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High-dose statin therapy: Benefits and safety in aggressive lipid lowering

Key Learning Points

- Low-density lipoprotein cholesterol (LDL-C) is a biomarker for atherosclerosis. Reductions in LDL-C are associated with reduced risk of adverse cardiovascular outcomes.
- Recent trials have shown the benefit of LDL-C lowering to <100 mg/dL and even <70 mg/dL. Based on these trials, the guidelines have been updated to suggest lower LDL-C goals for some at-risk patients.
- In patients without obvious coronary heart disease (CHD) or a CHD equivalent with ≥ 2 risk factors, it is critical to calculate their 10-year Framingham risk score to determine the LDL-C goal.
- The optimal LDL-C level for all patients with cardiovascular disease (CVD) appears to be <70 mg/dL. An LDL-C reduction of $\geq 50\%$ from baseline is the goal for non-CVD patients.
- LDL-C <70 mg/dL can be safely achieved in the majority of CVD patients if highly effective lipid-lowering agents are used.
- Statin therapy has been proven to be safe and well tolerated in millions of patients over almost 20 years of use.
- Physicians should select an agent that can achieve the appropriate level of LDL-C lowering, supported by clinical outcomes data, choose a robust starting dose, and titrate as needed to achieve goals.



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Despite the clear benefits of lipid-modifying drugs, current management of dyslipidemia remains suboptimal. Many at-risk patients fail to achieve guideline-recommended lipid goals, often as a result of either no or suboptimal statin therapy.¹ Family physicians have the opportunity to improve the quality of care for such patients. This supplement reviews the strength of recent trials supporting lower goals for low-density lipoprotein cholesterol (LDL-C) and the use of statins in high-risk patients with and without elevated LDL-C levels. Because the use of higher doses than those used to initiate therapy are often required, the safety of high-dose statin therapy will also be examined.

Disclosures

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TABLE 1
Updated NCEP ATP III LDL-C goals and cut points for therapy (2004)

Risk Category	LDL-C (mg/dL)		
	Goal	Initiation Level for TLC	Consideration Level for Drug Therapy
Very high risk: CHD + other risk factors	<70 (optional)	≥100	≥100 (<100: consider drug options)
High risk: CHD or CHD risk equivalents (10-yr risk >20%)	<100	≥100	≥100 (<100: consider drug options)
Moderately high risk: 2+ risk factors (10-yr risk 10%-20%)	<130 (optional: <100)	≥130	≥130 (100-129: consider drug options)
Moderate risk: 2+ risk factors (10-yr risk <10%)	<130	≥130	≥160
Lower risk: 0-1 risk factor	<160	≥160	≥190 (160-189: drug optional)

ATP III, Adult Treatment Panel III; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; TLC, therapeutic lifestyle change.

Adapted with permission from Grundy SM, et al. for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-239.

Indications for therapy based on cardiovascular risk

A patient's global cardiovascular disease (CVD) risk—the assessment of multiple CVD risk factors—should determine the need for and intensity of lipid-lowering therapy, with intensive treatments reserved for high-risk patients. Therapeutic lifestyle changes remain the foundation of primary prevention. Very high LDL-C levels or multiple risk factors elevate risk and require statin treatment to lower LDL-C.

To establish a patient's individual LDL-C goal, clinicians should determine the risk category, especially for patients without coronary heart disease (CHD) or a CHD risk equivalent (eg, diabetes). LDL-C is an intermediary target for the overall objective of reducing adverse CV events. Estimation of 10-year CVD risk—rather than counting risk factors—allows better targeting of intensive treatment for patients who will benefit most.² Determination can be made using the Framingham risk calculator, which can be found at <http://hp2010.nhlbi.nih.net/atpiii/calculator.asp?usertype=prof>. For example, the calculator shows that a 56-year-old male smoker with a total cholesterol of 210 mg/dL, a high-density lipoprotein cholesterol level of 32 mg/dL, and treated blood pressure (BP) (systolic BP of 132 mm Hg) has a 10-year risk of 25% and, therefore, an LDL-C goal of <100 mg/dL.

