Screening, Diagnosis and Treatment of Pediatric Dyslipidemia

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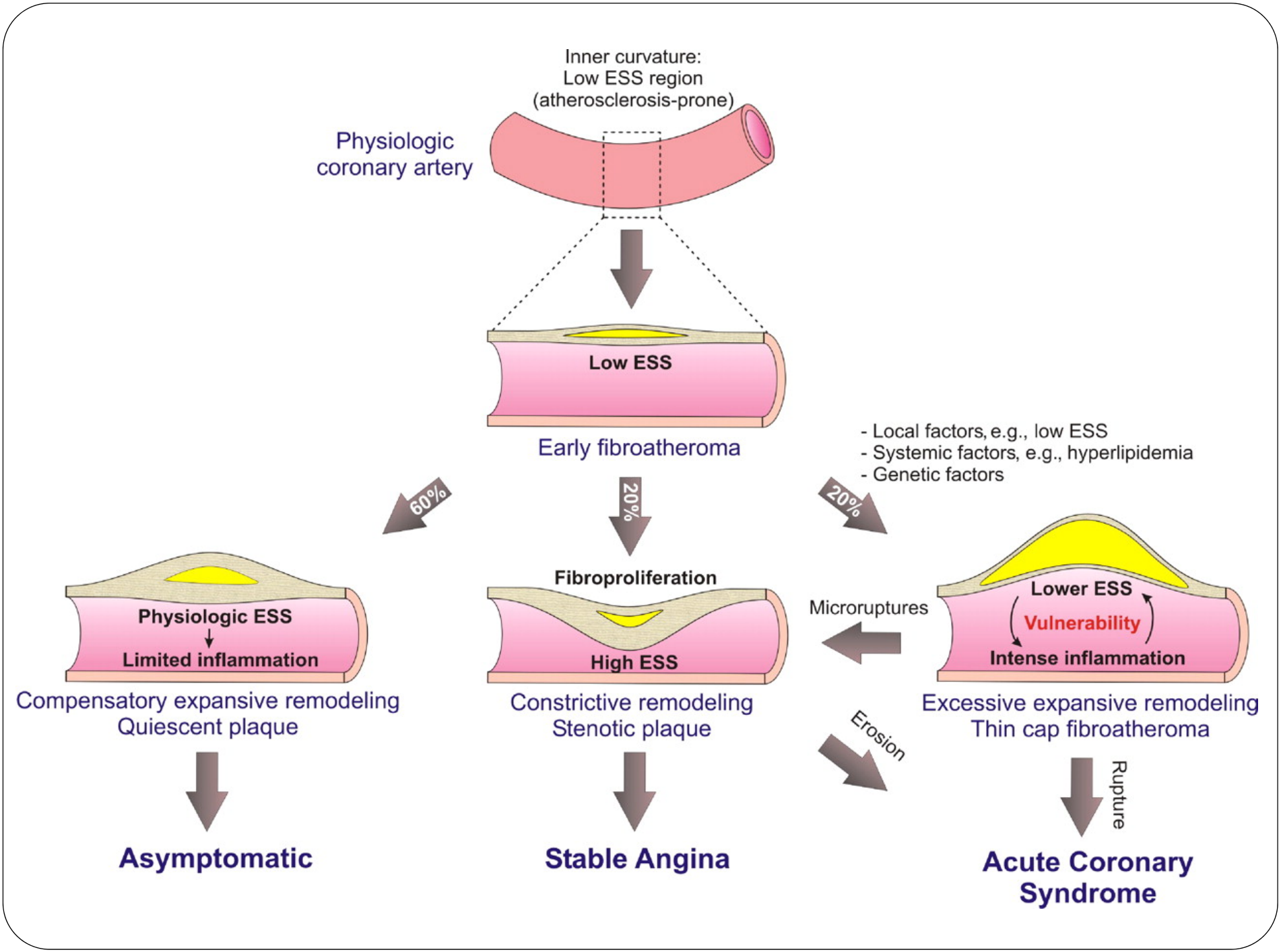
Introduction

- Atherosclerotic cardiovascular disease is the leading cause of death in the United States
- In patients with familial hypercholesterolemia (FH), lowering low-density lipoprotein cholesterol (LDL-C) levels greatly reduces CV disease events and mortality
- Only 20% of FH patients are diagnosed
- Only minority of diagnosed FH patients receive appropriate treatment
- Appropriate treatment of FH can markedly reduce morbidity and mortality from CV disease


Inner curvature:
Low ESS region
(atherosclerosis-prone)
Physiologic
coronary artery
Low ESS
Early fibroatheroma
- Local factors, e.g., low ESS
- Systemic factors, e.g., hyperlipidemia
- Genetic factors
60%
20%
20%
Physiologic ESS
Limited inflammation
Fibroproliferation
High ESS
Microruptures
Lower ESS
Vulnerability
Intense inflammation
Compensatory expansive remodeling
Quiescent plaque
Constrictive remodeling
Stenotic plaque
Erosion
Excessive expansive remodeling
Thin cap fibroatheroma
Rupture
Asymptomatic
Stable Angina
Acute Coronary
Syndrome

