

BISHOP LECTURE

Evolving Concepts of Dyslipidemia, Atherosclerosis, and Cardiovascular Disease

The Louis F. Bishop Lecture

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The controversies, successes, and unanswered questions that typify the unique, ongoing narrative history of dyslipidemia as a coronary risk factor have had profound effects on policy, patient care, and basic science (1,2). Although this lecture will draw from multiple sources, including my own personal experience, a brief synthesis of the state of the art such as this cannot possibly capture the contributions of all of the many investigators over the decades whose laboratories have delineated the diverse threads that intertwine dyslipidemia, atherosclerosis, and cardiovascular disease. Nevertheless, I will attempt to examine some of the most current and important topics as well as give my own personal perspective of how this field has evolved since I first came to it in 1967 at the National Institutes of Health (NIH), in the laboratory of Donald Fredrickson and Robert Levy.

WHAT IS THE LIPID HYPOTHESIS?

Based on a substantial body of observational, pathological, and clinical data, the lipid hypothesis holds that reducing high levels of cholesterol, particularly low-density lipoprotein cholesterol (LDL-C), decreases the risks for developing atherosclerosis. The pathologist Felix Marchand first proposed the term "atherosclerosis" in 1904, from the Greek "athero," meaning gruel or porridge, and "sclerosis," meaning hardening, to describe the fatty mush that he observed inside a hardened artery (3). Atherosclerosis begins as a disease primarily of the intima. The two main components believed to be involved in the atherosclerosis, or atherothrombosis, process were described in the mid-19th century by Karl von Rokitansky, who thought that atherosclerosis began with deposition in the intima of small blood clots with subsequent organization by the infiltration of fibroblasts and secondary lipid deposition, and by Rudolf Virchow, the German pathologist, who proposed that lipid insudation, vascular intimal injury, and inflammation in the arterial wall were the major mechanisms of plaque development (4).

Cholesterol, cholesteryl ester, and phospholipid circulate in blood in macromolecular complexes called lipoproteins. Michel Macheboeuf, in 1929, working at the Pasteur Institute, first described the plasma lipoproteins by using ammonium sulfate fractionation of horse serum to isolate alpha-lipoproteins, what today almost certainly would be recognized as high-density lipoprotein (HDL) (5). During the Second World War, the need to improve transfusion technologies for the battlefield helped spark a great effort to purify the constituents of blood plasma and serum. Two of the leading laboratories involved in this effort were those of Edwin J. Cohn and J. L. Oncley (6,7). Later on, I had the privilege to meet Professor Oncley and learned a great deal from him about those early days, when they were isolating huge amounts of plasma and serum with fractionation procedures that included precipitation under different acid and salt conditions, as well as electrophoresis. The original classification of the lipoproteins described an alpha- and a beta-fraction of lipids and lipoproteins in blood, based on their electrophoretic migration with the alpha- and beta-globulins. The alpha-lipoproteins correspond with HDL, and the beta-lipoproteins comprised mainly LDL. A pre-beta-fraction that migrated just in front of the beta-globulins has been characterized as including very low-density lipoprotein (VLDL) and then, subsequently, was shown to also contain a component called "sinking pre-beta" that was lipoprotein[a] (Lp[a]).

In 1951, Russ, Eder, and Barr (8,9), while at the New York Hospital, Cornell Medical Center, used the methodology of Cohn and Oncley to identify higher levels of alpha-lipoprotein in young women compared with men. They presciently postulated that these higher concentrations of the alpha-lipoprotein contributed to the lower cardiovascular disease event rate seen in pre-menopausal women.

In 1949, the noted biophysicist John Gofman and his colleagues at the University of California at Berkeley used the newly developed ultracentrifuge to separate plasma lipoproteins by flotation (10). Gofman observed that the lipoprotein fraction that corresponds with LDL was associated with increased risk for cardiovascular disease and showed that, in patients with familial hypercholesterolemia, the cholesterol elevation was all in the LDL and intermediate-density lipoprotein fractions.

At the NIH, Donald Fredrickson took advantage of the

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preparative ultracentrifuge and paper electrophoresis, which Robert Lees and Fred Hatch had shown could give a better separation of lipoproteins if an albuminated buffer was used, to characterize the lipoproteins further. In a series of landmark articles in the *New England Journal of Medicine* (11), Fredrickson, Robert Levy, and Robert Lees described a classification system based on which groups of lipoproteins were elevated. Fredrickson phenotyping has proved to be a popular schema for describing the dyslipidemias, although Fredrickson's categories made no attempt to distinguish between dyslipidemias with a primary or secondary etiology.

