

Cholesterol Guidelines: Review of Adult Treatment Panel (ATP) III Guidelines and Beyond

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Learning Objectives

- Review the components of the lipoprotein profile (LDL, non-HDL, HDL, Triglycerides), their normal ranges and target goals for treatment.
- Identify major risk factors for coronary heart disease (CHD) and CHD risk equivalents.
- Review risk categories and the corresponding LDL goal of therapy.
- Discuss therapeutic lifestyle changes (TLC) and drug therapies.
- Recognize issues beyond LDL lowering.

The Lipoprotein Profile

- Total cholesterol
 - LDL-C
 - HDL-C
 - Triglycerides
-
- Non-HDL (Total cholesterol – HDL)

Total Cholesterol

- Mean serum total cholesterol*
 - From 1999 to 2006 this value went from 204 mg/dL to 199 mg/dL in men aged 40 and older & women aged 60 and older
- ATP III Classification

< 200	Desirable
200-239	Borderline high
≥ 240	High

* CDC/NCHS, National Health and Nutrition Examination Surveys, 1999-2006.

LDL-C

- **The primary target of therapy**

- Elevated LDL-C is a major cause of CHD
- LDL-lowering therapy reduces risk

- **ATP III Classification**

<100 (mg/dl)	Optimal
100-129	Near optimal
130-159	Borderline high
160-189	High
≥ 190	Very High

LDL-C

- Follow up NCEP report in 2004:
 - “An LDL-C goal of < 70 mg/dl is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk.”
- “Very high risk”:
 - Multiple major risk factors
 - Severe and poorly controlled risk factors
 - Multiple risk factors of the metabolic syndrome
 - Patients with acute coronary syndrome

HDL-C

- Per ATP-III, not a primary or secondary target of therapy, but:
 - A low HDL-C is strongly and inversely associated with risk for CHD
 - Low HDL is a major risk factor for CHD

- ATP-III Classification

< 40 (mg/dl)	Low
≥ 60	High

HDL-C

- Causes of low HDL:
 - Elevated serum triglycerides
 - Overweight and obesity
 - Physical inactivity
 - Cigarette smoking
 - Very high carbohydrate intake
 - Type 2 diabetes
 - Medications (B-blockers, anabolic steroids)
 - Genetic factors

Triglycerides

- Elevated serum TGs are associated with increased risk for CHD.

- ATP-III Classification

< 150 (mg/dl)	Normal
150-199	Borderline-high
200-499	High
≥ 500	Very high

Note: For “very high” TGs – initial aim of therapy is to lower TGs to prevent acute pancreatitis. Return to LDL lowering after TG ≤ 500.

Triglycerides

- Causes of high triglycerides:
 - Overweight and obesity (central obesity)
 - Calculate BMI and measure waist circumference
 - Physical Inactivity
 - Cigarette smoking
 - Excess alcohol intake
 - Very-high carbohydrate diets
 - Other diseases
 - Rule out secondary causes if TG 250-1000 and no increase in LDL.
 - Medications
 - Genetic factors

Non-HDL

- Per ATP-III, a secondary target of therapy when triglycerides ≥ 200 mg/dl
- The sum of LDL + VLDL (or TC – HDL)
- ATP-III Classification

LDL Goal

< 100 (mg/dl)

< 130

< 160

non-HDL Goal

< 130

< 160

< 190

Risk Assessment

Coronary Heart Disease Risk

Risk Category

LDL Goal (mg/dl)

