

Management of Patients With Very High Cholesterol

ASFA

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Scotsdale, AZ

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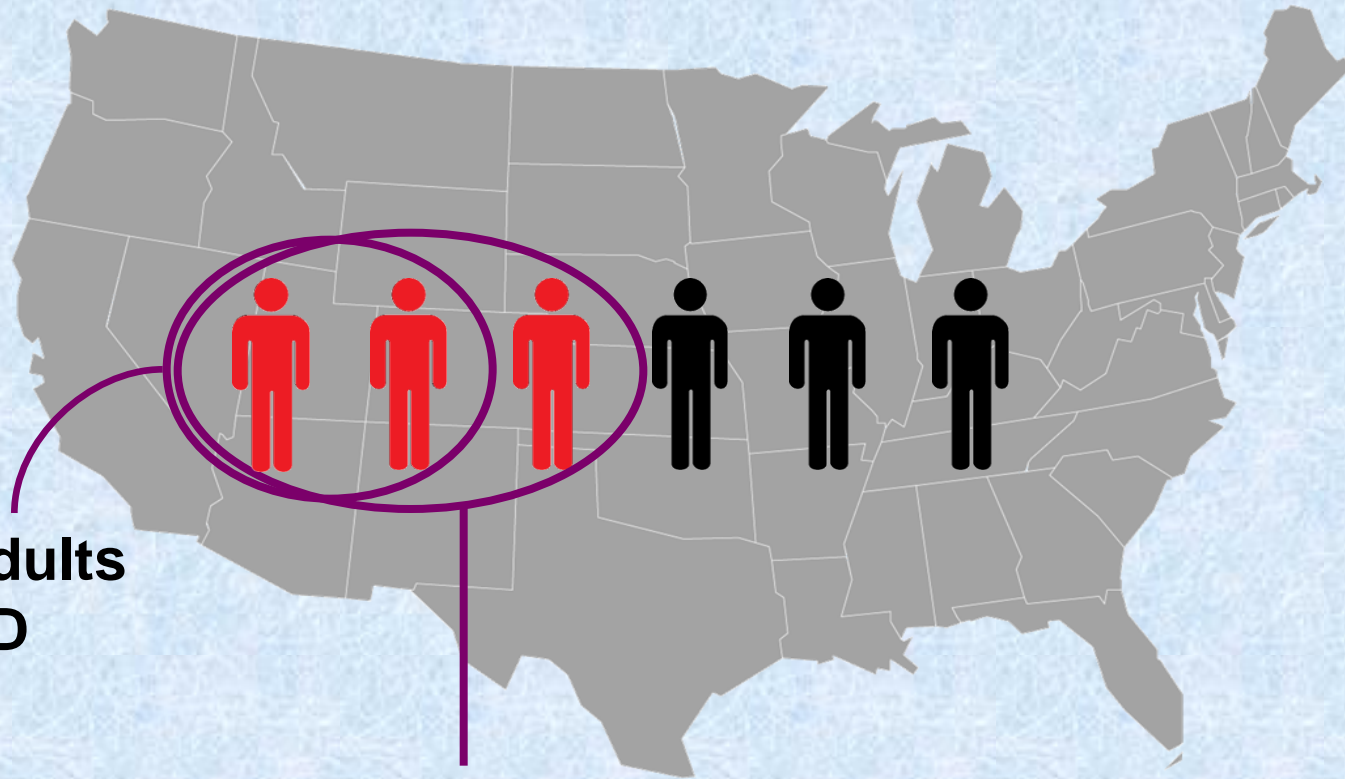
Dyslipidemia

- Dyslipidemia is a major risk factor for CHD, the leading cause of death in the United States¹
- The World Health Organization estimates that dyslipidemia is associated with >50% of global ischemic heart disease cases and >4 million deaths per year²

CHD = coronary heart disease.

