Lipid Management

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CVD is the number one killer

- **Leading cause of death in men and women**
- **Hyperlipidemia is a major modifiable risk factor for CVD**
- **Discussion today will include recommendations from ATP III (2004 update), the AHA/ACC guidelines on primary and secondary prevention and the Expert Panel of Lipid specialists consensus statement on advanced lipoprotein testing, convened by the National Lipid Association**

Lipids - Definition

- Lipids are organic compounds (include fats, oils, sterols, triglycerides)
- Principal structure of living things (along with proteins and carbohydrates)
- Essential to the body's function
- Transport system evolved to allow delivery of lipids to the organs that need them

- LDL
  - Primary carriers of cholesterol
  - Provide it to the body
- HDL
  - Carries cholesterol back to the liver
- VLDL and chylomicrons - lipids that are triglyceride rich
- Non-HDL is *Total cholesterol – HDL*
- Non-HDL also reflects cholesterol that is atherogenic

Overnutrition

- With overnutrition, lipids can become harmful
- Lipids (in particular LDL and chylomicron remnants) become “stuck” to the subendothelium of the vasculature
- Forms a “fatty streak,” the first step in the development of atherosclerosis

Risk Assessment

- ATP III- fasting lipid profiles
- Step-wise approach

Step 1

- Identify patients with clinical atherosclerosis
  - Clinical coronary artery disease
  - Peripheral arterial disease
  - Symptomatic carotid artery disease
  - Abdominal aortic aneurysm

Step 2

- Determine the presence of major risk factors
  - Smoking
  - Hypertension
  - Low HDL
  - Age (men $\geq$ 45 years, women $\geq$ 55 years)
  - Family history of premature coronary artery disease (males $\leq$ 55 years, females $\leq$ 65)

Step 3

- Assess 10 year risk in patients without coronary artery disease or an equivalent
- Framingham score- three levels
  - > 20% = coronary equivalent
  - 10% - 20%
  - < 10%

Other Risk Assessments

- Reynolds Risk Score
  - Gender, age, family history, blood pressure, smoking, HDL, hs-CRP
- PROCAM
  - Gender, age, family history, blood pressure, glucose > 120, weight, height and hypertension meds

Step 4

- **Identify metabolic syndrome**
  - **Abdominal obesity**
  - **Elevated triglycerides**
  - **Low HDL**
  - **Elevated blood pressure**
  - **Elevated fasting glucose**

Step 5: NCEP ATP III - LDL-C goals

Risk Category	Risk Factors	10 year CHD-risk	LDL-C Goal
Very High-Risk	CHD or CHD RE + RF	>20%	<70mg/dL
High-Risk	CHD or CHD RE	>20%	<100mg/dL
Moderately-high risk*	2 + RF	10-20%	<100mg/dL
Moderate risk	2 + RF	<10%	<130mg/dL
Low Risk	0-1		<160mg/dL

Step 6: ADA/ACC 2008 Consensus Statement

	LDL	Apo B
Highest risk patients -known CHD -DM with an additional CV risk factor	< 70	< 80
High Risk patients -no known CHD or DM but 2 clinical risk factors - DM but no other major CV risk factors	< 100	< 90

CV risk factors: smoking, hypertension, family history of premature CHD

Prioritize targets

- **If TG <500, LDL is primary target**
- **If TG >500, TG is primary target**
- **When LDL is at goal and TG 200-500, non-HDL is target**

Therapeutic Lifestyle Change

- Reduce saturated fat and cholesterol intake
- Plant stanols/sterols (2 g/d), increased viscous (soluble) fiber intake (10-25 g/d)
- Weight reduction
- Physical activity

Pharmacologic Therapy

- Statins
- Bile Acid Sequestrants
- Niacin
- Fibric Acid Derivatives
- Ezetimibe
- Omega-3 Fatty Acids

Statins

- **Mechanism of action**
  - **Inhibits B-hydroxy beta methyl glutaryl Co A reductase**
  - **Therefore decreases production of cholesterol**
  - **Leads to upregulation in LDL receptors that take up LDL out of the blood**
- **Statin effects**
  - **LDL levels ↓30-60%, TG levels ↓~20%, HDL levels ↑5-15%**
- **Side effects: Myopathy, increased liver enzymes**

