Hyperlipidemia

Be it known ....!

• “It should be noted that these guidelines are intended to inform, not replace, the physician’s clinical judgment, which must ultimately determine the appropriate treatment for each individual.”


Hyperlipidemia-Why do we care?

- Cardiovascular disease [CVD] is the number one cause for mortality in the United States

Cholesterol levels and Heart Disease

- The Framingham Heart Study, the Multiple Risk Factor Intervention Trial (MRFIT), and the Lipid Research Clinics (LRC) trial found a direct relationship between levels of LDL cholesterol (or total cholesterol) and the rate of new-onset CHD in men and women who were initially free of CHD.

- The same relationship holds for recurrent coronary events in people with established CHD.

Lipoprotein Subclasses

Atherogenic Particles – What are They?

Endogenous Lipid Transport

Lipid transport begins in the liver, where VLDL (very low-density lipoprotein) is synthesized. VLDL then enters the bloodstream and is converted to IDL (intermediate-density lipoprotein) and LDL (low-density lipoprotein) through a process involving lipoprotein lipase (LPL) and other enzymes. LDL is further converted to HDL (high-density lipoprotein) in the liver and extrahepatic tissues, completing the cycle of lipid transport.

Lipoprotein Subclasses

The lipoprotein subclasses can be categorized based on their density and composition. This classification is important for understanding their role in atherogenesis, as different subclasses are associated with different cardiovascular risks.

Atherogenic Particles

Atherogenic particles are a category of lipoproteins that are implicated in the development of atherosclerosis. They include Apolipoprotein B-containing particles, which are further divided into triglyceride-rich and cholesterol-rich categories. The measurement of these particles can provide valuable insights into the risk of cardiovascular disease.
The major classes of lipoproteins and their relative content of triacylglycerol (T), cholesterol (C), and protein (P):

- **Chylomicrons**
- **VLDL**
- **LDL**
- **HDL**

**Frederickson Classification of Hyperlipoproteinemias**

<table>
<thead>
<tr>
<th>Photype</th>
<th>Lipoprotein(s)</th>
<th>Serum cholesterol concentration</th>
<th>Serum triglyceride concentration</th>
<th>Relative frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>Normal</td>
<td>↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>↑↑↑</td>
<td>Normal</td>
<td>10</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL and VLDL</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>40</td>
</tr>
<tr>
<td>III</td>
<td>LDL</td>
<td>↑↑</td>
<td>↑↑</td>
<td>&lt;1</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>Normal</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>V</td>
<td>VLDL and chylomicrons</td>
<td>↑↑</td>
<td>↑↑</td>
<td>6</td>
</tr>
</tbody>
</table>

**LDL Cholesterol**

- Typically makes up 60–70 % of the total serum cholesterol.
- It has a single apo-B molecule in its structure.
- It is the major atherogenic lipoprotein.
- It is the primary target for therapy in most individuals, with few exceptions. [This focus on LDL has been strongly validated by recent clinical trials, which show the efficacy of LDL-lowering therapy for reducing risk for CHD.]

**LDL-C Lowering With Statins: Reduced CHD Events**

Hypercholesterolemia-Manifestations: Corneal Arcus and Tendon Xanthomata

- Normal makes up 20–30% of the total serum cholesterol.
- The major apolipoproteins of HDL are apo A-I and apo A-II.
- HDL-c levels are inversely correlated with risk for CHD.
- Some evidence indicates that HDL is anti-atherogenic, although a low HDL-c often reflects the presence of other atherogenic factors.

**HDL Cholesterol**

VLDL [not part of a lipid panel]

- Are triglyceride-rich lipoproteins, but contain 10–15 percent of the total serum cholesterol.
- The major apolipoproteins of VLDL are apo B-100, apo Cs (C-I, C-II, and C-III), and apo E.
- VLDL are produced by the liver and are precursors of LDL.
- VLDL remnants consist of partially degraded VLDL and are relatively enriched in cholesterol ester.
- VLDL remnants appear to promote atherosclerosis, similar to LDL.