In those early days, two large observational trials played a key role in establishing the cardiac dangers of excess cholesterol levels. Ancel Keys' Seven Countries Study (12), during the 1950s and 1960s, helped make the connection between dietary fat consumption, dyslipidemia, and coronary risk. In those populations that consumed a higher proportion of saturated fat as the total dietary caloric intake, there were higher levels of cholesterol in the blood and a higher incidence of congenital heart disease (CHD) mortality.

Between 1948 and 1951, under the aegis of the National Heart Institute (the precursor to the National Heart, Lung, and Blood Institute [NHLBI]), the Framingham Heart Study began to collect longitudinal data on 1,980 men and 2,421 women. In 1961, the Framingham investigators published their six-year follow-up data (13). The study showed that high blood pressure, smoking, and high cholesterol levels were major preventable factors in heart disease. The impact of the Framingham Heart Study on the recognition and management of atherosclerosis cannot be overstated: it is primarily responsible for the concept of "risk factors," both modifiable and nonmodifiable, and has guided the course of many decades of discussion of risk assessment.

The crux of the lipid hypothesis was that reducing cholesterol would reduce coronary events. The epidemiology had made a clear connection between cholesterol and coronary risk, but, as we have seen today with antioxidants and with hormone replacement therapy in CHD prevention, a relation established by epidemiologic or observational studies does not confirm a clinical benefit. An interventional trial was needed.

IS THE LIPID HYPOTHESIS CONFIRMED?

The Lipid Research Clinic Coronary Primary Prevention Trial (LRC-CPPT) (14), one of the most difficult trials in which I have participated, proved to be that trial. Each clinic site screened about 30,000 men in order to recruit 300 who qualified for entry by having very high levels of LDL-C, no evidence of coronary disease, and tolerance to the then-available preparation of cholestyramine, which patients compared in texture and palatability to sand. Overall, the trial recruited 3,806 middle-aged men with primary hypercholesterolemia. Although the drug was supposed to be administered as 24 g/day, patients could manage an average

dosage of around 12 g/day versus placebo. There was a 12% reduction in LDL-C and 9% in total cholesterol, corresponding to a reduction in CHD events of 19% after 7.4 years of follow-up.

Despite some investigators who criticized the trial's design and statistical analysis, LRC-CPPT confirmed for many others that the fundamental premise of the lipid hypothesis—that lipid modification was cardioprotective—was sound and enhanced public awareness of the issue of cholesterol and heart disease. Inspired by this trial, Dan Steinberg chaired an NIH committee to put together a National Cholesterol Consensus (15). The NHLBI launched a program that turned into the National Cholesterol Education Program. On September 1, 1987, lovastatin became the first statin to be introduced into the market. A year later, the positive results of the primary-prevention Helsinki Heart Study of gemfibrozil were announced (16). Thus, all evidence seemed to be moving toward affirmation of the lipid approach, although the lack of evidence showing total mortality benefit remained a key obstacle to wider acceptance.

In 1989, the investigative reporter Thomas Moore wrote a cover story for the *Atlantic Monthly* magazine entitled, "The Cholesterol Myth," with the tagline of "Lowering your cholesterol is next to impossible with diet, often dangerous with drugs, and it won't make you live any longer." (17). Since that article's publication, data have amassed that make it possible to challenge each of these three early criticisms. First, the lipid effects of diet are better understood. Dansinger et al. (18) recently assessed the lipid-modifying impact of four popular weight loss programs and also reported a one-year change in the LDL-C:HDL-cholesterol (HDL-C) ratio by approximately 10%, a reduction that is consistent with the lipid changes expected on the American Heart Association diet, which recommends low consumption of saturated fats. Regardless of the diet chosen, 12 months of weight loss was associated with improvements in the total cholesterol:HDL-C, C-reactive protein (CRP), and insulin levels. Poor patient adherence is the greatest impediment to optimal implementation of dietary therapy.

