Risk-Based Lipid Management

Andrew G. Bostom, MD, MS,
Associate Professor of Medicine
Diplomate, American Board of Clinical Lipidology

Framingham CHD Risk Assessment

Age	Points	Age	Points	Age	Points	
20-34	–7	50-54	6	65-69	12	
35-39	–3	55-59	8	70-74	14	
40-44	0	60-64	10	75-79	16	
45-49	3					Points ____

Total cholesterol (mg per dL)	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79	
<160	0	0	0	0	0	
160-199	4	3	2	1	1	
200-239	8	6	4	2	1	
240-279	11	8	5	3	2	
≥280	13	10	7	4	2	Points ____

Smoking	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79	
Nonsmoker	0	0	0	0	0	
Smoker	9	7	4	2	1	Points ____

HDL (mg per dL)	Points	
≥60	–1	
50-59	0	
40-49	1	
<40	2	Points ____

Systolic BP (mm Hg)	If untreated	If treated	
<120	0	0	
120-129	1	3	
130-139	2	4	
140-159	3	5	
≥160	4	6	Points ____
			Total points ____

Point total	10-year risk (%)	Point total	10-year risk (%)	Point total	10-year risk (%)
<9	<1	14	2	20	11
9	1	15	3	21	14
10	1	16	4	22	17
11	1	17	5	23	22
12	1	18	6	24	27
13	2	19	8	≥25	≥30

10-year risk ____%

ATP III 2006 Updated CHD Risk Categories & Treatment Goals*

Risk Category	LDL Goal(s)	Initiate TLC	Consider Drug Therapy
Very high risk**	**< 70 mg/dL**	**≥ 70 mg/dL**	**≥ 70 mg/dL**
High risk: CHD or CHD risk equivalents (10-yr *FHS* risk > 20%; also diabetes, or CKD)	**< 100 mg/dL**	**≥ 100 mg/dL**	**≥ 100 mg/dL**
Moderately high risk: ≥ 2 risk factors (10-yr *FHS* risk 10%-20%)	**< 130 mg/dL (optional goal < 100 mg/dL)**	**≥ 130 mg/dL**	**≥ 130 mg/dL (consider drug options if LDL 100-129)**
Moderate risk: ≥ 2 risk factors (10-yr *FHS* risk <10%)	**< 130 mg/dL**	**≥ 130 mg/dL**	**≥ 160 mg/dL**
Low risk: ≤ 1 risk factor	**< 160 mg/dL**	**≥ 160 mg/dL**	**≥ 190 mg/dL (consider drug options if LDL 160-189)**

[*From ***Circulation*** 2004; 110: 227-39, and 2006; 113: 2363-79]; TLC= therapeutic lifestyle changes; ****Very high risk*= *acute coronary syndrome*, or ***established CVD, plus any of the following***: (1) multiple major risk factors, esp. diabetes, (2) severe and poorly controlled risk factors (esp. continued cigarette smoking), (3) **multiple risk factors for the metabolic syndrome** (esp. triglycerides ≥ 200 mg/dl, plus non-HDL ≥ 130 mg/dl with HDL < 40 mg/dL)
Note: Goals for non-HDL at each risk category are 30 mg/dl above respective LDL goals

Criteria for Diagnosing Metabolic Syndrome

Measure	Categorical Cut Points*
Elevated waist circumference (population and country-specific definitions**)	[US**] Men: ≥ 102 cm (≥ 40 in) Women: ≥ 94 cm (≥ 37 in)
Elevated triglycerides (or drug treatment for)	≥ 150 mg/dl
Reduced HDL-C (or drug treatment for)	< 40 mg/dl in males < 50 mg/dl in females
Elevated blood pressure (or drug treatment for)	Systolic ≥ 130 and/or Diastolic ≥ 85 mm Hg
Elevated fasting glucose (or drug treatment for)	≥ 100 mg/dl

*** Presence of any 3 of these 5 risk factors constitutes a diagnosis of metabolic syndrome**

Treating to New Targets (TNT) Trial

Methods

A total of ***10,001 patients with clinically evident CHD and LDL cholesterol levels of < 130 mg/dl*** were randomly assigned to double-blind therapy and **received either 10 mg or 80 mg of atorvastatin per day**. Patients were ***followed for a median of 4.9 years***. The ***primary end point was the occurrence of a first major cardiovascular event***, defined as death from CHD, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

Results

The mean LDL cholesterol levels were 77 mg/dl during treatment with 80 mg of atorvastatin and 101 mg/dl during treatment with 10 mg of atorvastatin. A primary event occurred in 434 patients (8.7 percent) receiving 80 mg of atorvastatin, as compared with 548 patients (10.9 percent)receiving 10 mg of atorvastatin, representing ***an *absolute reduction in the rate of major cardiovascular events of 2.2 percent and a 22 percent relative reduction in risk (hazard ratio, 0.78; 95 percent confidence interval, 0.69 to 0.89; P<0.001).***

[*means NNT= 46]

N Engl J Med 2005;352:1425-35.

