

MARCH 23, 2006

Moderate Lifetime Reductions in LDL Cholesterol Dramatically Reduce Risk of Heart Disease

A new genetic analysis of more than 12,000 individuals has found that a decrease in low density lipoprotein (LDL) cholesterol, of as little as 15 percent, sustained over the long term can dramatically reduce the risk of coronary heart disease. The reduction in LDL observed in this study can easily be achieved with a low dose of cholesterol-lowering drugs called statins.

The analysis, which included both white and black populations, indicates that low levels of LDL cholesterol are protective even for people who have other significant risk factors for heart disease.

"Our prediction would be if that if you were to treat people earlier, you would magnify the effects of LDL reduction on coronary events."

— **Helen H. Hobbs**

What this study shows is that low plasma levels of LDL had a dramatic effect on the incidence of coronary events over a 15-year period. This is in individuals living in the same place, subjected to the same stresses, and having a similar prevalence of the major coronary risk factors - hypertension, diabetes, and smoking - and really high levels of those risk factors, said Helen H. Hobbs, a Howard Hughes Medical Institute investigator at the University of Texas Southwestern Medical Center in Dallas.

Hobbs led the study, in collaboration with colleagues at the University of Texas Southwestern, the University of Texas Health Science Center in Houston, and the University of Mississippi Medical Center. The work, which suggests that susceptible individuals may benefit from earlier medical intervention, was partially funded by the Donald W. Reynolds Foundation and is published in the March 23, 2006, issue of the *New England Journal of Medicine*.

In an accompanying editorial in the same issue of the journal, Alan R. Tall, a professor of medicine at Columbia University, wrote that the findings suggest that a one percent reduction in LDL cholesterol level over a lifetime translates into a reduction of more than two percent in the risk of cardiovascular disease.

LDL cholesterol, a waxy substance that can build up and clog arteries, is an essential factor in the initiation and progression of coronary heart disease (CHD). You have to have LDL to have atherosclerosis, Hobbs noted. Other risk factors exacerbate the effects of LDL, but LDL is central to the disease process.

The level of LDL in the blood varies widely among individuals, and is determined by a complicated interplay of genetic and environmental factors. It's clear, Hobbs said, that a high-fat, high-cholesterol diet can lead to a gradual increase in LDL over one's lifetime — but about 50 percent of the variability in cholesterol levels among individuals can be attributed to genetic factors. Eight different genes have so far been identified as major determinants of LDL levels in the blood, and there are likely many more yet to be identified.

Because so many factors influence LDL levels, it has been difficult for scientists to tease out LDL's precise role in heart disease. Traditionally, comparisons had been made between significantly different populations. For example, it's well established that people in China have very low levels of both LDL cholesterol and heart disease. But what you don't know, Hobbs said, is whether the lower levels of CHD are due to the lower level of LDL or to other factors that aren't accounted for.

The experiment we've wanted to do for years is to see the effect of a specific reduction in LDL-C in individuals subjected to the same environmental stresses as the rest of the population. Hobbs said. But until now, it had not been possible to compare two groups of people who differed only in their plasma levels of LDL.

A recent finding from the ongoing Dallas Heart Study, however, changed that. The study, headed by Hobbs, aims to uncover risk factors for heart disease and develop new treatments by collecting data from 3,000 Dallas County, Texas, residents, about half of whom are black. Hobbs and colleagues' analysis of this data allowed them to zero in on three forms of a gene known as *PCSK9* that are associated with significant reductions in plasma levels of LDL cholesterol. Individuals with *PCSK9* variations had low LDL levels that appeared to be independent of other risk factors for CHD.

The first two of these variations occurred fairly commonly in black participants - about once in every 40 individuals - but were rare in whites. These variations reduced LDL cholesterol levels by an average of 28 percent. A third gene variation, which reduced the level of LDL by about 15 percent, was found to be more prevalent in the white population. The *PCSK9* variants were a valuable discovery, because they occurred frequently enough to enable a meaningful study examining exactly what scientists have long

wanted to know: does a low level of LDL cholesterol really reduce the risk for coronary heart disease?

To answer that question, Hobbs and her colleagues turned to data collected in another large trial designed to investigate risk factors for heart disease in multiracial populations. The Atherosclerosis Risk in Communities (ARIC) Study has been following approximately 4,000 patients in each of four communities - Jackson, Mississippi; Minneapolis, Minnesota; Forsyth, North Carolina, and Washington County Maryland - since 1987. For the current study, the researchers examined samples from 3,363 black and 9,524 white study participants to determine whether they had *PCSK9* variations. They then compared that information to levels of LDL cholesterol and to the incidence of heart disease.

Their findings were dramatic. A 28 percent reduction in LDL cholesterol associated with *PCSK9* variants in black participants translated into an 88 percent decrease in coronary heart disease. In fact, only one of the 85 black participants (1.2 percent) who carried the *PCSK9* variant developed coronary heart disease during the ARIC study's 15 years of follow-up, compared with 9.7 percent of the participants without the variant. Among white participants, the more modest 15 percent reduction in LDL cholesterol correlated to a 50 percent decrease in coronary heart disease.

A major strength of this study, Hobbs said, is that you have two independent populations with different sequence variations in the same gene, that impact on a trait of interest, and you see similar kinds of effects.

The difference in LDL cholesterol between individuals with the normal form of *PCSK9* and those with these sequence variations is comparable to the reduction that can be achieved with a low dose of cholesterol-lowering statins, Hobbs said. However, the effect of the genetic variation on heart disease is more dramatic than what has been observed with statins. Hobbs and her colleagues attribute this to the fact that the gene variations keep LDL low over a lifetime, not just after statin treatment is begun - typically when a patient is in middle age. This, they say, may have important implications for clinical practice.

The new findings suggest the need to redouble our efforts to reduce LDL cholesterol levels in younger persons by promoting healthy diets and reducing obesity, Tall wrote in his editorial. Even small successes will probably be leveraged for later gains in lowering the risk of cardiovascular disease.

Hobbs added that medical intervention might also be more beneficial if begun earlier. Our prediction would be if that if you were to treat people earlier, you would magnify the effects of LDL reduction on coronary events, Hobbs said. For example, physicians might prescribe statins to patients whose LDL levels, while elevated, are not as high as the point at which the drugs are currently recommended, she said.

The threshold for treating people with medication - if we are unsuccessful in changing the eating habits of people in the United States - would be lower, she said. Hobbs cautions that further studies are essential to duplicate this study's findings in other populations before such a change can be recommended. She noted, however, that the medical community's extensive experience with statins has found them to be particularly safe drugs, suggesting that a longer course of treatment is unlikely to introduce harmful effects.

Finally, Hobbs said, PCSK9 is itself a good candidate for pharmacological intervention. Statin therapy increases the quantity of PCSK9 produced by cells, which in turn leads to degradation of the LDL receptor. This molecule is responsible for clearing the majority of LDL cholesterol from the blood, so its loss attenuates statins' cholesterol-lowering effects. Because results of the Dallas Heart Study show that people with a low level of PCSK9 are healthy, Hobbs is optimistic that combining statin therapy and drugs that target PCSK9 might be particularly effective at reducing the risk of heart disease.