The American Heart Association (AHA) 2009 Scientific Sessions hosted nearly 22,000 cardiologists, other health professionals, and industry exhibitors in Orlando, Florida, from November 14 to 18, 2009. This overview covers the late-breaking clinical trial presentation of ARBITER 6-HALTS, a lipid treatment strategy study that attracted more attention and controversy than others; a clinical trial of angiotensin–receptor blockers in heart failure; and two other sessions that examined the effects of lipids on both cardiovascular disease and cancer.

**The ARBITER 6-HALTS Trial (Ezetimibe and Niacin)**

- Allen J. Taylor, MD, Director, Advanced Cardiovascular Imaging, Walter Reed Army Medical Center, Washington, D.C.
- Mariel Jessup, MD, Associate Chief of Clinical Affairs, Division of Cardiovascular Medicine, and Professor of Medicine, Heart Failure & Cardiac Transplantation, University of Pennsylvania, Philadelphia, Pa.
- John Kastelein, MD, PhD, Professor of Medicine and Chairman, Department of Vascular Medicine; Strategic Chair, Genetics of Cardiovascular Disease; and Director, Atherosclerosis Research Group, Academic Medical Center, University of Amsterdam, Netherlands

Among high-risk patients receiving long-term statin therapy, niacin (Niaspan, Abbott) was superior to ezetimibe (Zetia, Merck, Schering-Plough) with respect to changes in carotid intima–media thickness (CIMT) and the incidence of major adverse cardiovascular events. The findings were reported in the ARBITER 6-HALTS trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol: HDL And LDL Treatment Strategies).

Although statins reduce low-density lipoprotein-cholesterol (LDL-C) blood levels and clinical events, residual cardiovascular risk with statin monotherapy may justify intensified therapy with niacin to increase high-density lipoprotein-cholesterol (HDL-C) levels or with ezetimibe to further reduce LDL-C levels. The investigators compared the effects of long-term lipid-lowering therapy with either extended-release niacin or ezetimibe on CIMT over 14 months. Between-group change in CIMT was the primary endpoint.

The mean age of the patients was 65 years (80% male). All patients had known cardiovascular disease with LDL levels below 100 mg/dL; HDL-C levels were below 50 mg/dL in men and below 60 mg/dL in women. Patients had been taking statins for a mean of six (± five) years. The mean LDL-C level of the patients was 130 mg/dL (± 60 mg/dL), and the mean HDL-C level was 40 mg/dL (± 10 mg/dL).

When evidence at a prespecified interim analysis showed that the primary endpoint was met, the Independent Data Advisory Committee terminated the study. At that point, 14-month data available on 208 patients showed varying cholesterol changes for the agents (Table 1). The final change in LDL-C with ezetimibe was −17.6 ± 20.1 mg/dL (0.5 ± 0.5 mmol/L) and −10.0 ± 24.5 mg/dL (0.3 ± 0.6 mmol/L) with niacin (P = 0.01). The final change in HDL-C in the ezetimibe patients was −7.5 ± 9.2 mg/dL (0.2 ± 0.2 mmol/L) and 7.5 ± 9.2 mg/dL (0.2 ± 0.2 mmol/L) in the niacin group (P < 0.001). Triglyceride levels were reduced in both groups.

For the primary endpoint of CIMT, subjects in the niacin arm achieved a greater change over 14 months (P = 0.003), with significant regression of both mean CIMT (P = 0.001) and maximal CIMT (P = 0.001). Paradoxically, among ezetimibe subjects, reductions in LDL-C levels with ezetimibe were associated with CIMT progression (P < 0.001). The incidence of cardiovascular events was lower with niacin than with ezetimibe (1.3% vs. 5.8%; P = 0.029).

Dr. Taylor concluded that the study provided clear and undeniable evidence of the superior clinical effectiveness of niacin over ezetimibe.

“Ezetimibe’s clinical efficacy remains unproven. HALTS further questions the proper role of ezetimibe, a less effective therapy, in clinical practice, and ezetimibe’s mechanism of action,” he said.

Although none among many experts commenting on the trial questioned its findings, Dr. Taylor’s conclusions—and this last statement, in particular—aroused considerable protest among experts.

