

The “D” in Dyslipidemia: How to Identify and Manage Childhood Dyslipidemia

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Disclosures

- I have no disclosures



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Learning Objectives

- **D**efine the lipoprotein subtypes
- Learn how to **d**iagnose dyslipidemia using the NHLBI screening guidelines for children and adolescents
- Understand appropriate **d**iet and lifestyle ("**d**oing") treatment options
- Identify which patients would qualify for **d**rug (statin) therapy



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Clinical Case I

- 13-year-old male
 - Lipids checked due to family history of hypercholesterolemia and premature coronary artery disease (CAD)
- Father with myocardial infarction at 41 years, s/p coronary artery bypass graft
- Paternal grandfather with hypercholesterolemia and premature CAD
- 15 yo brother with hypercholesterolemia, treated with statin



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Clinical Case II

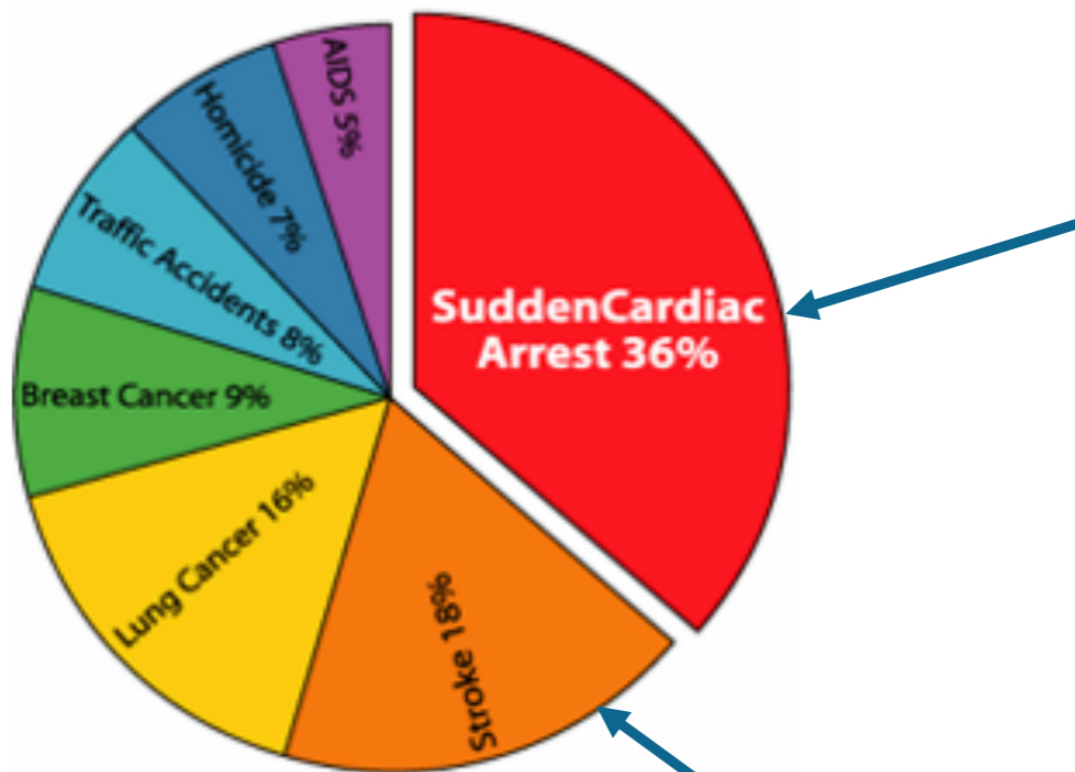
- 10-year-old female
 - Universal screening
- Family history:
 - Father and mother overweight
 - Maternal uncle treated for hypertriglyceridemia
 - Maternal grand-uncle had diabetes and bypass surgery in his 60s



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CVD and Death in the U.S.

