Dyslipidemia in Children

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None

Objectives

- Discuss guidelines regarding lipid screening and management in children and adolescents
  - Screening
  - Initiation of therapy
- Review statin therapy in children and adolescents.

Cholesterol Screening in Childhood

- **2011: National Heart, Lung, and Blood Institute (NHLBI) (endorsed by American Academy of Pediatrics and American Heart Association)**
  - **Universal screening for:**
    - **Ages 9 to 11 years**
    - **Ages 17 to 21 years**
  - **Selective screening at other ages**
- **2016: US Preventive Services Task Force**
  - **Insufficient evidence to make recommendation regarding benefits and harm.**

Limitations of Guidelines

- No long term studies demonstrating benefit of treatment.
- “Tracking”
- At risk children will be missed
- Efficacy of dietary therapy
- “Labeling”
- No stratification of risk based on:
  - Gender
  - Age at which premature CVD occurs in family

Cholesterol Screening in Childhood
Selective Screening

- **2 to 8 year olds and 12 to 16 year olds with:**
  - **Positive family history**
- **Premature cardiovascular disease (CVD)**

  Premature: < 55 years old in male
  < 65 years old in female
  in first- or second degree relative

  CVD: Cerebrovascular disease
  Documented MI or CVD
  Sudden cardiac death
  Angina

Cholesterol Screening in Childhood Selective Screening

- 2 to 8 year olds and 12 to 16 year olds with:
  - High-level risk factors
- Hypertension that requires drug therapy (BP ≥99th percentile + 5 mmHg)
- Current cigarette smoker
- Obesity with BMI ≥97th percentile
- Presence of a high risk condition: Diabetes (type 1 or type 2)
- Chronic kidney disease/end-stage renal disease/post-renal transplant
- Post-orthotopic heart transplant
- Kawasaki disease with current aneurysms

Cholesterol Screening in Childhood
Selective Screening

- **2 to 8 year olds and 12 to 16 year olds with:**
  - **Moderate-level factors**
- **Hypertension (defined as systolic and/or diastolic BP ≥95th percentile measured on three or more separate occasions) that does not require drug therapy**
- **Obesity:**
  - **For children age 2 to 11 years: BMI ≥95th to <97th %**
  - **For adolescents ≥12 years: BMI ≥85th to <97th %**
- **HDL cholesterol <40 mg/dL**

Cholesterol Screening in Childhood
Selective Screening

- **2 to 8 year olds and 12 to 16 year olds with:**
  - **Moderate-level factors**
- **Presence of a moderate risk condition: Kawasaki disease with regressed coronary aneurysms**
- **Chronic inflammatory disease (eg, systemic lupus erythematosus, juvenile idiopathic arthritis)**
- **HIV infection**
- **Nephrotic syndrome**
- **Adolescent depressive and bipolar disorders**

(2015 AHA recommendation)

Cholesterol Screening in Childhood

- **Preferred initial screening test in children:**
  - **With CV risk: fasting lipid profile (FLP).**
    - **Repeat every two years thereafter.**
  - **Without CV risk: non-HDL-C testing**
    - **Total cholesterol – HDL (non fasting)**
- **Selective screening during puberty due to poor sensitivity and specificity for predicting adult LDL-C levels and increase false-negative results.**

Classification Based on: non-HDL-cholesterol Level

Acceptable: <120 mg/dl

Borderline: 120-144 mg/dl

- **Repeat in 1 year (and average values)**

High: >145 mg/dl)

- **Fasting lipid profile**

Classification Based on: LDL-cholesterol Level

Acceptable: <110 mg/dl

- Repeat testing based on risk factors

Borderline: 110-129 mg/dl

- Lifestyle modification
- Repeat in 1 year

High: >130 mg/dl

- Repeat testing in 2 weeks to 3 months
- Average values of tests
- Provide: full evaluation and management

Very High: > 250

- Refer to a pediatric lipid specialist

Evaluation of Hypercholesterolemia

- **Exclude secondary causes of dyslipidemia.**

  Hypothyroidism, diabetes, renal or liver disease

  Medications: steroids, progestins, Accutane
- **Dietary evaluation**
- **Family history**

  Identify inheritable forms of dyslipidemias.

