

# New Therapeutic Options in the National Cholesterol Education Program Adult Treatment Panel III

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## **Abstract**

Coronary heart disease (CHD) is a common, costly, and undertreated disorder in the United States, and dyslipidemia is one of its most important modifiable risk factors. Recently, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) published updated guidelines for the treatment of lipid disorders, greatly expanding the number of patients eligible for therapy. In the new recommendations, several significant changes have been made in the identification and management of patients at risk for CHD. Although ATP III maintains that low-density lipoprotein (LDL) cholesterol should be the primary target of lipid-lowering therapy, it identifies non-high-density lipoprotein (HDL) cholesterol (total cholesterol minus HDL cholesterol) as a secondary target in patients with elevated triglycerides. Patients with  $\geq 2$  CHD risk factors should now be assessed for 10-year absolute CHD risk based on the Framingham Point Scale to identify those who require more aggressive treatment. The guidelines also designate a new category, CHD risk equivalent, which recognizes that certain patients have the same high risk as those with established CHD. Diabetes is now identified as a CHD risk equivalent, as are other forms of atherosclerotic disease and multiple risk factors comprising a CHD 10-year risk of  $>20\%$ . New lipoprotein classifications are given, and increased emphasis is placed on the metabolic syndrome, a constellation of metabolic risk factors, as a marker for CHD risk. Since adherence poses a major challenge in the management of patients with or at risk for CHD, the new guidelines provide physicians with several strategies for increasing patient compliance. The new guidelines should help physicians better identify and manage patients at risk for CHD, help more patients reach their lipid goals, and thereby decrease cardiovascular morbidity and mortality.

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Nearly 62 million people in the United States are estimated to have cardiovascular disease, including more than 12 million with known coronary

heart disease (CHD).<sup>1</sup> Despite advances in our understanding of its causes, prevention, and treatment, CHD is still the most frequent cause of death among men and women, accounting for about 1 of every 5 deaths in the United States. Each year, 650 000 people have an initial myocardial infarction (MI), and 450 000 suffer a recurrent attack. Of these people, 45% of patients will die within the first year post-MI; furthermore, women are more likely to die of an MI than men. Moreover, about 250 000 people, many of whom had no previous symptoms of the disease, died before they could be hospitalized. In addition to the morbidity and mortality associated with CHD, the economic consequences are staggering. The American Heart Association estimates that the total annual cost of CHD is \$111.8 billion, including \$58.2 billion in direct medical costs for hospitalization, nursing home care, physician and other professional fees, drugs, and home healthcare, and \$53.6 billion in indirect costs due to lost productivity and premature mortality.<sup>1</sup>

Numerous epidemiological and clinical studies show that CHD risk is associated with lipid abnormalities.<sup>2-9</sup> Accordingly, the National Cholesterol Education Program (NCEP) issued treatment guidelines in 1988 (Adult Treatment Panel I [ATP I]) and updated guidelines in 1993 (ATP II) that defined low-density lipoprotein (LDL) cholesterol as the principal target of therapy and established the LDL cholesterol levels at which diet and drug therapy should be initiated.<sup>10,11</sup> Nevertheless, the third National Health and Nutrition Examination Survey (NHANES III) showed that millions of people in the United States are not receiving treatment.<sup>12</sup> For example, of the estimated 8.4

**Table 1.** Classification of Lipoprotein Levels in ATP III

LDL Cholesterol (mg/dL)		Triglycerides (mg/dL)	
<100	Optimal	<150	Normal
100 to 129	Near or above optimal	150 to 199	Borderline high
130 to 159	Borderline high	200 to 499	High
160 to 189	High	≥500	Very high
≥190	Very high		
Total Cholesterol (mg/dL)		HDL Cholesterol (mg/dL)	
<200	Desirable	<40	Low
200 to 239	Borderline high	≥60	High
≥240	High		

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.  
 Source: Reference 14.

million CHD patients eligible for treatment, only 2.4 million have been prescribed diet therapy and 1.1 million have been prescribed drug therapy.<sup>12</sup> Moreover, only a small fraction of low-risk patients (<2 risk factors) or patients with multiple risk factors are receiving drug therapy. However, these numbers would be higher if ATP III goals were applied. Even among those being treated, many are not reaching LDL cholesterol treatment goals. The Lipid Treatment Assessment Project (LTAP) surveyed 4888 dyslipidemic patients between August 1996 and February 1997 who had been treated in primary care with the same lipid-modifying therapy for ≥3 months.<sup>13</sup> Overall, only 38% of patients had achieved their ATP II LDL cholesterol goal, including 68% of low-risk patients, 37% of high-risk patients (≥2 risk factors), and 18% of those with established CHD.<sup>13</sup>

