Dyslipidemias in Children: A Cardiologist's Perspective

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In pediatric cardiology we do take a family history!

- PPE/LH/syncope/SCD & arrhythmias…..
- SCD/SIDS
- LQTS/Brugada/VT
- Pacemaker/AICD
- Cardiomyopathies
- Syncope/seizures
- Marfan
- Cong. deafness
- History & Physical form…
- Cong. Heart disease & birth defects
- MI, CVA, hyperchol., htn., pacer, heart surg.
- SCD, stillbirths
- Seizures
- Not diabetes or obesity

Preventive Cardiology FH

- Pedigree added to table
- Aunts/uncles/cousins/greatgrandparents added to sibs/parents/grandparents/"others"
- Commorbidities: obesity, diabetes, smoking, physical inactivity, nutrition and...
- Expanded details of vascular disease (angina, stents, TIAs, meds, etc.), dyslipidemias and hypertension (#'s, dx., meds, response)

Epidemiology

- Plasma cholesterol values predicts risk for coronary heart disease (CHD)
- CHD is the most common cause of death in the US in both men and women
- CHD causes approximately 500,000 deaths/year (twice as many as cancer, 50 times as many as AIDS)

Epidemiology: Children

- Countries with higher dietary intakes of cholesterol and saturated fatty acids have higher average plasma cholesterols

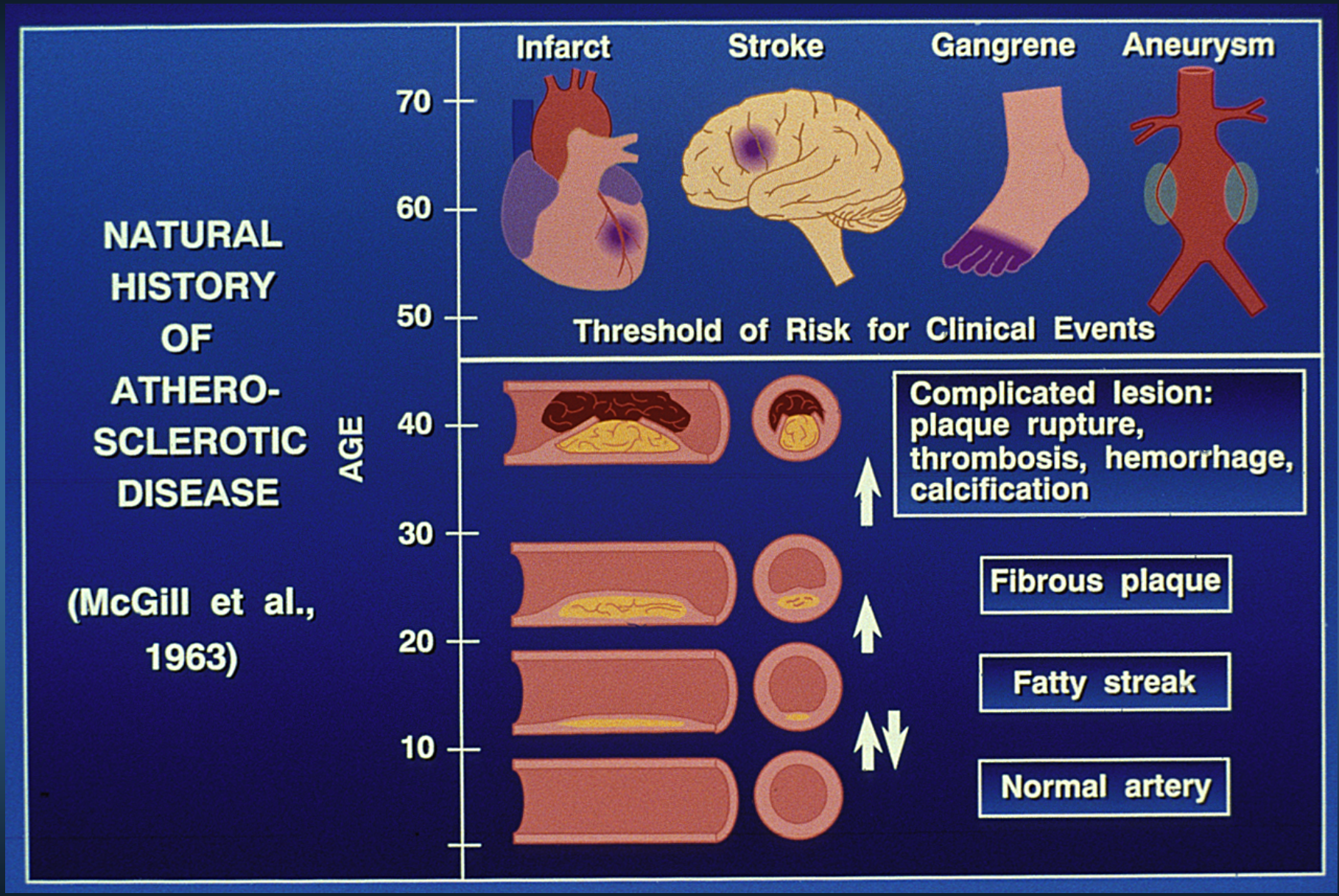
- 36% of US youth $\leq$ 19 years old have cholesterol $\geq$ 170 mg/dl

