American College of Cardiology, 59th Annual Scientific Session

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Among the 2,300 abstracts offered to 20,000 attendees at the American College of Cardiology (ACC) meeting in Atlanta, Georgia, from March 14 to 16, 2010, results for intensive therapies for blood pressure and lipids were disappointing; however, a new factor Xa agent (betrixaban) showed promise in late-breaking clinical trials. Other sessions reviewed here showed a possible safety deficit for one contrast agent used in cardiac catheterization, benefits for some early use of clopidogrel and a glycoprotein IIb/IIIa inhibitor (eptifibatide) in acute coronary syndromes, a new formulation of an older drug (diazoxide) for hypertriglyceridemia, and a more powerful lipid-lowering combination of rosuvastatin and ezetimibe.

Intensive Blood Pressure Control and Cardiovascular Events in Type-2 Diabetes (ACCORD Blood Pressure and Lipid Trial)

- William C. Cushman, MD, Veterans Affairs Medical Center, Memphis, Tenn.
- Henry C. Ginsberg, MD, College of Physicians and Surgeons, Columbia University, New York, N.Y.

In the context of good glycemic control, does a therapeutic strategy that targets a systolic blood pressure (BP) of below 120 mm Hg reduce the rate of cardiovascular events more than a strategy that targets a systolic BP of below 140 mm Hg? For that question—the primary one for the ACCORD trial (*A*ction to *C*ontrol *C*ardi*o*vascular *R*isk in *D*iabetes)— the answer was apparently negative for patients with type-2 diabetes at high risk for cardiovascular disease (CVD) events.

The ACCORD Blood Pressure trial, conducted at 77 clinical sites in the U.S. and Canada, included high-risk patients with type-2 diabetes who were randomly assigned to therapy designed to achieve a systolic BP goal of either less than 120 mm Hg (n = 2,362) or below 140 mm Hg (n = 2,371). The primary outcome measure was first occurrence of a major CVD event, such as nonfatal myocardial infarction (MI), nonfatal stroke, or CVD death, during a follow-up period of four to eight years.

After one year, the mean systolic BP was 119.3 mm Hg in patients receiving intensive therapy and 133.5 mm Hg in those receiving standard therapy. The incidence of CVD events for the primary outcome was similar between groups, occurring at annual rates of 1.87% for intensive therapy and 2.09% for standard therapy. The hazard ratio (HR) with intensive therapy was 0.88 ($P = 0.20$). Death from any cause was reported at annual rates of 1.28% with intensive therapy and 1.19% with standard therapy (HR = 1.07; $P = 0.55$). Although annual rates of stroke were lower with intensive therapy (0.32%) than with standard therapy (0.53%) (HR = 0.59; $P = 0.01$), Dr. Cushman pointed out that the number needed to treat to prevent one stroke with intensive treatment over five years was 89.

Serious adverse events (AEs) attributed to antihypertensive treatment occurred significantly more often with intensive therapy (in 3.3% of patients) than with standard therapy (in 1.3%) ($P < 0.001$). Hypotension was reported in 17 intensive-therapy patients and in one standard-therapy patient. Dr. Cushman concluded:

> The ACCORD BP trial results provide no conclusive evidence that a strategy targeting normal systolic blood pressure, compared with a standard systolic blood pressure goal, reduces a composite of major cardiovascular events in high-risk patients with type-2 diabetes in the setting of good glycemic control.

Regarding stroke, Dr. Cushman noted in an interview: "We have not yet analyzed stroke subgroups, but it may be that the elderly or African-Americans or some other group may show enough benefit to be considered clinically important."

A second major ACCORD investigation, the ACCORD Lipid Trial, included 2,765 patients who received fenofibrate (e.g., TriCor, Abbott) at a dose of 54 to 160 mg/day and 2,753 who received placebo. All participants received open-label simvastatin (Zocor, Merck) at doses of 20 to 40 mg/day.

After a mean follow-up of 4.7 years, major CVD events were reported at annual rates of 2.41% (310 events) for placebo and 2.24% for fenofibrate (HR = 0.92; $P = 0.32$). There were no significant differences in any secondary outcomes between the two study groups.

Annual death rates were 1.5% with fenofibrate and 1.6% with placebo (HR, 0.91; $P = 0.33$). Prespecified subgroup analyses suggested a treatment effect that favored men, with possible harm for women ($P = 0.01$ for interaction). There was also a possible interaction according to lipid subgroup, with a possible benefit for patients with both a high baseline triglyceride level and a low baseline level of high-density lipoprotein-cholesterol (HDL-C) ($P = 0.057$ for interaction).

AEs were similar between groups, with no differences in severe muscle aches or pains, myopathy, myositis, or rhabdomyolysis.

