# Hyperlipidemia in Primary Care

Step 1

Asses risk factors for atherosclerotic coronary heart disease:

Positive risk factors:

1. Age (males > 45 years, females > 55 years or menopause < age 40?)
2. Family history of premature coronary artery disease; definite myocardial infarction (MI) or sudden death before age 55 in father or other male first-degree relative, or before age 65 in mother or other female first-degree relative
3. Current cigarette smoker
4. Hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg confirmed on more than one occasion, or current therapy with antihypertensive medications)
5. Diabetes mellitus (DM)
6. High-density lipoprotein (HDL)-cholesterol < 40 mg/dL

Negative risk factor:

Elevated HDL cholesterol, > 60 mg/dL

Step 2

Identify patients with known CHD (history of myocardial infarction [MI], angina pectoris, other evidence of CHD) or a history of other kinds of vascular disease (such as stroke or claudication). Prevention of recurrent and fatal coronary events via aggressive lipid-lowering therapy has been demonstrated in large clinical trials.

Step 3

Age for screening:

1 Males: 35-75 years

2 Females: 45-75 years

Step 4

Determine if patient has Diabetes

Patients with DM are at significantly increased risk of CHD compared with non-diabetic patients of similar age.
DM patients without known CHD appear to have a risk for first MI similar to the risk for recurrent MI of non-DM patients with CHD and a prior coronary event.
Patients with type 2 diabetes commonly have other risk factors (hypertension, high LDL-C, low HDL-C, obesity) that increase risk for cardiac events.

Step 5

Obtain Total Cholesterol (TC) and HDL *or* TC, HDL, TG, LDL

To risk-stratify patients for targeted intervention versus follow-up screening.

Lipid levels may be obtained in a fasting or nonfasting state. TC levels and HDL-C can be measured in the nonfasting patient.

TG concentrations, however, are affected by recent food intake and will affect the calculation of LDL-C by the Friedewald equation: LDL-C = [TC] - [HDL-C] - [TG/5]. Therefore always order the lipid profile in a fasting state to avoid any errors.

Clinical decisions should be based on two lipid profiles, done 1 to 8 weeks apart, which have an LDL-C or TC difference of < 30 mg/dL.

Recent myocardial infarction, stroke, surgery, trauma, or infection may transiently lower cholesterol levels up to 40 percent. If a lipid profile cannot be obtained immediately (within 12 to 24 hours of the event), one must wait 8 weeks post-event to obtain an accurate reading.

Cholesterol levels increase by as much as 20 to 35 percent during pregnancy and should not be measured until three to four months after delivery.

Step 6

Evaluate the results:

A) An abnormal lipid profile:

LDL > 130 mg/dL
HDL < 40 mg/dL
TG > 400 mg/dL

B) Revaluate in 1-5 years if:

No ASCVD risk factors and
Total cholesterol < 200 mg/dL
LDL <130 mg/dL
HDL > 35 mg/Dl

C) Revaluate in 1-2 years if:

This patient will be of average risk for lipid-related events over a one to two year period.

Total cholesterol > 200 mg/dL
LDL <130 mg/dL
HDL > 40 mg/dL

Step 7

Identify Hypercholestrolemia associated with a familial disorder as aggressive lipid management is indicated for this group.

Familial hypercholesterolemia is characterized by severe elevations of LDL cholesterol (> 260 mg/dL), tendon xanthomas, and premature CHD.
Familial combined hyperlipidemia is characterized by elevations of total cholesterol, triglycerides, or both, in different members of the same family, and is associated with premature CHD.
Patients presenting with very severe hypercholesterolemia should undergo family screening to detect other candidates for therapy.
Therefore, a consultation with a specialist is recommended to assist the primary care clinician in co-managing these patients.