Atherosclerosis: *A Childhood Disease?*

- Bogalusa Heart Study (*N Engl J Med*. 1986)
  - pathological study
  - prevalence of fatty streaks was 50% during childhood, and 69% during young adulthood
- Vietnam war postmortem study (*JAMA*. 1971)
  - pathological study
  - 105 soldiers who died at a mean age of 22 years
  - 45% had gross evidence of coronary atherosclerosis (5% severe)

Obstacles and Opportunities

- Appropriate use of lipid lowering medications is currently not part of "typical" pediatric training
- Current deficiencies in the diagnosis and treatment of FH suggest:
  - Need for increased awareness and understanding of this disease -- both on the part of the public and of healthcare practitioners
  - Role for universal screening during childhood
  - Opportunity for cascade lipid screening of family members of known FH patients

Case Presentation: 15 yr female

- Asymptomatic. Mother concerned about family history
- Pediatrician documented total cholesterol 297 - 315 mg/dL since age 10 yr
- Father has hypercholesterolemia; no hx of heart attack or stroke
- Paternal uncle died at 29 yr from myocardial infarction in context of hypercholesterolemia
- Paternal grandfather had first myocardial infarction in his 20's in context of hypercholesterolemia
- Mother has normal lipid panel
- 12 yr-old brother has not been tested

Case Presentation: 15 yr female

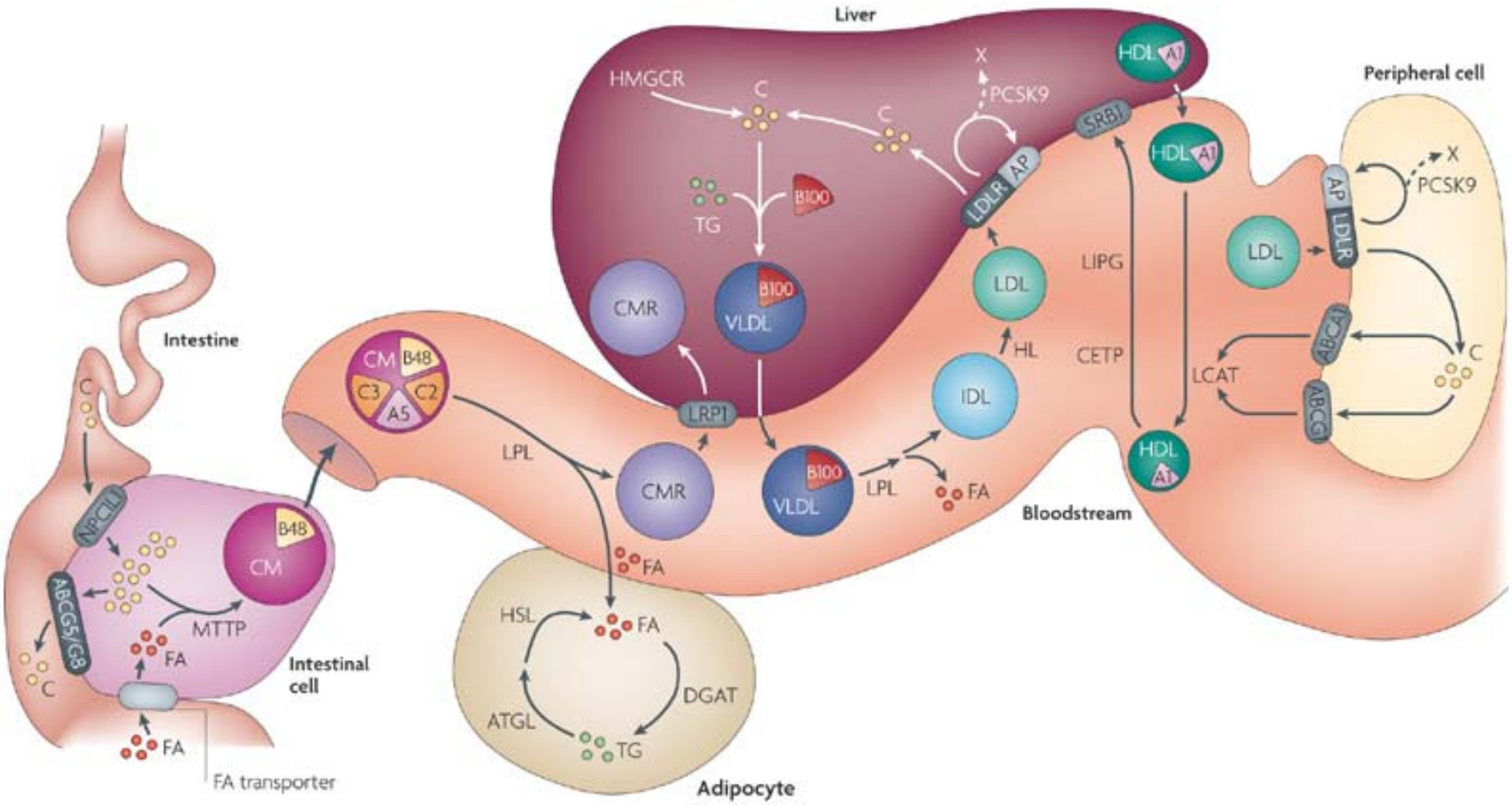
- Exam
  - BP 103/64 mmHg
  - Wt 58 kg (71st percentile)
  - BMI 27 kg/m2 (93rd percentile)
  - Normal CV exam
  - No tendon xanthomas, acanthosis nigricans or goiter
- Lab
  - TC 250, **LDL-C 204**, HDL-C 30, trig 79
  - Creatinine 0.7, ALT 31, glucose 98