**ATP III: Updated Guidelines With Important Changes**

The ATP III guidelines, published in 2001, build on ATP II with several new features. The assessment of 10-year absolute CHD risk based on the Framingham Point Scale is recommended to identify high-risk patients with multiple risk factors who also require aggressive LDL cholesterol lowering. ATP III emphasizes the identification of patients with metabolic syndrome who are candidates for intensified therapeutic lifestyle changes (TLC)

and potentially for drug therapy. The classification of lipoprotein levels has also been updated, including defining LDL cholesterol <100 mg/dL as optimal, raising the cutoff of low high-density lipoprotein (HDL) cholesterol to <40 mg/dL, and lowering triglyceride classification cut points to <150 mg/dL to emphasize moderate elevations (Table 1). In addition, non-HDL cholesterol is now identified as a secondary target of therapy in patients with elevated triglycerides.<sup>14</sup>

The designation of a new category, CHD risk equivalent, recognizes that certain patients have the same high risk as those with established CHD and require the same intensive LDL cholesterol lowering. Diabetes has been reclassified from a risk factor in ATP II to a CHD risk equivalent in ATP III. Other CHD risk equivalents include peripheral arterial disease, abdominal aortic aneurysm, thrombotic stroke, and transient ischemic attacks. Moreover, patients with multiple risk factors that confer a 10-year CHD risk >20% are also considered to be in the CHD risk equivalent category.

Positive risk factors include age (men ≥45 years and women ≥55 years), cigarette smoking, hypertension or blood pressure controlled with antihypertensive medication, low HDL cholesterol (<40 mg/dL), and family history of premature CHD. High HDL cholesterol (≥60 mg/dL) is a negative risk factor, with its presence allowing for 1 risk factor to be subtracted from the risk score. The 10-year CHD risk is calculated using the Framingham Point Scale for those patients with ≥2 risk factors for CHD. Points are assigned on the basis of age, total cholesterol, systolic blood pressure, HDL cholesterol, and smoking status, and are summed to determine the 10-year absolute risk (see sidebar). If the 10-year risk is >20%, the patient has a CHD risk equivalent. Patients with a 10-year risk of 10% to 20% are categorized as having moderate CHD risk and those with a 10-year risk of <10% are considered low risk. The LDL cholesterol goal is then defined on the basis of the person's risk classification (Table 2).<sup>14</sup>

ATP III also recognizes that CHD risk is influenced by life-habit and emerging risk factors, although these are not used in Framingham risk assessment. Life-habit risk factors include obesity, physical inactivity, and a high-fat diet. Emerging risk factors that may be useful in the future, but do not presently alter ATP-defined LDL cholesterol goals, include elevated lipoprotein (a); homocysteine, prothrombotic, and proinflammatory factors (eg, high-sensitivity C-reactive protein [hs-CRP]); impaired fasting glucose (110-125 mg/dL); and evidence of subclinical atherosclerotic disease, which is usually identified by imaging techniques such as carotid sonography.<sup>14</sup> These factors contribute to CHD risk to varying degrees and may be used to guide clinical decisions about the intensity of therapeutic intervention. In particular, CRP has been gaining attention because large epidemiologic studies have demonstrated its correlation with CHD risk.<sup>15,16</sup>

**Primary Approach to Treatment**

The effective management of dyslipidemia brings more patients under adequate lipid control, which in turn lowers the cost of CHD care and reduces cardiovascular morbidity and total mortality. According to ATP III, the management of dyslipidemia should include a multifaceted lifestyle approach that involves diet and exercise and then pharmacologic interventions, if necessary.<sup>14</sup> A number of different mechanisms effectively modify cholesterol levels; consequently, several approaches to drug therapy are available (Figure).<sup>17</sup> More important, these mechanisms are often complementary in lowering cholesterol levels, thus providing the basis for combination therapy.

