Aggressive LDL-C Lowering

Number 91 August 2004

"The lower the better for high risk people", is the message on low density lipoprotein cholesterol (LDL-C) from the recent clinical trials and the new NCEP guidelines. The NCEP panel updated the ATP III guidelines published in May 2001 based on the results of 5 major clinical trials of statins.

This *Heartbeat* will review the updated Adult Treatment Panel (ATP) III guidelines from the National Cholesterol Education Program (NCEP) based on evidence from recent statin trials.[1] These updated recommendations, which suggest more intensive LDL-C reduction for people at high risk of a cardiovascular (CV) event, are supported by the National Heart, Lung and Blood Institute (NHLBI), the American College of Cardiology (ACC) and the American Heart Association (AHA).

Guideline Highlights

Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. This more aggressive use of cholesterol-lowering drugs is to be used in conjunction with TLC–diet and exercise, which have enormous benefits beyond lowering LDL-C cholesterol, such as elevating levels of *good* cholesterol (HDL-C), lowering triglycerides (TG), improving diabetes, and reducing inflammation. Moreover, any person at high-risk who has lifestyle-related risk factors (eg obesity, physical inactivity, elevated TG, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C levels.

The updated guidelines (summarized in Table 1) preserve the same general goal of cholesterol-lowering treatment for high-risk individuals as in the 2001 guidelines—to reduce LDL-cholesterol levels to less than 100 mg/dL. The recommendations go even further, however, with the panel recommending that in very high-risk patients, aggressively lowering LDL-C to < 70 mg/dL is now a therapeutic option for clinicians and is encouraged by most experts.

TABLE 1. ATP III LDL cholesterol cutoffs for lifestyle interventions and drug therapy in different risk categories.

Risk category	LDL cholesterol goal	Initiate therapeutic lifestyle changes	Consider drug therapy
High risk: CHD, PAD, carotid vasc dx, AAA or CHD risk equivalents (diabetes or 10-year risk >20%)	<100 mg/dL **New:** optional goal of <70 mg/dL) in very high risk patients*	≥100 mg/dL	≥100 mg/dL (consider drug options if LDL-C <100 mg/dL)
Moderately high risk: two or more risk factors (10-year risk 10%-20%)	<130 mg/dL **New:** optional goal of <100mg/dL	≥130 mg/dL	≥130 mg/dL (consider drug options if LDL-C 100-129 mg/dL)
Moderate risk: two or more risk factors (10-year risk <10%)	**No change** <130 mg/dL	≥130 mg/dL	>160 mg/dL
Low risk: ≤1 risk factor	**No change** <160 mg/dL	≥160 mg/dL	≥190 mg/dL (consider drug options if LDL-C 160-189 mg/dL)

***Very high risk: Those with established coronary heart disease who have multiple risk factors including diabetes, tobacco dependence, metabolic syndrome, or severe or poorly controlled risk factors (eg HBP) and recent MI or acute coronary syndrome.**

These therapeutic options extend to those who have a baseline LDL-C < 100mg/dL.Treatment with statins is indicated in all high-risk patients regardless of LDL-C levels. Moreover, when a high-risk patient has high triglycerides—> 30mg/dL above the LDL-C goal and/or low high density lipoprotein cholesterol (HDL-C)—< 40mg/dL), combining a fibrate or niacin with a statin should be considered. Current documentation of risk reduction through controlled, clinical trials is not sufficient to warrant setting a specific goal value for raising HDH-C. Concern about developing myopathy with the statin-fibrate combination has lessened somewhat by the recent finding that one fibrate (fenofibrate [*Tricor*]) does not interfere with catabolism of statins and is therefore less likely to increase the risk of myopathy in patients treated with moderate doses of statins. The added risk of myopathy with niacin appears to be a least as low as it is with fenofibrate.

The updated guidelines now use a 10yr risk of coronary heart disease (CHD) with Framingham scoring as an added risk assessment tool (last page after references). In moderately high-risk patients defined as those with two or more risk factors for CHD and a 10—20% risk of CHD within 10 years, the NCEP targets remain LDL-C < 130mg/dL but now doctors have the option to bring the LDL-C down further, below 100mg/dL. The panel recommends that when LDL-C lowering is employed, the intensity of therapy be sufficient to at least lower LDL-C levels by 30% to 40%. *All the experts agree that more aggressive lipid lowering is beneficial especially in high-risk patients. These interventions to lower cholesterol level are often effective and justified even in older individuals.*

Recommendations for treating individuals at low or moderate risk (< 10% risk of CHD within 10 years) are unchanged from the 2001 Guidelines.

