Discrepancies and Barriers Related to Screening and Treating Hypercholesterolemia in Primary Prevention

Catherine J. McNeal, M.D., Ph.D.
Department of Internal Medicine, Division of Cardiology and Department of Pediatrics
Scott & White, Temple, TX
DISCLOSURE

• I have no disclosures to report.
Overview

• Comparison of pediatric & adult guidelines
  Youth - 2011 NHLBI Expert Panel Guidelines
  Adults – 2013 ACC/AHA Guideline

• Barriers and unknowns related to screening & treatment of dyslipidemia in youth to prevent future CVD

• Should pediatric and adult guidelines be harmonized?
Unique Aspects of the Pediatric Population

• The relation of age to disease expression
• Differences in risk, benefit and cost-effectiveness
• For each risk factor, recommendations must be specific to age, gender (percentile based values) and developmental stage.
Cholesterol Levels and Age

Universal Lipid Assessment

- TC and LDL-C levels fall as much as 10-20% or more during puberty.
- Based on this normal pattern of change in lipid and lipoprotein levels with growth and maturation, age 10 years (range age 9-11 years) is a stable time for lipid assessment in children.
Importance of CVD Prevention in Youth

• The “footprints of premature atherosclerosis” begin in youth and the progression throughout the lifespan is correlated with the number and intensity of risk factors.

• Risk factors for atherosclerosis can be identified in youth. “A population that enters adulthood with lower risk will have less atherosclerosis and lower CVD events.” (NHLBI 2011 Guidelines).

• The primary emphasis in the pediatric population is identification of youth with FH and/or multiple moderately abnormal CVD risk factors.
Progression with Time

Progression over time (yrs):

Normal Artery
Lesion Initiation
Fibro-fatty Stage
Vulnerable Plaque
Plaque Rupture
Fibrous, Calcified Plaque
Endothelial Erosion

Libby. Circulation 2001;104: 365
What is the Evidence?

Paucity of outcomes data:

• Screening vs. no screening; targeted vs. universal screening; treatment vs. no treatment of abnormal risk factors.
• Longitudinal trials over the life-span are impractical and unethical.
• Compared to adults, there is a much smaller pool of available children for inclusion in studies.
• Children are not as static as adults necessitating larger sample sizes for comparable power.
Pediatric Screening & Treatment Guidelines

1992
• Targeted screening based on family history

2006
2008
• Identification of high risk youth + targeted screening based on family history

2011
• Identification of high risk youth + Targeted screening based on family history + Universal screening
  • National Heart, Lung and Blood Institute Expert Panel Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents
  • Pediatrics 2011;128:S1-S44
  • www.nhlbi.nih.gov/guidelines/cvd_ped
**Adult Screening & Treatment Guidelines**

**1988**
- Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults
- Focus on primary prevention in adults with LDL-C ≥160 mg/dL or borderline elevation ≥130 mg/dL and 2+ RF

**1994-2004**
- NCEP-ATPII Intensive management of LDL-C in adults with CHD to lower LDL-C ≤ 100 mg/dL.
- NCEP-ATP III: Introduces CHD risk equivalent diseases, uses 10 y FRS to stratify treatment, identifies adults with MetSyn, non-HDL-c, HDL-c and triglycerides are secondary targets.
- NCEP-ATPIII Update: Definition and treatment of very high risk populations.

**2013**
- ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
- Identifies 4 groups who have definitive benefit from statin Rx in place of LDL-C targets (other groups based on clinical judgment).
2013 American College of Cardiology–American Heart Association Guidelines for Use of Statin Therapy in Patients at Increased Cardiovascular Risk, “ATP IV”

Patients >21 yr of age without heart failure (NYHA class II, III, or IV) or end-stage renal disease (undergoing hemodialysis)
Screen for cardiovascular risk factors
Measure LDL cholesterol

- Clinical atherosclerotic CVD
  - High-intensity statin therapy

- Diabetes mellitus (type 1 or type 2) and age of 40–75 yr and LDL cholesterol 70–189 mg/dl
  - Calculate 10-yr risk of atherosclerotic CVD
    - If risk <7.5%, moderate-intensity statin therapy
    - If risk ≥7.5%, high-intensity statin therapy

- No diabetes mellitus and age of 40–75 yr and LDL cholesterol 70–189 mg/dl
  - Calculate 10-yr risk of atherosclerotic CVD
    - If risk ≥7.5%, moderate-to-high-intensity statin therapy

