

## Effects of Statin Therapy in Children with Familial Hypercholesterolemia

Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004;292:331–7.

### Study Overview

**Objective.** To determine the 2-year efficacy and safety of pravastatin therapy in children with heterozygous familial hypercholesterolemia.

**Design.** Prospective, randomized, double-blind, placebo-controlled trial.

**Setting and participants.** 214 children with familial hypercholesterolemia seen at an academic medical center in the Netherlands who were sequentially recruited between 7 December 1997 and 4 October 1999. Patients were followed for 2 years. Eligible participants were aged 8 to 18 years, had 1 parent with a definite clinical or molecular diagnosis of familial hypercholesterolemia, and had 2 fasting samples with low-density lipoprotein (LDL) cholesterol levels of at least 155 mg/dL after 3 months on a fat-restricted diet. Participants were excluded if they had homozygous familial hypercholesterolemia, hypothyroidism, or abnormal levels of muscle or liver enzymes.

**Intervention.** All participants were encouraged to follow a fat-restricted diet and to engage in regular physical activity. Children were then assigned to receive treatment with pravastatin ( $n = 106$ ) 20 mg (age < 14 years) or 40 mg (age  $\geq 14$  years), or placebo ( $n = 108$ ).

**Main outcome measures.** The primary efficacy outcome was the change from baseline in mean carotid intimal media thickness (IMT) compared between the 2 groups over the 2-year study period. The principal safety outcomes were participant growth, including height and weight, maturation-sexual development, and hormone level measurements over 2 years, as well as liver and muscle enzyme levels.

**Main results.** Compared with baseline, the carotid IMT suggested regression with pravastatin (mean standard deviation [SD],  $-0.010$  mm [0.048];  $P = 0.049$ ). The placebo group had a tendency toward an increased IMT (mean SD,  $+0.005$  mm [0.044];  $P = 0.28$ ). The overall change in carotid IMT differed significantly between the 2 groups (mean SD,  $0.014$  mm

[0.046];  $P = 0.02$ ). The pravastatin group had significantly reduced mean LDL cholesterol levels compared with placebo ( $-24.1\%$  versus  $0.3\%$ ;  $P < 0.001$ ). There were no differences in growth, sexual development, Tanner staging, endocrine function, or muscle and liver enzymes between the 2 groups.

**Conclusion.** Two years of pravastatin therapy induced a change in carotid IMT in children with heterozygous familial hypercholesterolemia with no adverse effects on growth, sexual development, hormone levels, or muscle or liver enzymes.

### Commentary

Familial hypercholesterolemia is a monogenic autosomal dominant disorder caused by a mutation in the LDL cholesterol receptor. Heterozygous familial hypercholesterolemia is common, occurring in approximately 1 out of every 500 people in Europe and North America. Adults typically present with an increased serum cholesterol concentration and premature coronary heart disease. The median age of coronary heart disease onset is approximately 50 years in men and 59 years in women [1]. In adults, treatment of elevated LDL cholesterol with statins has had a beneficial effect on patient cholesterol profiles and outcomes [2].

Wiegman et al studied heterozygous children with familial hypercholesterolemia who are at high risk for a cardiovascular event based on their family history. In their study population, 34% of affected parents had confirmed cardiovascular disease and 10% of affected parents had already died of cardiovascular disease. The accumulation of LDL cholesterol can lead to endothelial dysfunction, which gives rise to increased IMT and leads to important arterial stenosis.

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Therefore, these children were treated with pravastatin or placebo, and the thickness of the carotid intimal media layer was measured as a surrogate marker of atherosclerotic vessel wall changes.

Weigman and colleagues found that pravastatin was safe in this pediatric population and did not have any adverse effects on growth or development. Second, they determined that there was an overall change in carotid IMT of 0.014 mm. This was statistically significant; however, the clinical significance of this small change leads to an important limitation of this study. The carotid IMT is a surrogate marker of future vascular disease. The authors recognize that they could not assess clinical endpoints, such as cardiovascular events, in their population. They note in a previous study, however, that IMT is a strong marker of future disease in these children since it is part of the pathophysiologic pathway from elevated LDL cholesterol to endothelial dysfunction, atherosclerosis, and premature cardiovascular disease [3]. Further follow-up, especially of clinical endpoints, is necessary in these high-risk children.

### Applications for Clinical Practice

The result of the statin therapy trial in children with familial hypercholesterolemia demonstrates reduced progression of carotid IMT; however, clinical endpoints such as cardiovascular events were not followed. Use of statin therapy in children with familial hypercholesterolemia can only be recommended after more extensive studies are conducted on the long-term safety and clinical outcomes.

—Review by *Christianne L. Roumie, MD*

### References

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