

# Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines

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## Purpose of review

In 2001, the Adult Treatment Panel III of the National Cholesterol Education Program issued recommendations, which were updated in 2004 to reflect knowledge from five major clinical trials completed after 2001. This review discusses the results of key clinical trials released in 2005 and their potential impact on the guidelines.

## Recent findings

Three major clinical trials, one subgroup analysis, and one meta-analysis were published in 2005 that can potentially affect the existing guidelines. The Treating to New Targets and the Incremental Decrease in End Points Through Aggressive Lipid Lowering trials demonstrated the incremental benefit of more aggressive low-density cholesterol lowering in stable coronary heart disease. The Cholesterol Treatment Trialists' Collaboration meta-analysis of statin trials supported the importance of low-density lipoprotein cholesterol reduction, irrespective of initial lipid profile, in reducing cardiovascular events. A subgroup analysis of the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm demonstrated statin benefits in diabetes, whereas the Fenofibrate Intervention and Event Lowering in Diabetes study failed to show overall treatment benefits with a fibrate in diabetes.

## Summary

Lowering of low-density lipoprotein cholesterol remains central in reducing cardiovascular risk; however, the recent trials support a target of less than 2.0 mmol/l (<80 mg/dl), rather than the less than 1.8 mmol/l (70 mg/dl) suggested by the 2004 update, for all high-risk patients and not, as recommended previously, just for those with additional factors. For individuals with diabetes, recent data support the use of statin therapy, even in those at less than high risk. First-line therapy should remain statins and not fibrates.

## Keywords

lipid lowering, National Cholesterol Education Program Adult Treatment Panel III guidelines, statin therapy

## Abbreviations

<b>ALLHAT-LLT</b>	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid Lowering Trial
<b>ASCOT-LLA</b>	Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm
<b>ATP III</b>	Adult Treatment Panel III
<b>CARDS</b>	Collaborative Atorvastatin Diabetes Study
<b>CHD</b>	coronary heart disease
<b>CTT</b>	Cholesterol Treatment Trialists group
<b>FIELD</b>	Fenofibrate Intervention and Event Lowering in Diabetes study
<b>HPS</b>	Heart Protection Study
<b>IDEAL</b>	Incremental Decrease in End Points Through Aggressive Lipid Lowering study
<b>LDL-c</b>	low-density lipoprotein cholesterol
<b>MI</b>	myocardial infarction
<b>NCEP</b>	National Cholesterol Education Program
<b>PROSPER</b>	Prospective Study of Pravastatin in the Elderly at Risk
<b>PROVE-IT TIMI 22</b>	Pravastatin or Atorvastatin Evaluation and Infection – Thrombolysis in Myocardial Infarction 22 trial
<b>RRR</b>	relative risk reduction
<b>TNT</b>	Treating to New Targets trial

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## Introduction

Over the past three decades, multiple clinical trials have demonstrated the link between cholesterol and cardiovascular disease. In an attempt to synthesize the wealth of data and to integrate the information into clinical practice, several organizations around the world developed guideline recommendations for the management of dyslipidemia. The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) [1] issued a set of recommendations in 2001 incorporating the evidence to date. After 2001, several major clinical trials were completed that affected the recommendations and thus, an update was released in 2004 [2]. The update suggested optional more aggressive low-density lipoprotein cholesterol (LDL-c) targets for very high-risk and moderately high-risk patients. These were not official modifications in the recommendations, however, but rather suggested therapeutic options to consider. Since the 2004 update, other clinical trials have been published that add to the wealth of evidence and may have significant impact on future guideline recommendations. This review discusses these recent trials and their potential implications.