Step 8

Identify and Treat Secondary Causes of Elevated LDL-C

| Disorder/Patient Characteristic | Effect on Lipids | Laboratory Test for Diagnosis |
|---|---|---|
| Chronic renal failure/ Postrenal transplantation | TG, TC, HDL-C | $S_{Cr}$ |
| DM | TG, TC, HDL-C | Glucose, HbA1c |
| Ethanol use | TG, HDL-C | |
| HIV/AIDS[b] | TG, TC, HDL-C, LDL-C | |
| Hypothyroidism[c] | TG, TC, LDL-C | TSH, thyroid hormones |
| Inactivity | HDL-C | |
| Nephrotic syndrome | TC, LDL-C | Urinalysis, serum albumin |
| Obesity | TG, HDL-C | |
| Obstructive liver disease | TC | LFTs |
| Estrogen therapy | TG, LDL, HDL | |

[a]AIDS = acquired immune deficiency syndrome; DM = diabetes mellitus; HbA1c = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; LFTs = liver function tests; $S_{Cr}$ = serum creatinine; TC = total cholesterol; TG = triglycerides; TSH = thyroid-stimulating hormone.
[b] Effects more pronounced with the addition of protease inhibitors
[c]Primary and secondary.

EVIDENCE

Address secondary causes: Stone, 1997; NCEP III, 2001

Step 9

Identify and Treat Secondary Causes of Hypertriglyceridemia

The most common secondary causes of **hypertriglyceridemia** are alcohol, diabetes, and hypothyroidism. Addressing these underlying conditions can improve or normalize triglyceride levels, and failure to address these can render therapy ineffective.

Recognize the fact that if TG is greater than 400mg/dl than the calculation of LDL-C is not reliable. Friedwald LDL calculation [LDL-C = total cholesterol - (HDL-C + TG/5)] yields unacceptably inaccurate estimation of the LDL cholesterol in these patients. Non-HDL cholesterol can be estimated using the simple formula [Non-HDL cholesterol = Total cholesterol – HDL] or by direct measurement of the LDL.

Since non-HDL cholesterol levels tend to be approximately 30 mg/dL greater than estimated LDL levels, the estimated LDL from this equation will be approximately 30 points lower and LDL goals need to be interpreted accordingly. For example, if the goal LDL is <130 mg/dL, then the non-HDL cholesterol goal should be < 160 mg/dL instead. One can also continue to use specified guidelines for LDL levels if an adjusted version of the non-HDL cholesterol equation is followed

Patients with triglycerides >1,000 are at increased risk of pancreatitis Therefore they should be treated promptly with

A. strict avoidance of alcohol and dietary fat, as well as restriction of calories
B. Fibrates: first choice, which are contraindicated in severe renal disease.
C. Alternative Niacin, which is contraindicated in hepatic disease and relatively contraindicated in DM, gout, and history of complicated/active peptic ulcer disease

Step 10

**Determine Goal of Therapy; Initiate/Modify Therapy to Achieve Goal**

Select an appropriate therapy based on LDL-C baseline level and other risk factors for ASCVD. CHD risk factors are age, family history, current smoker, hypertension, diabetes, and HDL-C < 40 mg/dL. Patients with CHD or multiple risk factors require more aggressive treatment.

1. Select an appropriate LDL-C target
2. Initiate non-pharmacologic therapy
3. For patients who do not reach LDL target, initiate pharmacotherapy.

**LDL-C Thresholds for Initial Dyslipidemia Treatment**

| | Baseline LDL-C [mg/dL] | | | |
|---|---|---|---|---|
| Risk for ASCVD | >100 | >130 | >160 | >190 |
| Known CHD | Diet/exercise Consider drug | Diet/exercise + drug | Diet/exercise + drug | Diet/exercise + drug |
| Diabetes (without known CHD) | Diet/exercise Consider drug | Diet/exercise+ drug | Diet/exercise + drug | Diet/exercise + drug |
| No known CHD but > 2 risk factors | ____ | Diet/exercise | Diet/exercise + drug | Diet/exercise + drug |
| No known CHD but < 2 risk factors | ____ | ____ | Diet/exercise | Diet/exercise + drug |

Adapted from NCEP III, 2001
Note: If one risk factor is diabetes, the diabetes category is used to determine threshold and goal.

