2 Hyperlipidemia

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INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of overall mortality in America for both men and women. A major risk factor for CVD is hyperlipidemia, a condition referring to elevated levels of at least one of five families of plasma lipoproteins–chylomicrons, very low-density lipoproteins, intermediate-density lipoproteins, low-density lipoproteins (LDL), and high-density lipoproteins (HDL).

The guidelines for the treatment of hyperlipidemia have been dynamic, starting from initial studies to the more recent and accepted recommendations of the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults *(1)*. Additionally, since the findings of Adult Treatment Panel III, five major clinical trials have been recognized and have subsequently enriched the guidelines further. These studies include the Heart Protection Study (HPS), the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), the Antihypertensive and Lipid-Lowering Treatment to Prevent

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Heart Attack trial—lipid-lowering trial, the Anglo-Scandinavian Cardiac Outcomes Trial—lipid-lowering arm, and the Pravastatin or Atorvastatin Evaluation and Infection—Thrombolysis in Myocardial Infarction 22 trial (PROVE-IT—TIMI 22) *(2)*.

Screening

Universal screening for hyperlipidemia is recommended for all persons aged 20 or older. Screening should consist of a fasting lipoprotein profile, which includes total cholesterol (TC), LDL-cholesterol, HDL-cholesterol, and triglyceride (TG) levels. Blood work should be obtained every 5 yr, unless otherwise indicated.

If the specimen that is collected is nonfasting, only TC and HDL-cholesterol are valid. If the TC is greater than 200 or the HDL cholesterol is less than 40, then a follow-up fasting lipid profile should be performed. Much of the guidelines revolve around LDL-cholesterol, and therefore a follow-up fasting profile is recommended for formal evaluation.

Table 1
Classification

Total cholesterol (mg/dL)	*Category*
<200	Desirable
200–239	Borderline high
>240	High

LDL-cholesterol (mg/dL)	*Category*
<100	Optimal
100–129	Near optimal
130–159	Borderline high
160–189	High
>190	Very high

HDL-cholesterol (mg/dL)	*Category*
<40	Low, increases cardiac risk
40–60	Normal
>60	High, decreases cardiac risk

RISK CATEGORIES AND TARGET LDL-CHOLESTEROL

The treatment of LDL-cholesterol is not solely based on its value. For instance, a healthy 25-yr-old female with an LDL of 174 should be treated differently than a 75-yr-old male with a history of hypertension and stroke having the same LDL. Thus, in addition to the number, treatment is also guided by cardiac risk factors. These risk factors are as follows:

Major cardiac risk factors that modify LDL goals:

- Age
  - Male >45, female >55
- Family history of premature coronary disease in first-degree relative.
  - Male <55, female <65.
- Cigarette smoking.
- Hypertension.
- Low HDL-cholesterol (<40).

Notes:

- High HDL-cholesterol (>60) counts as a negative risk factor l.
- Diabetes mellitus counts as an independent coronary heart disease equivalent, not merely a risk factor.

Appropriate LDL-cholesterol levels exist for individual patients based on these cardiac risk factors. In patients without coronary disease, having fewer than two cardiac risk factors confers a low risk. For this group, a goal LDL of less than 160 exists.

Having two or more cardiac risk factors confers a moderate to a moderately high risk. For these patients, as further described later, the Framingham score should be used to distinguish those at higher risk. For both of these risk groups, the goal LDL is below 130. However, for those with a moderately high-risk class, or a 10-yr risk of between 10 and 20% based on Framingham, a stronger emphasis is placed on pharmacotherapy.

In patients with a history of coronary disease, or for those with a coronary heart disease equivalent, which is defined as a 10-yr risk of developing a coronary heart event or recurrent event of more than 20%, a goal LDL of less than 100 has been established.

Coronary heart disease includes:

- Myocardial infarction.
- Unstable angina.
- Evidence of underlying myocardial ischemia.
- Status-post angioplasty or bypass surgery.

Coronary heart disease equivalents include:

- Peripheral arterial disease.

