Best of the AHA Scientific Sessions 2005

Highlights from the American Heart Association Scientific Sessions, November 13-16, 2005, Dallas, TX

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Key words: ACTIVATE • ASSENT-4 PCI • EASY • Erythropoietin • Fenofibrate • JELIS • Levosimendan • Lipids • Obesity • PREVENT IV • PROactive • RECAST • REPAIR-AMI • REVIVAL • REVIVE-2 • Stem cells • SURVIVE-W

The 2005 American Heart Association (AHA) Scientific Sessions brought together experts from across the globe to discuss the latest findings and advances in cardiovascular treatment and research. Here our board members report on some of the most important findings from Dallas.

Levosimendan in Acute Decompensated Heart Failure

REVIVE-2 and SURVIVE-W

Acute decompensated heart failure (HF) remains a clinical challenge. None of the current standard-of-care therapies have been demonstrated to reduce mortality or the risk of rehospitalization in randomized clinical trials. Indeed, clinical trials and observational studies of the use of inotropic agents such as dobutamine and milrinone, which increase intracellular calcium, have demonstrated increased mortality risk in patients with decompensated HF without cardiogenic shock.

Levosimendan is an intravenous myofilament calcium-sensitizing agent that increases inotropic response without changing intracellular calcium levels.[1] It is also a potassium channel agonist, promoting peripheral vasodilation.[1] The Levosimendan Infusion versus Dobutamine (LIDO) study suggested that the administration of levosimendan in acute decompensated HF patients resulted in a lower mortality risk than did the use of dobutamine.[2]

The Randomized Evaluations of Levosimendan (REVIVE-2) was a randomized, double-blind, placebo-controlled trial evaluating clinical course during the hospitalization of patients with acute decompensated HF who were randomized to either levosimendan or placebo, both added to standard care. The trial included 600 patients with acute decompensated HF, left ventricular ejection fraction (LVEF) of 35% or less, and resting dyspnea despite intravenous diuretic therapy. Patients were randomized to a 12 μg/kg bolus dose followed by a 24-hour 0.1 to 0.2 μg/kg/min infusion of levosimendan or to similar administration of placebo. For patients in both groups, physicians continuously

adjusted conventional background HF therapy as needed. The trial was conducted at 103 sites in the United States, Australia, and Israel. The primary endpoint consisted of changes in symptoms, death, or worsening HF over 5 days. Worsening HF was defined as death from any cause; persisting or worsened HF despite therapy with vasodilators, diuretics, or inotropes; or moderately or markedly worse patient global assessment at 6 and 24 hours and at 5 days.

The results were presented by Dr. Milton Packer of the University of Texas Southwestern Medical Center in Dallas, TX, at the AHA Late Breaking Clinical Trials Plenary Session. Mean patient age was 63, 72% were male, and average LVEF measured at 25%. At day 5, 33% more patients in the levosimendan group had improved and 30% fewer had worsened compared with patients in the control group ($P = .015$ for both differences). About the same number of patients in both groups showed an unchanged clinical status. Worsening acute HF requiring rescue intravenous therapy developed in 15% of patients in the levosimendan group and 26% of patients in the control group. Patient global assessment score was improved in the levosimendan group at 24 hours ($P = .026$). Average duration of hospitalization was shorter in the levosimendan group (7.0 days vs 8.9 days for controls, $P = .006$).

Table 1
Adverse Events in REVIVE-2

Selected adverse events	Levosimendan (%)	Placebo (%)
Hypotension	49.2	35.5
Ventricular tachycardia	24.1	16.9
Cardiac failure	22.4	26.6
Atrial fibrillation	8.4	2.0
Ventricular extrasystoles	7.4	2.0

Levosimendan appeared to be associated with an increased risk of serious adverse events, such as symptomatic hypotension and atrial/ventricular arrhythmias. See Table 1. There was also a potential signal of an increased mortality risk. At 1 week, there were 15 deaths in levosimendan patients versus only 6 deaths in placebo patients. The secondary endpoint of 90-day all-cause mortality was 15.1% in the levosimendan group and 11.6% among controls. In addition, there was a reduction in plasma levels of brain-type natriuretic protein (BNP), a secondary endpoint, seen at day 1 and sustained for 5 days but not at 30 days in the levosimendan group.

Worsening acute HF requiring rescue intravenous therapy developed in 15% of patients in the levosimendan group and 26% of patients in the control group.

A second trial with levosimendan was also presented at the Scientific Sessions. The Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE-W) enrolled 1327 patients with acute decompensated HF and an LVEF of 30% or less who were judged in need of inotropic support after failing to respond to vasodilators or diuretics. They were randomized in a double-blind manner to receive levosimendan as a 12 μg/kg bolus followed by a 24-hour 0.1 to 0.2 μg/kg/min infusion or dobutamine at greater than or equal to 5 μg/kg/min for at least 2 hours, on top of standard HF medications. The primary endpoint was all-cause mortality at 180 days. The trial was conducted in 8 European countries and Israel.