Thus, the higher a patient's global risk, the greater the overall benefit of reducing LDL-C levels, particularly at levels >100 mg/dL. The 2001 National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines (2001) defined the LDL-C goal as <100 mg/dL for high-risk patients (those with established CHD, peripheral arterial disease, abdominal aortic aneurysm, history of ischemic cerebrovascular accidents, >50% obstructive carotid atheromatous plaque, diabetes mellitus, or a 10-year CHD risk >20%).² Based on trial data, NCEP ATP III guidelines were updated in 2004 to include an optional LDL-C goal of <70 mg/dL in patients with established CHD that is complicated by diabetes mellitus, metabolic syndrome, poorly controlled standard risk factors, and current smoking.³ An LDL-C goal <100 mg/dL was also recommended as an option for primary prevention in patients with ≥2 risk factors and a 10-year CV risk of 10% to 20%. The update states that at least a 30% to 40% reduction from baseline LDL-C is warranted to significantly reduce CV risk.³ **TABLE 1** summarizes the updated LDL-C goals and cut points for initiating therapy.

Evidence for intensive statin therapy

Recent large clinical trials have established that additional CV risk reduction is achievable with high-dose (intensive) versus moderate-dose (standard)

TABLE 2
Benefits of high-dose versus moderate-dose statin therapy: Key results of 3 trials

Trial	Statin Dose		Achieved LDL-C Level (mg/dL)		RR (P value)	
	High	Moderate	High	Moderate	All-Cause Mortality	Total CV Events*
IDEAL (N=4439) ^a	80 mg atorvastatin	20 mg simvastatin	81	104	.98 (.80)	.87 (.02)
TNT (N=10,001) ^b	80 mg atorvastatin	10 mg atorvastatin	77	101	1.01 (.92)	.78 (<.001)
PROVE IT—TIMI 22 (N=4162) ^c	80 mg atorvastatin	40 mg pravastatin	62	95	.72 (.07)	.84 (.005)

CV, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; RR, relative risk. *Cardiovascular events defined as: IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering): Major coronary event (composite of coronary death, confirmed nonfatal acute myocardial infarction (MI), or cardiac arrest with resuscitation) + stroke at 5-year follow-up; TNT (Treating to New Targets): Death from coronary heart disease, nonfatal, non-procedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke at 5-year follow-up; PROVE IT—TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22): Death from any cause, MI, documented unstable angina requiring rehospitalization, revascularization, and stroke at 2-year follow-up.
^aPedersen TR, et al. JAMA. 2005;294:2437-2445. ^bLaRosa JC, et al. N Engl J Med. 2005;352:1425-1435. ^cCannon CP, et al. N Engl J Med. 2004;350:1495-1504.

statin therapy in patients with CHD.⁴⁻⁶ The principal results of these secondary-prevention trials show that high-dose statin therapy can achieve serum LDL-C levels substantially lower than the currently recommended level of <100 mg/dL, and that these lower levels result in greater protection against future CV events (TABLE 2). These trials show that high-dose statin therapy provides an additional 11% to 22% relative risk (RR) reduction of CV events compared with moderate-dose therapy; patients treated with high-dose statin therapy safely lowered LDL-C levels to a mean of 62 to 81 mg/dL, and no increased risk of serious adverse effects occurred with high-dose therapy. These trials confirm the benefit of this approach in patients with acute coronary syndrome (ACS), CHD, and past myocardial infarction (MI).

The Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT—TIMI 22) study showed the benefits and tolerability of high-dose statin therapy. In patients hospitalized with recent ACS (unstable angina [UA], MI), intensive treatment with atorvastatin (80 mg) provided greater protection against death or major CV events than did standard treatment with pravastatin (40 mg).⁶ Rates of the primary end point at 2 years were 26.3% in the pravastatin group and 22.4% in the atorvastatin group, reflecting a 16% reduction

in the hazard ratio (HR) in favor of atorvastatin ($P=.005$; 95% confidence interval [CI], 5%-26%). The number needed to treat (NNT) was 26 for major CV events and 40 for stroke.⁷

A subsequent subanalysis evaluated only atorvastatin-treated patients in groups: those who achieved LDL-C levels >100 mg/dL, >80 to 100 mg/dL, >60 to 80 mg/dL, >40 to 60 mg/dL, and <40 mg/dL.⁸ Patients who achieved very low LDL-C levels (<40 mg/dL and 40-60 mg/dL) had fewer major CV events (20.4%) than did patients with LDL-C levels of >80 to 100 mg/dL (26.1%), with no significant differences in safety. These data suggest that there is no lower limit of achievable LDL-lowering therapy that does not provide incremental benefit. Advantageous HRs for lower levels of LDL-C were 0.67 (CI, 0.50-0.92) for those achieving >40 to 60 mg/dL and 0.61 (CI, 0.40-0.91) for those achieving ≤40 mg/dL compared to the referent >80 to 100 mg/dL.