- Abdominal aortic aneurysm.
- Symptomatic carotid artery disease (transient ischemic attack [TIA]/ cerebrovascular accident [CVA] from carotid origin; >50% carotid occlusion).
- Diabetes mellitus.
- Multiple coronary risk factors that confer a 10-yr risk for disease greater than 20% based on Framingham results.

Since the release of ATP III, an optimal LDL goal of less than 70 has been established for those at very high risk, which includes those with established coronary heart disease plus either:

- Multiple major risk factors, especially diabetes.
- Severe and poorly controlled risk factors, especially active cigarette smoking.
- Multiple risk factors of the metabolic syndrome.
- Acute coronary syndrome (ACS).

TREATMENT OF LDL-CHOLESTEROL

The major options for LDL-lowering therapy include therapeutic lifestyle changes (TLCs) and pharmacotherapy. TLCs remain an essential modality in the clinical management of hyperlipidemia and should be initiated for all patients not at goal LDL. In addition, any person at even moderately high risk who has lifestyle-related risk factors (obesity, physical inactivity, elevated TG, low HDL-cholesterol, or metabolic syndrome) is a candidate for TLC to modify these risk factors, regardless of LDL-cholesterol level.

TLC has the potential to reduce cardiovascular risk through several mechanisms beyond purely lowering LDL. The TLC diet emphasizes dietary restriction of saturated fats (<7% of total calories) and cholesterol (<200 mg daily). In addition, weight reduction and increased physical activity are recommended. Physicians are encouraged to refer patients to registered dieticians or other qualified nutritionists.

After 6 wk of TLC, LDL-cholesterol should be remeasured. If the goal has not been achieved, other options should be considered to further lower LDL, such as adding plant stanol/sterols (2 g/d) and viscous soluble fiber (10–25 g/d).

Pharmacotherapy provides the other option in the treatment of elevated LDL-cholesterol. This option should be considered for all patients who have not achieved target levels after TLC implementation.

When LDL-lowering drug therapy is initiated, the intensity of therapy should be aimed at achieving at least a 30–40% reduction in LDL. In patients without coronary disease or the equivalent, recommendations for consideration of drug therapy are again based on the number of cardiac risk factors. For patients with fewer than two risk factors, whose goal LDL is less than 160, drug therapy should be considered when LDL is 190 or higher. Clinical judgment is recommended when LDL is between 160 and 189. Calculation of 10-yr coronary risk is not useful in this group.

For those with two or more risk factors, the Framingham Coronary Risk Assessment Score has been developed to identify individuals at a higher risk, in which consideration should be given to more intensive treatment. The ATP III stratification system uses Framingham calculations to divide persons into those with 10-yr risks for coronary disease of more than 20%, between 10 and 20%, and less than 10%. Scoring calculators can be found in this chapter, on the Internet (at www.nhlbi.nih.gov/guidelines/cholesterol), and for PDAs.

For all patients with two or more risk factors, target LDL-cholesterol is less than 130, as described earlier. For those with a 10-yr risk of less than 10% based on Framingham, drug therapy should be considered when LDL is 160 or more. However, for those with a 10-yr risk of 10–20%, consideration should be given for earlier pharmacotherapy, when LDL is 130 or more. Clinical judgment is reserved for those individuals with LDL levels between 100 and 129; an LDL goal of less than 100 is an option based on the available clinical trial evidence.