Relative LDL Lowering of Statins

Atorva	Fluva	Pitava	Lova	Prava	Rosuva	Vytorin	Simva	% LDL decrease
--	40 mg	1 mg	20 mg	20 mg	--	--	10 mg	30%
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	--	--	20 mg	38%
20 mg	--	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%
40 mg	--	--	--	--	10 mg	10/20 mg	80 mg	47%
80 mg					20 mg	10/40 mg		55%
					40 mg	10/80 mg		63%

Muscle and Statin Safety

- Baseline CK only for high risk pts
- Counsel pt to report any muscle symptoms
- Do not measure CK if asymptomatic
- Check CK in symptomatic pts
- Evaluate muscle symptoms or ↑ CK level for other causes

Liver and Statin Safety

- Check LFTs at baseline and as clinically indicated
- Evidence of liver injury
  - d/c statin, etiology should be sought/refer pt to gastroenterologist/hepatologist
- Isolated, asymptomatic ↑ LFTs
  - 1-3 X ULN, no need to d/c statin
  - > 3 X ULN, test should be repeated
- According to the Expert Liver Panel, pts with chronic liver disease, nonalcoholic fatty liver disease, or NASH may safely receive statin therapy.

FDA. FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. February 28, 2012. http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm.

Risk versus Benefit of Statins

- **Risks from fatal and non-fatal rhabdomyolysis are ~ 0.3 and 3 per 100,000 person years respectively**
- **Acute Liver Failure 0.5-1 per 100,000 person years (~ equal to background rate of liver failure in the general population)**
- **No evidence that statins cause:**
  - **Acute or chronic kidney damage**
  - **Peripheral neuropathy**
  - **Impairment of memory or cognition**

Secondary Prevention Statin Trials

Trial	Population	Results
MIRACL	3086 patients with ACS Given: Atorva 80	16% relative risk reduction in death, nonfatal acute MI, cardiac arrest, recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency hospitalization
4S	4444 men and women with prior MI Given: Simva 20	30% relative risk reduction in death, 42% reduction in coronary deaths, 37% reduction in revascularization procedures
CARE	4159 men and women with prior MI Given: Prava 40	CHD death and nonfatal MI reduced 24%; 26% reduction in CABG; 22% reduction in PTCA

Heart Protection Study	20,536 men and women with MI or other forms of CHD, DM, or treated HTN. Entry cholesterol > 135 Given: Simva 40	Simva group had reduction in all-cause, CHD deaths, and all vascular mortality.
LIPID	9014 men and women with known CHD Intervention: Prava 40	CHD death reduced 24%, total mortality reduced 23%, fatal CHD and nonfatal MI reduced 23%
PROVE-IT TIMI 22	4162 patients with ACS Intervention: Prava 40 vs. Atorva 80	16% reduction in death from any cause, MI, unstable angina, revascularization, and stroke
TNT	10,001 patients with stable CHD Intervention: Atorva 10 vs. Atorva 80	Significant reductions in primary endpoint of major cardiovascular event (defined as death from CHD, nonfatal non procedure related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke)

Primary Prevention Statin Trials

Trial	Population	Results
WOSCOPS	High-risk men Intervention: Prava 80	31% reduction in fatal and nonfatal MI; 32% reduction from all CV causes; 22% reduction in all-cause mortality
AFCAPS/TexCAPS	6605 men and women Intervention: Lovastatin 20 to 40	36% reduction in first coronary event; 26% reduction in fatal and nonfatal MI; 33% reduction in revascularization (CABG, PTCA)
CARDS	2838 Type 2 diabetic patients without known CHD Intervention: Atorva 10	Cardiovascular events were reduced by 37%

ASCOT-LLA	10, 305 increased risk patients Intervention: Atorva 10	34% reduction in nonfatal MI and fatal CHD 21% reduction in total cardiovascular events 27% reduction in fatal and nonfatal stroke
JUPITER	17, 802 men and women with LDL < 130 and CRP > 2 Intervention: Rosuva 20	Primary endpoint of a first major CV event reduced by 44% Mortality reduced by 20%.