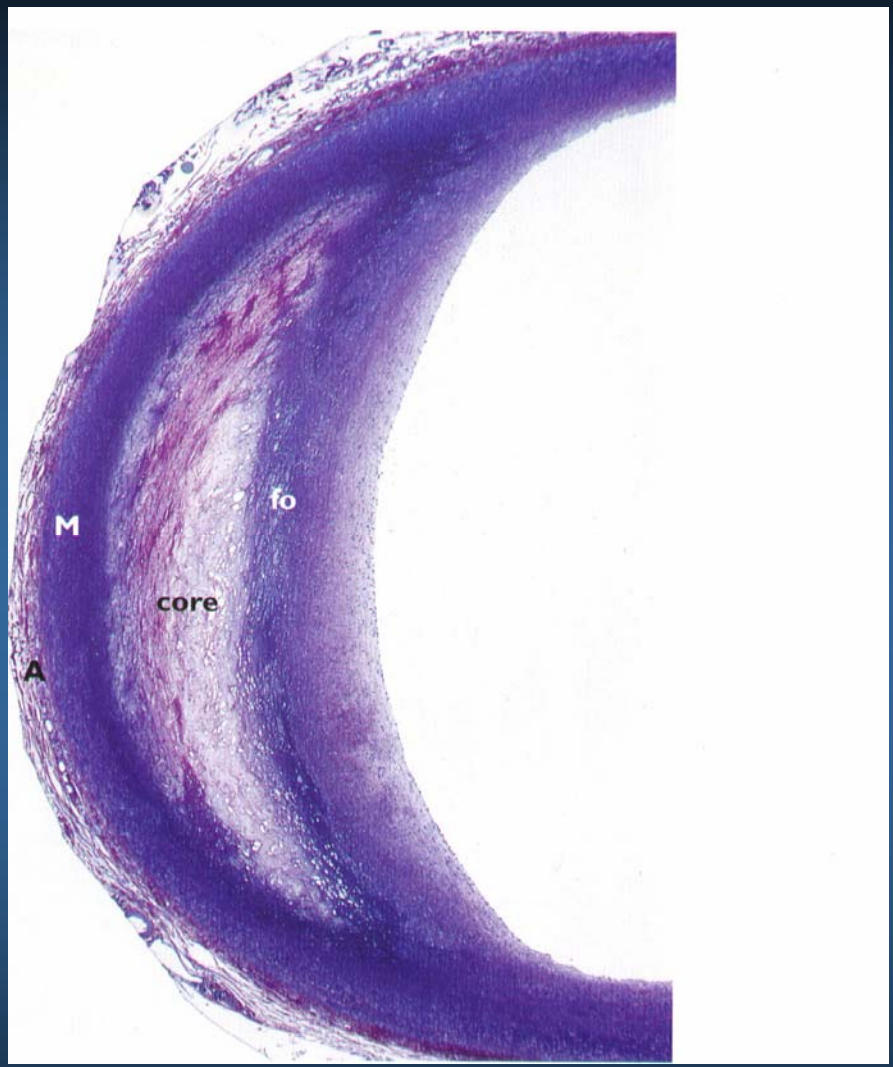
Epidemiology

	Boys	Girls
Whites	27%	31%
Blacks	37%	46%

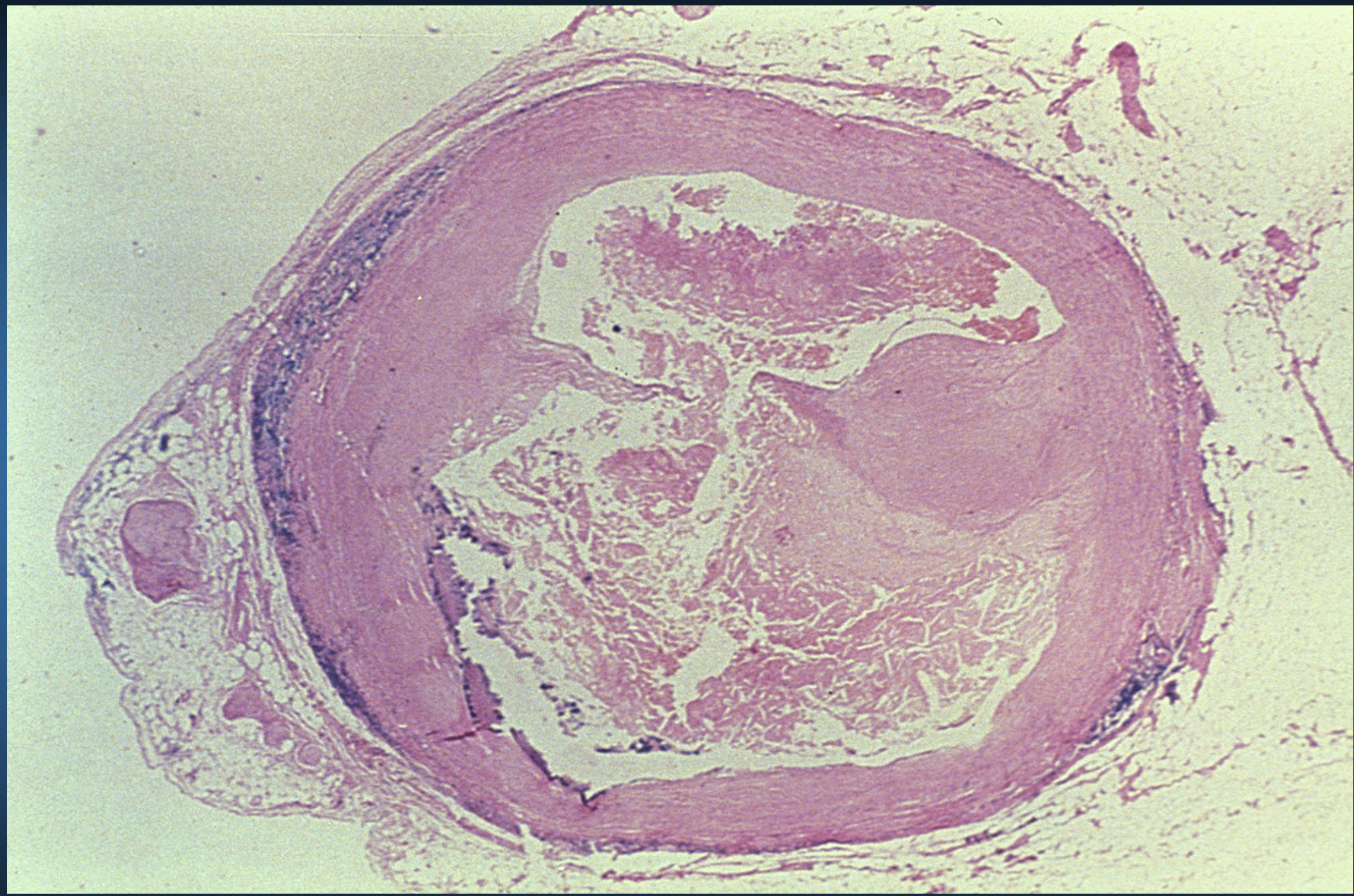
Epidemiology: Coronary Heart Disease

- Clinical sequelae ≥ middle age
- Arterial lesions-origins in childhood
- Aorta-fatty streaks in early childhood
- Coronary arteries-fatty streaks-many in 2nd decade
- Coronary arteries-fibrous plaques-some in 2nd decade
- Coronary arteries-fibrous plaques in many after age 20


NATURAL HISTORY OF ATHERO-SCLEROTIC DISEASE
(McGill et al., 1963)
AGE
70
60
50
40
30
20
10
Infarct
Stroke
Gangrene
Aneurysm
Threshold of Risk for Clinical Events
Complicated lesion: plaque rupture, thrombosis, hemorrhage, calcification
Fibrous plaque
Fatty streak
Normal artery



23 Year old male, Type IV lesion



Vascular Pathology: Endothelial Dysfunction

- Carotid arterial intima-media wall thickness
- LDL-c is a strong independent predictor of carotid arterial intima-media thickness in children with heFH
- 5-fold more rapid increase vs. nl. sibs
- Impaired flow-mediated dilatation of the brachial artery in children with heFH vs. controls

Statins and Endothelial Dysfunction

- Statins associated with carotid arterial wall intima-media thickness regression
- Statins may inhibit or reduce faster progression of atherosclerosis
- Short term statin (simvastatin) results in improved flow mediated dilatation of the brachial artery to a level similar to non-heFH controls

Common Genetic Disorders Ranked by Predominant Lipid Abnormality

- High LDL-cholesterol
  - Familial hypercholesterolemia
  - Familial defective apo B-100
  - Familial combined hyperlipidemia
  - Polygenic primary elevation of LDL

Common Genetic Disorders Ranked by Predominant Lipid Abnormality

- High triglycerides of mild to moderate severity
  - Familial combined hyperlipidemia
  - Familial dysbetalipoproteinemia (type III)
  - Familial hypertriglyceridemia

Common Genetic Disorders Ranked by Predominant Lipid Abnormality

- Low HDL-cholesterol
  - Familial hypoalphalipoproteinemia
- Excess lipoprotein(a) [Lp(a)]
- Very high triglycerides
  - Familial hypertriglyceridemia

Genetic Conditions Causing Elevated LDL

- Familial Hypercholesterolemia (FH): defective or deficient LDL receptors; retarded clearance of LDL from plasma.

- Familial Combined Hyperlipidemia (FCH): increased secretion of apo B-100.

