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REFINEMENTS AND INNOVATIONS ENHANCE SAFETY, EFFECTIVENESS OF CARDIOVASCULAR THERAPIES

ATLANTA, GA (March 12, 2006) — Research presented today at the American College of Cardiology's 55th Annual Scientific Session offers new insight into the most effective therapies for acute coronary syndromes, atrial fibrillation and heart failure, and sheds light on simple ways to prevent the harmful effects of inflammation in patients who have cardiac surgery. ACC.06 is the premier cardiovascular medical meeting, bringing together more than 30,000 cardiologists to further breakthroughs in cardiovascular medicine.

"Together these studies cover an enormous therapeutic range, but each has the potential to change the day-to-day management of patients with cardiovascular disease," said Matthew R. Wolff, M.D., F.A.C.C., University of Wisconsin.

Prospective, Randomized Comparison of Heparin Plus IIb/IIIa Inhibition and Bivalirudin With or Without IIb/IIIa Inhibition in Patients With Acute Coronary Syndromes: The ACUITY Trial

When the final results of the ACUITY trial are unveiled, they are expected to show whether a synthetic version of an anti-clotting compound can improve on existing medical therapy for patients with acute coronary syndromes (ACS). The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial compared the direct thrombin inhibitor bivalirudin, with or without a glycoprotein IIb/IIIa inhibitor (GPI, which prevents platelets from clumping together to form a blood clot), to the indirect thrombin inhibitor heparin, plus a GPI. The study is part of ongoing research aimed at improving clinical outcomes in ACS therapy while limiting the risk of serious bleeding.

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Acute coronary syndrome is an umbrella diagnosis that encompasses both unstable angina and a type of heart attack known as non-ST elevation myocardial infarction (NSTEMI). Today, drug therapy typically consists of aspirin, clopidogrel, heparin, and a GPI. Each of these medications interferes at a specific point in the blood clotting process in the coronary artery. Patients also typically have angiography within a few days to determine whether further, invasive treatment with angioplasty or bypass graft surgery is needed to restore full blood flow to the heart.

The ACUITY trial was led by Gregg W. Stone, M.D., F.A.C.C., Columbia University Medical Center and the Cardiovascular Research Foundation, New York City. He and his colleagues from 448 medical centers in 17 countries randomly assigned 13,820 patients with moderate-to-high-risk ACS to one of three treatments: heparin (conventional, unfractionated or a low-molecular-weight alternative, enoxaparin) plus GPI, bivalirudin plus GPI, or bivalirudin alone. One month after treatment, investigators measured the net clinical benefit, which balances the risks of ACS itself—death, heart attack, or an unplanned procedure to open the blocked coronary artery—against the major bleeding risks of anti-clotting therapy.

Dr. Stone will present the results of the ACUITY trial in a Late Breaking Clinical Trials session on Sunday, March 12, at 11:36 a.m.

[Pexelizumab, a Terminal Complement Inhibitor in Coronary Artery Bypass Graft Surgery: Results From the Pexelizumab for the Reduction of Infarction and Mortality in CABG II Trial \(PRIMOCABG II\)](#)

Use of a cardiopulmonary bypass (CPB) machine to circulate blood outside the body enables surgeons to stop the heart during coronary artery bypass grafting (CABG), but it also provokes an inflammatory response that increases the risk of heart attack and death. In addition, cardiac surgery subjects the heart itself to inflammatory injury when the blood supply is re-established. The international PRIMOCABG II trial will shed light on whether treatment with pexelizumab, a medication that inhibits one pathway in that inflammatory process, can improve outcomes in high-risk patients.

"The inflammatory response is natural and sometimes protective, but it can be harmful," said Peter K. Smith, M.D., chief of thoracic and cardiovascular surgery at Duke University Medical Center, Durham, NC.

"We are hoping that by inhibiting inflammation, we can make heart surgery and cardiopulmonary bypass safer."

One of the key participants in the inflammatory response is a family of proteins known as complement, which become activated in a cascade that results in an enzyme reaction and the release of the C5 portion of the protein.

One particularly harmful portion of the complement protein is C5a, which causes activation of white blood cells, vasoconstriction and ultimately, cell death. Pexelizumab binds to the C5 complement protein, inhibiting its cleavage that results in C5a and other complement fractions. A smaller previous study, PRIMOCABG I, showed that in moderate-risk patients, pexelizumab significantly reduced the risk of heart attack, but did not significantly reduce mortality.

In the PRIMOCABG II trial, Dr. Smith and colleagues from North America and Europe randomly assigned treatment with pexelizumab or placebo to more than 4,000 CABG patients with at least two risk factors, including diabetes, previous CABG, a recent heart attack, an urgent need for CABG surgery, and female gender. In this high-risk group, investigators evaluated the influence of pexelizumab treatment on the combined risk of death or heart attack within 30 days of surgery, as well as on the risk of heart failure during hospitalization and within 30 days, and on the risk of death within 90 days.

Dr. Smith will present the PRIMOCABG II trial at a Late Breaking Clinical Trial session on Monday, March 13, at 3 p.m. ET.

A Controlled Randomized Trial of Circumferential Pulmonary Vein Ablation versus Antiarrhythmic Drug Therapy for Curing Paroxysmal Atrial Fibrillation: The Ablation for Paroxysmal Atrial Fibrillation (APAF) Trial

A catheter procedure that uses radiofrequency energy to burn a blockade of scar tissue around the source of abnormal electrical impulses has proven superior to anti-arrhythmic drug therapy for the treatment of an intermittent form of atrial fibrillation, or heart flutter, the most common type of cardiac arrhythmia.

