The peak-interest clinical trials at the American College of Cardiology (ACC) Scientific Sessions, which took place from March 29 to April 2, 2008, are generally ushered into the high-profile Late-Breaking Clinical Trials sessions. This year, the ENHANCE trial (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) was precluded from the “Late-Breakers” because a peek at the unexpectedly disappointing data had already been afforded in January.

Amid pre-meeting publicity about allegedly inappropriate data delays (and a Congressional hearing delving into them), the ACC created a special plenary session “Showcase” presentation of the data with a review panel for comment. The ENHANCE findings intensified interest in both non–lipid-lowering benefits of statins and non-statins for lipid lowering. This 57th ACC conference hosted a record 29,000 attendees in Chicago, Illinois.

### ENHANCE, a Scientific Showcase Presentation, Sets the Statin Stage

**ENHANCE: Ezetimibe/Simvastatin (Vytorin) versus Simvastatin (Zocor) Alone**

- John Kastelein, MD, PhD, Professor of Medicine and Chairman, Department of Vascular Medicine, Academic Medical Centre, Amsterdam, The Netherlands
- Steven Nissen, MD, Chairman, Department of Clinical Cardiology, Cleveland Clinic, Cleveland, Ohio
- Michael Davidson, MD, Professor of Medicine, Rush University Medical Center, Chicago, Ill.
- Harlan M. Krumholz, MD, Professor of Internal Medicine, Yale University, New Haven, Conn.

Dr. Kastelein, ENHANCE lead investigator, reported that among 720 patients with familial hypercholesterolemia who were receiving a combination of ezetimibe 10 mg (Zetia) plus simvastatin 80 mg (Vytorin, Merck/Schering-Plough) or 80 mg of simvastatin (Zocor) alone, low-density lipoprotein-cholesterol (LDL-C) levels declined by an incremental reduction of 16.5% \((P < 0.01)\) with Vytorin versus simvastatin (simvastatin, 318 mg/dL at baseline, 193 mg/dL at 24 months; Vytorin, 319 mg/dL at baseline, 141 mg/dL at 24 months).

Other cholesterol changes favored Vytorin to a significant degree as well (Table 1). High-sensitivity C-reactive protein (hs-CRP) levels also fell (by an incremental reduction of 26%) with Vytorin.

Despite the drop in LDL-C levels, the primary endpoint—the change in carotid intima media thickness—was essentially the same in both groups (0.0111 mm with simvastatin alone and 0.0058 mm with Vytorin; \(P = 0.29\)). Possible explanations, according to Dr. Kastelein, were that the measurement technique had not been accurate enough, that ezetimibe had no favorable vascular effects, and that patients had already received effective pharmacotherapy at enrollment.

Dr. Nissen, former ACC President, projected a slide with the heading “Corporate Misconduct” at a Society for Vascular Biology and Medicine symposium the previous day. Among the bulleted items, he discussed (1) delays in reporting the data (18 months from the study’s end to the first release of the data), (2) changes in methodology after data review and an attempt to change the primary endpoint, and (3) a denial of data access to investigators because of suspected unfavorable findings.

At a Merck/Schering-Plough press briefing following the Showcase presentation, Dr. Davidson called the evidence in support of the benefits of LDL-C lowering “overwhelming” and said that the most likely explanation for the lack of a benefit on carotid artery intima thickness was that it was impossible to see an effect because “the population was so well treated even before the study started.”

At the same briefing, Dr. Kastelein stated emphatically that all data had remained blinded until December 2007. Problems with reading the 40,000 B-mode ultrasonography images, he explained, had contributed strongly to the delay in presenting the data. In addition, he had recused himself from some discussions associated with these difficulties, he said later in an interview.

Dr. Krumholz spoke for the Showcase Panel following the ENHANCE presentation. He said that ENHANCE suggests that the way in which LDL-C levels are lowered might matter.

He concluded: “For clinicians who may have employed this

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Table 1. Changes from Baseline after Therapy With Zocor versus Vytorin

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin 80 mg</th>
<th>Ezetimibe/Simvastatin 10/80 mg</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cholesterol</strong>, %</td>
<td>–31.9</td>
<td>–45.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>LDL-cholesterol</strong>, %</td>
<td>–39.1</td>
<td>–55.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Triglycerides (median)</strong>, %</td>
<td>–23.2</td>
<td>–29.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The author is a medical writer living in New York, New York.
medication (i.e., ezetimibe) before exhausting the options with statins, the strongest recommendation we can make on this panel is, ‘Turn back to statins, especially those with favorable outcomes data.’"

Outcomes data from another trial—IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)—comparing Vytorin with simvastatin alone among 18,000 patients recovering from acute coronary syndromes are expected in 2012.

