

Current Concepts in Managing Dyslipidemia

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Summary

The guidelines for managing dyslipidemia are continuing to evolve. Currently, very aggressive lowering of low density lipoprotein cholesterol is recommended for many patients. To achieve these aggressive goals, maximized statins or combination lipid lowering therapy is necessary.

Key Points

- Aggressive LDL cholesterol lowering with a goal of less than 100 mg/dl for high-risk patients and a goal less than 70 mg/dl for very high-risk patients provides clinical outcome benefits.
- Achieving aggressive LDL cholesterol goals will require high dose statins or combination lipid lowering medication.
- Major outcomes trials are needed to determine whether combination therapy results in significantly greater reductions in cardiovascular events than monotherapy with statins alone.

MULTIPLE STUDIES HAVE SHOWN A relationship between low density lipoprotein cholesterol (LDL-C) reduction and coronary heart disease (CHD) relative risk (Exhibit 1).¹ Current lipid treatment guidelines focus primarily on LDL-C management.²⁻⁴ By incorporating new studies, these guidelines have evolved significantly over the years (Exhibit 2). Treatment recommendations have become more aggressive as studies have pushed for lower and lower LDL-C levels.

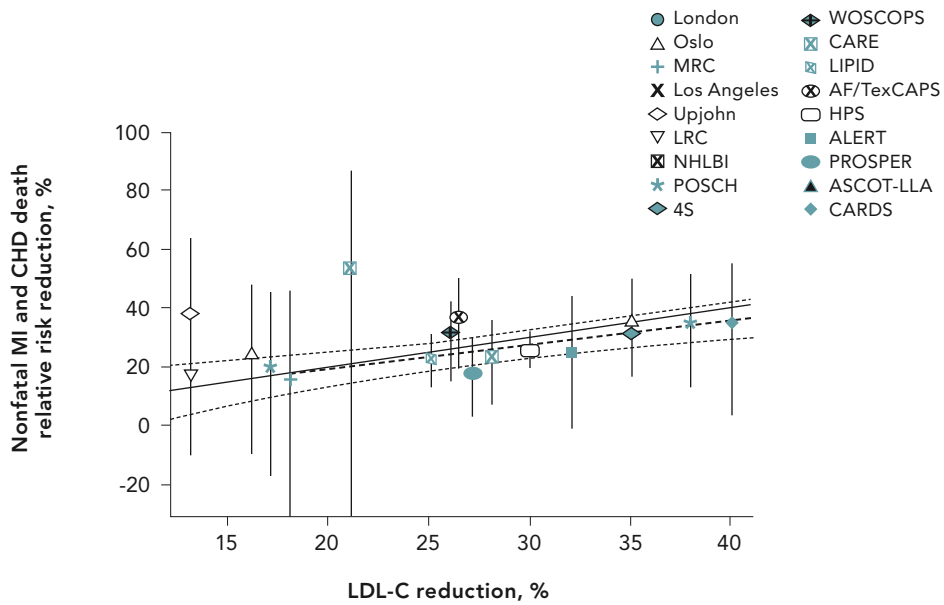
The Heart Protection Study was one of the studies to promote more aggressive treatment. This study found that statin therapy in patients starting with LDL-C less than 100 mg/dl was beneficial.⁵ The PROVE-IT study also was important to changing the guidelines.⁶ This study compared two different statins (atorvastatin 80 mg versus pravastatin 40 mg) in a group of very high-risk patients with acute coronary syndrome. It was found that the lower the LDL-C, the higher the benefit in CVD reduction. The benefit began within three to six months of beginning treatment, which is different from other studies. This was likely due to the high-risk nature of the subjects included in this trial. Most other secondary prevention trials show it takes 12 to 18

months to achieve benefit with statins.