## National Cholesterol Education Program Adult Treatment Panel III 2004 update

In the 2004 NCEP report, five major clinical trials were reviewed. These included the Heart Protection Study

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(HPS) [3]; the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) [4]; the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid Lowering Trial (ALLHAT-LLT) [5]; the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) [6]; and the Pravastatin or Atorvastatin Evaluation and Infection – Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) trial [7]. It was determined that these major trials supported the LDL-c goal of less than 2.6 mmol/l (100 mg/dl) for high-risk patients and the inclusion of patients with diabetes in the high-risk group, as well as confirming the benefits of lipid lowering in older patients. In addition, a new LDL-c goal of less than 1.8 mmol/l (<70 mg/dl) was deemed a therapeutic option in patients determined to belong to a newly defined, very high-risk group. They included established coronary heart disease (CHD) plus multiple major risk factors (especially diabetes); severe and poorly controlled risk factors (especially cigarette smoking); multiple risk factors of the metabolic syndrome; or patients with an acute coronary syndrome. This suggestion was based mostly on the HPS and PROVE-IT trials, which demonstrated further benefit of LDL-c lowering beyond 2.6 mmol/l, with a median LDL-c of only 1.6 mmol/l (62 mg/dl) in the intensive arm of PROVE-IT. It was recognized, however, that HPS and PROVE-IT could not be taken as the final word on the benefit of reducing LDL-c to such low levels [2], and thus the suggestion to reduce the LDL-C goal was left as a therapeutic option instead of a strong recommendation, pending the results of ongoing trials.

Based on the data from ASCOT-LLA and ALLHAT-LLT, a new therapeutic option was also proposed for moderately high-risk patients, which includes patients with two or more risk factors and a 10-year calculated CHD risk of 10–20%. Previously, ATP III did not recommend lipid-lowering therapy for this group of patients in whom LDL-c is less than 3.36 mmol/l (130 mg/dl). The 2004 report, however, suggested a LDL-c goal of less than 2.6 mmol/l (100 mg/dl) for moderately high-risk patients with baseline LDL-c between 2.6 and 3.36 mmol/l as a therapeutic option based on clinical judgement. No modifications were suggested for the lower risk category.

### **Review of recent studies with cardiovascular end points**

This section examines Treating to New Targets (TNT), Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL), Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis, Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm (ASCOT-LLA) – type 2 diabetes subgroup, and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD).

### **'Treating to New Targets'**

The TNT clinical trial [8\*\*] was carried out in 10 001 patients with clinically evident stable CHD and LDL cholesterol levels at baseline of less than 3.4 mmol/l while on atorvastatin 10 mg daily. The purpose of this study was to determine if aggressive lowering of LDL-c levels to 2.0 mmol/l (80 mg/dl) with high-dose statin was associated with better cardiovascular outcomes than a goal LDL-c of 2.6 mmol/l (100 mg/dl) with moderate statin therapy. Eligible patients were randomly assigned to receive either 10 mg or 80 mg of atorvastatin daily with a median follow-up of 4.9 years. The primary outcome was occurrence of first major cardiovascular event, defined as CHD death, nonfatal myocardial infarction (MI), resuscitation after cardiac arrest, or fatal or nonfatal stroke. The achieved LDL-c levels were 2.0 mmol/l (77 mg/dl) for the 80-mg group and 2.6 mmol/l (100 mg/dl) for the 10-mg group. At study end, there was a 22% relative risk reduction (RRR) and 2.2% absolute risk reduction in occurrence of the primary end point. Overall mortality was no different between the groups, although mortality rates were quite low in both groups. As for safety, the group treated with 80 mg of atorvastatin experienced more adverse events leading to discontinuation of study drug (7.2 vs. 5.3%) and more episodes of liver enzyme elevation (1.2 vs. 0.2%) but no difference in myalgia, rhabdomyolysis, or serious adverse events.

