SOUTHWESTERN NEWS

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THREE STATIN DRUGS FOUND TO REDUCE NEW MARKER OF HEART DISEASE

DALLAS – April 17, 2001 – Three common cholesterol-lowering drugs significantly reduce a relatively new, independent marker of inflammation in the coronary arteries called C-reactive protein (CRP), researchers at UT Southwestern Medical Center at Dallas have discovered.

Inflammation in the coronary arteries has only recently been shown to be a major cause of heart attack and stroke.

More than 70 percent of the participants in a UT Southwestern study, the results of which are published in today's issue of *Circulation*, responded positively to at least one of three statin drugs – pravastatin, simvastatin, and atorvastatin. The participants' CRP levels decreased an average of 23 percent while on the statin therapy.

Only one study to date has evaluated statin therapy on CRP. Results from this study, about the effects of pravastatin on CRP levels, showed a 17 percent reduction when a single blood sample was drawn at baseline and after five years of therapy.

The study conducted at UT Southwestern is the first definitive study to evaluate three statin drugs and to establish whether this previous observation is specific only for pravastatin.

"For the first time, we can comment on individual response to three statin drugs," said Dr. Ishwarlal Jialal, lead author of the study, professor of pathology and internal medicine, and head of clinical biochemistry and human metabolism at UT Southwestern.

"Previously these drugs have been shown to lower low-density lipoprotein (LDL) cholesterol. We have now shown that they have anti-inflammatory effects by lowering CRP. These results are very encouraging for the population and provide an additional way of lowering the risks of cardiovascular disease. This is important for both primary and secondary prevention of cardiovascular disease."

Twenty-two patients who had combined hyperlipidemia – high cholesterol and high triglyceride levels – participated in the study. The participants followed the American Heart Association's Step One Diet – a low-fat, high-carbohydrate diet – for six weeks prior to beginning drug therapy and then throughout the study. Each drug was given for six weeks, with a

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period of three weeks between them. Multiple blood samples were taken throughout the study.

The reductions in CRP levels with pravastatin, simvastatin and atorvastatin were 20 percent, 23 percent, and 28 percent, respectively. The percentage of patients who responded to the pravastatin, simvastatin and atorvastatin were 73 percent, 82 percent and 82 percent, respectively.

Physicians assess CRP levels by administering a simple blood test and using a highly sensitive assay. Normal ranges are between 0.6 to 2 milligram per liter. A reading of 2 mg/L or greater doubles the likelihood of developing cardiovascular disease. Increased levels of CRP, which is produced by the liver, are present in the bloodstream only during periods of inflammation.

"The results of this study lead to a better understanding of inflammation. We are now seeing that the reduction in cardiovascular events such as heart attack and stroke are not all due to the reduction of LDL cholesterol levels. It's also related to the lowering of CRP," said Jialal.

The statin therapy did not have a significant effect in lowering interleukin-6, which elicits the secretion of CRP from the liver, or its soluble receptor. This finding led the researchers to believe that the mechanism by which statins lower CRP is by direct effect on the monocyte cell, which causes plaque to form in the wall of the arteries. Jialal and his collaborators are currently studying this theory.

A correlation between the reduction of CRP levels and triglyceride levels was evident in this study. Triglyceride reduction appears to account for 34 percent of the reduction in CRP levels.

"Because of the small sample size, this finding about triglyceride reduction still needs to be confirmed," Jialal said.

Fifty percent of individuals who have cardiovascular-related illnesses do not have the established risk factors that include diabetes, hypertension, smoking and high cholesterol, Jialal said. In addition to the standard measurements for assessing heart disease risks – measuring HDL and LDL cholesterol levels and triglycerides – high-sensitive CRP tests should be administered as well to more efficiently evaluate a person's risk of developing cardiovascular disease, he added.

In a previous study, Jialal found that a high intake of the antioxidant vitamin E also significantly reduces levels of CRP. He believes a combination therapy of vitamin E and statin drugs can have a powerful effect on reducing heart disease.

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UT Southwestern has a long history in the research of statin drugs. Nobel laureates Drs. Michael Brown and Joseph Goldstein discovered the basic mechanism of cholesterol metabolism, which led to the development of today's statin drugs. Dr. Scott Grundy, director of the Center for Human Nutrition at UT Southwestern, and other center researchers were instrumental in testing these cholesterol-lowering drugs.

Other UT Southwestern researchers who worked on the *Circulation* study are Dr. David Balis, assistant professor of internal medicine; Dr. Sridevi Devaraj, assistant professor of pathology; Grundy; and Beverley Adams-Huet, faculty associate in internal medicine. Dr. Dan Stein, formerly on the UT Southwestern faculty, and now a researcher at the Albert Einstein College of Medicine of Yeshiva University, also collaborated on the project.

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