The American Heart Association (AHA) Scientific Sessions 2011 attracted nearly 20,000 attendees (8,103 domestic; 7,467 professional) to Orlando, Fla., from November 12–15, 2011, with its program of cutting-edge research on clinical and interventional cardiology. Key sessions reflect the continued elusiveness of broadly successful drug trials, a drug-eluting balloon trial showing that less might be more, and an analysis suggesting that giving free drugs to patients saves money in the long run.

**Extended-Release Niacin and Statins For LDL-Cholesterol: The AIM-HIGH Trial**

• William E. Boden, MD, Professor of Medicine and Preventive Medicine, Schools of Medicine and Public Health, State University of New York at Buffalo, N.Y.

• Discussant: Philip Barter, MD, PhD, Director, The Heart Research Center, Sydney, Australia

The direct relationship between elevated levels of low-density lipoprotein-cholesterol (LDL-C) and an increased cardiovascular risk is firmly established, as is the important role of statins in reducing cardiovascular events by 25% to 35%. Although statins, when recommended, help patients achieve goal LDL-C levels, a residual risk persists. A significant inverse relationship also exists between low levels of high-density lipoprotein-cholesterol (HDL-C) and cardiovascular events.

Previous placebo-controlled trials have supported the use of niacin or fibrates. The objective of the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health) trial was to determine whether the residual risk associated with low HDL-C levels would be mitigated in patients with coronary heart disease (CHD) whose LDL-C levels were already optimized through statin use, namely with simvastatin (Zocor, Merck) (40 to 80 mg/day), with or without ezetimibe (Zetia, Merck/Schering Plough), when extended-release niacin (1,500–2,000 mg/day) or placebo was added.

Enrolled patients (N = 3,414), 45 years of age and older, had CHD, cerebrovascular disease (CVD), or peripheral artery disease (PAD), low HDL-C levels (below 40 mg/dL for men; below 50 mg/dL for women), triglyceride levels between 150 and 400 mg/dL, and LDL-C levels below 180 mg/dL. The LDL-C target was 40 to 80 mg/dL. The duration of follow-up was 12 months.

The primary outcome was the time to the first occurrence of events (i.e., CHD death, nonfatal heart attack, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven revascularization). The event-driven trial was designed with an 85% power to detect a 25% reduction in events, based on a projected 800 primary outcomes over a period of 2.5 to 7.0 years of follow-up. The trial was stopped after an average of 36 months of follow-up because of a lack of medication efficacy and a higher rate of ischemic stroke in the niacin group.

The primary outcome was reported at rates of 16.4% in the combination therapy arm and 16.2% in the monotherapy arm. The hazard ratio (HR) was 1.02, and the 95% confidence interval (CI) was 0.87 to 1.21 (P = 0.79).

Dr. Boden noted, “Prior therapy in patients receiving statins (94%) and niacin (20%) may have limited our ability to demonstrate a favorable treatment effect with niacin.”

An unexpected 9.8% increase in HDL-C levels in the placebo-treated patients, he added, could have minimized differences in the rate of adverse events. In this patient population, Dr. Boden concluded, there was no incremental clinical benefit from the addition of niacin to statin therapy.

Dr. Barter said, “At the outset, I would like to say that this study seriously disturbs me. … It was a study designed in such a way that it was not possible to get a positive result.”

He explained that to generate the desired statistical power would have required a follow-up period of 15 to 20 years or a much larger sample size. Furthermore, with an actual on-treatment difference of 4 mg/dL in HDL-C levels between the two groups and a 5-mg/dL difference in LDL-C levels between the groups, the predicted event rate reduction would have been 12.5%, half of that on which the power calculations were based. With the early stopping of the trial after 550 events, AIM-HIGH “in no way had the power to detect a 12.5% reduction in events,” Dr. Barter said.

He concluded: “AIM-HIGH has not tested the HDL hypothesis, nor was it powered sufficiently to test the potential benefits of niacin.”

The much larger HPS2–THRIVE trial (Heart Protection Study—Treatment of HDL to Reduce the Incidence of Vascular Events) is currently investigating that question, he added, in a comparison of extended-release niacin/laropiprant 2 g (previously known as MK-0524A).