In patients with established coronary disease, or risk equivalents, including a 10-yr risk of more than 20%, therapy is favored when LDL is 100 or more. Clinical judgment is recommended for patients whose baseline LDL is less than 100 prior to treatment. Optimal LDL goal for those at very high risk is less than 70. This recommendation evolved from the findings of the PROVE-IT and HPS trials. The PROVE-IT trial evaluated intensive LDL lowering in patients with ACS with high-dose atorvastatin (80 mg/d) against standard-dose pravastatin (40 mg/d). Whereas pravastatin 40 mg lowered median LDL from 106 to 95, atorvastatin 80 mg lowered the median to 62 and was associated with a statistically significant reduction in major cardiovascular events in only 2 yr. The HPS trial found that in a population of high-risk patients with coronary disease, other occlusive arterial disease, or diabetes, with a baseline LDL of less than 116, even in the subgroup with LDL less than 100, there was significant risk reduction with statin therapy. Thus, LDL-cholesterol of 70 seems preferable for very high-risk patients compared with an LDL of 100. In the past, there has been some concern regarding the potential dangers of lowering LDL-cholesterol to very low levels. Early epidemiological studies suggested that very low serum cholesterol levels are associated with an increase in total mortality, largely because of cerebral hemorrhage. This has not been supported in recent clinical trials with statin therapy. No significant side effects from LDL lowering have been formally identified to date. The decision to achieve very low LDL levels in very high-risk patients should be based on clear evidence of benefit with current lack of evidence of harm.

Statins (HMG-CoA reductase inhibitors) are the drugs of choice for elevated LDL, not only for their LDL-reduction capability but also for their anti-inflammatory properties and because of the strength of clinical trial evidence

Table 2
ATP III LDL-Cholesterol Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence *(3)*

Risk category	*LDL goal*	*Initiate TLC*	*Consider drug therapy*
High risk: CHD or CHD risk equivalent (10 yr risk >20%)	100 mg/dL (optional goal <70 mg/dL)	≤100 mg/dL	≥100 mg/dL (consider if <100 mg/dL)
Moderately high risk: 2 + risk factors (10 yr risk 10–20%)	<130 mg/dL (optional LDL goal <100 mg/dL)	≥130 mg/dL	≥130 mg/dL (consider drug therapy if 100–129 mg/dL)
Moderate risk: 2 + risk factors (10 yr risk <10%)	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0–1 risk factors	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (optional if 160–189 mg/dL)

CHD, Coronary heart disease.

supporting their use. When statin therapy is introduced, the goal should be a reduction in LDL by at least 30–40%. Numerous statins are on the market, each with varying degrees of efficacy.

Table 3
Doses of Statin Required to Obtain a 30–40% LDL-Cholesterol Reduction

Drug	*Dose (mg/d)*	*LDL reduction (%)*
Atorvastatin	10	39
Lovastatin	40	31
Pravastatin	40	34
Simvastatin	20–40	35–41
Fluvastatin	40–80	25–35
Rosuvastatin	5–10	39–45

Alternative classes of antihyperlipidemia therapy include nicotinic acid, bile–acid sequestrants, and ezetimibe. These agents should be considered as second-line therapies or, perhaps, first-line therapy for those with intolerance to statins. In addition, some of these agents may be more beneficial should dyslipidemia (depressed HDL, elevated TG) rather than hyperlipidemia exist.

After 6 wk starting pharmacotherapy, LDL should be remeasured. If goal has been achieved, the patient should continue on the present dose. Otherwise, LDL-lowering therapy can be intensified by increasing the dose of the primary medication, or by adding a second medication. If after 12 wk of therapy, LDL levels are not at goal, further intensification should be pursued. Referral to a lipid specialist should be considered if goal LDL is unobtainable.

SPECIAL CONSIDERATIONS

Diabetes

According to ATP III guidelines, patients carrying the diagnosis of diabetes are considered to have an independent coronary heart disease equivalent, not just a risk factor. In the HPS, higher-risk populations of patients with diabetes or other occlusive arterial disease were found to have a risk for coronary events, which was approximately that of nondiabetic patients with established coronary disease. Therefore, for these patients, optimal LDL is less than 100.

However, not all patients with diabetes can be considered to have a 10-yr cardiac risk of more than 20%. For example, an otherwise healthy 20-yr-old male with type 1 diabetes would not be expected to have a significant 10-yr risk. This potentially lower-risk patient was not studied in the HPS; however, and so no formal data have been collected. A potential option remains to use clinical judgment about whether to initiate LDL-lowering therapy if this patient's baseline LDL is below 130. Of note, maximal TLC therapy is clearly indicated.