Specific patient populations

Evaluations of statin therapy have also focused on specific patient populations. Few trials have investigated the effects of statin therapy on CV morbidity and mortality in patients with metabolic syndrome. A post hoc analysis of the Treating to New Targets (TNT) trial showed a 29% reduction in CV event risk in such patients given

TABLE 3**Reported rates of discontinuation of study medication due to drug-related adverse events, number needed to harm, and number needed to treat**

Study	Treatment	Mean Achieved LDL-C (mg/dL)	Withdrawals due to Drug-Related AEs (% patients)	NNH to Result in Discontinuation for Drug-Related AEs	NNT to Prevent 1 Event (Any CV event/hard event ^a)
TNT	Atorvastatin 80 mg	77	7.2	53	19/44
	Atorvastatin 10 mg	101	5.3		
IDEAL	Atorvastatin 80 mg	81	9.6	19	23/60
	Simvastatin 20-40 mg	104	4.2		
4S	Simvastatin 20-40 mg	122	6	0 ^b	NR/10
	Placebo	190	6		
CARE	Pravastatin 40 mg	98	3.2	0	NR/24
	Placebo	136	3.5		

AE, adverse event; CARE, Cholesterol and Recurrent Events; CV, cardiovascular; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; LDL-C, low-density lipoprotein cholesterol; NNH, number needed to harm; NNT, number needed to treat; NR, not reported; 4S, Scandinavian Simvastatin Survival Study; TNT, Treating to New Targets.

^aHard event is defined as a nonfatal myocardial infarction, stroke, or CV-related death. ^bRate of discontinuation higher in placebo group. Adapted from J Am Coll Cardiol, vol 49, Davidson MH, et al. Safety of aggressive lipid management, 1753-1762. © 2007, with permission from Elsevier.

intensive therapy with atorvastatin (80 mg) beyond that achieved by standard therapy with atorvastatin (10 mg) (9.5% vs 13.0%, $P<.0001$).⁹ As shown in **TABLE 3**, the NNT for a CV event was 19, and for a hard event (defined as nonfatal MI, stroke, or CV death), the NNT was 44 for the overall TNT trial.¹⁰

A recent post hoc analysis of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial compared the benefits of atorvastatin 80 mg in older (≥ 65 years, mean age 74 \pm 6 years) and younger (< 65 years) patients with ACS.¹¹ Reductions in primary end point RR were similar in both the younger and older patients (22% vs 14%, respectively). Similar efficacy and safety findings were reported in a secondary analysis of the TNT trial: absolute risk for major CV events was reduced by 2.3% and RR by 19% for the high-dose (80 mg) atorvastatin group versus low-dose (10 mg) atorvastatin group (HR, 0.81; $P=.032$) in patients ≥ 65 years.¹² The improved clinical outcome was achieved without persistent elevation in creatine kinase levels. This analysis suggests that additional clinical benefit can be achieved safely in older patients with CHD by reducing LDL-C levels to < 100 mg/dL.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial enrolled patients with recent stroke or transient ischemic

attack and LDL-C levels of 100 to 190 mg/dL, but without known CHD. In this double-blind, placebo-controlled trial, treatment with atorvastatin 80 mg significantly reduced the overall incidence of stroke and CV events, despite a small increase in the incidence of hemorrhagic stroke.¹³ The 5-year absolute risk reduction in major CV events was 3.5% (HR, 0.80; 95% CI, 0.69-0.92; $P=.002$). The 5-year absolute risk reduction in fatal events was 2.2% (adjusted HR, 0.84; 95% CI, 0.71-0.99; $P=.03$; unadjusted $P=.05$). Importantly, the increase in hemorrhagic stroke was limited to patients who had a prior history of hemorrhagic stroke and/or inadequate blood pressure control.

The Heart Protection Study demonstrated the benefit of treating patients at high risk of a coronary event with simvastatin 40 mg daily, regardless of baseline LDL-C levels.¹⁴ Substantial reductions in CV events occurred at various patient ages: < 65 years, 24%; 65 to 69 years, 23%; and > 70 years, 18%. The NNT to prevent all deaths was 57, and the NNT to prevent CV events was 19. The availability of generic simvastatin, with its lower therapy costs, may allow greater patient access to therapy.