The LDL cholesterol levels at which TLC and drug therapy should be initiated for each risk category are shown in Table 2. The TLC diet includes reducing saturated fat intake to <7% of total calories, restricting polyunsaturated and monounsaturated fats to ≤10% and ≤20% of caloric intake, respectively, with total fat and carbohydrates representing 25% to 35% and 50% to 60% of total calories, respectively. Trans

**Assessment of 10-Year CHD Risk in Patients With Multiple Risk Factors**

Risk assessment is done based on risk factors and the Framingham Points Scale, available at <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>.

A 52-year-old man (6 points) has a total cholesterol of 150 mg/dL (0 points) and an HDL cholesterol of 35 mg/dL (2 points). He doesn't smoke (0 points), but he has a systolic blood pressure of 135 mm Hg after treatment with hydrochlorothiazide (2 points). This subject has a total score of 10 points, giving him a 10-year CHD risk of 6% and placing him in the low-risk category.

**Framingham Point Scores for Estimating 10-Year CHD Risk in Men and Women**

Age (yrs)	Systolic Blood Pressure (mm Hg)			HDL Cholesterol (mg/dL)	
	Untreated	Treated			
20-34	-9/-7			≥60	-1/-1
35-39	-4/-3	<120	0/0		
40-44	0/0	120-129	0/1	50-59	0/0
45-49	3/3	130-139	1/2	40-49	1/1
50-54	6/6	140-159	1/3	<40	2/2
55-59	8/8	≥160	2/4		
60-64	10/10		3/6		
65-69	11/12				
70-74	12/14				
75-79	13/16				

**Total Cholesterol**

Age	20-39 yrs	40-49 yrs	50-59 yrs	60-69 yrs	70-79 yrs
<160 mg/dL	0/0	0/0	0/0	0/0	0/0
160-199 mg/dL	4/4	3/3	2/2	1/1	0/1
200-239 mg/dL	7/8	5/6	3/4	1/2	0/1
240-279 mg/dL	9/11	6/8	4/5	2/3	1/2
≥280 mg/dL	11/13	8/10	5/7	3/4	1/2

**Smoking Status**

No	0/0	0/0	0/0	0/0	0/0
Yes	8/9	5/7	3/4	1/2	1/1

CHD indicates coronary heart disease; HDL, high-density lipoprotein.

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**Assessment of 10-Year CHD Risk in Patients With Multiple Risk Factors** (Continued)

Men		Women	
Points	10-Year CHD Risk	Points	10-Year CHD Risk
<0	<1	<9	<1
0-4	1	9-12	1
5-6	2	13-14	2
7	3	15	3
8	4	16	4
9	5	17	5
10	6	18	6
11	8	19	8
12	10	20	11
13	12	21	14
14	16	22	17
15	20	23	22
16	25	24	27
≥17	≥30	≥25	≥30

CHD indicates coronary heart disease.

**Table 2.** Target LDL Cholesterol Levels and Cut Points for Initiation of TLC and Consideration of Drug Therapy

Risk Category	LDL Goal (mg/dL)	LDL Level (mg/dL) at Which to:	
		Initiate TLC	Consider Drug Therapy
CHD or CHD risk equivalent	<100	≥100	≥130 (100 to 129; optional*)
≥2 risk factors (10-year CHD risk ≤ 20%)	<130	≥130	≥130 if 10-year risk is 10% to 20% ≥160 if 10-year risk is <10%
0 risk factors or 1 risk factor	<160	≥160	≥190 (160 to 189, optional)

\*Some experts recommend LDL cholesterol-lowering drug therapy if goal cannot be achieved with TLC alone, whereas others prefer to use drugs that primarily modify triglycerides and HDL cholesterol, such as niacin or fibrates. TLC indicates therapeutic lifestyle changes; LDL, low-density lipoprotein cholesterol; CHD, coronary heart disease. Source: Reference 14.