Second, a substantial body of evidence now illustrates the safety of the most potent class of lipid-modifying drugs, the statins. Although one agent of this class, cerivastatin, was removed from the market in 2001 because of an enhanced risk for fatal rhabdomyolysis, the rates of adverse events with the remaining are low and do not exceed the potential benefits of therapy. An analysis of pharmacy benefit data from 11 managed-care health plans concluded that the rhabdomyolysis rate was low and similar for atorvastatin, pravastatin, and lovastatin (0.44 per 10,000 person-years of treatment) (19).

Finally, three of the landmark statin trials were sufficiently powered to determine an effect on total mortality of active treatment against placebo: a 30% reduction in the Scandinavian Simvastatin Survival Study (4S); 22%, in the

Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial; and 13%, in the Heart Protection Study (20–22). Therefore, it may be said conclusively that lipid modification can help improve survival in high-risk patients.

EMERGING ROLE OF NON-LDL LIPID MARKERS IN CHD RISK MANAGEMENT

Although the clinical trials of statins have established that targeting LDL-C yields coronary benefit, statin treatment does not completely abolish CHD risk, and many receiving statins nevertheless proceed to clinical coronary events. Thus, although LDL-C remains the primary “bad actor” in atherogenesis and is the first lipid target of therapy, research has moved beyond LDL alone to include other lipid fractions that may be contributing to the risk, such as HDL-C and triglycerides.

The Framingham Heart Study was one of the first to observe the inverse correlation between HDL-C and coronary risk: the higher the HDL-C, the lower the risk for an event, to the extent that a 1-mg/dl increment in HDL-C corresponded with 1% decrement in CHD risk (13).

There have been a number of trials with fibric acid derivatives, the lipid-modifying drug class with primary HDL-C-raising and triglyceride-lowering effects (23). None of these trials were powered to look at all-cause mortality, but two of them have reported coronary risk reductions with fibrate treatment compared with placebo: the Helsinki Heart Study and the Veterans Affairs HDL-C Intervention Trial (VA-HIT), a secondary-prevention study with gemfibrozil in post-myocardial infarction (MI) men. In the VA-HIT, there was no reduction in LDL-C, but a significant reduction in coronary events, attributed in part to the effect of gemfibrozil on HDL-C (24). An interesting finding from both studies was the post-hoc description of a certain subgroup of patients who appeared to benefit more acutely from intervention than the overall cohort. In the Helsinki Heart study, high triglycerides, low HDL-C, and high LDL-C characterized the subgroup that experienced the greatest relative risk reduction (25). This subgroup with the “lipid triad” would be comparable to patients with the metabolic syndrome, based on current criteria. In the VA-HIT, the patients who most benefited were those who either were diabetic or who had the metabolic syndrome (26). Therefore, fibrate treatment appears to be of particular benefit in patients who have or are susceptible to diabetes or who have the metabolic syndrome.

Over a five-year period in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), treatment with lovastatin, 20 to 40 mg/day, reduced the risk for a first acute major coronary event by 37% in low- to moderate-risk men and women with below-average HDL-C (27). Logistic regression modeling to identify which lipids or apolipoproteins correlated best to event reduction suggested that apolipoprotein A1, the major protein of HDL, and apolipoprotein B, the major protein of

atherogenic lipoproteins, were the most consistently predictive (28). These data have contributed to the ongoing debate about identifying the optimal lipid markers of CHD risk, particularly with regard to apolipoprotein B, which many studies have proposed to be superior to LDL-C. Unfortunately, the primacy of LDL in research and guidelines and the entrenchment of its use in clinical practice have made it very difficult for new lipid markers to gain a foothold.

PROGRESS IN HDL THERAPIES

There may be several aspects to the cardioprotection associated with HDL, including reverse cholesterol transport and an antioxidant effect that prevents the modification of the LDL particle, with consequent anti-inflammatory implications. Three major pathways have been described (29) that could mediate cholesterol efflux from peripheral tissue with HDL: a passive diffusion pathway of cholesterol from the vessel wall in the macrophage into a mature HDL particle; a pathway that involves scavenger receptor B-1 (SR-B1); and a third pathway involving adenosine triphosphate-binding cassette A1 (ABCA1) transporter, which is abnormal and deficient in the low HDL-C syndrome Tangier disease, first described by Donald Fredrickson and his colleagues.