Genetic Conditions Causing Elevated LDL

- Familial Defective Apo B-100: mutant apo B-100 poorly recognized by LDL receptor; retarded clearance of LDL from plasma.

- Polygenic Primary Elevation of LDL: heterogeneous group of conditions; clearance of LDL usually retarded; E4 allele of apo E sometimes plays a role

Familial Type III Hyperlipoproteinemia (Familial Dysbetalipoproteinemia)

- Pathogenesis: defective apo E (usually E-II/II phenotype)

- Lipoproteins: hypercholesterolemia and hypertriglyceridemia; elevated remnants of VLDL and chylomicrons.

Pathophysiologic Mechanisms of Hypertriglyceridemias

Mechanism	Impact on physiology
* Increased apo B-100 secretion	*Increased number of VLDL (familial combined hyperlipidemia) particles
* Increased hepatic triglyceride production (familial hypertriglyceridemia)	* Increased size of VLDL particles
* Increased expression of apo C-III or C-II	* Reduced VLDL clearance
* Heterozygosity for lipoprotein lipase (some cases of familial hypertriglyceridemia)	* Reduced clearance of deficiency triglyceride-rich lipoproteins
* Lipoprotein lipase deficiency (type I hyperlipoproteinemia) (rare)	* Reduced clearance of triglyceride-rich lipoproteins
* Apolipoprotein C-II deficiency hyperlipoproteinemia)triglyceride-rich lipoproteins (rare)	* Reduced clearance of (type I (type I or type V

Inherited Dyslidemias--Incidence

Lipid disorder:	Approximate incidence:
Familial hypercholesterolemia	
-homozygotes	1/1,000,000
-heterozygotes	1/500
Familial Combined Hyperlipidemia	0.5-1 %
Familial Defective apo B-100	rare to 1/600
Polygenic Hypercholesterolemia	1/20 to 1/100
Familial Dysbetalipoproteinemia	1/100 (occurs 1/5000)
Familial Hypertriglyceridemia	rare to 1/300
Familial Chylomicronemia	rare
Familial Hypoalphalipoproteinemia	rare

Causes of Secondary Hypercholesterolemia

- Exogenous
  - Drugs
  - Alcohol
  - Obesity
- Storage diseases
  - Glycogen storage diseases
  - Sphingolipidoses
- Endocrine and Metabolic
  - Hypothyroidism
  - Diabetes mellitus
  - Lipodystrophy
  - Pregnancy
  - Idiopathic hypercalcemia

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Causes of Secondary Hypercholesterolemia

- Obstructive Liver Diseases
  - Biliary atresia
  - Biliary cirrhosis
- Chronic Liver Diseases
  - Nephrotic syndrome
- Others
  - Anorexia nervosa
  - Progeria
  - Collagen disease
  - Klinefelter syndrome

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Preventive Cardiology

- Primary Prevention
- Should be practiced in the primary care setting
- Population Approach vs. High-Risk Approach
- Secondary Prevention
- Not practiced in pediatrics with regard to atherosclerosis (with rare exceptions)

