

Management of Hyperlipidemia

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Evaluation for Hyperlipidemia

- All men and women after the age of 20, should have a fasting lipoprotein profile obtained once every five years
- Requires a 12-15 hour fast:

$$\text{LDL-C} = \text{TC} - (\text{HDL-C} + \text{TG}/5)$$

(Friedewald formula)

- Should the triglyceride concentration exceed 399 mg/dL, a direct LDL assay is required for accurate LDL-C determination

JAMA 2001;285(19):2486-2497

Definition of Hyperlipidemia

- Clinical definition of hyperlipidemia is based on the blood concentrations of LDL-C (*not total cholesterol*) and triglyceride (in a fasting state)
- Hyperlipidemia categories:
 - hypercholesterolemia (elevated LDL-C; IIa)
 - hypertriglyceridemia (elevated TG and TC, normal LDL-C; IV)
 - combined hyperlipidemia (elevated TG and LDL-C; IIb)
 - mixed hyperlipidemia (elevated TC and TG due to IDL; III)
 - chylomicronemia (TG > 1000 mg/dL; I or V)
 - Lp(a) excess (Lp(a) > 30 mg/dL)

Causes of Hyperlipidemia

HYPERLIPIDEMIA

SECONDARY HYPERLIPIDEMIA

- Obesity
- Insulin resistance (type 2 diabetes)
- Insulin deficiency (type 1 diabetes)
- Hypothyroidism
- Nephrotic syndrome
- Renal insufficiency
- Dysglobulinemias
- Cholestasis (LpX)
- Primary biliary cirrhosis (LpX)
- Anorexia nervosa
- High saturated/trans fat diet
- Excess alcohol ingestion
- Beta blockers/thiazides

PRIMARY HYPERLIPIDEMIA

- Polygenic hypercholesterolemia
- Familial combined hyperlipidemia
- Familial hypercholesterolemia
- Sporadic hypertriglyceridemia
- Familial hypertriglyceridemia
- Lipoprotein lipase deficiency
- Apo C-2 deficiency
- Familial mixed hypertriglyceridemia
- Dysbetalipoproteinemia

LDL-C Categories Based on CHD Risk (NCEP ATP III Guidelines)

Risk Category:	LDL Goal* (mg/dl)	Therapeutic Option† (mg/dl)
CHD and CHD risk equivalents	< 100	< 70
Multiple (2+) risk factors	< 130	< 100
0 – 1 risk factor	< 160	

* JAMA 2001;285(19):2486-2497
 † Circulation 2004;110:227-239

Categorization of Serum Triglycerides

< 150	Normal
150 – 199	Borderline – High
200 – 499	High
≥ 500	Very High

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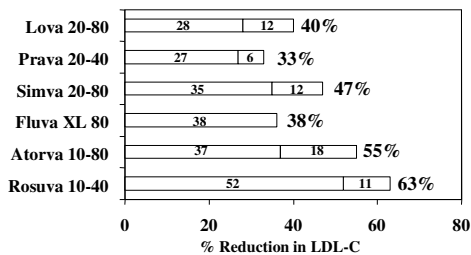
Pharmacotherapy for Hyperlipidemia

- HMG CoA reductase inhibitors (statins)
- Bile acid binding sequestrants (resins)
- Intestinal cholesterol absorption inhibitors (ICAI)
- Niacin
- Fibric acid derivatives
- Omega-3-acid ethyl esters

Pharmacotherapy for Hyperlipidemia

Classification of Hyperlipidemia	Drug Class(es)
Elevated LDL-C (IIa)	Statins, resins, ICAIs
Elevated TG and TC (IV)	Fibrates, niacin, omega-3-FAs
Elevated TG and LDL-C (IIb)	Statins, niacin, fibrates, ICAIs
IDL accumulation (III)	Fibrates, niacin
Chylomicronemia (I and V)	Fibrates, omega-3-FAs, niacin
Lp(a) excess	Niacin, oral estrogens

Mean Percent Reductions in LDL-C With Statins

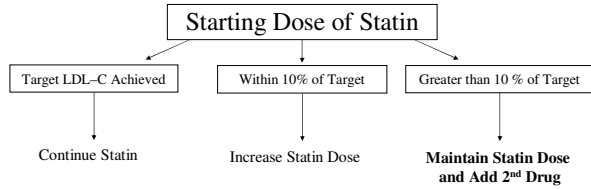


Colored Bars: Usual Starting Doses
 White Bars: Dose Titrations to Maximum Approved Doses

Illingworth, D.R. *Med Clin N Amer* 2000;84:23-42
 McKenney JM, et al. *Cur Med Res Opin* 2003;19:689-698

“10% Rule”

- Initiate starting dose of statin.
- Evaluate lipid profile and safety chemistry analytes at 6 to 8 weeks post-treatment.