The study was presented by Dr. Alexandre Mebazaa of the Lariboisiere Hospital, Paris, France. Baseline characteristics were similar in both groups, with 88% of patients having a history of HF, 86% in New York Heart Association Class IV, and a mean baseline LVEF of 24%. Median BNP levels were 1178 pg/mL and 1231 pg/mL, in the levosimendan and dobutamine groups, respectively. Levosimendan was infused for a mean of 23 hours and dobutamine for 39 hours.

There was no difference in the primary endpoint of all-cause mortality at 180 days (26.1% in levosimendan group and 27.9% in dobutamine group; hazard ratio [HR] 0.92, $P = 0.401$). Likewise, there was no difference at 5 days (4.4% vs 6.0%; HR 0.72, P = NS) or 31 days (11.9% vs 13.7%; HR 0.85, P = NS). See Table 2 for other 31- and 180-day statistics. Among the adverse events, atrial fibrillation occurred more often in the levosimendan group (9% vs 6%), whereas cardiac failure occurred less often in the levosimen-

Table 2
All-Cause Mortality in the SURVIVE-W Trial

Interval	Analysis	Levosimendan, n = 664 (%)	Dobutamine, n = 663 (%)	HR (95% CI)
180 d	Primary end point	26	28	0.91 (0.74-1.13)
31 d	Secondary end point	12	14	0.85 (0.63-1.15)

dan group (12% vs 17%). There was no difference in hypotension (16% vs 14%) or ventricular tachycardia (8% vs 7%). Rates of adverse renal events or of changes in serum creatinine levels did not differ between groups. There were no differences in symptoms of dyspnea or global score between the two treatments.

Levels of BNP plunged by nearly 50% soon after commencing the levosimendan infusion and stayed low for at least 5 days, whereas the BNP drop in the dobutamine group was less pronounced or consistent ($P < .0001$ for the difference between treatment groups).

These 2 trials, taken together, suggest that levosimendan improves symptoms in acute decompensated HF, with symptom relief and a mortality rate comparable to dobutamine, but also with significantly more serious adverse events and potentially increased mortality compared to placebo. It appears levosimendan improves symptoms in patients with acute decompensated HF, but so do a number of other therapies. There were signals of adverse effects from the drug, especially for short-term mortality and ventricular arrhythmias, compared to placebo. If there is assurance that there is no excess mortality compared with placebo, then improvement of symptoms with an acute HF medication is very worthwhile. Further studies with this agent will be necessary to better evaluate its safety, as well as strategies to reduce the risk of serious adverse events.

[Gregg C. Fonarow, MD, FACC]

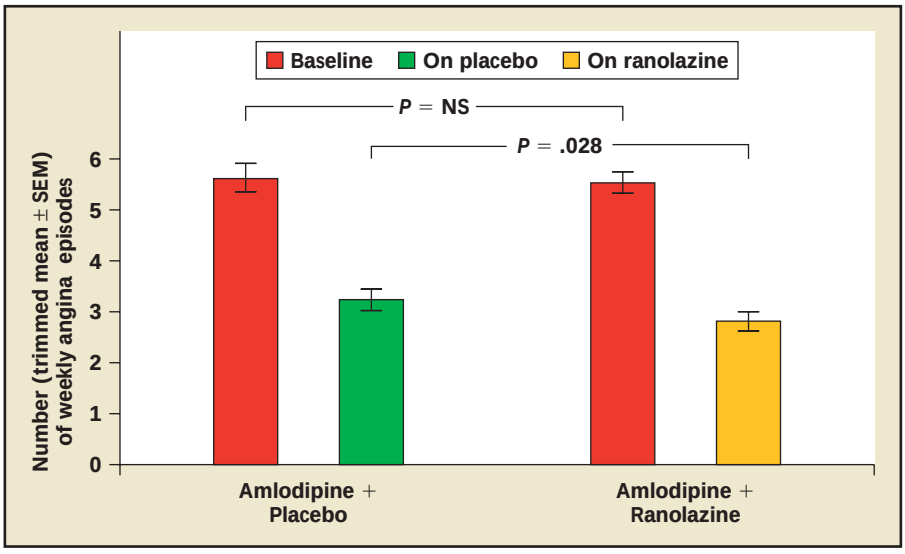
Dr. Fonarow discloses that he has received speaker's honoraria as well as research and consulting grants from Scios, Inc.