**Vorapaxar Reduces Events in Acute Coronary Syndrome: The TRA-CER Trial**

• Kenneth W. Mahaffey, MD, Physician; Associate Professor of Medicine, Duke Clinical Research Institute; and Co-Director of Cardiovascular Research, Duke University, Durham, N.C.

• Robert O. Bonow, MD, former AHA president and Professor of Medicine, Northwestern University, Chicago, Ill.

The platelet protease-activated receptor-1 (PAR-1), the main thrombin receptor, is a novel target for the treatment and prevention of arterial thrombosis. The TRA-CER trial (Thrombin
MEETING HIGHLIGHTS: American Heart Association

Receptor Antagonist for Clinical Events Reduction) was conducted to compare the efficacy and safety of vorapaxar, a first-in-class, orally active, potent selective PAR-1 antagonist, with placebo in 12,942 high-risk patients with non–ST-segment elevation (NSTEMI) acute coronary syndrome (ACS). These patients, enrolled in 37 countries, had received the current standard of care (aspirin and P2Y12 inhibition). In previous trials, the incidence of myocardial infarction (MI) was reduced with vorapaxar without increased bleeding, Dr. Mahaffey noted.

Vorapaxar (40 mg) or placebo was given as a loading dose, followed by a maintenance dose (2.5 mg daily). The primary endpoint was the composite of cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, and urgent coronary revascularization.

Safety-related endpoints included the composite of moderate and severe GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator) bleeding and clinically significant TIMI (Thrombolysis in Myocardial Infarction) bleeding.

Among the 6,471 patients (28% female; mean age, 64 years) receiving placebo, 97% were taking aspirin and 87% were taking a thienopyridine. For the 6,473 patients who were taking vorapaxar (mean age, 64 years), 96% were taking aspirin and 88% were taking a thienopyridine.

The primary combined endpoint was reported at a rate of 19.9% in the placebo group and at 18.5% in the vorapaxar group, an 8% reduction (HR 0.92; 95% CI, 0.85–1.01; P = 0.072). Although the key secondary endpoint of combined cardiovascular death, MI, and stroke significantly favored vorapaxar (18.4% placebo, 17.7% vorapaxar; P = 0.018), because the primary endpoint was not met, superiority could not be claimed, according to the prespecified criteria.

Bleeding rates were significantly higher (P < 0.001) in the vorapaxar group, compared with the placebo group, for GUSTO moderate or severe bleeding (5.2% vs. 7.2%), clinically significant TIMI bleeding (14.6% vs. 20.2%), GUSTO severe bleeding (1.6% vs. 2.9%), TIMI major bleeding (2.5% vs. 4.0%), and intracranial hemorrhage (0.24 vs. 1.07%).

In the small group of patients who did not receive a thienopyridine, however, GUSTO moderate or severe bleeding was not increased in the vorapaxar group (P value for interaction = 0.044), and the benefit was not significantly more pronounced (P = 0.13).

Dr. Mahaffey concluded that in this population, the use of aspirin, P2Y12 inhibition, and vorapaxar did not significantly reduce the combined endpoint, but it did increase the rates of bleeding and intracranial hemorrhage.

Commenting on the benefit in the dual antiplatelet therapy subgroup in an interview, Dr. Bonow expressed strong interest in upcoming results with vorapaxar in the TRA-2P (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) study. If what was seen in TRA-2P is borne out in TRA-2P, he suggested, “it might justify a new trial, one testing aspirin plus a PAR-1 inhibitor against aspirin and prasugrel (Effient Eli Lilly/Daiichi Sankyo). It may be that three antiplatelet drugs at this dose are too many.”

The percentage of patients in the TRA-2P trial who received dual antiplatelet therapy (12%–13%) was small, Dr. Bonow cautioned.

Drug-Eluting Balloons Replace Drug-Eluting Stents In Patients With a High Risk of Bleeding Complications

- Mariusz Zadura, MD, Senior Cardiologist, Heart and Diabetes Center of Mecklenburg-Vorpommern, Karlsruhe, Germany

There is a strong indication for oral anticoagulants in patients receiving a mechanical prosthetic heart valve and for those with atrial fibrillation or pulmonary embolism. When these patients also receive a drug-eluting stent and simultaneous combined antiplatelet therapy with aspirin and clopidogrel (Plavix, Bristol-Myers Squibb/Sanoﬁ) or prasugrel (Effient), for 12 months, the risk of bleeding complications is high. Those patients receiving a drug-eluting balloon, however, need only 4 weeks of dual antiplatelet therapy instead of the usual year.