Causes of Death Annually for all Americans

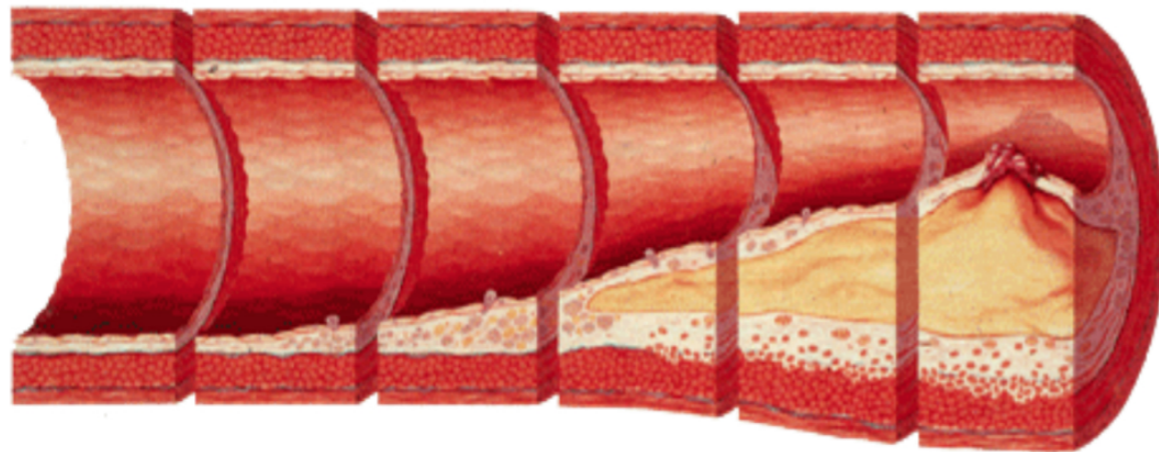


It begins in childhood

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Lipids and Risk Factors

- Children with abnormal lipid levels are more likely to have lipid abnormalities in adulthood
- The number of cardiovascular risk factors is proportionate to the severity of asymptomatic coronary and aortic atherosclerotic heart disease



Benson et al N Eng J Med 1998,338:1650-1656



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"Definitions"



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Lipoprotein Subtypes

- LDL-C (low density lipoprotein; “bad or L=lousy”)
 - Formed from VLDL or chylomicrons
 - Saturated, *trans* fats increase LDL-C
 - Major carrier of cholesterol into body tissues
- HDL-C (high density lipoprotein; “good or H=heart healthy”)
 - Synthesized in liver and gut
 - Major carrier of cholesterol *away* from body tissues
- Triglycerides (TG)
 - Major form of fat in body
- Non-HDL-C*
 - Includes all atherogenic apolipoprotein B-containing lipoproteins: VLDL, intermediate-density lipoprotein (IDL), LDL, and lipoprotein(a)



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Most Recent NHLBI Guidelines

- Integrated age-specific cardiovascular risk reduction guidelines published 12/2011
 - Lipids and lipoproteins ← **Universal Screening**
 - Overweight/obesity
 - Hypertension
 - Diabetes mellitus and metabolic syndrome
 - Nutrition/diet
 - Physical activity
 - Tobacco

Kavey REW, Simons-Morton DG, de Jesus JM and the Expert Panel. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics 2011;128: S1-44.



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Rationale for Universal Screening

- Early atherosclerosis exists in young patients with elevated cholesterol
- Early treatment of CVD risk factors in youth is effective
- Screening with family history alone misses 30-60% of children with dyslipidemia
- Lipid disorders are common in children
 - Increasing with overweight and obesity

Kavey REW, Simons-Morton DG, de Jesus JM and the Expert Panel. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics 2011;128: S1-44.



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Prevalence of Dyslipidemia

- 20% of adolescents have at least one lipid abnormality
 - 8% high LDL-C
 - 8% low HDL-C
 - 10% high triglycerides



National Health and Nutrition Examination Survey III (NHANES) (2010). Prevalence abnormal lipid levels among youth: US 1999-2006.



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Laboratory Testing

- **Non-fasting lipid profile (non-FLP)**
 - Total-C, HDL-C
 - Calculate Non-HDL-C = Total cholesterol – HDL-C
- **OR**
- **12-hr fasting lipid profile (FLP)**
 - Total-C, HDL-C, TG
 - If fasting TG < 400 mg/dL:
 - Calculate LDL-C = (Total-C) – (HDL-C) – (TG/5)
 - If fasting TG ≥ 400 mg/dL
 - Calculate Non-HDL-C = Total cholesterol – HDL-C



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Use of Non-HDL-C

- Accurate in non-fasting state
- In adults:
 - Non-HDL-C = better predictor of CV events than LDL-C
- In children:
 - Non-HDL-C and LDL-C are equally good predictors of adult lipid levels
- In epidemiologic studies:
 - Non-HDL-C correlates with raised lesions and subclinical atherosclerosis on vascular imaging in childhood and at autopsy



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Diagnosis

WHEN AND HOW TO SCREEN
FOR DYSLIPIDEMIA



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Lipid Screening < Age 2 years