Several novel therapies are in development that will try to exploit the risk-reducing effect of HDL. Many of these involve developing infusions of variants of apolipoprotein AI. A synthetic version of apolipoprotein AI Milano, a genetic mutation first identified in a long-lived Italian community with low HDL-C levels, has suggested the promise of this approach (30). In a multicenter, randomized, double-blind phase II trial of this agent (ETC-216), 47 subjects were randomized within two weeks of a coronary event to weekly intravenous infusion of ETC-216 (15 or 45 mg/kg) or placebo. Patients received a maximum of five doses, and intravascular ultrasonography was performed before the first dose and after the fifth. The primary end point, percent change in plaque volume at end of treatment versus baseline, was significantly reduced by the treatment. The infusion yielded net regression of plaque burden, an exciting but preliminary benefit that warrants additional research. Another approach that is in the pipeline is the development of peptides that mimic the active part of apolipoprotein A1. Such a peptide would need to possess: the ability to activate lecithin:cholesterol acyltransferase (LCAT), a key enzyme in reverse cholesterol transport; cholesterol-efflux capability; the ability to elevate HDL-C in vivo; and anti-atherosclerotic activity. In 1974, Dr. Jere Segrest at the NIH and Drs. Richard Jackson, Joel Morrisett, and I at Baylor College of Medicine published an amphipathic helical model to describe lipid-protein interactions in plasma lipoproteins (31). This model helped inspire later research into the synthesis of consensus peptides, one of which is currently under investigation (ESP24218, Esperion Therapeutics, personal communica-

tion, Marianne Andreach, March 5, 2005) as an HDL-based anti-atherosclerosis therapy. A number of other synthetic analogues of apolipoprotein AI are also being studied.

Finally, inhibition of cholesteryl ester transfer protein (CETP), another key enzyme in HDL catabolism, is gaining acceptance as a novel treatment (32). The first CETP inhibitor, torcetrapib, is being tested in a number of large trials. The evidence so far suggests that this drug will raise HDL-C by 16% to 91%, depending on dosage, but whether this will result in fewer coronary events remains to be seen.

IS LOWER BETTER?

The relation between cholesterol and coronary risk appears to be linear, with no apparent threshold yet described below which cholesterol reduction would not yield further benefit. In 2004, the Adult Treatment Panel of the National Cholesterol Education Program (NCEP) revised its guidelines to permit an optional goal of <70 mg/dl for the highest-risk patients, which is lower than the <100-mg/dl target advocated in previous iterations (33). Although several clinical trials helped shape this change, two studies were of particular relevance. First was the Heart Protection Study, which showed consistent coronary benefit in high-risk patients with moderate cholesterol elevations across the tertiles of baseline LDL-C (22). On the basis of the Heart Protection Study results, the U.S. Food and Drug Administration approved a revised indication for simvastatin that allowed treatment of any high-risk patient, regardless of LDL-C. The other study, the Pravastatin or Atorvastatin Evaluation And Infection Therapy (PROVE-IT) trial in acute coronary syndrome patients assessed the effect of pravastatin 40 mg/day versus atorvastatin 80 mg/day on recurrent events (34). There was a statistically significant 16% risk reduction in favor of atorvastatin, thus suggesting that more intensive lipid-lowering regimens have greater clinical benefits over moderate lipid-lowering regimens.

The results of the Treating to New Targets (TNT) trial have added further support to the claim of “lower is better” (35). A total of 10,003 patients in the TNT trial, ages 35 to 75 years, with LDL-C 130 to 250 mg/dl and triglycerides \leq 600 mg/dl were treated with either atorvastatin 10 mg/day or atorvastatin 80 mg/day. The LDL-C target for the atorvastatin 10-mg group was 100 mg/dl, and for the atorvastatin 80-mg group, 75 mg/dl. The primary end point was time-to-occurrence of CHD death, non-fatal MI, resuscitated coronary arrest, and fatal or non-fatal stroke. All-cause mortality was a secondary end point, but the study was not powered to show a reduction in all-cause mortality.

WHAT NEW AREAS HAVE BEEN OPENED BY THE CONCEPT OF THE VULNERABLE PLAQUE?

For many years, atherosclerosis was thought to be an inevitable accompaniment of aging. Russell Ross, among others, introduced the concept of atherosclerosis as a re-

sponse to endothelial injury of the vessel wall (36). Monocytes penetrate the intima, then differentiate into macrophages that scavenge minimally modified or oxidized LDL particles and convert to foam cells. Apoptosis of these lipid-laden cells account for deposition of a necrotic lipid core in the atheroma. Furthermore, activated macrophages and foam cells secrete cytokines growth factors and metalloproteinases, resulting in matrix degradation of the connective tissue in the plaque. This vulnerable plaque is susceptible to rupture, precipitating a cascade of thrombotic events that result in vessel occlusion and a vascular event.

