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Familial Hypercholesterolemia: A Decade of Progress

Samuel S. Gidding, MD

Thomas Jefferson University and A.I. duPont Hospital for Children, sgidding@nemours.org

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Samuel S. Gidding, MD

Cardiology Division Head

Nemours Cardiac Center

A.I. duPont Hospital for Children

Professor of Pediatrics, Thomas Jefferson University

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Contact Information

Nemours Cardiac Center

1600 Rockland Road

Wilmington, DE 19803

sgidding@nemours.org

302 651 6639 (5345, fax)

Natural history studies of familial hypercholesterolemia (FH), a genetic disorder associated with elevated cholesterol and premature coronary artery disease, and with a frequency of about 1:500 in the general population, were first conducted in the 1970s.¹ Homozygotes, with cholesterol levels in excess of 500 mg/dl experience coronary events as early as adolescence and heterozygotes (with one normal and one abnormal gene) are affected prematurely in middle age. The first major breakthrough in understanding the disease came with the discovery of the low density lipoprotein (LDL) receptor by Brown and Goldstein, work that won the Nobel prize.²

Over the last 20 or so years, several hundred separate defects have been identified as causes of elevated LDL cholesterol via alteration of function of the LDL receptor. These defects fall into several groups. Most common are defects of receptor function ranging from the absence of receptor expression (the most severe) to abnormalities in receptor function. The second most common group are defects in the formation of apolipoprotein B, the major protein on LDL, so that binding of the protein to the receptor is impaired.³ Finally, genes related to the regulation of LDL receptor function have recently been uncovered, PCSK9 is important in this process, and defects that impair receptor function increase LDL levels and risk for heart disease while those that enhance LDL receptor function lower the risk for heart disease.⁴ In Europe, genotyping of patients suspected of having FH is common and a genetic defect is identified at least 80% of the time.⁵

Though cholesterol-lowering treatment has been well established in coronary disease prevention in adults, it has taken until this decade for work establishing evidence for the importance of early recognition and treatment of FH in childhood. Premature

atherosclerosis in adolescents has been demonstrated by radiologic assessment of subclinical atherosclerosis. About 25-30% have measurable coronary calcium.⁶ Carotid intima media thickness is increased in affected individuals and increases faster in affected individuals compared to unaffected siblings.⁷ The Pathobiological Determinants of Atherosclerosis in Youth Study has demonstrated that for every 30 mg/dl increase in non-HDL cholesterol, the coronary vasculature develops the equivalent of 2-3 years of accumulation of atherosclerosis; since the average LDL cholesterol in FH is 100-200 mg/dl above the population median, the development of premature coronary disease with this genetic disorder is easily explained.⁸

Effective treatment for elevated cholesterol, particularly for children, did not exist until the development of the statins, a class of drugs that inhibit cholesterol synthesis in hepatic cells (and elsewhere) and, in consequence, increase LDL receptor expression and thus lower serum cholesterol levels.⁹ Clinical trials of 1 to 2 years duration have now been conducted in children for all the important statins leading to FDA approval for lovastatin, pravastatin, simvastatin, and atorvastatin use in childhood; all lower cholesterol safely for the duration of the trials. Trials of rosuvastatin, the most potent statin on a mg for mg basis, are nearing completion. This experience has recently been reviewed in an American Heart Association scientific statement that provides guidelines for their use in those with elevated cholesterol.⁹

Medications that inhibit bile acid or cholesterol absorption have also been used to lower LDL cholesterol; because they work by a different mechanism of action, they are synergistic with statins and can significantly increase LDL cholesterol reduction when used in combination. Cholestyramine, a resin that inhibits bile reabsorption, has been

used for decades though gastrointestinal side effects are common. Ezetimibe, a cholesterol absorption inhibitor, has been studied in conjunction with simvastatin and adds to LDL lowering achieved by that medication.¹⁰ In this issue of the Journal of Pediatrics, Stein et al report the use of colesevelam, an inhibitor of bile acid reabsorption, to safely and effectively lower cholesterol in a dose dependent fashion in FH children. (ref) All of these drugs lower LDL cholesterol in the range of 10-15% in comparison to the 20-50% lowering achieved by statins (depending on the potency of the individual statin). The current role for these medications has not been firmly established, but it is likely they will be important in two settings: primary treatment for patients who are statin intolerant or preferred treatment for those who have genetic defects that are particularly suited to the mechanism of action of these drugs (e.g. sitosterolemia). A third pediatric role, use as adjuncts to statins to help achieve LDL targets, is not yet firmly established but may emerge as important if future primary prevention trials both in young and older adults can show increments of prevention of events related to achieving target LDL cholesterol goals (as opposed to settling for significant % reduction but not achieving LDL levels below 130 mg/dl).

An important limitation of the conduct of the colesevelam trial relates to the lack of tight control of statin use during the course of the study.¹¹ Concomitant statin treatment was allowed but not monitored for compliance and doses of statins were adjusted during the study. Paradoxically, patients receiving both a statin and low dose colesevelam actually had a slight rise in LDL cholesterol. This result points out a common problem in pediatric lipid lowering treatment; poor compliance with recommendations. The most likely explanation for the paradoxical finding is

discontinuation of statins in preference for study drug (or placebo) during the trial. The benefits of cholesterol lowering therapy cannot be achieved without regularly using the medication.

Given the substantial progress in understanding the early natural history of FH in the last decade or so, what progress can be anticipated in the next decade? In Europe, where natural history studies of statin treatment have been underway for many years, it is highly likely that the benefits of LDL lowering for coronary artery disease prevention in this disease will be conclusively established. A second advance will likely be the incorporation of genetic testing into standard clinical practice to diagnose FH and risk stratify based on the particular genetic defect. Future research should also be directed towards understanding whether clinicians should be satisfied with substantial cholesterol lowering from low to moderate statin dosing or if it will be necessary to achieve specific LDL target levels to achieve prevention of events. Safety evaluations will be critical in these trials.

Research to date has allowed the United Kingdom to develop cholesterol lowering guidelines specific for FH, the NICE guidelines.¹² This approach is different than the approach in the United States that is linked specifically to LDL cholesterol levels and not to the diagnosis of FH. Cost benefit analysis has shown that the combination of genotype screening of potentially affected individuals and subsequent lipid lowering therapy of affected individuals is justified. Perhaps the time has come in the United States to separate out those individuals with known high risk for premature coronary artery disease from more general population-based guidelines. This may allow for the development of clinical trials specifically directed towards these high risk patients, those with FH,

diabetes mellitus, and multiple risk states created by interactions of genetics with obesity and/or tobacco use.

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