Patients Differ in Their Vascular Sensitivity to LDL

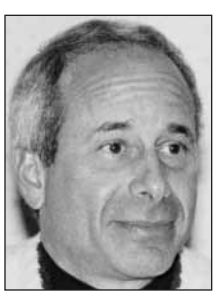
ARTICLES BY
BRUCE JANCIN
Denver Bureau

ORLANDO, FLA. — Why do some individuals live well into their 90s free of heart disease despite an untreated serum cholesterol of 350 mg/dL, while on a daily basis physicians see numerous patients with normal or even low cholesterol who have advanced coronary disease at a relatively young age?

The answer appears to be that people differ in their vascular sensitivity to cholesterol. And that characteristic has major implications for treatment guidelines, which don't acknowledge these individual differences, Robert A. Vogel, M.D., said at the annual meeting of the American College of Cardiology.

This was the provocative implication of a new substudy of the previously reported Reversal of Atherosclerosis with Lipitor (REVERSAL) trial, said Dr. Vogel, professor of medicine and director of clinical vascular biology at University of Maryland, Baltimore.

The primary REVERSAL result was that intensive LDL-cholesterol lowering using 80 mg/day of atorvastatin (Lipitor) halted progression of coronary artery disease (CAD) as assessed by intravascular ultrasound during 18 months of follow-up. CAD continued to worsen in patients randomized to moderate LDL lowering with 40 mg/day of pravastatin (Pravachol). This finding paved the way for the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT TIMI-22) trial, which showed fewer cardiovascular events with 80 mg/day of atorvastatin than with 40 mg/day of pravastatin after hospitalization for acute coronary syndrome.



Heart disease treatment guidelines do not acknowledge these individual differences.

DR. VOGEL

The new REVERSAL substudy involved 214 participants with CAD whose endothelial function was assessed using the brachial artery flow–mediated dilation test at 21 medical centers. The purpose was to learn whether 3 months of intensive LDL lowering would improve endothelial function more than moderate LDL lowering. And, indeed, it did. Atorvastatin at 80 mg/day boosted flow-mediated dilation by 72%, while 40 mg/day of pravastatin increased it by 32%. But the substudy also yielded a completely unexpected and counterintuitive finding: Those CAD patients with the lowest pretreatment LDL-cholesterol levels had the worst baseline endothelial function. And they also responded much more dramatically to intensive LDL lowering than did patients with higher LDL levels.

"We found in the overall trial that the difference between intensive and moderate therapy was concentrated in people who started with low cholesterol. As clinicians, we tend not to look at intensive therapy when the cholesterol is low to start out with. But we found in REVERSAL that those were the patients who actually benefited to the greatest degree," he explained.

The presence of CAD in REVERSAL participants with low baseline LDL-cholesterol levels couldn't be accounted for by an increased prevalence of any of the traditional or novel cardiovascular risk factors. These patients differed from the others only in their low LDL levels and worse endothelial dysfunction.

"We think the explanation is that we're all different and that if you get coronary disease and your LDL is low, it's because you're really sensitive to cholesterol," he continued. "Your goal in cholesterol may be very different from my goal in cholesterol."

This is a reality the National Cholesterol Education Program guidelines will have to find a way to acknowledge, assuming the new REVERSAL finding is confirmed. But that doesn't mean measurement of endothelial dysfunction is likely to find its way into routine clinical practice as a risk-stratification tool.

"Measuring brachial artery blood flow is a complicated technique. We've been doing this now for 13 years. We have one technician who's been doing it the whole time. That's all he does. One of the disappointments in REVERSAL is we found the variability of even well-trained centers to be more than we would have expected. That makes doing clinical trials, let alone individual decision making about patients, very, very difficult. At the present time, I don't see brachial artery ultrasound as a clinically oriented technique," he said. ■

Statins May Up Survival in Patients With Advanced Heart Failure

ORLANDO, FLA. — Statin therapy may markedly improve survival in patients with advanced heart failure, whether or not the etiology is ischemic, Andrew D. Sumner, M.D., said at the annual meeting of the American College of Cardiology.

This enhanced survival appears to be due primarily to a reduced incidence of arrhythmic death, added Dr. Sumner of Pennsylvania State University, Hershey.

Statins' effect on heart failure mortality may arise in part from their anti-inflammatory action.