Inflammation is an integral participant in atherogenesis, and microbial infection by *Chlamydia pneumoniae* has been postulated to play a role in this process (37); however, the benefits of anti-inflammatory agents, with the exception of aspirin, in the therapy of atherosclerosis remain speculative. Trials of anti-chlamydial agents have been generally negative, and cyclooxygenase (COX)-2 inhibitors, despite being anti-inflammation drugs, may have deleterious cardiovascular effects (38–41). Statins may reduce the evidence of inflammation, as measured by high-sensitivity CRP, but whether or not this alone may protect against cardiovascular disease remains to be established.

A post-hoc analysis of the AFCAPS/TexCAPS trial examined first coronary event rates in subgroups defined by LDL-C values above or below the median and CRP values above or below the median (42). The subgroup that had LDL-C above the median, regardless of whether CRP was elevated, had a trend toward benefit from lovastatin therapy, and the subgroup that had a CRP above the median had a trend toward benefit regardless of whether the LDL-C was above or below the median. In the subgroup where both LDL-C and CRP were below the median ($n = 1,448$), however, the event rate in the lovastatin group was no better than that in the placebo group, suggesting that it may be possible to discriminate individuals in a population who may not benefit from statin therapy using both LDL-C and CRP.

Based on a post-hoc analysis of the PROVE-IT trial, Ridker et al. (43) have put forth the argument that CRP has moved from an inflammatory marker to a therapeutic target in a “dual goal” approach to management. In the PROVE-IT trial, patients achieving on-treatment LDL-C >70 mg/dl had a greater number of events than those <70 mg/dl. At the same time, those who had on-treatment CRP >2 mg/l experienced a greater number of events than those <2 mg/l. There was no correlation ($r = 0.18$) between achieved LDL-C and CRP. Choice of statin appeared to be less important than achieving the goals of LDL-C <70 mg/dl and CRP <2 mg/l, although atorvastatin resulted in more patients achieving both goals. Of the entire cohort in the PROVE-IT trial, 27% achieved both LDL-C <70 mg/dl and CRP <2 mg/l. This subgroup, after adjustment for age, gender, smoking, diabetes, hypertension, obesity, and HDL-C, had a 29% lower risk for recurrent MI or

cardiovascular death ($p = 0.04$) (44). Further research is needed to answer the question of whether changes in CRP, and by extension in inflammation, account for any of the coronary benefit observed with the statins.

Even more intriguing are data that suggest hypothetical benefits of statins in other disease states with features of inflammation, such as a number of immune-mediated disorders like multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and graft rejection in organ transplantation (45). A small study reported fewer gadolinium-enhancing lesions and fewer new lesions in a group of patients with relapsing multiple sclerosis treated with 80 mg/day of simvastatin (46). The Trial of Atorvastatin in Rheumatoid Arthritis (TARA) reported modest improvements in rheumatoid arthritis disease activity scores and swollen joint counts in a small number of patients who received atorvastatin 40 mg/day, versus placebo (47). Furthermore, a potential anticancer effect has been reported in some observational analyses that warrant additional consideration (48).

CONCLUSIONS

Atherosclerosis was once thought to be an irreversible, inevitable consequence of aging. The recognition of dyslipidemia as a major modifiable risk factor introduced the possibilities of both treatment and prevention. The advent of the statins ushered in an era of landmark trials that affirmed the basic tenets of the lipid hypothesis and established a definitive mortality benefit with cholesterol control. Furthermore, the statin trials helped extend the view of atherosclerosis management beyond the coronary arteries to include both other cardiovascular manifestations, such as carotid disease and peripheral arterial disease, and diabetes, whose associated cardiovascular risk justifies aggressive intervention.

The improved understanding of the role of lipid disorders in cardiovascular disease over the decades has generated new insights into the pathology of atherosclerosis, opened new areas of investigation, and created new opportunities for intervention. Although the successes of the last 50 years have been extraordinary, much of the landscape of atherosclerosis remains uncharted and poorly understood. Tackling the challenges of that exploration will shape the future of the field, with the best yet to come.

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