  Establish age(s) of onset of premature CVD.

ADA Position

- **Obtain a fasting lipid profile in children ≥10 years of age soon after the diagnosis (after glucose control has been established).**
- **If lipids are abnormal, annual monitoring is reasonable.**
- **If LDL cholesterol values are <100 mg/dL repeat lipid profile every 3–5 years.**
- **Initial therapy:**
  - **Optimize glucose control**
  - **Medical nutrition therapy using a Step 2 American Heart Association diet.**

ADA Clinical Practice Recommendations 2017
Diabetes Care 2017;

Dietary Modifications

- **Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents**
  - **Total fat: < 30% of total calories**
  - **Saturated fat: < 8 to 10% of total calories**
  - **Dietary cholesterol: <300 mg/day**
  - **Avoid trans fat as much as possible**
- **Step 2 American Heart Association Diet**
  - **Total fat: < 30% of total calories**
  - **Saturated fat: ≤ 7% of total calories**
  - **Dietary cholesterol: < 200 mg/day.**

Who Should be Treated?

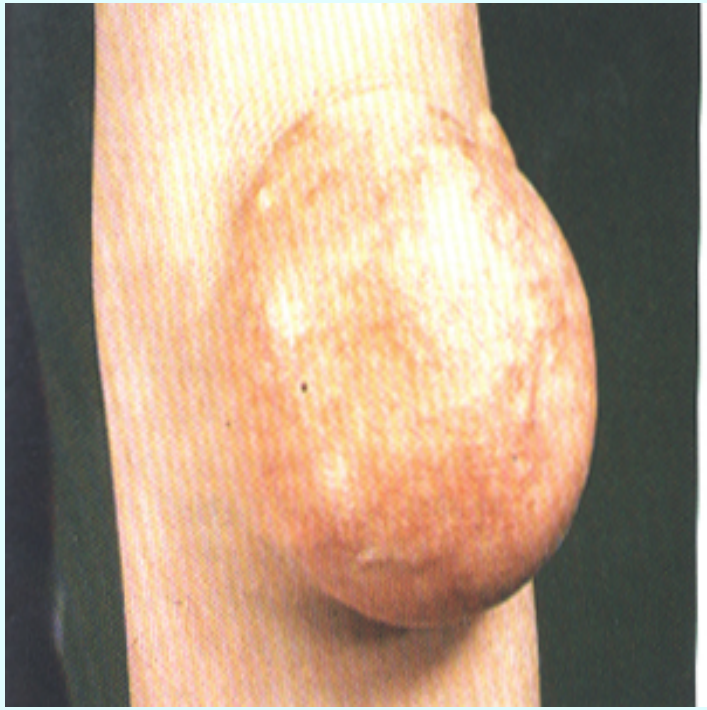
- Children clearly at risk for premature CV disease.
  - Familial hypercholesterolemia (FH)
  - Diabetes
  - Others?
- At what age?
- What medication?

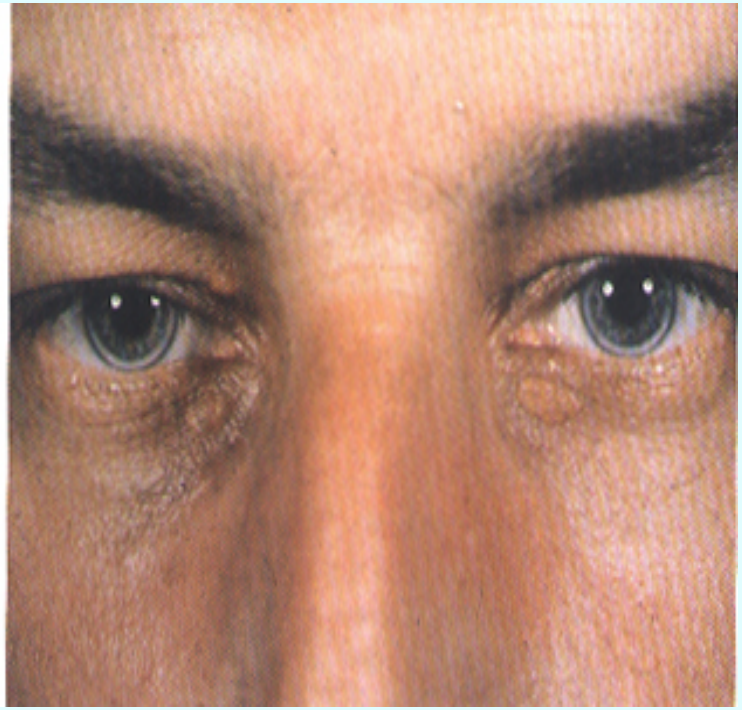
Heterozygous Familial Hypercholesterolemia (FH)