Dr. Ginsburg concluded: "ACCORD Lipid does not support use of the combination of fenofibrate and simvastatin compared to simvastatin alone to reduce cardiovascular events."

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In the ACC press conference, he further noted that in his own practice, he sees patients with the worst lipid disorders and the highest risk.

"In those people whose triglycerides are over 200 mg/dL and whose HDL-C is in the mid-30s, I add a fenofibrate to a statin," he said.

Betrixaban versus Warfarin (Coumadin) For Atrial Fibrillation (EXPLORE-Xa)

- Michael D. Ezekowitz, MD, PhD, Lankenau Institute for Medical Research, Wynnewood, Pa., and Professor of Medicine, Jefferson Medical College, Philadelphia, Pa.
- Ralph Brindis, MD, President, American College of Cardiology

EXPLORE-Xa, a randomized, parallel-group, dose-finding, multicenter, multinational study, compared the safety and tolerability of three doses of betrixaban (PRT-054021, Portola/Merck/Millennium) at 40, 60, and 80 mg once daily with dose-adjusted warfarin (Coumadin, Bristol-Myers Squibb). The study involved 506 patients (median age, 74 years) with nonvalvular atrial fibrillation or atrial flutter and at least one additional risk factor for stroke, such as age, diabetes, or hypertension.

The primary endpoint was the time to major and clinically relevant non-major bleeding. Dr. Ezekowitz, the lead investigator, said that patients using betrixaban did not require monitoring or dose adjustments for renal impairment. Because the drug is metabolized by the cytochrome P450 system, major drug interactions are not expected.

"In addition, an antidote for betrixaban is being co-developed, which makes it unique among these anti-Xa agents," Dr. Ezekowitz said.

Patients received either warfarin or one of the three betrixaban doses. After a median follow-up of 147 days, there were fewer reports of major bleeding and clinically relevant non-major bleeding with betrixaban 40 mg daily (in one patient) compared with warfarin (in seven patients) (Table 1). At doses of betrixaban 60 and 80 mg daily, bleeding rates were similar to those in the warfarin group. One patient in each treatment group died.

Levels of d-dimer, a measurement of the activity of the anticoagulation system, consistently decreased from baseline as the betrixaban dose increased from 40 to 80 mg. D-dimer levels rise in direct proportion to thrombotic activity. One patient withdrew from betrixaban treatment because of gastrointestinal side effects.

Speaking at an ACC press conference, Dr. Ezekowitz added, "It's my view, based on the evidence, that all of the doses of the drug are active."

Dr. Ralph Brindis, MD, ACC President and moderator, said, "What appeals to me about this drug is that it's oral and once daily, it requires no dose adjustments for renal impairment, and an antidote for someone who would need quick reversal is in development."

Table 1 Betrixaban and Warfarin Effects in the EXPLORE-Xa Trial

	Betrixaban			
	40 mg	*60 mg*	*80 mg*	Warfarin
*Bleeding**	1	5	5	7
Stroke	0	1	1	1
Death	1	0	0	1

* Includes major and clinically relevant non-major bleeding.

Invasive Cardiac Catheterization With Low-Osmolar Contrast Agents (Iopamidol, Iohexol, and Ioversol)

- James K. Min, MD, Weill Cornell Medical College, New York, N.Y.

When three low-osmolar contrast iodinated media agents were compared in patients undergoing cardiac catheterization, the risk of in-hospital mortality was similar for all three. The agents used in this multicenter study of almost 208,000 patients were iopamidol (Isovue, Bracco), iohexol (Omnipaque, Sterling-Winthrop/ GE Healthcare), and ioversol (Optiray, Mallinckrodt).

Although the risk of hemodialysis was lower for iohexol, Dr. Min, the study author, stopped short of making recommendations based on the preliminary finding. He said, "These agents show low rates of need for inpatient hemodialysis and inpatient mortality."

Large numbers of patients are exposed to iodinated contrast media during cardiac catheterization procedures. Deciding which medication to use is often based on reported rates of contrast-induced acute kidney injury (CI–AKI) for the various agents. Data on CI–AKI, however, have focused primarily on comparing iso-osmolar media with low-osmolar media. To date, head-to-head trials comparing CI–AKI rates among the various contrast media are lacking.

To determine the relative rates of in-hospital mortality and in-hospital hemodialysis, Dr. Min retrospectively reviewed inpatient medical data from the Premier Perspective Comparative Database; 36,089 patients received iopamidol; 36,118 received iohexol; and 135,619 received ioversol. Among factors that the researchers controlled for in the multivariate logistic regression analyses were age, sex, race, type of admission, severity of illness, cardiac risk, and major comorbidities.

