EDITORIAL COMMENT

Shifting the Diagnosis and Treatment of Atherosclerosis to Children and Young Adults: A New Paradigm for the 21st Century*

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Over the past century, the practice of medicine has largely been reflexive, primarily focusing on treating acute manifestations of disease. Advances in the diagnosis and treatment of coronary heart disease have increased the lifespan and quality of life for many of our patients. However, despite these laudable achievements, the treatment of coronary atherosclerosis has largely been palliative, treating the end-stage sequelae. This is illustrated by the fact that the first manifestation of cardiovascular disease (CVD) in approximately 50% of patients is still sudden death or acute myocardial infarction (MI). A dramatic example of this is the recent sudden death of 33-year-old star baseball pitcher Darryl Kile of the St. Louis Cardinals. Although he was asymptomatic until his sudden death, autopsy discovered 80% to 90% stenoses in two of his coronary arteries.

A large body of evidence demonstrates that subclinical atherosclerosis is present and progresses for many decades before the onset of clinical manifestations. In a series of groundbreaking studies, Palinski, Napoli, and colleagues have provided direct evidence of the fetal origins of atherosclerosis by showing that over 50% of the fetuses of mothers who were hypercholesterolemic during pregnancy had already developed aortic fatty streaks (1). Strong correlations were noted between fetal and maternal plasma cholesterol levels up to the second trimester, which in turn were proportional to the extent of lesion formation in the fetus. Of interest, oxidized low density lipoprotein (LDL) was present even in the earliest lesions, in some cases before the presence of monocyte/macrophages, supporting a role for oxidation in the pathogenesis of lesion formation even in fetal life. They extended these results by showing that aortic atherosclerosis in children of hypercholesterolemic (during pregnancy) mothers progressed much more rapidly than did children of mothers who had been normocholesterolemic, despite the fact that plasma cholesterol levels of the children were similar. Further studies in animals have shown that lesion formation in offspring can be significantly diminished by treating hypercholesterolemic pregnant mothers with cholestyramine or antioxidants. These studies demonstrate that fetal exposure to maternal hypercholesterolemia, rather than selection of genetic hypercholesterolemia per se, results in altered gene expression and artery wall metabolism, which may affect the subsequent response of the artery to atherogenic stimuli, particularly during childhood and adolescence (1).

Autopsy studies of soldiers dying in combat in Korea and Vietnam and the PDAY and Bogalusa Heart Studies have confirmed the presence of aortic and coronary atherosclerotic lesions, even advanced and obstructive lesions, in young and clinically robust individuals (2–5). Similarly, Nissen, Tuzcu, and colleagues have demonstrated with intracoronary ultrasound that 17% of otherwise healthy heart donors <20 years of age, 37% of those age 20 to 29, 60% of those 30 to 39, 71% of those 40 to 49, and 85% of those >50 years old had evidence of coronary atherosclerosis, even without “overt” hypercholesterolemia (6). In contrast, only 8% of these individuals had angiographic evidence of disease, and none had obstructive disease.

Familial hypercholesterolemia (FH) is an autosomal dominant disorder resulting from the absence of functional LDL receptors (7). The homozygous form of this disorder (HFH) is rare (1:1,000,000) but is the best proof of the primacy of LDL in contributing to the pathogenesis of atherosclerosis. Patients with HFH, maintaining plasma LDL cholesterol levels of 500 to 1,000 mg/dl, have been documented to have MIs as early as 18 months of age and usually succumb to various manifestations of ischemic cardiovascular disease by the third decade of life. Heterozygous FH (1:500) results in LDL cholesterol levels of 200 to 350 mg/dl and greatly accelerated atherosclerosis, with 30% of affected males having a major cardiovascular event by age 30. By age 60, 60% of FH males will be affected compared with only 10% of non-affected male siblings. Even 30% of FH females will have coronary artery disease by age 60 (7).

One of the earliest manifestations of subclinical atherosclerosis is endothelial dysfunction, which is a strong marker for underlying vascular disease and, in adults, predicts risk of subsequent cardiovascular events (8,9). The common underlying distal defect in most cases of endothelial dysfunction is the inability to preserve nitric oxide responsiveness, either through decreased production or increased destruction such as through increased oxidative stress (10). There is evidence that both acute and long-term reductions in LDL cholesterol, both with diet or pharmacologic therapy, improve endothelial function. For example, Tama1 et al. (11) showed in patients with FH that significant increases in brachial artery acetylcholine-induced flow mediated dilation (FMD) were noted within 4 h following a single session of LDL apheresis, which reduced LDL cholesterol from 142

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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to 33 mg/dl. Interestingly, plasma levels of oxidized LDL and the production in nitrate/nitrite most strongly correlated with the degree of FMD (11). Similarly, the extent of susceptibility of plasma LDL to oxidation and the presence of elevated plasma OxLDL levels, measured by antibody E06, has been strongly correlated with endothelial dysfunction (12,13). Other studies have shown that statins, fibrates, cholestyramine, probucol, intraarterial infusion of antioxidants, and dietary therapy also improve endothelial function. Interestingly, statins may have additional cholesterol-independent “pleiotropic” effects in preserving endothelial function by acutely enhancing eNOS activity (14).