Extent of the Problem

Toth P.P. et al. “Prevalence of lipid abnormalities in the United States: The National Health and Nutrition Examination Survey 2003-2006”, *J Clin Lipidol* 2012; 6: 325-330

“…For LDL-C, an estimated 23 million adults with CHD or a CHD risk Equivalent, and 17 million with ≥ 2 risk factors but a Framingham risk ≤ 20% are *not* at goals of < 100 and < 130 mg/dl, respectively.”

Therapeutic Lifestyle Changes

For all patients:

- **Start dietary therapy. Reduce intake of saturated fats (to < 7% of total calories), trans fatty acids, and cholesterol (to < 200 mg/d)**

- **Adding plant stanols/sterols (2g/d) and viscous fiber (≥ 10g/d) will further lower LDL-C**

- **Promote daily physical activity and weight management**

- **Encourage increased consumption of omega-3 fatty acids in the form of fish or as capsules (1g/d) for risk reduction. For treatment of elevated TGs, higher doses (~3.4 g/d) are usually required**

Lipid Management

Assess fasting lipid profile in all patients, and within 24-h for those presenting with an acute coronary syndrome. For hospitalized patients, initiate lipid-lowering drugs as recommended below prior to discharge:

- **LDL-C should be < 100 mg/dl, and further reduction to < 70 mg/dl is reasonable**
- **If baseline LDL-C is ≥ 100 mg/dl, initiate LDL-lowering drug therapy**
- **If on-treatment LDL-C is ≥ 100 mg/dl, intensify LDL-lowering drug therapy (this may require combination LDL-lowering drug therapy)**
- **If baseline LDL-C is 70 to 100 mg/dl, it is reasonable to treat LDL-C < 70 mg/dl**

Lipid Management II

<u>Non-HDL guidelines</u> (esp. relevant in setting of metabolic syndrome)*:

- **If TGs are 200 to 499 mg/dl, non-HDL-C should be < 130 mg/dl**
- **Further reduction of non-HDL to < 100 mg/dl is reasonable**
- **Therapeutic options to reduce non-HDL are:**
  - **More intense LDL-C-lowering therapy, or**
  - **Niacin (after LDL-C-lowering therapy), or**
  - **Fibrate therapy (after LDL-C-lowering therapy)**
- **If TGs are ≥ 500 mg/dl, therapeutic options to prevent pancreatitis are fibrates or niacin (or possibly, high dose omega-3 fatty acids, [for eg., EPA 465 mg/DHA 375 mg per capsule, 4 capsules per day]) *<u>before</u>* LDL-lowering therapy; and treat LDL-C to goal after TG-lowering therapy. Achieve non-HDL-C < 130 mg/dl, if possible**

A recent joint consensus report by the American Diabetes Association (ADA) and the American College of Cardiology (ACC) Foundation concluded that <u>non–HDL-C was a better measure than LDL-C for identifying patients at high risk who had multiple cardiometabolic risk factors</u>** [J Am Coll Cardiol*** 2008;51:1512–24.]

Case Study & Question 1

A 58 y/o women is referred to you with persistently elevated TG on simvastatin 40 mg/d. She has a h/o of newly diagnosed type 2 diabetes and hypertension, which is well-controlled. Current meds are simvastatin 40 mg/d, metformin 500 mg/d, lisinopril 20 mg/d, and aspirin 81 mg/d. Her fasting labs are:

Total cholesterol	**335 mg/dl**
HDL-C	**33 mg/dl**
LDL-C	**Cannot calculate due to TGs**
Triglycerides	**813 mg/dl**
Non-HDL-C	**302 mg/dl**
Glucose	**167 mg/dl**
HgbA1c	**8.4%**
ALT	**75 U/L (3-50 U/L)**

Which ***one*** of the following statements is **CORRECT** regarding initial TG-lowering management in this patient as per NCEP ATP III guidelines?