Palmar Crease Xanthoma-Pathognomonic of Dysbetalipo-Proteinemia or Type III Hyperlipidemia

- Normally makes up 20–30% of the total serum cholesterol.
- The major apolipoproteins of HDL are apo A-I and apo A-II.
- HDL-c levels are inversely correlated with risk for CHD.
- Some evidence indicates that HDL is anti-atherogenic, although a low HDL-c often reflects the presence of other atherogenic factors.
Eruptive Xanthoma—Seen in Patients with Very High Triglycerides [VLDL / Chylomicrons]

Evanescent pin-head or larger yellow papules with an erythematous base occurring most commonly on the buttocks, shoulders and extensor surfaces of the extremities.

Lipemia—Excess Triglycerides

Lipemic fasting serum usually means the excess presence of either VLDL or chylomicron [types I, V and rarely IV]

Lipid Profile The Basic Test

- The first step is to obtain a fasting lipid profile usual components are
  1. Triglycerides [measured]
  2. HDL cholesterol [measured] = [HDL-c]
  3. Total Cholesterol [measured] = [T.Chol]
  4. LDL cholesterol [calculated] = [LDL-c] calculation usually based on the Friedewald’s formula (T. Chol — HDL-c — TG/5)

Lipid Profile The Basic Test

- Calculated serum triglycerides are not reliable when tg levels are elevated above 350-400 mg/dl
- ‘Direct Idl-c’ measurement is possible and can be requested in those with hypertriglyceridemia [icd-9 code for pure hypertriglyceridemia 272.1]
Serum triglycerides are affected by food intake. Hence the need for a fasting blood sample.

Non-HDL-c [T.Chol — HDL-c] is a measure of all apolipoprotein-B [apo-B] containing particles [LDL-c, IDL-c and VLDL-c] and does not need a patient to fast.

Who Should Get a Lipid Panel?

<table>
<thead>
<tr>
<th>Screening group</th>
<th>Begin screening</th>
<th>Frequency</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD, CHD risk equivalent, or ≥ 2 risk factors</td>
<td>Age 20 years or at onset</td>
<td>1-2 years</td>
<td>Fasting lipid panel</td>
</tr>
<tr>
<td>Familial dyslipidemia or family history of premature CHD</td>
<td>Age 20 years</td>
<td>2 years</td>
<td>Fasting lipid panel</td>
</tr>
<tr>
<td>None of the above</td>
<td>Age 20 years</td>
<td>5 years</td>
<td>Fasting lipid panel or non-fasting total cholesterol and HDL-C</td>
</tr>
</tbody>
</table>

Lipid Screening Patient Request

- “I want you to check my blood cholesterol levels”
- Pre-test counseling
- ICD-9 codes and billing issues: reimbursement issues must be discussed beforehand
- Relevant in those with a family h/o premature CHD, hyper-lipidemia, sudden cardiac death etc.
## National Cholesterol Education Program [NCEP] Adult treatment Panel [ATP]

- ATP I: published 1988
- ATP II: published 1993
- ATP III: published 2002
- ATP III Update: 2004

## ATP III Classification of T. Chol

- < 200 desirable
- 200-239 borderline high
- > 240 high

## ATP III Classification of LDL-c [mg/dl]

- < 100 optimal
- 100-129 near optimal / above optimal
- 130-159 borderline high
- 160-189 high
- > 190 very high

## ATP III Classification of HDL-c

- < 40 Low
- > 60 High
Treatment Principles in Dyslipidemia Patients

- CV risk stratification
- Define targets for therapy
- Determine intensity of treatment needed
- Lifestyle measures
- Pharmacotherapy
- Screening for complications of disease and therapy
- Comprehensive cardiometabolic approach

Non-Lipid Risk Factors for CHD

<table>
<thead>
<tr>
<th>MODIFIABLE RISK FACTORS</th>
<th>NON-MODIFIABLE RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension*</td>
<td>Age*</td>
</tr>
<tr>
<td>Cigarette smoking*</td>
<td>Male sex*</td>
</tr>
<tr>
<td>Prothrombotic states†</td>
<td>Family history of premature CHD</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Physical inactivity</td>
<td></td>
</tr>
<tr>
<td>Atherogenic diet</td>
<td></td>
</tr>
</tbody>
</table>

* Included in ATP III risk assessment † Inferential [anti-platelet drugs / anticoagulants seem to reduce CHD events]