In a newsroom interview, Dr. Nissen recommended that in the future, when approval of a drug is based on surrogate endpoint trials (as was the case with ezetimibe), such approval should be contingent upon the immediate launch of an outcomes trial.

**DUAAL: Amlodipine and Atorvastatin (Caduet)**

- John Deanfield, MD, Professor of Cardiology, University College, London, United Kingdom

Interest in results from the Double-blind Atorvastatin Amlodipine (DUAAL) study was also heightened by ENHANCE’s suggestion of pleiotropic statin effects. DUAAL findings point to statin benefits in endothelial function that translate into reductions in transient myocardial ischemia (TMI), according to Dr. Deanfield.

In CAD patients with stable angina, TMI is associated with increased morbidity and mortality and may reflect disturbed arterial biology. The calcium antagonist amlodipine besylate (Norvasc, Pfizer) can have potent antianginal effects, and statins have a favorable effect on vascular function.

Dr. Deanfield also said that the combination of amlodipine and atorvastatin (Caduet, Pfizer) demonstrated synergistically favorable effects on the endothelium and, in an antihypertensive regimen, reduced the number of cardiovascular events.

The objective of DUAAL was to evaluate the anti-ischemic and antianginal effects of atorvastatin 10 → 80 mg (Lipitor, Pfizer) and amlodipine 5 → 10 mg, separately and in combination. The randomized, double-blind, parallel-group multinational trial included a two-week run-in phase and 24 weeks of active therapy with a dose titration at the sixth week. DUAAL included 311 patients with stable angina, a history of coronary artery disease, and three TMI episodes and/or 15 minutes of ischemia during 48-hour Holter monitoring.

Investigators assessed changes in TMI by Holter monitoring, exercise ischemia, and inflammatory biomarkers at 26 weeks. Holter-recorded median TMI episodes decreased in a similar fashion from baseline values in all three groups at week 26 as follows: –5.0 at baseline, –0.5 with amlodipine, 0.0 with atorvastatin, and –1.0 with the combination (P < 0.001).

Patient diaries showed significant decreases in angina episodes (from five attacks per week to about one attack per week) and nitroglycerin use (from about three attacks per week to 0.75 attacks per week), as well, in all groups.

Levels of hs-CRP increased in the amlodipine patients and fell significantly in the atorvastatin group when compared with baseline values and when compared with amlodipine. Peripheral edema was the only adverse drug event, occurring in 2% or more of the patients (5.8% with amlodipine; 0.0% with atorvastatin; and 10.6% with the combination).

The complementary mechanisms of atorvastatin and amlodipine may be advantageous in the management of patients with CAD and TMI, Dr. Deanfield concluded. He pointed out that within 18 weeks, statin use virtually eliminated any evidence of ischemia during patients’ normal daily activities.

“What we found, very unexpectedly, was that the statin was as effective an antianginal and anti-ischemic drug as the traditional medications we use for treating angina and ischemia.”

**Niacin and Laropiprant (Cordaptive)**

- Michael J. Koren, MD, Jacksonville Center for Clinical Research, Jacksonville, Fla.

Interest in lipid-lowering agents other than those from the statin class was piqued by the ENHANCE findings suggesting that the way in which LDL-C is lowered might be important. Side effects from those agents, however, have been a major impediment to their uptake and a major factor behind the widespread prescribing of ezetimibe as an alternative to high-dose statins. With niacin, its favorable effects on LDL-C and HDL-C levels are confounded by the flushing that occurs in 90% of patients, Dr. Koren said.

Laropiprant, a potent, highly selective prostaglandin D1, subtype 1 (DP1)-receptor antagonist that has been shown to significantly reduce niacin-induced flushing, is added to extended-release (ER) niacin in Merck’s Cordaptive. Dr. Koren presented data from a multinational, double-blind, randomized, parallel-group study of 1,455 dyslipidemic patients who were treated for 16 weeks with ER niacin (Niaspan, Abbott).

The study involved multistep titration to 2 g with aspirin plus nonsteroidal anti-inflammatory drugs (NSAIDs) to mitigate flushing or a forced titration of a 1-g fixed dose of ER niacin/20 mg laropiprant for four weeks, advanced to 2 g ER niacin/40 mg laropiprant for 12 weeks. The primary endpoint was the number of days per week during which patients experienced moderate-to-severe or extreme flushing (according to the Global Flushing Severity Scale) during the treatment period.

Of those patients in the ER niacin/laropiprant group, 47% had no moderate-to-extreme flushing episodes, compared with 22% in the ER niacin group (P < 0.001). Twenty-eight percent of patients had between zero and 0.5 or more episodes per week with ER niacin/laropiprant, compared with 34% who received ER niacin (Niaspan).