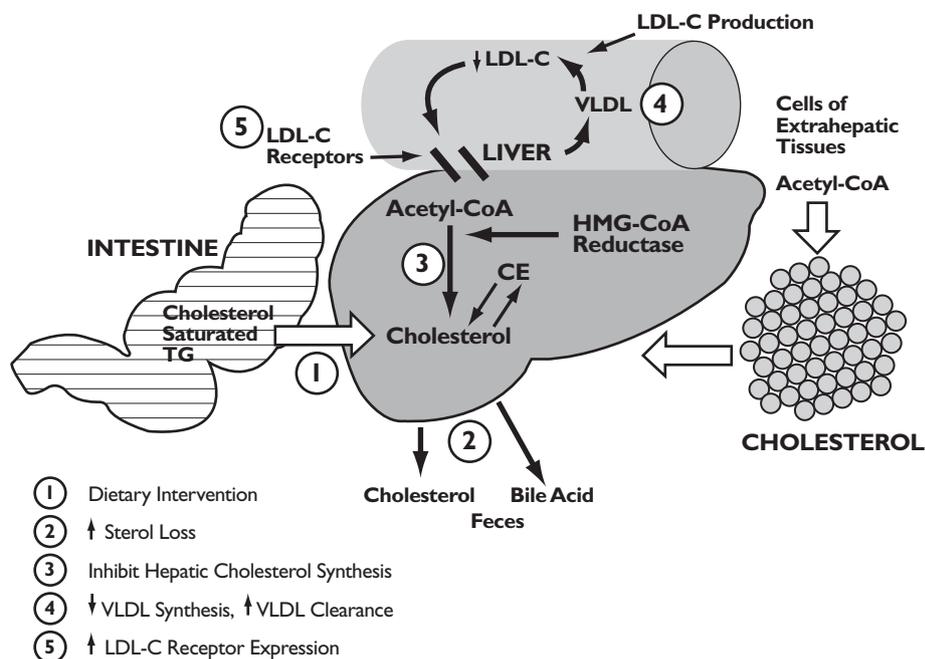
fatty acids, which also raise LDL cholesterol, should be kept to a minimum. Protein should account for approximately 15% of the caloric intake, and fiber should be maintained at 20 to 30 g/day. Finally, cholesterol intake should be limited to <200 mg/day. TLC interventions are highly effective in lowering LDL cholesterol and often underemphasized in routine management of patients with lipid disorders. If these dietary measures are undertaken, the estimated LDL cholesterol reductions through dietary reduction of saturated fat, reduction of dietary cholesterol, and weight loss are 8% to 10%, 3% to 5%, and 5% to 8%, respectively.<sup>14</sup> The cumulative reduction in LDL cholesterol with these measures plus viscous fiber (5-10 g/day) and plant sterol/stanol esters (2 g/day) may equal 20% to 30%.

Four classes of lipid-modifying drugs are currently available: statins, bile acid sequestrants, niacin, and fibrates. High LDL cholesterol should be managed first with TLC, and if appropriate, drug therapy. On initiation of drug therapy, attention to TLC should be maintained and healthcare providers should constantly enforce its importance. Statins are widely used as the initial drug because they have the greatest LDL cholesterol-lowering activity and are generally well tolerated. If the patient does not achieve his or her LDL cholesterol target on statin monotherapy, either the statin dose should be escalated or a bile acid sequestrant or niacin should be added.<sup>14</sup>

**Treating Other Lipid Abnormalities**

ATP III identifies metabolic syndrome as an important consideration for reducing CHD risk. Diagnosis of metabolic syndrome is made when ≥3 of the following risk factors are present: abdominal obesity (defined by a waist circumference >40 inches in men and >35 inches in women); elevated serum triglycerides (≥150 mg/dL); low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women); blood pressure ≥130/85 mmHg; and impaired fasting blood glucose (110-125 mg/dL). Treatment of metabolic syndrome starts with weight loss and increased physical activity.<sup>14</sup> For the many patients with metabolic syndrome

**Figure 1.** Potential Mechanisms of Cholesterol Lowering



LDL-C indicates low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein; Acetyl-CoA, acetyl-coenzyme A; HMG-CoA, 3-hydroxy-3-methylgluteryl coenzyme A; TG, triglycerides.  
 Source: Reference 17.

who are overweight, weight loss is extremely important to improve metabolic risk factors. Thereafter, each metabolic abnormality should be addressed: antihypertensive medications to reduce blood pressure; aspirin to reduce prothrombotic state in CHD patients and, as many experts would add, diabetic patients as well; and management of elevated triglycerides and low HDL cholesterol.