1. Smith DG. *Am J Manag Care*. 2007;13:S68-S71. 2. World Health Organization. *The World Health Report*. 2002;4:47-97.

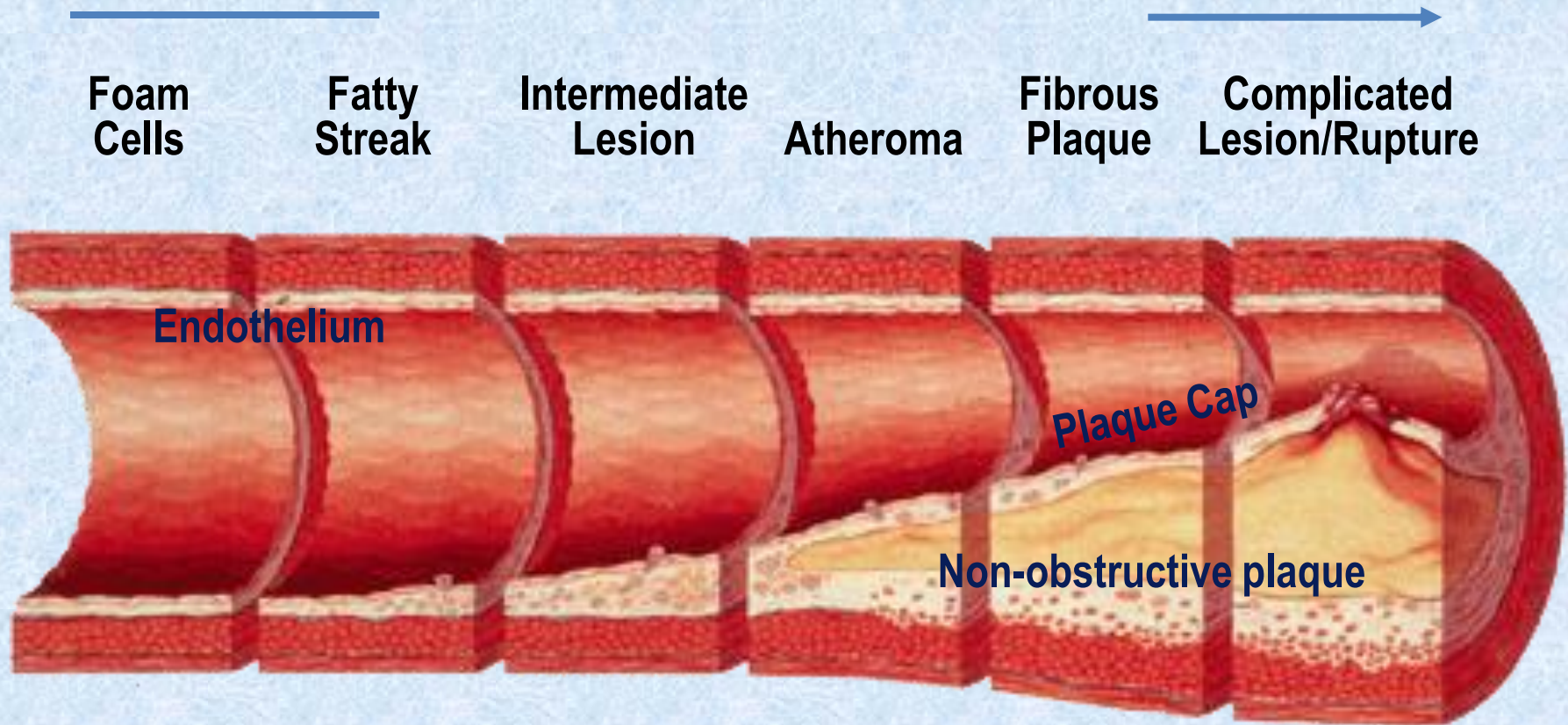
Current Estimates of the Impact of CVD and Dyslipidemia in the US



- **1 in 3 adults has CVD**

- **1 in 2 adults has total cholesterol ≥ 200 mg/dL**

Endothelial Dysfunction



From first decade	From third decade	From fourth decade	
Growth mainly by lipid accumulation		Smooth muscle & collagen	Thrombosis hematoma