- LDL cholesterol ≥190 mg/dl
  - High-intensity statin therapy

Synopsis - 2011 Pediatric Guideline

• Prevent the acquisition of risk factors (primordial prevention).
• Dyslipidemia guidelines are integrated with universal screening of all risk factors to identify those with the highest risk of developing premature CVD.
• Guideline recommendations are enmeshed in general pediatric practice, facilitating practice at the primary care level.
Synopsis - 2011 U.S. Pediatric Guidelines

- Calculate BMI annually ≥ 2 years of age
- Measure blood pressure annually ≥ 3 years of age
- Screen high-risk children for hyperglycemia per ADA guidelines age 10+ years
- Screen all children for lipid abnormalities with a fasting (LDL-C) or nonfasting (non-HDL-C) between 9-11 and 17 – 21 years of age in addition to targeted screening in high-risk youth > 2 years of age.
How Do We Justify Recommendations for Universal Lipid Screening in Children?

• In the U.S., significant evidence exists that using family history to screen for premature CVD or evidence of cholesterol disorders as the primary factor in determining lipid screening in children misses approximately 30-60% of children with dyslipidemia. In other countries cascade screening is far more effective with less need for universal screening.

• In the absence of a clinical or historic marker, identification of children with lipid disorders that predisposes them to accelerated atherosclerosis requires universal lipid assessment.

• Conclusion: In the U.S., accurate and reliable measures of family history are often not available.
Justification of Universal Screening: Reverse Cascade Screening

• “Cascade screening fails to achieve sufficient coverage to be a practical method of populations screening.”

• Universal screening in childhood may identify the most families affected by FH.

After ~30 years of screening children, enough adults will be identified for cascade screening to be effective.

Arguments Against Universal Screening

• A selective approach will identify the majority of children with elevated LDL-C and would be the most cost-effective approach.

• On balance there is insufficient evidence of benefit and risks:
  – USPSTF concluded that data were insufficient to make a definitive recommendation for universal screening in children and adolescents
  – Inadequate evidence to show that interventions based on abnormal screening results in youth would be more efficacious than interventions later in the disease process.

• Identification of youth with abnormal values will not result in positive changes in risk factor values.
How are we doing with lipid screening in the U.S. so far?

Pediatric Lipid Study Consortium
Cardiovascular Research Network (CVRN)
Setting: 4 CVRN sites

Population: 539,782 unique boys and girls (51%), 2-20 years old during 2002-2012

- 34% Non-Hispanic White
- 15% Non-Hispanic Black
- 8% Asian/Pacific Islander
- 5% Hispanic
- 38% Other/Unknown
Trend in Pediatric Lipid Testing

p<0.001
Overall Prevalence Trends

- Expected FH prevalence
- Point Prevalence LDL > 190 mg/dL

p = 0.003
# Fundamental Differences

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>Primordial and primary prevention.</td>
<td>Primary and secondary prevention.</td>
</tr>
<tr>
<td><strong>Relationship to Outcome</strong></td>
<td>Distant &gt; 30 yr in most cases.</td>
<td>10-30 yr</td>
</tr>
<tr>
<td><strong>Screening</strong></td>
<td>Targeted screening after 2 yr with FLP.</td>
<td>Universal screening ≥ 20y, FLP. USPTF: FLP men ≥ 35 yr women ≥45 yr.</td>
</tr>
<tr>
<td><strong>Risk Estimate</strong></td>
<td>PDAY risk score represents the odds of having advanced plaque.</td>
<td>10 yr risk of coronary death or nonfatal MI, or stroke age 40 – 75 yr; lifetime (30 yr risk) 20 – 59 yr.</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Based on number of risk factors/conditions</td>
<td>Treatment based on presence/absence of CVD, DM, FH and risk score.</td>
</tr>
</tbody>
</table>
Treatment
“A population that enters adulthood with lower risk will have less atherosclerosis and lower CVD events.”

Unknown: Can lipid lowering therapy starting in youth achieve similar benefits as naturally occurring low levels of LDL-C?
Kaplan-Meier Curve Estimates of Cumulative CHD-survival for hzFH

Versmissen J et al. BMJ 2008;337:bmj.a2423
Statin Therapy in Children

A Systematic Review and Meta-Analysis of Statin Therapy in Children With Familial Hypercholesterolemia


Objective—Functional and morphological changes of the arterial wall already present in young children with heterozygous familial hypercholesterolemia (HeFH) suggest that treatment should be initiated early in life to prevent premature atherosclerotic cardiovascular disease. The purpose of this study was to assess the efficacy and particularly safety of statin therapy in children with HeFH.

