INTRODUCTION

Our children are being relentlessly exposed to a cardiotoxic environment. High calorically dense, fat-enriched foods, and technologically aided sedentary lifestyles predispose future generations to cardiovascular insult. An idea once considered unimaginable a generation ago, more and more children are developing risk factors for coronary artery disease at an alarming rate.

Although children with cardiac risk factors may be asymptomatic, the data reveal the presence of significant early vascular changes in the form of fatty streaks, precursors to early plaque formation, in the coronary arteries of older children (above 10 years of age) and adolescents. The good news is that routine implementation of methods of early detection of coronary artery changes are on the horizon; these include intravascular ultrasound, cardiac magnetic resonance imaging (MRI), and 64-slice computed tomography (CT) imaging, which may aid physicians in deciding whether to prescribe cholesterol-lowering drugs. However, with the new technology, new questions will arise and decisions will have to be made regarding the validity and ultimate utility of these drugs in directing treatment.

A DILEMMA: TO TREAT OR NOT TO TREAT

Today, health care providers must ask themselves these questions:

- Should we consider at-risk children for medical management with hypercholesterolemic drugs, particularly the class reputed to be the most effective, the HMG-CoA reductase inhibitors (statins)?
- Should we recommend only lifestyle modification along with a low-fat or a low-carbohydrate diet and daily vigorous aerobic exercise?
- Should we do neither—and possibly wait for the manifestations of cardiovascular risks that affect millions of adults yearly?

Certainly, lifestyle changes have little down side, and their benefits extend far beyond the cardiovascular system. Experts debate constantly about the optimal nutritional approach to lowering cholesterol levels and weight. Short-term results have suggested that the low-carbohydrate approach might help to increase weight loss and lower total and low-density lipoprotein-cholesterol (LDL-C) levels. However, meta-analyses of the various popular low-fat and low-carbohydrate nutritional plans reveal little advantage to either when these regimens are extended for one year or greater. This is, in large part, a result of the difficulties in the long-term compliance with these diets. Although the concepts behind them are well intended and worthy of consideration, the public in general often sees only the extreme form of them on display. Compliance with lifestyle modifications, including diet and exercise, is discussed later in this article.

Prescribing the optimal exercise program is also an imprecise art, and recommendations for the amount of time that should be devoted to physical activity vary among practitioners. Most health care professionals suggest one hour or more of moderate-intensity exercise on most days of the week. This exercise may include activities resulting in heavy breathing or being able to speak in short sentences upon exertion. However, this is not an evidence-based recommendation by any means.

Because of the scarcity of studies on the safety of statin therapy in older children and adolescents, the known side-effect profile in adults, the unknown long-term effects on growth and development, and the virtual lack of any prospective efficacy studies of cardiac or all-cause mortality and morbidity in children have limited the use of statins in adolescents.

The fundamental question arises: Is coronary artery disease actually present if the individual in question has no symptoms whatsoever? If the answer is “no,” the decision to treat hypercholesterolemia in childhood would be an easy one—it would be a resounding “no.”

However, the reality is that our society recognizes that a disease can exist even when an individual is asymptomatic. For example, physicians and nutritionists give nutritional supplements or recommend dietary alterations for newborns when their initial screening reveals a deficiency in a vital enzyme. This practice may successfully prevent serious health consequences later. Hypertensive adults are often completely asymptomatic yet are treated to lower their blood pressure so as to minimize the occurrence of cardiovascular disease. Smoking cessation is a form of treatment of a very significant cardiovascular risk factor years prior to any onset of symptoms. These forms of primary prevention are the most effective tools for treating diseases—by averting their occurrence in the first place.

Thus, identifying a well-researched risk factor, such as ele-
vated cholesterol, should prompt the same philosophical approach to prophylactic treatment. Data collected decades ago from hundreds of Korean War and Vietnam War casualties revealed that coronary atherosclerotic plaques were well formed by the time the soldiers were 20 years of age. Unfortunately, correlative data on dyslipidemia were not available for most of these men. However, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) report and the Bogalusa studies demonstrated a direct correlation of dyslipidemia and coronary artery plaque formation in 15- to 34-year-olds.

Studies utilizing intracardiac ultrasound in vivo demonstrate the presence of increased intimal thickness in dyslipidemic older children (above 10 years of age) and adolescents. Further diagnostic modalities, such as electron-beam CT, demonstrate significantly increased coronary calcium scores in individuals with familial hypercholesterolemia. The higher the calcium levels, the higher the correlation with more advanced coronary artery disease.

So, back to our earlier question: should we treat all children who have hypercholesterolemia? Unfortunately, the answer is not simple. The difficulties may lie in the following: screening, compliance, and medical management.

