Trials and Tribulations of Statin Use in Children

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## Disclosures

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Statins for Children with FH

- How did we come to statins for children?
- What is the evidence for efficacy and safety of statin use for children with FH?
- Will we create an epidemic of statin use in children?
- What further evidence is needed?
Statins for Children with FH

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A little history of little people:

- First statin developed in Japan in 1971 – mevastatin
- This work was picked up by Merck which developed lovastatin in 1978, approved by FDA and marketed in 1987
- The Lipid Research Clinics Coronary Primary Prevention Trial published in 1984 used cholestyramine, and established the benefit of lipid-lowering drug therapy
Statins for Children with FH

A little history of little people:
- The first NCEP pediatric guidelines published 1992 suggested a bile acid sequestrant as the only recommended med (considered safe as not systemically absorbed, concerns about fat soluble vitamins)
A little history of little people:
- Combinations including pravastatin + colestipol (2002), simvastatin + ezetimibe (2008)
- Additional trials with
  - rosuvastatin (with CIMT, baseline results published)
  - pitavastatin (EU Clinical Trials Register 2011-004962-32)
Statins for Children with FH

A little history of little people:

- AHA Scientific Statement (2007) recommended statin as first line therapy
- AAP statement (2008) described meds but did not specifically recommend statins over other meds
- NHLBI commissioned integrated pediatric guidelines (2011) gave detailed guidance regarding who and how of statins
Statins for Children with FH

Little people, little evidence:

PubMed search citations:

FH in adults 3,895
FH in children 838
Statin and FH in adults 651
Statin and FH in children 179
Statins for Children with FH

Little trials for little people:
- FDA Modernization Act (1997) – exclusivity principle (6 month patent extension for pediatric study)
- Renewed and amended FDA Amendments Act (2007)
Economic return of clinical trials performed under the pediatric exclusivity program. (Li et al. JAMA 2007; 297:480)

- n=9 drugs reviewed that had been granted Pediatric Exclusivity (no statins included); 5 drugs associated with yearly US sales >$1 billion
- 8 drugs achieved a labeling change
- 27 completed trials with 16 evaluating efficacy
- Median patients enrolled 140
- Median cost per written requests $12.24 million
- Median net economic benefit $134 million
- Median 6 month benefit to cost ratio 12.44 (up to 73.63)
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## Statins for Children with FH

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<th>Study</th>
<th>T Chol</th>
<th>LDL</th>
<th>HDL</th>
<th>TGs</th>
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<tr>
<td><strong>McCrindle 2003</strong></td>
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<tr>
<td>atorvastatin 10-20 mg</td>
<td>-30%</td>
<td>-40%</td>
<td>+6%</td>
<td>-13%</td>
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<td><strong>Avis et al 2009</strong></td>
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<td>rosuvastatin 5 mg</td>
<td>-30%</td>
<td>-39%</td>
<td>+5%</td>
<td>+3%</td>
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<tr>
<td>10 mg</td>
<td>-34%</td>
<td>-44%</td>
<td>+10%</td>
<td>-14%</td>
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<tr>
<td>20 mg</td>
<td>-39%</td>
<td>-50%</td>
<td>+9%</td>
<td>-8%</td>
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Early statin therapy restores endothelial function in children with familial hypercholesterolemia
(de Jongh et al, JACC 2002; 40:2117-21)

n=50 children with FH, age 9-18 yrs; 19 controls

Double-blind randomized clinical trial 40 mg simvastatin for 28 weeks; assessed FMD at baseline and 28 weeks
Efficacy and safety of statin therapy in children with familial hypercholesterolemia. (Wiegman et al, JAMA 2004; 293:331-337)

n=214 children with FH, age 8-18 yrs

Double-blind randomized clinical trial 20-40 mg pravastatin for 2 years; assessed CIMT at baseline and 2 years

LDL at 2 years – 180 mg/dL

Change from baseline in mean CIMT:

- Pravasatin: -0.010 (0.048) p=0.02
- Placebo: +0.005 (0.044)

No difference in academic performance, growth, Tanner stage, safety labs, hormones
STATINS