Dr. Jessup, chairperson of the program committee for the AHA Annual Scientific Sessions, objected not to the findings but to the strength and range of the conclusions. She stated in an interview:

“I think people are distressed in particular about the post hoc analysis that looked at the relationship between ezetimibe’s lowering of LDL and the actual increase in intimal wall thick-

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<th>Change in LDL-C</th>
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LDL-C = low-density lipoprotein-cholesterol; HDL-C = high-density lipoprotein-cholesterol; TG = triglycerides.
The HEAAL Study (Low-Dose and High-Dose Losartan)

- Marvin A. Konstam, MD, Professor, Tufts University School of Medicine, Boston, Mass.
- Karl Swedberg, MD, Sahlgrenska Academy, Goteborg, Sweden

In the first study to investigate the effects of angiotensin-receptor blocker (ARB) doses on clinical outcomes in heart failure (HF), higher ARB doses had a favorable impact on rates of death and hospitalization for HF. Patients in HEAAL (Heart Failure Endpoint evaluation with the Angiotensin II Antagonist Losartan) had New York Heart Association (NYHA) Class II–IV HF with a left ventricular ejection fraction (LVEF) of 40% or lower and intolerance to angiotensin-converting enzyme (ACE) inhibitors.

To test the hypothesis that higher ARB doses would be associated with improved clinical outcomes in HF, patients were given 12.5 to 25 mg of losartan (Cozaar, Merck) once daily for two weeks. The dose was then randomly titrated upward over three weeks to either 150 mg (n = 1,927) or to 50 mg (n = 1,919). The primary endpoint was death or hospitalization for HF.

The mean patient age was approximately 64 years (about 70% male). Mean ejection fraction was 31.6%, and 64% of the patients had ischemic heart disease. Most patients (70%) were receiving ARBs at screening.

After a median follow-up of 4.7 years, the primary endpoint expressed in rate per 100 person-years was reported as 11.1 for 150 mg and 12.4 among those receiving losartan 150 mg and as 12.9, 11.5 vs. 12.9, P = 0.027. Among secondary endpoints, differences in HF hospitalizations (6 vs. 7, P = 0.025) and cardiovascular hospitalizations (11.5 vs. 12.9, P = 0.023) also favored the higher dose significantly. Mortality rates were similar for both doses (7.6 for 150 mg and 8.2 for 50 mg, P = 0.94).

Although rates of adverse events were significantly higher for hyperkalemia, hypotension, and renal impairment with the 150-mg dose, discontinuations for adverse events (also in per 100 person-years) were low (7.7 for 150 mg; 7 for 50 mg) and were nonsignificant.

Dr. Konstam concluded, “In patients with HF, reduced LVEF and ACE-inhibitor intolerance, incremental value is derived from up-titrating ARB doses to levels demonstrated to confer benefit on clinical outcomes.”

AHA discussant Dr. Swedberg concurred with Dr. Konstam’s conclusion.

“The clinical implication is that all patients on losartan today need to be evaluated and probably up-titrated,” he commented.

The same is true for other ARBs, he added. Dr. Swedberg then posed two other still unanswered questions: What is the effect of losartan versus placebo in these patients? Is this dose of losartan more effective than an ACE-inhibitor?

Statins May Not Benefit Increased Cardiovascular Risk Linked to Low HDL-Cholesterol Levels

- Haseeb Jafri, MD, Tufts Medical Center, Boston, Mass.

According to an analysis of 20 randomized, controlled trials involving 137,000 participants, increases in the risk of cardiovascular events that occur with progressively lower HDL-C levels were similar, whether or not patients were taking a statin.

Although statins do reduce the risk of cardiovascular disease, rates of cardiovascular events persist at unacceptably high levels. In an effort to determine whether statin therapy might alter the relationship between HDL-C levels and cardiovascular disease risk, Dr. Jafri and colleagues conducted a Medline search among statin trials with 1,000 years or more of follow-up. The median duration of follow-up was 3.9 years. The median baseline HDL-C level was 45 mg/dL, and the on-treatment HDL-C level was 48 mg/dL (P < 0.001). Baseline and on-treatment HDL-C levels did not differ in the control arms. Investigators evaluated the relationship between HDL-C levels and risk of myocardial infarction (MI) in the statin and control groups.