What is the Most Likely Diagnosis?

- Heterozygous familial hypercholesterolemia (FH)
- Polygenic dyslipidemia
- Metabolic syndrome
- Obesity causing secondary dyslipidemia

The Cynic's Alternate Answer Key

- *I hated biochemistry in college, and I'd really rather not look any more stupid than I already feel!* ☹
- *I'll grant you that this is probably something important, but c'mon, she's just a kid. We can punt this to the internist!*
- *I never paid attention to all this lipid hysteria, and I'll be damned if I am going to start now!*



Nature Reviews | Genetics

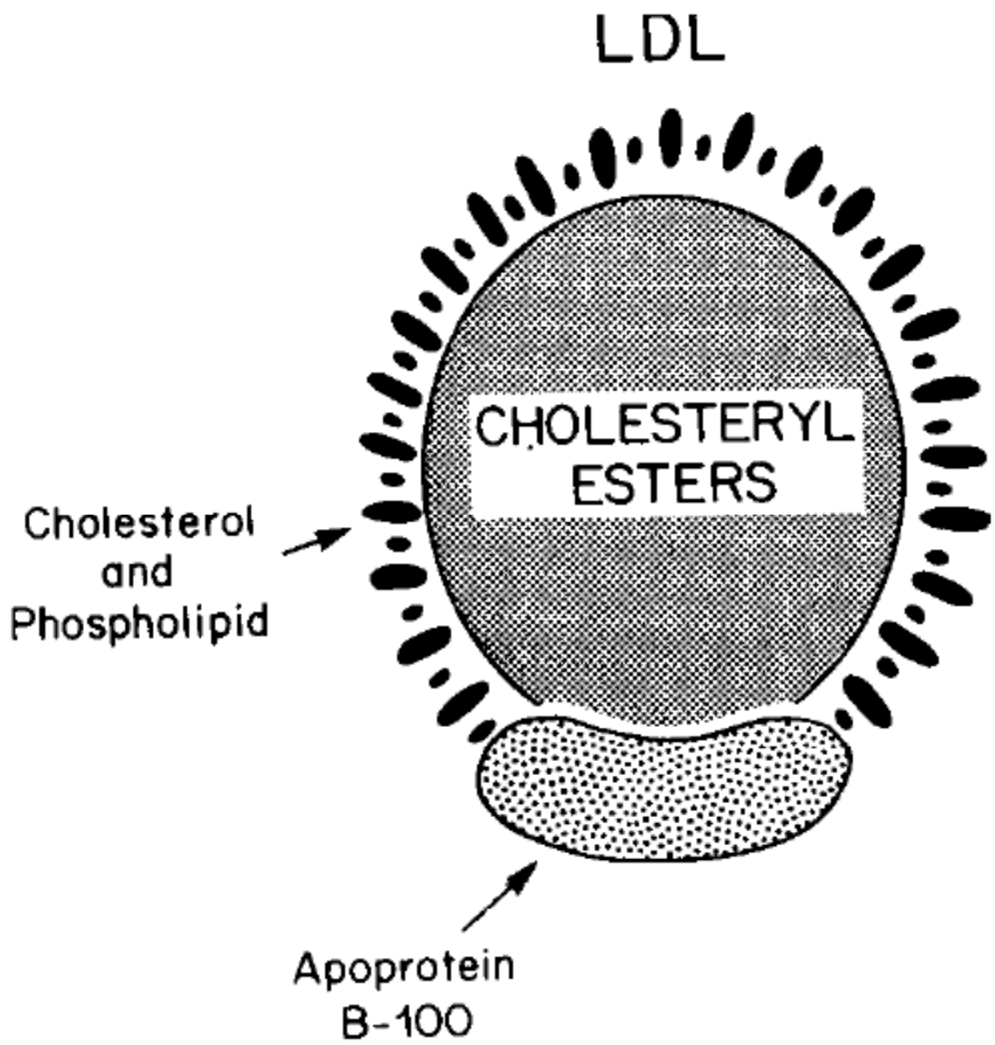
Cholesterol Metabolism: Overview

- Where it comes from…
  - Dietary cholesterol intestinal absorption
  - Hepatic cholesterol biosynthesis
- Where it goes…
  - Hepatic production of bile acids excreted into the intestine is major route of cholesterol elimination, but this is countered by bile acid reabsorption
  - Regulatory feedback mechanisms that decrease hepatic cholesterol biosynthesis
- How it gets there…*serum transport via lipoproteins*

