on Atherosclerosis: Safety and Efficacy (ERASE) trial (Tardif et al. *JAMA*. 2007 doi:10.1001/jama.297.15. jpc70004) were presented by Jean-Claude Tardif, MD, of the Montreal Heart Institute.

Patients with recent acute coronary syndrome (ACS) were randomly assigned to either 4 weekly infusions of CSL-111 (40 mg/kg or 80 mg/kg) or volume-matched placebo. Patients were assessed via intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) at baseline and follow-up. The primary endpoint was the percentage change in atheroma volume as measured by IVUS. Secondary efficacy endpoints included nominal change in plaque volume on IVUS, change in plaque characterization on IVUS, and change in coronary score of QCA. The original statistical analysis plan was to compare the differences between all 3 treatment groups, but the safety review committee recommended stopping the 80 mg/kg arm because of observed liver function test abnormalities. The statistical plan and protocol were therefore amended to adjust the primary analysis to the change from baseline to final assessment within the active treatment group.

Twelve (12) patients were randomly assigned to the 80 mg/kg group (before the treatment group was discontinued), 60 to placebo, and 111 to CSL-111 40 mg/kg. Patients treated with CSL-111 40 mg/kg had a statistically significant reduction in the median percent and nominal changes in atheroma volume compared with baseline ($p<0.001$), but these changes were not significant when compared to placebo. The change in plaque composition characterization and change in coronary score ($p=0.03$) were significantly different between the treatment groups.

Thirty-three percent (33%) of the 80 mg/kg group had an ALT >10 times the upper limit of normal, compared with 0.9% in the 40 mg/kg group. Dr. Tardif noted that the liver enzyme elevations were transient, returned to normal after CSL-111 discontinuation, and there was no evidence of hepatic dysfunction/failure. The most common adverse events in the 80 mg/kg group were fatigue (25%) and diarrhea (16.7%), and the most frequent adverse events in the 40 mg/kg group were hypotension (13.8%) and fatigue (10.1%).

Dr. Tardif concluded by saying that, although the clinical significance of these findings is not fully understood, the compound demonstrated great promise in this small, proof-of-concept study.

Metabolic Syndrome Needs Intervention

Roger S. Blumenthal, MD, Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland, described the six risk conditions associated with the metabolic syndrome, and their appropriate interventions:

Risk	Interventions
Abdominal obesity	Diet and exercise
Atherogenic dyslipidemia	Statins, fibrates
Elevated blood pressure	ACE inhibitors, angiotensin receptor blockers
Insulin resistance/glucose intolerance	Lifestyle changes, thiazolidinedione, metformin
Proinflammatory state	Diet, statins
Prothrombotic state	Aspirin

Intensive lifestyle changes can reduce the progression to diabetes by nearly 60%, Dr. Blumenthal noted, largely through robust dietary interventions and a regular exercise program of 30 minutes of moderate activity per day—or "10,000 steps." "These actions are just as important as giving aspirin or a cholesterol-lowering pill every day," he remarked.

Gail Underbakke, MS, RD, of the University of Wisconsin, Madison, noted that diet has an effect on endothelial function. Fruits, vegetables, folic acid, and omega-3 fatty acids improve vascular function, while high-fat diets (especially saturated and trans fats) worsen postprandial vascular function. Studies with antioxidant vitamins show mixed results, she said.

In the optimal diet, calories should be appropriate for weight management. Carbohydrates should be <60% of calories (high fiber, limit concentrated sugars), fat should be 25% to 35% of calories (emphasize monounsaturated fat, omega-3 from fish and plants, and 1 ounce of nuts per day), protein should be 15% to 20% of calories (from

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NSAIDS and the Kidney: What is the Danger?

Michael E. Farkouh, MD, Mt. Sinai Heart Clinical Trials Unit, New York, emphasized that dose-dependent renal effects also occur in up to 5% of patients following long-term use of NSAIDS. In light of the coxib controversy, concerns over renal toxicity are increasing, he said.

Problems include acute renal failure, hypertension, congestive heart failure, fluid and electrolyte abnormalities, nephritic syndrome, and papillary necrosis. Patients most at risk include those with age-related decline in glomerular filtration rate, hypovolemia, loop diuretic use, heart failure, cirrhosis and nephrosis.

Risk for acute renal failure with NSAIDS varies by the preparation, according to a recent epidemiologic study (*Am J Epidemiol*. 2006;164:881-9). Naproxen and rofecoxib carry the highest adjusted relative risk over non-exposure (about 2.3 fold); celecoxib's risk is 1.5 and meloxicam's risk is nearly 1.3. Multiple studies have demonstrated that adverse renal effects with rofecoxib are dose-related.

Another significant problem is the aggravation of hypertension with NSAIDS. When patients require treatment with both antihypertensive agents and NSAIDS, Dr. Farkouh advised, "Don't disregard the blood pressure effects of these drugs and make sure your office measures blood pressure reliably." He recommended using lower doses of the NSAID (nonselective or coxib), titrating the antihypertensive, reducing salt intake, questioning patients about over-the-counter NSAID use, and considering aspirin or a non-opioid analgesic instead.

In contrast to current agents, a new agent, lumiracoxib (Prexige®), has a greatly improved renal safety profile and, especially at low doses, is associated with less heart failure compared with other agents, Dr. Farkouh said.

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low-saturated fat sources and plant proteins), vegetables and fruits should be consumed in abundance, and processed foods should be minimized.

Steven M. Haffner, MD, University of Texas Health Science Center, San Antonio, posed three "key questions" regarding the metabolic syndrome: 1) Does the presence of impaired fasting glucose suggest the need for intensification of cardiovascular risk factor management? 2) Is pharmacologic treatment of impaired fasting glucose and/or impaired glucose tolerance justified to prevent or delay type 2 diabetes? 3) Does therapy for prevention or delay of diabetes decrease cardiovascular disease?

Unfortunately, the answers to these questions, at this point, are "ambiguous," he said. The increase in coronary heart disease risk is "modest" in the setting of impaired fasting glucose, therefore, intensification of risk factor management in this population is not formally recommended. Treatment for impaired fasting glucose or impaired glucose tolerance is only recommended in very-high-risk subjects who have more than a 10% per year risk of developing diabetes. Finally, there is little evidence that preventing diabetes will also prevent cardiovascular disease.

Furthermore, added Lynda Powell, PhD, of Rush University Medical Center, Chicago, it is difficult to motivate patients to make even those changes that clearly prevent cardiovascular disease. "For every 100 patients treated, we achieve success in terms of blood pressure control in only 33, lipid lowering in only 17, and weight loss in only 10 patients," she observed.

Clinicians can help motivate patients toward healthier lifestyles by focusing on one change at a time, keeping the message very simple and repeating it often, she said. They should also emphasize the immediate benefits of change, rather than the long-term goals. The immediate benefits of walking, for example, are the opportunity to breathe fresh air, undisturbed, and reflect on life and thus reduce stress. In addition, she advocates a "coping peer" program that uses fellow patients as a support system for lifestyle modification.