DR. SUMNER

He presented a retrospective analysis of data from the previously reported prospective Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. In COMPANION, 1,520 patients with advanced heart failure (HF) at 128 U.S. centers were randomized 1:2:2 to optimal drug therapy alone, in conjunction with a cardiac resynchronization pacemaker, or with a combined cardiac resynchronization pacemaker/implantable cardioverter defibrillator (ICD).

There were 313 deaths during a median 16 months of follow-up. Unadjusted all-cause mortality among the 40% of COMPANION participants on a statin was 18%, compared with 22% in those who weren't on a statin. After controlling for numerous variables—including New York Heart Association class, left ventricular ejection fraction, QRS duration, blood pressure, gender, age, diabetes and other comorbidities, HF duration and etiology, and treatment assignment—statin use was associated with a highly significant 28% reduction in all-cause mortality.

Statin use was associated with an adjusted 33% reduction in all-cause mortality among patients randomized to device therapy, but with no gain in survival in patients who received only optimal pharmacologic therapy. Statin-treated patients on cardiac resynchronization therapy without an ICD had a 46% relative risk reduction in all-cause mortality and a 63% reduction in sudden cardiac death, compared with those not on a statin.

In contrast, statin therapy did not appear to have any effect upon all-cause mortality or sudden cardiac death in patients on cardiac resynchronization therapy plus an ICD. This is to be expected, since the ICD already protects against sudden cardiac death, which together with pump failure constitute the two chief causes of mortality in patients with advanced HF.

Dr. Sumner stressed that COMPANION participants were not randomized to statin therapy, and as a retrospective analysis, his study must be considered hypothesis generating. "Hopefully, there will be a randomized, placebo-controlled trial to confirm these observations," he added.

Although statins are best known for their potent LDL-lowering effect, they also reduce markers of inflammation, normalize endothelial dysfunction, and improve production of nitric oxide.

"Because heart failure is characterized by decreased cardiac performance, with activation of neurohormones, release of proinflammatory cytokines, and abnormalities in nitric oxide biosynthesis, treating patients with chronic heart failure with statins is potentially attractive," the cardiologist observed. ■

Pilot Study: Coenzyme Q_{10} Relieved Statin-Induced Pain

ORLANDO, FLA. — Coenzyme Q_{10} markedly improved statin-induced myopathic pain in a randomized, double-blind controlled trial with 41 patients.

"I was surprised at the strength of the outcome; I'd been skeptical," Patricia Kelly, D.O., told this newspaper at the annual meeting of the American College of Cardiology.

Dr. Kelly reported on 41 statin-treated patients who had myopathic pain and whose creatine phosphokinase (CPK) levels were normal or minimally elevated. The patients were randomized to 400 IU vitamin E (control group) or 100 mg coenzyme Q_{10} daily for 30 days.

On a validated pain scale of 0-10, self-rated muscle pain fell from a mean of 6.2 to 3.1 in the group taking coenzyme Q_{10} but remained unchanged in controls. Pain improved in 18 of 21 patients treated with coenzyme Q_{10}, compared with 3 of the 20 taking vitamin E, said Dr. Kelly, a cardiology fellow at Stony Brook (N.Y.) University Hospital.

Severity of muscle pain was unrelated to CPK level, which didn't change significantly in either study arm. LDL cholesterol concentrations and liver function tests also remained unchanged. Both treatments were well tolerated and free of side effects.

Based on these findings, Dr. Kelly concluded that coenzyme Q_{10} may provide an alternative to halting statins in patients with muscle pain. Although the incidence of myopathic pain in clinical trials sponsored by drug companies is often as low as 5%, the experience of Dr. Kelly and her colleagues has been that it's more like 25%, or even higher, in clinical practice.

The rationale for studying coenzyme Q_{10} stems from the fact that all statins not only reduce production of cholesterol but also reduce the biosynthesis of coenzyme Q_{10}, or ubiquinone, a component of the electron transport system and a key early player in mitochondrial ATP production. Other investigators have previously documented 25%-40% reductions in serum and plasma coenzyme Q_{10} levels in statin-treated patients.

Oral coenzyme Q_{10} supplementation therefore seemed like a potential way to boost skeletal muscle high-energy phosphate metabolism—and thereby reduce myopathic pain symptoms—without interfering with the potent LDL cholesterol–lowering ability of statins, she explained.

A month's supply of coenzyme Q_{10} costs at least $30 in health food stores. Based upon the encouraging results of this unsponsored randomized pilot study, Dr. Kelly and her coinvestigators have applied to the National Institutes of Health for a grant to conduct a larger, definitive study. ■