CENTER FOR CARDIOVASCULAR DISEASE PREVENTION: RISK ASSESSMENT AND REDUCTION

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INTRODUCTION

Cardiovascular disease is the number one cause of death in the United States, accounting for more than 1.4 million deaths each year (American Heart Association. Heart and Stroke Statistics-2004 Update. Dallas, Texas: American Heart Association, 2003). The Center for Cardiovascular Disease Prevention (CCDP) was created in 2000, as a partnership between the Methodist DeBakey Heart Center and Baylor College of Medicine, to identify and implement new preventive and therapeutic strategies to reduce pain, suffering and death from cardiovascular disease. In clinical and translational research, investigators at the CCDP use a comprehensive approach directed at improving both risk assessment and risk reduction.

IMPROVING RISK ASSESSMENT

Because many individuals who develop cardiovascular disease do not have traditional risk factors such as elevated low-density lipoprotein cholesterol (LDL-C), research has increasingly focused on additional factors chat may refine risk assessment, to identify high-risk patients before they have a cardiovascular event. In particular, the importance of inflammation in both atherogenesis and atherothrombosis has led to the investigation of inflammatory mediators as markers of risk. A recent srudy conducted at the CCOP examined the relationship between lipoprotein-associated phospholipase A2 (Lp-PLA2)-a proinflammatory enzyme secreted by macrophages-and incident coronary heart disease (CHO) m middle-aged Americans.1

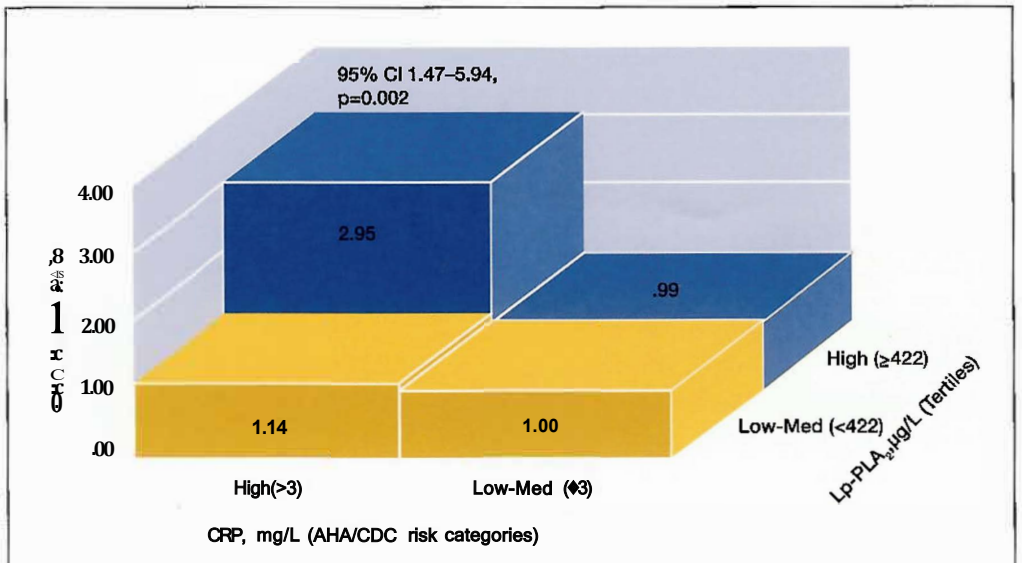

Figure 1.
Association of lipoprotein-associated phospholipase A2 (Lp-PLA2), C-reactive protein (CRP), and risk for incident coronary heart disease (CHO) among individuals with low-density lipoprotein cholesterol (LDL-C) <130 mg/dl in the Atherosclerosis Risk in Communities Study. Reprinted with permission from Ballantyne CM et al. Circulation 2004;109:837-842.1

In this examination of participants in the Atherosclerosis Risk in Communities (ARIC) study, Lp-PLA2 levels were higher in individuals who developed incident CHO. Among individuals with low LOL-C (<130 mg/dL, the study median), Lp-PLA2 levels were independently associated with incident CHO, even after adjustment for traditional risk factors and C-reactive protein (CRP), an inflammatory marker previously shown to be an independent predictor of CHO. Also, among individuals with low LOL-C, high levels of both Lp-PLA2 and CRP indicated the greatest risk for CHO-almost three times that of individuals with low to medium levels of both inflammatory markers (Figure I).I

IMPROVING RISK REDUCTION

While the benefit of lipid-modifying therapy on cardiovascular disease prevention has been established in multiple large clinical trials, in practice, many patients do not achieve the LOL-C recommendations of the National Cholesterol Education Program Adult Treatment Panel III (ATP Ill).2 Researchers at the CCOP continue to lead clinical investigations that evaluate the effectiveness

of new lipid-modifying therapies.

