates may be associated with an increased risk of death from noncardiovascular causes.[19] Reductions in LDL-C levels observed with bile acid sequestrants appear to be sufficient to reduce risk of CVD over a long period. In male patients receiving cholestyramine, reductions of 8% in plasma total cholesterol levels and 12%

Table II. LDL-C Reduction and Reduction in Risk for Nonfatal MI and Coronary Heart Disease in ASCOT-LLA and ALLHAT-LLT

	Population	Intervention	LDL-C, mg/dL Baseline	LDL-C, mg/dL End Point	Percent Reduction	Follow-Up, y	Outcome	HR (95% CI)
ALLHAT-LLT[29]	Hypertension plus ≥2 other CV risk factors; LDL-C 120–189 mg/dL with no CHD history, or 100–129 mg/dL with CHD history	Pravastatin 40 mg/d	146	105	28%	8	Nonfatal MI or fatal CHD (secondary end point)	0.91 (0.79–1.04); *P*=.16
		Usual care	146	129	11%			
ASCOT-LLA[23]	Hypertension plus ≥3 other CV risk factors; total cholesterol ≤6.5 mmol/L	Atorvastatin 10 mg/d	133	90	31%	3.3	Nonfatal MI or fatal CHD (primary end point)	0.64 (0.50–0.83); *P*=.0005
		Placebo	133	127	5%			

Abbreviations: ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

in LDL-C levels were associated with a 19% reduction in CHD incidence after 7 years.[20] Some evidence is also available that a statin/niacin combination reduces risk of cardiovascular events (composite end point of death from cardiovascular causes, nonfatal myocardial infarction [MI], stroke, or revascularization procedure) compared with placebo,[21] and statin/bile acid sequestrant and niacin/bile acid sequestrant combinations have been shown to reduce the risk of cardiovascular events compared with usual care.[22]

A great deal of clinical trial data demonstrate that statins reduce cardiovascular risk compared with placebo. To date, most evidence for reduction in clinical outcomes has been from trials evaluating atorvastatin,[23,24] lovastatin,[25] pravastatin,[26] or simvastatin.[5,27] Trials with fluvastatin have been smaller or more specialized[28] and no outcome data are available as yet from trials of rosuvastatin.

Because of their simple dosing regimen, excellent safety record, superior LDL-C–lowering efficacy, and demonstrated ability to reduce CVD events in a wide range of patients, statins are presently the therapy of choice for lowering LDL-C.

POSSIBLE PLEIOTROPIC EFFECTS WITH STATIN THERAPIES

The reduction in cardiovascular events observed with statin treatment may be due, in part, to effects independent of their LDL-C–lowering capacity. At present, opinions differ regarding this possibility, but data from several clinical studies may lend some support to the concept that statins may exert pleiotropic effects.

Comparison of the results from 2 large-scale clinical trials, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial (ALLHAT-LLT)[29] and Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA),[23] suggests that statins may have pleiotropic effects. It should be noted that in addition to the different treatment regimens, the populations studied in these 2 trials differed considerably: ASCOT-LLA included patients at higher cardiovascular risk than the patients in ALLHAT-LLT. In ALLHAT-LLT, 10,355 patients with CHD or at least 3 cardiovascular risk factors received pravastatin 40 mg/d or usual care in addition to antihypertensive therapy for a mean of 4.8 years, while in ASCOT-LLA 10,305 patients with hypertension and at least 3 other cardiovascular risk factors received atorvastatin 10 mg/d or placebo in addition to antihypertensive therapy for a median of 3.3 years. In ASCOT-LLA, atorvastatin reduced LDL-C levels from baseline by 31%, compared with 28% with pravastatin in ALLHAT-LLT. Although statin treatment generated similar LDL-C reductions in both studies, the reduction in the rate of nonfatal MI and fatal CHD was greater in ASCOT-LLA (Table II) and was in addition to the reduction that may have been gained with antihypertensive therapy; systolic BP control was comparable in the placebo and atorvastatin groups (≈138.4 mm Hg). Caution must be used when comparing the outcomes of these trials, particularly since greater benefit is usually noted with risk factor interventions in patients at greater risk.

