Guidelines and Pharmacologic Treatment of Pediatric Dyslipidemia

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Disclosures

No relevant disclosures
Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. The statements contain recommendations that are based on evidence from a rigorous systematic review and synthesis of the published medical literature.

*Institute of Medicine, 1990*
DEFINITION

Guidelines are a constructive response to the reality that the practicing physician requires assistance to assimilate and apply the exponentially expanding, often contradictory body of medical knowledge.

Sniderman AD et al. JAMA 2009;301:429-431
History of Clinical Practice Guidelines

- Developed by organizations with established expertise in a subject
- No standards for committee composition
- No standards for scientific review → evidence review often selective/supportive
- Conclusions presented as unanimous
- Review process inconsistent, not independent
- Conflict of interest issues inconsistently addressed

Sniderman AD et al. JAMA 2009;301:429-431
Modern Approach to Clinical Guidelines

- Balanced Committee membership
- Potential issues of conflict addressed
- Complete evidence review
- Transparency of committee discussion (minority report)
- Graded Evidence and Graded Recommendations
Guideline Development Cycle

- Define critical questions
- Literature search
- Evidence tables
- Evidence review
- Serial guideline drafts
- External review
- Problem analysis
- Dissemination

Implementation

Feedback
Problem Analysis/Defining Critical Questions:

- Evidence re: development of atherosclerosis relative to presence and intensity of RFs: 9 questions
  - e.g. What is the evidence that atherosclerosis begins in childhood?

- Evidence re: RF change/impact on atherosclerotic process: 5 questions
  - e.g. What is the evidence that control of hypertension in childhood will decrease clinical CV disease in adult life?
Atherosclerosis: A Progressive Process

- Normal
- Fatty Streak
- Fibrous Plaque
- Occlusive Atherosclerotic Plaque
- Plaque Rupture/ Fissure & Thrombosis

Endothelial dysfunction and plaque progression due to risk factor exposure

Blood levels of inflammatory markers (e.g., CRP)

Clinically silent
10 20 30 40 50

Increasing age

Unstable Angina
MI
Coronary Death
Stroke
Critical Leg Ischemia
NEWBORN FETAL EXPOSURE

GENETIC INPUT

BIOLOGIC FACTORS
   Genetic input
   (Family history)
   Lifestyle

RISK FACTOR DEVELOPMENT

CHILDREN AT RISK

INTERMEDIATE OUTCOMES:
   Atherosclerosis; subclinical atherosclerosis (increased CIMT, reduced FMD, increased Ca score on EBCT, decreased arterial distensibility); increased LV mass

LIFESTYLE CHANGE

PHARMACOLOGIC INTERVENTION

ADULTS AT RISK

CLINICAL CARDIOVASCULAR DISEASE OUTCOMES:
   Morbidity    Mortality    Quality of Life
Integrated Pediatric CV Risk Reduction

CONSIDERATIONS

- Wide age range: Birth to 21 yrs
- Multiple risk factors to be addressed
- Clinical endpoint remote
- Epidemiologic studies = Important evidence
- Goal: Prevention of risk factors
  - Prevention of future disease
  - Primordial and primary prevention
- Acknowledged gaps in the evidence base but recommendations needed to guide patient care
Integrated Pediatric CV Risk Reduction

RISK FACTORS ADDRESSED

- Family history
- Age
- Gender
- BP/ Hypertension
- Lipids
- Obesity
- Diet
- Physical Activity
- Smoking
- Diabetes mellitus
- Inflammation
- Metabolic syndrome
- Other disease processes
Integrated Pediatric CV Risk Reduction

EVIDENCE REVIEW

- Search of relevant databases
  - (e.g. Pub Med, Cochrane)
- Identification of meta-analyses, reviews, RCTs, important observational studies
  - (NHANES; Bogalusa; Muscatine; Beaver County; PDAY; Princeton; Minnesota BP study; Fels; NGHS; Young Finns)
- Abstraction of key elements for panel review
- Expert panel review and grading
  - (at least 2 members/paper)
Integrated Pediatric CV Risk Reduction