- Lipid lowering
- Pleiotropic Actions
  - Endothelial Function
  - Oxidative Stress
  - Inflammation
  - Platelet Aggregation
  - Coagulation Fibrinolysis

CARDIOVASCULAR
Morbidity and mortality
Statin treatment in children with familial hypercholesterolemia. The younger, the better. (Rodenburg et al. Circulation 2007; 116:664)

n=186 children with FH, age 8-18 yrs

Double-blind randomized clinical trial 20-40 mg pravastatin for 2 years; open label treatment thereafter with pravastatin for mean of 4.5 yrs for mean reduction in LDL-C of -29%

Multivariable regression for greater mean CIMT at F/U:
Greater CIMT at statin initiation
Males
Older age at statin initiation
Longer duration of statin treatment
(Vuorio et al. Atherosclerosis 2013; 226:315)
Conclusions:

- No firm evidence regarding when to initiate statin treatment or what target LDL-C should be obtained.
- Due to lack of evidence pediatricians should be cautious in interpreting current (AAP) guidelines.
- Studying high risk groups (obese or diabetic patients) and incorporating composite end points including surrogate markers of atherosclerosis may help define treatment guidelines.
Statins for Children with FH

Systematic reviews and meta-analyses:
- ~12 RCT’s → ~6 reviews
- Cochrane review, Kuoppala et al. 2010
  Included 9 placebo-controlled RCTs with 897 patients
  - Statins efficient in lipid-lowering in FH
  - Safe in the short-term, unknown in the long-term
  - Treated patients should be followed carefully
  - Large long-term trials needed to establish long-term safety
A systematic review and meta-analysis of statin therapy in children with FH.
Avis et al. ATVB 2007; 27:1803

6 trials met inclusion criteria
- No difference between placebo and statin regarding discontinuations.
- 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
- Liver toxicity: RR of > 3 times the ULN for AST 0.98; 95% CI: 0.23 to 4.26 and for ALT 2.03; 95% CI: 0.24 to 16.95
- Height change (statin vs. placebo): +0.33 cm; 95% CI: +0.03 cm to +0.63 cm
n=365 trials of 153 drugs under Pediatric Exclusivity incentive 1997 to 2007

137 labeling changes; 33 products (26%) had pediatric safety information added to labeling

12 products had neuropsychiatric safety findings; 21 other important safety findings

Only 48% of these trials were reported in the peer-reviewed literature; of those reported 44% did not include the important safety findings
Safety monitoring of drugs receiving pediatric marketing exclusivity.
(Smith et al. Pediatrics 2008; 122:e648)

Best Pharmaceuticals for Children Act (2002)

- Requires the FDA to report to the Pediatric Advisory Committee on adverse events occurring during the 1 year period after granting pediatric exclusivity

- Safety information is obtained from the electronic Adverse Event Reporting System (supports post-marketing safety surveillance)
Safety monitoring of drugs receiving pediatric marketing exclusivity.
(Smith et al. Pediatrics 2008; 122:e648)

Best Pharmaceuticals for Children Act (2002)
- Review PAC recommendations for 67 of 130 drugs granted exclusivity up to 2007
- Recommendations made for 23 of drugs reviewed, 11 with pediatric specific findings (remainder returned to routine monitoring):
  - Labeling changes for 12
  - Continued monitoring for 10
  - MedGuide production for 9
  - Update of labeling changes for 1
Safety monitoring of drugs receiving pediatric marketing exclusivity.
(Smith et al. Pediatrics 2008; 122:e648)

Best Pharmaceuticals for Children Act (2002)

- Several statins reviewed
  - Fluvastatin  Routine monitoring
  - Pravastatin  Routine monitoring
  - Simvastatin  Continued monitoring
  - Atorvastatin  Continued monitoring

- Majority of drugs had no adverse events of a frequency or severity to prevent a return to routine adverse event monitoring
Statin treatment in children with familial hypercholesterolemia. The younger, the better. (Rodenburg et al. Circulation 2007; 116:664)

n=186 children with FH, age 8-18 yrs

Double-blind randomized clinical trial 20-40 mg pravastatin for 2 years; open label treatment thereafter with pravastatin for mean of 4.5 yrs for mean reduction in LDL-C of -29%

No serious lab adverse events
No discontinuations for lab adverse events
2 males had CPK >10xULN (extreme fitness)
4 subjects with normal CPK had myalgia
No relevant impact on growth, development, hormones
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Concentrations of LDL-C and total cholesterol among children and adolescents in the U.S.