Risk Factors that Modify LDL-c Goals

Positive risk factors:
1. Age
2. Male >45; Female >55
3. Family h/o premature CHD [MI/SCD < 55 in father/male 1st degree relatives; < 65 in mother/other 1st degree relatives]
4. Current smoker
5. Hypertension [> 140/90 or on medications]
6. Low HDL-c [< 40 mg/dl both genders]

Negative risk factor:
1. HDL-c > 60 mg/dl in both genders
### NCEP ATP 3 Risk Categories

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very-high risk</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>Moderately-high risk</td>
</tr>
<tr>
<td>Moderate risk</td>
</tr>
<tr>
<td>Low risk</td>
</tr>
</tbody>
</table>

### Very High Risk Patients

1. Recent acute coronary syndromes
2. Established cardiovascular disease and
   - Multiple major risk factors (especially Type 2 DM)
   - Severe and poorly controlled risk factors (especially cigarette smoking)
   - Multiple risk factors of the metabolic syndrome (abdominal obesity, increased Tg, decreased HDL, blood pressure ≥130/85, glucose > 100)

### High Risk Patients

1. History of CHD
2. Type 2 diabetes
3. Symptomatic carotid disease
4. Peripheral vascular occlusive disease
5. Abdominal aortic aneurysm

### Coronary Risk Categorization in Patients without Established CHD

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>&gt;20% 10 year CHD risk</td>
</tr>
<tr>
<td>Moderately-high risk</td>
</tr>
<tr>
<td>2 or more risk factors and 10-20% 10 year risk</td>
</tr>
<tr>
<td>Moderate risk</td>
</tr>
<tr>
<td>2 or more risk factors and &lt; 10% 10 year risk</td>
</tr>
<tr>
<td>Lower risk</td>
</tr>
<tr>
<td>0-1 risk factors and &lt; 10% 10 year risk</td>
</tr>
</tbody>
</table>
CHD/CHD Risk Equivalents
10-year CAD risk exceeds 20%

- Established CAD
- Stroke and stroke variants
- Peripheral arterial disease
- Atherosclerotic aortic aneurysms
- Post-op CABG / carotid endarterectomy / peripheral arterial revascularization
- Diabetes mellitus

For Those without CHD

- Determine presence of major risk factors aside from LDL-C
  - Current cigarette smoking
  - BP ≥ 140/90 or on anti-hypertensive medication
  - HDL-C < 40 mg/dl (if ≥ 60 count as negative RF)
  - CHD in 1st degree relatives < 55, or first degree relatives < 65
  - Age ≥ 45 or ≥ 55
- Calculate Framingham Risk Score in those with 2 or more risk factors

NCEP/Framingham risk scores:
Estimate of 10-yr Hard CHD risk in men without CHD

NCEP/Framingham risk scores:
Estimate of 10-yr Hard CHD risk
in men without CHD

- Total cholesterol (mg/dL)
- HDL cholesterol (mg/dL)
- Systolic blood pressure (mm Hg)
- Age in years
- Gender
- Current cigarette smoking

Framingham Risk Score

For those with 2 or more risk factors:
Calculate Framingham Risk Score

Treatment Principles in Dyslipidemia Patients

- CV risk stratification
- Define targets for therapy
- Determine intensity of treatment needed
- Lifestyle measures
- Pharmacotherapy
- Screening for complications of disease and therapy
- Comprehensive cardiometabolic approach

NCEP ATP III Targets for Therapy-Which Order?

- LDL-first target for therapy
- Non-hdl – second target for therapy
- HDL-third target for therapy
- LDL particle number and small dense LDL particle number-???

Clinical Studies Supporting Use of LDL as Primary Target

| Intervention | No. trials | Cholesterol Lowering Therapy
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>7</td>
<td>4.084 22 -43 -20</td>
</tr>
<tr>
<td>Sequestrants</td>
<td>3</td>
<td>1.962 9 -21 -21</td>
</tr>
<tr>
<td>Diet</td>
<td>12</td>
<td>14.491 11 -24 -21</td>
</tr>
<tr>
<td>Statins</td>
<td>12</td>
<td>17.45 8.123 24 -30 -24</td>
</tr>
</tbody>
</table>

* This table is adapted from the meta-analysis of Cochrane.1

1 Intended among those clinical trials that are those employing fibrates, nicotinic acid, and hormones. The major sources of fibrates and nicotinic acid are in triglycerides and HDL, whereas for these trials no effects beyond usual effects.