- **Prevalence is 1:250 to1:500**
- **First clinical manifestation (CAD) often in 2nd to 3rd decade (by age 50: 45% of men, 20% of women)**
- **23% of men experience FATAL heart attacks <50 yrs of age** (Stone et al Circulation 1974. 49;476)
- **90% have a MI before age 60**
- **Most adults have: tendon xanthomas or corneal arcus**

Xanthomas rarely occur before age 10

FH Skin Manifestations

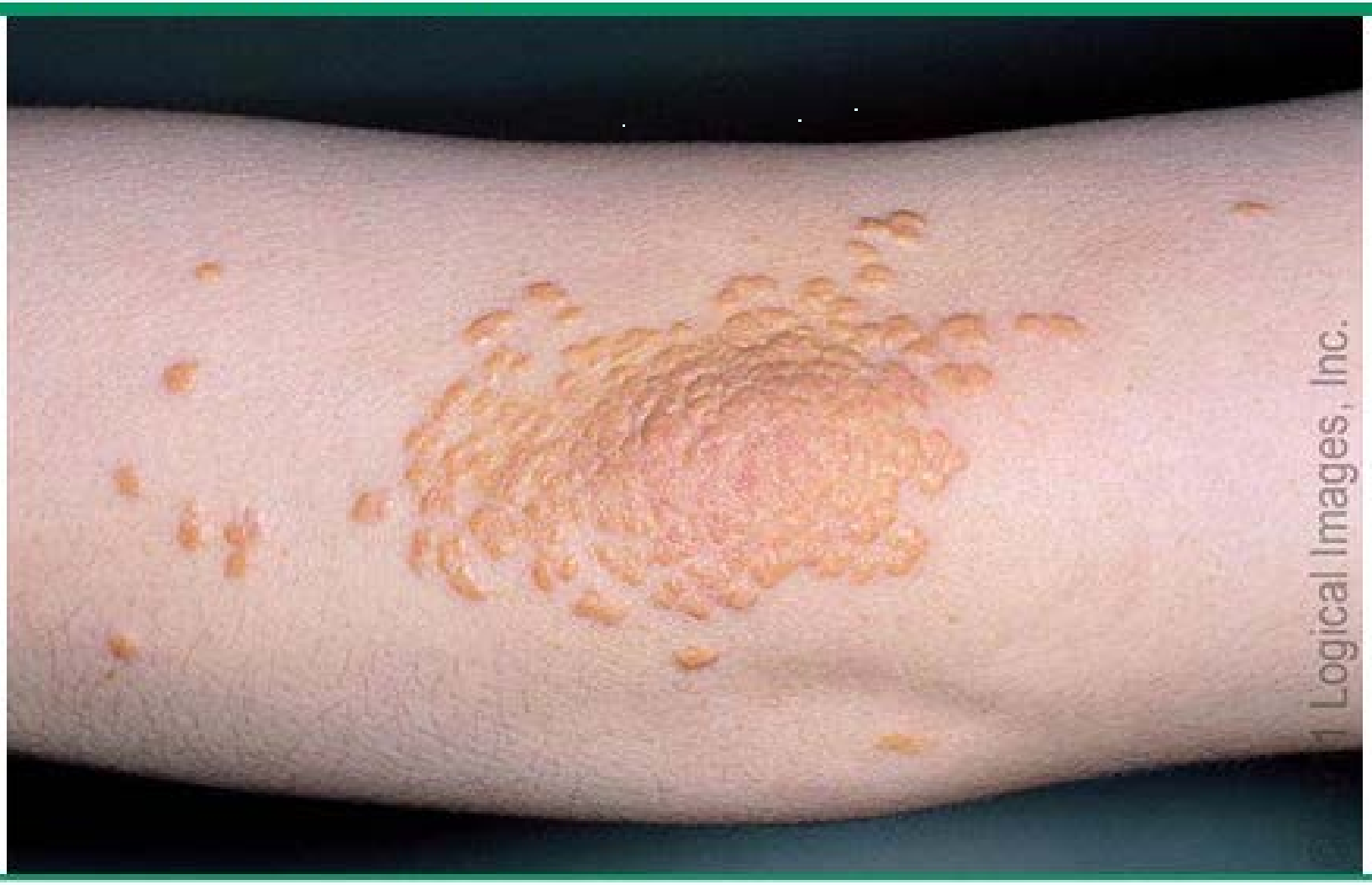




Corneal arcus

Corneal arcus is a white or grey arc or ring around the cornea due to deposition of cholesterol. It is commonly seen in older adults (called arcus senelis), but is an abnormal finding in individuals under age 40.

Tuberous xanthoma



Yellow papules on the elbow in a case of tuberous xanthoma.

Heterozygous Familial Hypercholesterolemia (FH)

Diagnosis

- Autosomal dominant inheritance pattern
- Skin manifestations in family members
- LDL $\geq$ 160mg/dl) with family hx CVD
- LDL $\geq$ 190mg/dl) without family hx CVD
  - Minimizes misclassification between those with and without FH
  - LDL over which medical therapy indicated if other risk factors present

Approximately 12% will not have familial history of hypercholesterolemia or premature CVD

Heterozygous Familial Hypercholesterolemia (FH)