Screening

The first hurdle to clear is to identify who should be screened for hypercholesterolemia. Most practitioners agree on the American Heart Association’s recommendation of screening all children after two years of age who meet at least one of the following historical criteria:

- any parent or grandparent with cardiovascular, cerebrovascular, or peripheral vascular disease before age 55 years
- either parent with a total cholesterol level above 240 mg/dL
- an unknown medical history of the biological family

Although this approach would be beneficial in detecting many children who are at high risk for adult cardiovascular disease, it could detect some children with elevated lipids that might spontaneously resolve without any aggressive lifestyle modifications or medical therapy. Conversely, many children who ultimately develop adult dyslipidemia may be missed when these criteria are used. The likelihood of correctly identifying more children at risk for hypercholesterolemia increases if we set the parents’ cholesterol level to 200 mg/dL instead of the previously suggested 240 mg/dL.

The alternative approach involves universal screening. Even though this approach undoubtedly would find more children with dyslipidemia, there are significant drawbacks. One problem involves the significant cost associated with screening all children. More important, if dyslipidemia is detected, the decision to treat is an even more onerous one.

Most practitioners who detect dyslipidemia in children with a strong family history believe that aggressive intervention is warranted to help prevent a similar fate. However, the universal screening approach might identify an individual with dyslipidemia but with no family history of concern, thereby making the need to treat much less clear.

The timing of screening also is an important variable. Older children and adolescents normally have a physiological nadir in lipid levels that climbs into adulthood. Generally speaking, cholesterol levels are higher in preadolescents than in older adolescents. Therefore, the age at which children undergo screening has a definite impact on the decision to treat.

Health care professionals might choose not to prescribe medications for a preadolescent with a borderline high cholesterol level, knowing that the patient’s lipid profile might naturally improve in the upcoming adolescent years. Although health care providers might decide not to intervene, they must be cognizant of a possible rebound worsening of the lipid profile into early adulthood.

Compliance

Let us now assume that we identify the child with an elevated lipid profile via the targeted-screening approach and that we are now considering treatment. Certainly, few would disagree with recommending lifestyle changes; however, many practitioners hold little confidence in the ability of their patients to actually achieve target goals solely with lifestyle modifications. Many health care professionals say that diet and exercise “just don’t work.” This is a common misperception; in reality, however, lifestyle modification is highly effective—the real problem is that compliance with lifestyle changes is difficult to achieve.

Why is compliance so difficult for patients to achieve?

Shouldn’t the goal of a healthier body be enough motivation? Noncompliance may be prevalent because of the following:

- Lifestyle changes are not a quick fix to the problem.
- Eating and activity habits are deeply ingrained.
- Lifestyle changes are not fun, pleasant, or exciting.
- Early cardiovascular disease may be asymptomatic, painless, and not outwardly visible, thereby not providing significant motivation to change.

Therefore, we are left with medical management—or are we?

Medical Management

Certainly in adult medicine, persistent dyslipidemia may be countered with the addition of cholesterol-lowering drugs. Also, intrinsic to the decision to prescribe medications is a consideration of comorbidities such as diabetes, obesity, smoking, hypertension, along with knowledge of the patient’s pre-existing cardiovascular or peripheral vascular disease. Aside from the growing predisposition toward obesity, children rarely exhibit the same comorbidities that afflict the adult population.

This being said, the incidence of type-2 diabetes mellitus and of the poorly defined metabolic syndrome is skyrocketing in obese older children and adolescents and is becoming a recognized comorbidity in this population. The syndrome is not well defined in children; it is an evolving diagnosis, and it perceived by many to be a future problem. Children with truncal obesity, elevated triglyceride levels, and insulin resistance have the syndrome, but we don’t know what constitutes significant enough truncal obesity and insulin resistance for a child to receive the diagnosis. We cannot use the adult woman’s “35-inch waist” and the adult man’s “40-inch waist” as criteria.

Much of the data on the efficacy of statin drugs in terms of cardiovascular morbidity and mortality exists in secondary prevention studies (i.e., in patients with already established coro-
nary artery disease). However, on the basis of limited primary prevention analyses in adult medicine, the consensus is that cholesterol-lowering attempts are warranted even in the absence of other risk factors or of pre-existing cardiovascular disease. Furthermore, primary prevention studies have not conclusively determined the desired target goal for lipid levels in younger people. Unfortunately, primary prevention studies involving adults cannot be extrapolated properly to children for whom medical treatment is being considered for primary prevention of cardiovascular disease.

Further confounding the entire matter: although studies of adults reveal reductions in cardiovascular mortality, cholesterol-lowering drugs have not uniformly demonstrated significant reductions in all-cause mortality. Thus, lowering one’s cholesterol level might prevent some forms of heart disease, but some other disease will still get us in the end. It is important to state that there has never been a demonstrated direct causality of statins to noncardiovascular mortality.