NHANES data 1999-2006, ages 6 to 17 years
Prevalence based on cutpoints:
Lipid Research Clinics Prevalence Study
  5.2% for LDL-C, 10.7% for total cholesterol
National Cholesterol Education Program
  6.6% for LDL-C, 9.6% for total cholesterol
~0.8% eligible for drug therapy
  42% had LDL>190 mg/dL
  58% had LDL>160 mg/dL + ≥1 risk factor
Only one subject on meds (cholesterolamine)
Will obesity increase the proportion of children and adolescents recommended for a statin?
McCrindle et al. Circulation 2013; 128:2162

NHANES data 1999-2010, ages 12 to 17 years
n=4151 with non-fasting lipid values
24.6% would have high non-HDL-c ± low HDL-c
n=3315 with fasting lipid values
20.3% would have high non-HDL-c ± low HDL-c
6.6% would have LDL-c ≥130 mg/dL
5.2% ≥130 but <160
1.0% ≥160 but <190
0.4% ≥190
Will obesity increase the proportion of children and adolescents recommended for a statin? McCrindle et al. Circulation 2013; 128:2162

Following the guidelines, the proportion recommended for a statin:

Expert Panel 2011: 0.85%
AAP 2008: 1.0%
NCEP 1992: 0.5%
Will obesity increase the proportion of children and adolescents recommended for a statin? 
McCrindle et al. Circulation 2013; 128:2162

Stratifying by BMI percentile, statin recommended for:
- 0.6% if BMI <95th %ile
- None if BMI ≥95th but <97th %ile (small n)
- 3.1% if BMI ≥97th %ile (3.6% males, 2.4% females)

- 32% had LDL-c 130 to 159 (smokers)
- 60% had LDL-c 160 to 189
- 8% had LDL-c ≥190
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Statins for other high risk populations:

- Type 1 diabetes with atorvastatin: Possible reduction in arterial stiffness ($p=0.06$), no effect on endothelial function (Haller et al. J Pediatr Endocrinol Metab 2009)

- Atorvastatin in pediatric heart transplant recipients reduced graft coronary artery disease (observational study) (Chin et al. Pediatr Transplant 2006)

- Atorvastatin in pediatric SLE patients did not improve CIMT (Schanberg et al. Arthritis Rheum 2012)
Statins for Children with FH

Statins for other high risk populations:

- Statins (pravastatin, fluvastatin, simvastatin) improved endothelial function in Kawasaki disease patients with important coronary artery abnormalities (Huang et al 2008; Hamaoka et al 2010; Duan et al 2014)

- Statins improved lipids in chronic renal disease, nephrotic syndrome and renal transplantation (Sanjad et al 1997; Argent et al 2003; Butani et al 2003; Prescott et al 2004; Butani 2005; Garcia-de-la-Puente et al 2009)
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There will likely never be direct evidence that treating risk factors in children reduces cardiovascular events in adults.

We need a shift from preventing events to preventing atherosclerosis.
Statins for Children with FH

More and stronger links in the chain of evidence
- Longitudinal data – safety, vascular/events
- Evidence for cutpoints and targets
- Personalized medicine for FH
- Trials of statins in other high risk populations
Statins for Children with FH

NHLBI Pediatric Heart Network DO IT! Trial
- Rosuvastatin vs. placebo x 2 years
- Obese adolescents with combined dyslipidemia:
  - LDL-C <160 mg/dL
  - TG <500 mg/dL
  - TG/HDL-C ratio ≥ 3.0
  - non-HDL-C ≥145 mg/dL
- Primary outcome: PWV, CIMT
- Secondary outcomes: safety, lipids
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