Elevated triglycerides independently increase CHD risk, suggesting that some triglyceride-rich lipoproteins, most likely partially degraded very low-density lipoprotein (VLDL) cholesterol, are atherogenic.<sup>18</sup> Accordingly, ATP III identifies the sum of LDL and VLDL cholesterol (ie, non-HDL cholesterol) as a secondary target of therapy in patients with high triglycerides ( $\geq 200$  mg/dL). Non-HDL cholesterol can be simply calculated by subtracting HDL cholesterol from total cholesterol. Based on the premise that VLDL cholesterol  $\leq 30$  mg/dL is normal, the non-HDL

cholesterol goal is set at 30 mg/dL higher than the LDL cholesterol goal. Therefore, non-HDL cholesterol should be lowered to  $<130$  mg/dL in patients with CHD or CHD risk equivalents,  $<160$  mg/dL in those with  $\geq 2$  risk factors, and  $<190$  mg/dL in those with no risk factors or 1 risk factor.<sup>14</sup>

Treatment of elevated triglycerides depends on the cause and severity. When triglycerides are borderline high (150-199 mg/dL), weight reduction and increased physical activity should be emphasized. In those with high triglycerides (200-499 mg/dL), drug therapy should also be considered to achieve the non-HDL cholesterol goal. This may be accomplished either by intensifying LDL cholesterol-lowering therapy or adding a fibrate or niacin. Finally, in patients with very high triglycerides ( $\geq 500$  mg/dL), the initial goal should be to reduce triglycerides to prevent pancreatitis. In addition to weight loss and physical activity, patients should be prescribed a low-fat diet, with fats rep-

representing  $\leq 15\%$  of caloric intake, and a triglyceride-lowering drug, specifically either niacin or a fibrate.<sup>14</sup>

Low HDL cholesterol ( $< 40$  mg/dL) is also an independent risk factor for CHD. Although ATP III does not identify a specific treatment goal, it does recommend that low HDL cholesterol receive clinical attention. In all patients with low HDL cholesterol, the LDL cholesterol goal should first be achieved. Second, in patients with the metabolic syndrome, emphasis should shift to weight loss and physical activity once the LDL cholesterol goal has been reached. In patients with high triglycerides, the non-HDL cholesterol goal should be achieved. Finally, niacin or fibrates may be considered for raising HDL cholesterol in those patients with borderline high triglycerides or isolated low HDL cholesterol, especially in patients with CHD or CHD risk equivalents.<sup>14</sup>

**Adherence**

Recognizing that patient adherence to treatment poses a major challenge in managing lipid disorders, ATP III recommends several strategies for its improvement. For optimum effectiveness, healthcare providers should use  $\geq 2$  of the following approaches with their patients:

- Keep medication regimens simple (ideally 1 dose per day)
- Provide explicit instructions
- Suggest prompts to help patients remember their treatment regimens
- Use systems that maintain contact with patients
- Encourage support from family and friends
- Reinforce and reward adherence
- Increase visits for those who cannot reach their treatment goal

One suggestion is to have patients create a graph of their LDL cholesterol levels and tape it to their refrigerator doors as a constant reminder of the things they need to do to avoid an MI or stroke. Other strategies for improving adherence should focus on the healthcare provider and delivery system.

For the provider:

- Use prompts as a reminder of the importance of lipid management
- Identify a patient advocate in the medical office
- Educate and involve patients in their preventive care program
- Use feedback from past performance to modify future patient care
- Remind patients of their appointments and follow up any missed appointments

For the healthcare delivery system:

- Provide lipid management through a lipid clinic
- Utilize case management by nurses
- Implement telemedicine procedures for patient follow-up
- Involve pharmacists in collaborative care
- Develop in-hospital critical care pathways

ATP III guidelines suggest that patients should have a fasting lipoprotein panel performed in the hospital following an MI. Even though LDL cholesterol may be reduced by acute illness,<sup>14</sup> this represents an important educational opportunity and an ideal time to get patients started on lipid-lowering therapy.

**Conclusion**

Coronary heart disease is a common, costly, and undertreated disorder. As shown in numerous clinical trials, treatment of lipid abnormalities reduces total mortality as well as cardiovascular morbidity and mortality. Moreover, treatment of lipid abnormalities is cost effective, especially among high-risk patients. ATP III guidelines build on ATP II by recommending ways to better identify and manage patients with CHD risk. The updated guidelines give new lipoprotein classifications; recommend 10-year CHD risk assessment for patients with multiple risk factors; define CHD risk equivalents; and suggest strategies for patient adherence. Healthcare providers should regard ATP

III as a valuable tool for identifying patients at risk for CHD, managing their treatment, helping them achieve their lipid goals, and ultimately reducing their risk for future CHD events.

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