Angio-graphic Studies Supporting use of LDL as Primary Target

- Statin trials: LCAS, CIS, CARS, Post-CABG, REGRESS, PLAC I, CCAIT, MAAS, MARS
- Surgical therapy: POSCH
- Sequestrant trials: STARS, NHLBI Type II
- Lifestyle intervention: Heidelberg, STARS, Lifestyle Heart Trial
- Combination drug therapy: HARP, SCRIP, SCOR, FATS (lovastatin/colestipol),
- FATS (nicotinic acid/colestipol), CLAS
- Calcium channel blocker monotherapy trials: Montreal Heart Institute Study, INTACT
### Remember the Exception...

When serum triglyceride exceeds 500 mg/dl, the primary aim is to lower the triglyceride first to reduce / prevent pancreatitis

### NCEP ATP III Targets for Therapy-Which Order?

- LDL-first target for therapy
- Non-hdl – second target for therapy
- HDL-third target for therapy
- LDL particle number and small dense LDL particle number-???

### Non-HDL

- Target for therapy if triglyceride > 200 mg/dl
- Non HDL=total cholesterol—HDL cholesterol
- Represents all apolipoprotein b containing particles
- Can be estimated in the non-fasting state

### NCEP ATP III Targets for Therapy-Which Order?

- LDL-first target for therapy
- Non-hdl – second target for therapy
- HDL-third target for therapy
- LDL particle number and small dense LDL particle number-???
Heart Disease and HDL

• 20% of all individuals with lipid disorders have low levels of HDL-cholesterol
• 50% of all CHD patients have low HLD-c
• Paucity of drugs that efficiently increases HDL-c

CHD risk associated with HDL, and its independence from triglycerides in the PROCAM study

Predictivity of Non-HDL-C for CAD Events in the Bypass Angioplasty Revascularization Investigation (BARI)

• Baseline lipids available in 1514 patients with multivessel CAD
• Randomization in overall study to CABG (n=769) or PTCA (n=745)
• Outcomes: all-cause mortality, nonfatal MI, combined endpoint of death or nonfatal MI, angina, revascularization
• Follow-up: 5 years

Independent Baseline Lipid Predictors of Nonfatal MI in BARI

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>1.043</td>
<td>1.001–1.087</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.900</td>
<td>0.763–1.082</td>
<td>0.3</td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.023</td>
<td>0.981–1.069</td>
<td>0.2</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>1.640</td>
<td>1.006–1.993</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TG</td>
<td>1.016</td>
<td>1.001–1.031</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*For each 10 mg/dL increment in lipid variables. Covariance in BARI model: age, sex, race, CHD, HTN, prior MI, smoking, body surface area, number of significant coronary lesions, DPM treatment assignment.
Treatment Principles in Dyslipidemia Patients

- CV risk stratification
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- Comprehensive cardiometabolic approach

ATP III Update 2004: LDL-C Goals and Cutpoints for Therapy in Different Risk Categories

Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
<th>Non-HDL Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD Risk Equivalent (10-year risk for CHD &gt; 20%)</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Multiple (2+) Risk Factors and 10-year risk &lt; 20%</td>
<td>&lt;130</td>
<td>&lt;160</td>
</tr>
<tr>
<td>0-1 Risk Factor</td>
<td>&lt;160</td>
<td>&lt;190</td>
</tr>
</tbody>
</table>

Treatment Principles in Dyslipidemia Patients

- CV risk stratification
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Initiate Therapeutic Lifestyle Changes (TLC) if LDL is Above Goal

**TLC Features**

- **TLC diet:**
  - Saturated fat <7% of calories, cholesterol <200 mg/day
  - Consider increased viscous (soluble) fiber (10-25 g/day) and plant stanols/sterols (2 g/day) as therapeutic options to enhance LDL lowering
- Weight management
- Increase physical activity