“That makes the balloons a potentially attractive alternative to the stents,” Dr. Zadura said.

He reported on the first 63 patients (41 men, 22 women; mean age, 67.2 years) who were treated for coronary restenosis with a paclitaxel-eluting balloon (Taxol, Bristol-Myers Squibb; SeQuent Please, B. Braun) instead of a drug-eluting stent. At 6 to 9 months, 94.5% of patients experienced no significant loss of the gain achieved with angioplasty.

Restenosis (by more than 50%) was observed in four of 91 lesions. Only two patients (3%) required target lesion revascularization. One patient was treated successfully with a drug-eluting stent, and the other underwent surgery.

Dr. Zadura concluded: “This is a major benefit, especially in elderly or noncompliant patients. Due to the reduced need for dual platelet inhibition, drug-eluting balloons seem to be an interesting alternative.” Rates of restenosis and target lesion revascularization were as low as with the drug-eluting stents, he added.

Dr. Zadura pointed to a further advantage of the balloon over the stent for treating restenosis:

The current approach of placing a metal drug-eluting stent inside an old bare metal stent essentially creates a metal sandwich. With drug-eluting balloons, we can reduce the body’s reaction to a ‘full-metal jacket’ placed in an artery because the biodegradable balloon coating matrix decomposes in 24 hours and appears to create less of an immune reaction.

Preventive Medications After Myocardial Infarction: The MI FREEE Trial

- Niteit K. Choudhry, MD, PhD, Associate Professor, Harvard Medical School; and Associate Physician, Division of Pharmacoepidemiology and Pharmacoeconomics and the Hospitalist Program, Brigham and Women’s Hospital, Boston, Mass.
- Discussant Eric D. Peterson, MD, MPH, Fred Cobb, MD, Distinguished Professor of Medicine, Division of Cardiology, Duke University Medical Center; and Associate Director, Duke Clinical Research Institute, Durham, N.C.

Within 2 years of initiating therapy in the MI FREEE trial (Post-Myocardial Infarction Free Rx Event and Economic
Evaluation), only 50% of patients were found to be adherent to their prescribed statins, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin-receptor blockers (ARBs). Even among patients with medical insurance, the usage of these drugs varied according to the comprehensiveness of coverage.

To test the hypothesis that adherence and outcomes might be improved by eliminating copays for statins, the investigators prescribed beta blockers and ACE inhibitors or ARBs to post-myocardial infarction (MI) patients and evaluated possible effects on major vascular event rates and health spending. The patients (mean age, 54 years; 75% men) were randomly assigned to receive, in a 1:1 fashion, full coverage (free drugs; n = 2,845) or usual coverage (copays; n = 3,010). The patients were insured beneficiaries who had been discharged a mean period of 49 days after the MI, and they were observed for a median period of 394 days.

Mean monthly baseline copays in the usual-coverage group were $13.35 for ACE inhibitors and ARBs, $12.83 for beta blockers, and $24.92 for statins. Medication adherence in the full-coverage (free drugs) arm was significantly higher for all three drug classes (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>ACE Inhibitors and ARBs</th>
<th>Beta Blockers</th>
<th>Statins</th>
<th>All Three Drug Classes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full adherence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% difference in days)</td>
<td>↑5.6%</td>
<td>↑4.4%</td>
<td>↑6.2%</td>
<td>↑5.4%</td>
</tr>
<tr>
<td>41.1</td>
<td>49.3</td>
<td>55.1</td>
<td>43.9</td>
<td></td>
</tr>
<tr>
<td><strong>Usual adherence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% difference in days)</td>
<td>35.9</td>
<td>45.0</td>
<td>49.0</td>
<td>38.9</td>
</tr>
</tbody>
</table>

P < 0.001 for all comparisons.
ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker.

Dr. Choudhry concluded, “Eliminating copayments improved adherence, reduced rates of major vascular events, reduced patient out-of-pocket spending for drugs and other non-drug services, and did not increase insurer or total spending.”

The composite outcome of major vascular events plus revascularization was not lowered significantly.

Dr. Peterson said, “MI FREEE showed that providing free post-MI medications could reduce total vascular events and pay for itself! Thus, widespread adoption is recommended.”

REFERENCES