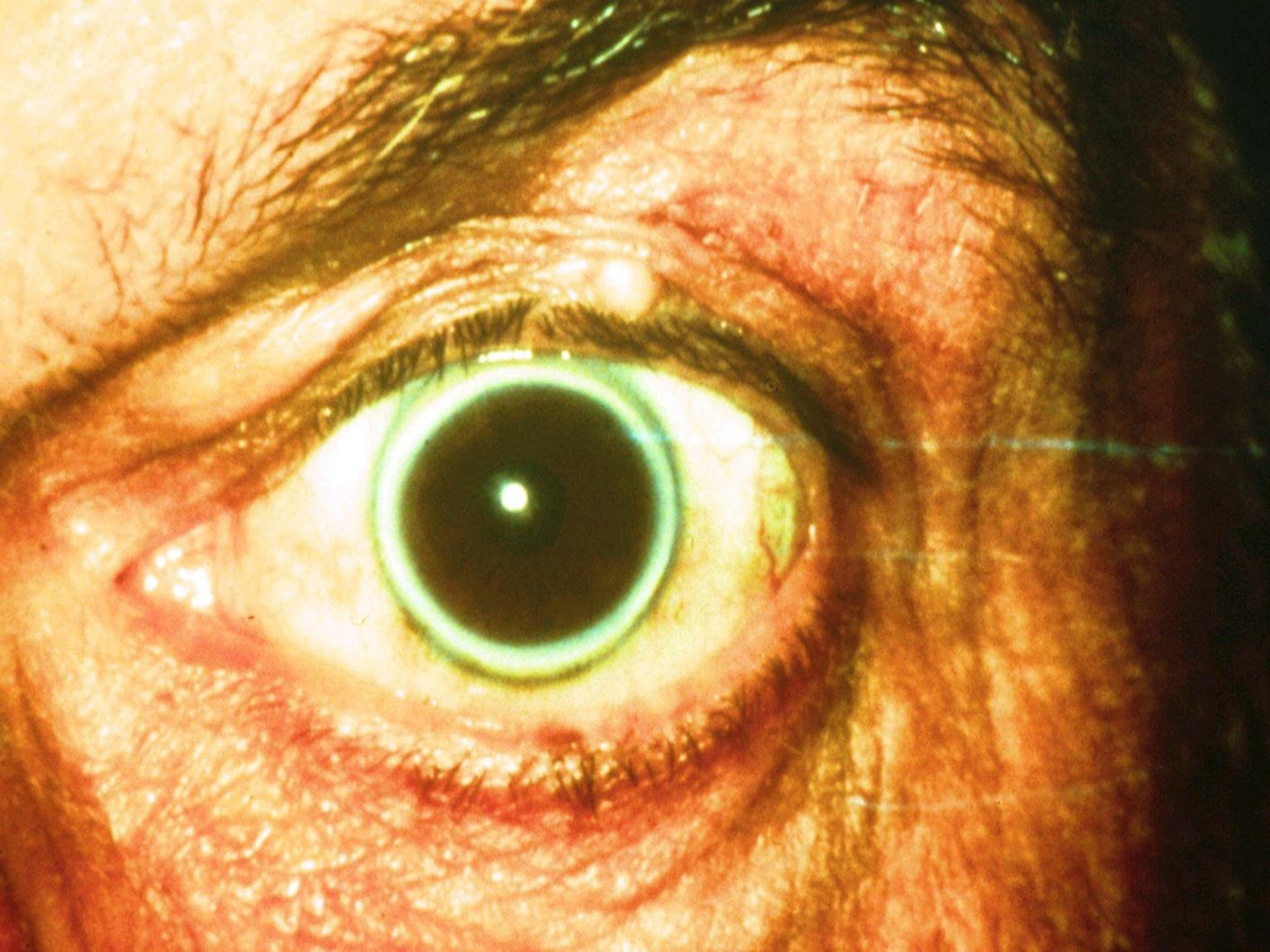
Sources of High Cholesterol

- Primary and Secondary Causes
 - Primary are related to genetics

Disorders Affecting LDLR Activity

- Familial Hypercholesterolemia: Deficient or defective LDL receptors (chromosome #19); impaired LDL removal from plasma
- Familial Defective Apo B 100: Mutant apo B 100 poorly recognized by LDL receptor – impaired LDL removal from plasma
- Autosomal recessive hypercholesterolemia: Very rare due to a mutation in the LDL receptor adaptor protein - markedly elevated LDL levels





Causes of Lipid Disorders

- Secondary may be related to medical disorders, and medications, that effect specific parameters of the lipid profile
 - Metabolic endocrine
 - Diabetes
 - Thyroid disease
 - Renal
 - Hepatic
 - drugs

Overview of Secondary Causes of Dyslipidemia

Secondary cause	High cholesterol High LDL-C	Low HDL-C
Dietary	Saturated fat caloric excess, anorexia	Low fat diet, high sugar diet
Drugs	Diuretics, cyclosporine, sirolimus glucocorticoids, rosiglitazone, fibrates,	Anabolic steroids, progestins, B-blockers, cigarettes, retinoic acid
Disorders of metabolism	Hypothyroidism pregnancy, DM	Obesity, type 2 DM
Diseases	Nephrotic syndrome, biliary obstruction (Lp-X) Type 2 DM	Chronic renal failure, dialysis, type 2 DM

Secondary Causes of Dyslipidemia

Secondary Cause	Triglyceride Excess mild – mod (high VLDL)	Severe Triglyceride Excess: Chylomicronemia syndrome
Dietary	Weight gain, alcohol, simple carbohydrates	Alcohol, fat plus genetic lipid disorder
Drugs	Retinoic acid, B-blockers, estrogens, glucocorticoids, sirolimus, protease inhibitors	Estrogens, tamoxifen, glucocorticoids plus genetic lipid disorder
Disorders of metabolism	Obesity, type 2 DM, pregnancy (3 rd trimester)	DM, hypothyroidism plus a genetic lipid disorder
Diseases	Chronic renal failure ± dialysis, nephrotic syndrome	Systemic Lupus, lymphoma (rare)

Refractory Patient with Known History of CAD

- JE 57 year old gentleman with family history notable for father's death at age 47 with first MI, all four of the paternal uncles died secondary to CAD by age 60. No premature CAD on maternal side
- Patient has been forced into early retirement related to his anginal symptoms and high anxiety state caused by CAD
- Medications at presentation included Cardizem 240, Imdur 30 mg., Ecotrin 325 mg., and prn sl nitro