---

**Lifestyle Weight Management**

**Classification of Overweight and Obesity by BMI**

<table>
<thead>
<tr>
<th>Obesity Class</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
</tr>
<tr>
<td>Obesity I</td>
<td>30.0 – 34.9</td>
</tr>
<tr>
<td>Obesity II</td>
<td>35.0 – 39.9</td>
</tr>
<tr>
<td>Extreme Obesity</td>
<td>III</td>
</tr>
</tbody>
</table>

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**Exercise**

- At least 150 minutes a week
- Mixture of aerobic exercise and weights
- Seek ways and means to expend energy / increase exercise during a typical work day and when not working
- Pedometers helpful-clock 15000 steps daily

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**Lifestyle Weight Management**

- Dietary discipline is key
- Exercise therapy is an important component.
- Often requires a ‘culture’ change
- Best implemented in steps and avoid drastic changes over short periods of time.
**Behavioural Modification**

*Behavior Therapy:* Strategies, based on learning principles such as reinforcement, that provide tools for overcoming barriers to compliance with dietary therapy and/or increased physical activity are helpful in achieving weight loss and weight maintenance. Specific strategies include self-monitoring of both eating habits and physical activity, stress management, stimulus control, problem solving, contingency management, cognitive restructuring, and social support.

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**Treatment Principles in Dyslipidemia Patients**

- CV risk stratification
- Define targets for therapy
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- Comprehensive cardiometabolic approach

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### LDL Cholesterol Goals and Outcomes for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)</th>
<th>LDL Level at Which to Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD Risk Equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL</td>
<td>≥100 mg/dL</td>
<td>≥190 mg/dL (110-129 mg/dL, drug optional)</td>
</tr>
<tr>
<td>2+ Risk Factors (10-year risk ≥20%)</td>
<td>&lt;100 mg/dL</td>
<td>≥130 mg/dL</td>
<td>10-year risk ≥20%: 190 mg/dL, ≥70 mg/dL</td>
</tr>
<tr>
<td>0-1 Risk Factors</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL (110-129 mg/dL, drug lowering drug optional)</td>
</tr>
</tbody>
</table>

* Some authorities recommend use of LDL-lowering drugs in this category of LDL cholesterol ≥100 mg/dL, cannot be achieved by therapeutic lifestyle changes. Often prefer use of drugs that mainly lower triglycerides and HDL, e.g., niacin and/or fibrate.
* Clinical judgment is key for defining drug therapy in this category.
* Almost all people with 0-1 risk factor have 10-year risk <10%. Five 10-year risk assessment in people with 0-1 risk factor is not necessary.

### Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

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<td>&lt;130</td>
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<td>&lt;160</td>
</tr>
<tr>
<td>0-1 Risk Factor</td>
<td>≤160</td>
<td>≤190</td>
</tr>
</tbody>
</table>
Pharmacologic Agents Available

- Statins: Atorvastatin, Simvastatin, Lovastatin, Rosuvastatin, Pravastatin and Fluvastatin.
- Fibric acid derivatives: fenofibrate, Bezafibrate & Gemfibrozil
- Niacin: Immediate release, sustained release and Extended release forms
- Fish oil
- Bile acid sequestrants

Effect of Lipid-Lowering Drugs on LDL-C Levels

<table>
<thead>
<tr>
<th>Pharmacologic Agent</th>
<th>Effect on LDL-C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>↓ 20-62%</td>
</tr>
<tr>
<td>Bile acid resins</td>
<td>↓ 15-25%</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↓ 15-30%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>↓ 15-25%</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>↓ 10-25%</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>↓ 10-15%</td>
</tr>
</tbody>
</table>

Statin Preparations Efficacy

<table>
<thead>
<tr>
<th>Statin</th>
<th>10mg</th>
<th>20mg</th>
<th>40mg</th>
<th>80mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorva</td>
<td>38%</td>
<td>46%</td>
<td>51%</td>
<td>54%</td>
</tr>
<tr>
<td>Fluva</td>
<td>--</td>
<td>17%</td>
<td>23%</td>
<td>29%</td>
</tr>
<tr>
<td>Lova</td>
<td>--</td>
<td>29%</td>
<td>31%</td>
<td>48%</td>
</tr>
<tr>
<td>Prava</td>
<td>19%</td>
<td>24%</td>
<td>34%</td>
<td>37%</td>
</tr>
<tr>
<td>Rosuva</td>
<td>51%</td>
<td>57%</td>
<td>63%</td>
<td>65%</td>
</tr>
<tr>
<td>Simva</td>
<td>28%</td>
<td>35%</td>
<td>41%</td>
<td>46%</td>
</tr>
<tr>
<td>Vytorin</td>
<td>47%</td>
<td>51%</td>
<td>57%</td>
<td>59%</td>
</tr>
</tbody>
</table>

