ed with the 80 mg rather than 10-mg dose of atorvastatin for 5 years to prevent one additional major cardiovascular event. TNT participants received state-of-the-art background secondary prevention therapy. This was reflected in the fact that mortality in both treatment arms was lower than in any prior major secondary prevention trial. It’s a measure of the recent advances made in secondary prevention in recent years that in this population of 10,000 patients with documented CHD followed for 5 years, atorvastatin, cardiovascular disease was not the number-one cause of death, Dr. LaRosa observed.

The safety profile of 80 mg/day of atorvastatin was noteworthy. The incidence of persistently elevated liver enzyme tests more than three times the upper limit of normal was 1.2%. Treatment-related myalgia was reported by 4.8% of patients. There were no cases of rhabdomyolysis meeting ACC/American Heart Association criteria in either treatment arm. This was particularly reassuring because in the Aggrastat to Zocor (A to Z) trial, roughly 1 in 250 patients on high-dose simvastatin developed serious muscle complications, David D. Watkins, M.D., a TNT steering committee member, told CARDIOLOGY news. Discussant Carl J. Vaughan, M.D., of the University of Cork (Ireland), said TNT is best appreciated in the context of the earlier Heart Protection Study (HPS) and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trials. Subgroup analysis in the nearly 21,000-patient HPS showed that patients with relatively low baseline LDL-cholesterol levels had the same clinical benefit from intensive statin therapy as those with higher levels. Last year PROVE-IT showed the superiority of high-intensity moderate-intensity statin therapy in acute coronary syndrome patients, again regardless of baseline LDL-cholesterol level.

TNT corroborates those studies, provides confirmatory evidence of the “lower is better” treatment strategy, extends its applicability to the majority of CHD patients having stable disease, and thereby expands the population of candidates for intensive lowering of LDL cholesterol to an estimated 20–30 million patients in the United States alone.

“The aggregate data from HPS, PROVE-IT, and TNT help convict even so-called normal cholesterol [levels] as deleterious and worthy of treatment in secondary prevention,” Dr. Vaughan added.

“This is a very impressive trial,” Sidney C. Smith, Jr., M.D., told this newspaper. “We’re going to have to get this information into our revised guidelines,” added the cardiologist, who is director of the center for cardiovascular science and medicine at the University of North Carolina at Chapel Hill, a former AHA president, and a member of the committee responsible for the influential joint American Heart Association/AHA secondary prevention guidelines.

The only question remaining in many observers’ minds was when the National Cholesterol Education Program (NCEP) will get around to formally revising its target LDL-recommendations for patients with known CHD. Michael H. Davidson, M.D., director of preventive cardiology at Rush University Medical Center, Chicago, predicted the panel will wait on results, which are expected soon, from two other large trials similar to TNT—the Airway Management Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), with simvastatin and folic acid/ vitamin B₁₂. Those results will provide NCEP’s cardiologists with additional side effect data and an opportunity to fine-tune their new LDL-cholesterol target goals.

“I think those studies are going to be positive, too,” he told this newspaper.

Many physicians feel no need to wait for revised guidelines from NCEP. “There are always more data coming along, but I would say this, taken together with HPS and PROVE-IT, is enough,” said Dr. Watkins, professor of medicine at the University of California, San Francisco, and chief of the cardiology section at San Francisco General Hospital.”I’m going to go home and start putting my patients on 80 mg of atorvastatin.”

The TNT results were published concurrently with the presentation in the online edition of the New England Journal of Medicine (http://content.nejm.org/cgi/reprint/NEJMoa050461v1.pdf).

**Lowering LDL Target Cuts Risks**

**TNT Trial from page 1**

**Patient Event Rates in TNT**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>10 mg atorvastatin</th>
<th>80 mg atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>All major CV events</td>
<td>2.3%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>10.9%</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

**The data help convict even so-called normal cholesterol [levels] as deleterious and worthy of treatment in secondary prevention.**

**Vascular Protection After the PEACE Trial**

Has PEACE ever before caused such havoc? The Prevention of Events With Angiotensin Converting Enzyme Inhibition trial has been widely misinterpreted, to the detriment of patient care. PEACE involved the double-blind randomization of patients with stable coronary artery disease (CAD) and normal left ventricular systolic function to the ACE inhibitor trandolapril or placebo on top of modern conventional therapy with other drugs of proven effectiveness. Surprisingly, the trandolapril group experienced no reduction in clinical atherosclerotic events, compared with placebo. Many physicians have concluded as a result that the study casts doubt upon the overall vasculoprotective effects of ACE inhibition.

So what effect, then, has PEACE had on my own clinical practice? None whatsoever. I continue to place essentially all my patients with CAD or any other form of vascular disease and normal left ventricular systolic function on an ACE inhibitor, giving preference to those agents that have demonstrated compelling evidence of benefit in this setting—namely, ramipril and perindopril. And in talking with cardiologists opinion leaders, I find most of them are doing the same. Why are many of us not more willing to give PEACE a chance? Because the permissive bulk of the randomized clinical trial data, including the nearly 10,000-patient Heart Outcomes Prevention Evaluation (HOPE) trial as well as the 12,218-patient European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPAC), has shown that ACE inhibitor therapy results in a highly significant 20–22% reduction in atherosclerotic events in patients with CAD or other vascular disease but no history of heart failure or depressed left ventricular systolic function. This demonstrated clinical efficacy has a compelling mechanistic basis: ACE inhibitors not only lower blood pressure, they also have antithrombotic properties, have antioxidant effects, potentiate 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, and perhaps even those coronary-vasculopathic patients. To put it plainly, because of changing practice patterns, the patients we were much better treated in terms of guideline-recommended therapies for their coexisting risk factors. The use of statins, however, was significantly more common in PEACE than in the earlier HOPE and EUROPA trials. The PEACE participants on statin therapy were also treated to lower target LDL-cholesterol values. Similarly, PEACE participants had higher rates of antplatelet therapy than those in HOPE and EUROPA. They also had better blood pressure control, greater utilization of β-blocker therapy, and a higher rate of coronary revascularization procedures prior to study enrollment.

PEACE has raised an important question in my mind and in those of other observers: If we treat our patients in exemplary fashion with all of the other guideline-recommended risk-reduction therapies, do we still obtain added value from ACE inhibitor therapy, or does it become redundant? The verdict is still out on that. But because the weight of the evidence to date still supports the vascular-protective role of ACE inhibitors, I’m not planning to change my own practice unless a future randomized trial replicates the PEACE findings.

I don’t expect that to happen. In fact, that kind of a trial will be virtually impossible to conduct. It would be a no-win situation for a sponsoring pharmaceutical company, and the National Institutes of Health usually does not conduct competitive trials.

**Guest Editorial**

**Vascular Protection After the PEACE Trial**

By Prakash Deedwania, M.D.