DEVELOPMENT OF RECOMMENDATIONS

- Review of evidence tables by RF subpanels
- Age-specific recommendations based on the evidence – integrated across RFs
- Recommendations accompanied by grades – grading by study and for the body of evidence
- Full panel review of recommendations/evidence – Pre-defined consensus process
- Final draft guideline with scientific rationale
# Integrated Pediatric CV Risk Reduction

## EVIDENCE GRADING SYSTEM

American Academy of Pediatrics *Pediatrics* 2004;114:874-877

<table>
<thead>
<tr>
<th>Grade</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>A</td>
<td>Well-designed randomized, controlled trials in a population similar to the guideline’s target population</td>
</tr>
<tr>
<td>B</td>
<td>Randomized, controlled trials with minor limitations; genetic natural history studies; overwhelmingly consistent evidence from observational studies</td>
</tr>
<tr>
<td>C</td>
<td>Observational studies (case-control and cohort design)</td>
</tr>
<tr>
<td>D</td>
<td>Expert opinion, case reports or reasoning from first principles (bench research or animal studies)</td>
</tr>
</tbody>
</table>
## Integrated Pediatric CV Risk Reduction

### STRENGTH OF RECOMMENDATION

<table>
<thead>
<tr>
<th>Statement</th>
<th>Definition</th>
<th>Implication</th>
</tr>
</thead>
</table>
| Strong recommendation         | Evidence grade A or B  
Benefit clearly exceeds harm                                                 | Should follow                                    |
| Recommendation                | Evidence grade B or C  
Benefit exceeds harm but evidence is not as clear                           | Should generally follow                           |
| Optional                      | Well-performed studies (Grade A, B, C) show no clear advantage; or evidence is suspect (grade D) | Flexible response including pt preference        |
| No recommendation             | Evidence lacking or balance between benefit and harm is unclear            | Independent decision; need new evidence          |
Guideline Implementation Program

I. Guideline publication/ Media release/ Dissemination to pediatric care providers

II. On-line educational program

III. NHLBI website → Linked access to specific guideline sections from CV Schedule

IV. Pocket/ virtual tool-kit to facilitate guideline adoption

V. Outcome evaluation

VI. Public education campaign
Familial Hypercholesterolemia

An important consideration is the group of individuals with Genetic Dyslipidemia, including Familial Hypercholesterolemia. However, this was not specifically addressed in the Integrated Guidelines.
Familial Hypercholesterolemia

- Most adults and children with heterozygous FH remain undiagnosed and are asymptomatic

Treatment: diet, physical activity, pharmacologic (statins)
NLA Guidelines Regarding Pharmacological Treatment of Dyslipidemia in Children and Adolescents
What is the effectiveness of pharmacologic interventions in lowering abnormal lipid values in children and adolescents?

Vuorio A et al. The Cochrane Collaboration 2014
- Used randomized controlled clinical trials, including participants up to 18 years old comparing statin treatment to placebo or to diet alone.
- Eight studies were high quality
- 1074 participants
- Range of follow-up was 6 weeks-2 years
Key Question 1

Findings: Statins reduced LDL-C at all time points

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>Mean Relative Reduction</th>
</tr>
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<tbody>
<tr>
<td>1 month</td>
<td>24.6%</td>
</tr>
<tr>
<td>6 months</td>
<td>35.0%</td>
</tr>
<tr>
<td>12 months</td>
<td>27.0%</td>
</tr>
</tbody>
</table>

Pooled estimate of the difference in mean relative reduction at the end of follow-up:
32.15% (95% CI -34.9 to -29.4)

Studies are considered clinically comparable
Key Question 1a

- Which agents are most effective?
- Which agents are contraindicated?
Key Question 1a

- Available Agents
  - Statins
  - Bile acid sequestering agents
  - Cholesterol absorption inhibitors

Key Question 1a

- Best LDL-C Reduction—Statins
- Best tolerability—Statins
- Very little evidence regarding cholesterol absorption inhibitors in children and adolescents.
Key Question 1b

- What is the effectiveness of pharmacologic intervention in improving intermediate markers of atherosclerosis (endothelial function, carotid IMT?)