- No lipid screening



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Lipid Screening: Ages 2-8 years

- **No Routine Screening**
- Measure FLP twice & average results if:
 - Parent with total cholesterol ≥ 240 mg/dl
 - Premature CVD in first or second degree relatives
 - < 55 years males and < 65 years females
 - Diabetes (Type I or II)
 - Hypertension
 - BMI > 85 th percentile
 - Cigarette smoking (or secondhand smoke)
 - Chronic/end-stage kidney disease/post-renal transplant
 - Nephrotic syndrome
 - Post-orthotopic heart transplantation
 - Kawasaki disease, with current or regressed aneurysm
 - Chronic inflammatory disease
 - HIV infection

Kavey REW et al. Pediatrics 2011;128: S1-44



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Lipid Screening: Ages 9-11 years

- Universal Screening
 - Measure once between 9-11 years
 - Non-FLP:
 - Obtain FLP twice if
 - non-HDL \geq 145 mg/dL
 - HDL $<$ 40 mg/dL
- OR**
- FLP:
 - Repeat FLP if
 - LDL-C \geq 130 mg/dL
 - non-HDL-C \geq 145 mg/dL
 - HDL-C $<$ 40 mg/dL
 - TG \geq 100 mg/dL ($<$ 10 yrs) or TG \geq 130 mg/dL (\geq 10 yrs)



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Lipid Screening: Ages 12-16 years

- **No routine screening**
- If new knowledge of CV risk (same as 2-8 years), measure FLP twice and average results



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Lipid Screening: 17-21 years

Universal Screening

Measure once between 9-11 years:

Ages 17-19 yrs

- Non-FLP:

- Obtain FLP twice if
 - non-HDL \geq 145 mg/dL
 - HDL $<$ 40 mg/dL

OR

- FLP:

- Repeat if
 - LDL-C \geq 130 mg/dL
 - non-HDL-C \geq 145 mg/dL
 - HDL-C $<$ 40 mg/dL
 - TG \geq 130 mg/dL

Ages 20-21 yrs

- Non-FLP:

- Obtain FLP twice if
 - non-HDL \geq 190 mg/dL
 - HDL $<$ 40 mg/dL

OR

- FLP:

- Repeat if
 - LDL-C \geq 160 mg/dL
 - non-HDL-C \geq 190 mg/dL
 - HDL-C $<$ 40 mg/dL
 - TG \geq 150 mg/dL



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Lipid Levels in Children and Adolescents

Category	Acceptable mg/dL	Borderline mg/dL	High mg/dL	Low mg/dL
TC	<170	170-199	≥200	
LDL-c	<110	110-129	≥130	
Non HDL-c	<120	120-144	≥145	
TG				
0-9yr	<75	75-99	≥100	
10-19yr	<90	90-129	≥130	
HDL-c	>45	40-45		<40

Cut points for a high or borderline high value are 95th and 75th percentile, respectively. Cut points for a low or borderline low value are 5th and 25th percentile, respectively.

*Kwiterovitch P, J Clin Endocrinol Metab 2008,
Kavey REW et al. Pediatrics 2011;128: S1-44*



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Lipid Levels in Young Adults 20-24

Category	Low mg/dL	Borderline mg/dL	Acceptable mg/dL	Borderline mg/dL	High mg/dL
TC	—	—	<190	190–224	≥225
LDL cholesterol	—	—	<120	120–159	≥160
Non-HDL cholesterol	—	—	<150	150–189	≥190
Triglycerides	—	—	<115	115–149	≥150
HDL cholesterol	<40	40–44	>45	—	—

Cut points for a high or borderline high value are 95th and 75th percentile, respectively. Cut points for a low or borderline low value are 5th and 25th percentile, respectively.

*Kwiterovitch P, J Clin Endocrinol Metab 2008,
Kavey REW et al. Pediatrics 2011;128: S1-44*



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Clinical Case I (continued)

- Physical Exam:
 - Vitals:
 - BMI 19.4 (50th %)
 - Blood pressure 120/74 (86th %)
 - Pulse 72 bpm
 - PE: benign, no xanthomas, Tanner Stage II
- Labs, mg/dL (average of 2)
 - TC 444 (> 95%), HDL-C 64 (50-75%), LDL-C 366 (> 95%), TG 69 (50-75%)
 - Thyroid functions, UA, Glucose, Insulin, AST/ALT, CK: normal