Bile acid sequestrants

- **Colesevelam, cholestyramine, and colestipol**
- **Decrease LDL 15-30%**
- **Raise HDL 3-5%**
- **No change or increase in TG**
- **Side effects: GI distress, constipation, decreased absorption of other drugs**
- **Contraindicated in hypertriglyceridemia**

Nicotinic acid

- Decrease LDL 5-25%
- Raise HDL 15-35%
- Decrease TG by 20-25%
- Side effects- Flushing, hyperglycemia, hepatoxicity

Fibric acids

- Decrease LDL 5-20% (may increase LDL in patients with high TG)
- Raise HDL 10-20%
- Decrease TG 20-50%
- Side effects: GI distress

Ezetimibe

- Cholesterol absorption inhibitor
- Decreases LDL by 18%
- Increases HDL by 1%
- Decreases TG by 2%
- Additive to statins

Omega-3 Fatty Acids

- Mechanism of Action
  - Slows the release of TG rich VLDL into plasma
  - Accelerates clearance of TG rich lipoproteins via enhanced lipolysis
- Effects
  - 2000-4000mg of EPA + DHA , TG ↓17-47% (45% if TG >500)
  - Most OTC 1-g fish oil contain 300mg to 500mg of EPA + DHA
- Side effects
  - GI (burping/belching, diarrhea), fishy after taste
  - ↑ALT and LDL-C
  - Monitor BS
  - Mildly inhibit platelet fxn at high doses

Outcome Data on Non-statins

Drug	Results
Cholestyramine	• Effective in primary prevention (Lipid Research Clinics 1984) and secondary prevention in men (Watts 1992)
Colestipol	• Significantly reduces cardiovascular events compared to placebo (Insull 2006)
Ezetimibe	• No cardiac outcomes data and ezetimibe did not reduce regression of carotid intima-media thickness (surrogate marker) when added to a statin (Kastelein 2008, Taylor 2009)

Fenofibrate	• In type 2 diabetics, did not reduce primary outcome of fatal MI or CHD mortality. Improved secondary outcomes of non-fatal MI and coronary revascularization, a reduction in albuminuria, reduced laser treatments for retinopathy (FIELD 2005) • Added on to statin, did not lower risk of non-fatal MI, non-fatal stroke, or CV death, more than statin alone in patients with type 2 diabetes at high risk for CV disease. May be a subgroup (high TG, low HDL) that benefits (ACCORD 2010)
Gemfibrozil	• Effective in primary prevention in men (Helsinki Heart Study 1987) and in secondary prevention in men with low HDL (VA-HIT 1999)

Niacin	• Effective in secondary prevention (Coronary Drug Project 1975) • Niacin and simvastatin decreased atherosclerosis, coronary death, MI, stroke, or revascularization (HATS 2001) • Added on to statin, niacin decreased CIMT (ARBITER-2 2004, ARBITER-6 HALTS 2009) • In patients with stable CVD and LDL < 70, no benefit to addition of niacin to statin therapy (AIM-HIGH 2011)
Omega-3 fatty acids	• Effective in secondary prevention (GISSI-Prevenzione 2002); however, recent meta-analysis did not show that omega-3 fatty acids reduce cardiovascular events or mortality (Rizos 2012)

Future Directions

- **PCSK9 inhibitors**
- **PCSK9 enzyme that degrades the LDL receptor, raising serum LDL levels.**
- **If PCSK9 is inhibited, LDL levels fall.**
- **Dramatic drops in LDL in Phase II trials**
- **Phase III trials underway**

Conclusions

- Hyperlipidemia is a major modifiable risk factor
- Risk assessment
- Cholesterol targets
- Pharmacologic therapy

Lipid Cases

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Patient Case Outline

- **Case #1**
  - **High TG**
  - **Drug Interactions**
  - **Statin Adverse Effects**
- **Case #2 – Intermediate Risk**

Patient Case #1

- **55 yo male**
- **PMH: HTN, newly diagnosed DM**
- **FH/SH/ROS: Non contributory**
- **Labs:**

Component	11/15/2011
CHOLESTEROL	280
TRIGLYCERIDES	567 (H)
HDL CHOLESTEROL	28 (L)
LDL CHOLESTEROL	----
NON-HDL CHOLESTEROL	182
GLUCOSE	135
HbA1c	7.3

Patient Case #1

- Nutrition Assessment reveals
  - No breakfast
  - Sweet tea and fruit throughout the day
  - Few crackers, pop, for lunch
  - Large dinner, including white meat, large portion of white pasta/rice/bread/potatoes