Exhibit 3 shows the current LDL-C goals and cut points for therapeutic lifestyle changes and drug therapy.^{2,3} The changes that were recommended in the 2004 update to the 2001 National Cholesterol Education Program (NCEP) guidelines are highlighted. Additional studies that support lower LDL-C levels (~70 mg/dL) being beneficial have been published since the 2004 update to the guidelines. Based on these studies, the American Heart Association (AHA) and the American College of Cardiology (ACC) published recommendations for intensive LDL-C goals for high-risk patients (Exhibit 4).^{3,4} Although the 2004 update to the NCEP guidelines suggested a goal of less than 70 mg/dL for very high-risk patients, the AHA/ACC recommendations state the lower LDL-C level is appropriate for all patients with evidence of CHD or atherosclerosis.

Unlike the NCEP guidelines, the American Diabetes Association consensus statement for patients with diabetes mellitus or cardiometabolic risks provides specific goals for non-high density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (Exhibit 5).⁷ In addition to a LDL-C goal of less than 100 mg/dL for patients with diabetes, this state-

Exhibit 1: Multiple Studies Showed a Relationship Between LDL-C Reduction and CHD Relative Risk



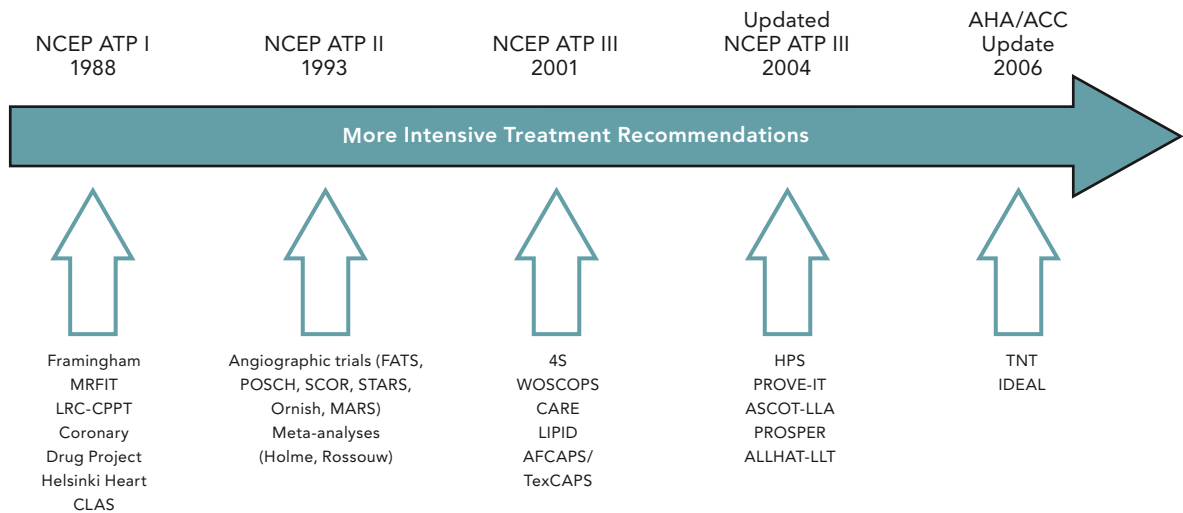
MI – myocardial infarction.

ment suggests lowering triglycerides to less than 150 mg/dL and raising HDL-C to more than 40 mg/dL in men and more than 50 mg/dL in women.

Several lipid lowering agents are available and have differing effects on the various lipid components (Exhibit 6).^{8,9} To achieve an aggressive goal

of less than 70 mg/dL for LDL-C, the treatment options are higher doses of the more potent statins (simvastatin, atorvastatin, rosuvastatin) or combination therapy. Using higher doses of statins has limitations because each doubling of the statin dose only lowers LDL-C another 6 to 7 percent. If it is not