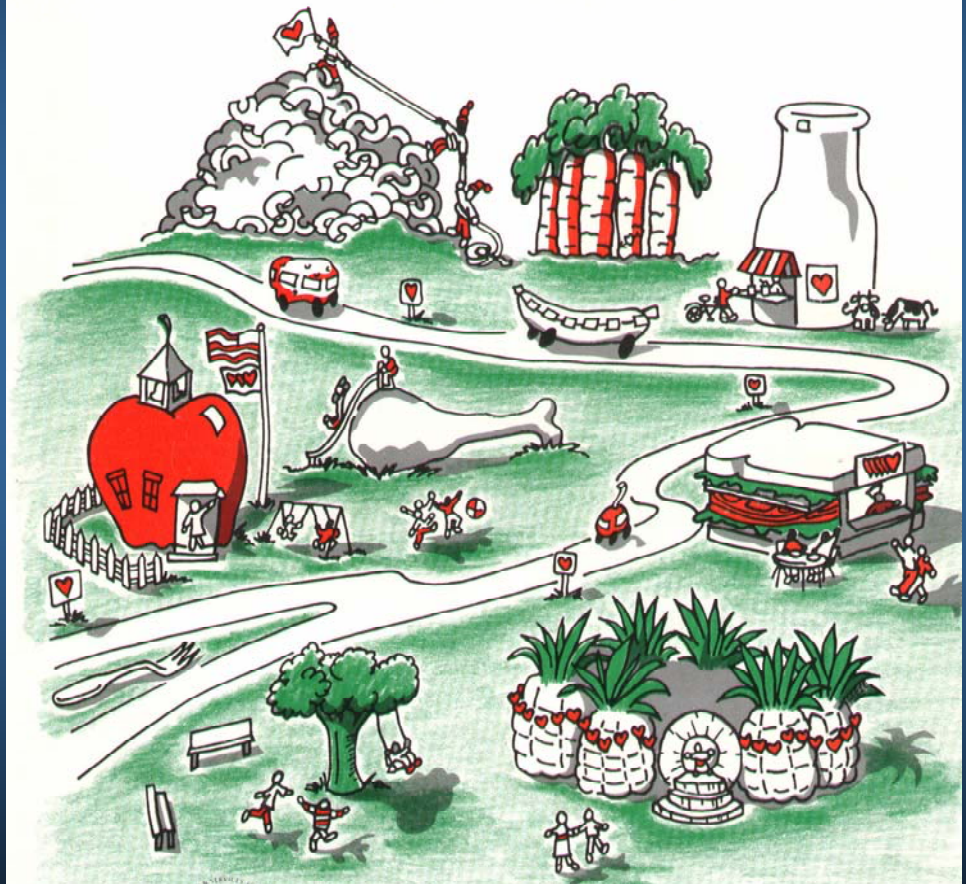
Primary Prevention

- Population Approach
- NCEP/AHA recommends a well-balanced diet low in saturated fat for everyone

- High-Risk Approach
- Identify high risk individuals by family history:
- Parental hypercholesterolemia
- Early atherosclerosis in 1st degree relatives

National Cholesterol Education Program

Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Risk Assessment

- Positive family history → Lipoprotein analysis
- Parental hypercholesterolemia (≥240 mg/dL) → total cholesterol

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Referral Scenarios from PCPs

- FH, TC/FLP, algorithms, therapy, goals met, continued F/U
- FH, TC/FLP, algorithms, therapy, goals *not* met → refers
- FH, TC/FLP, initiates therapy → refers
- FH, TC/FLP, *no* therapy → refers
- FH, *no* TC/FLP, *no* therapy → refers

Risk Assessment

- Acceptable cholesterol (<170 mg/dL) → repeat every 5 years and education
- Borderline cholesterol (170-199 mg/dL) → repeat and average with lst
- High cholesterol (≥200 mg/dL) → lipoprotein analysis

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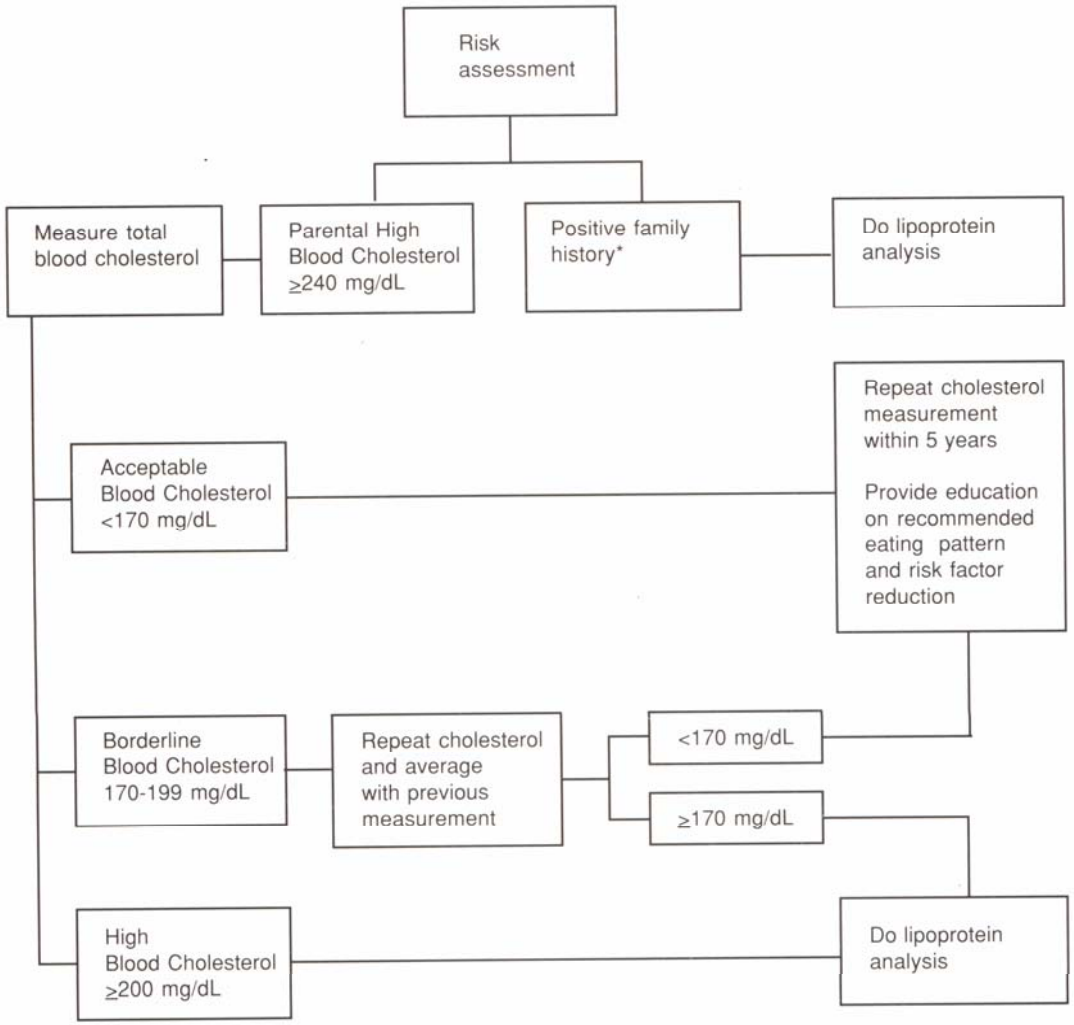
Risk Assessment