### **'Incremental Decrease in End Points Through Aggressive Lipid Lowering'**

In the prospective, open-label IDEAL trial [9\*\*], 8888 patients, all with previous MI and stable CHD, were randomly assigned to high-dose atorvastatin (80 mg daily) or usual-dose simvastatin (20–40 mg daily) and followed for a median of 4.8 years. The primary outcome was occurrence of a major coronary event, defined as CHD death, nonfatal MI, cardiac arrest, or resuscitation – but not stroke. Achieved LDL-c levels were 2.1 and 2.7 mmol/l, respectively. The difference in the primary outcome failed to reach statistical significance (hazards ratio 0.89; 95% CI, 0.78–1.01;  $P=0.07$ ). Several pre-specified secondary outcomes were statistically different between the groups, however. These included a 13% RRR in major cardiovascular events (primary event plus stroke – the primary end point in TNT); 16% RRR in any coronary event (any primary event, revascularization, or hospitalization for unstable angina); 16% RRR in any cardiovascular disease (primary event plus congestive heart failure and peripheral arterial disease); and a 17% RRR in nonfatal MI. Again, no difference was demonstrated in mortality. As for safety, more patients in the 80-mg atorvastatin group discontinued medication secondary to adverse events (9.6 vs. 4.2%) and experienced myalgias or elevations in liver enzymes, but it should be noted that this may be as a result of a selection

bias as more than 50% of the patients at baseline had previously been treated with simvastatin. No rhabdomyolysis was reported in either group.

### **Cholesterol Treatment Trialists' Collaboration meta-analysis**

A prospective meta-analysis of data from more than 90 000 patients in 14 randomized trials of statin therapy from 1994–2004 was performed by the CTT Collaboration [10\*\*]. A 12% RRR in all-cause mortality was demonstrated for every mmol/l reduction in LDL-c over 5 years, due in large part to the 19% RRR in coronary mortality. There were also corresponding reductions in MI or coronary death by (23% RRR), coronary revascularization (24% RRR), fatal or nonfatal stroke (17% RRR), and any major vascular event (21% RRR). Benefits were seen within the first year of treatment but increased over subsequent years. In other words, for every mmol/l reduction in LDL-c achieved, there were 48 fewer major vascular events per 1000 patients for secondary prevention and 25 fewer events per 1000 patients for primary prevention. There was no evidence of reduction in nonvascular mortality and no increase in the incidence of cancer.

### **Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm type 2 diabetes subgroup**

In ASCOT-LLA [6], 10 305 patients with hypertension and no history of CHD and at least three additional cardiovascular risk factors were randomly assigned to receive either 10 mg of atorvastatin or placebo for a median follow-up of 3.3 years. All of these patients had baseline nonfasting total cholesterol levels of 6.5 mmol/l or below ( $\leq 251$  mg/dl). The main results of the LLA were published in 2004 and supported the use of statin therapy in this group of patients who would have been categorized as moderately high risk by ATP III criteria, to reduce cardiovascular events. A prespecified subsidiary aim of the trial was to analyze data on the 2532 patients with type 2 diabetes, and this detailed analysis was published in 2005 [11\*\*]. At study end, the atorvastatin-treated group had an LDL-c of 2.15 mmol/l (83 mg/dl) compared with the placebo group with LDL-c of 3.02 mmol/l (117 mg/dl). Total cardiovascular events and procedures were reduced by 23% in the atorvastatin group. After excluding the 306 patients who had preexisting vascular disease, there remained a significant 25% reduction in events and procedures. This reduction was similar to reductions in the total ASCOT-LLA population. ASCOT was also designed to compare the effects of two antihypertensive regimens (atenolol with and without bendroflumethiazide and amlodipine with and without perindopril) for the prevention of CHD among 19 342 patients with hypertension, and the blood pressure part of the study was also stopped prematurely because of a significant decrease

in mortality observed in the amlodipine with-or-without perindopril arm. A two-by-two factorial design with the lipid arm allowed for detection of interaction between the treatments, and interestingly, an interaction was detected [12]. In the group receiving amlodipine-based treatment, there was a significant 53% reduction in the primary end point in those also receiving atorvastatin compared with placebo. In the group receiving atenolol-based therapy, however, the benefit of atorvastatin did not achieve statistical significance. This was true for the primary end point as well as several secondary end points.