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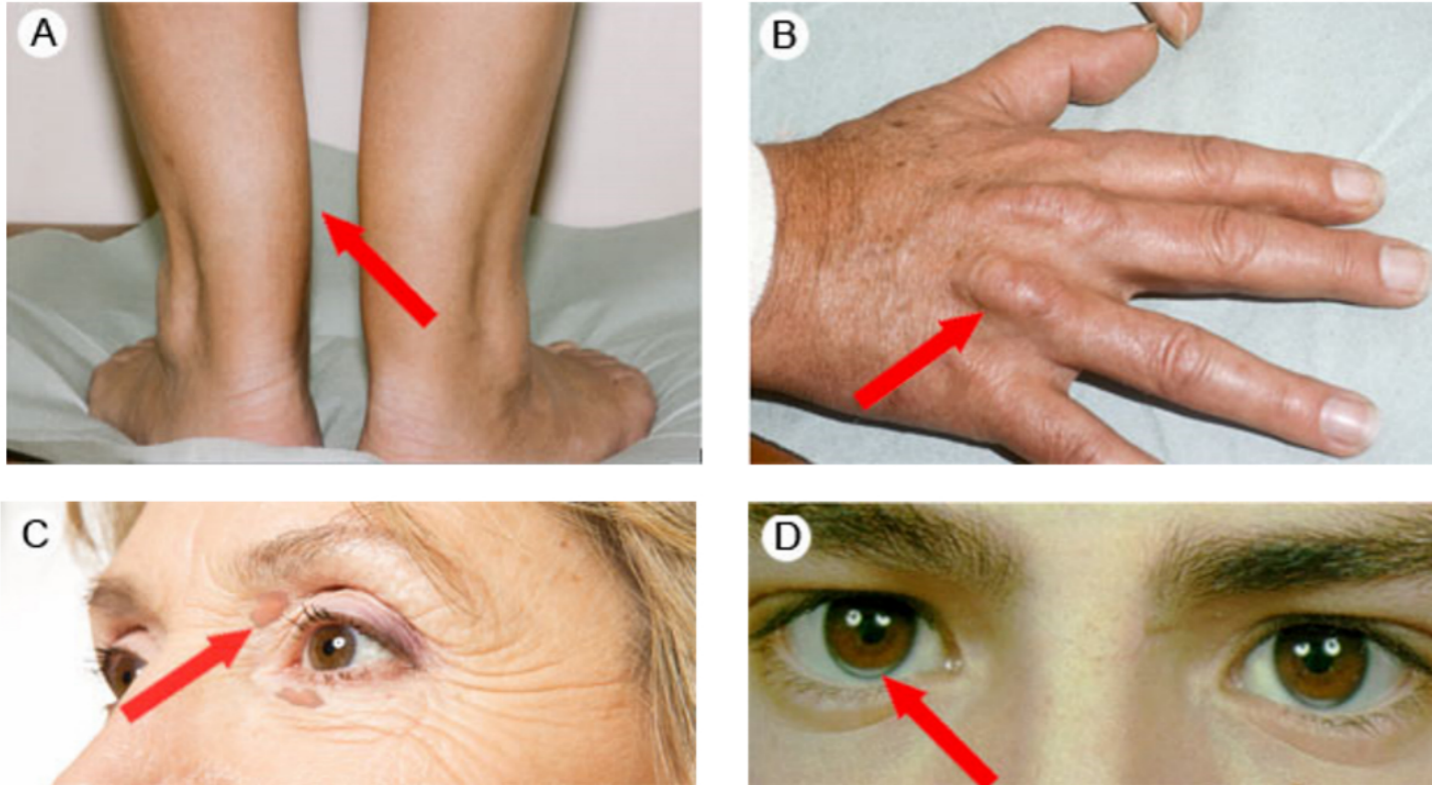
Familial Hypercholesterolemia (FH)

- Autosomal dominant inheritance
 - ~1:200-1:500 prevalence (heterozygous), ~1:1,000,000 (homozygous)
- Mutation in LDL-C receptor or apoB-100
- Heterozygous FH
 - TC \geq 270 mg/dL, LDL-C \geq 160 mg/dL
 - If untreated, risk of CVD
 - Men: 80% by 60 years old
 - Women: 45% by 60 years old
- Homozygous FH
 - TC > 700-1200 mg/dL, LDL-C > 400 mg/dL
 - Death from MI < 30 if untreated
 - Usually requires LDL apheresis



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Physical Manifestations of FH



