Impact of Early Evidence of Atherosclerotic Changes on Early Treatment in Children With Familial Hypercholesterolemia

Željko Reiner

Heterozygous familial hypercholesterolemia (HeFH) is the most common genetic metabolic disorder and is an important cause of premature atherosclerosis, particularly coronary artery disease. This is because of lifelong elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) that result in deposition of LDL-C in tissues (xanthelasmas, xanthomas, and particularly tendinous xanthomas and corneal arcus), most importantly in arteries, forming atherosclerotic plaques. The affected subjects typically have LDL-C about at least double that of their unaffected siblings, and therefore clinically HeFH is most often recognized by finding very high LDL-C. It is well known that in patients with HeFH, high plasma LDL-C levels are present from birth, and because there are few other causes of increased LDL-C in childhood, such a finding is virtually diagnostic in children (unlike in adults), particularly if family history of premature cardiovascular disease is positive. In children with HeFH, clinical signs such as xanthomas and corneal arcus are not pathognomonic because they appear later in life. Because children in families where ≥1 member has FH are likely to be on a particular lipid-lowering diet and thus have lower LDL-C than expected, all children from such families should be checked by identification of the causative mutation in the LDL receptor, apolipoprotein B, or PCSK9 genes, which provides definitive diagnosis. Recently, a high-resolution melting method for mutation detection in patients with HeFH has been developed as a sensitive, rapid, and robust technique that could significantly reduce the time and cost of screening. This method was successfully used in screening of some populations that were previously underdiagnosed.

Sectioning of Children for FH

Different screening strategies are currently suggested to identify children with FH. European guidelines are not recommending universal screening of children by either LDL-C measurement or some other approach. Although such a screening has often been suggested, for example at the time of infant immunization, in Europe it is considered that this concept is yet to be proven in clinical practice, particularly because of the high cost and possibility of a high false-positive rate. However, relatively recently in United States, the National Heart, Lung, and Blood Institute panel endorsed by American Academy of Pediatrics recommended universal screening of 9- to 11-year-old children with a lipid profile plus targeted screening with 2 lipid profiles of children aged 2 to 8 years and 12 to 16 years. This approach drew a lot of criticism, and many argued that there are no evidence-based estimates of the health benefits, possible harms, and increased costs that might result from such a screening and that these recommendations are predominantly based on expert opinion and not on hard data.

Kusters et al have in this issue of Circulation Research reported that children with FH have greater mean carotid intima-media thickness (cIMT) values compared with their unaffected siblings even before the age of 8 years (some of them were between 6 and 8 years old). They have also found that age, sex, and the presence of FH were independent predictors of carotid arterial wall atherosclerosis. The comparison with non-FH siblings is crucial because by this genetic and environmental variation between the 2 groups was kept to minimum. Why might these findings be important?

cIMT and Cardiovascular Risk

cIMT, as assessed by B-mode ultrasound, is a measurement not only of early atherosclerosis but also of smooth muscle hypertrophy/hyperplasia and is considered to be a good surrogate marker of coronary artery disease. Because there is a graded increase in cardiovascular risk with rising cIMT, it is generally accepted that the measurement of cIMT and screening for atherosclerotic plaques by carotid artery ultrasound can add information beyond assessment of traditional risk factors, including elevated LDL-C, in asymptomatic adults at moderate cardiovascular risk. The importance of cIMT measurement for risk assessment in this population is similar to the importance of ankle brachial index or coronary artery calcium measurement by computed tomography. It is well known that adult patients with FH are not at moderate but rather at high or at very high risk, so there is no point in screening them by cIMT measurement to improve their risk assessment. However, there are not much data on cIMT values in children with FH, particularly not when compared with the healthy children.

cIMT Measurement in Children

Although some reports on cIMT in children with FH were published quite a long time ago, the most important resource of this is data analysis of 4 prospective studies initiated in
Cardiovascular Risk in Young Finns Study (Finland), Childhood Determinants of Adult Health study (Australia), Bogalusa Heart Study (United States), and Muscatine Study (United States). This analysis showed that the strength of the associations between childhood risk factors and cIMT is dependent on childhood age. In this analysis, LDL-C and non–high-density lipoprotein cholesterol were significantly associated with cIMT among 12-, 15-, and 18-year-old subjects. Taken in general, risk factor measurements obtained at or after 9 years of age were predictive of subclinical atherosclerosis in adulthood. All these studies, and particularly the Cardiovascular Risk in Young Finns Study, have shown that exposure to high LDL-C in childhood and adolescence predicts increased cIMT and decreased elasticity in young adulthood.