Diagnosis

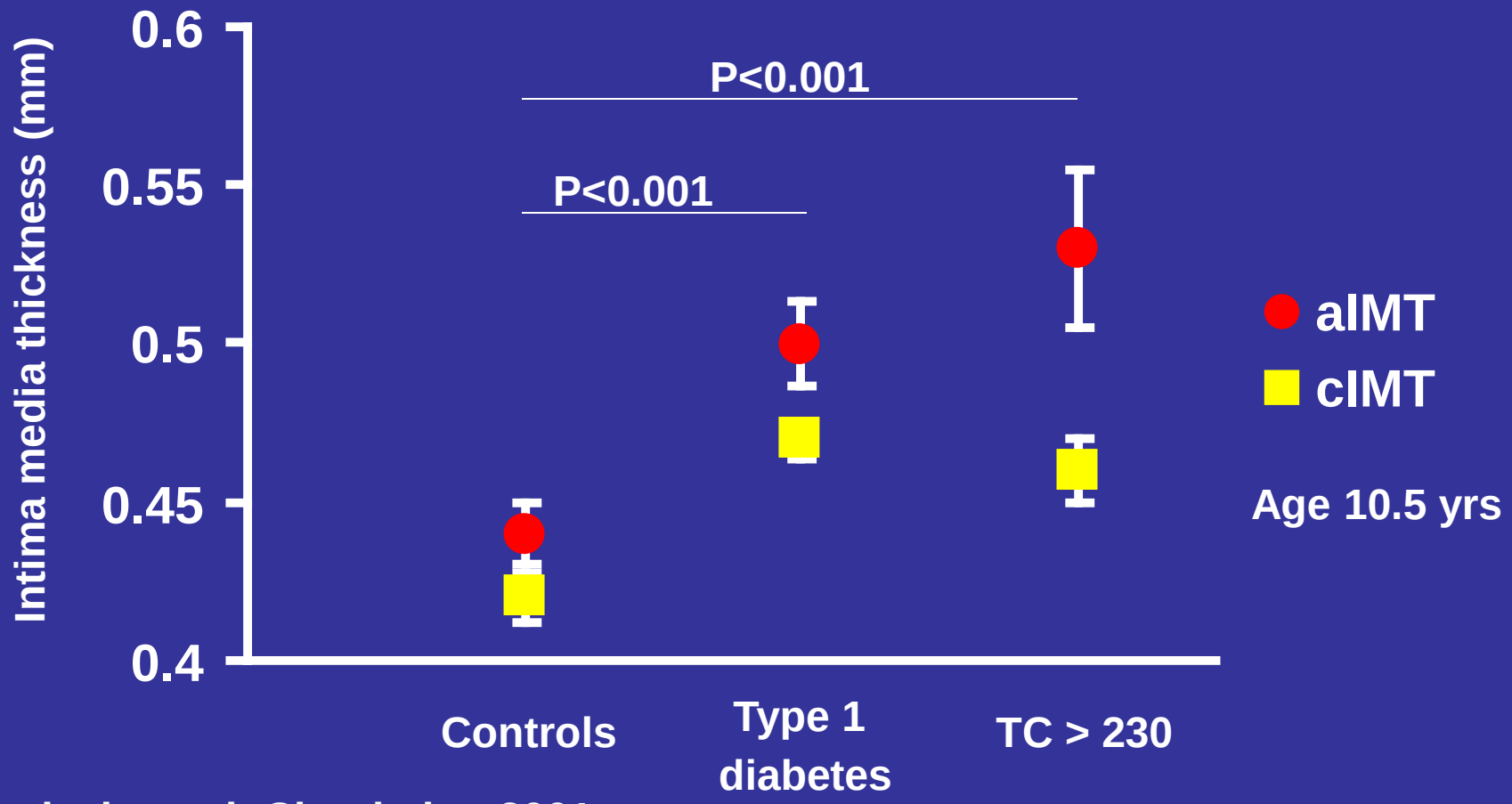
- **Genetic testing is available**
  - **Includes loss of function variants in *APOB***
  - ***PCSK9* pathogenic variants**
  - **Cost of entire panel: $1390**

ADA Position

- **After the age of 10 years, addition of a statin after medical nutrition therapy and lifestyle changes. continue to have**
  - **LDL cholesterol >160 mg/dL**