Methods and Results—We performed a meta-analysis of randomized, double-blind, placebo-controlled trials evaluating statin therapy in children aged 8 to 18 years with HeFH. Six studies (n=798 children) with 12 to 104 weeks of treatment were included. Total cholesterol, LDL cholesterol, and apolipoprotein B were significantly reduced, whereas HDL cholesterol and apolipoprotein A1 were significantly increased by statin therapy. No statistically significant differences were found between statin- and placebo-treated children with respect to the occurrence of adverse events (RR 0.99; 95% CI: 0.79 to 1.25), sexual development (RR of advancing ≥1 stage in Tanner classification 0.96; 95% CI: 0.79 to 1.17), muscle toxicity (RR of CK ≥10 times the upper limit of normal [ULN] 1.38; 95% CI: 0.18 to 10.82), or liver toxicity (RR of ≥3 times the ULN for ASAT 0.98; 95% CI: 0.23 to 4.26 and for ALAT 2.03; 95% CI: 0.24 to 16.95). We found a minimal difference in growth in favor of the statin group (0.33 cm; 95% CI: 0.03 cm to 0.63 cm).

Conclusion—In addition to the fact that statin treatment is efficacious, our results support the notion that statin treatment in children with HeFH is safe. Thus, even though further studies are required to assess lifelong safety, statin treatment should be considered for all children aged 8 to 18 with HeFH. (Arterioscler Thromb Vasc Biol. 2007;27:1803-1810.)

Key Words: familial hypercholesterolemia ■ children ■ statins ■ safety ■ meta-analysis
Study Inclusion

537 potentially eligible publications

- 527 studies did not meet the following inclusion criteria:
  - Indication: HeFH
  - Population: ≤ 18 years of age
  - Intervention: any statin
  - Study design: randomized placebo-controlled trial

- Ten RCT's on statin therapy in children and adolescents with HeFH

- Four RCT's met ≥ one of the following exclusion criteria:
  - Lipid lowering co-medication
  - Unblinded treatment
  - Duplicate or preliminary report
  - No outcome on lipids, lipoproteins, safety or IMT

= Six RCT's included

CONTROVERSIES

• “…starting aggressive treatment during early childhood, as is currently done and advised by the American Academy of Pediatrics, is probably not necessary to reduce coronary heart disease risk.”

• “Although atherosclerosis is present in children, this process is to a certain extent reversible…”

• “It is probably safe to limit statin treatment of children with heterozygous familial hypercholesterolemia to those whose first degree relatives have severe premature coronary heart disease.”

Versmissen J et al. BMJ 2008;337:bmj.a2423
<table>
<thead>
<tr>
<th>Question</th>
<th>Youth</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decisions for treatment based on specific LDL-C targets?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Decisions for treatment based on number of risk factors and risk conditions?</td>
<td>Yes</td>
<td>No. Decisions for treatment based only on risk conditions</td>
</tr>
<tr>
<td>When to treat with a statin?</td>
<td>Children ≥ 10 yr should be treated with a statin to achieve LDL-C &lt; 130 mg/dL</td>
<td>Adults ≥ 21 yr should be treated with *high-dose statin therapy “if they have not already been diagnosed and treated before this age.” Goal is to achieve ≥50% LDL-C reduction.</td>
</tr>
</tbody>
</table>

“Use of LDL-C targets may result in under-treatment with evidence-based statin therapy or overtreatment with non statin drugs that have not been shown to reduce ASCVD events.”
Defining Risk Factors in Youth

**High-Level Risk Factors**
- Hypertension requiring drug therapy (BP $\geq 99^{th} \% + 5$ mmHg)
- Current cigarette smoker
- Body Mass Index (BMI) $\geq 97^{th} \%$
- Presence of high risk conditions
- Family History of premature CVD

**Moderate-Level Risk Factors**
- Hypertension not requiring drug therapy
- BMI $\geq 95^{th}$ percentile but $< 97^{th} \%$
- HDL-C $< 40$ mg/dl
- Presence of moderate risk conditions

Diabetes mellitus (DM) is also a high-level risk factor but it is classified here as a high-risk condition to correspond with ATP III recommendations