- Weight 200 lbs, height 5'9", BMI = 30, B/P 140/108, HR 64
- Laboratory Values:
 - TG 188
 - TC 330
 - LDL 253
 - HDL 39
 - Glucose 98
 - Lp(a) 111 <30)
 - Uric Acid 5.3
 - ALT/AST 32/24
 - TSH within normal range
- Patient very reluctant to try other medications R/T “problems in the past” but understands his high risk

Triggers that may be influenced by/associated with statin intolerance

- Strenuous exercise
- Fasting
- Dehydration
- Extremes in temperature
- Sleep deprivation
- Disease states
 - Hypothyroidism
 - Muscular disorders
 - Neurological disorders
- Viral infection
- Certain medications (e.g., statins)

Cholesterol-Lowering Drug Therapy

- More than 102 million Americans have total cholesterol levels >200 mg/dL
 - 41 million with total cholesterol >240 mg/dL
- In 2005, 29.7 million people in U.S. on statin therapy
- By 2010, approximately 39 million taking statins

Consequences of Adverse Reactions to Statin Therapy

- Risk of statin therapy withdrawal from >2.3 million patients based on myalgias alone
- 30% (690,000) may develop earlier cardiovascular events secondary to withdrawal of statin therapy
 - Statins reduce cardiovascular endpoint events by 30%

QUESTIONS ? ? ?

- What is the patient's LDL target?
- What options are open for this patient?
- Should another trial of statin therapy be implemented?
- What medications were prescribed, how much, any combination therapy?
- What other class of anti-hyperlipidemia medication could be considered for this patient?
- What would be the expected outcome on the LDL cholesterol?

ADA/ACC Consensus Statement: Treatment Goals

	LDL-C (mg/dL)	Non- HDL-C (mg/dL)	Apo B (mg/dL)
Highest-risk patient – Known CVD – Diabetes plus ≥ 1 additional major CVD risk factor*	<70	<100	<80
High-risk patients – No diabetes or known CVD but ≥ 2 major CVD risk factors* – Diabetes but no other major CVD risk factors*	<100	<130	<90

*Major risk factors beyond dyslipidemia include smoking, hypertension, and family history or premature CHD.

Lipid Therapy Options for Dyslipidemia

Drug Class	LDL-C	HDL-C	TG	Key Limitations
Statins ¹	↓ 18%–55%	↑ 5%–15%	↓ 7%–30%	Myositis, ↑ LFTs
Bile acid sequestrants ¹	↓ 15%–30%	↑ 3%–5%	No effect or ↑	Upper/lower GI complaints (eg, constipation)
Nicotinic acid ¹	↓ 5%–25%	↑ 15%–35%	↓ 20%–50%	Flushing, hyperglycemia, hyperuricemia/gout
Fibric acid derivatives ¹	↓ 5%–20%	↑ 10%–20%	↓ 20%–50%	Upper GI complaints, myopathy
Cholesterol-absorption inhibitors ²	↓ 18%	↑ 1%	↓ 8%	↑ LFTs in combination with statins; lack of outcomes data
Omega-3 fatty acids ^{3*}	↑ 45%	↑ 9%	↓ 45%	↑ LDL-C; lack of outcomes data

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497. 2. Zetia® (ezetimibe) [package insert]. Merck/Schering-Plough Pharmaceuticals. North Wales, PA; 2008.
3. Lovaza™ (omega-3 acid ethyl esters) capsules [package insert]. Reliant Pharmaceuticals. Durham, NC; 2007.

*Based on use in patients with very high TG levels (≥500 mg/dL)

STATINS: Mechanism of Action

- Inhibit the rate-limiting enzyme HMG-CoA in cholesterol biosynthesis
- The associated decrease in synthesis stimulates production of LDL receptors
- Also possible increased removal of VLDL and IDL remnants which accounts for some decrease in triglycerides
- Other effects

Current Research theories with

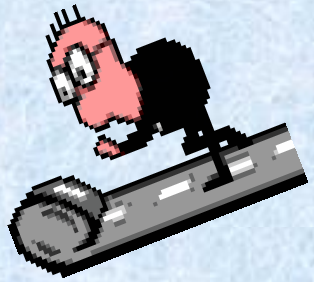
HMG Co-reductase inhibitors

- anti-inflammatory effects
- plaque stabilization
- decreased thrombus formation
- endothelial restoration

NEWSFLASH !!!!!

All Statins Are Not Created Equal

- How are they different ?
 - strength at starting dose
 - way the body metabolizes it
 - hydro/lipophilic



Taking a walk on the Cytochrome P450 Pathway



Role of CYP450 3A4 in Drug Metabolism

- Responsible for converting lipophilic substrates to water-soluble products to facilitate urinary excretion
- High potential for drug-drug interactions, as approximately 50% of drugs are metabolized by this enzyme
- Hydrophilic agents do not require clinically significant metabolism through this pathway

Dose Efficacy of Statin-Based Therapies for LDL-C Reduction (%)¹

Drug	Dose Efficacy in STELLAR ^{1*}			
	10 mg	20 mg	40 mg	80 mg
CRESTOR [®] (rosuvastatin calcium)	46	52	55	
Lipitor [®] (atorvastatin calcium)	37	43	48	51
Pravachol [®] (pravastatin sodium)	20	24	30	*
Zocor [®] (simvastatin)	28	35	39	46

- Vytorin[™] (ezetimibe 10 mg/simvastatin)* reduces LDL-C by 46% to 59%^{2*}
- Data derived from the prescribing information for Vytorin

Mechanisms of Statin Induced Muscle Injury ?