CHD & CHD risk equivalent

< 100

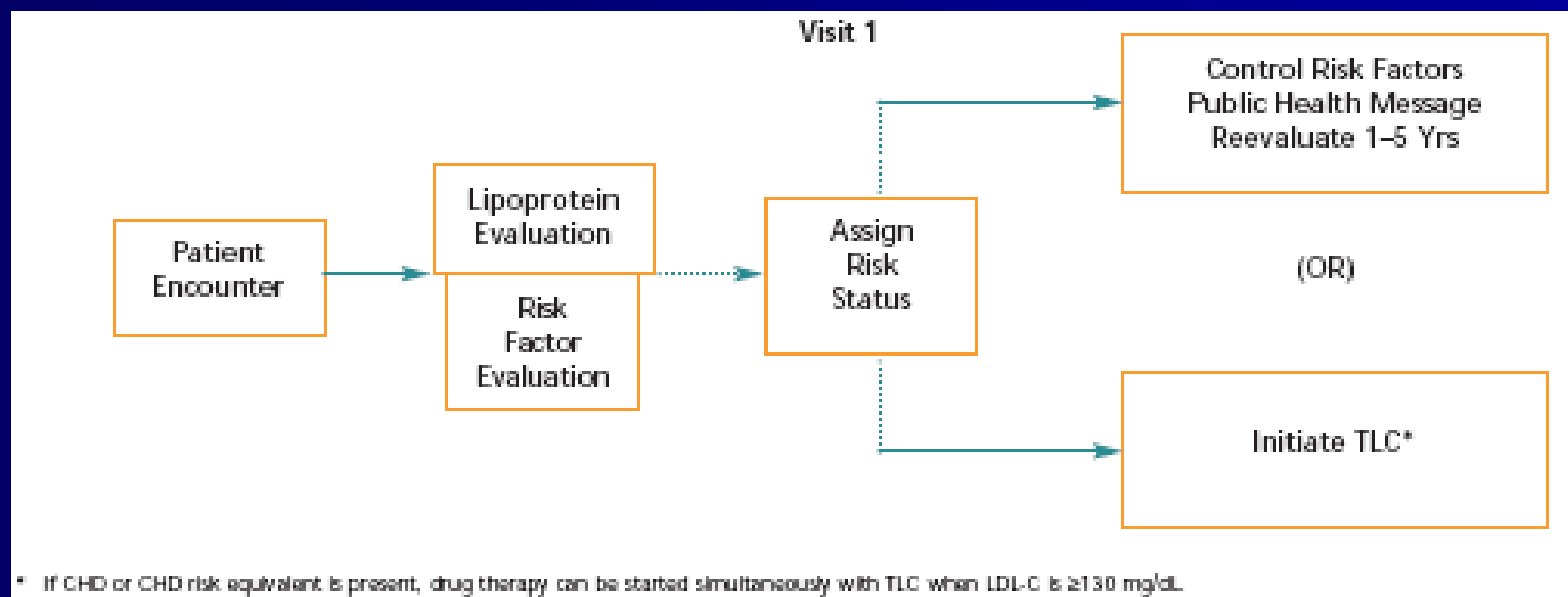
2 or more major risk factors

< 130

0 to one major risk factor

< 160

Risk Assessment



Determining a Risk Category

1. Lipoprotein evaluation
2. Risk factor evaluation
 - “The intensity of LDL-lowering therapy should be adjusted to the individual’s absolute risk for CHD”
3. Assign a risk status

Lipoprotein evaluation

■ USPSTF

- (2001) Routinely screen men > 35 and women > 45 for lipid disorders (younger men and women if there are risk factors).
- (2007) Update in progress.

■ ATP-III

- All adults aged ≥ 20 should have a fasting lipoprotein profile every 5 years.

In 2005-2006, 65% of men and 70% of women had been screened within past 5 years - CDC/NCHS, National Health and Nutrition Examination Surveys, 1999-2006.

Lipoprotein evaluation

- ATP-III recommends a complete, fasting lipoprotein profile as the preferred initial test
- If nonfasting opportunity:
 - Only TC and HDL will be of use.
 - If $TC \geq 200$ or $HDL < 40$, obtain fasting profile.
- Repeat every 5 years, or more often if multiple risk factors

Lipoprotein evaluation

- ATP III supports ruling out secondary causes of dyslipidemia in persons presenting with elevated LDL:
 - Diabetes
 - Hypothyroidism
 - Obstructive liver disease
 - Chronic renal failure
 - Medications (progestins, anabolic steroids & corticosteroids)

Risk factor evaluation

1. Identify CHD or CHD risk equivalent
2. Count major risk factors
3. (What about other risk factors?)

Risk factor evaluation

CHD and CHD risk equivalent identification

- Coronary heart disease
- Atherosclerotic diseases
- Diabetes mellitus
- Multiple risk factors and 10-yr risk > 20%

LDL Goal of Therapy is < 100 mg/dl

Risk factor evaluation

Major risk factor counting

- Cigarette smoking
- Hypertension
- Low HDL cholesterol*
- Family history of premature CHD
- Age (men ≥ 45 , women ≥ 55)