*Pediatrics 2011;128:S1-S44*
Defining Risk Conditions in Youth

High-Level Risk Conditions

• T1 and T2 DM
• Chronic kidney disease/end-stage renal disease/post renal transplant
• Postorthotopic heart transplant
• Kawasaki Disease with current aneurysms

Moderate-Level Risk Conditions

• Kawasaki disease with regressed coronary aneurysms
• Chronic inflammatory disease
  • Systemic lupus erythematosus
  • Juvenile rheumatoid arthritis
• HIV
• Nephrotic syndrome

With the exception of DM, these risk conditions are not carried forward in the adult guidelines.
Differences in Cut Points For Statin Use
## Fundamental Differences in Recommendations for Treatment

<table>
<thead>
<tr>
<th>Youth Criteria</th>
<th>Adult Criteria</th>
<th>Action</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C ≥ 130-189 mg/dL, no FHx, no RF.</td>
<td>LDL-C &lt; 190 mg/dL, no DM, ≤ 7.5% 10-yr ASCVD risk.</td>
<td>Dietary Rx only</td>
<td>Dietary Rx only</td>
</tr>
<tr>
<td>LDL-C ≥ 190 mg/dL.</td>
<td>LDL-C ≥ 190 mg/dL.</td>
<td>Treat with statin</td>
<td>Treat with statin</td>
</tr>
<tr>
<td>LDL-C ≥ 130 mg/dL, age ≥ 10 yr + DM.</td>
<td>Any LDL-C, age 40-75 yr, +DM.</td>
<td>Treat with statin</td>
<td>Treat with statin</td>
</tr>
<tr>
<td>LDL-C ≥ 160-189 mg/dL, + FHx or 1 HL-RF/RC or ≥ 2 ML-RF/RC.</td>
<td>Any LDL-C, with ASCVD.</td>
<td>Treat with statin</td>
<td>Treat with statin</td>
</tr>
<tr>
<td>LDL-C ≥ 130-159 mg/dL + 2 HL-RF/RC or 1 HL + ≥2 ML-R/RCF or CVD.</td>
<td>ASCVD risk above 7.5%</td>
<td>Treat with statin</td>
<td></td>
</tr>
</tbody>
</table>

HL-RF/RC = high level risk factor/risk condition  
ML-Rf = moderate level risk factor/risk condition
Fundamental Differences in Recommendations for Treatment

Case:
• 20 yr old Caucasian male, BMI > 97%tile (41.5 kg/m$^2$)
• +FHx premature CVD
• Lipids:
  TC 198 mg/dL, LDL-C 130 mg/dL, HLD-C 50 mg/dL, TG 90 mg/dL

PEDiATRIC
• LDL-C ≥ 130-159 mg/dL +2 high level RF
• TREATMENT: START STATIN

ADULT
• 10 year risk estimate: 0.0% (< 7.5%) and no CVD, FH, or DM
• Lifetime risk 36.4%
• Statin benefit uncertain
What is the trend in statin treatment of pediatric lipid disorders in the U.S.?

Pediatric Lipid Study Consortium
Cardiovascular Research Network (CVRN)
Harmonizing Guidelines – Pros and Cons

• As with HTN and DM, blending adult & pediatric lipid guidelines would:
  – Improve provider knowledge and application of guidelines for both populations.
  – Provide justification for universal screening in childhood to potentially improve detection of younger adults (parents).

• Should high risk conditions in the pediatric population be carried into adult guidelines?
  – Requires higher burden of proof and better outcomes data in the pediatric population.
    • FH registry
    • Lipid Rx registry
  – Consistency is critical in the transition from pediatric to adult healthcare. Diagnoses must be carried forward into adult health history to allow tracking and appropriate monitoring.

• Need for lifetime risk data beginning in younger populations.
Harmonizing Guidelines

- When/how could lipid guidelines be harmonized into one consistent guideline across all ages?
- What agency/organization/society should be responsible?
- How could the impact of harmonization be measured & tracked?
“Catch the wave early!”

LONG RIDERS

SHORT RIDERS
Collaborators

Justin Zachariah
Laurel Copeland
Ying Fang
Fang Fang Sun
Jeffrey Tom

Andrea Cassidy-Bushrow
Jeffrey VanWormer
Don Wilson
Piers Blackett
Discrepancies and Barriers Related to Screening and Treating Hypercholesterolemia in Primary Prevention

Catherine J. McNeal, M.D., Ph.D.
cmcneal@sw.org