Five Trials

Evidence from five clinical trials was used to revise the ATP III recommendations:

1. **HPS: H**eart **P**rotection **S**tudy, a UK secondary prevention study of adults aged 40 to 80 years showing a risk reduction of 13% for all cause mortality, 24% for major vascular events, 27% for coronary death rate, and 25% for coronary revascularization with 40 mg of simvastatin daily compared with placebo.[2] The key finding was that these benefits were sustained even in those with baseline LDL-C levels below 100mg/dL.

2. **PROSPER: PRO**spective **S**tudy of **P**ravastatin in the **E**lderly at **R**isk, a 3.2-year study of secondary prevention in the elderly aged 70 to 82 years showing LDL-cholesterol reduction of 34% with risk reduction of 19% for coronary events and 24% for CHD mortality with 40 mg of pravastatin daily compared with placebo.[3]

3. **ALLHAT: A**ntihypertensive and **L**ipid-**L**owering Treatment to Prevent **H**eart **A**ttack **T**rial, a study of older adults with hypertension and moderate hypercholesterolemia that showed similar six-year mortality and CHD events for the pravastatin and the placebo groups with significant protection only for the African-American subgroup.[4]

4. **ASCOT-LLA: A**nglo-**S**candinavian **C**ardiac **O**utcomes **T**rial **L**ipid-**L**owering **A**rm, a primary prevention study prematurely terminated at 3.3 years because of a reduced risk of 36% for all CHD events, 21% for cardiovascular events, and 27% for stroke for atorvastatin compared with placebo.[5]

5. **PROVE IT:** Pravastatin and Atorvastatin Evaluation and Infection, a two-year head-to-head comparison of atorvastatin, 80 mg, (intensive dose) with pravastatin, 40 mg, (standard dose) showing a 16% improvement of cardiovascular endpoint for atorvastatin compared with pravastatin with better lowering of LDL-cholesterol level (endpoint, 62 mg/dL compared with 95 mg/dL).[6]

Four of these trials (along with others[7]) demonstrated that effective LDL-C reduction significantly reduces CHD risk and one (ALLHAT) failed to show any significant decrease in LDL-C between the treatment and control groups and was not associated with risk reduction. Overall the new evidence strongly reinforced ATP III recommendations, in particular the benefit of LDL-C lowering for patients with diabetes and the elderly. And beyond that, they provide new evidence for the efficacy of risk reduction with statins in high-risk patients with relatively low LDL-C levels.

Summary of Implications of Recent Clinical Trials for ATP III Treatment Algorithm:

- TLC remains an essential modality in clinical management. TLC has the potential to reduce CV risk through several mechanisms beyond ↓ LDL.

- In high-risk persons, the recommended LDL-C goal is <100 mg/dL.
  - –An LDL-C goal of <70 mg/dL is a recommended therapeutic option on the basis of new evidence, especially in the very high risk.
  - –An LDL-lowering drug (statin) is indicated regardless of LDL-C level simultaneously with TLC.
  - –If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with a statin. When triglycerides are ≥200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal (i.e. TG < 130mg/dL in a high-risk patient).

- For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL. When L DL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a recommended therapeutic option on the basis of the new evidence.

- For every 1% ↓ in LDL-C level, relative risk of CHD is ↓ by 1%. A 30%-40% reduction in LDL-C is advised when LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons; this translates into a similar 30-40 %CHD risk reduction of more than 5 years.
  - –Doses of statins used in the secondary prevention trials achieve LDL-C lowering to < 100mg/dL in just more than half the patients, and the statin dose may need to be increased or a second agent added in the remaining half.
  - –LDL-C reductions of > 50% often cannot be achieved. Thus a high-risk patient with a baseline LDL-C >150mg/dL, would not be able to get to < 70mg/dL.
  - –For intensive LDL-C lowering, the dose of statin should first be maximized, than a second agent such as an intestinal absorption inhibitor (ezetimibe-[*Zetia*]) or niacin or a fibrate may be added.

- Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC.

- For people in lower-risk categories, recent clinical trials do not modify the goals and cut points of tx.

Conclusion: LDL-C goals are intensified for very high-risk and high-risk moderate risk patients and include the elderly. Recommendations include statins, a second agent and TLC.

Mario L Maiese, DO, FACC, FACOI
Associate Professor of Medicine UMDNJSOM
Mail to: maiese1@comcast.net

[1] Grundy SM et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* July 13 2004; 110: 227-239.
[2] Heart Protection Study (HPS) Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet.* 2002; 360: 7–22.
[3] Shepherd J, et al; PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. PROspective Study of Pravastatin in the Elderly at Risk. *Lancet.* 2002; 360: 1623–1630.
[4] ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA.* 2002; 288: 2998–3007.
[5] Sever PS, et al; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. *Lancet.* 2003; 361: 1149–1158.
[6] Cannon CP, Braunwald E, et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* April 8 2004; 350: 1495–1504.
[7] Maiese ML. Extra-low cholesterol. April 2004 *Heartbeat*: 88.