Classification of Total and LDL-Cholesterol in Childen/Adolescents

Category	Total Cholesterol (mg/dL)	LDL-Cholesterol (mg/dL)
Acceptable	< 170	< 110
Borderline	170-199	110-129
High	≥ 200	≥ 130

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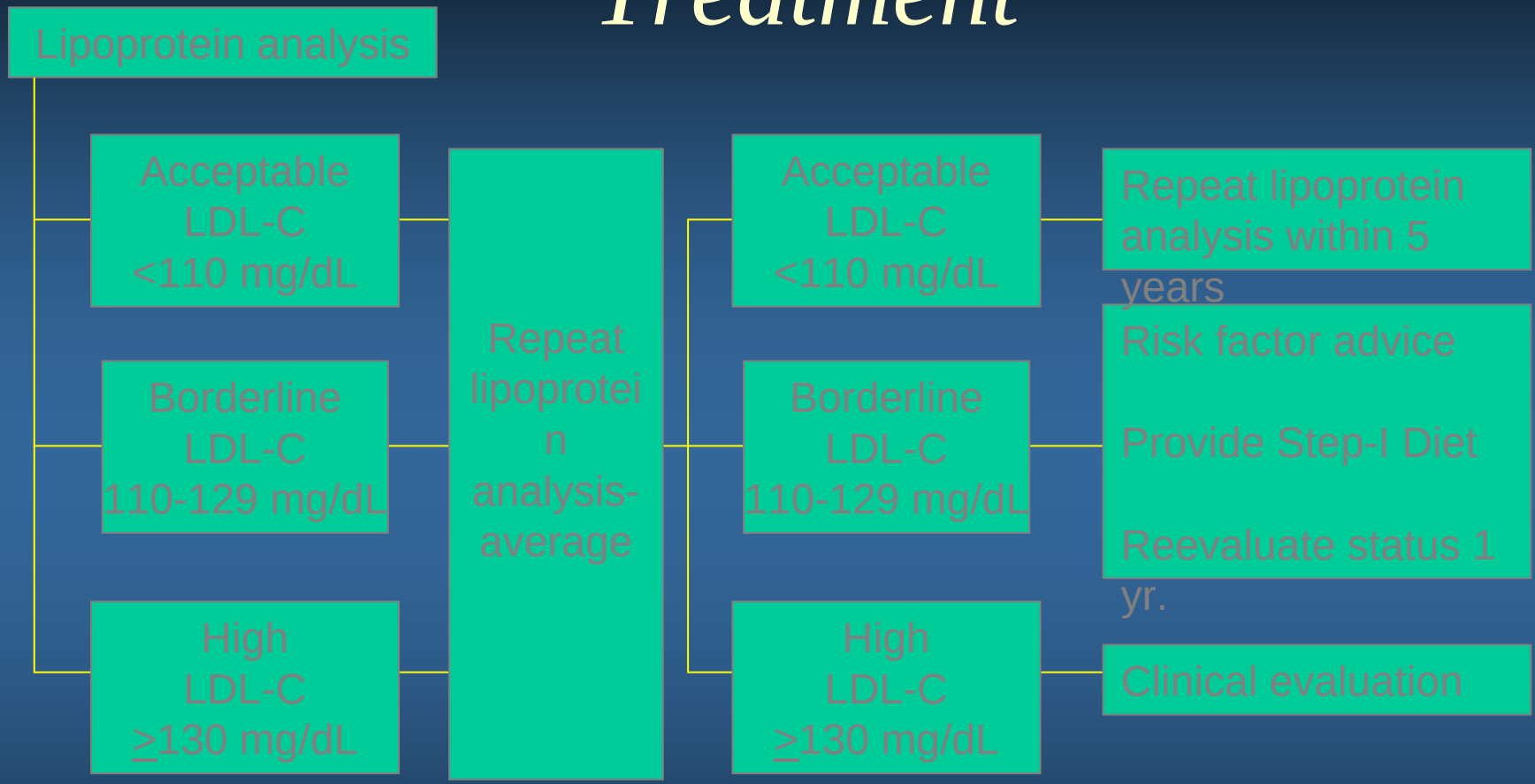
Treatment



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Hypercholesterolemia

- In 15% of children with TC = 200-240 mg/dl, LDL-C is below 15th percentile, but HDL-C is increased (hyperalphalipoproteinemia) associated with decreased risk of atherosclerotic disease