*If HDL-C ≥ 60 mg/dl, subtract one risk factor from the count

Risk factor evaluation

Major risk factor counting

a. If 0-1 risk factor

LDL goal of therapy is < 160 mg/dl

b. If 2+ risk factors

Calculate the 10-year CHD risk

Risk factor evaluation

10-year CHD risk calculation

- Framingham Point Scores
 - Age, total cholesterol, HDL-C, systolic BP, treatment for hypertension and cigarette smoking
- 10-yr risk categories
 - >20% (CHD risk equivalent)
 - 10-20%
 - <10%

Men Estimate of 10-Year Risk for Men

(Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points				
	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	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

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

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

10-Year risk _____%

Women Estimate of 10-Year Risk for Women

(Framingham Point Scores)

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

Total Cholesterol	Points				
	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				
	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

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

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
< 9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30

10-Year risk _____%

Age

Total Cholesterol

Smoker?

HDL

Systolic BP



10-yr risk

From National Cholesterol Education Project, NHLBI, NIH

Risk factor evaluation

10-year CHD risk calculation

- Quick desk reference

<http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf>

- Online risk calculator

<http://hp2010.nhlbihin.net/atpiii/calculator.asp>

Assign a risk status

<u>Risk Category</u>	<u>LDL Goal</u> (mg/dl)
CHD & CHD risk equivalent (10-yr risk >20%)	< 100
Multiple (2+) risk factors (10-yr risk \leq 20%)	< 130
Zero to one risk factor	< 160

Other risk factors for CHD

- Modifiable:
 - Overweight/obesity
 - Physical inactivity
 - Atherogenic diet
- Emerging:
 - Homocysteine
 - Thrombogenic factors
 - Inflammatory markers
 - Impaired fasting glucose

•Targets for clinical interventions

**What about the metabolic
syndrome?**

Metabolic Syndrome

- Multiple, inter-related factors that raise the risk for CHD.
 - Abdominal obesity
 - Atherogenic dyslipidemia (low HDL + high TG)
 - Elevated blood pressure
 - Insulin resistance
 - Prothrombotic state
 - Proinflammatory state
- Increasing prevalence of the syndrome threatens to reverse the reduction in CHD risk.

Metabolic Syndrome

Any 3 of 5 criteria below

- Elevated waist circumference
 - ≥ 102 cm in men, ≥ 88 cm in women
- Elevated TG
 - ≥ 150 mg/dl or on treatment
- Reduced HDL
 - < 40 mg/dl in men, < 50 in women
- Elevated BP
 - ≥ 130 mm Hg systolic or ≥ 85 diastolic or on tx
- Elevated fasting glucose
 - ≥ 100 mg/dl or on tx

Metabolic Syndrome

- Does the presence of the metabolic syndrome change the LDL goal of therapy?

No, but

“ATP III places increased emphasis on the metabolic syndrome & on its favorable modification through changes in life habits....the full benefit of risk reduction will be lost if the metabolic syndrome is ignored.”

Treatments

Therapeutic Lifestyle Changes (TLC)

- A lifestyle approach to reducing risk for CHD:
 - Reduced intake of saturated fats and cholesterol
 - Dietary options for enhancing LDL lowering
 - Weight reduction
 - Increased regular physical activity

Therapeutic Lifestyle Changes

“TLC remains an essential modality in clinical management.”

“TLC has the potential to reduce CHD risk through several mechanisms beyond LDL lowering”

“Any person at high risk or moderately high risk of CHD is a candidate for TLC regardless of LDL level.”