A) Initial aim of therapy is to achieve LDL goal

B) Initial aim of therapy is to achieve HDL goal

C) Initial aim of therapy is to achieve non-HDL goal

D) Initial aim of therapy is to prevent pancreatitis

E) None of the above

Case Study & Answer to Question 1

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NCEP ATP III Classification of TGs	
Normal TGs	**< 150**
Borderline high TGs	**150-199**
High TGs	**200-499**
Very high TGs	**≥ 500**

Initial aim in this patient is to prevent the pancreatitis associated with marked hypertriglyceridemia, which may be caused by inadequately controlled diabetes, EtOH abuse, drugs (i.e., thiazides, beta-blockers, estrogens, isotretinoin, glucocorticoids) . Goal is to lower TG to < 500 mg/dl with fibrates, and/or niacin, OM3 FAs, and then LDL becomes primary target

Case Study & Question 2

She returns for 3-mo follow-up. Current meds are simvastatin 40 mg/d, fenofibrate 160 mg/d, metformin 2 g/d, pioglitazone 45 mg/d, lisinopril 20 mg/d, and aspirin 81 mg/d. She now walks 30 min/d most days. Her fasting labs are:

Total cholesterol	**238 mg/dl**
HDL-C	**33 mg/dl**
LDL-C	**129 mg/dl**
Triglycerides	**350 mg/dl**
Non-HDL-C	**199 mg/dl**
Glucose	**128 mg/dl**
HgbA1c	**7.0%**
ALT	**46 U/L (3-50 U/L)**

What are her ***non-HDL and LDL goals, respectively***, as per NCEP ATP III guidelines?

A) < 190 mg/dl & < 160 mg/dl

B) < 160 mg/dl & < 130 mg/dl

C) < 130 mg/dl & < 100 mg/dl

D) < 100 mg/dl & < 70 mg/dl

E) None of the above

Case Study & Answer to Question 2

What are her ***non-HDL and LDL goals, respectively***, as per NCEP ATP III guidelines?

A) < 190 mg/dl & < 160 mg/dl

B) < 160 mg/dl & < 130 mg/dl

C) < 130 mg/dl & < 100 mg/dl

D) < 100 mg/dl & < 70 mg/dl

E) None of the above

As per current NCEP ATP III risk-based guidelines, diabetes is a CHD risk equivalent which confers high risk (but in the absence of concurrent known CVD, *not* very high risk), so the goal for non-HDL is < 130 mg/dl, and for LDL < 100 mg/dl

Case Study & Question 3

Which *one* statement represents the next **most appropriate step** to for this patient to help her achieve are her NCEP ATP III therapeutic goals?

A) Increase simvastatin to 80 mg/d

B) Change simvastatin to rosuvastatin 20 mg/d

C) Maintain current drug regimen without changes

D) Change fenofibrate to gemfibrozil 600 mg twice daily

E) Add cholestyramine resin 8 g twice daily

Total cholesterol	**238 mg/dl**
HDL-C	**33 mg/dl**
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A) Doubling simva dose only yields an additional 6% LDL reduction, when goals is additional ~20%, and 80 mg dose is assoc. with increased risk of muscle injury

C) Now that patient's TGs are < 500, her LDL goal of < 100 merits attention

D) Use of gemfibrozil with simva at was contraindicated by the FDA 6/8/11 (mechanism may be competition for liver glucuronidation which potentially increases risk for muscle injury); But current use of fenofibrate/statin combination is supported by safety and even subgroup efficacy (i.e., those with an HDL ≤ 34 mg/dl & TGs ≥ 204 mg/dl) data from the ACCORD-LIPID trial (total n=5518 pts with diabetes followed for median 4.7 yrs)

E) Bile acid sequestrants, such as cholestyramine can increase VLDL production and worsen pre-existing hypertriglyceridemia

B) Changing to rosuvastatin 20 mg/d could confer as much as a 52-55% reduction in LDL compared to the current 40 mg/d simva which affords an ~ 40% reduction

Relative potency of statins

Dose (mg) of drug					*% Reduction**	
Atorva**	**Simva**	**Lova**	**Prava**	**Fluva**	**TC**	**LDL-C**
-	**10**	**20**	**20**	**40**	***22***	***27***
10	**20**	**40**	**40**	**80 XL**	***27***	***36***
20	***40***	**80**			***32***	***42***
40	**80**				***37***	***48***
80					***42***	***54***

*** "Rule of 6s": Additional ~ 6% LDL-C reduction per doubling of statin dose**

**** Rosuvastatin 5, 10, *20*, 40 mg reduces LDL-C by *45, 52, 55, and 63%* , respectively**