Clinical Evaluation

- History, physical exam, lab tests
  - Evaluate for secondary causes
  - Evaluate for familial disorders
- Intensive clinical intervention

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Clinical Evaluation

- Clinical Evaluation (history, physical exam, lab tests
  - Evaluate for secondary causes
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Clinical Evaluation

- Screen all family members
- Set goal LDL-cholesterol
  - minimal: <130 mg/dL
  - ideal: <110 mg/dL
- Step-One Diet, then Step-Two Diet

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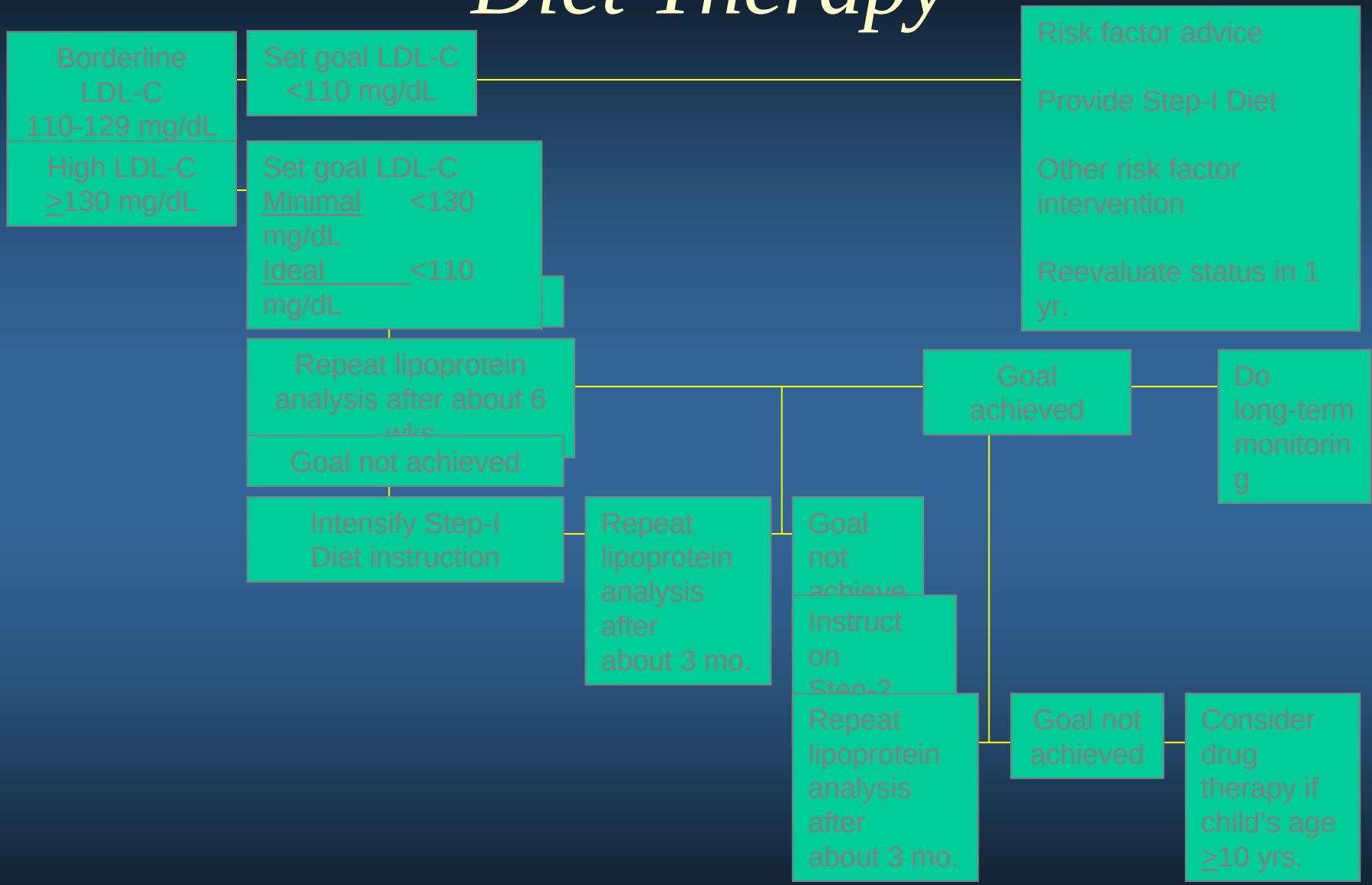
Diet Therapy



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The TLC Diet

Nutrient	Recommended Intake
Saturated fat*	< 7% of total calories
Polyunsaturated fat	up to 10% of total calories
Monounsaturated fat	up to 20% of total calories
Total fat**	25-35% of total calories
Cholesterol	< 200 mg/day
Carbohydrate***	50-60% of total calories
Fiber	20-30 g/day
Protein	15% of total calories
Total calories	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain.