In the HPS, patients with both diabetes and coronary disease had a very high risk for recurrent coronary disease. This category of patient benefited greatly from statin therapy and thus the data suggests initiation of a statin regardless of baseline LDL levels. For this very high-risk class, optimal LDL is less than 70.

Metabolic Syndrome

The metabolic syndrome, a disease characterized by increased insulin resistance and therefore increased risk for coronary heart disease, is defined by meeting at least three of the following five criteria:

1. Abdominal obesity (males >40 in., females >35 in.).
2. Elevated TG (>150 mg/dL).
3. Depressed HDL (males <40 mg/dL, females <50 mg/dL).
4. Blood pressure above 130/85 mmHg.
5. Impaired fasting glucose (>110 mg/dL).

Treatment of the metabolic syndrome involves TLC therapy (weight reduction and increased physical activity) in an effort to manage the disorder (abdominal obesity, hypertension, depressed HDL), but also to gain control of LDL-cholesterol.

Low HDL-Cholesterol

Low HDL-cholesterol is a strong independent risk factor for heart disease. ATP III specifies low HDL-cholesterol as being a level below 40 mg/dL, a change from the level of 35 mg/dL that was described in ATP II. ATP III does no specify a goal for appropriate elevation of HDL because there is currently no sufficient evidence to define the degree to which HDL should be raised by treatment and available drugs have not been studied sufficiently to make recommendations regarding their use for raising HDL-cholesterol. Reduction of LDL-cholesterol remains the main goal of treatment. Low HDL modifies the risk category, which is assigned to determine goal LDL level.

For all persons with depressed HDL levels, the primary target of therapy remains LDL. After the LDL goal has been attained, emphasis should shift to weight reduction and increased physical activity.

If TGs are between 200 and 499, goal should be to achieve non-HDL goal cholesterol, which is set at 30 mg/dL more than LDL-cholesterol goals. If TGs are less than 200, meaning that the dyslipidemia is solely isolated to low HDL, drugs for HDL raising can be considered. These drugs include nicotinic acid or fibrates. Pharmacotherapy for isolated low HDL is mostly reserved for persons with coronary disease or risk equivalents.

Elevated Serum Triglycerides

Elevated serum TGs are also considered an independent risk factor for coronary disease.

Table 5
Classification of Triglycerides

Serum triglycerides (mg/dL)	*Category*
<150	Normal
150–199	Borderline high
200–499	High
>500	Very high

Remember that the primary treatment of elevated TGs is to reach LDL goal. Any borderline TGs should be addressed through TLC therapy (weight reduction, increased physical activity). After goal LDL is reached, a secondary goal for non-HDL-cholesterol of 30 mg/dL higher than that of the LDL-cholesterol should be set. Note that non-HDL-cholesterol is the TC–HDL.

For those with high TGs, non-HDL-cholesterol becomes a secondary target for therapy. Weight reduction and increased physical activity should be implemented. Pharmacotherapy can be considered in high-risk persons to achieve the

non-HDL-cholesterol goal. This can be achieved by intensifying therapy with an LDL-lowering drug, or by adding nicotinic acid or a fibrate.

The immediate goal of therapy for the patient with very high TGs is to prevent acute pancreatitis through TG lowering. This is usually done through a TG-lowering agent (fibrate or nicotinic acid) in addition to weight reduction, increased physical activity, and a very low-fat diet (15% of total caloric intake). Only after TG levels have fallen to below 500 should LDL lowering be targeted to reduce cardiac risk.

OLDER AND YOUNGER ADULTS

Most cardiovascular events occur in individuals older than 65 yr of age. Elevated LDL-cholesterol and low HDL-cholesterol are predictive for the development of coronary disease in the elderly as well as in the young. ATP III states that older persons should not be denied the benefits of LDL-lowering therapy accorded to other age groups. This recommendation has additional support through both the HPS and the PROSPER trials, which demonstrated that intensive lipid-lowering management for elderly patients with established coronary disease yields similar outcomes as that achieved in younger populations.