Exhibit 2: Evolution of NHLBI Supported Guidelines



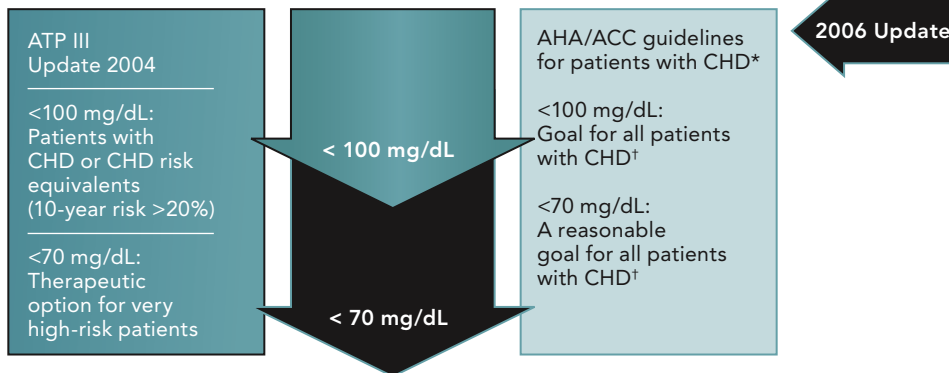
NHLBI = National Heart, Lung, and Blood Institute.
 NCEP ATP = National Cholesterol Education Panel Adult Treatment Panel.
 AHA = American Heart Association.
 ACC = American College of Cardiology.

Exhibit 3^{2,3}: LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy: 2004

Risk Category	LCL Goal (mg/dL)	Initiate TLC (mg/dL)	Consider Drug Therapy (mg/dL)
CHD or CHD risk Equivalents (10-year risk > 20%)	< 100 (optional goal: < 70)	≥ 100	> 100 (< 100: consider rug options)
2+ risk Factors: Moderately high risk (10-year risk 10-20%)	< 130 (optional goal: < 100)	≥ 130	≥ 130 (100-129: consider drug options)
Moderate Risk (10-year risk < 10%)	< 130	≥ 130	≥ 160
0-1 Risk factor	< 160	≥ 160	≥ 190 (160-189: LDL-lowering drug optional)

Exhibit 4^{3,4}: Intensive LDL-C Goals for High-Risk Patients

Recommended LDL-C treatment goals



*And other forms of atherosclerotic disease.

†Factors that place a patient at very high risk: established cardiovascular disease (CVD) plus: multiple major risk factors (especially diabetes); severe and poorly controlled risk factors (eg, cigarette smoking); metabolic syndrome (triglycerides [TG] >200 mg/dL + non-HDL-C >130 mg/dL with HDL-C <40 mg/dL); and acute coronary syndromes.

possible to attain an LDL-C less than 70 mg/dL because of a high baseline LDL-C, it is possible and recommended to achieve reductions of more than 50 percent with more intensive LDL-C-lowering therapy, including drug combinations.⁴

When seeking aggressive lipid lowering, many patients will require combination therapy to achieve

their goal. Statins can be combined with bile acid binding resins, niacin, fibrates, or ezetimibe, a cholesterol absorption inhibitor. Little data on clinical outcomes with combination therapy exist. A small study of triple therapy (niacin, colestipol, lovastatin) demonstrated reductions in cardiovascular deaths.¹⁰ The HATS trial, using a combination of simvastatin

Exhibit 5⁷: ADA Consensus Statement for Patients With Diabetes Mellitus or Cardiometabolic Risks

Cardiometabolic Risk	LDL Goal (mg/dl)	Non-HDL (mg/dl)	apoB (mg/dl)
Highest risk 1) Known CVD or 2) Diabetes plus one or more additional CVD risk factor(s)	< 70	< 100	< 80
High-risk patients 1) No diabetes or known CVD but ≥ 2 CVD risk factors 2) Diabetes: no other CVD risk factors	< 100	< 130	< 90