In this issue of the Journal, de Jongh and colleagues (15) have performed a seminal study showing normalization of endothelial function with simvastatin in children with heterozygous FH (age 14 years, LDL = 205 mg/dl). They randomized 50 children with FH in a double-blinded manner to an escalating dose of simvastatin (maximum dose 40 mg/day) versus matching placebo. After 28 weeks of treatment, coincident with a 40% reduction in LDL cholesterol (to 123 mg/dl), there was normalization of FMD to levels observed in non-FH controls. Because of ethical concerns, niacin was not administered to rule out endothelium-independent vasodilation, although this is unlikely to have contributed. In this short treatment period, no adverse clinical events, hepatic toxicity, or rhabdomyolysis were noted. Although endothelial dysfunction has been previously noted in children, this is the first study to show that endothelial function can be normalized with statin therapy in children. Although data are not currently available, it seems reasonable to infer that endothelial dysfunction will be a prognosticator of CVD in children as in adults, although the expression of cardiovascular events will be delayed.

Can the findings from de Jongh et al. (15) be applied to children and young adults with moderate elevations of LDL cholesterol? A strong case can be made that any total plasma cholesterol level above 150 mg/dl is elevated and places one at risk, depending on the presence of other risk factors. For example: 1) LDL levels in most animals and even in human umbilical cord blood are ~40 mg/dl; 2) individuals with hypobetalipoproteinemia with plasma LDL levels 5 to 10 mg/dl seem never to develop atherosclerosis and are long-lived; 3) atherosclerosis cannot be induced in animals, without exception, unless their LDL cholesterol levels are significantly increased; 4) data from epidemiologic studies in multiple countries have shown that, in general, the increase in risk for MI starts above a total cholesterol of 150 mg/dl; 5) lowering LDL is proportional to lowering cardiovascular risk (16); and 6) lowering LDL cholesterol in adults decreases risk at all levels of LDL studied (17).

In light of the arguments given above, it seems likely that all would agree that identification and treatment of FH children and those with moderately elevated LDL cholesterol levels should begin at an “early age.” The key question is: “How early should this occur?” Should this be in the teenage years? Should it be in children before puberty? Unless we intend to initiate therapy, be it lifestyle modifications or drug therapy, it makes little sense to identify patients at such a young age. Such a position requires the demonstration that the use of hypolipidemic drugs at such a young age, particularly the statins, fulfills two criteria: first, that the use of statins and other hypolipidemic agents are safe in both the short and long term, and second, that treatment at such a young age has some demonstrable benefits, both short- and long-term. There is little data to support the latter is now available with the study of de Jongh et al. (15). Although there are several studies showing short-term (48 weeks) safety and efficacy of statins in children (18), long-term data are unavailable (19); nor is there information on the long-term safety of the use of bile acid binding resins, fibrates, niacin, or ezetimibe in such groups. Thus, demonstration projects to determine the safety of hypolipidemic drugs in this patient population, and in particular the use of statins, are urgently needed before the wide-scale adoption of this aggressive approach can be advocated.

Cholesterol lowering probably provides protection by multiple mechanisms, some working very quickly, as noted in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (20), and others by decreasing the progression of atherosclerosis itself and even inducing long-term regression (21,22). Thus, initiating diagnosis and treatment early in life in the highest risk individuals, such as children and young adults with type 1 diabetes, seems the most rational approach. In addition, children and young adults with multiple risk factors, metabolic syndrome, strong family history such as a first-degree relative dying in their 40s or 50s, and those on the extremes of high LDL (>160 mg/dl), low HDL (<35 mg/dl), or elevated Lp(a) (>50 mg/dl), would be reasonable candidates for early and aggressive therapy. Although the approximate 30% relative risk reduction in the statin cholesterol-lowering trials may seem large, the actual incidence of major cardiovascular events after statin therapy remains very high, at least during the 5-year duration of these trials (16,17). However, there was continued separation of survival curves at the end of the study period, and it is quite likely that further significant benefit would have accrued with longer treatment, or more importantly, with earlier initiation of treatment.

Assuming that effective treatments are available for children and adolescents, how will subclinical atherosclerosis be diagnosed? It is unlikely the simply measuring plasma cholesterol levels, except in children with FH, will provide enough prognostic power. Additional surrogate markers of atherosclerosis, such as C-reactive protein, markers of oxidized LDL (23), or inflammatory markers, may provide additional predictive power. In addition, direct non-invasive imaging of the vessel wall will likely play an important role in deciding who should be targeted for more aggressive treatment. Future imaging techniques, however, will need to
provide prognostic information above and beyond any easily measured plasma marker of risk.

Potential difficulties in targeting young, asymptomatic, overtly healthy but at-risk individuals may include poor compliance, uncertainty of long-term safety and efficacy, the predictive ability of diagnostic modalities, cost effectiveness in an era of cost containment, insurability, the potential adverse effects of statins in pregnancy, and many others.

Armed with knowledge that atherosclerosis starts in childhood and is directly responsible for the death of nearly 50% of Americans, a change in the paradigm to initiate early diagnosis, treatment, and prevention should be instituted. As we move into the 21st century, the challenge before the cardiovascular community as a whole will be to continue to improve treatments for CVD but, even more importantly, to develop cost-effective means to prevent, treat and subclinical disease before death and disability ensue.

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