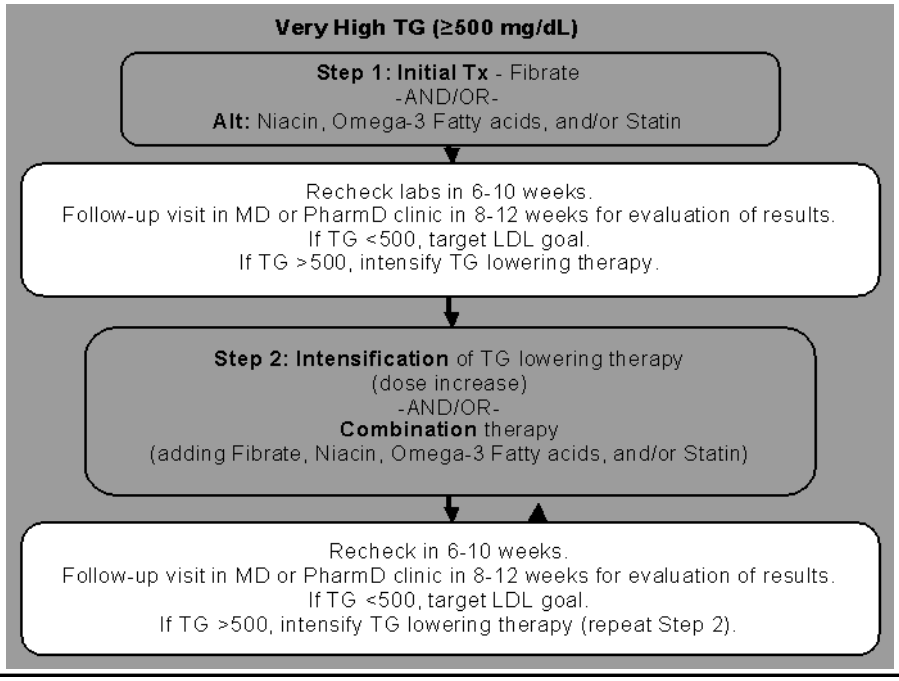
Patient Case #1

- Step 1: Define Risk
  - Diabetes
  - Metabolic Syndrome
- Step 2: Prioritize goals

Patient Case #1

- **Step 3: Treatment Considerations**
  - **Secondary causes of dyslipidemia**
    - **Impaired Fasting Glucose**
    - **Hypothyroidism**
  - **Therapeutic Lifestyle Changes**
  - **Medication Considerations**

Patient Case #1



Patient Case #1

- **Discuss TLC w/ small, quantifiable goals**
- **Started on gemfibrozil 600mg twice daily**
- **Returns to clinic in 8 wks with following labs:**

Component	1/15/2012	11/15/2011
CHOLESTEROL	240	280
TRIGLYCERIDES	350 (H)	567 (H)
HDL CHOLESTEROL	31 (L)	28 (L)
LDL CHOLESTEROL	139 (H)	----
NON-HDL CHOLESTEROL	209	182
GLUCOSE	132	135
HbA1c	7.1	7.3

Patient Case #1

- **Combination Therapy**
  - **Compelling Indications**
  - **Cost**
  - **Drug Interactions**

Statins and Drug Interactions

- **Risk of myopathy ↑ when statins are coadministered with medications that inhibit their metabolism**
- **Choosing a noninteracting medication or switching to a non-interacting statin may be the safest option**

Statins and Drug Interactions

- **Focus on Simvastatin**

Contraindicated with simvastatin:	Itraconazole , Ketoconazole , Posaconazole, Erythromycin , Clarithromycin Telithromycin , HIV protease inhibitors, Nefazodone, **Gemfibrozil,** Cyclosporine, Danazol
Do not exceed 10mg daily of simvastatin with:	Verapamil, Diltiazem
Do not exceed 20mg daily of simvastatin with:	Amiodarone, Alodipine (New), Ranolazine (New)
Limit use of simvastatin 80mg daily	Increased risk of muscle damage may exceed benefits, and safer alternatives are available

Patient Case #1

Component	1/15/2012	11/15/2011
CHOLESTEROL	240	280
TRIGLYCERIDES	350 (H)	567 (H)
HDL CHOLESTEROL	31 (L)	28 (L)
LDL CHOLESTEROL	139 (H)	----
NON-HDL CHOLESTEROL	209	182
GLUCOSE	132	135
HbA1c	7.1	7.3