  - **LDL cholesterol >130 mg/dL and one or more cardiovascular disease risk factors. (following reproductive counseling and implementation of effective birth control due to the potential teratogenic effects of statins).**

ADA Clinical Practice Recommendations 2017
Diabetes Care 2017;

Increased Aortic Intima-Media Thickness in Children



Jarvisalo et al; Circulation 2001

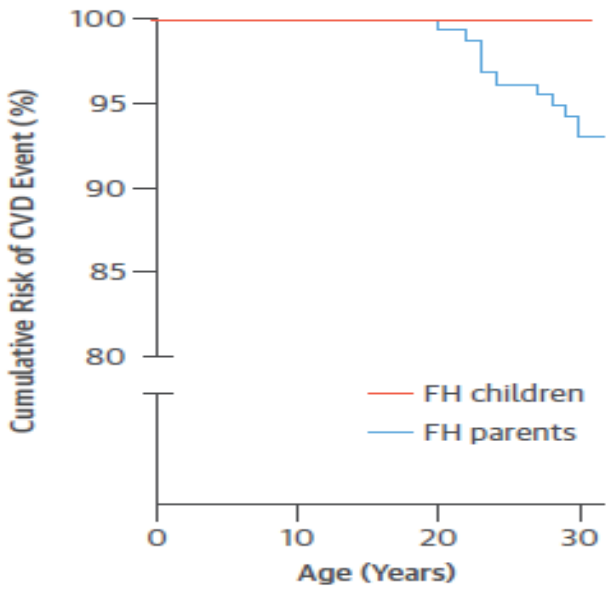
Can Statin Therapy Decrease CV Disease if Started in Childhood?