This finding thus illustrates the importance of emphasizing the quality—but not necessarily the quantity—of one’s years in terms of disease prevention. Although we are merely speculating, we would think that reducing cardiovascular disease in adults should improve their ability to remain vigorous, active, and content. These are all desirable goals, even though we do not have evidence to conclude that improving cholesterol levels reduces overall mortality.

After taking all of these facts into account, medical providers may consider medication therapy for children older than 10 years of age. The choice of medication is another challenge.

For a long time, the bile acid–binding resins were the staple of pharmaceutical management in children. These were preferred because of their impressive safety profile; however, poor palatability, significant gastrointestinal side effects, and limited cholesterol-reducing effects made this class of drugs a poor choice.

Along came the statins, which act in the liver to block cholesterol synthesis, thereby resulting in up-regulation of LDL-C receptor expression. This in turn results in more cholesterol-laden LDL-particles being pulled out of the blood.

Recent exciting data also suggest a pleiotropic effect of statins as anti-inflammatory agents against atherosclerosis.6 By acting to inhibit precursor metabolites of cholesterol that trigger inflammation, statins may have a significant vascular protective effect. A growing number of double-blinded, placebo-controlled pediatric studies have demonstrated excellent LDL-C-lowering effects of this class of medications. Safety profiles have been excellent, and reports about possible growth or maturational interference have not been confirmed.8 Unfortunately, these studies have relatively short-term follow-up periods.

Let us revisit the hypothetical adolescent male who is being medically treated with statins. We can assume that he has experienced excellent lowering of LDL-C and total cholesterol levels as well as a modest elevation in high-density lipoprotein-cholesterol (HDLC). Now additional questions arise:

- How long do we treat this adolescent with statins?
- What if there is a significant rise in liver enzymes?
- What if creatine phosphokinase levels rise significantly after vigorous sporting activities or muscle trauma?

In general, our knowledge about statins in children is based on a few clinical studies that followed children for six months to two years after initiation of the study drug.9 Approximately 1% to 5% of children show significant increases in liver enzymes, and fewer develop rhabdomyolysis. In most older children and adolescents without underlying liver disease, the elevation of liver enzymes greater than three-fold warrants discontinuing the statin. In a significant majority, enzyme levels return to normal after the medication is stopped. However, the rest of our questions are not yet answered.

**DISCUSSION**

We are left with these facts about the use of statin drugs in adolescence:

- Statins are highly effective for the short-term lowering of cholesterol and LDL-C levels.
- They have a favorable side-effect profile and are well tolerated.

However, their use in this age group also poses these dilemmas:

- Studies demonstrating reductions in cardiovascular mortality exist exclusively in adults and primarily in secondary prevention studies.
- It is unknown whether the pleiotropic beneficial effects of statins apply to older children (above 10 years of age) and to adolescents, as demonstrated in adults.
- Long-term systemic and developmental effects have not yet been assessed in older children or adolescents.

Therefore, dyslipidemia in these older children and adolescents will continue to pose a dilemma to concerned health care professionals. In actual practice, if the adolescent has significant dyslipidemia (total cholesterol, 240 mg/dL; LDL-C above 190 mg/dL) and a strong family history of first-degree relatives with premature cardiovascular disease, we would not hesitate to medically prescribe statins after a failed six-month trial of lifestyle modification.

It is the child with borderline values whose total cholesterol level only slightly exceeds the recommended 170 mg/dL and whose LDL-C level exceeds 110 mg/dL (e.g., total cholesterol, 180 mg/dL; LDL-C, 140 mg/dL) and no other comorbid risk factors who poses a treatment conundrum.

If premature disease is suspected in the family history, one would certainly consider medical management after failed attempts at lifestyle modification. However, the use of a resin binder, such as cholestyramine (Questran, Par), may adequately achieve results without subjecting patients to the more potent statins. This drug class—the antilipemic agents—inhibits local intestinal absorption of cholesterol without creating problems relating to systemic absorption, hepatic or muscle injury, or the need to monitor blood work; however, its cholesterol-lowering effects are not as potent as those associated with statins.

**CONCLUSION**

It seems evident that the use of statins for primary prevention of coronary artery disease will benefit older children and adolescents in the same way that it benefits young adults. Prospec-
It will probably also benefit patients to use the newer, non-invasive modalities such as ultra-fast electron beam CT, cardiac MRI and magnetic resonance angiography (MRA), and intravascular ultrasound to monitor the progression or regression of coronary artery disease, with surveillance assessments beginning in childhood.

Finally, it bears repeating that pharmacotherapy should never replace lifestyle modification as the primary focus in the management of dyslipidemia in children.

REFERENCES