*intake of trans-fatty acids should be low (not on food labeling)
**TG $\geq$ 500 mg/dl , fat intake should be $\leq$ 15% of total calories
***derived predominantly from foods rich in complex carbohydrates, including grains (especially whole grains), fruits, and vegetables

NCEP ATP III

Major Cardiovascular Risk Factors

- Age (male >45; female > 55 or premature menopause without estrogen replacement)
- Family history of premature atherosclerosis in 1st degree relative (<55 male; <65 female)
- Cigarette smoking
- Hypertension
- Diabetes mellitus

Major Cardiovascular Risk Factors

- Elevated LDL-cholesterol
- Low HDL-cholesterol (<40 mg/dl)
- -Note: high HDL-C >60 mg/dl is considered a negative risk factor
- Physical inactivity
- Obesity

Emerging Risk Factors

- Elevated lipoprotein (a) [Lp(a)]
- Hyperhomocysteinemia
- Proinflammatory factors (eg, CRP)
- Prothrombotic factors (eg, fibrinogen)
- Impaired fasting glucose (the metabolic syndrome

The Metabolic Syndrome

- Genetic and Environmental influences cause hyperinsulinemia, which causes:
  - Glucose intolerance
  - Small, dense LDL
  - Increased triglycerides
  - Decreased HDL-C
  - Hypertension
  - Increased fibrinogen and Plasminogen activator inhibitor 1
  - Microalbuminuria, hyperuricemia

Most or all of which, contribute to Coronary Heart Disease

Treatment of Dyslipidemias

- Diet
  - Step I American Heart Association Diet
  - Step II American Heart Association Diet
  - ? Therapeutic Lifestyle Change (TLC) Diet
  - Decrease calories
  - Decrease simple sugars
  - Increase dietary fiber
- Increase physical activity
  - Aerobic
  - Daily living
  - Decrease sedentary time

Treatment of Dylipidemias in Chidren: Beyond NCEP

- Carefully consider medications beyond bile acid sequestrants
  - Age: “> 10 years” or earlier
  - Significant family history
  - Inadequate response to TLC with good compliance
  - Inadequate response to bile acid sequestrant if used

Treatment of Dylipidemias in Chidren: Beyond NCEP

- Assess and treat multiple risk factors (ATP III)
  - Dyslipidemia-LDL & TC, but also TG or non-HDL and HDL; consider Lp(a)
  - Weight/adiposity-consider The Metabolic Syndrome (hyperinsulinemia)
  - Physical inactivity
  - Hypertension
  - Family history
  - Smoking
  - Consider homocysteine

Indications for Drug Therapy

- LDL-c ≥ 190 mg/dl
- LDL-c ≥ 160 mg/dl AND family history of premature cardiovascular disease (<55 yrs) or 2 or more other risk factors present after vigorous attempts to control these risk factors
- Risk factors: smoking, hypertension, low HDL-C (< 35 mg/dl), severe obesity (≥ 95th %-ile; ? BMI ≥ 95th %-ile), diabetes mellitus, metabolic syndrome, physical inactivity

Treatment of Dyslipidemias

- Specific nutrients
  - Phytosterols and phytostanols
  - Fish oil (omega-3 fatty acids)
  - Antioxidants
  - Folate (1 mg/Day)
  - Soy proteins

Treatment of Dyslipidemias

- Medications
  - Non-absorbed
    - Supplemental fiber (psyllium)
    - Bile acid sequestrants
    - Cholestyramine (Questran, etc.)
    - Colestipol (Colestid)
    - Colesevelam (WelChol)

- Absorbed
  - HMG-CoA reductase inhibitors (“statins”)
    - Atorvastatin (Lipitor)
    - Simvistatin (Zocor)
    - Pravastatin (Pravachol)
  - Nicotinic acid (niacin)
    - Niaspan
  - Fibric acid derivatives (“fibrates”)
  - Cholesterol absorption inhibitors
    - Ezetimibe (Zetia)

Pharmacotherapy: Lipid Modifying Effects

	LDL-C	HDL-C	TG
Bile acid Sequestrants	↓ 15-20%	↑ 5%	variable
HMG-CoA Reductase Inhibitors	↓ 20-60%	↑ 5-15%	↓ 10-40%
Fibric acid Derivatives	variable, ↓ 10-15%	↑ 5-20%	↓ 20-50%
Nicotinic acid	↓ 20-30%	↑ 15-35%	↓ 20-50%

Dyslipidemias in Children: Principles of Therapy

- Emphasize that it is NOT a disease or disorder (generally)
- Reassure that it does NOT doom one to heart disease
- Adopt a different time scale from acute problems
- Prescribe Therapeutic Lifestyle Changes for ALL

Dyslipidemias in Children: Principles of Therapy

- Don’t just treat the numbers-base pharmacotherapy on patient/family readiness/probable compliance, family history, physical examination, the lipid profile (and other data)
- Make small changes/use moderation/allow “cheating”

Dyslipidemias in Children: Principles of Therapy

- Assess and address other risk factors
- Follow-up/assess compliance
- Keep a positive attitude
- Keep patient safety 1st and foremost

THANKS!