**LDL-C Goals in the Treatment of Dyslipidemia.**

| Risk for ASCVD | LDL-Cholesterol Goal |
|---|---|
| Known CHD | <100 mg/dl* |
| Diabetes (without known CHD) | <100 mg/dl* |
| No known CHD, but > 2 risk factors | <130 mg/dl |
| No known known, CHD, but ≤ 2 risk factors | <160 mg/dl |

*NCEP III recommends an LDL-C goal of < 100 mg/dL in patients with known CHD and CHD equivaltents (i.e., type 2 diabetes mellitus)

Step 10

# Treatment

A) **Therapeutic life style changes** indicated in :
   a. Patients with 0-1 risk factor and LDL-C > 160mg/dl
   b. patients with 2 risk factors and LDL > 130mg/dL
   c. patients with known CHD or diabetes and LDL-C > 100mg/dl.

For primary prevention of ASCVD, patients whose initial treatment is diet/exercise should be given three to six months on dietary therapy prior to beginning medication and longer if lipids are improving and nearing LDL thresholds.

Patients failing clinician-initiated efforts may benefit from a MNT consult prior to initiating medications (See Appendix 1 titled "Medical Nutrition Therapy" of the original guideline document).

For secondary prevention of recurrent ASCVD events, non-pharmacologic therapy is always indicated, but should not delay appropriate pharmacotherapy.

## Expected Percent Change in Serum Lipids in Response to Diet Therapy

| | Expected Response to Therapy | | | |
|---|---|---|---|---|
| | Step I Diet | Step II Diet | Very Low Fat | High MUFA[a] |
| LDL | -5 to -20 % | -10 to -25 % | -0 to -20 % | -5 to -20 % |
| TG | +5 to -10 % | +10 to -10 % | Decrease with weight loss<br>Increase without weight loss | No change or slight decrease |

[a]MUFA = Monounsaturated fatty acids.
Cardiovascular Nutrition, ADA, 1998

### B) Pharmacotherapy:

Drug therapy is indicated in CHD/ASCVD patients and moderate-high risk primary prevention patients who remain above LDL thresholds with non-pharmacologic measures.

HMG-CoA reductase inhibitors (statins) are first line agents in most situations. They are cost-effective in secondary prevention and high-risk primary prevention risk groups.

**The dose should be adjusted at 4 to 6 week intervals until the individually-determined LDL-C goals are met**.

Other agents have been shown to reduce CHD events and angiographic progression, but have had minimal impact on total mortality.

The first line drugs and alternatives for lipid disorders are summarized below and in Table below.

| LIPID DISORDER | MONO THERAPY | EFFICACY | | CONSIDERATIONS |
|---|---|---|---|---|
| LDL-C<br>Initial | Statins | LDL<br>-22 to -60% | | Caution using statins in hepatic disease<br>Niacin is contraindicated in hepatic disease and relatively contraindicated in DM, gout, and history of complicated/active PUD.<br>Resins may increase TG |
| Alternate | Niacin | -13 to -21% | | |
| | Bile acid resin (resin) | -10 to -20% | | |
| LDL-C and TG<br>Initial | Niacin | LDL<br>-13 to -21% | TG<br>-10 to -24% | For high TG, use fibrates or niacin |
| | or statin | -22 to -60% | -06 to -37% | |

| | | | | |
|---|---|---|---|---|
| Alternate | Fibrates | +10 to -35% | -32 to -53% | For high LDL, use statins |
| LDL and HDL | Niacin<br>or statin<br>or fibrates | LDL<br>-13 to -21%<br>-22 to -60%<br>+10 to -35% | HDL<br>+10 to +24%<br>+2 to +12%<br>+2 to +34% | No preferences in terms of efficacy |
| TG 400-1000 mg/dL | Consider gemfibrozil if HDL-C < 40 mg/dL[a] | | | For high TG, use direct LDL-C measurement or non-HDL-C as lipid disorder to guide therapy |

Adapted from PBM-MAP, 1997.
[a]VA-HIT, 1999.

**For CHD/ASCVD Patients**

For patients with known CHD/ASCVD who have HDL < 40 mg/dL pharmacotherapy with gemfibrozil is recommended (VA-HIT, 1999)

| | | | | |
|---|---|---|---|---|
| LDL-C 130 mg/dL<br>And<br>HDL-C < 40 mg/dL | Gemfibrozil | LDL<br>+10 to – 35% | HDL<br>+2 to 34% | Outcome data for secondary prevention only |

Adapted from PBM-MAP, 1997.