(A) Achilles tendon xanthoma, (B) extensor tendons xanthoma, (C) palpebral xanthelasma, (D) Corneal arcus

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"Diet"



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Children with Dyslipidemia, Overweight, or at Risk for CVD

- Total fat 25%-30% daily kcals
- Saturated fat < 10% daily kcals
 - Aim for < 2 grams saturated fat/serving
- Mono- and poly-unsaturated fats up to 20% daily calories
- Avoid *trans* fats
- Zero sweetened beverages
- ≥ 5 servings fruits & vegetables daily
- Fiber: Age + 5 g/day (2-10 yrs)
 - 14 g/1000kcal (11-21 yr)
 - Goal: 2-3 grams of fiber/serving or slice



NCEP expert panel of blood cholesterol levels in children and adolescents. Pediatrics 1992;89:495-501.

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Diet: High LDL-c

- After 3-6 months of low-saturated fat diet and LDL-C remains >130 mg/dL
 - Reduce saturated fat intake to $\leq 7\%$ of total calories
- Recommend meeting with dietitian
 - Make changes without compromising nutrition
 - Food choices at home and other places
 - Friend's houses, restaurants, school, etc.
- Soluble fiber
 - Psyllium (enriched cereal or supplements, Metamucil)
 - 6 g/d for children 2–12 years
 - 12 g/d for those ≥ 12 years



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Clinical Case II

- Physical exam:
 - Vitals:
 - BMI: 27.0 kg/m² (>95%)
 - Blood pressure 114/70 (<90%)
 - Pulse: 75 bpm
 - PE: innocent murmur
- Labs, mg/dL:
 - TC: 213 mg/dL (>95%), HDL-C: 27 (<5%), LDL-C: 140 (>95%), TG: 229 (>95%)
 - Thyroid functions, ALT/AST, glucose, insulin, UA: normal



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Familial Combined Hyperlipidemia

- Very common lipid disorder
 - 0.5% - 2% of the population
 - Autosomal dominant
 - Phenotypic variability between family members
- Common lipid phenotype:
 - TC 250-350 mg/dL, LDL-C > 160 mg/dL, TG 200-400 mg/dL, low HDL
- No unique clinical features
- 10% of all patients with MI < 60 years



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Obesity-related Dyslipidemia

- Difficult to differentiate from familial combined dyslipidemia
- More common with obesity epidemic
- Common lipid phenotype:
 - High TG, low HDL, normal to mildly increased LDL
- Improves with diet, weight loss, exercise
 - Usually no pharmacologic therapy needed, just hard work!
 - Focus on reducing simple carbohydrates and saturated fat, increasing complex carbohydrates



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Diet: High Triglycerides

- Limit simple sugars and carbohydrates
- Increase fiber and complex carbohydrates
- Omega-3 fatty acids
 - Foods such as: wild salmon, ground flaxseed, walnuts, winter squash
 - EPA + DHA, 2-4 grams/day
 - Hard to get through diet alone
 - OTC or prescription
 - DHA component *may* slightly raise LDL-C
- Weight loss or stabilization

Kris-Etherton PM et al, Circulation 2002.



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"Doing"



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Activity Recommendations

- All children ≥ 2 years should participate in 1 hour of enjoyable, moderate-vigorous intensity activities **daily**
- Limit sedentary activity (computer, television, texting, etc) to < 2 hr/day



www.cdc.gov



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"Drugs"



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When to Consider Medications?

- After intensive diet and lifestyle changes for 6 months in children ≥ 10 years, ≥ 8 years in high-risk patients
- Statin is first-line therapy
- Target LDL
 - Goal < 130 mg/dL
 - Ideal < 110 mg/dL



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Recommendations for Statin Therapy

Risk Factor

- No risk factors for premature CVD
- Positive family history of premature CVD, *or* 1 high-risk factor/condition *or* ≥ 2 other moderate-risk factors/conditions
(see Risk Factor/Condition Table)
- ≥ 2 high risk factors/conditions *or* 1 high + 2 moderate risk factors/conditions *or* clinical cardiovascular disease
(see Risk Factor/Condition Table)

Recommended LDL-C Cut Points

LDL-C ≥ 190 mg/dL

LDL-C ≥ 160 mg/dL

LDL-C ≥ 130 mg/dL



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Risk Factors/Conditions: Statin Initiation

• High risk

- Hypertension requiring drug therapy
- Cigarette smoking
- Severe obesity (BMI \geq 97th percentile)
- Diabetes (Type I and Type 2)
- Chronic/end-stage kidney disease/post-renal transplant
- Post-orthotopic heart transplantation
- Kawasaki disease, currently with aneurysm

