The Cholesterol Controversy Continues

By Hoefner, Daniel M

In 1985, during the Nobel Lecture, Brown and Goldstein, stated, "Cholesterol is the most highly decorated small molecule in biology," a comment supported by 13 Nobel Prizes having been awarded to individuals who devoted a significant part of their lives to cholesterol research. Whether or not the structure is remembered, probably every student of the biomedical sciences in the last several decades has at one time become familiar with the cyclopentanophenanthrene ring that makes up the cholesterol backbone from which all the steroid hormones are derived. In the late 1700s, French researcher Francois Poulletier de la Salle first discovered it in solid form from gallstones; and around 1815, another French chemist, Michel Eugene Chevreul, was the first to isolate and purify this sterol (as well as several other lipids). Chevreul, incidentally, is also credited as the first person to demonstrate that the sugar in diabetics' urine is glucose. In 1843, J. Vogel showed that cholesterol was present in atherosclerotic arteries; a few years later, Virchow suggested that atherosclerosis was caused by blood lipid accumulation in arterial walls. Early 20th-century discoveries

The current era of atherosclerosis research began in 1913 when Nikolai Anitschkow demonstrated that, when fed large amounts of cholesterol, rabbits developed vascular lesions similar to atherosclerosis seen in humans. Over the ensuing years, Anitschkow and colleagues established or proposed that foam cells were leukocytes that had infiltrated the arterial wall where they engulfed lipids and developed into atherosclerotic fatty streaks, which would eventually develop into fibrous plaques; that cholesterol also entered the arterial wall from the blood; that disease progression began at the root of the aorta and aortic arch and was proportional to blood-cholesterol concentrations; and that the early stages of the disease process were somewhat reversible. Steinberg has suggested if the full significance of Anitschkow's findings had been grasped at the time, "We might have saved more than 30 years in the long struggle to settle the 'cholesterol controversy' and Anitschkow might have won a Nobel Prize." Unfortunately, his work remained either ignored or unknown for several decades, and lipid research continued at a modest pace until the middle of the 20th century.

According to the "lipid hypothesis," dyslipidemia - primarily manifested as elevated levels of blood cholesterol, elevated concentrations of low-density lipoprotein cholesterol (LDL-C), or abnormal proportions of LDL-C and high-density lipoprotein cholesterol (HDL-C) (high and low, respectively) - is not only associated with the development but also is the cause of atherosclerosis and other cardiovascular diseases (CVD). It is also believed that the lipid imbalance can be remedied via a healthy diet, exercise, and, if necessary, pharmaceutical intervention. In the past 50 years, a plethora of studies have led most medical scientists and clinicians to accept the lipid hypothesis as truth. A small yet vocal group maintains, however, that there has been a significant amount of bias in the studies and that the hypothesis has never been properly substantiated. And, while many other mechanisms have ample evidence to their credit as major causes of CVD (e.g., vascular inflammatory processes), the major therapeutic focus of contemporary healthcare guidelines has been to lower LDL-C. Thus, the "cholesterol controversy."

Although the dispute has continued for more than four decades, it is the use/overuse of drugs (especially statins) to lower LDL-C that seems to goad much of the current debate. In addition, there are a number of other recent issues that fuel the fire. Whereas research in the 1970s and 1980s was dominated by efforts that linked lipids to atherogenesis, it is now generally recognized that inflammation plays a key role in its pathophysiology. Over the last decade, considerable work has focused on the inflammatory mechanisms that couple dyslipidemia to atherogenesis; and it is now well established that inflammation plays a key role in essentially all aspects of atherothrombotic disease. In addition, two recent clinical trials have generated results that defy the current dogma of the lipid hypothesis, much to the disappointment of (and cost to) the pharmaceutical sponsors.