Sratins are first-line therapy for reducing LDL-C in most patients. The newest statin, rosuvastatin, was compared with atorvastatin, simvastatin and pravastatin in the multicenter Starin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial. Rosuvastatin was found to provide significantly greater reductions in LDL-C than the other statins (Figure 2) and to enable more patients to achieve LDL-C goals.3

Although the primary effect of statins is to lower LDL-C levels, statins also have been shown to reduce levels of CRP. In the multicenter Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial,4 which is ongoing at the CCDP, individuals with low LDL-C (<130 mg/dL) and elevated CRP (mg/1) are randomized to receive rosuvastatin (20 mg/day) or placebo. Patients will be followed up for 3.5 years to assess the effect of rosuvastatin on risk for a first cardiovascular event. Although patients in the JUPITER trial would not be considered for drug therapy by the ATP III guidelines, they may be at increased risk because of a heightened inflammatory response. The results of this ongoing investigation should help clarify mechanisms by which statin therapy reduces cardiovascular risk across a range of LDL-C levels, including levels not considered elevated by the current guidelines.

The LDL-C-lowering effectiveness of statins may be limited not only by drug efficacy but also by concerns about the safety of high-dose therapy. Combination therapy using agents with complementary mechanisms of action may provide a safer option. Combining a statin, which inhibits cholesterol synthesis in the liver, with a cholesterol absorption inhibitor, which inhibits cholesterol absorption in the intestine, may enable more patients to safely achieve optimal LDL-C levels for CHO risk reduction.

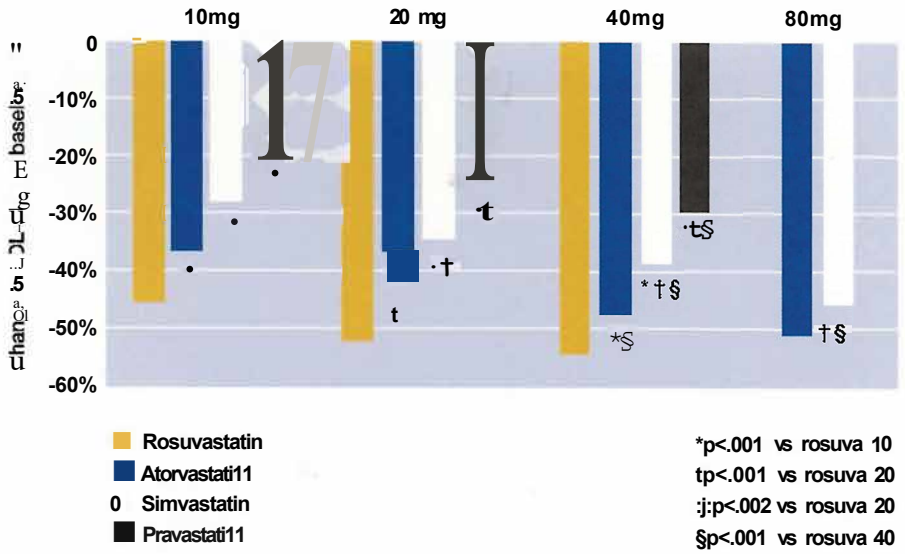

Figure 2.
Comparative LDL-C-lowering efficacy of statins in the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial.3

In a recent study conducted at the CCDP, atorvastatin monotherapy was compared with the combination of atorvastatin and rhe cholesterol absorption inhibitor ezetimibe across a range of atorvastatin doses in patients with hypercholesterolemia.5 Depending on atorvastatin dose, ezetimibe plus atorvastatin provided LDL-C reductions of 50-60% (Figure 3), and in an analysis that pooled all atorvastatin doses, coadministration of atorvastatin and ezetimibe provided an additional 12% reduction in LDL-C compared with atorvastatin alone. Further, combination therapy of ezetimibe plus atorvastatin at its lowest dose (10 mg) provided similar LDL-C reduction to maximum-dose atorvastatin monotherapy (80 mg): 50% and 51%, respectively.5 Combination therapy with ezetimibe and a statin therefore offers a new treatment option to achieve recommended LDL-C goals.