Step 11

**Follow Up, Repeat Lipid Evaluation at Least Annually**

When dyslipidemia is identified and the care provider and patient undertake dietary and/or pharmacologic treatment, it is pertinent clinically and economically to periodically repeat measurement of serum lipids to ensure that initially desirable response to therapy continues.
Total and LDL cholesterol tend to increase with advancing age, even in intensively treated patients. Thus, an initially favorable response to treatment may not be maintained over time.

Step 11:

**Address Adherence to Therapy**

Patients should be questioned about adherence to treatment at each visit. They should be asked about side effects of the medications and the reasons for non-compliance should be sought.
A minimum of 3-6 months of intensive diet and exercise is recommended before medications are initiated for primary prevention.

Shorter trials of MNT and exercise are appropriate for patients with severe hyperlipidemia or ASCVD, since aggressive drug therapy is of demonstrated efficacy in these high risk groups.

Step 12:

**Modify Drug Therapy; Consider Combination Therapy**

Modify drug therapy to achieve LDL-C goal.
Niacin and resins are considered alternative therapy in patients who do not tolerate initial therapy.
If the patient has not achieved the LDL-C goal with initial therapy, consider the addition of a second agent.
Clinical judgment must be used to balance patient issues, side effects, and monitoring parameters.

Step 13;

**Reschedule Lipids Evaluation at Appropriate Time and Follow Up until Goal is Met**

Nadir values of LDL cholesterol and triglycerides may not be achieved until after three to six months on a Step I or Step II diet.
Pharmacotherapy likewise may not result in lower lipid values until after at least one month of treatment.
Remeasurement of serum lipids after at least one month of drug therapy, or after at least three months of dietary therapy, allows for the documentation of efficacy, the identification of unfavorable effects of treatment, and the dose titration of medication.

Step 14

**Identify patients with ASCVD who are candidates for aggressive treatment of hypercholesterolemia**.

Patients with known ASCVD (secondary prevention) have significant risk of coronary or peripheral vascular events and are therefore candidates for aggressive lipid management.
Multiple prospective intervention trials have consistently demonstrated reduction in atherosclerotic event rates with treatment of hypercholesterolemia.
For this group, the reduction in clinical endpoints is particularly compelling, based on the demonstration of mortality benefit in some studies. In the major clinical trials published to date, actual LDL-C attained with statin therapy has ranged between 98 mg/dL and 118 mg/dL. As noted above and the target lipid levels in secondary CHD prevention are:

- LDL-C < 100 mg/dL* and
- HDL-C > 40 mg/dL.

*NCEP III and the American Diabetes Association guidelines support initiation of LDL-lowering therapy for patients with LDL in the 100-130 mg/dL range. Absolute risk reduction in CHD events for drug treatment initiated at this threshold has not yet been established, except in the setting of HDL-C < 40 mg/dL (VA-HIT Study, 1999).
In the VA-HIT Study, the average LDL-C of treated patients was 112 mg/dL and the average HDL-C was 33 mg/dL.

Step 15

**Repeat Evaluation in patients with risk factors of CHD other than hyperlipidemia in 1 to 2 Years as Indicated.**

Because total and LDL cholesterol tend to increase with advancing age, patients with initially borderline LDL values may evolve frankly elevated LDL with the passage of 1 year, or may develop concurrent health conditions (nephrotic syndrome, hypothyroidism, diabetes mellitus) that can declare as hyperlipidemia.
Patients known to be at high risk for CAD based on multiple risk factors other than hyperlipidemia are candidates for early and aggressive dietary and pharmacologic therapy; thus annual reevaluation of serum lipid status is prudent and cost-effective.

Step 16

Treatment of low HDL cholesterol (<40mg/dl)

First reach HDL goal then:
Intensify weight management and increase physical activity.
If triglyceride 200-499 mg/dl, achieve non-HDL goal.
If triglyceride <200 mg/dl (isolated low HDL) in CHD or CHD equivalent consider nicotinic acid or fibrate.

## ADAPTATION

Executive summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001 May 16;285(19):2486-97. See the related National Guideline Clearinghouse (NGC) summary.
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