Therapeutic Lifestyle Changes

Risk Category

LDL level (mg/dl)

to start TLC

CHD & CHD risk equivalent

≥ 100

(10-yr risk >20%)

Multiple (2+) risk factors

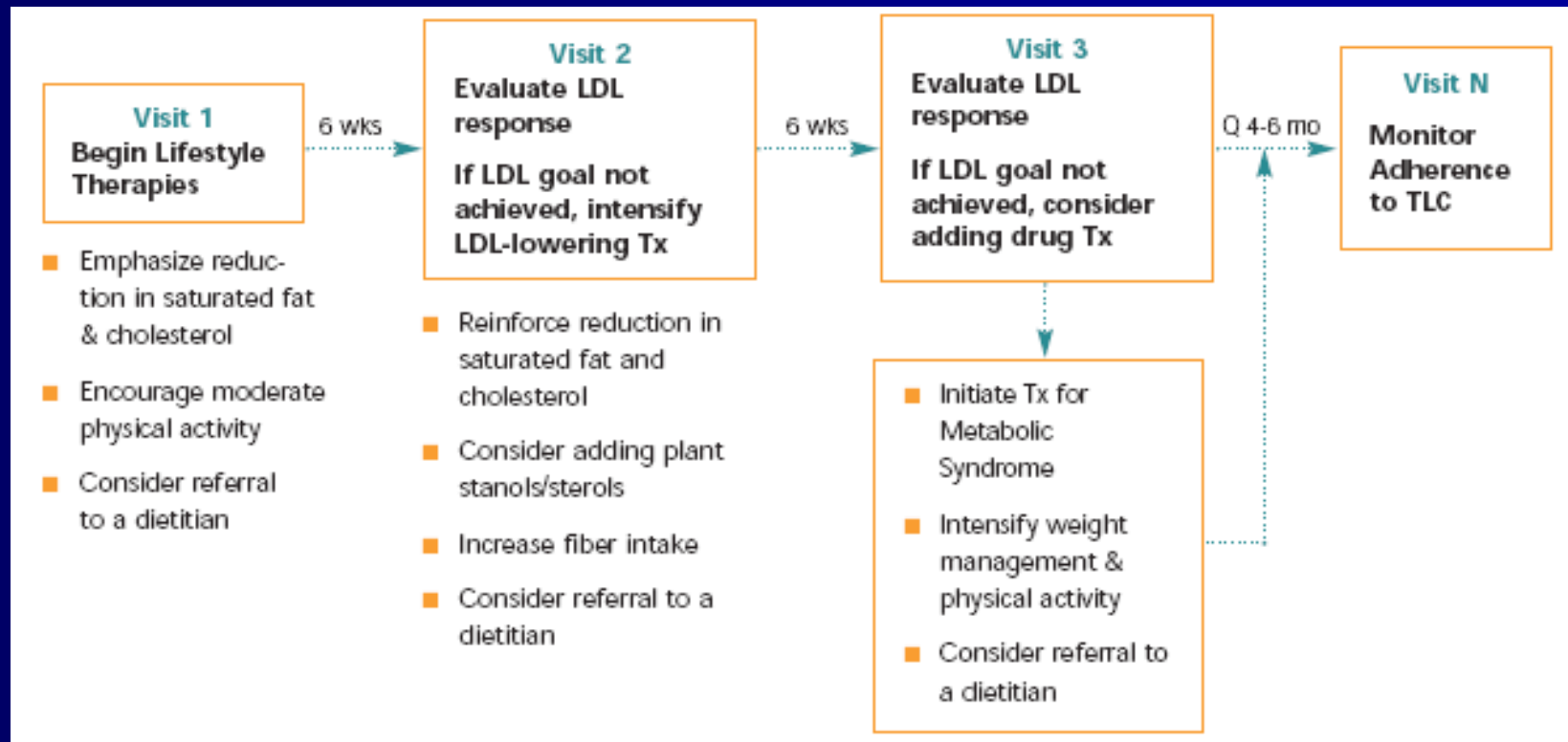
≥ 130

(10-yr risk ≤ 20%)

Zero to one risk factor

≥ 160

Therapeutic Lifestyle Changes



First Visit

- Emphasize a reduction of saturated fat & cholesterol:
 - CAGE questions
 - Cheese (and whole milk, 2% milk, ice cream, whole fat yogurt)
 - Animal fats (hamburger, ground meat, hot dogs, sausage, fried foods, fatty cuts of meat)
 - Got it away from home (eating or ordering out)
 - Eat (extra) high-fat commercial products
- Encourage moderate physical activity
- “Consider” referral to a dietician
- Follow up with patient in 6 weeks

Dietary Recommendations

- Total fat - 25-35% of total calories
 - Saturated fat < 7% of total calories
 - Reduce trans fats
- Carbohydrate – 50-60%
 - Simple sugars should be limited
- Cholesterol - < 200 mg/d
- Dietary fiber – 20-30 grams/day
- Protein – 15%
- Limit sodium intake to < 2400 mg/d