Recent clinical trials

Late in 2006, Pfizer announced that it was pulling the plug on a clinical trial of torcetrapib, a drug that
inhibits cholesterol ester transfer protein (CETP), thereby increasing HDL-C levels. Prior to the study, it was demonstrated that this drug could prevent aortic atherosclerosis in animal models by significantly increasing circulating HDL-C concentrations. In addition, numerous studies have shown elevated levels of HDL to be a "negative risk factor" - that is, beneficial at reducing CVD risk. A few months ago, an article in the New England Journal of Medicine described the details of the torcetrapib trial, which had been halted prematurely due to adverse events. The concern was that, after a year and a half, the number of patients with CVD-related morbidity and mortality (as well as death from any cause) in the torcetrapib arm of the study actually increased. One suggestion for the poor outcome was attributed to torcetrapib causing a small increase in blood pressure and electrolyte changes by unknown mechanisms. Other possibilities that could have caused the adverse outcome include an undesirable influence from CETP inhibition (e.g., functional impairment of HDL) and other unknown insidious side effects of the drug.

It was hoped that this new class of drugs would be the latest vanguard in the armament of medicines that allow physicians greater opportunities to reduce heart disease by raising the "good cholesterol." Ultimately, it caused an upset to the current views of most mainstream lipidologists and rendered ammunition to the opposers of the lipid hypothesis. Since adverse events, however, were actually lowest in the group of torcetrapib-treated patients who realized the greatest increase in HDL-C, it could be that the benefits of HDL were simply overshadowed by untoward toxic side effects.

In January of this year, Merck/Schering-Plough Pharmaceuticals announced the results of its ENHANCE trial in which two drugs were compared (an ezetimibe/simvastatin combination versus simvastatin alone) over a two-year period. The cohort consisted of patients with heterozygous familial hypercholesterolemia - an uncommon genetic disorder (~1/500 people in the United States) characterized by elevated levels of LDL and the propensity to develop early CVD. Both drugs had been known to lower LDL-C, and the hope was that the additional lowering by the ezetimibe would prove beneficial to the outcome, which was an endpoint based on the mean carotid intima-media thickness, or the formation of plaque in the arteries of the neck (a surrogate for coronary heart disease, CHD). Even though the efficacy of the drug combination was almost 30% greater than simvastatin alone at lowering LDL-C, there was no apparent benefit to the outcome.

Although there are some caveats to the ENHANCE trial (this was a biomarker study with an endpoint not based on CVD-related morbidity and mortality in a group of patients with a rare condition), it is likely that these "limitations" were preselected so as to give the biggest bang for the buck. After all, it is generally easier to show a therapeutic biological change in a group that naturally manifests disease more readily than, say, in those with a "normal" level of LDL-C. In addition, the use of surrogate markers is commonplace and much less expensive and time consuming. While it is well recognized that the Merck/Schering-Plough Pharmaceuticals trial was underpowered in regard to the endpoint and that the reduction in LDL-C still did not achieve the levels that are recommended in the current guidelines, it nevertheless lends credence to those who claim that the lipid hypothesis is flawed. The results of this study do not prove that ezetimibe has no therapeutic value, but it does cast a shadow on its broad utility. It could well be that the recent "setbacks" of the ezetimibe and torcetrapib trials are actually in the study design. It is possible that there is a high degree of efficacy in specific subpopulations.

What is the problem?

Even though all cells have the ability to manufacture cholesterol, the liver synthesizes most of what is present in our bodies, and humans only derive about one-fourth of their cholesterol from dietary sources. Therefore, a reduction in dietary cholesterol would not appear to have a substantial impact on reducing plasma concentrations of cholesterol, and there are only a paucity of studies to suggest that reducing cholesterol intake has an impact on CVD risk reduction. The mechanism of action for ezetimibe is different from statins - its target is the sterol transporter, which is involved in the intestinal uptake of cholesterol and plant sterols. Ezetimibe inhibits cholesterol absorption, which causes a decrease in the delivery of intestinal cholesterol to the liver (analogous to a dietary reduction), whereas statins act as HMG-CoA reductase inhibitors. Perhaps the outcome of the trial was a "failure" because reducing cholesterol in this manner does not have a significant impact on the reduction of cardiovascular disease. Another major point of contention with the lipid hypothesis is that many patients today are funneled into statin-centric monotherapy treatment regimes, yet they continue to be at risk for and experience adverse CHD events. For several years, atorvastatin (Lipitor) has been the No. 1 selling drug in the United States and was the best-selling drug in the world in 2006 with ~$13 billion in sales. This is not the case because it is a miracle drug that apparently benefits all who use it. Rather, it seems to be driven by marketing hype and an oblique presentation of the data. A review of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) illustrates the point. In this study of over 10,000 patients (about half given placebo and half atorvastatin) who were followed for a median duration of 3.3 years, the drug reduced the rate of coronary events (either fatal CHD or non-fatal myocardial infarction) with a relative
risk reduction of 36%.