**Lipid-Lowering Treatment in Children With FH**

It is well known that the risk of premature atherosclerotic vessel changes related to HeFH can be substantially ameliorated by early start of cholesterol-lowering treatment. But the question remains—how early? It is also important to establish what is the clinical relevance of making an early assessment of vascular changes in children with FH by using the imaging techniques such as cIMT and whether this might influence the treatment approach?

To date, 3 trials have been performed showing an improvement of vascular dysfunction and a regression of cIMT in children with FH treated with statins compared with progression in placebo-controlled groups as well as demonstrating that earlier initiation of treatment is associated with reduced cIMT. However, there is still no hard evidence that treatment of children of any age, other than those with homozygous FH and extremely high LDL-C, really prevents cardiovascular events and saves lives. Also, almost all the trials on children with FH were directed only toward the determination of statin efficacy and safety and not toward clinical outcomes. Therefore, it is still not clear how early we should start with lipid-lowering treatment in these patients to prevent cardiovascular events later in their lives.

In particular, there are no data to show whether statin treatment should be initiated before the age of 8 to 10 years or not, except for anecdotal reports. The main concerns on statin treatment in young children (ie, <8 years) are not only well-known adverse effects of statins that occur in adults as well but much more the fact that inhibiting endogenous cholesterol synthesis by statins might in children have serious multiorgan consequences like those in Smith–Lemli–Opitz syndrome. Characteristics of this syndrome are prenatal and postnatal growth retardation, microcephaly, intellectual disability, and multiple major and minor malformations. In this disease, they occur because of decreased endogenous cholesterol synthesis caused by 7-dehydrocholesterol reductase mutations. Thus, cholesterol has numerous essential functions in normal cell physiology especially during the developmental period of childhood. Cholesterol is a major component of cell membranes and the central nervous system, which accounts for ≈25% of total body cholesterol, and it promotes myelin formation, synaptogenesis, and neuronal plasticity. It is also a precursor of steroid hormones and bile acids. The cholesterol pool in the brain is isolated because the blood–brain barrier prevents the uptake of lipoproteins from the circulation. Therefore, all the cholesterol in the brain originates from de novo synthesis, and the need of brain cells for cholesterol cannot be covered by uptake of cholesterol-rich lipoproteins by these cells as it can be, at least partially, by the cells of other tissues. Despite these potential concerns, to date there are no reports that statin treatment of children with FH might cause any harm to their central nervous system or any change similar to those described in these syndromes.

**When to Start Statin Treatment in Children With FH?**

Although it has been shown that atherosclerotic changes can be detected already early in life, the benefits of statin treatment for children with FH are not yet clearly proven. It might be speculated that such a therapy would prevent the development of significant atherosclerotic disease later and subsequent cardiovascular events. It is clear, however, that homozygous patients with FH should be treated as early as possible because they have an extremely high risk of premature cardiovascular disease and death. The youngest patient with homozygous FH who was treated with statins was only 3 years old at the initiation of treatment. This boy was also the youngest patient treated by a combination of statin and ezetimibe as well as with apheresis above statin therapy, and he is today, 11 years later, still alive and did not have any cardiovascular event so far.

It has been shown that even with more potent statins available today, only 40% of FH children achieve the LDL-C target of <110 mg/dl (=2.8 mmol/L), reflecting these patients’

### Table. Statin Therapy in Children According to the US Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Might Be Considered if</th>
<th>Should be Considered if</th>
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</thead>
<tbody>
<tr>
<td>8–9</td>
<td>≥190 (≈4.9)</td>
<td>≥190 (≈4.9)</td>
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<tr>
<td></td>
<td>+ positive family history</td>
<td>or</td>
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<tr>
<td></td>
<td>≥1 high-level CVD RF</td>
<td>or</td>
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<tr>
<td></td>
<td>≥2 moderate-level CVD RF</td>
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<tr>
<td>LDL-cholesterol mg/dL (mmol/L)</td>
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<tr>
<td></td>
<td>&gt;160–189 (≈4.1–4.9)</td>
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<tr>
<td></td>
<td>+ positive family history</td>
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<td></td>
<td>≥1 high-risk CVD RF</td>
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<td>≥2 moderate-level CVD RF</td>
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<td></td>
<td>&gt;130–159 (≈3.4–4.1)</td>
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<td>≥2 high-level CVD RF</td>
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<tr>
<td></td>
<td>≥2 moderate-level CVD RF</td>
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CVD RF indicates cardiovascular disease risk factor; and LDL, low-density lipoprotein.
Diagnosis of Atherosclerosis in Children With FH

Reiner

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