- **Stop gemfibrozil**
- **Start fenofibrate 200mg daily with food**
- **Start atorvastatin 10mg every evening**

Patient Case #1

- **Returns to clinic in 8 wks, labs below**
- **Pt complains of constant myalgias bilaterally and difficulty standing up from the seated position**

Component	3/15/2012	1/15/2012	11/15/2011
CHOLESTEROL	199	240	280
TRIGLYCERIDES	249 (H)	350 (H)	567 (H)
HDL CHOLESTEROL	34 (L)	31 (L)	28 (L)
LDL CHOLESTEROL	115 (H)	139 (H)	----
NON-HDL	165	209	182
GLUCOSE	120	132	135
HbA1c	7.0	7.1	7.3

Patient Case #1

Statin-related muscle effects occur in the significant minority of pts, mostly myalgias with normal CK

- **Myalgia management**
  - **Re-challenge/Reduce statin**
  - **Try different statin**
    - **Ultra-low dose statin and/or Hydrophilic statin**
  - **Assess 25-OH Vitamin D**
    - **Consider replacement if low**
  - **Consider non-statin or combination**

Patient Case #1

- **Patient was switched to rosuvastatin and was able to titrate up to 20mg daily**
- **Most recent labs reveal:**

Component	7/15/12	3/15/12	1/15/12	11/15/11
CHOLESTEROL	178	199	240 (H)	280 (H)
TRIGLYCERIDES	230 (H)	249 (H)	350 (H)	567 (H)
HDL-C	37 (L)	34 (L)	31 (L)	28 (L)
LDL CHOLESTEROL	95	115 (H)	139 (H)	----
NON-HDL	141 (H)	165 (H)	209 (H)	252 (H)
GLUCOSE	140	120	132	135
HbA1c	7.3	7.0	7.1	7.3

Patient Case #1

- Non-HDL still not at target
- Consider add-on therapy
- Options & considerations of each
  - Lovaza
  - BAS
  - Zetia
  - Niaspan – yes!

Patient Case #1: Niaspan Education

- Describe as "prickly heat"
  - Head, neck, and shoulders
  - 15-30 min after ingestion of IR, 30-120 after ER, highly variable after SR
- Expect it
  - Reassure it is "normal" and "harmless"
  - Short-lived
- Prevent it
  - Concurrent ASA 81-325mg or ibuprofen 200, 30-60 min before niacin
  - Bedtime snack
    - Whole wheat crackers or skim milk
  - Avoid high-fat meals, alcohol, spicy food
- Rapidly abort flushing with NSAID
  - For example, ibuprofen 200 mg
  - Caution in pts w/ renal or active peptic disease

Patient Case #1

- **Niaspan was added and pt was able to titrate up to 1500mg daily**
- **Most recent labs reveal all at goal levels:**

Component	10/15/12	7/15/12	3/15/12	1/15/12	11/15/11
TC	154	178	199	240 (H)	280 (H)
TG	145	230 (H)	249 (H)	350 (H)	567 (H)
HDL-C	40	37 (L)	34 (L)	31 (L)	28 (L)
LDL-C	85	95	115 (H)	139 (H)	----
NON-HDL	114	141 (H)	165 (H)	209 (H)	252 (H)
GLUCOSE	112	125	120	132	135
HbA1c	6.9	7.0	7.0	7.1	7.3

Patient Case #2

- **51 yo male presents to clinic on no meds**
- **BP 137/85, waist 38'', sedentary, father with MI at age 53**
- **Laboratory values**

Component	11/15/2011
CHOLESTEROL	190
TRIGLYCERIDES	175
HDL CHOLESTEROL	40
LDL CHOLESTEROL	115
NON-HDL CHOLESTEROL	150
GLUCOSE	110

Patient Case #2

- **Step 1: Define Risk**
  - **Risk Factors that modify LDL-C goal = 2**
  - **Framingham 10-year risk score = 6%**
  - **Metabolic Syndrome**
  - **ATP III & Update recommend LDL-C target <130mg/dL and non-HDL target of <160mg/dL**

In pt with intermediate risk, esp with positive family history, are we doing enough??

Patient Case #2

Step 1: Define Risk (cont.)

