A Summary of Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines

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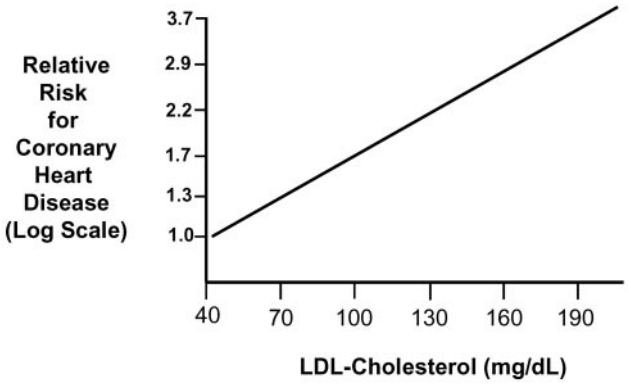
The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) issued an evidence-based set of guidelines on cholesterol management in 2001. Since the publication of ATP III, five major clinical trials of statin therapy with clinical end points have been published. These trials addressed issues that were not examined in previous clinical trials of cholesterol-lowering therapy. An NCEP working group reviewed the results of these recent trials and assessed their implications for cholesterol management. These clinical trials strongly support the ATP III recommendation that LDL-cholesterol (LDL-C) should be the primary target of lipid-lowering therapy. The trials confirm the benefit of cholesterol-lowering therapy in high-risk patients and support the ATP III treatment goal of LDL-C <100 mg/dL. In fact, they add to the growing evidence supporting the concept that, for LDL-C in high-risk patients, "the lower, the better" for reducing risk for major cardiovascular events (Figure). Although recent clinical trials focused on drug therapies for LDL lowering, the NCEP update affirms that therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering. Recent clinical trials support the inclusion of patients with diabetes in the high-risk category and confirm the benefits of LDL-lowering therapy in these patients. They further confirm that older persons benefit from therapeutic lowering of LDL-C. The major recommendations for modifications to footnote the ATP III treatment algorithm for LDL lowering are presented in the Table 1 and are summarized in Table 2. In *high-risk persons*, ATP III established that the recommended LDL-C goal is <100 mg/dL; when triglycerides are high (≥200 mg/dL), a secondary goal is a non–HDL-C <130 mg/dL. According to the update, when risk is *very high*, an LDL-C goal of <70 mg/dL is a therapeutic option, ie, a reasonable clinical strategy, based on available clinical trial evidence. This therapeutic option extends also to patients at very high risk who have a baseline LDL-C <100 mg/dL. For those very high risk patients who have a high triglyceride, a level of non–HDL-C of <100 mg/dL corresponds to an LDL-C level of <70 mg/dL. Identifying a very high risk patient depends on clinical judgment. Examples of such patients include those with established cardiovascular disease plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high triglyceride ≥200 mg/dL plus non–HDL-C ≥130 mg/dL with low HDL-C [<40 mg/dL]) and (4) those with acute coronary syndromes. Moreover, when any high-risk patient has high triglyceride or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug.

See page e149

For *moderately high-risk persons* (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL; but an LDL-C goal <100 mg/dL is a therapeutic option based on recent trial evidence. The latter option extends also to moderately high risk persons with a baseline LDL-C of 100 to 129 mg/dL. When LDL-lowering drug



Log-linear relationship between LDL-cholesterol levels and relative risk for coronary heart disease (CHD). This relationship is consistent with a large body of epidemiological data and with data available from clinical trials of LDL-lowering therapy. These data suggest that for every 30 mg/dL change in LDL-C, the relative risk for CHD is changed in proportion by ≈30%. The relative risk is set at 1.0 for LDL-C=40 mg/dL

The financial disclosure of the writing group panel of the ATP III update can be viewed on the National Heart, Lung, and Blood Institute website at http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3upd04.htm

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TABLE 1. ATP III LDL-Cholesterol Goals and Cut Points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence

Risk Category	LDL-C Goal	Initiate Therapeutic Lifestyle Changes (TLC)	Consider Drug Therapy[††]
CHD* or CHD Risk Equivalents[†] (10-year risk >20%) *High Risk*	<100 mg/dL (optional goal: <70 mg/dL)[¶]	≥100 mg/dL**	≥100 mg/dL[‡‡] (<100 mg/dL: consider drug options)[††]
2+ Risk Factors[‡] (10-year risk 10%–20%) *Moderately High Risk*	<130 mg/dL[‖]	≥130 mg/dL**	≥130 mg/dL (100–129 mg/dL; consider drug options)[§§]
2+ Risk Factors[‡] (10-year risk <10%) *Moderate Risk*	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
0–1 Risk Factor[§]	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

*Coronary heart disease (CHD) includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or by-pass surgery), or evidence of clinically significant myocardial ischemia.

†CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.

‡Risk factors include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years), and age (men ≥45 years; women ≥55 years)

§Almost all people with 0–1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with 0–1 risk factor is thus not necessary.

¶Very high risk favors the optional LDL-C goal of <70 mg/dL

‖Optional LDL-C goal <100 mg/dL.

**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 therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

††When LDL-lowering drug therapy is used, it is advised that intensity of therapy be sufficient to achieve at least a 30%–40% reduction in LDL-C levels.

‡‡If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option based on available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

§§For moderately high-risk persons, when LDL-C level is 100–129 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 therapeutic option based on available clinical trial results.

therapy is used in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels. Moreover, 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 to modify these risk factors regardless of LDL-C level.

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

TABLE 2. Recommendations for Modifications to Footnote the ATP III Treatment Algorithm for LDL-Cholesterol (LDL-C)

Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.

In high-risk persons, the recommended LDL-C goal is <100 mg/dL.

An LDL-C goal of <70 mg/dL is a therapeutic option based on available clinical trial evidence, especially for patients at very high risk.

If LDL-C is ≥100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.

If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug to achieve an LDL-C level <70 mg/dL is a therapeutic option based on available clinical trial evidence.

If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. 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

For moderately high-risk persons (2+ risk factors and 10-year risk 10%–20%), the recommended LDL-C goal is <130 mg/dL; an LDL-C goal <100 mg/dL is a therapeutic option based on available clinical trial evidence. When LDL-C level is 100–129 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 therapeutic option based on available clinical trial evidence.

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 therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

When LDL-lowering drug therapy is used in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%–40% reduction in LDL-C levels.

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