In-hospital hemodialysis rates were low after exposure to any of the three agents (0.8% for iohexol, 1% for iopamidol, and 1% for ioversol). Adjusted odds ratios (ORs), however, showed an increased risk for ioversol compared with iohexol (1.28) but not for iopamidol when compared with iohexol (OR = 1.05). In-hospital mortality risk was similar after use with iopamidol (OR = 0.94) and with ioversol (OR = 0.94), compared with iohexol as a reference.

Dr. Min commented, "Hemodialysis risk did not differ between iopamidol and iohexol but was higher for ioversol."

In an interview, he cautioned that even though the trial was large and was based on a real-world use of contrast agents, differences might not hold up after an analysis matching the cohorts is conducted; therefore, he could not yet make any recommendations.

He concluded, "This [finding] is hypothesis-generating and speaks to the need for a randomized trial."

Early Clopidogrel and Eptifibatide (Integrilin) In Acute Coronary Syndromes: Early ACS Trial

• Tracy Wang, MD, and Kristin Newby, MD, both from Duke Clinical Research Institute, Durham, N.C.

Patients in the EARLY ACS (*A*cute *C*oronary *S*yndromes) study were randomly assigned to receive eptifibatide (Integrilin, Schering/Millennium)—a glycoprotein IIb/IIIa inhibitor (GPI)—or placebo 12 or more hours before undergoing angiography. Last year's presentation of EARLY ACS results showed that the benefits of routine early eptifibatide over delayed provisional eptifibatide were nonsignificant for the primary endpoint of combined death, reinfarction, and recurrent ischemia requiring urgent revascularization or thrombotic bailout (10% vs. 9.3%, respectively; $P = 0.23$). Similarly, the routine early use of eptifibatide was not significantly better than delayed provisional use (12.4% vs. 11.2%, respectively) for the secondary endpoint of 30-day death or MI ($P = 0.079$).

However, a new analysis that took clopidogrel use into account led EARLY ACS senior investigator Dr. Newby to state in an interview that for patients with a positive marker for refractory chest pain, the combination may offer benefits.

"Particularly in patients where you're pretty certain they will be going to the [catheter] lab, the combination of clopidogrel with eptifibatide looks good, with a modest increase in bleeding."

Dr. Wang pointed out that clopidogrel use and timing in EARLY ACS were determined by the treating physician. That raised the question of whether clopidogrel administration preceding angiography influenced the benefit or safety of routine early eptifibatide. For the primary endpoint, the adjusted difference was marginal between those receiving and those not receiving clopidogrel.

For the endpoint of death or MI at 30 days, however, even though the interaction was not statistically significant ($P = 0.23$), there was a 15% reduction in patients receiving routine early eptifibatide (OR = 0.85 [0.80–1.30]). Again, major bleeding with pre-treatment eptifibatide was amplified in the presence of clopidogrel, as was the need for transfusions (for eptifibatide alone, OR =1.23; with clopidogrel, OR = 1.36).

Dr. Wang concluded that giving eptifibatide before a procedure (i.e., percutaneous coronary intervention) may be associated with a reduced 30-day death or MI in patients with non–ST-segment (NSTE) ACS who received pretreatment with clopidogrel. The use of eptifibatide is also associated with an increased risk of bleeding.

Diazoxide Choline Controlled Release in Hypertriglyceridemia: Lipid and Other Metabolic Effects

• Harold Bays, MD, Medical Director and President, Louisville Metabolic and Atherosclerosis Research Center, Louisville, Ky.

A new formulation of diazoxide (Essentialis, Inc.), an approved drug that has been used for hypertensive emergencies and hyperinsulinemia for nearly half a century, demonstrated significant ability to improve moderately severe hypertriglyceridemia.

A once-daily diazoxide choline controlled-release (DCCR) tablet was evaluated in a double-blind, randomized study among 90 subjects with baseline triglyceride levels between 200 and 650 mg/dL. In dosages equivalent to 200, 300, or 400 mg/day, DCCR was compared with placebo for eight weeks. Patients with glucose concentrations of 126 mg/dL or higher or glycosylated hemoglobin (HbA_{1c}) levels above 6.5% were excluded from the study. Patients receiving steady doses of statins at baseline (N = 19) continued with the statins throughout the study. The primary endpoint was the median percentage of change in triglyceride levels.

Compared with placebo, DCCR 200 mg reduced median triglyceride levels by 21.4% ($P = 0.076$); the 300-mg dose, by 30.1% ($P = 0.0003$); and DCCR 400 mg, by 32.1% ($P < 0.0001$). In subjects with baseline triglycerides of 400 mg/dL or more (n = 14), DCCR reduced median triglycerides by 42.5%. DCCR showed nonsignificant but consistent reductions in non–HDL-C and total cholesterol values, with a modest rise in HDL-C levels.