Reference: Vuorio et al. Cochrane Collaborative 2014
Key Question 1b

- Statins: Change in Carotid IMT
  - 1 study reported this outcome (Wiegman 2004, Pravastatin)
  - Small but statistically significant regression of IMT compared to placebo
    - 0.01 mm (95% CI -0.03 to 0.00)
  - Placebo group had an increase in CIMT
What are the risks of pharmacologic intervention to improve lipid levels?

Reference: Vuorio et al. The Cochrane Collaborative 2014
Key Question 1c

- Statins (risks)
  - Liver dysfunction
    - Serum AST, ALT did not differ between intervention and control groups at any time point
  - Myopathy/serum creatine kinase
    - Creatine kinase concentrations did not differ between intervention and control group at any time point
  - Rhabdomyolysis
    - There were no cases of rhabdomyolysis
  - Quality of Life
    - No study reported this outcome
Key Question 1c

- Growth and maturation
  - There was no adverse impact on measures of growth (3 studies).
  - There was no adverse impact on progression of puberty (2 studies).

- Adverse Events
  - Six studies reported adverse clinical events
    - At one month, the estimate of the risk ratio was 0.86 (95% CI 0.65-1.13)
    - At 6 months, the estimate of the risk ratio was 1.02 (95% CI 0.82-1.27)
    - At 1 year, the estimate of the risk ratio was 1.01 (95% CI 0.81-1.26)

- Bile acid sequestrants
  - Adverse events limited to gastrointestinal events, including cramping, constipation, bloating and abdominal pain

- Cholesterol absorption inhibitors
  - Very limited data in pediatric patients
Key Question 1c

Best evidence for long term safety

- Longest clinical trials were 24 months
- Observational data – 10-year follow-up after a clinical trial.

Kusters DM et al *JAMA* 2014
Key Question 1c

10-year Follow-up

- No adverse effects on height, weight, maturation
- No adverse effects on laboratory measures
- 4 had myalgia without ↑ CPK
- 2 had ↑ CPK with high physical activity
- Younger age at initiation of statin was associated with lower CIMT at 10 years of follow-up

Kusters DM et al. *JAMA* 2014
At what age should lipid lowering medication be started?

There is essentially no high level evidence to inform an answer to this question.

Observational studies and Mendelian randomization studies suggest younger is better.
Key Question 2

- What is the target level of lipids for lifestyle intervention and pharmacologic treatment?

Essentially, there is no high level evidence.

- Observational studies and Mendelian randomization studies suggest lower is better
Key Question 2a

Should the target lipid level for treatment differ by the number of risk factors for cardiovascular disease or in other high risk conditions?

Essentially, there is no high level evidence.
Key Question 2b

- Should the target of treatment be both LDL-C and non HDL-C?

Essentially, there is no high level evidence.
Observational Studies that Inform Questions
Prediction of Lifetime Risk for Cardiovascular Disease by Risk Factor Burden at 50 Years of Age

- The absence of established risk factors at 50 yrs. of age is associated with very low lifetime risk for CVD and markedly longer survival.

- These results should promote efforts aimed at preventing development of risk factors in young individuals.

### Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease

<table>
<thead>
<tr>
<th>Subjects</th>
<th>LDL–C Reduction</th>
<th>↓ in CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>28%</td>
<td>40 mg/dl (1 mmol/L)</td>
</tr>
<tr>
<td>White</td>
<td>15%</td>
<td>20 mg/dl (0.5 mmol/L)</td>
</tr>
<tr>
<td>Statin Trials</td>
<td>38.7 mg/dl (1 mmol/L)</td>
<td>36%</td>
</tr>
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</table>

These data suggest that lifelong reduction of LDL levels confers greater benefit than does a similar reduction instituted later in life. This finding is consistent with the observation that coronary atherosclerosis develops early in life and suggests that earlier introduction of an intervention that lowers lipid levels even moderately may confer increased protection from CHD.

“...lifetime exposure to an LDL level lowered by 40 mg/dl because of mutations in 1 or more of these alleles could reduce CHD risk by almost 55%.”