While lowering LDL-C has been shown to slow or even stop atherosclerotic progression, raising high-density lipoprotein cholesterol (HDL-C) may actually reverse the disease progress.6 The cholesteryl ester transport protein (CETP) inhibitor torcetrapib has been shown to increase HDL-C levels by 15-90%;[7] by comparison, statins usually increase HDL-C by only 5-10%. In ongoing studies at the CCDP, the potential benefit of combining LDL-C-lowering stacin therapy with HDL-C-raising torcetrapib is being examined in two high-risk populations: patients with mixed dyslipidemia and those with a family history of CHO, total cholesterol 00 mg/dl, and LDL-C >200 mg/dl. Patients are randomized to receive atorvascatin plus torcetrapib or atorvastatin plus placebo and monitored by carotid ultrasound to measure change in intima-media thickness.

Other agents under development that are being studied ac

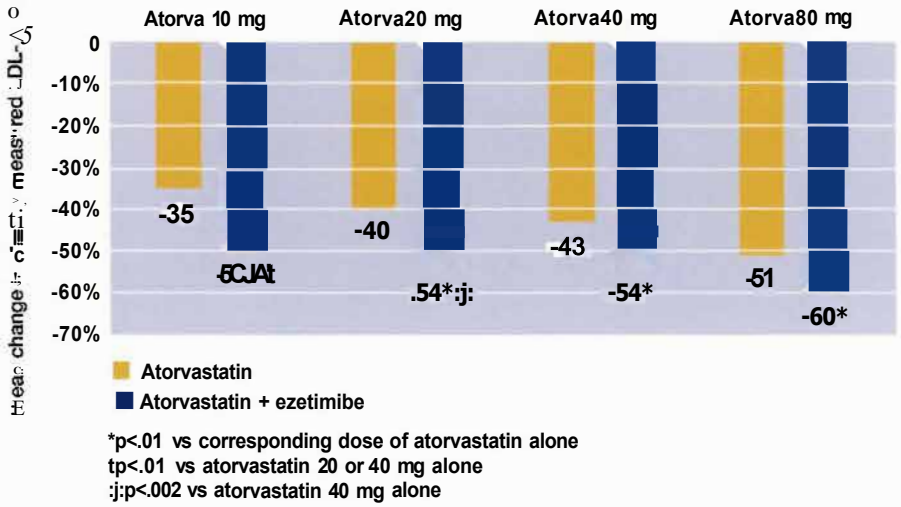

Figure 3.

Effect of combination therapy with ezetimibe and atorvastatin compared with atorvastatin monotherapy on directly measured LDL-C.5 Reprinted with permission from Ballantyne CM et al. Circulation 2003;107:2409-2415.

the CCDP include an acyl-CoA: cholesterol acyltransferase (ACAT) inhibitor, which is being studied in patients with heterozygous familial hypercholesterolemia to determine whether it will reduce progression of carotid atherosclerosis as assessed by ultrasound. In addition, an immunomodulatory approach to cardiovascular disease prevention, using a procedure that targets the underlying chronic inflammation involved in atherosclerosis, is being studied in patients with peripheral arterial disease.

Imaging modalities provide noninvasive assessment of therapeutic efficacy. Investigators at the CCDP have begun a large National Institutes of Health (NIH) trial, in collaboration with the Section of Vascular Surgery of Baylor College of Medicine, to determine whether triple therapy with a statin, ezetimibe, and niacin can stop or reverse atherosclerosis. The Effect of Lipid Modification on Peripheral Arterial Disease after Intervention Trial (ELIMIT) will test the hypothesis that additional reductions in atherogenic lipoproteins and increases in HDL-C with combination therapy will stop or even regress atherosclerosis more effectively than statin monotherapy. Patients with peripheral arterial disease will be randomized to receive either simvastatin 40 mg monotherapy or triple therapy with simvastatin 40 mg, extended-release niacin 1500 mg and ezecimibe 10 mg. The primary endpoint of peripheral arterial disease progression will be assessed by magnetic resonance imaging (MRI); secondary endpoints include walking time, ankle-brachia! index, clinical events, and inflammatory and thrombotic markers.

RESEARCH OPPORTUNITIES

With more than 20 ongoing clinical trials, the Center for Cardiovascular Disease Prevention is currently recruiting patients with high cholesterol, high triglycerides, mixed hyperlipidemia, metabolic syndrome, diabetes or peripheral arterial disease. To refer a patient for a study, please call 713-798-3171 or 713-798-3330.

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