Exhibit 6^{8,9}: Effects of Drug Classes on Serum Lipids

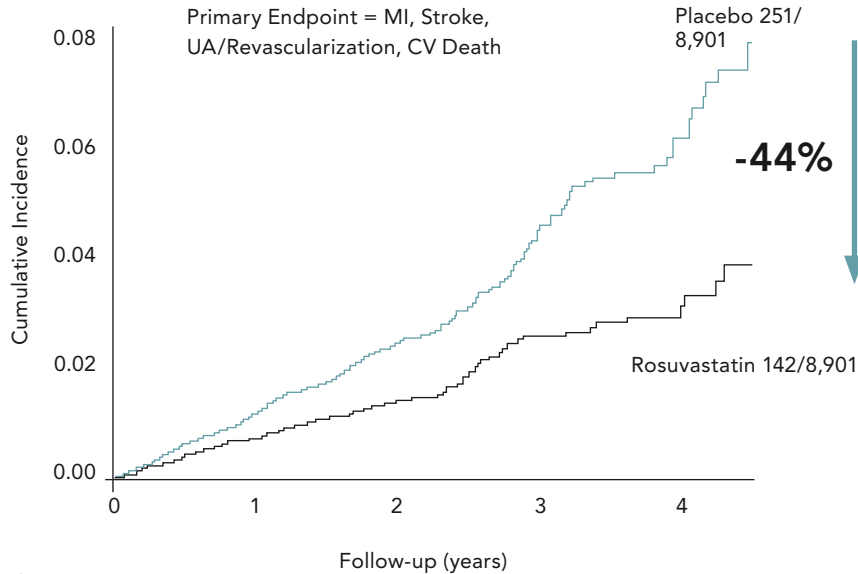
Drug class	TC	LDL	HDL	TG
Resins	↓ 20%	↓ 10-20%	↑ 3-5 %	Variable
Nicotinic acid	↓ 25%	↓ 10-15%	↑ 15-35%	↓ 20-50%
Fibrates	↓ 15%	Variable	↑ 6-15%	↓ 20-50%
Statins	↓ 15-60%	↓ 20-60%	↑ 3-15%	↓ 10-40%
Ezetimibe	↓ 20-22%	↓ 18-20%	↑ 1-3%	↓ 8-10%

and niacin, found reduced risk of coronary death, MI, stroke, and revascularization compared with placebo.¹¹ There are data on the use of fibrates which suggests that patients with diabetes or metabolic syndrome would benefit most in terms of clinical outcomes from these agents because both patient groups tend to have high triglycerides and low HDL-C. There are ongoing studies to determine the clinical outcomes of various combinations.

There are some challenges for clinical trial design to show clinical outcomes of lipid lowering in the post-statin trial era. Placebo controlled trials are unethical in patients where clinical benefit of statins is known. Now, the only trials that can be done are those using surrogate outcomes with intravascular ultrasound or carotid intima thickness (CIMT) or placebo controlled outcomes trials in patient populations where benefits of statins/lipid lowering are unknown.

Two recently published trials have received a lot of attention in both the lay and medical press. The ENHANCE trial was in patients with familial hypercholesterolemia and with severely elevated LDL-C (mean 317 mg/dL) and normal CIMT at baseline.¹² The subjects were treated for two years with simvastatin 80 mg plus ezetimibe 10 mg versus simvastatin 80 mg. Even on high doses of simvastatin, the subjects did not achieve recommended LDL-C levels. The mean LDL-C after treatment was 193 ± 60 mg/dL in the simvastatin group and 141 ± 53 mg/dL in the combination therapy group. The addition of ezetimibe to simvastatin did lead to expected changes in LDL-C, but did not reduce any CIMT parameter. There were problems with the design of this study—eight percent of the subjects had been treated with statins previously and none of the subjects had thickened CIMT at baseline. With-

Exhibit 7¹⁶: JUPITER Primary Trial Endpoint



		Number at risk									
		0	1	2	3	4	5	6	7	8	9
7	Rosuvastatin	8,901	8,631	8,412	6,540	3,893	1,958	1,353	983	544	157
	Placebo	8,901	8,621	8,353	6,508	3,872	1,963	1,333	955	534	174

out some increase in CIMT at baseline or reduction of LDL-C to less than 70 mg/dL, it was impossible to show an effect of drug therapy. The results of this trial are not grounds for questioning the benefits of LDL lowering.

