Although the debate about when, whom, and how to treat adults with elevated low-density-lipoprotein cholesterol (LDLc) is essentially over because of a huge amount of data generated by large, clinical end-point, placebo-controlled trials with HMG CoA reductase inhibitors (statins),1–3 the issue in children and adolescents is not yet settled. In this issue of Circulation, Rodenburg and colleagues4 provide important further evidence for both the potential benefit of long-term LDLc reduction and the safety of treating children and adolescents with familial hypercholesterolemia (FH) with statins. This latest trial is an extension of an earlier double-blind, placebo-controlled, 2-year study in just over 200 FH children 8 to 17 years of age at entry.5 The initial trial was the first demonstration that even a moderate reduction in LDLc of 25% to 30% resulted in a significant decrease in the rate of thickening of the carotid artery intima thickness and thus moved the focus of lipid-lowering therapy in children from a plasma marker to a well-established anatomic surrogate of atherosclerosis. In the present 2-year extension in which all children were treated with the statin, Rodenburg and colleagues demonstrate that the age at which statin treatment was started was positively associated with carotid artery intima thickness on follow-up and strongly argue that, on the basis of their data, when it comes to treating children with FH, “the earlier, the better.” This would by implication include children at least as young as 8 years of age, the entry age in their trial. This is a few years younger than all current recommendations, including the recently released scientific statement on drug therapy of high-risk lipid abnormalities in children and adolescents from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young,6 which states “In general, do not start [drug therapy] before 10 years of age in boys and preferably after onset of menses in girls. Patients should ideally be at Tanner stage II or higher.”

The 4 statins currently approved for use in FH children by the US Food and Drug Agency (FDA) all with labeling consistent with the recent AHA pediatric statement in terms of age when treatment should be started are lovastatin, simvastatin, pravastatin, and atorvastatin. Between these 4 statins, randomized placebo-controlled trials of at least 24 weeks have been reported in >750 male and female children.13–16 Careful and regular safety monitoring of numerous biochemical, endocrine, and hematological parameters, along with growth and sexual development, has been examined. No significant findings have been reported, including in the nearly 200 patients in this latest trial, which lasted >4 years. Two additional statins, fluvastatin and rosuvastatin, are currently undergoing similar evaluation in FH children, which, in just over a year, will bring the global statin experience in FH children to >1000 subjects. This should allow a fairly comprehensive assessment of these agents in a pediatric population, in fact making the statins one of the best-studied therapeutic agents in children for any chronic disorder. However, the vast majority of these data, including the

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growth and sexual development information, will have been generated on children >10 years of age and at Tanner stage II or later at the time of entry. The evidence for younger children and those prepubertal is, and will remain, sparse.

Data on individual statins are obviously too few to allow comparisons of safety; however, it can be stated that the very few side effects actually seen in pediatric trials do not appear to differ with the statin used, the dose used, or the amount of LDLc reduction. The caveat is that in pediatric trials the top doses of statins (80 mg of lovastatin, pravastatin, simvastatin, and atorvastatin) have not been studied or approved by the FDA in children, and the top dose of rosuvastatin (40 mg) also is not being studied in FH children. However, even with these lower doses, the range of LDLc achieved in children is the same as in adults, providing pediatricians LDLc reductions from ∼20% at the lower doses of the less effective statins to close to 50% at the higher doses of the most effective agents. The range of LDLc reduction can be extended further by 12% to 18% with the combined use of a statin with bile acid sequestrants or ezetimibe; however, none of these agents have yet received FDA approval for use in FH children, although colesevelam and ezetimibe are currently undergoing pediatric FH trials.

As in adults with severe forms of LDLc elevation such as FH, we will soon have the tools to reach virtually any LDLc target in children that is found to be “optimal.” Rodenburg and colleagues in this latest trial and their colleagues in Amsterdam in the earlier trials have demonstrated that the rate of carotid thickening can be markedly reduced, stopped, and even reversed in FH with aggressive LDLc, even in adults. Thus, given the residual uncertainty of the impact on safety, growth, and sexual development in the younger age groups and the fact that clinical events do not appear until the mid to late 20s at the earliest, it would still appear prudent to delay the start of statin and other lipid-lowering drug therapy until the age and sexual development stage outlined by the recent AHA consensus statement.

However, the optimal answer to the question of whether “the younger, the better” or “later but greater” is the better approach should be determined by an evidenced-based clinical trial, presumably with a surrogate end point such as carotid artery intima thickness. This is unlikely ever to be undertaken by a pharmaceutical company but would be an important public health issue that I hope would be undertaken by a not-for-profit agency such as the National Institutes of Health. Until then, the debate will continue to be based on indirect evidence mostly from the relative safety of past and ongoing statin studies in FH children and adults.

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