The Lipoproteins

- Lipoprotein classes:
  - Very low density lipoprotein (VLDL)
  - **Low density lipoprotein (LDL)**
  - Intermediate density lipoprotein (IDL)
  - High density lipoprotein (HDL)

- Packaging serum cholesterol esters into lipoproteins prevents nonspecific cholesterol partitioning into cell membranes


LDL
CHOLESTERYL
ESTERS
Cholesterol
and
Phospholipid
Apoprotein
B-100

A RECEPTOR-MEDIATED PATHWAY FOR CHOLESTEROL HOMEOSTASIS

Nobel lecture, 9 December, 1985

By
MICHAEL S. BROWN AND JOSEPH L. GOLDSTEIN

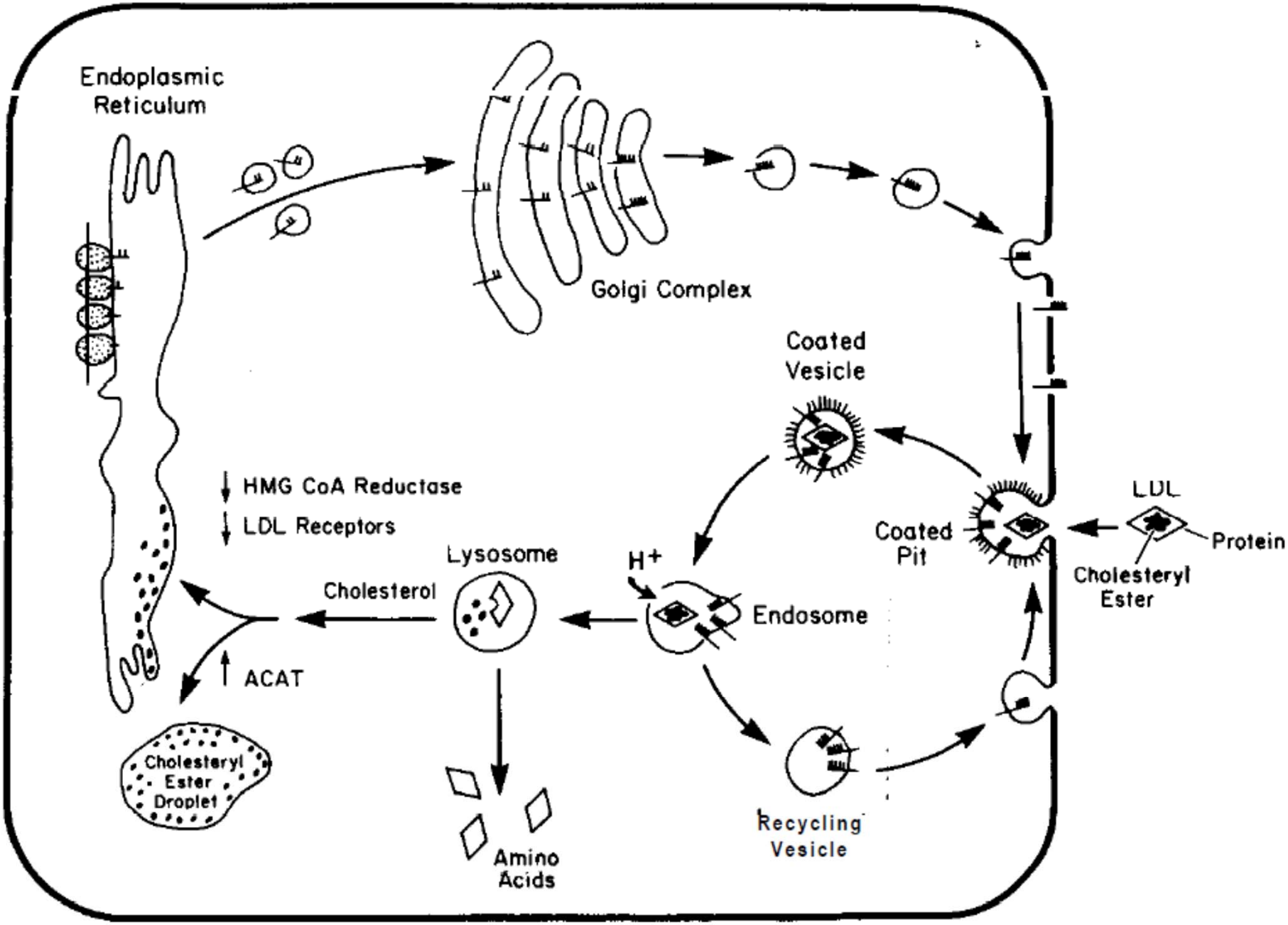
Department of Molecular Genetics, University of Texas Health Science Center, Southwestern Medical School, 5323 Harry Hines Blvd. Dallas, Texas,
U.S.A.