- 214 pts mean age 14 ± 3 years (8-18 years old) with FH treated with pravastatin 20-40 mg QD.
- 10 year follow up:
  - Mean age 24 + 3 years (18-30 yo)
  - Statin still used by 84%
  - CV disease events determined in pts and parents (mean age 54 years old)
  - Carotid IMT measured in pts and unaffected sibs
  - Outcomes: parents (tx with statin unknown)
    - 14 deceased
    - 41.6% had a CV event

Journal American College of Cardiology 2016;67:455-56.

Can Statin Therapy Decrease CV Disease if Started in Childhood?

FIGURE 1 Kaplan-Meier Curve of CVD-Free Survival



No. at risk				
FH children	214	214	193	3
FH parents	156	156	156	146

Cumulative risk of cardiovascular disease (CVD) events in 213 young adults patients with familial hypercholesterolemia (FH) who started statin therapy in childhood (**orange**) and their 156 affected FH parents (**blue**) for whom statins were available much later in life.

Can Statin Therapy Decrease CV Disease if Started in Childhood?

- **Carotid intimal-medial thickness (IMT) in pts with FH vs unaffected sibs**
  - **Carotid IMT significantly greater in patients compared to unaffected siblings.**
  - **Progression in carotid IMT similar in both groups.**
  - **Age of statin initiation significantly associated with carotid IMT at follow up.**

    JAMA 2014;312:1055-57.

When and How to Treat: NHLBI

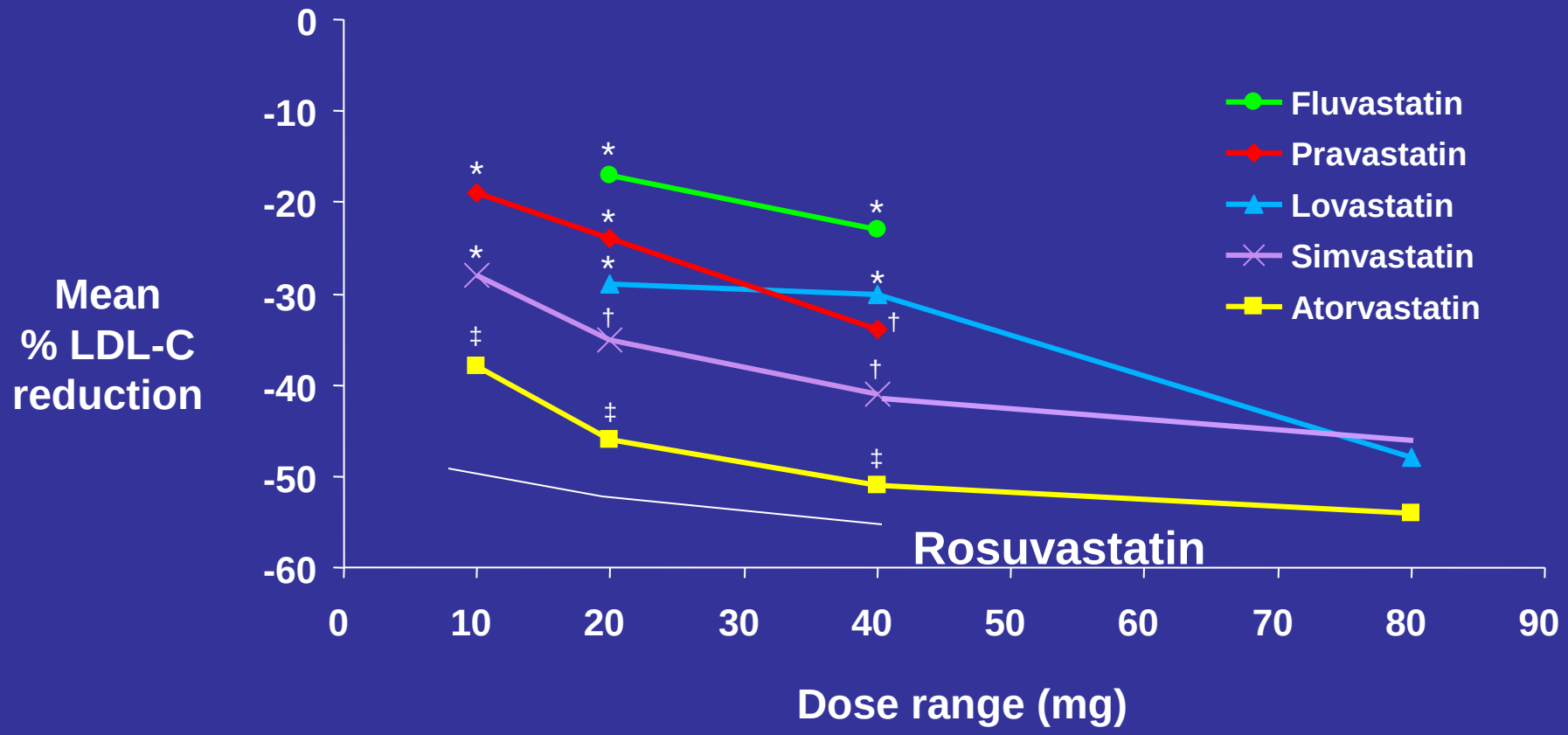
- **LDL cholesterol:**
  - **≥ 190 mg/dl**
  - **≥ 160-189 mg/dl plus**
    - **1 high-level risk factor (H-L RF)**
    - **≥ 2 moderate-level risk factors (M-L RF)**
  - **> 130-159 mg/dl plus**
    - **2 H-L RFs or**
    - **1 H-L RF and ≥ 2 M-L RFs**
- **Age: 10 years old**
- **Statin:**
  - **Monitoring ALT and AST**
  - **Baseline CK and then prn**