	Initial Clinical Assessment					
	CRP	Lp-PLA$_2$	Apo B	LDL-P	Lp(a)	HDL or LDL Subfractions
Low risk (<5% 10-year CHD event risk)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Intermediate risk (5-20% 10-year CHD event risk)	Recommended for routine measurement	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended
CHD Equivalent	selected patients	selected patients	selected patients	selected patients	selected patients	
Family History	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommended
Recurrent Events	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommended

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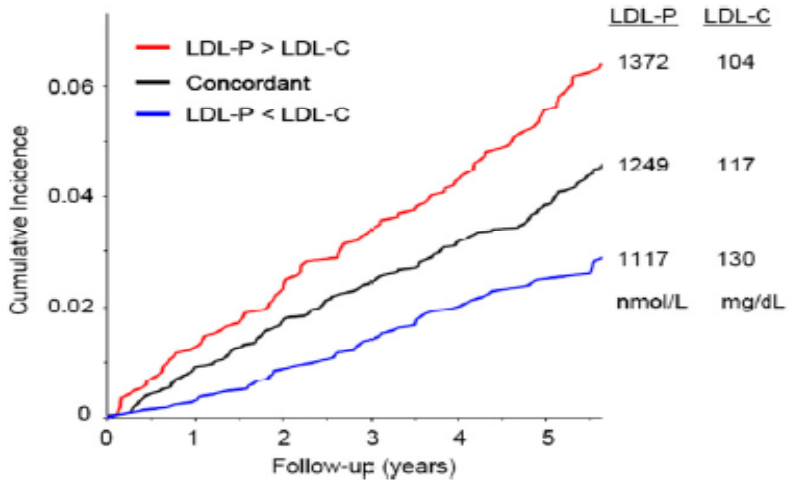
Patient Case #2

Step 1: Define risk (cont)

- **LDL-P or ApoB**
  - **Direct measure of atherogenic particles**
  - **Measures residual risk**
  - **Useful in positive family history**
  - **Useful in intermediate risk**
    - **Framingham 5-20%**

Patient Case #2

- **LDL-C & LDL-P discordance**



Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *J Clin Lipidol*. 2011;5:105–113.

Patient Case #2

When LDL-P is discordant, consideration should be given to intensifying LDL-C lowering therapy

- **Discordance expected in:**
  - **Hypertriglyceridemia**
  - **Abdominal obesity**
  - **Metabolic Syndrome**
  - **Insulin resistance**
  - **Low HDL**

Patient Case #2

- **For this patient, NMR reveals:**

Component	11/15/2011
CHOLESTEROL	190
TRIGLYCERIDES	175
HDL CHOLESTEROL	40
LDL CHOLESTEROL	115
NON-HDL CHOLESTEROL	150
GLUCOSE	110
Total LDL-P	**1527**

Patient Case #2

Step 1: Define risk (cont)

- **Intermediate Risk**
  - **Consider other advanced testing**
    - **Lp(a)**
    - **Crp-hs**
  - **Consider imaging**
    - **CIMT**
    - **Coronary Calcium Scoring**

Patient Case #2

- **Step 2: Prioritize / Set goals**
  - **At least LDL-C <130mg/dL**
  - **Consider LDL-C <100mg/dL**
  - **Consider target LDL-P/ApoB <1000/<80**

Patient Case #2

- **Step 3: Treatment Considerations**
  - **Medication**
    - **Statins, Zetia, and BAS tend to lower LDL-C more**
    - **Niacin and Fibrates tend to lower LDL-P more**
  - **Combination therapy may be necessary**

Patient Case #2

- **Start simvastatin 10mg po qhs**
- **Therapeutic Lifestyle Changes**
- **10 week follow-up laboratory values**

Component	2/15/2012	11/15/2011
CHOLESTEROL	167	190
TRIGLYCERIDES	148	175
HDL CHOLESTEROL	40	40
LDL CHOLESTEROL	97	115
NON-HDL CHOLESTEROL	127	150
GLUCOSE	105	110
Total LDL-P	1096	1527

Cardiovascular Risk Reduction and Lipid Clinic

- **Cardiovascular event risk reduction**
- **Medication intolerance**
- **Management of drug interactions**
- **Familial hypercholesterolemia**
- **Hypertriglyceridemia**

To make an appointment: 888-293-7677