### **Fenofibrate Intervention and Event Lowering in Diabetes**

The FIELD study [13\*\*] was a multinational, randomized controlled trial of 9795 patients with type 2 diabetes, not on statin therapy at study entry, comparing the effects of fenofibrate and placebo on coronary events (CHD death or nonfatal MI). Of the 9795 patients, 7664 did not have preexisting cardiovascular disease. Baseline total cholesterol was less than 6.5 mmol/l ( $<251$  mg/dl) and the mean LDL-c was 3.1 mmol/l (119 mg/dl). The patients' primary care physicians were permitted to modify therapy, including lipid-lowering therapy, at their discretion. After a median follow-up of 5 years, 17% of the patients in the placebo group and 8% in the fenofibrate group were also receiving other lipid-lowering therapy, 93% of which were statins. The primary end point was the first occurrence of either nonfatal MI or CHD death. At study end, the difference in primary outcome did not achieve statistical significance. Although non-fatal MI was reduced significantly by 24% (hazards ratio 0.76; 95% CI 0.62–0.94;  $P=0.01$ ), CHD mortality was increased by a nonsignificant 19% (hazards ratio 1.19; 95% CI 0.90–1.57;  $P=0.22$ ). Some of the other secondary outcomes also achieved statistical significance including total cardiovascular disease (CHD events, stroke, cardiovascular death, coronary and carotid revascularization) (hazards ratio 0.89; 95% CI 0.80–0.99;  $P=0.035$ ). There was no difference in total mortality. Interestingly, there were some positive tertiary outcome benefits of fenofibrate use, including reduced progression of albuminuria and retinopathy requiring laser treatment.

### **Potential implications of recent trials on the National Cholesterol Education Program Adult Treatment Panel III guidelines**

This section examines very high-risk and high-risk patients and patients with diabetes mellitus.

#### **Very high-risk and high-risk patients**

The 2004 report suggested the creation of a 'very high-risk' group based on the coexistence of other major factors in a high-risk patient. For this group, the LDL-c goal was reduced to less than 1.8 mmol/l ( $<70$  mg/dl) as

a therapeutic option. This number appears to have been chosen arbitrarily based on the LDL-c level achieved in PROVE-IT [2] of 1.6 mmol/l (62 mg/dl) and the suggestion from HPS that reducing LDL-c by 30% starting at 2.6 mmol/l (100 mg/dl) can achieve a further 20–30% RRR in CHD. TNT, IDEAL, and the CTTC meta-analysis [8\*\*–10\*\*] further support the notion that lowering the LDL-c level plays a direct and central role in reducing risk of cardiovascular disease. Therefore, the lowering of LDL-c goals from the previously recommended 2.6 mmol/l (100 mg/dl) is appropriate, but to what extent? TNT and IDEAL suggest that lowering LDL-c below 2.6 mmol/l (100 mg/dl) provides further benefit, but they do not directly support the threshold of 1.8 mmol/l (70 mg/dl) proposed in the 2004 NCEP report. In TNT, the intensively treated group only achieved a LDL-c of 2.0 mmol/l (77 mg/dl). Although the primary outcome of IDEAL did not achieve statistical significance, the secondary outcome of major cardiovascular events, which included stroke and was identical to the primary outcome of TNT, did reach statistical significance with a 13% RRR. When interpreted in that light, IDEAL also supports the benefit of reducing LDL-c below the 2.6 mmol/l (100 mg/dl) threshold, but its high-dose treatment arm achieved a LDL-c of 2.1 mmol/l (80 mg/dl). Thus, the recent evidence would support lowering the target below 2.6 mmol/l (100 mg/dl) to about 2.0 mmol/l (77 mg/dl), rather than 1.8 mmol/l (70 mg/dl). In addition, the majority of the patients in TNT and IDEAL would have been considered ‘high risk’ but not ‘very high risk’ according to the factors outlined in the 2004 report. Therefore, the reduced targets should be applied to all high-risk patients, not only those with additional factors. In addition, although TNT and IDEAL do not directly support the lower target of 1.8 mmol/l (70 mg/dl), the results of PROVE-IT are important and should be taken into consideration for one of the ATP III Update’s very high-risk groups – those with acute coronary syndrome. Marked differences in LDL-c were achieved within 30 days of the acute coronary syndrome event and differences in cardiovascular outcome were also achieved early within 30 days of the event. Thus, perhaps the therapeutic option of lowering LDL-c to less than 1.8 mmol/l (70 mg/dl), and perhaps the 1.6 mmol/l achieved in PROVE-IT, should be reserved at the present time for those patients with acute coronary syndrome.