Older patients, in general, are at higher risk of developing coronary disease than are younger patients. Quantitative risk assessment in elderly patients without established coronary disease is not as reliable as it is in younger patients. Clinical judgment is therefore recommended when deciding on lipid-lowering therapy. A host of factors must be weighed for these patients, including efficacy, safety, and tolerability. Of note, both the PROSPER and Anglo-Scandinavian Cardiac Outcomes Trial support the efficacy of statin therapy in older, high-risk persons without established CVD.

For all younger adults (males age 20–35, females age 20–45), TLC should be instituted and emphasized when LDL levels surpass 130. Particular attention should be given to young males who smoke and have a high LDL (160–189), as they may be candidates for earlier intervention with LDL-lowering drugs. When young adults have very high LDL levels (>190), pharmacotherapy should be considered, as in other adults.

ADDITIONAL STUDIES SINCE GUIDELINE PUBLICATION

Subsequent to the publication of the 2004 update to ATP III, two trials have been published that futher support intensive treatment of LDL-cholesterol. The Collaborative Atorvastatin in Diabetes Study (CARDS) looked at middle-aged patients with type 2 diabetes without pre-existing cardiovascular disease and at least one other cardiovascular risk factor and mean baseline LDL of 117 *(4)*. Results of CARDS showed that in this group of patients with diabetes and a low LDL-cholesterol, treatment with atorvastatin 10 mg, led to a decrease in first

cardiovascular events including MI and stoke. This study, along with the results of the HPS led the American Diabetes Association *(5)* to recommend that all patients older than 40 yr old with diabetes and with a TC over 135 mg/dL be treated with a statin to reduce LDL-cholesterol by 30–40%.

The Treating to New Targets study looked at patients with cardiovascular disease who where already on a statin, and randomized patients to atorvastatin 10 mg vs atorvastatin 80 mg. During the wash-in period, when all patients received atorvastin 10 mg, the mean LDL-cholesterol level was 98 mg/dL. Over the 4.9 yr of the study, there was a relative decrease in cardiovascular events of of 22% (absolute decrease –2.2%) in the group of patients randomized to atorvastatin 80 mg.

In summary, these two studies, both published since the most recent update to ATP III, lend further support to the recommendations of ATP III to pursue aggressive lipid lowering with a target goal consideration of an LDL-cholesterol of less than 70 mg/dL.

SOURCES

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APPENDIX

Framingham Coronary Risk Assessment Male Based on LDL-Cholesterol

Step 1

Age	*Points*
30–34	–1
35–39	0
40–44	1
45–49	2
50–54	3
55–59	4
60–64	5
65–69	6
70–74	7

Step 2

LDL-cholesterol	*Points*
<100	–3
100–129	0
130–159	0
160–189	1
>190	2

Step 3

HDL-cholesterol	*Points*
<35	2
35–44	1
44–49	0
50–59	0
>60	–1

Step 4

	Blood pressure				
Systolic	*Diastolic*				
	<80	80–84	85–89	90–99	>100
<120	0 pts	–	–	–	–
120–129	–	0 pts	–	–	–
130–139	–	–	1 pts	–	–
140–159	–	–	–	2 pts	–
>160	–	–	–	–	3 pts

When systolic and diastolic measures provide different point scores, use the higher number.

Step 5

Diabetes	*Points*
No	0
Yes	2

Step 6

Smoker	*Points*
No	0
Yes	2

Step 7

Add up all of the points

Step 8

Coronary heart disease risk	
Point total	*10-Yr risk (%)*
≤–3	1
–2	2
–1	2
0	3
1	4
2	4
3	6
4	7

(Continued)

Step 8 *(Continued)*

Point total	*10-Yr risk (%)*
5	9
6	11
7	14
8	18
9	22
10	27
11	33
12	40
13	47
≥14	≥56

Framingham Coronary Risk Assessment Male Based on Total Cholesterol

Step 1

Age	*Points*
30–34	–1
35–39	0
40–44	1
45–49	2
50–54	3
55–59	4
60–64	5
65–69	6
70–74	7

Step 2

Total cholesterol	*Points*
<160	–3
160–199	0
200–239	1
240–279	2
>280	3

Step 3

HDL-cholesterol	*Points*
<35	2
35–44	1
44–49	0
50–59	0
>60	–2

Step 4

	Blood pressure				
Systolic	*Diastolic*				
	<80	80–84	85–89	90–99	>100
<120	0 pts	–	–	–	–
120–129	–	0 pts	–	–	–
130–139	–	–	1 pts	–	–
140–159	–	–	–	2 pts	–
>160	–	–	–	–	3 pts

When systolic and diastolic measures provide different point scores, use the higher number.