A subanalysis of the TNT trial found that intensive treatment of patients with stable CHD with atorvastatin (80 mg) significantly reduced hospitalization for heart failure (HF) among

patients with a history of HF ($P=.008$) compared to atorvastatin 10 mg.¹⁵ This clinical approach may, therefore, reduce the high rate of mortality associated with hospitalization among these patients.

Dosage and titration for statin therapy

Estimated changes in LDL-C levels with dosing of available statins are shown in **TABLE 4**.¹⁶ Starting doses generally provide LDL-C reductions of 21% to 26%; only starting doses of atorvastatin (10-40 mg) and rosuvastatin (5-10 mg) generate LDL-C reductions of 40% to 50%. Prescribing information data and clinical experience suggest that only a few statins used as monotherapy can lower LDL-C levels by $\geq 50\%$, eg, atorvastatin 40 to 80 mg, rosuvastatin 10 to 40 mg. Most patients at moderately high to very high risk need high-dose statin therapy or combination therapy to achieve LDL-C levels < 70 mg/dL, or even < 100 mg/dL.

The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration 2 (ACTFAST-2) study matched the starting dose of atorvastatin to a patient's baseline LDL-C value. This allowed high-risk patients to achieve LDL-C targets within 12 weeks of the initial dose or in a single uptitration.¹⁷ The flexible starting dose allowed 68% of patients to achieve LDL-C targets of < 100 mg/dL safely within the study parameters. The dosing recommendations are summarized in

TABLE 5.

The New Atorvastatin Starting Doses: A Comparison (NASDAC) study evaluated the safety and efficacy of atorvastatin at starting doses of 10, 20, 40, and 80 mg.¹⁸ The LDL-C levels were reduced in a dose-dependent manner across the 10- to 80-mg dose range; each higher dose significantly reduced LDL-C levels compared with all lower doses ($P<.01$) (**FIGURE**). Nearly all patients achieved NCEP ATP III LDL-C goals with atorvastatin 40 mg. The agent was well tolerated at all dosages. This study indicates that high-risk patients may benefit from a higher starting dose rather than starting low and titrating up.

In the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study, aggressive treatment with atorvastatin produced a 17% reduction in risk of CV events versus usual care ($P=.02$).¹⁹ The key driver of this overall reduction was the 47% decrease in nonfatal MI versus

TABLE 4
Estimated changes in LDL-C levels with dosing of current statins

Statin	Dose (mg/d)	Change in LDL-C (%)	
Atorvastatin	10	-39	
	20	-43	
	40	-50	
	80	-60	
Fluvastatin	20	-22	
	40	-25	
	80 (40 twice daily)	80 ^a	-36
			-35
Lovastatin	10	-21	
	20	-27	
	40	-31	
	80	-42	
Pravastatin	10	-22	
	20	-32	
	40	-34	
	80	-37	
Rosuvastatin	5	-45	
	10	-52	
	20	-55	
	40	-63	
Simvastatin	5	-26	
	10	-30	
	20	-38	
	40	-41	
	80	-47	

LDL-C, low-density lipoprotein cholesterol.

^aExtended-release formulation.

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usual care ($P<.0002$). Patients in the atorvastatin group were titrated to LDL-C goals of < 80 mg/dL or a maximum atorvastatin dose of 80 mg. The mean dose of atorvastatin over the course of the study was 40.5 mg; 545 patients (45%) received 80 mg. Usual-care patients received any treatment deemed appropriate by their physicians.

To determine a starting dose for statin therapy, the clinician should calculate the patient's level of risk (low, moderate, moderately high, or high), determine the percentage of LDL lowering needed, choose an appropriate agent, then titrate as needed (follow-up in 6-12 weeks, on the shorter end if the patient has had tolerability or other issues).

TABLE 5**Atorvastatin initial dose recommendation based on LDL-C levels and statin use**

Baseline LDL-C (mg/dL)	Statin-Naïve Patients	Patients Previously Taking Statins
100-149	10 mg	20 mg
150-159	20 mg	40 mg
160-169	40 mg	80 mg
170-220	80 mg	80 mg

LDL-C, low-density lipoprotein cholesterol. Adapted with permission from Farsang C, et al. *Curr Med Res Opin.* 2007;23:1945-1956.