When cholesterol targets are lowered, we must also consider the safety of aggressive lowering, which virtually always requires the use of high-dose statin therapy. The CTTC meta-analysis [10\*\*] examined safety issues pertaining to statin use. In the meta-analysis, no increase in nonvascular death or cancer was demonstrated in the statin-treated group over 5 years compared with placebo. The incidence of rhabdomyolysis was also found to be

very low, with a 5-year excess of 0.01%. None of the high-dose statin trials (PROVE-IT, TNT, IDEAL) were included in this meta-analysis, however. A substudy of PROVE-IT examined the safety of achieving very low LDL-c levels [14\*\*] and found no difference in muscle, liver, retinal abnormalities, intracranial hemorrhage, or death in the group with LDL-c lower than 1.0 (40 mg/dl) compared with those with higher LDL-c levels. Interestingly, however, the fewest cardiac events were seen in that group as well as those with values lower than 1.55 mmol/l. In both TNT and IDEAL, the higher-dose statin therapy was associated with higher rates of discontinuation secondary to drug-related adverse events and with more liver enzyme abnormalities. There was no difference in myalgia, rhabdomyolysis, or incidence of clinical liver disease, however. Therefore, it would appear that the significant clinical benefits of higher-dose statin therapy and lower LDL-c levels outweigh the slight increase in adverse events, none of which were permanent or catastrophic.

#### Patients with diabetes mellitus

The NCEP ATP III, like many other guidelines, identifies diabetes mellitus as a high-risk condition and places the vast majority of patients with diabetes mellitus whether with or without CHD in the high-risk category. In the 2004 update, this designation was supported further by data from HPS clearly demonstrating that patients with both diabetes mellitus and CHD deserve aggressive LDL-c lowering. Treatment with lipid-lowering drugs was not necessarily recommended for individuals with diabetes mellitus and no CHD who were considered to be only moderately high risk [2], however. With the support of data from the Collaborative Atorvastatin Diabetes Study (CARDS) [15], and more recently the diabetes subgroup analysis of ASCOT-LLA [11\*\*], it would be appropriate to recommend statin therapy even in the moderately high-risk group with diabetes mellitus. Furthermore, we now have evidence that statin therapy should be recommended as first-line treatment for reduction of cardiovascular outcomes in patients with diabetes mellitus and not fibrate therapy based on the overall negative results of FIELD [13\*\*]. The benefits seen in many of the secondary outcomes of FIELD are interesting and would support further trials to look for additional benefits of fibrate therapy, perhaps when added to statins. We await the results of the ongoing National Institutes of Health-sponsored ACCORD trial (protocol abstract, 14 November 2002, available at: <http://www.accordtrial.org/public/purpose.cfm>) to further address the issue of combination fibrate and statin use in type 2 diabetes.

#### Conclusion

Since the publication of the 2004 NCEP update of ATP III, several important lipid outcome trials as well as a

long-awaited meta-analysis have been released. TNT, IDEAL, and the CTTC meta-analysis have provided further support to the central role of LDL-c lowering with high-dose statin therapy to reduce cardiovascular risk. Rather than supporting the aggressive goal of less than 1.8 mmol/l (70 mg/dl) suggested by the 2004 update, they point to a target closer to 2.0 mmol/l (< 77 mg/dl) and for all high-risk patients, not just those with additional factors. The diabetes subgroup analysis of the lipid portion of ASCOT supports the previously recommended aggressive approach to treating individuals with diabetes and also supports the use of statin therapy even in patients with diabetes in the moderately high-risk category, consistent with the results of CARDS. Furthermore, the first-line therapy should remain statins and not fibrates given the negative primary results of FIELD. Unanswered questions for future studies include the appropriate targets for lower-risk patients as well as the role of combination therapy.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 422).

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