A recent comparative analysis of 11 studies examining the efficacy of statin treatments

Table III. Percent Reductions in CRP When LDL-C Reductions Across Therapies Are Comparable

Treatment Regimen	LDL-C Reduction, %	CRP Reduction, %
Treatments with similar LDL-C Reductions		
Atorvastatin 80 mg	54	43
Atorvastatin 10 mg/ezetimibe 10 mg	53	25
Atorvastatin 80 mg/ezetimibe 10 mg	61	62
Simvastatin 80 mg/ezetimibe 10 mg[a]	60	36
Simvastatin 10 mg/ezetimibe 10 mg[b]	47	21
Atorvastatin 40 mg[b]	48	29
Treatments with differing LDL-C Reductions		
Atorvastatin 80 mg	54	43
Atorvastatin 80 mg/ezetimibe 10 mg	61	62
Atorvastatin 40 mg[b]	48	29
Simvastatin 80 mg/ezetimibe 10 mg[b]	59	27

Abbreviations: CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol. Data from Ballantyne et al[35] unless otherwise indicated. [a]Data from Sager et al.[38] [b]Data from Ballantyne et al.[36]

concluded that although treatment with any statin produces substantial clinical benefits, treatment with atorvastatin provides the greatest benefit, since atorvastatin produced the greatest estimated 5-year reductions in cardiac morbidity and stroke and the fastest onset of clinical benefit. The authors speculated that this may be due to the ability of atorvastatin to slow plaque progression or to other, as yet unknown, features of the action of atorvastatin in metabolism.[30] At present, no comparative data are available with rosuvastatin.

Reductions in CVD Events With Reductions in C-Reactive Protein

The estimated differences between lipid-lowering therapies in their ability to reduce the rate of CVD events may be partly due to differences in pleiotropic and anti-inflammatory effects. C-Reactive protein (CRP), a marker of inflammation, has received attention as a potential predictor of CVD risk, although, at present, there are few outcome studies to determine whether reducing CRP levels without other interventions will influence cardiovascular outcome. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial, 4162 patients hospitalized with acute coronary syndromes (ACS) were randomized to atorvastatin 80 mg/d or pravastatin 40 mg/d.[31] Patients who achieved lower CRP levels (<2 mg/L) after statin therapy had a significantly lower rate of death from coronary causes or recurrent MI than those with higher CRP levels (2.8 events/100 person-years vs 3.9 events/100 person-years; P=.006), independent of achieved LDL-C level.[32] Patients with CRP and LDL-C levels in the lowest range (<1 mg/L and <70 mg/dL, respectively) after statin therapy experienced the greatest cardiovascular benefit (1.9 events/100 person-years vs 4.5 events/100 person-years for patients with CRP level ≥1 mg/L and LDL-C level ≥70 mg/dL).[32]

In Phase Z of the A to Z trial, which randomized 4497 patients with ACS to intensive simvastatin treatment (40 mg/d for 30 days, then 80 mg/d) or a less intensive regimen (placebo for 4 months, then simvastatin 20 mg/d), there was no significant difference in the primary end point (cardiovascular death, MI, readmission for ACS, or stroke) between the 2 treatment groups (11% risk reduction, P=.14).[33] One could speculate that the more modest reductions in CRP levels observed with simvastatin therapy may in part explain the lack of significance in the rate of reduction of major cardiovascular events with intensive vs moderate therapy in this trial. At month 1, LDL-C levels were significantly reduced with simvastatin 40 mg/d compared with placebo, but differences in CRP levels between the 2 groups were not statistically significant.[33]

A large-scale trial is under way to determine prospectively whether CRP reductions with statin treatment impact clinical outcomes, by comparing the risk of first-ever CVD events in patients with elevated CRP but without raised LDL-C receiving either rosuvastatin 20 mg/d or placebo.[34]

CRP Reductions With Statins

Clinical trials with several of the statins have demonstrated reductions in CRP levels of up to 60%,[35] but the degree of CRP reduction observed, as with LDL-C, varies depending on the agent used.[35,36] The relative reductions in CRP levels with different statins appear to be independent of the magnitude of LDL-C reductions, with treatments that produce

similar LDL-C reductions sometimes resulting in differing reductions in CRP (Table III).