Step 5

Diabetes	*Points*
No	0
Yes	2

Step 6

Smoker	*Points*
No	0
Yes	2

Step 7

Add up all of the points

Step 8

Coronary heart disease risk	
Point total	*10-Yr risk (%)*
≤ –1	2
0	3
1	3
2	4
3	5
4	7
5	8

(Continued)

Step 8 *(Continued)*

Point total	*10-Yr risk (%)*
6	10
7	13
8	16
9	20
10	25
11	31
12	37
13	45
≥14	≥53

Framingham Coronary Risk Assessment Female Based on LDL-Cholesterol

Step 1

Age	*Points*
30–34	–9
35–39	–4
40–44	0
45–49	3
50–54	6
55–59	7
60–64	8
65–69	8
70–74	8

Step 2

LDL-cholesterol	*Points*
<100	–2
100–129	0
130–159	0
160–189	2
>190	2

Step 3

HDL-cholesterol	*Points*
<35	5
35–44	2
44–49	1
50–59	0
>60	–2

Step 4

	Blood pressure				
Systolic	*Diastolic*				
	<80	80–84	85–89	90–99	>100
<120	–3 pts	–	–	–	–
120–129	–	0 pts	–	–	–
130–139	–	–	0 pts	–	–
140–159	–	–	–	2 pts	–
>160	–	–	–	–	3 pts

When systolic and diastolic measures provide different point scores, use the higher number.

Step 5

Diabetes	*Points*
No	0
Yes	4

Step 6

Smoker	*Points*
No	0
Yes	2

Step 7

Add up all of the points

Step 8

Coronary heart disease risk	
Point total	*10-Yr risk (%)*
≤–2	1
–1	2
0	2
1	2
2	3
3	3
4	4
5	5
6	6

(Continued)

Step 8 *(Continued)*

Point total	*10-Yr risk (%)*
7	7
8	8
9	9
10	11
11	13
12	15
13	17
14	20
15	24
16	27
≥17	≥32

Framingham Coronary Risk Assessment Female Based on Total Cholesterol

Step 1

Age	*Points*
30–34	–9
35–39	–4
40–44	0
45–49	3
50–54	6
55–59	7
60–64	8
65–69	8
70–74	8

Step 2

Total cholesterol	*Points*
<160	–2
160–199	0
200–239	1
240–279	1
>280	3

Step 3

HDL-cholesterol	*Points*
<35	5
35–44	2
45–49	1
50–59	0
>60	–3

Step 4

	Blood pressure				
Systolic	*Diastolic*				
	<80	80–84	85–89	90–99	>100
<120	–3 pts	–	–	–	–
120–129	–	0 pts	–	–	–
130–139	–	–	0 pts	–	–
140–159	–	–	–	2 pts	–
>160	–	–	–	–	3 pts

When systolic and diastolic measures provide different point scores, use the higher number.

Step 5

Diabetes	*Points*
No	0
Yes	4

Step 6

Smoker	*Points*
No	0
Yes	2

Step 7

Add up all of the points

Step 8

Coronary heart disease risk	
Point total	*10-Yr risk (%)*
≤ –2	1
–1	2
0	2
1	2
2	3
3	3
4	4
5	4
6	5

(Continued)

Step 8 *(Continued)*

Point total	*10-Yr risk (%)*
7	6
8	7
9	8
10	10
11	11
12	13
13	15
14	18
15	20
16	24
≥17	≥ 27

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