"Cholesterol is the most highly decorated small molecule in biology"

"If cholesterol is to be transported safely in blood, its concentration must be kept low, and its tendency to escape from the bloodstream must be controlled."

Back to Basics: LDL Receptor

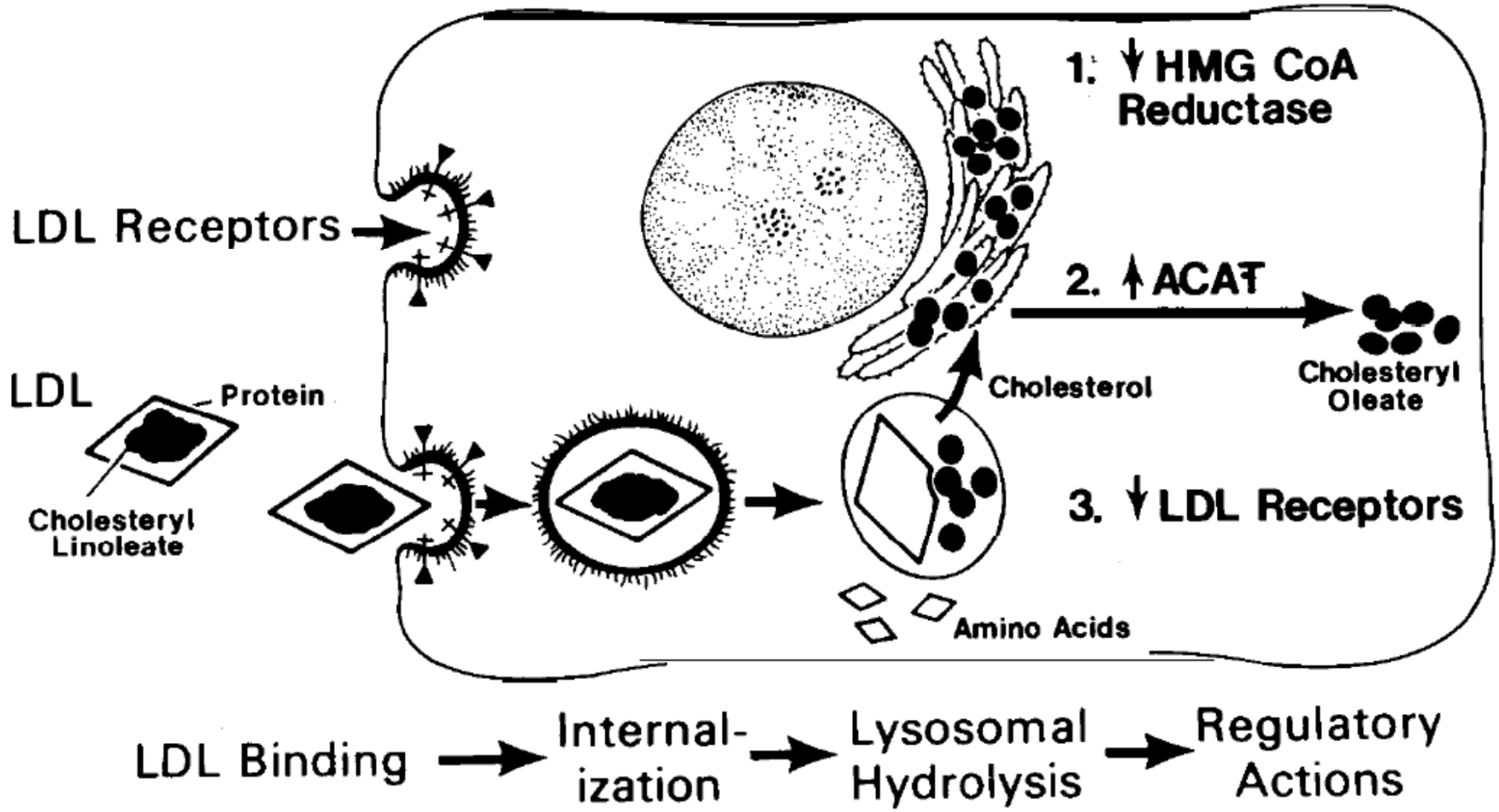
- LDL-C particles are cleared from bloodstream by LDL-receptor (LDLR) mediated endocytosis
- Internalized cholesterol esters are delivered to lysosomes for plasma membrane, bile acid, and sterol hormone synthesis
- LDLR proteins rapidly cycle to and from the cell surface
- LDLR mutations or regulatory signals can reduce cell surface LDLR recycling and diminished clearance of serum LDL-C
- FH patients have twice a many circulating LDL-C particles in their bloodstream from birth to death