- 1. Reduced Sarcolemmal Cholesterol**
- 2. Reduced T-Tubule & Sarcoplasmic Reticulum Cholesterol** Draeger JPath 2006
- 3. Reduced Isoprenoids: Ubiquinone - Co-enzyme Q10**
- 4. Reduced Prenylation of GTP Binding Proteins - Ras, Rac and Rho - Cell Maintenance, Growth & Reduced Apoptosis** Coleman Cell Death Differ 2002
- 5. Changes in Fat Metabolism**
(Phillips P Atherosclerosis 2005)
- 6. Increased Muscle Cholesterol & ? Plant Sterol 2nd to LDL Receptor Activity** (Paiva Clin Pharmacol Ther 2005)
- 7. Failure to Appropriately Repair Damaged Muscle**
(Urso Thompson ATVB 2005)
- 8. Vitamin D Deficiency**
- 9. Inflammation (Inflammatory Myopathy)**

Plan

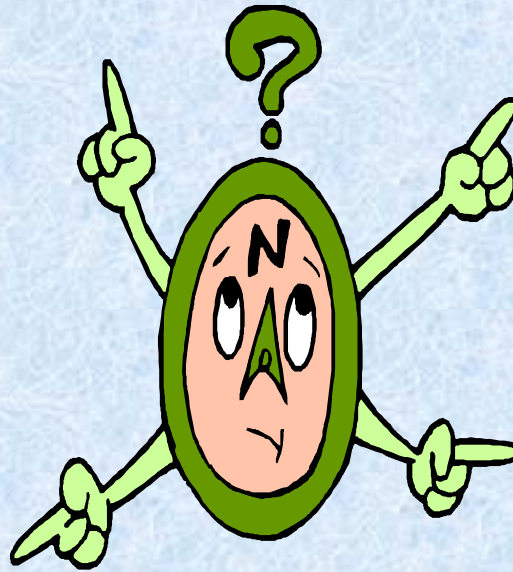
- Referral to Lipid Specialist – Initial Consultation
 - Review of current health history
 - Review of all current medications
 - Review of previous treatment plans
 - Issues with statin therapy evaluated
 - Muscle ache and pain
 - Elevations in liver transaminases
 - CPK elevated but $< 3 \times \text{UL}$

The Plan

- Options for reducing cholesterol
 - Re–challenge treatment with statin therapy
 - Unable to tolerate statin therapy even in very low dose
 - Add Niacin therapy
 - Had several GI issues and developed issue with gout
 - Add BAS
 - Had GI issues similar to that when taking Niacin therapy
 - Add Absorption Inhibitor
 - Was able to tolerate and achieve about a 20% of LDL

Exercise
And
Diet

LDL Apheresis



Medication

LDL Apheresis

- LDL apheresis is an underutilized (<1 % in the United States who would benefit) and approved modality for removing ApoB containing lipoproteins (LDL, Lp(a), VLDL) from the blood
- Treatment is recommended for patients with severe Homozygous Familial Hypercholesterolemia, those with Severe Heterozygous Familial Hypercholesterolemia, or those who are not able to tolerate traditional lipid lowering medication regimens.

LDL Apheresis

- The process involves separation of the patient's plasma, followed by selective removal of apoB containing atherogenic lipoproteins. After separation, the blood is pumped into one of the two LDL adsorption columns.
- ApoB containing lipoproteins are then selectively removed and flow into the waste line while the remaining plasma is returned back to the patient without significant loss of essential plasma components such as HDL-C and albumin.

LDL APHERESIS SYSTEM

<u>Lipid/Lipoprotein</u>	<u>Acute Reduction (%)</u>
Total Cholesterol	61 - 71
LDL-C	73 - 83
HDL-C	3 - 14
Lp(a)	53 - 76
Triglycerides	47 - 68