• Moderate risk

- Hypertension (blood pressure $>$ 95th percentile for gender and age) not requiring drug therapy
- Obesity (BMI \geq 95th percentile but $<$ 97th percentile)
- HDL-C $<$ 40 mg/dL
- Kawasaki disease with regressed aneurysm
- Chronic inflammatory disease
- HIV infection
- Nephrotic syndrome



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Statins Approved for Children

Pravastatin (Pravachol ®) <i>*generic*</i>	10-20 mg/day (8-13 yrs) 10-40 mg/day (14-18 yrs) 20-80 mg/day (> 18 yrs)
Lovastatin (Mevacor ®)	10-40 mg/day (10-17 yrs)
Simvastatin (Zocor ®) <i>*generic*</i>	5-40 mg/day (10-17 yrs)
Atorvastatin (Lipitor ®) <i>*generic*</i>	10-20 mg/day (10-17 yrs) 10-80 mg/day (≥ 18 yrs)
Rosuvastatin (Crestor ®) <i>*generic*</i>	5-40 mg/day (10-17 yrs)



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Possible Statin Side Effects

- Myalgia, myositis, rhabdomyolysis
 - Obtain baseline CK, and follow symptoms
- Elevation of LFTs (monitoring recommendation changed Feb 2012)
 - Obtain baseline LFTs, after medication initiation and any change in medication
- Increased fasting glucose and HgbA1c (potential side effect added Feb 2012)
 - Baseline fasting glucose. Monitor glucose and HgbA1c if child has risk factors for developing diabetes
- Teratogenic
 - Consider birth control for girls/abstinence

*Pasternak RC et al, Circulation 2002;
Thompson ED et al, JAMA 2003.*



Caption text

Clinical Case I

- Severe heterozygous FH: LDL goal < 130 mg/dL
- Labs I (in mg/dL):
 - TC 444 (> 95%), HDL-c 64 (50-75), LDL-C 366 (> 95), TG 69 (50-75), ALT/AST, CK: normal
- Atorvastatin 10mg
- Labs II, 2 months later:
 - TC 275 (> 95), HDL-c 63 (50-75), LDL-C 202 (> 95), TG 51 (5-50)



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Clinical Case I

- Atorvastatin 20mg
- Labs III, 2 months later
 - TC 244 (> 95), HDL-c 66 (50-95), LDL-C 165 (> 95), TG 67 (50-75)
- Atorvastatin 40mg
- Labs IV, 3 months later
 - TC 221 (> 95), HDL-c 73 (50-95), LDL-C 138 (> 95), TG 51 (5-50)



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Clinical Case II

- Familial combined vs obesity-related dyslipidemia
- Lab I:
 - TC: 213 (>95), HDL-C: 27 (<5), LDL-C: 140 (>95), TG: 229 (>95)
- Increase physical activity, decrease soda, 10 lb weight loss
- Lab. II, 6 months later:
 - TC: 172 (>95), HDL-C: 32 (<5), LDL-C: 125 (90-95), TG: 73 (60)



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Summary: Screening

- **Universal screening once age 9-11 yrs and 17-21 yrs**
 - Fasting lipid profile or a non-fasting lipid profile
- **At-risk 2-8 yr and 12-16 yr olds**
 - Fasting lipid profile



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Summary: Optimal Lipid Levels

- LDL-C: < 110 mg/dL
- TG: < 75 mg/dL if < 10 yrs old
TG: < 90 mg/dL if \geq 10 yrs old
- HDL-C: \geq 45 mg/dL
- Non-HDL-C: < 120 mg/dL



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Summary

- Consider statin therapy
 - If despite lifestyle changes and age ≥ 10 years
 - LDL-C remains ≥ 190 , ≥ 160 , or ≥ 130 based on risk factor profile
- Hypertriglyceridemia
 - Usually responds to decreased simple carbs, increased physical activity, weight loss/stabilization
 - Consider high-dose fish oil if after focused lifestyle changes
 - TGs remain 250-499 mg/dL



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Lipid Heart Clinic

- Located at CHOP Main and Virtua at Voorhees, NJ
- New patients 2-18 years with lipid abnormalities; established patients followed through college, if desired
- If labs not in CHOP system, please fax to: 215-590-4978
- Parents can call 215-590-4040 to schedule
- Questions? 215-590-1804



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