Endoplasmic Reticulum
Golgi Complex
Coated Vesicle
HMG CoA Reductase
LDL Receptors
LDL
Protein
Coated Pit
Cholesteryl Ester
Lysosome
H+
Cholesterol
Endosome
ACAT
Cholesteryl Ester Droplet
Amino Acids
Recycling Vesicle

Regulation of Cholesterol Synthesis

- 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase) is the rate-determining enzyme involved in cholesterol biosynthesis within the hepatocyte

- LDL-C internalization (mediated by the LDLR) and subsequent lysosomal liberation of free cholesterol down-regulates HMG CoA reductase activity


1. ↓HMG CoA Reductase
LDL Receptors
2. ↑ACAT
LDL
Protein
Cholesterol
Cholesteryl Oleate
Cholesteryl Linoleate
3. ↓LDL Receptors
Amino Acids
LDL Binding
Internal-ization
Lysosomal Hydrolysis
Regulatory Actions

Common Dyslipidemias

- **Familial hypercholesterolemia (FH)**
- Polygenic hypercholesterolemia
- Familial combined hyperlipidemia
- Familial hypertriglyceridemia
- Lipoprotein lipase deficiency
- Apoprotein C-II deficiency
- Secondary dyslipidemia (i.e., consequent to hypothyroidism, nephrotic syndrome, diabetes, hepatic disease)

Familial Hypercholesterolemia (FH)

- Inherited genetic defects resulting in severely elevated serum cholesterol concentrations
- First recognized 1938 (Carl Müller, Oslo)
- Autosomal dominant (heterozygous) inheritance
  - **LDLR defects – 85 to 90% of cases (1600+ known LDLR mutations)**
  - Apolipoprotein (Apo) B defects – 5 to 10% of cases
  - Proprotein convertase subtilisin/kexin type 9 (PCSK9) defects – 5% of cases
  - *Others yet to be described*

Epidemiology

- FH is one of the most commonly occurring congenital metabolic disorders:
  - **Heterozygous FH: 1 in 300 to 500 people**
    - French Canadians, Dutch Afrikaners, Christian Lebanese, Ashkenazi Jews all have founder effects and higher rates of disease
  - Homozygous FH: 1 in 1,000,000 people
- 620,000 FH patients currently living in US
- Risk of premature CHD is increased 20-fold in untreated FH patients
- Males typically have CHD events in their 30s-40s
- Females typically have CHD events in their 40s-50s

Clinical Diagnosis

- Heterozygous FH: TC 350 to 550 mg/dL
- Homozygous FH: TC 650 to 1000 mg/dL
- 80% probability of heterozygous FH if LDL-C:
  - Greater than 250 mg/dL in patients > 30 yr
  - Greater than 220 mg/dL in patients 20 to 29 yr
  - **Greater than 190 mg/dL in patients < 20 yr**

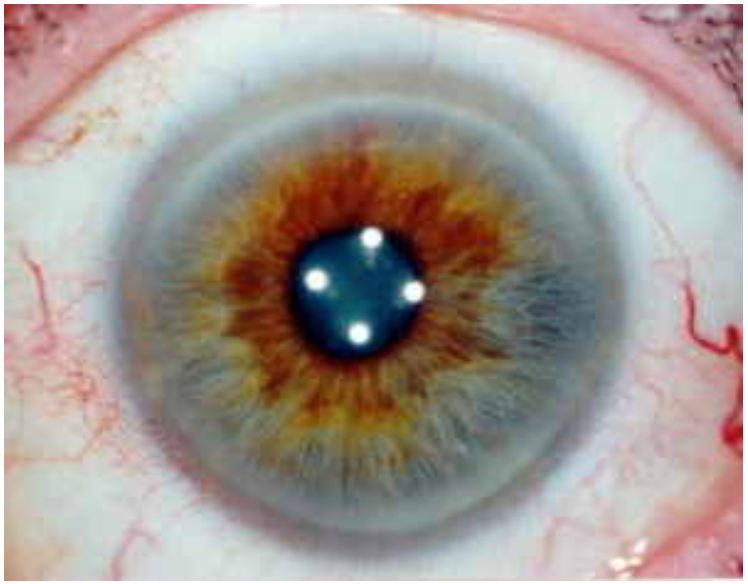
- Be suspicious for FH if child has LDL-C >160 mg/dL
- **Average two results**

Clinical Diagnosis

- Clinical diagnosis of FH is most likely when:
  - ≥ 2 first-degree relatives have elevated LDL-C
  - pediatric relatives have dyslipidemia
  - patient or a close relative has tendon xanthomas
  - family history of hypercholesterolemia or premature CHD (i.e., onset in men before age 55 years and women before age 65 years)
- FH patients can also have elevated triglycerides – *elevated triglycerides does not exclude diagnosis of FH*

Physical Examination

- Physical signs of FH are insensitive, but can be quite specific
- **Tendon xanthomas at any age**
  - most common in Achilles tendon and finger extensor tendons
  - can also occur in patellar and triceps tendons
- Arcus corneae in a patient *under age 45 yr*
- Tuberous xanthomas or xanthelasma in a patient *under age 20 to 25 yr*



Genetic Testing for FH?