"The APAF trial is the first to compare medicinal therapy to catheter ablation for paroxysmal atrial fibrillation using a formal and appropriately powered randomized controlled

study," said Carlo Pappone, M.D., Ph.D., chief of the division of cardiac pacing and electrophysiology, San Raffaele University Hospital, Milan, Italy. "This study convincingly demonstrates superior efficacy with catheter ablation, even though we used intense, daily transtelephonic monitoring during follow-up."

The APAF study enrolled 198 patients who were experiencing, on average, three episodes of atrial fibrillation per month and had been unable to control the arrhythmia with medication. Researchers randomly assigned study participants to drug treatment with amiodarone, flecainide, or sotalol, or to a catheter procedure known as circumferential pulmonary vein ablation (CPVA). This technique uses a special catheter passed into the left side of the heart that can deliver radiofrequency energy, which is used to burn circular patterns around each of the four pulmonary veins where the abnormal electrical activity often originates. The resulting scar tissue prevents electrical impulses from escaping into the left atrium. Researchers also created three linear lesions, two at the back wall of the left atrium and one at near mitral valve that separates the left atrium from the left ventricle.

Early results from the first 99 patients followed-up for at least nine months showed that 84 percent of those who had catheter ablation were no longer experiencing paroxysmal atrial fibrillation, as compared to only 24 percent of patients treated with anti-arrhythmic medication.

Dr. Pappone will report clinical findings on 135 patients with a minimum follow-up of nine months at a Late Breaking Clinical Trial session on Sunday, March 12, at 10:30 a.m.

A Randomized Trial of Atorvastatin for Reduction of Post-operative Atrial Fibrillation in Patients Undergoing Cardiac Surgery. Results From the ARMYDA-3 (Atorvastatin for Reduction of Myocardial Dysrhythmias After Cardiac Surgery) Study

Atrial fibrillation, or heart flutter, is an arrhythmia that develops in 40 to 50 percent of patients who have cardiac surgery, and increases the risk of complications and lengthens hospitalization. New evidence from a randomized controlled study shows that pretreatment with atorvastatin one week before heart surgery significantly reduces the risk of postoperative atrial fibrillation, perhaps by limiting the body's inflammatory response to the surgery and to cardiopulmonary bypass.

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"Inflammatory mechanisms may be involved in the development of atrial fibrillation after cardiac surgery," said Germano Di Sciascio, M.D., a professor and chairman of cardiology and director of the Department of Cardiovascular Sciences, Campus Biomedico, University of Rome, Italy. "Our study suggests that statins can help prevent such arrhythmic episodes."

The ARMYDA-3 study enrolled 200 patients who were scheduled for coronary artery bypass grafting, or repair or replacement of a heart valve. Patients were randomly assigned to one week's pretreatment with 40 mg of atorvastatin, or to placebo. Atorvastatin is most often prescribed for lowering blood cholesterol levels, but has also been shown to prevent inflammation.

Investigators found that atorvastatin reduced the rate of atrial fibrillation from 57 percent in the placebo group to 35 percent in the atorvastatin group, a highly significant difference. The benefits of atorvastatin were apparent even when taking into account patient characteristics that might have inflated the risk of atrial fibrillation, including advanced age and high blood pressure. Investigators also found that blood levels of C-reactive protein, a marker of inflammation, were significantly higher in patients who developed atrial fibrillation compared to those who did not.

"This study could influence preoperative pharmacological management of patients undergoing elective cardiac surgery," Dr. Di Sciascio said. "The low cost and low risk of statin therapy may support its routine, early use in these patients."

Dr. Di Sciascio will present the ARMYDA-3 study at a Late Breaking Clinical Trials session on Sunday, March 12, at 2 p.m.

Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD)

There are approximately one million hospital admissions for heart failure each year in the United States, 90 percent as a consequence of fluid overload in the lungs and other body tissues. Aggressive treatment with diuretics is a mainstay of therapy. Now, a new study suggests that a more effective approach is to withdraw the patient's blood through tubing in a small vein, circulate it through a filtering system that removes excess fluid, then return the blood through a tube in another vein.

"Diuretics have never before been challenged in a controlled clinical trial of acute decompensated heart failure," said Maria Rosa Costanzo, M.D., medical director of the Edward Hospital Center for Heart Failure, Naperville, IL, a suburb of Chicago.

"We found that ultrafiltration was more effective in removing fluid and that patients were less likely to be readmitted to the hospital within three months."

Dr. Costanzo and her colleagues randomly assigned 200 patients hospitalized for uncontrolled heart failure to aggressive treatment with intravenous diuretics or to ultrafiltration. They evaluated patients during treatment, upon discharge from the hospital, and at 10, 30, and 90 days. Patients lost significantly more water weight with ultrafiltration, required fewer medications to maintain a stable blood pressure, were less likely to be hospitalized again within 90 days, and were hospitalized for shorter periods of time. Dr. Costanzo speculated that ultrafiltration may be associated with better clinical outcomes because, unlike diuretics, it does not activate some of the harmful hormonal changes that worsen heart failure.

Dr. Costanzo will present the UNLOAD trial at a Late Breaking Clinical Trial session on Tuesday, March 14, at 9:15 a.m.

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The American College of Cardiology (www.acc.org) represents the majority of board certified cardiovascular physicians in the United States. Its mission is to advocate for quality cardiovascular care through education, research, promotion, development and application of standards and guidelines- and to influence health care policy. ACC.06 and the ACC inaugural i2 Summit, the first-ever meeting for interventional cardiologists, will bring together more than 30,000 cardiologists and cardiovascular specialists to share the newest discoveries in treatment and prevention, while helping the ACC achieve its mission to address and improve issues in cardiovascular medicine.