Evidence Mandating Earlier and More Aggressive Treatment of Hypercholesterolemia

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The long-standing controversy over the validity of the lipid hypothesis of atherosclerosis has been settled.1–3 In several large-scale, 5-year trials, statins have reduced coronary heart disease (CHD) morbidity and mortality by ≈30%, and the magnitude of the protective effect mirrored the magnitude of the low-density lipoprotein (LDL) lowering.4 However, as has been quite correctly pointed out,5–6 some 70% of those expected to have an event (based on the number of events in the control group) went on to have one during the 5 years of the trial despite statin therapy. For example, in the Scandinavian Simvastatin Survival Study, 502 events occurred in the untreated group and 353 in the statin-treated group. The number of events prevented (n=149), as a percentage of the number expected, was 29.7% (149/502×100); the number of events in the statin group that were not prevented (353) amounts to 70.3% (353/502×100). Looked at this way, the results are admittedly not quite so impressive. In fact, some investigators are now taking the position that we can expect to achieve higher salvage rates only if we supplement LDL-lowering therapies with alternative interventions such as the use of antiinflammatory agents or immunotherapy. This may turn out to be true. However, it is much too early to reach that conclusion for reasons we discuss here. The search for alternative or supplementary therapies is already in full swing and should continue.6–8 We are confident that one day these additional therapies will take their place alongside cholesterol-lowering agents in our armamentarium. However, we believe that the results of the statin trials to date considerably underestimate the full potential of cholesterol-lowering strategies. It would be unfortunate if efforts to fully exploit that potential faltered because of a misplaced pessimism based on the statin results to date. Our current approaches may be a case of “too little, too late.”5,9–14 How much further can we expect to decrease risk by treating dyslipidemia (ie, lowering LDL levels and/or raising high-density lipoprotein levels)?

Why Do We Think We Can Do Better?

One important line of evidence comes from a consideration of the Japanese experience. In 1952, mortality from CHD among Japanese men 55 to 64 years of age was <10% of what it was in the United States.15,16 Their total cholesterol levels at the time averaged ≈160 mg/dL (estimated LDL, ≈80 mg/dL). It is noteworthy that the Japanese enjoyed this relative immunity to CHD despite the fact that the prevalence of one of the major risk factors—cigarette smoking—was much higher in Japan than in Western countries,17 and another—hypertension—was just as high.18 Even the diabetic population in Japan fares better than the diabetic population in Western countries. In 1985, almost 30% of British male diabetics but only ≈15% of the Japanese male diabetics had CHD.19 The implication is that if blood cholesterol levels are sufficiently low, the other dominant risk factors, including cigarette smoking, hypertension, and diabetes mellitus, constitute much less of a threat.

Are these large differences in incidence between Japan and Western countries based primarily on genetic factors? No. Two cleverly designed epidemiological studies showed that the Japanese who had migrated and taken up permanent residence in Hawaii had higher blood cholesterol levels and a higher incidence of CHD than those who remained on the home island. For those who migrated even further, on to California, the differences were even more striking.20,21 This and other migration studies22 showed that the differences in CHD risk among different populations are certainly not entirely genetic. Which environmental factors are at play? A number of factors could be involved, but there is reason to believe that the major factors are changes in diet and exercise patterns that predispose to elevated blood cholesterol and obesity. Keys23 reported as early as 1957 that the fat content of the diet, as a percentage of total calories, rose from 10% to 15% in Japanese on the home island to ≈30% in Japanese migrants to Hawaii and to almost 40% in migrants to Los Angeles.

A crucially important point needs to be noted here: For whatever reasons, the Japanese have their lower cholesterol levels for their entire lifetimes. Lowering the cholesterol level of a 50-year-old American for just 5 years, even if his cholesterol is successfully brought down to a Japanese-like level, is unlikely to convert his risk to a Japanese-like risk. At 50 years of age, he most likely enters the study with well-established, extensive arterial disease.24,25 It would be unreasonable to expect that all that damage could be reversed in just 5 years. The canonical 5-year trials have given us a minimum estimate of the impact of preventive management. Only after longer trials with younger subjects will we have...
some estimate of the maximum potential. We will return later to this key issue, the need for earlier treatment.