Relative to controls, statin therapy was associated with a median reduction in the rate of MIs of 26.2% and with a median reduction in the rate of cardiovascular disease events of 24.5% (P < 0.01) for both comparisons. In terms of HDL-C concentrations, after the researchers adjusted for on-treatment LDL-C levels and age, for every 10-mg/dL decrement in HDL-C levels, there was an associated increase of 7.6 (95% confidence interval [CI], 3.9–11.3) and 7.8 (95% CI, 2.8–13.0) MIs per 1,000 person-years in statin-treated patients and non-statin controls, respectively (P = 0.45). In contrast, statin treatment reduced MIs by a median of 4.4 per 1,000 person-years.

Dr. Jafri concluded: “The residual cardiovascular disease risk in statin-treated patients could be partly explained by the effects of low levels of HDL-C.”

Higher HDL-C Levels, Lower Cancer Risk

- Richard Karas, MD, PhD, Professor; Vice-Chairman of Medicine; Director, Preventive Cardiology Center; Co-Director, Women’s Heart Center; and Associate Director, Molecular Cardiology Research Institute, Tufts Medical Center, Boston, Mass.

Independent of LDL-C levels, age, body mass index (BMI), and smoking status, there is a significant inverse relationship between HDL-C levels and the incidence of cancer. The finding emerges from a Medline search that identified lipid intervention in randomized, controlled trials involving 1,000 or more person-years of follow-up and providing baseline HDL-C data and rates of incident cancer.

The association of low HDL-C levels with increased cancer risk has been known for many years. For Dr. Karas, it aroused interest in whether a similar relationship exists for HDL-C.

“We realized that no one had really ever looked systematically at whether HDL-C levels are associated with an increased risk of death and hospitalization for HF.
risk of cancer,” he said.

Twenty-one eligible studies with more than 73,000 patients were identified. Median follow-up was five years, and cumulative exposure was 586,528 person-years. During the follow-up period, 7,928 cancers were reported.

The analysis revealed a significant inverse relationship between baseline HDL-C levels and the rate of incident cancer, as follows: every 10-mg/dL increase in HDL-C was associated with a 24% relative reduction in the cancer rate (95% CI, 1%–41%; \( P = 0.05 \)). After investigators adjusted for baseline LDL-C levels, age, BMI, and smoking status, the relationship remained, showing that every 10-mg/dL increase in HDL-C level was associated with a 21% relative reduction in incident cancer (95% CI, 8%–33%; \( P = 0.004 \)).

LDL-C levels also demonstrated an inverse relationship to cancer incidence cancer. Every 10-mg/dL reduction in LDL-C levels was associated with a 14% relative increase in the cancer rate (95% CI, 9%–18%; \( P < 0.001 \)).

Both age and BMI were factors with a significant, direct relationship to the rate of cancer. For every five-year increase in age, there was an associated 28% relative increase in cancer (95% CI, 16%–42%; \( P < 0.001 \)). In addition, for every 1-kg/m² increase in BMI, there was an associated 18% relative increase in the cancer rate (95% CI, 6%–31%; \( P = 0.003 \)).

Dr. Karas concluded: “The current systematic analysis is the first to report a strong and significant inverse relationship between baseline HDL-C and the rate of incident cancer, which is independent of LDL-C, age, BMI, and smoking status.”

In an interview, Dr. Karas pointed out that although low LDL-C levels are associated with higher cancer rates, lowering LDL-C with statins does not contribute to an increased cancer risk. Dr. Karas suggested that the relationship between HDL-C levels and the incidence of cancer is strong, significant, and inverse and is independent of LDL-C levels, age, BMI, or smoking status.

He concluded:

This first systematic analysis to show a strong and significant inverse relationship between HDL-C and the rate of incident cancer does not test whether or not raising HDL-C levels lowers cancer risk. Insight into that question may come from future clinical trials, such as the ongoing AIM-HIGH trial [Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes].

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**MEETING HIGHLIGHTS: AHA**

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