In the SANDS trial, a reduction in CIMT was seen with the addition of ezetimibe to other lipid lowering medications at 36 months in previously untreated patients,¹³ which shows how study design is important to the results of a study. Additional clinical outcomes trials with ezetimibe are underway including Improve-It with a goal of 18,000 subjects.

An up and coming predictor of cardiovascular events is highly specific C reactive protein (hs-CRP). In some studies, hs-CRP is a better predictor than LDL-C alone.^{14,15} It adds to predictive value of the total cholesterol to HDL-C ratio in determining risk of first myocardial infarction.¹⁵

JUPITER was a randomized trial of rosuvastatin 20 mg per day versus placebo in the primary prevention of cardiovascular events among individuals with low levels of LDL-C and elevated levels of hs-CRP (> 2 mg/l).¹⁶ Included subjects had to have an LDL-C less than 130 mg/dL; the mean LDL-C was 108 mg/dL. Recruitment of the subjects for this study was a long process. More than 80,000 people had to be screened to identify 17,802 subjects. Because elevated hs-CRP is a marker for inflammation, 41

percent of the selected subjects had metabolic syndrome. Overall in this study, LDL-C decreased 50 percent, HDL-C increased 4 percent, hs-CRP decreased 37 percent, and TG decreased 17 percent with 12 months of rosuvastatin therapy compared with placebo. There was a 44 percent reduction in the primary endpoint of myocardial infarction, stroke, unstable angina, revascularization, or cardiovascular death (Exhibit 7).¹⁶ Due to the dramatic benefit, this study was halted early.

Overall, treatment with rosuvastatin of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels significantly reduced the incidence of major cardiovascular events.^{16, 17} Clinical benefits were maximized when both LDL-C and hs-CRP were reduced. Achievement of target concentrations of LDL cholesterol less than 70 mg/dL and hs-CRP less than 2 mg/L was associated with improved event-free survival compared with achievement of neither target or with achievement of reduced LDL cholesterol alone. An additional finding was a reduction in the occurrence of symptomatic venous thromboembolism with rosuvastatin therapy.¹⁸

There are some limitations to the results from JUPITER. This study did not include patients with low levels of hs-CRP. The data provides only limited information regarding use of hsCRP in practice.

The study did not compare use of hs-CRP with other markers of cardiovascular risk. Because the study was stopped after 1.9 years, the early termination may have exaggerated the results to some degree. Additionally, there was a high rate of screening failures, which suggests identifying similar patients may require a lot of screening. These types of subjects represent only about 4 percent of National Health Survey populations. Lastly, there also was an increase in the rate of physician-reported diabetes and a slight increase in hemoglobin A1C in patients treated with rosuvastatin.

The fourth revision of the NCEP guidelines is underway. It will be interesting to see how hs-CRP will be utilized in these guidelines. Currently, the AHA suggests using hs-CRP in patients with moderate risk for CVD to provide an additional measure of risk.¹⁹

Conclusion

Aggressive LDL cholesterol lowering with statins should be extended to high-risk patients with LDL-C less than 100 mg/dL and with a goal of less than 70 mg/dL for very high-risk patients. Many high-risk patients will require more effective LDL cholesterol lowering to achieve the ATPIII goal of LDL less than 100 mg/dL (or less than 70 mg/dL). Combination therapy may be required to achieve these aggressive goals. Major outcomes trials are needed to determine whether combination therapy results in significantly greater reductions in cardiovascular events than monotherapy with statins alone. **JMCM**

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