Physical Activity

■ Adults 18-65:

- Moderate intensity aerobic activity **30 minutes at least 5 days/week** OR vigorous activity **20 minutes at least 3 days/week**
 - Can accumulate in shorter sessions (10 min. bouts)
- Muscle strengthening a minimum of 2 days/week
 - 8-10 exercises on 2 nonconsecutive days

■ Adults > 65:

- Same, except adjust intensity based on fitness level
- Add in activities that increase flexibility & balance

Second Visit

- Evaluate LDL response
- If LDL goal not achieved:
 - Reinforce reduction in saturated fats and cholesterol
 - Consider plant stanols/sterols
 - Increase soluble fiber intake
 - If not already done, consider referral to a dietician
- Follow up with the patient in 6 weeks

Third Visit

- Evaluate LDL response
- If LDL goal achieved:
 - Continue TLC
- If LDL goal not achieved:
 - Consider LDL-lowering drug
 - If not already done, referral to a dietician
 - Initiate management of metabolic syndrome.

Drug therapies

- From ATP-III
 - Consider drug therapy simultaneously with TLC for CHD and CHD risk equivalents.
 - Consider adding drug to TLC after 3 months for other risk categories.

Drug therapies

Risk Category (mg/dl)

LDL level to start meds

CHD & CHD risk equivalent
(10-yr risk >20%)

≥ 130

Multiple (2+) risk factors

10-yr risk 10-20%

≥ 130

10-yr risk < 10%

≥ 160

Zero to one risk factor

≥ 190

Drug therapies

- Recommended in ATP-III:
 - HMG CoA reductase inhibitors (statins)
 - Bile Acid Sequestrants
 - Fibrates
 - Nicotinic Acid
- Updates on new therapies:
 - Cholesterol absorption inhibitors
 - Squalene synthase inhibitors
 - CETP inhibitors
 - Rx Omega-3 fatty acids

Statins – inhibit cholesterol synthesis

- Major use for lowering LDL
- Lipid effects:
 - LDL down by 18-55%
 - HDL up by 5-15%
 - TG down by 7-30%
- Contraindications:
 - Absolute: active or chronic liver disease
 - Relative: other meds (cyclosporine, gemfibrozil, macrolides, anti-fungals)

Statins

- Side effects minimal in clinical trials
 - Elevations in transaminase (AST,ALT)
 - Measure before starting therapy
 - Repeat 12 weeks after starting
 - Repeat annually or more frequently if indicated
 - Muscle soreness or tenderness
 - Measure CK before starting therapy
 - Evaluate symptoms 6-12 weeks after starting
 - Repeat CK if symptoms appear

Statins

- Increased risk of myopathy:
 - Older age
 - Presence of multisystem disease
 - Multiple medications
 - Alcohol abuse
 - Specific medications
 - Cyclosporine, erythromycin, clarithromycin, verapamil, amiodarone, protease inhibitors

Bile Acid Sequestrants – block reuptake of bile acid in gut

- Lipid effects:
 - LDL down by 15-30%
 - HDL up by 3-5%
 - No effect on TG
- Add to the LDL lowering effect of other drugs (12-16% decrease in combination with statin)
- Contraindications:
 - Absolute: Familial dyslipoproteinemia or TG > 400 mg/dl
 - Relative: TG > 200 mg/dl

Bile Acid Sequestrants

- Benefits:

- Lack systemic side effects
- Added LDL lowering benefit

- Challenges:

- GI upset (bloating, constipation, etc.)
- Interferes with other medication absorption
- Complicated administration with powder forms

Nicotinic Acid

- Lipid effects:
 - LDL down by 5-25%
 - HDL up by 15-35%
 - TG down by 20-50%
- Nicotinic Acid & Statin – TG down by 36%
- Contraindications:
 - Absolute: chronic liver disease, severe gout
 - Relative: hyperuricemia, high doses in Type 2 DM

Nicotinic Acid

- Most effective HDL raising medication
- Side effects:
 - Flushing & itching of the skin, GI distress, hyperuricemia, hepatotoxicity and glucose intolerance.
- Flushing may be minimized with use of extended release niacin.
- Glucose elevations in Type 2 diabetics:
 - ADA (2008): If HDL < 40 and LDL 100-129, recent studies have found modest glucose elevations with low doses of niacin (750-2,000 mg/day) that are amenable to diabetes medication adjustments.