LDL Apheresis

Treatment Frequency

- Once every 2 weeks

Plasma Volume Treated

- 4 - 5 liters

Heparin Dosage

- Priming, loading and continuous dose
-

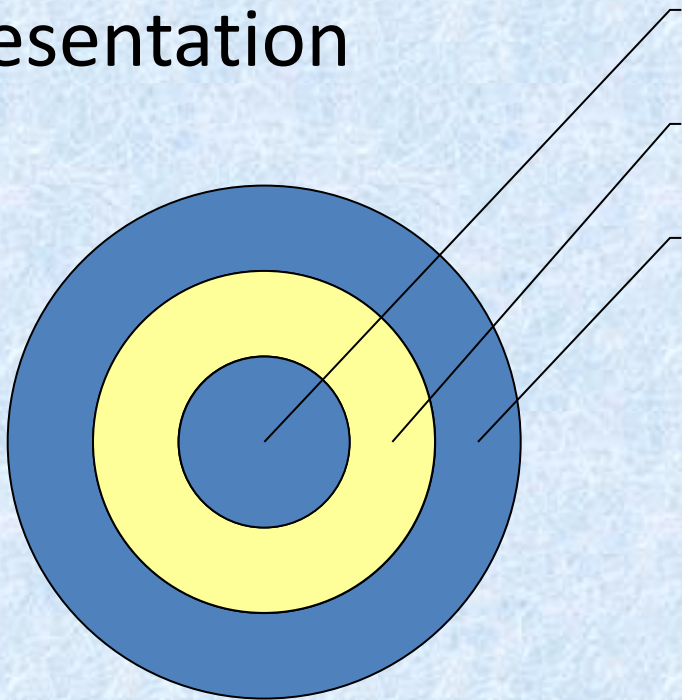
LDL Apheresis

PATIENT REACTIONS
(During Clinical Study)

(74 Patients 4,936 Treatments)

Events	Episodes	Percentage
Hypotension	41	0.8%
Nausea/vomiting	27	0.5%
Flushing	20	0.4%
Angina	10	0.2%
Fainting	9	0.2%

- Patient met criteria for procedure and was started a about a month after initial presentation



- Pre treatment lipids:
- TG 143, TC 287, LDL 212, HDL 46
- Post treatment lipids:
- TG 48, TC 107, LDL 50, HDL 47

Pre - treatment Values

TG 90, TC 275, LDL 209,
HDL 40

Post - treatment Values

TG 47, TC 106, LDL 53, 39

After 1 year

TG 91, TC 225,
LDL 170, HDL 42

TG 49, TC 110,
LDL 62, HDL 38

After 2 years

TG 104, TC 251,
LDL 195, HDL 44

TG 74, TC 115,
LDL 55, HDL 39

- Initially patient reported:
 - Poor quality of life with little hope for the future related to inability to tolerate medications for his cholesterol
 - Had substantial anginal symptoms with need for frequent stress tests/caths and further revascularization

- After the first year of treatment patient reported:
- Approx. a 50 % increase in ability to walk and participate in social events
- Approx. a 60 % reduction in anginal symptoms
- Increased hope for the future



Case 2

Patient with known CAD and refractory to traditional treatment

Ms. S is a 72 year old women with history of markedly elevated cholesterol, Referred by her local cardiologist for evaluation and treatment recommendations for her refractory hyperlipidemia. Total cholesterol levels off treatment 500-600 range

PMH:

CAD – angioplasties 1990, angina approximately 1 time weekly with exertion, HTN, Stroke, Syncope, Impaired fasting glucose, GERD, Obesity, OA, PAD, and Metabolic Syndrome

- Social History:
 - Married homemaker, 6 children
 - Non smoker
 - No ETOH
 - Exercises generally 3 Xs a week walking for 30 minutes – has been difficult with “leg pain” in the past
- Family History:
 - Mother died from, breast cancer in her 40’s, but there is history of extensive heart disease in her Mother’s siblings
 - Father died from CAD at 76

- Medications at presentation
 - Niacin (Niaspan) 2 Gm.
 - Lisinopril 5 mg.
 - Metoprolol 25 mg daily
 - MVI – one daily
 - Omeprazole 20 mg daily
 - Clopidrogrel 75 mg
- Past Experience with antihyperlipidemic medications
 - Lovastatin, Atorvastatin and Gemfibrozil resulted in myositis
 - Able to tolerate Simvastatin for a number of years but did not have adequate LDL lowering with a 40 mg dose, (LDL 190-200)

Endogenous Risk Factors for ADRs Associated with Statins

- Advanced age (>80 yrs)
- Small body frame & fragility
- Female sex
- Multisystem disease (e.g., renal function impairment, hypothyroidism, diabetes)
- History of metabolic muscle disease
- Medications metabolized through P-450 3A4

- Physical Exam
 - Height 4'11" Weight 179, BMI 36, BP 122/70, HR 78
 - Head and neck: + bilateral arcus cornea without xanthelasma or carotid bruits
 - COR: normal first and second sounds, negative murmurs
 - Abdomen: soft, non-tender, neg. bruit, organomegaly, masses
 - Peripheral pulses were 1+, no peripheral edema
 - + bilateral achilles tendon xanthomas
- Labs:
 - TG 269
 - TC 461
 - HDL 58
 - LDL 349
 - Glucose 113
 - ALT - WNL
 - AST - WNL
 - Creatinine: 0.5
 - TSH - WNL
- ECG: sinus rhythm, otherwise normal study