Lowering LDL earlier in life, using diet and/or drug approaches, could prevent not just 30% of events, as in the statin trials, but possibly more like 60%.

Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease

As compared with non-carriers, carriers of any of four APOC3 mutations had:

- ↓ Triglyceride levels (39%)
- ↓ LDL cholesterol levels (16%)
- ↓ APOC3 levels (46%)
- ↑ HDL cholesterol levels (22%)

The risk of coronary heart disease was reduced 40%.
No evidence that LDL-C at very low levels (50mg/dL) is harmful

Normal growth and development
Observational studies and studies of Mendelian randomization suggest that lower lifetime LDL-C and TG and higher lifetime HDL-C reduce the risk of coronary heart disease.

This would suggest that cholesterol lowering should be considered early in childhood.
## Drug Therapy

Consider drug therapy at 10 years and older, and after an adequate trial of diet therapy (6 months—1 year)

<table>
<thead>
<tr>
<th>LDL Cholesterol</th>
<th>Initiation Level (mg/dL)</th>
<th>Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No family history of premature CVD and no other CVD risk factors in child or adolescent</td>
<td>≥190</td>
<td>&lt;130 minimal &lt;110 ideal</td>
</tr>
<tr>
<td>Family history of premature CVD or child or adolescent has ≥1 other CVD risk factor</td>
<td>≥160</td>
<td>&lt;130 minimal &lt;110 ideal</td>
</tr>
</tbody>
</table>

**Other potential risk factors**

Hypertension, obesity, strong family history, diabetes, cigarette smoking

Dyslipidemia—Intervention

Elevated LDL-C

Pharmacologic treatment focused on reduction of LDL-C

- Bile acid resins
- Hmg COA reductase inhibitors (statins)
Dyslipidemia—Intervention

Elevation of triglycerides and low HDL-C

- There are few pharmacologic interventions recommended in pediatric patients with atherogenic dyslipidemia.

- Pharmacologic treatment for elevated triglycerides is only recommended when TG’s are very high (>500 mg/dL), which is usually the result of a genetic hypertriglyceridemia. The concern is risk for pancreatitis.
Dyslipidemia—Intervention

Bile Acid Sequestrants

Dosage

- The best approach is to start with a low dose and advance over time on the basis of efficacy and tolerance.

1 - 4 grams/day \(\rightarrow\) Children < age 10

1 - 8 grams/day \(\rightarrow\) Adolescents

1 scoop = 4 grams cholestyramine

1 Colestipol tablet = 1 gram
Dyslipidemia—Intervention

Bile Acid Sequestrants

Mechanism of Action

- Binds with bile acid, which is then excreted in stool
- Interrupts the enterohepatic circulation of bile
Dyslipidemia—Intervention

Bile Acid Sequestrants (continued)

Side Effects

- Constipation, abdominal cramping
  - Recommended that patients drink appropriate fluids
  - Increasing fiber (psyllium 2-4 gm/day) may be helpful

- Binding with other medications
  - Other drugs should not be taken at the same time
Dyslipidemia—Intervention

Elevated LDL-C

Statin Agents

HMG-COA reductase inhibitors

Action

➢ Inhibits cholesterol synthesis

➢ Induces LDL receptors in the liver
Statin Agents (continued)

Side Effects

- Headaches, rash
- Elevated hepatic aminotransferases
- Elevated muscle enzymes – myositis (muscle aches)
- Side effects reversible with discontinuation of the medication
- Teratogenicity – unknown. These drugs are not recommended for adolescent females who are sexually active without contraceptives and are at risk of becoming pregnant.
Dyslipidemia—Intervention

Statin Agents (continued)

Cholesterol Reduction

- Up to 30% (LDL-C)
- May be used in combination with a bile acid sequestrant. (This may result in a lower dose of both medications.)
Dyslipidemia—Intervention

Goal for pharmacologic treatment

- Initial: LDL-C < 190 mg/dL

- Target: LDL-C < 160 mg/dL or LDL-C < 130 mg/dL
"I don’t think of it as laying an egg. I think of it as lowering my cholesterol!"