Statin Overview

STATIN	NAME	GENERIC	AGE [1]	COST [2]
Atorvastatin	Lipitor	Yes	≥ 10	$99
Fluvastatin	Lescol	Yes	≥ 10	$127
Lovastatin	Mevacor	Yes	≥ 10	$4
Pravastatin	Pravacol	Yes	≥ 8	$84
Rosuvastatin	Crestor	Yes	≥ 8	$225
Simvastatin	Zocor	Yes	≥ 10	$72

1 = Age (years) approved for use
2 = Cost of starting dosage at KY Clinic pharmacy (2017)

Which Statin?



Jones P et al. *Am J Cardiol.* 1998;81:582-587.

Clinical Trials and Review

- **Familial hypercholesterolemia**
  - **Meta-analysis and review of 9 randomized placebo controlled trials (1177 children, aged 4-18; study duration 12-104 weeks)**
    - **Statins showed significant efficacy in lowering LDL cholesterol**
    - **Therapy well tolerated with no significant adverse reactions**

  Cochrane Database of Systematic Reviews 2017; Issue 7.
- **Children and adolescents with diabetes**
  - **No outcome studies**

Lipid-Lowering Medications in Pediatric Type 1 Diabetes

- Retrospective, longitudinal study
- 360 subjects (1994-2004)
- 23 treated with lipid-lowering medications (19 statin only, 3 ezetimibe, 1 fibrate)
- Results:
  - No major adverse effect
  - Premedication mean LDL 203 ± 59 lowered -19% ± 23% after treatment
  - "40%-63% of children with abnormal lipids remain abnormal"

J Pediatr 2007;150:146-50.

Hypertriglyceridemia

- TG: ≥ 200- 499 mg/dL
  - Consider omega-3 fish oil therapy after dietary modification
- Average TG levels >500 mg/dL or a single TG level >1000 mg/dL
  - Risk of pancreatitis
  - Fibric acid derivatives
    - Gemfibrozil
    - Fenofibrate

Conclusion

- There is strong pathological data confirming that CAD starts in youth.
- Many at risk FH children will be missed based on family history alone.
- Cholesterol reduction in children with FH likely reduces or delays CHD.
- There are no long-term studies of cholesterol reduction in children with diabetes.
- Best approach: individualized management.