In a study comparing the effects of statins on CRP levels in patients with CHD, atorvastatin 40 mg/d produced significantly greater CRP reductions than 40 mg/d of fluvastatin, lovastatin, pravastatin, or simvastatin; this reduction was independent of LDL-C changes.[37] Again, no data with rosuvastatin are available at present. Studies of statins combined with ezetimibe have also shown CRP reduction to be independent of LDL-C lowering. Ballantyne and colleagues[35] examined whether coadministration of ezetimibe and atorvastatin resulted in greater LDL-C and CRP reductions than atorvastatin alone. In 628 patients with a baseline LDL-C level of 145 to 250 mg/dL and triglyceride level ≤350 mg/dL, intensive atorvastatin therapy (80 mg/d) and combined atorvastatin 10 mg/ezetimibe 10 mg produced similar LDL-C reductions, but the use of atorvastatin 80 mg/d monotherapy resulted in greater CRP reductions than the combination (Table III). Adding ezetimibe to atorvastatin 80 mg/d resulted in greater reductions in both LDL-C and CRP than did monotherapy with atorvastatin 80 mg/d,[35] which suggests that combination therapy with high dosages may be beneficial in patients who do not reach LDL-C goals with intensive statin monotherapy.

A similar study examined the effects of simvastatin monotherapy and simvastatin/ezetimibe combination therapy on LDL-C and CRP levels. In 668 patients with an LDL-C level of 145 to 250 mg/dL and triglyceride level ≤350 mg/dL, a simvastatin 80 mg/ezetimibe 10 mg combination produced similar LDL-C reductions to those noted with atorvastatin 80 mg/ezetimibe 10 mg in the previous study, but CRP reductions were greater with the atorvastatin 80 mg/ezetimibe 10 mg combination (Table III).[38] An atorvastatin/ezetimibe combination produced greater reductions in CRP when compared with a simvastatin/ezetimibe combination.

A larger study in 1229 patients with type 2 diabetes and hypercholesterolemia compared monotherapy with atorvastatin 10 and 20 mg with a combination of ezetimibe 10 mg/simvastatin 20 mg, and monotherapy with atorvastatin 40 mg with a combination of ezetimibe 10 mg/simvastatin 40 mg. The use of simvastatin 20 mg/ezetimibe 10 mg resulted in significantly greater reductions in both LDL-C and CRP levels than atorvastatin 10 mg, but atorvastatin 20 and 40 mg monotherapies gave comparable CRP reductions to the simvastatin milligram-equivalent combinations with ezetemibe (simvastatin 20 mg/ezetimibe 10 mg and simvastatin 40 mg/ezetimibe 10 mg), despite greater LDL-C reductions with the combination regimen.[39] No data are available from this study to indicate whether atorvastatin 80 mg monotherapy would be more efficacious for lowering both LDL-C and CRP than a lower-dose simvastatin/ezetimibe combination.

A randomized double-blind study compared atorvastatin monotherapy with simvastatin/ezetimibe combination therapy in 1902 patients with LDL-C levels above NCEP ATP III goals. Even when LDL-C reduction was greater with simvastatin 80 mg/ezetimibe 10 mg combination therapy than with atorvastatin 40 mg monotherapy (59% compared with 48%), CRP reduction was 2% greater with atorvastatin 40 mg monotherapy (29% compared with 27%) (Table III).[36] In a subanalysis of this study, only a small proportion of patients in either group reached target levels for both LDL-C and CRP (LDL-C <70 mg/dL, CRP <2 mg/L).[40] If combination therapy is required to meet goals, an atorvastatin/ezetimibe combination may be more efficacious than a simvastatin/ezetimibe combination if a CRP reduction is considered to be important in determining outcome.

It is worth noting that there is now substantial evidence to address safety concerns, particularly the concerns about severe muscle-related adverse effects, with high-dose statin therapy. A recent review of high-dose statin therapy found that in more than 40 trials (nearly 12,000 patients) with high-dose atorvastatin, the statin most extensively studied at high doses, there were 2 cases of myopathy.[41] No cases of myopathy were reported, however, in controlled trials of high-dose fluvastatin, while high-dose simvastatin appeared to be associated with a perceptible, but small, increase in the risk of myopathy; further trials will more definitively answer safety concerns with high-dose simvastatin.[41]

CONCLUSIONS

Managing LDL-C levels in patients with hypertension and additional cardiovascular risk factors reduces the patients' risk of cardiovascular events. Statins are the most effective available medications for lowering LDL-C; however, the degree of LDL-C lowering varies considerably among the statins. In addition to their LDL-C–lowering effects, some statins may also exert a lowering effect on CRP, a marker for inflammation that may also be a marker for CVD risk. Data to support definitive conclusions are not yet available, but some evidence suggests that reductions in CRP may lead to reductions in CVD risk, independent of LDL-C

changes. As with their effects on LDL-C, the effects of statins on CRP level are variable. High-dose monotherapy with atorvastatin appears to be as or more effective than combination therapy in reducing CRP than monotherapy with a different cholesterol-modifying medication.

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