- **Generally not needed for diagnosis or management**
- May be useful when diagnosis is uncertain, or to motivate some patients to implement treatment
- Negative genetic test does not exclude FH (20% of clinically definite FH patients are genotype-negative)

Executive Summary

Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients

Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

Anne C. Goldberg, MD, FNLA, Chair*, Paul N. Hopkins, MD, MSPH,
Peter P. Toth, MD, PhD, FNLA, Christie M. Ballantyne, MD, FNLA,
Daniel J. Rader, MD, FNLA, Jennifer G. Robinson, MD, MPH, FNLA,
Stephen R. Daniels, MD, PhD, Samuel S. Gidding, MD, Sarah D. de Ferranti, MD, MPH,
Matthew K. Ito, PharmD, FNLA, Mary P. McGowan, MD, FNLA,
Patrick M. Moriarty, MD, William C. Cromwell, MD, FNLA,
Joyce L. Ross, MSN, CRNP, FNLA, Paul E. Ziajka, MD, PhD, FNLA

Journal of Clinical Lipidology (2011) 5, S1–S8

There Are All Kinds of Prevention

- *Primordial prevention* (avoid risk factors)
- *Primary prevention* (manage established risk factors)
- *Secondary prevention* (manage established CV disease)

New Dyslipidemia Screening Guidelines

- Universal screening (non-fasting, non-HDL-C or fasting lipoprotein profile) recommended at age 9 - 11 yr
- Cost-effective (cost per year of life saved) ***IF*** effective cholesterol-lowering treatment is applied to all those identified with dyslipidemia
- Screening should begin earlier (i.e., ≥ 2 yr) when there are parents, grandparents or aunts/uncles with CV disease or dyslipidemia

Cascade Screening Comes Next

- **Lipid panel testing for all first-degree relatives of diagnosed FH patients**
- Newly identified FH cases provide clues to additional relatives who are in turn considered for screening
- Most cost-effective means of finding previously undiagnosed FH patients

Management Overview

- **FH is a treatable disease**
- **Early treatment of FH is highly beneficial, lowering CHD event rates to near that seen in the unaffected population**
- Exclude causes of secondary dyslipidemia
- Target LDL-C reduction of ≥ 50% (even greater target LDL-C reductions may be necessary for high-risk FH patients)
- Life-long commitment to treatment and follow-up

High-Risk FH

- Clinically evident CHD or other atherosclerotic disease
- Diabetes
- Family history of very early CHD (male relative <45 yr; female relative <55 yr)
- Current smoker or close quarters tobacco smoke exposure
- High lipoprotein(a) >50 mg/dL
- Homozygous FH

Treatment Principles

- All FH patients require diet and lifestyle management
- Majority will eventually require lipid-lowering drug therapy
- Consider therapeutic targets
  - Inhibition of intestinal reabsorption of bile acids
  - Inhibition of hepatic cholesterol synthesis
- Consider pharmacological options
  - **Statins**, bile acid sequestrants, ezetimibe, niacin, fibrates
  - LDL apheresis (homozygous FH, high-risk heterozygous FH)
  - Liver transplantation (homozygous FH)

Therapeutic Lifestyle & Diet

- Reduced intakes of saturated fats and cholesterol:
  - total fat 25-35% of energy intake
  - saturated fatty acids <7% of energy intake
  - dietary cholesterol <200 mg/day
- Use of plant stanol or sterol esters 2 g/day
- Use of soluble fiber 10-20 g/day
- Physical activity and caloric intake to achieve and maintain a healthy body weight
- Emphatic recommendation to avoid use of any tobacco products and second-hand smoke

Health Services and Outcomes Research

Cost-Effectiveness of Statin Therapy for Primary Prevention in a Low-Cost Statin Era

Lawrence D. Lazar, MD; Mark J. Pletcher, MD, MPH; Pamela G. Coxson, PhD;
Kirsten Bibbins-Domingo, MD, PhD; Lee Goldman, MD, MPH

Conclusions—Low-cost statins are cost-effective for most persons with even modestly elevated cholesterol or any coronary heart disease risk factors if they do not mind taking a pill daily. Adverse effects are unlikely to outweigh benefits in any subgroup in which statins are found to be efficacious. (***Circulation*. 2011;124:146-153.**)