Statin safety

Overall, currently marketed statins have a favorable benefit-to-risk relation with respect to liver, muscle, and renal concerns. Discontinuation of therapy because of adverse events with intensive treatment is no more frequent than is discontinuation with standard treatment.^{7,20} Results from the TNT (LDL to 70 mg/dL) and PROVE IT-TIMI 22 (LDL to <40 mg/dL) trials also show that adverse events are unrelated to the degree of LDL lowering.^{7,20} A retrospective analysis of pooled data from 49 clinical trials of atorvastatin in 14,236 patients treated for a mean of 2 weeks to 52 months demonstrated that the incidence of treatment-associated adverse events and withdrawals due to treatment-related adverse events for atorvastatin 80 mg was similar to that of both atorvastatin 10 mg and placebo.²¹ The incidence of treatment-related myalgia was $\leq 1.5\%$ across groups and was not dose-related, and elevation in liver enzymes was $\leq 0.6\%$ across groups. Thus it appears that rates of clinically significant myopathy and elevated hepatic enzymes are extremely low with high-dose atorvastatin therapy. However, a review by Waters showed that, while simvastatin 40 mg is associated with low rates of elevated hepatic enzymes and myopathy, simvastatin 80 mg carries a risk of myopathy of ~ 1 in 250.²²

Hepatotoxicity

Although transaminase levels increase in a dose-related fashion with statins, the risk of hepatic effects is not related to the magnitude of LDL lowering, and a definitive correlation between statin therapy and hepatotoxicity is not supported by statin trials to date.²³

Muscle toxicity

Statin-induced myopathy and rhabdomyolysis are relatively rare events (1 in 1000 and 1 in 10,000, respectively) that have been shown to be unrelated to the degree of LDL lowering.^{23,24} In a review of 49 trials, treatment-associated myalgia was observed in 1.4%, 1.5%, and 0.7% of patients in the atorvastatin 10 mg, atorvastatin 80 mg, and placebo groups, respectively.²¹ In a clinical trial database of 41,050 patients treated with simvastatin, the incidence of myopathy was approximately 0.02%, 0.08%, and 0.53% at 20, 40, and 80 mg/day, respectively.²⁵ Rhabdomyolysis, although rare with statins, is a serious side effect of statin-fibrate and statin-niacin combination therapy. Patients receiving these combination treatments should have their liver transaminase levels monitored and should be instructed to report any symptoms that might suggest myopathy.²⁶

Cancer

The Cholesterol Treatment Trialists' (CTT) collaborators collected data on 90,056 patients from 14 randomized statin trials and evaluated 5103 new cases of cancer. They concluded there was no evidence that statin therapy increased the overall risk of developing cancer (RR, 1.0; 95% CI, 0.95-1.06; $P=.9$), nor was there an excess in the development of cancer at any particular site.²⁷ Another meta-analysis of 26 randomized controlled trials showed that statins have a neutral effect on the risk of cancer and cancer death.²⁸

Drug interactions

The drugs that most commonly increase the risk of toxicity with statin therapy are cyclosporine and those that are metabolized via the cytochrome P450 (CYP) pathway or glucuronidation. Drugs that are metabolized via the CYP pathway include digitalis, diltiazem, verapamil, itraconazole, and ketoconazole, whereas gemfibrozil inhibits glucuronidation.²⁹ Atorvastatin has not been reported to interact with warfarin, whereas a recent case study suggests that simvastatin may interact with warfarin.³⁰ Dietary supplements such as St. John's wort and grapefruit juice (≥ 1 quart per day) also increase the risk of statin toxicity.^{10,31} Physicians should be vigilant for muscle-related complaints in patients taking a statin and amiodarone concomitantly, especially older patients taking

multiple medications.³² In these cases, use of a statin that is not metabolized through the CYP3A4 pathway (eg, pravastatin and rosuvastatin) may be appropriate.^{10,32} Atorvastatin, lovastatin, and simvastatin are metabolized mainly through the CYP3A4 pathway, whereas fluvastatin is metabolized mainly through the CYP2C9 pathway.¹⁰

Physicians are appropriately concerned about the potential of statins to interact with other lipid-lowering agents such as fibrates and niacin (nicotinic acid), which may be used in patients with mixed dyslipidemia. For example, the use of fenofibrate is preferred to gemfibrozil in combination with statins, since fenofibrate does not interfere with statin metabolism.³³ However, an analysis of data from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study found no evidence to support the concern for a statin-clopidogrel interaction.³⁴ In addition, a review of adverse events did not support a clinically significant interaction between extended-release niacin and statins.³⁵