### How Much More Aggressive Should Treatment Be?

In the 1940s, many clinical laboratories defined a total cholesterol level of 280 mg/dL as the upper limit of normal. That number has come tumbling down over the decades as epidemiological and clinical trial experience has accumulated. Currently, for individuals at high risk, the widely accepted rule is becoming "the lower, the better."4,11,26–31 The National Institutes of Health (NIH) now recognizes that an LDL of $\leq 70$ mg/dL confers more benefit than the canonical 100 mg/dL originally recommended in the Adult Treatment Panel III 2001 guidelines.32,33 Careful analysis of the statin data makes it clear that further benefit is conferred when LDL is reduced even to 40 to 60 mg/dL.29 Although limited, data are available suggesting that patients with initial LDL levels $<40$ mg/dL show lower all-cause mortality after 2 years of statin therapy.34

With combination therapy, it is now possible to reach these low LDL goals; they are not unrealistic.35 Yet, most patients outside specialty clinics are not reaching those goals, in part because of poor compliance but also in part because practitioners are still hesitant to be more aggressive. There continue to be concerns about safety and side effects despite the wealth of evidence that they are not serious problems in the vast majority of patients.36

### Do Adverse Effects Accompany Cholesterol Lowering?

Is lowering LDL levels intrinsically dangerous? That possibility has been suggested in the past, but no hard evidence exists for such a concern, and a number of considerations make such an effect quite improbable.

First, levels of intracellular cholesterol are jealously guarded by the wonderfully efficient LDL receptor homeostatic mechanism elucidated by Brown and Goldstein.37 Consequently, lowering plasma cholesterol levels does not decrease intracellular cholesterol levels. The LDL receptor has a very high affinity for its ligand, so much so that even at plasma LDL cholesterol concentrations of 10 mg/dL, the LDL receptors in peripheral tissues would still be 50% saturated and uptake would continue unabated.

Second, we know that most mammalian species have LDL levels well below those reached in humans during even the most aggressive treatment of hypercholesterolemia (mean value, 42 mg/dL).38 Obviously, these animals’ cells do just fine. In addition, cord-blood LDL levels in humans are $<20$% of adult levels,39 showing that growth and development of the fetus are just fine at LDL cholesterol levels $<40$ mg/dL.

Third, in some kindreds with hypobetalipoproteinemia, LDL cholesterol levels can be $<15$ mg/dL throughout life, yet the affected members show perfectly normal growth and development and actually have increased longevity.40,41

We know now from the large-scale statin trials that lowering LDL values to well below 100 mg/dL not only is safe but actually decreases overall mortality significantly.4,11,29,42–46 Thus, there should be no hesitation at all about lowering LDL levels through attention to lifestyle changes (ie, diet and exercise), in which the intervention itself carries no risks. Here, the only rule necessary is “the lower, the better.”

However, when it comes to drug therapy, we must take a hard look at risks and benefits. In patients at high or moderate risk of CHD, the risk-to-benefit ratio with statins is obviously favorable, and their use should be expanded. If target goals are not achieved, combination therapies with other hypolipidemic agents should be aggressively pursued. In short, for most subjects, hypolipidemic agents, alone or in combination, are on hand to lower cholesterol levels to meet current guidelines and even the more aggressive guidelines that are sure to come.

### Should We Be Starting Preventive Measures Earlier?

Fatty streak lesions are already extensive by 30 years of age.24,25 These lesions are themselves asymptomatic and clinically nonthreatening at that early stage. Consequently, some have proposed that intervention can be deferred and that treatment will somehow “catch up.” This is shortsighted. It overlooks the fact that the early lesions are the precursors of the later, clinically threatening lesions. Thus, the risk factors that predict the extent of fatty streaks in the young, including hypercholesterolemia, are the same as those that predict coronary heart disease risk and myocardial infarction in adults.47,48 It is not as though we were dealing with two different diseases, one early and clinically benign (and, by implication, therefore not requiring our immediate attention) and 1 late that now carries a more imminent threat of angina and infarction (and therefore demands our immediate attention). No, we are dealing with a single disease entity that evolves slowly over decades. Mapping in the Pathobiological Determinants of Atherosclerosis in Youth study49 confirmed what was known from animal model studies, namely that the anatomic sites favored for fatty streak development are much the same as those favored for fibrous plaque development. In short, the fatty streak is indeed the precursor of the plaque. The disease is a continuum, so prevention of (or slowing the development of) fatty streaks will prevent (or slow the development of) the later, clinically significant lesions. So, why wait for the clinical expression to be just around the corner? No one would seriously propose deferring cancer therapy until the tumor had reached a certain size. No one would advocate deferring treatment of diabetes mellitus until microvascular disease was evident. Why not slow things down early in the game, as urged by McGill and McMahan9 and by Domanski44? The hope is that doing so might prevent clinical expression or at least defer it into the 9th or 10th decade.