“Second Drug” Options With Statin Therapy for LDL Reduction

Bile Acid Binding Resin (colesevelam, cholestyramine)

- Non-systemic
- 3.8 grams (6 tablets, qd) provides additional 20-25% reduction in LDL-C
- No requirement for increased frequency of safety laboratory assessment

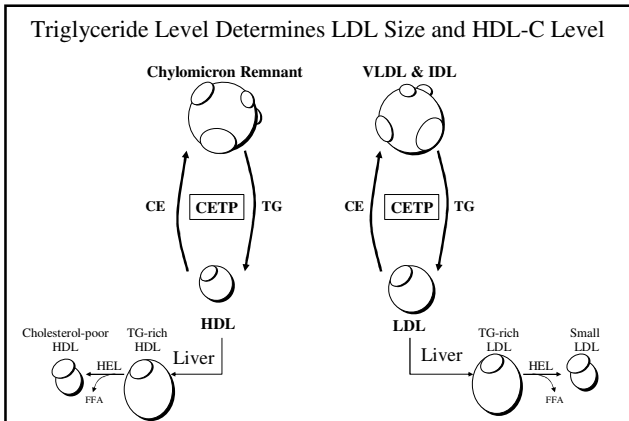
Nicotinic Acid (extended-release niacin)

- Reduces LDL-C and triglyceride
- Increases HDL-C (+25%)
- 1 gram provides additional 15% reduction in LDL-C
- Requires increased frequency of safety laboratory assessment (e.g., 3-4 times per year)
- Must be used with caution in patients with a history of diabetes or gout

Intestinal Cholesterol Absorption Inhibitors (ezetimibe)

- 10 mg dose reduces LDL-C by 20-25%
- No requirement for increased frequency of safety laboratory assessment

Hypertriglyceridemia



Apolipoprotein B-100

- The only protein component of LDL; one molecule of apo B-100 per LDL particle
- The different sizes of LDL are determined by the number of cholesteryl ester molecules

Large, buoyant LDL Small, dense LDL

Plasma LDL-C Level Inadequately Predicts ASCVD Risk in Hypertriglyceridemia

- A more accurate way to capture risk posed by LDL in hypertriglyceridemic subjects (≥ 200 mg/dL) is to measure apo B-100
- A recent ADA/ACC consensus statement suggests measuring and treating apo B-100 to at least 10% lower than the LDL-C goal in patients with elevated triglycerides

LDL-C Goal	Apo B-100 Goal	Non-HDL-C Goal
< 100 mg/dL	< 90 mg/dL	< 130 mg/dL

Brunzell JD et al. *Diabetes Care* 2008;31:811-822
Brunzell JD et al. *JACC* 2008;51:1512-1524

Pharmacological Treatment for Elevated Triglycerides

- Fibric acid derivatives (-50% to -70%)
 - gemfibrozil
 - fenofibrate
- Nicotinic acid (-30%)
- Omega-3-acid ethyl esters (-45%)
 - Lovaza (formerly Omacor)

Treatment of Moderately Elevated Triglycerides (≥ 150 -499mg/dL)

- Primary aim of therapy is to reach LDL (or apo B) goal
- Intensify weight management
- Increase physical activity
- Should triglycerides exceed 199mg/dL after the LDL (or apo B) goal is reached, set secondary goal for non-HDL-cholesterol (total – HDL) at 30mg/dL higher than LDL goal

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Combination Therapy Options for Mixed Hyperlipidemia

- Statin and fenofibrate or Lovaza
 - Highly effective
 - Statin dosages above starting dose (i.e., 10 or 20mgs) are generally not recommended
 - Assess safety chemistry analytes 3 to 4 times per year (LFTs, alk. phos., CK)
- Fibrate or Lovaza and either a resin or ezetimibe
 - Effective
 - No increased risk of side effects beyond the fibrate only (safety and efficacy labs: 2 times per year)
- Niacin and either a resin or ezetimibe
 - Modest effect on triglyceride reduction; effective for LDL-C reduction
 - No increased risk of side effects beyond niacin only (safety and efficacy labs: 2 times per year)

Treatment of Very High Triglycerides ($\geq 500\text{mg/dL}$)

- Lower triglycerides to prevent pancreatitis (fibrate, nicotinic acid or omega-3-FAs)
- Evaluate for an attempt to correct secondary causes
- If TGs are $> 1000\text{ mg/dL}$, reduce caloric from fat to $< 10\%$ of calories. Also,
 - Restrict refined carbohydrates
 - Reduce or eliminate alcohol intake
- When triglycerides are less than 400mg/dL , turn to LDL-lowering therapy

Pharmacotherapy for Hyperlipidemia

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HDL-C as a Target of Treatment?