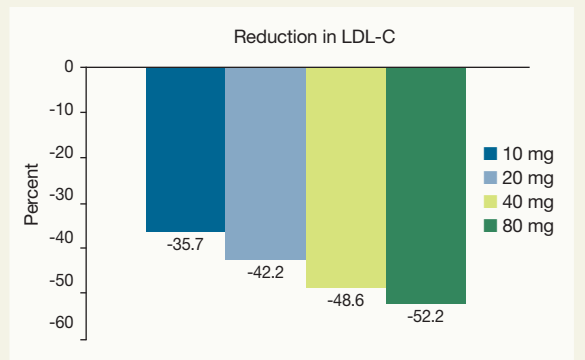
Weighing the efficacy and safety of statin therapy

Based on data summarized in **TABLE 3**, high-dose statin therapy is more effective in reducing mean LDL-C levels, is only marginally associated with a greater rate of discontinuation due to adverse events, and is unequivocally associated with reduced risk of acute events.¹⁰

The patient characteristics likely to enhance the safety of high-dose statin therapy include: prior statin use and tolerability, normal thyroid function, left ventricular ejection fraction $\geq 30\%$, and no fibrate use (especially gemfibrozil).¹⁰ In Asian patients, the starting dose of rosuvastatin should be 5 mg because of the decreased systemic clearance in this population.¹⁰ Statins should be used with caution in frail patients or those with small body frames (especially women) and in patients with a history of muscle disease. They should be avoided in patients receiving immunosuppressive agents (particularly cyclosporine), macrolide antibiotics (especially erythromycin or clarithromycin), antiviral drugs (especially HIV protease inhibitors), systemic azole antifungals (itraconazole and ketoconazole), and in patients with hepatic or renal disease or a history of alcoholism.¹⁰ Statins should be discontinued before intravenous dye

FIGURE

Dose-dependent reductions in LDL-C with atorvastatin



LDL-C, low-density lipoprotein cholesterol. Adapted from Am Heart J, vol 149, Jones PH, et al. Comparison of the efficacy and safety of atorvastatin initiated at different starting doses in patients with dyslipidemia, e1-e8. © 2005, with permission from Elsevier.

administration and before strenuous exercise (eg, a marathon), and their use should be discontinued during severe illness, major surgery, or trauma until after the patient has recovered.¹⁰ The concomitant use of simvastatin at doses >20 mg daily with either verapamil or amiodarone is not recommended because of increased risk of adverse events.¹⁰ Weak or moderately potent CYP3A4 inhibitors (eg, verapamil and diltiazem) can be used cautiously with small doses of CYP3A4-dependent statins.³⁶

Combination therapy to achieve LDL goals

Although lifestyle changes (eg, diet, exercise) remain important for achieving LDL goals, and statin monotherapy is effective for many patients, some patients may require combination drug therapy. Results of a recent meta-analysis of 5 randomized controlled studies enrolling a total of 5039 patients suggest that adding ezetimibe to ongoing statin therapy in patients who cannot achieve their LDL-C goal on statin monotherapy provides sufficient additional lipid lowering to allow more patients to reach their LDL-C goal.³⁷ No outcomes or long-term safety data are available for combination therapy of ezetimibe and simvastatin at this time. Recent controversy has been raised with the full report of the ENHANCE study. The limitations of the ENHANCE study include the patient population studied—patients who had familial hypercholesterolemia with an average baseline LDL-C of 319 mg/dL. Furthermore,

the ENHANCE trial was not powered to examine differences in clinical outcomes. The American College of Cardiology (ACC) has issued a statement that recommends that physicians adhere to the ACC/American Heart Association Guidelines, which recommend statins to the maximally tolerated dose or to goal as first-line treatment for patients with coronary artery disease.³⁸

Conclusion

Evidence-based data indicate that the optimal LDL-C level for all patients with CHD appears to be <70 mg/dL. This level of lipid lowering can be achieved safely in most patients using a high-dose

statin monotherapy, assuming appropriate patient selection. The clinical benefits of preventing vascular events, MI, stroke, and other CV outcomes far outweigh the low risk of adverse events associated with high-dose statin therapy in high- and intermediate-risk patients. The relationship between LDL-C reduction and reduction in risk for CV events is among the most exhaustively investigated issues in all of medicine—more patients, more years of follow-up, more clinical trials. Therefore, physicians can be confident that implementing high-dose statin therapy can achieve appropriate LDL lowering and reductions in CV morbidity and mortality in their patients. ■

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