Fibrates - PPAR alpha agonists

- Lipid effects:
 - LDL down by 5-20%
 - HDL up by 10-35%
 - TG down by 20-50%
- Contraindications:
 - Absolute: Severe liver or kidney insufficiency
- Side effects: gallstones, myositis, GI upset
- Early concern of higher non-CHD mortality have not been supported in more recent, long term studies

Fibrates

- Major uses:
 - Reduce risk for pancreatitis when TG high
 - Treat atherogenic dyslipidemia (low HDL + high TG)
- CHD outcomes in clinical trials:
 - Decreased rates of non-fatal MI
 - Recent clinical trials have not shown fibrates to decrease rates of fatal MI or total mortality

Newer drug therapies

Cholesterol absorption inhibitor - Ezetimibe

- Primary target is LDL lowering beyond statin therapy alone.
- Additional 20-25% reduction in LDL.
- Side effect profile similar to statins.
 - Addition of ezetimibe did not increase adverse events
- Recent ENHANCE trial results:
 - Simvastatin vs. Simvastatin/Ezetimibe
 - Despite lower LDL, no difference in atherosclerotic plaques seen on ultrasound.

Squalene synthase inhibition

- Lapaquistat acetate:
 - In phase III clinical trials, lapaquistat was shown to reduce LDL levels by 20%.
 - Minimal differences in adverse events between lapaquistat, placebo and lapaquistat with atorvastatin, except:
 - Higher rate of transaminase elevation with 100 mg dose of lapaquistat.
 - This dose has been removed from development.

CETP Inhibition

- CETP – Cholesterol Ester Transfer Protein
 - Primary lipid effect: Raise HDL
- Torcetrapib – CETP inhibitor
- Combination with atorvastatin resulted in 61% increase in HDL and 20% decrease in LDL.
- **But:**
 - Torcetrapib resulted in an increased risk of morbidity and mortality (NEJM, 2007)

Rx Omega-3 Fatty Acids

- Studies report a reduction in CHD mortality for post-infarction patients who increased their consumption of fish or took fish oil supplements.
- Japanese study of EPA (JELIS trial):
 - Used capsules with 300 mg purified EPA.
 - After 5 years, a 19% reduction in major coronary events was seen in EPA + statin group as compared with those taking statin alone.
 - (Lancet, 2007:369)

Drug Therapies

■ LDL

- Statins
- Bile Acid Sequestrants
- Fibrates

- Nicotinic acid
- Ezetimibe
- (Squalene synthase)

■ HDL

- Nicotinic acid
- Statins
- Fibrates

- Combination therapies with statins and niacin
- (~~CETP inhibitors~~)

■ TG

- Statins

- Nicotinic acid
- Combination statin/niacin

■ Non-HDL

- Same as LDL list
- (Rx Omega 3 FAs)

Secondary targets of therapy

Elevated Triglycerides

- $TG \geq 500$:
 - Very low fat diet
 - Weight management & physical activity
 - Fibrate or nicotinic acid
 - Return to LDL after $TG < 500$
- If TG 200-499, reach non-HDL goal:
 - Intensify therapy for LDL, or
 - Add nicotinic acid or fibrate

Metabolic syndrome

- Treat underlying causes:
 - Dietary changes
 - Intensify weight management
 - Increase physical activity
- Treat lipid and non-lipid risk factors:
 - Treat hypertension
 - Aspirin for CHD patients; consider prophylaxis in high risk patients
 - Treat elevated TG and/or low HDL

Low-HDL

- Clinical trials are lacking to show a reduction in incidence of CHD events through HDL elevation.
- Per ATP-III,
 - 1st reach LDL goal
 - Intensify weight management and physical activity
 - Address non-HDL if TG > 200
 - If TG < 200 and HDL is low, consider nicotinic acid or fibrate.

Promoting healthy lifestyles

- Smoking cessation
- LDL-lowering diet
- Weight control
- Regular physical activity

Thank you!