This might sound rather notable, but the catch is hidden in the word relative. There was actually only an absolute risk reduction of 1.1% between the two groups. That is, the rate of adverse events was 1.9% in the group of patients taking the drug and 3.0% in the placebo group (1.9 is about 36% less than 3.0). So, the difference in deaths was only 1.1%. Another calculation can be used to determine the number needed to treat (NNT), which is an epidemiological gauge to indicate how many patients would need to be treated with a drug in order for one patient to get the expected benefit (i.e., to be "saved" from a coronary event). It is simply calculated by taking the inverse of the absolute risk reduction (as a percent). Based on the ASCOT results, for every 91 people who took the drug for 3.3 years, only one person would realize a benefit, roughly two would still suffer a coronary event, and 88 would see no advantage (yet, be at risk of potential side effects). The NNT appears to be universally poor for many of the statin drugs, with results that average from about 50 to greater than 100.9

Today, there are many who would suggest that atherosclerosis is a man-made disease, viz., a product of the modern lifestyle. This does not appear, however, to be the case. About a century ago, the mummified remains of persons who lived thousands of years ago were unearthed from the Nile Valley and examined. Remarkably, due to the Egyptian embalming processes and ideal environmental factors, the integrity of the tissue was such that it still rendered acceptable histological studies to be performed on the aorta and other major arterial vessels. Reports of those investigations clearly indicate that atherosclerosis has been a common condition throughout antiquity, and that the histopathology of disease is independent of "race, diet, and the stresses of survival" with the arterial lesions in mummified remains being "no different from those we see today." Other paleopathology studies of preserved human remains include those of Chinese and Alaskan Inuit ancestry, all of which showed evidence of atheromatous plaques and other indications of CVD. Although atherosclerotic disease was present, was it as fatal as today? There are many factors that have changed over the years ... nutrition (especially sugar consumption), physical exertion, lifespan, and many other components play heavily on the relative burden of CVD.

Endpoints and guidelines

The laboratory measurement of cholesterol is a surrogate marker for lipoprotein particles, which can be considered a proxy for the degree of atheromatous deposits, which is a surrogate for the endpoint of atherosclerosis-related morbidity and mortality. The further a marker is removed from the endpoint of interest, the less accurate it becomes in its utility. In light of that and given cardiovascular diseases are so multifactorial (many genetic and lifestyle factors contribute to its development), it is no wonder that total cholesterol, LDL-C, and HDL-C are such poor markers for heart disease and other associated conditions. For years, the Food and Drug Administration (FDA) has allowed the use of surrogate endpoints (such as LDL-C reduction) to prove efficacy and clear new drugs. One problem is that endpoint studies (diseaserelated morbidity and mortality) take many years to complete and can cost many millions of dollars. So, the problem is not so much that the FDA uses surrogate endpoints but that the entire industry continues to rely so heavily on old inferior markers (primarily LDL-C and, to a lesser extent, HDL-C). This seems to be driven by historical precedent - their use in this regard ignores much of what has been discovered in the past few decades regarding the complex nature and interactions of the lipoprotein particle subspecies as well as the relevant inflammatory mechanisms.

In the United States, much of the current focus on LDL-C testing can be attributed to the National Cholesterol Education Program (NCEP) guidelines put forth in the Adult Treatment Panel III report (ATP III). In ATP III, the primary focus was on lowering elevated LDL-C as a means of either treatment for or prevention of CHD. The full report is nearly 300 pages in length; and, no doubt, many clinicians have found this document overbearing and confusing. Therefore, incumbent on the framers of the forthcoming ATP IV guidelines (in the planning stages with an expected release date in 2009) will be to consider all the current scientific evidence and propose easy-to-use guidelines. Since consensus guidelines generally maintain a conservative position with a significant lag behind much of the leading-edge research, it will be interesting to see whether this new report continues to focus primarily on the reduction of LDL-C. NCEP's strategic plan looks promising in that the group intends to develop an integrated set of practice guidelines focusing on CVD risk reduction that is comprehensive (across all cardiovascular risk factors) and evidence-based. In addition, its members intend to focus on developing a more practical format so that clinicians and patients will be better able to implement the proposals.