Diagnosis & Treatment Plan

- Lipid Diagnosis:
 - Severe Heterozygous Familial Hypercholesterolemia
 - Super-imposed hypertriglyceridemia
- Treatment Plan:
 - 6 month trial of combination lipid lowering medication and TLC
 - Start Simvastatin 40 mg continue prescription Niacin at 2 Gm and then add Colesevelam after first labs to evaluate tolerability to see if adequate LDL level can be obtained
 - Meet with Registered Dietician – focus on weight reduction, recommendations for reduction of TG, glucose
 - Discuss Potential for Implementation of LDL Apheresis
 - Continue with aerobic exercise program
 - Blood work in 6 weeks, Full lipid panel, CMP, TSH, Hema1c
 - Contact patient with results and have follow up appointment 4 months

First Follow up appointment

- 4 month appointment
- Changes in status: continues with anginal symptoms unchanged with intensity or frequency
- Current Meds: Simvastatin 80 mg (increased by PCP), Prescription Niacin 2 Gms, Lisinopril 5 mg, Metoprolol 25 mg, Omeprazole 20 mg, Clopidrogrel 75 mg
- PE: Weight 183, BMI 36, BP 140/80, HR 76, otherwise unchanged from previous visit
- Labs: TGs 225, TC 327, HDL 56, LDL 266, down from 350, Glucose 97, LFTs WNLs, Creatinine 0.9

Impression and Plan

- Impression
 - Severe Heterozygous Familial Hypercholesterolemia
 - Sub-optimal LDL with some lowering with the addition of Simvastatin at 80 mg but clearly well above target of < 70 mg/dL given her vascular disease and other co-morbidities
- Plan:
 - Paperwork completed for LDL apheresis, insurance coverage verification completed
 - Vessels evaluated for access at the unit
 - Colesevelam added and other LLMs continued at current doses
 - Return appointment 3 months

Return Visit

- **Current Meds:** Simvastatin 80 mg, Prescription Niacin 2 Gms, Lisinopril 5 mg, Metoprolol 25 mg, Omeprazole 20 mg, Clopidogrel 75 mg, Welchol 625 (4) tabs 2 Xs daily, complaining of some diffuse muscle ache which are unchanged in character or quantity, feels that they are tolerable.
- **New Problems:** Nocturnal leg cramps, leg pain with walking 1 block in R leg, relieved with stopping of activity. Increased GI complaints of nausea. No change with anginal pain with exertion and 1 episode of atria fibrillation
- **PE:** Weight 185, BMI 36, BP 140/82, HR 72
- **Labs:** Improved with TG 107, TC 269, HDL 71, LDL 177, LFTs WNLs, glucose WNL

Impression and Plan

- Impression & Plan
 - CAD, angina, FH, HTN, PAD, muscle symptoms, increased GI complaints, patient is somewhat hesitant about the potential for LDL apheresis.
 - Follow up with local cardiologist for recurrent anginal symptoms and intermittent claudication
- Lipids: continue with current medications but add Ezetimibe 10 mg. for optimal control of LDL at least until decision for LDL apheresis is made. Encouraged to contact office if muscle symptoms increase or feels that GI problems continue or escalate
- RTC 4 months

Follow up appointment

- 4 month FUA
- Isosorbide mononitrate added by local cardiologist, medications otherwise unchanged
- Continues to have “muscle ache/pain” and would like to consider stopping some of the lipid lowering medication
 - Ezetimibe, Prescription Niacin, Colesevelam 625 mg., Simvastatin 80 mg
 - Current labs on the 4 medication regimen:
 - TG 162, TC 259, HDL 55, LDL 172
- Impression and Plan:
 - Severe FH with still sub-optimal LDL cholesterol on 4 medication regimen
 - Stop Niacin, Ezetimibe, Colesevelem, and continue with Simvastatin but decrease to 40 mg for relief of symptoms
 - Proceed to LDL aphaeresis

Lipid Values on LDL Apheresis

Pre - treatment Value

TG 144

TC 311

HDL 57

LDL 225

Post - treatment Value

TG 29

TC 124

HDL 59

LDL 59

Impression:

FH, tolerated LDL Apheresis without difficulty, less fatigue reported off of all but Simvastatin at 40 mg. Patient well pleased with process and outcome.

Plan:

No change with medications, treatment every other week as scheduled

Follow up appointment in 3 months

Pre - treatment Values

TG 144
TC 311
HDL 57
LDL 225

Post - treatment Values

TG 29
TC 124
HDL 59
LDL 59

1 year later – pre treatment

TG 284
TC 276
HDL 56
LDL 163

1 year later – post treatment

TG 69
TC 97
HDL 45
LDL 38

3 years later – pre treatment

TG 292
TC 325
HDL 50
LDL 216

3 years later - Post treatment

TG 67
TC 117
HDL 45
LDL 59

Five Years Later

- No further cardiac disease progression
- Greatly Improved anginal symptoms
- Tolerating the procedure and now looking forward as we all are to
 - New medications to further lower LDL with/without need for LDL apheresis every other week
 - Ongoing work with her children and grandchildren so they will not need to walk a mile in her shoes

What does the future hold?