Drug Rx Thresholds and Targets

- Over age 8 yr with LDL-C >190 mg/dL despite diet and lifestyle changes (>160 mg/dL with personal risk factors or positive family history of premature CHD)
- Low-risk children and adults
  - **Treatment goal is ≥ 50% LDL-C reduction or <130 mg/dL**
- High-risk children and adults
  - **Treatment goal is LDL-C reduction < 100 mg/dL**

Statins Approved for Children

- FDA currently approves one statin* for children 8 yr old; all others approved for children older than 10 yr
- Simvastatin, atorvastatin, pravastatin*, fluvastatin, rosuvastatin, and lovastatin
- All statins recommended by the FDA are approved for treatment of children with FH

Safety & Efficacy: Statin Rx in Kids

- Clinical trials with medium-term follow-up suggest statin Rx in children is safe and effective

- No evidence of impaired growth, delayed pubertal development, or abnormal cognitive development with long-term statin therapy in children >8-10 yr (Tanner II puberty males and post-menarchal females)

Practical Statin Prescribing

- Choice of statin is largely one of preference
- Measure baseline CK, ALT, and AST
- Start with the lowest dose once daily at bedtime
- Instruct patient to report potential side-effects (e.g., muscle cramps, weakness, asthenia)
- Counsel females regarding pregnancy and contraception
- Advise about drug interactions (e.g., cyclosporine, fibrates, niacin, erythromycin, azole antifungals, HIV protease inhibitors)

Monitoring Statin Therapy

- After 4-8 wk, repeat fasting lipoprotein profile, CK, ALT, and AST
- If target LDL levels are not achieved, double the dose up to max recommended dose, repeat blood work in 4 wk
- If target LDL levels are achieved, repeat blood work in 3-6 mos
- Worrisome CK, ALT and AST are values 10 times above upper limit of normal

Other Benefits from Statins???

- No widespread consensus – only intriguing biochemical evidence that statins *might*:
  - Improve endothelial dysfunction (e.g., improves myocardial vasodilation into ischemic segments)
  - Increase nitric oxide bioavailability (e.g., prevent down-regulation of endothelial nitric oxide synthase)
  - Have antioxidant properties (e.g., decrease activity of macrophage CD36 – a receptor for oxidized LDL)
  - Inhibit inflammatory responses (e.g., lowers CRP)
  - Stabilize atherosclerotic plaques (e.g., down-sizing lipid core)

Statins May Not Be Enough

- **Only 40% of children with heterozygous FH will attain target LDL-C values with a statin alone**

- Doubling any statin dose only lowers LDL-C by an additional ~7%

- Other LDL lowering medications will often be needed to reach target LDL-C values

Ezetimibe

- Selectively inhibits absorption of cholesterol at the small intestinal brush border
- Does not inhibit absorption of TG or fat-soluble vitamins
- No identified problems with growth or pubertal development
- Controversy exists regarding whether the cholesterol-lowering efficacy is accompanied by real reduction cardiovascular risk

Bile Acid Sequestrants

- One of the first therapies applied to dyslipidemia
- Prevents reabsorption and recirculation of bile acids
- Inhibits absorption of fat-soluble vitamins
- Largely replaced by newer drugs with fewer gastrointestinal side-effects
- Colesevelam has lower incidence of side-effects, and is also FDA approved for lowering HbA1c (may be useful in patients with hypercholesterolemia and diabetes)

Niacin

- Hydrophilic B complex vitamin that increases HDL-C levels and reduces VLDL-C
- Not commonly used in pediatric patients and data on its efficacy for children are limited
- Side-effects include flushing, impaired glucose tolerance, liver failure, and myopathy

Omega-3 Fatty Acids and Fibrates

- Primary pharmacologic agents for hypertriglyceridemia
- Demonstrated efficacy and safety of omega-3 fatty acid and fibrate Rx during childhood
- Incremental approach to treatment of severe pediatric hypertriglyceridemia:
  1) Start with omega-3 fatty acid Rx
  2) Add a cholesterol-lowering medication (e.g., statin)
  3) Add a fibrate

Females of Childbearing Age

- **Provide contraception and pregnancy counseling**

- Instruct to stop statins, ezetimibe, and niacin at least four weeks before discontinuing contraception, and to not use these medications during pregnancy and lactation

- Other lipid lowering medications (e.g., colesevelam) can be used during pregnancy

Summary

- **FH (and other dyslipidemias) are very manageable diseases with childhood onset and poor prognosis if inadequately treated**
- All primary health care providers and relevant specialists have a responsibility to:
  - screen all children and adults for hypercholesterolemia
  - initiate diet, lifestyle and drug therapy in patients with FH and severe hypercholesterolemia
- For children with FH, consultation with a lipid specialist may be helpful

Is your
indecision final?

The Economist