Good science to end controversy?

Despite all the controversy and frequent setbacks in the field of lipidology, it seems that researchers are on the right track. Since 1950, when the link between cholesterol levels and CVD were becoming...
formalized and therapeutic endeavors were put into place, it took just 45 years for the death rate (all ages) for heart disease in the United States to be cut in half. In 2004, the death rate for heart disease was 217 per 100,000 population, a drop to below 37% of what it was in 1950.13 Much of the benefit, however, may simply be the result of an individual’s healthier lifestyle (better diet, exercise, not smoking, and so forth) and overall advances in the care of his health.

There is little argument concerning the utility of LDL-C as a key risk factor for CVD. Also, lowering LDL-C and raising HDL-C is clearly beneficial for lowering that risk. There is, however, much more to the multifactorial cardiovascular diseases. The literature is replete with markers other than LDL-C that have shown significant ties to risk and the development of CVD, including ratios of HDL and LDL subspecies particles; the total number of LDL particles (as opposed to simply LDL-C); apolipoprotein concentrations; the overall influence of inflammation and use of appropriate markers for such; and genetic studies for factors that influence the metabolic fate of the lipoproteins, plaque stabilization factors, lipid oxidation, thrombotic and fibrinolytic factors, diabetes, and others. In fact, over a quarter of a century ago, a review was published entitled "A survey of 246 suggested coronary risk factors."14 Since then, the list has no doubt increased significantly. So, it should be no surprise that a few biochemical parameters in human blood are not enough for the accurate prediction of all patients who will develop CVD or to monitor those who are being treated.

The scientific method is a tool for formalizing ideas into a hypothesis, testing those postulations, analyzing the data, and considering the outcome (while correcting and integrating the new knowledge) to test the hypothesis, and then revising the hypotheses to begin the process again. In science, controversy frequently promotes new discoveries and advancement by bringing forth new ideas to be tested with this process. There is a downside in that scientific funding is frequently in the hands of those who also have chips on the table. Hopefully, good science will win out and the long-lived cholesterol controversy will finally be put to rest.

The History of Cholesterol

1760
Francois Poulletier de la Salle discovered cholesterol in solid form from gallstones.

1815
Michel Eugene Chevreul isolated and purified the sterol from gallstones and named it "cholesterol" (Greek, chol for bile plus stereos for solid).

1838
Louis Rene Lecanu confirmed the presence of cholesterol in human blood.

1843
J. Vogel showed that cholesterol was present in arterial plaques.

1913
Nikolai Anitschkow demonstrated that cholesterol caused rabbits to develop vascular lesions similar to atherosclerosis seen in humans.

1932
Adolf Windaus elucidated the structure of cholesterol.

1964
Konrad Bloch and Feodor Lynen received the Nobel Prize for their research on the mechanism and regulation of cholesterol and fatty-acid metabolism.

1985
Michael S. Brown and Joseph L Goldstein received the Nobel Prize for their discoveries concerning the role of the LDL receptor in cholesterol metabolism and regulation.
Lovastatin Mevacor was the first statin drug to be cleared for use by the FDA.

1988

The CDC’s National Cholesterol Education Program published its first set of guidelines. Adult Treatment Panel, to educate patients and physicians on the importance of treating high cholesterol.

1994

Scandinavian Simvastatin Survival Study (4S) showed that statin treatment of patients with coronary heart disease lowered morbidity and mortality. 2002

The Heart Protection Study showed that high-risk patients with cholesterol levels previously considered low could benefit from statin treatment.

2006

The best-selling drug in the world atorvastatin (Lipitor) grosses ~$13 billion in sales.

References


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