LDL-C Therapy: Pointers

- Use a statin dose that would achieve 30-40% reduction in LDL-c
- “Start Low – Go slow” in high risk cases—the elderly, people with liver disease, renal disease, post-transplant patient etc.
- Combination therapy—achieve synergy, while minimizing side-effects
- When “not efficacious” first make sure that patient is compliant, before increasing dose!
Factors That Increase the Risk of Statin-Induced Myopathy

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Statin Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>High systemic exposure</td>
</tr>
<tr>
<td>Female sex</td>
<td>Lipophilicity</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>High bioavailability</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>Limited protein binding</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Potential for drug-drug interactions metabolized by CYP pathways (particularly CYP450 3A4)</td>
</tr>
<tr>
<td>Diet (i.e., grapefruit juice)</td>
<td></td>
</tr>
<tr>
<td>Polypolymyarin</td>
<td></td>
</tr>
</tbody>
</table>

Attaining Non-HDL Goals by Lowering Triglycerides: Traditional Therapeutic Options

- **Niacins**
  - 25-40% decrease in [TG]
- **Fibrates**
  - Fenofibrate: 50% decrease in [TG]
  - Gemfibrozil: 40% decrease in [TG]
- **Omega – 3 fatty Acids**
  - 30-40% decrease in [TG]
- **Statins**
  - 7-30% decrease in [TG]

CKD Dyslipidemia Pharmacotherapy Dose Adjustments

<table>
<thead>
<tr>
<th>Agent</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>60-90</th>
<th>15-59</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>No</td>
<td>↓ by 50%</td>
<td>↓ by 50%</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>No</td>
<td>↓ by 50%</td>
<td>↓ by 50-75%</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>↓ by 50%</td>
<td>↓ by 75%</td>
<td>AVOID</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Principles in Dyslipidemia Patients

- CV risk stratification
- Define targets for therapy
- Determine intensity of treatment needed
- Lifestyle measures
- Pharmacotherapy
- Screening for complications of disease and therapy
- Comprehensive cardiometabolic approach
Clinical Identification of the Metabolic Syndrome – Any 3 of the Following:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity*</td>
<td>Waist circumference/2</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≤130/85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

* Overweight and obesity are a correlate with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more tightly correlated with the metabolic risk factors than an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similar to men with a more marked increase in waist circumference.

CVD Mortality Increased in the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>Cardiovascular disease mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>4</td>
<td>4%</td>
</tr>
<tr>
<td>6</td>
<td>6%</td>
</tr>
<tr>
<td>8</td>
<td>8%</td>
</tr>
<tr>
<td>10</td>
<td>10%</td>
</tr>
<tr>
<td>12</td>
<td>12%</td>
</tr>
</tbody>
</table>

RR (95% CI), 3.55 (1.96-6.43)

Treatment of Metabolic Syndrome

- Treat underlying causes (overweight/obesity and physical inactivity):
  - Intensify weight management
  - Increase physical activity
- Treat lipid and non-lipid risk factors if they persist despite these lifestyle therapies:
  - Treat hypertension
  - Use aspirin for CHD patients to reduce prothrombotic state
  - Treat elevated triglycerides and/or low HDL (as shown in Step 9)

IGT/IFG = Prediabetes [ADA]
Too much fat in all the wrong places

<table>
<thead>
<tr>
<th>FAT</th>
<th>FATTER</th>
<th>FATTEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>Liver</td>
<td>Muscle</td>
</tr>
</tbody>
</table>

Obesity  AFLD/NASH  Diabetes  Cardiomyopathy

**Dyslipidemia in Diabetes and Prediabetes**

**Atherogenic Triad**
- High Triglyceride
- Low HDL
- Increased small dense LDL [Pattern B]

**IGT Progressively increases risk of CHD Mortality**

Paris Prospective Study 10-year follow-up

![Chart showing CHD mortality risk over 10 years for different BMI categories.]