We already treat very high-risk patients in childhood (eg, patients with familial hypercholesterolemia), and evidence is building to show that early treatment works and is safe. In children 8 to 18 years of age, pravastatin treatment for 2 years lowered LDL levels by 24% and significantly slowed the rate of progression of intima-media thickening of the carotid artery.50 No adverse effects on growth, hormone levels, or sexual maturation were found. A follow-up study when the...
whole cohort had been on statin treatment for an additional 2.5 years showed that the results were significantly better in the children entered into the study at younger ages. Until long-term studies have been done, we cannot say with certainty how much better the cardiac end-point results will be as a result of starting earlier. Still, some exciting new results suggest that we may be pleasantly surprised.

A new gene importantly involved in regulation of the LDL receptor has recently been identified. This gene, PCSK9, codes for a secreted proprotein that acts to decrease the number of LDL receptors expressed in the liver. Overexpression of the gene (or gain-of-function mutations) lowers LDL receptor number and thus raises plasma LDL levels; knocking out the gene (or a loss-of-function mutation) increases LDL receptor number and thus lowers LDL levels. PCSK9 does not regulate at the transcriptional or translational level but rather in some fashion suppresses the level of expression of the LDL receptor at the surface of the hepatocyte. The precise molecular mechanisms are still uncertain.

The key point here is that Cohen and colleagues have studied CHD risk in subjects with nonsense mutations in PCSK9 that cause low plasma LDL levels, presumably from birth. The LDL levels in these subjects were reduced by 28%. The CHD risk, on the other hand, was reduced by fully 88%. In the 5-year statin trials, the drop in LDL (25% to 35%) was similar, but the decrease in risk was only \( \approx 30\% \), not 88%. As nicely pointed out by Brown and Goldstein, the implication is that having a low LDL from birth almost triples the magnitude of the effect on risk compared with the risk reduction found in a 5-year trial of middle-aged people. Nonsense mutations were much less common in the white subjects in the Cohen et al cohort, but a missense mutation (R46L) occurred in 3.2% of the whites. This mutation was associated with a 15% lower LDL and a 47% reduction in CHD risk. Again, the large impact of this modest reduction in LDL on risk is striking. The protective effect of the R46L mutation has been confirmed by 2 groups. These findings strongly support a mandate to treat earlier. Drugs that regulate the expression and function of PCSK9 may well be treated as a result of starting earlier. Still, some exciting new results suggest that we may be pleasantly surprised.

We have no idea yet how long it will take to cause a vulnerable plaque in humans to revert to a stable plaque, and that would seem to be the most relevant datum. There may be only poor correlation between measures of anatomic regression and risk of infarction. However, the fact that in some trials the event rate in the experimental group has become significantly lower within the first 6 months of lipid lowering strongly suggests that even a relatively small degree of anatomic regression and/or “plaque stabilization” is enough to significantly reduce risk.

Recently, striking evidence of the reversibility of lesions has been seen in mouse models. Desurmont and coworkers showed that the hypercholesterolemia in apolipoprotein E-null mice crossed into immunodeficient (nude) mice can be rapidly corrected by introducing the human apolipoprotein E gene via an adenoviral vector. The plasma cholesterol level returned to almost normal within a week or 2, from 400 down to 100 mg/dL, and because no immune response occurred, it stayed down for at least 100 days. Lesion size in the proximal aorta at 17 weeks, which is when the adenoviral vector was injected, was \( \approx 10^4 \mu m^2 \); over the next 28 weeks, in the controls (LacZ vector), it further increased 6-fold. However, in the mice receiving the apolipoprotein E vector, lesion size decreased by almost 90%. Moreover, there was a virtual disappearance of foam cells and cholesterol from the lesions and reendothelialization of the aorta.

Reis and colleagues have shown equally dramatic regression in mice. They devised a technique for transplanting a lesion-containing thoracic aortic graft from a hypercholesterolemic apolipoprotein E–null mouse into either a syngeneic normocholesterolemic recipient or another syngeneic hypercholesterolemic apolipoprotein E–null recipient. This allowed the investigators to suddenly change the environment in which the aortic lesion finds itself to whatever the recipient blood offers. In this study, the donors had been on a Western-type diet for a full 9 months, so they had advanced, complicated lesions containing foam cells, intimal smooth muscle cells, extracellular matrix, and lipid pools. Nine weeks after transplantation into normocholesterolemic recipients, atherosclerotic changes had all but disappeared; in contrast, after 9 weeks in the hypercholesterolemic apolipoprotein E–null recipient, the lesions had increased further in size.

Finally, we call attention again to an impressive series of articles showing that returning cholesterol-fed rabbits to a Chow diet—and thus lowering their blood cholesterol without pharmacological intervention—markedly reduced many proinflammatory processes associated with lesion progression.
Taken together, all of these findings suggest that the inflammation associated with atherogenesis is not sufficient in itself to cause further lesion progression or even to maintain lesions at a steady state once the hypercholesterolemia has been fully corrected. In other words, many (or even most) of the inflammatory processes in the advancing lesion are downstream responses ultimately traceable to hyperlipidemia and its consequences. Consequently, early and aggressive correction of hypercholesterolemia may be sufficient. On the other hand, if hypolipidemic therapy is initiated at, say, 40 or 50 years of age, optimal intervention will no doubt also require attention to inflammation, thrombosis, and hemodynamic factors.