Safety profiles were similar for both groups. Discontinuation rates for flushing were 7.4% with ER niacin/laropiprant and 12.4% for ER niacin, Dr. Koren reported.

In an interview, he stated: "The take-home message is that the number of severe flushes in the Cordaptive group was about one per month, as compared with one per week with ER niacin."

The trial’s regimen should allow more patients to reach and maintain a 2-g dose of niacin, he added.

On April 28, 2008, the FDA issued a “not approvable” letter to Merck regarding its Cordaptive application. Merck has announced that it is providing additional information to the FDA.
ISAR–REACT3: Bivalirudin (Angiomax) versus Unfractionated Heparin

- Adnan Kastrati, MD, Deutsches Herzzentrum, Munich, Germany
- Harvey D. White, DSc, Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand
- Marc Cohen, MD, Professor of Medicine, Mount Sinai School of Medicine, New York, New York

In the ISAR–REACT3 (Intracoronary Stenting and Anti-thrombotic Regimen–Rapid Early Action for Coronary Treatment) trial, although bleeding was significantly reduced with bivalirudin (Angiomax for Injection, The Medicines Company), this agent did not improve net clinical benefit significantly, compared with unfractionated heparin (UFH), at 30 days after percutaneous coronary intervention (PCI). Net clinical benefit is a measure that balances clinical gains and adverse events.

In a Late-Breaking presentation, Dr. Kastrati said that previous clinical trials had not reflected current anticoagulant or antithrombotic practices and had not included higher-risk populations. It was hypothesized that ISAR–REACT3 would find bivalirudin superior to UFH for biomarker-negative patients undergoing PCI after optimal pretreatment with clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Synthelabo).

In this trial, 4,570 patients with a mean age of 67 years (76.5% men and 80% with multivessel disease) were negative for biomarkers (troponin T levels below 0.03 mcg/L or creatine kinase [CK-MB] below the upper limit of normal [ULN]) with stable or unstable angina. These patients had been treated with aspirin at a dose of 325 mg or higher and with clopidogrel 600 mg for two hours or more before the procedure.

The patients received bivalirudin as an intravenous (IV) bolus at 0.75 mg/kg before PCI, followed by continuous IV infusion during the procedure at 1.75 mg/kg per hour. Patients in the UFH arm received UFH as an IV bolus of 140 units/kg, followed by a continuous infusion of placebo for the duration of the procedure. All patients received clopidogrel 75 to 150 mg/day until discharge or for the first three days after the procedure, then 75 mg/day for at least six months and aspirin 80 mg to 325 mg indefinitely.

The primary endpoint was a composite of death, myocardial infarction (MI), urgent target vessel revascularization (UTVR), and major bleeding, according to REPLACE-2 criteria (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events).

Dr. Kastrati reported that ischemic events (death, definite ST elevation, MI, UTVR) were similar for both treatment groups. The primary endpoint was also similar between the two groups, at rates of 8.7% with UFH and 8.3% with bivalirudin ($P = 0.57; \text{relative risk} [RR], 0.94$).

In the secondary combined endpoint (death, MI, UTVR), differences were also nonsignificant (UFH, 5.0%; bivalirudin, 5.9%). The frequency of bleeding, however, was higher in the UFH group, with major bleeding affecting 4.6% of patients, minor bleeding affecting 9.9%, and transfusions needed in 1.8%) than in the bivalirudin group, with major bleeding affecting 3.1% ($P = 0.008$), minor bleeding affecting 6.8% ($P = 0.0001$), and transfusions needed for 1.3% ($P = 0.15$).

A prespecified subgroup analysis of age, sex, diabetes, creatinine, and stable or unstable angina revealed no differences, and the incidence of thrombocytopenia was also similar between the two groups.

Concluding that bivalirudin had not improved net clinical benefit, Dr. Kastrati nevertheless said that it did reduce bleeding. He suggested that for some subgroups (e.g., older patients, the bleeding risk might make bivalirudin the better choice. Cost, however, could make UFH the preferred agent overall.

Although ISAR–REACT3 was a trial with negative outcomes, ACC commentator Dr. White said that bivalirudin could be an appropriate antithrombotic choice in this setting. He added, “I think bleeding should have been the primary endpoint.”

Dr. Cohen pointed out in an interview that the trial’s UFH dose was about double the starting dose used in the U.S., and probably produced higher bleeding rates in the UFH group. He emphasized bivalirudin’s extra cost, compared with UFH ($450–$500), and said that no evidence was given to suggest that the small bleeding increase with UFH led to any major added utilization of health care resources.