Muscle Nerve 34: 153–162, 2006

GENETIC RISK FACTORS ASSOCIATED WITH LIPID- LOWERING DRUG-INDUCED MYOPATHIES

GEORGIRENE D. VLADUTIU, PhD,¹ ZACHARY SIMMONS, MD,² PAUL J. ISACKSON, PhD,¹
MARK TARNOPOLSKY, MD, PhD,³ WENDY L. PELTIER, MD,⁴ ALEXANDRU C. BARBOI, MD,⁴
NAGANAND SRIPATHI, MD,⁷ ROBERT L. WORTMANN, MD,⁶ and PAUL S. PHILLIPS, MD⁷

Implications of Increased Carrier Status in Statin Myopathy

Disorder	Carrier Frequency	Homozygote Frequency	-fold increase in risk
CPT II deficiency*	1/270	1/300,000	>1,000
McArdle disease**	1/170	1/100,000	>500

*Derived from data generated in the Guthrie Laboratory

**Haller RG. Arch Neurol 2000;57:923-4

Is the finding of genetic risk factors for statin myopathy good news for drug manufacturers?

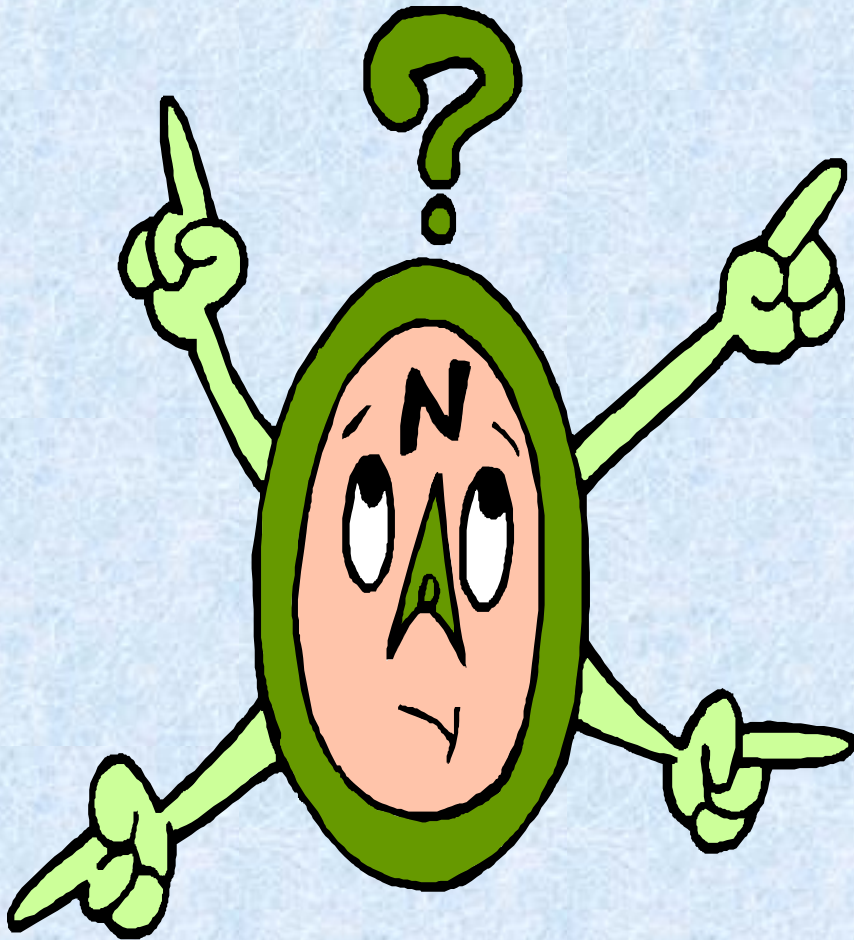
- ADRs are not necessarily due to statins
- ADRs may be due, in large part, to genetic susceptibility for muscle disease
- Alteration of dosage or statin type may help reduce or prevent symptoms

Is the finding of genetic risk factors for statin myopathy good news for healthcare providers?

- Selected testing of high risk individuals will identify many of those at risk for ADRs and allow better medical management with potential to move to LDL apheresis sooner to protect the patient when necessary

The Robert Guthrie Biochemical Genetics Laboratory

- Molecular testing for triggerable metabolic myopathies
 - Carnitine palmitoyltransferase (CPT) II deficiency
 - McArdle disease (myophosphorylase deficiency)
 - Myoadenylate deaminase deficiency
 - Exercise Intolerance Mutation Profile



Thank you for your
kind attention

We will now open the
floor to questions &
discussion