**Implications for Management**

Progress in this area of medicine has been rapid. As a result, public health policies and guidelines for practitioners have tended to lag behind. The time is ripe for a fresh look at the issues, taking a longer-term view. At the top of the agenda should be the issue of early treatment of hypercholesterolemia. We know the disease is already well on its way by 30 years of age, yet current guidelines do not take into account the natural history of the disease. How shall we change our approach? Lloyd-Jones and colleagues make a cogent argument for using lifetime risk rather than short-term, 10-year risk as the arbiter of how intensive therapy should be. Their analysis of data from the Framingham cohort shows that for men 40 years of age with a total cholesterol level of 200 to 239 mg/dL, the 10-year risk for CHD is only 5%, but the lifetime risk is 43%.

Eliminating age from risk prediction models includes both pros and cons. In many respects, it is an attractive way to encourage earlier intervention in patients with high-risk profiles. Other algorithms should be evaluated, taking into account all the relevant risk factors and leading to intervention at the appropriate level of intensity. Initiation of therapy at least by 30 years of age would seem to be warranted in any patient with a lifetime risk >40%.

Of course, children with familial hypercholesterolemia should be started very early in life on statins, and other agents if necessary, to lower their LDL to 50 mg/dL. Adults with existing CHD or multiple risk factors also should strive to lower their LDL to 50 mg/dL. In fact, on the basis of the accumulated evidence reviewed above, it would be reasonable to recommend that an “ideal” LDL cholesterol level should be defined as ≤50 mg/dL. That goal is currently attainable in many patients with the treatment regimens now available, which include statins alone or in combination with other hypolipidemic drugs, including bile acid sequestrants, niacin, fibrates, and ezetimibe. In the future, new agents should become available to help reach these lowered goals in almost everyone.

**The Ultimate Long-Term Solution**

If indeed the low pre-Westernization CHD rate in Japan was, as discussed above, due primarily to lifestyle differences (diet and exercise), then our long-term goal should be to alter our lifestyle accordingly, beginning in infancy or early childhood. Is such a radical proposal totally impractical? It would, of course, take generations to achieve and would require an all-out commitment of money and manpower to reeducate and modify the behavior of the nation. Is that impossible? No. We have already shown that even a frankly addictive behavior like cigarette smoking can be overcome (eventually) with the right combination of education, peer pressure, and legislation. Would it be safe? Data are now available to show that instituting a low-saturated-fat, low-cholesterol diet in infancy (7 months) is perfectly safe without adverse effects on growth, development, and sexual maturation.

The importance of early intervention is becoming apparent in another common chronic disease entity, type 2 diabetes mellitus. Early treatment has been shown to prevent progression of prediabetes to frank clinical diabetes. Interestingly, intensive intervention on lifestyle factors (ie, diet and exercise) was just as effective as or more effective than intervention with drugs (metformin). It is now considered best practice to anticipate the conversion of prediabetes (impaired glucose tolerance) to frank diabetes mellitus and to forestall that conversion by early intervention. In much the same way, it should become best practice to anticipate the conversion of the fatty streak to the fibrous plaque by treating hypercholesterolemia at a much earlier age.

The NIH has already committed itself to “wars” on obesity and diabetes mellitus. The weapons for those wars—education and behavior modification—are the same as those needed for a war on CHD. The overlaps are obvious. A concerted national public health program might dramatically reduce morbidity and mortality resulting from these 3 major chronic diseases.

**Summary**

With the advent of the statins, enormous progress has been made in the management of hypercholesterolemia. However, some authorities point out, quite correctly, that statin treatment reduces event rates by “only” 30% and suggest that preventing the other 70% will require more than just control of hypercholesterolemia (eg, adjunctive use of antiinflammatory or immunologic interventions). This may discourage clinicians from pressing on to do the best that can be done with the interventional tools already at hand. This review has summarized the evidence, drawn from a variety of sources, that the results of the 5-year statin trials seriously underestimate the ultimate potential of cholesterol-lowering therapy. We suggest that this evidence mandates continuing and more aggressive use of lipid-lowering regimens and, even more important, intervention at an earlier stage in the development of the atherosclerotic lesion.

**Disclosures**

Drs Witztum and Glass are on the Merck Speakers’ Bureau. Dr Witztum is a consultant to AtheroGenics Inc. Dr Steinberg reports no conflicts.

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