Mean low-density lipoprotein-cholesterol (LDL-C) levels did not increase. Among patients with baseline LDL-C levels of 160 mg/dL or higher (n = 23), DCCR reduced LDL-C values by 9.2%. Lipid effects were generally similar with or without statins. DCCR raised median fasting glucose levels by 12.4% (12 mg/dL) and HbA_{1c} by 0.1%. Although patients' weight did not change, DCCR appeared to reduce waist circumference, BP, liver enzymes, and homeostasis model assessment of insulin resistance.

AEs, typically mild to moderate, resolved at the end of treatment. Side effects were noted in 45% of patients receiving placebo, in 59% receiving DCCR 200 mg, in 74% using DCCR 300 mg, and in 78% receiving DCCR 400 mg.

Dr. Bays said:

> We asked, 'Is there something more to this drug?' and we found that, consistent with previous reports of favorable diazoxide effects on cardiovascular risk factors, this study suggests that DCCR significantly reduces TG without raising LDL-C.

He added that he would like to see a larger clinical trial confirming the efficacy and safety findings.

Rosuvastatin (Crestor) plus Ezetimibe (Zetia) Versus Simvastatin plus Ezetimibe (Vytorin): GRAVITY Results

• Christie M. Ballantyne, MD, Center for Prevention of Cardiovascular Disease, Baylor College of Medicine, Houston, Tex.

Improvements in lipid levels were greater and more patients reached LDL-C goals with ezetimibe 10 mg (Zetia, Merck/Schering-Plough) plus rosuvastatin 20 mg (Crestor, AstraZeneca) compared with ezetimibe 10 mg/simvastatin 40 or 80 mg (Vytorin). Dr. Ballantyne, lead investigator of the GRAVITY study (*G*auging the lipid effects of *R*osuv*A*statin plus ezetimibe *V*ersus s*I*mvastatin plus ezetimibe *T*herap*Y*), noted earlier studies in which rosuvastatin, compared with other statins,

enabled more patients to reach lipid goals.

"If you look at a patient who's hard to get to target, 'how do you do this?' is the bottom line issue for doctors," Dr. Ballantyne said.

Reaching the more stringent lipid targets in guidelines for patients with high-risk CVD, however, may necessitate combination therapy. Combining a statin with ezetimibe, which inhibits cholesterol absorption, has been shown to facilitate more substantial reductions in LDL-C levels.

GRAVITY included 814 patients (mean age, 62 years, 56% male) at high risk for coronary heart disease (CHD). This trial was conducted to test the efficacy and safety of rosuvastatin 10 and 20 mg plus ezetimibe 10 mg against simvastatin 40 and 80 mg in a fixed-dose combination with ezetimibe 10 mg. All participants had hypercholesterolemia and a history of CHD or its risk equivalent, fasting LDL-C levels between 130 and 220 mg/dL, and fasting triglyceride levels below 400 mg/dL. The primary endpoint was the mean percentage of change in LDL-C levels from baseline to week 12.

Subjects receiving rosuvastatin 20 mg/ezetimibe 10 mg achieved significantly greater reductions in LDL-C (–59.7%) ($P < 0.001$) and greater improvements in most other lipid parameters, compared with those receiving simvastatin 40 mg/ezetimibe 10 mg (LDL-C, –55.2%) or simvastatin 80 mg/ezetimibe 10 mg (LDL-C, –57.4%).

Rosuvastatin 10 mg/ezetimibe 10 mg resulted in significantly greater reductions, when compared with simvastatin 40 mg/ ezetimibe 10 mg, in the following parameters:

- LDL-C ($P < 0.05$).
- total cholesterol (–43.0% vs. –39.6%)
- triglycerides (–28.9% vs. –23.0%)
- non–HDL-C (–54.7% vs. –49.9%)
- apolipoprotein B (–46.1% vs. –42.0%)

Furthermore, at the end of the study, significantly more patients achieved LDL-C goals of below 100 mg/dL ($P < 0.05$) and below 70 mg/dL ($P < 0.001$) with rosuvastatin 20 mg/ezetimibe 10 mg (95.6%/77% for below 100 mg/dL and below 70 mg/dL) than with simvastatin 40 mg/ezetimibe 10 mg (87.4%/55.3%, respectively) or simvastatin 80 mg/ezetimibe 10 mg (88.6%/67.7%, respectively).

Patients receiving rosuvastatin 10 mg plus ezetimibe 10 mg were more likely to achieve the LDL-C goal of below 100 mg/dL (93.3% vs. 55.3%, respectively; $P < 0.05$) than those receiving simvastatin 40 mg/ezetimibe 10 mg/dL.

About 2% of patients receiving combination therapy experienced myalgia, the most commonly reported AE.

"This a very good option for people who are hard to get to targets, with good effects on all the lipids," Dr. Ballantyne concluded.

Unlike the rosuvastatin/ezetimibe combination, the ezetimibe/simvastatin combinations are available in a single tablet (Vytorin). ■