HDL Controversy

- The disparity between the strong, independent, inverse correlation between HDL-C levels and risk of ASCVD observed in epidemiologic studies, and the weak effect on reducing this risk in clinical trials where HDL-C has been increased
- Lack of interventions (e.g., pharmacologic, hygienic) that raise HDL-C without having major effects on other lipid parameters

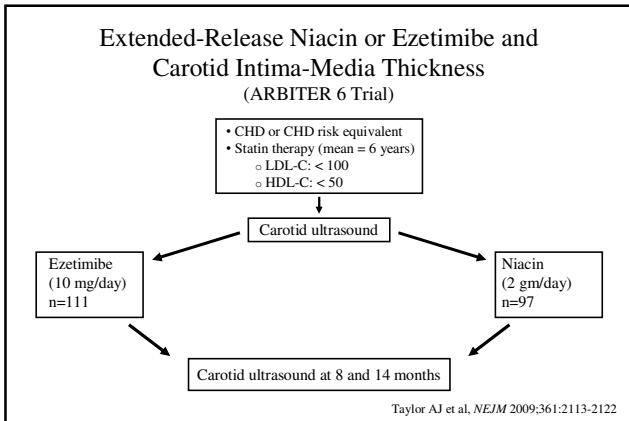
Brown WF *J Clin Lipidol* 2010;4:1

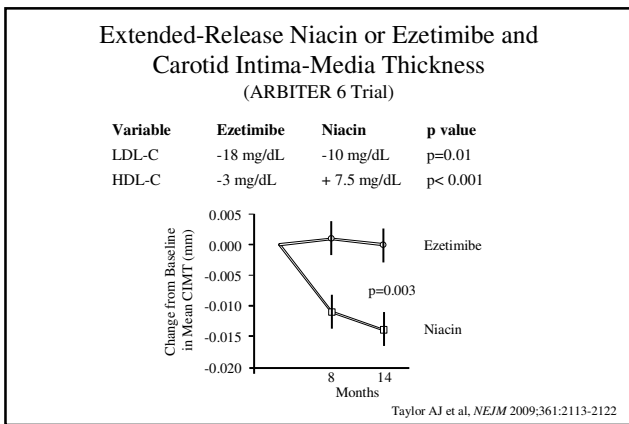
HDL Metabolism

High Density Lipoprotein Composition

- A heterogeneous mixture of lipoproteins differing in size and density, lipid and apolipoprotein composition, and function
- Classification:

Density ultracentrifugation	Electrophoresis
HDL ₂ : 1.063-1.125 g/mL	HDL _L HDL _{2a} HDL _{3a}
HDL ₃ : 1.125-1.210 g/mL	HDL _{2b} HDL _{3b}
	HDL _{3c}
Apolipoprotein composition	Vertical autoprofiler (VAP)
Lp A-I: A-II	HDL _L HDL ₂ HDL _{3L}
Lp A-I	HDL _{3D}
- Clinically, HDLs are measured as the fraction of cholesterol associated with all HDL particles; that is HDL-cholesterol





Association Between HDL-C and CVD Morbidity and Mortality: Systematic Review and Meta-regression Analysis

- Purpose: to determine whether a relationship exists between treatment-induced changes in HDL-C and CVD events (including death) in randomized, controlled clinical trials
- A total of 108 lipid-modifying clinical trials were included in the analysis which involved 146,890 participants in the intervention groups and 152,420 in the control groups

Briel, M et al, *BMJ* 2009;338:1-8

Association Between HDL-C and CVD Morbidity and Mortality:
Systematic Review and Meta-regression Analysis

- Statins (n=54)
- Fibrates (n=9)
- Resins (n=3)
- Niacin with a statin, fibrate or resin (n=6)
- Omega-3-FA (n=9)
- ACAT inhibitors (n=2)
- Probucol (n=2)
- TZDs (n=2)
- Hormones (n=5)
- Torcetrapib (n=2)
- Low-fat diets (n=5)

Briel, M et al, *BMJ* 2009;338:1-8

Association Between HDL-C and CVD Morbidity and Mortality:
Systematic Review and Meta-regression Analysis

• **Results:**

- Change in LDL-C was associated with the risk of CVD events in a multi-variate analysis adjusted for change in HDL-C and different drug classes. The risk ratio for CHD events was reduced by 7.1% ($p < 0.001$) per 10 mg/dL reduction in LDL-C
- No significant association between the change in HDL-C and the risk of CVD events was found in a multi-variate analysis after adjustment for changes in LDL-C and different drug classes

Briel, M et al, *BMJ* 2009;338:1-8

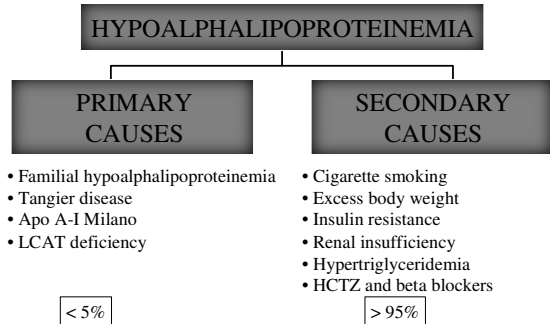
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• **Conclusion:**

- Available data indicate that simply increasing the level of circulating HDL-C does not reduce the risk of CVD events or all-cause mortality

Briel, M et al, *BMJ* 2009;338:1-8

Management of Hypoalphalipoproteinemia



Conclusions and Recommendations

- Determine the cause(s) of the low HDL-C
- Therapeutic lifestyle changes should be the first approach for elevating HDL-C
- Attempt to correct any of the secondary causes
- Pharmacologic approach: rather than targeting HDL-C consider lowering LDL-C to a greater degree