**HbA1c as a Predictor of Micro- and Macrovascular Disease in Type 2 Diabetes**

![Graph showing HbA1c levels and estimated risk of microvascular and myocardial infarction.]

*Retinopathy requiring photo-coagulation, vitreous hemorrhage, fatal or nonfatal renal failure
HbA1c as a Predictor of Micro- and Macrovascular Disease in Type 2 Diabetes

UKPDS: Order of Importance for Prediction of Coronary Artery Disease (Baseline Epidemiologic Data)

Type 2 Diabetes and CHD: 7-year Incidence of Fatal/Nonfatal MI (East West Study)

CVD Death and Number of Risk Factors

Age-adjusted CVD death rate and number of risk factors (cholesterol, blood pressure, smoking)
**Medicare Cardiovascular Screening**

- 80061 lipid panel (total cholesterol, HDL cholesterol and triglycerides)
- 82465 cholesterol, serum or whole blood, total
- 84478 triglycerides
- 63718 lipoprotein, direct measurement, HDL cholesterol

**Special codes that apply...**

- V81.0 Special screening for cardiovascular disease, ischemic heart disease
- V81.1 Special screening for cardiovascular disease, hypertension
- V81.2 Special screening for cardiovascular disease, other and unspecified cardiovascular conditions

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**ICD-9 Disorders of lipoid metabolism code 272**

- 272.0 Pure hypercholesterolemia [Familial hypercholesterolemia, Fredrickson Type Ia hyperlipoproteinemia, Hyperbetalipoproteinemia, Hyperlipidaemia, Group A, Low-density-lipoid-type (LDL) hyperlipoproteinemia]
- 272.1 Pure hyperglyceridemia [Endogenous hyperglyceridemia, Fredrickson Type I, IIa, hyperlipoproteinemia, Hyperlipidaemia, Group B, Hyperbetalipoproteinemia, Hyperglyceridemia, essential, Very-low-density-lipoid-type (VLDL) hyperlipoproteinemia]
- 272.2 Mixed hyperlipidemia [Broad- or floating betalipoproteinemia, Fredrickson Type IIb or III hyperlipoproteinemia, Hypercholesterolemia with endogenous hyperglyceridemia, Hyperbetalipoproteinemia with prebeta-lipoproteinemia, Tubo-eruptive xanthoma, Xanthoma tuberosum]
- 272.3 Hyperchylomicronemia [Bürger-Grütz syndrome, Fredrickson type I or V hyperlipoproteinemia, Hyperlipidaemia, Group D, Mixed hyperglyceridemia]
- 272.4 Other and unspecified hyperlipidemia [Alpha- lipoproteinemia, Combined hyperlipoproteinemia, Hyperlipidaemia NOS, Hyperlipoproteinemia NOS]

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**Treatment Principles in Dyslipidemia Patients**

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- Comprehensive cardiometabolic approach
Steno-2 Supports Aggressive Multifactorial Intervention in Type 2 Diabetes

- Target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria
  - Blood pressure < 130/80 mm Hg
  - A1C < 6.5%
  - Total cholesterol < 175 mg/dL
  - Triglycerides < 150 mg/dL
- Produced risk reductions in CV and microvascular outcomes
  - Primary outcome (combined CV disease) 53% decrease
  - Nephropathy 61% decrease
  - Retinopathy 58% decrease
  - Autonomic neuropathy 63% decrease

Lipid Clinic Referral-Who Should be Referred?

- Inability to achieve effective control of serum lipid levels despite using multiple agents
- Very high serum lipid levels, including genetic hyperlipidemias
- Established cardiovascular disease
- Intolerance to lipid lowering agents
- Liver disease, renal disease
- Transplant patients
- The elderly.

Complex Dyslipidemia Clinic at The Ohio State University [Cramblett Clinic]

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Diplomate, Am. Board of Internal Medicine [subspecialty: Endocrinology, Diabetes & Metabolism]

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Call 614-292-3800 or fax 614 292 1550