ERICA Study

The Evaluation of Ranolazine in Chronic Angina (ERICA) study[3] was a placebo-controlled, double-blind, randomized trial to evaluate the effectiveness of ranolazine (Ranexa,® CV Therapeutics, Palo Alto, CA) in 565 patients with chronic angina. Ranolazine is a unique, anti-anginal agent that does not rely on a blood pressure or heart rate effect for its therapeutic efficacy. Patients were eligible if they had at least 3 episodes of angina per week, despite a maximal dose regimen of amlodipine (10 mg per day). The results of this trial were presented by Peter H. Stone, MD, of Brigham and Women's Hospital, Boston, MA. The primary endpoint of the trial was angina frequency with secondary endpoints including consumption of nitrates as a measure of anti-anginal effectiveness and the safety and tolerability of the 1000 mg, twice daily ranolazine dosage. Results of the study showed a significant reduction in mean angina episodes per week compared to placebo, as well as a reduction in the use of nitroglycerin per week (Figure 1).

The mechanism of action of ranolazine relates to its ability to reduce the late inward sodium current that, through an effect on calcium current, prevents an increase in left ventricular diastolic tension. In practice, we are often limited in the use of contemporary anti-anginal therapies by their dependence on blood pressure and heart rate effects. Ranolazine, by not affecting these

Figure 1. *Results from the Evaluation of Ranolazine in Chronic Angina (ERICA) study, showing average rates of angina over the 6-week study period.*



parameters, should be an effective add-on to contemporary therapy, to prevent the occurrence of disabling anginal symptoms.

PROactive Trial

Diabetic and Previous-MI Subgroup Analyses

The Proactive Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) was designed to determine the effects of pioglitazone on mortality and morbidity associated with cardiovascular disease progression in high-risk Type 2 diabetes patients whose treatment was optimized during the study, according to International Diabetes Federation (Europe) guidelines. Optimization included the appropriate use of antihypertensives, anti-platelet drugs, lipid-modifying medicines, and glucose-lowering agents, including insulin. The original results of PROactive were published in the *Lancet*[4] and focused on 2 key endpoints: a primary combination endpoint of 7 different macrovascular events of varying clinical importance and a principal secondary combination endpoint of the most serious events (death, stroke, and heart attack).

Patients received aggressive background medical therapy with 55% on β-blockers, 70% on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, 85% on antiplatelet medication, and 53% on statins and/or fibrates. The primary endpoint was reduced by 10% but was not statistically significant ($P = .095$). The principal secondary combination endpoint showed that pioglitazone (Actos,® Eli Lilly and Co., Indianapolis, IN) significantly reduced the risk of death, stroke, or myocardial infarction by 16% ($P = .027$).

A subgroup analysis of patients with type 2 diabetes and myocardial infarction was presented at AHA by Erland Erdman, MD, of the University of Cologne, Cologne, Germany. Of the total PROactive cohort (N = 2245), 1230 in the pioglitazone and 1215 in the placebo group had a previous MI within 6 months of randomization. At 3 years in this subgroup, there was a significant reduction of 28% in fatal and nonfatal MI in the pioglitazone group compared with placebo, with only trends toward reductions of the other prespecified endpoints (Table 3).

Table 3
Endpoint Analysis in PROactive: High Cardiovascular Risk Subgroup

Endpoint	Pioglitazone (%)	Placebo (%)	HR	*P* value
Fatal or nonfatal MI*	5.3	7.2	0.72	.045
CV death or nonfatal MI*	9.3	10.9	0.84	.164
CV death, nonfatal MI,* or stroke	11.1	13.1	0.84	.123

*Excluding silent MI. CV, cardiovascular; MI, myocardial infarction.

Incidence of ACS was also significantly reduced (by 37%) in the pioglitazone group, and a composite cardiac endpoint of cardiac death, nonfatal MI, coronary revascularization, or ACS was significantly reduced by 19% in the pioglitazone group compared with placebo. Although more patients on pioglitazone were hospitalized for heart failure, the PROactive investigators believe that some of these patients were misdiagnosed, probably due to observed edema in patients on pioglitazone, mistakenly seen as a sign of decompensated heart failure. There has been no evidence that the thiazolidinediones (TZDs) induce ventricular dysfunction.

This substudy shows the cardiovascular benefit of this agonist of the peroxisome proliferator-activated receptor (PPAR) -γ in patients with diabetes and a history of myocardial infarction. It would therefore seem reasonable to consider the first-line use of a TZD such as pioglitazone in patients with diabetes and coronary artery disease for treatment of hyperglycemia where there are no contraindications. The question of how other agents in this class (including the dual-PPAR agonist tesaglitazar [Galida,® AstraZeneca, LP, Wilmington, DE] that activates both PPAR-α and PPAR-γ receptors) reduce atherogenic triglycerides, raise cardioprotective HD_1 levels, and improve insulin resistance, awaits Phase III clinical trial evaluation.

ACTIVATE Trial

The ACAT Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE) study evaluated the ability of the acyl-coenzyme A:cholesterol acyltransferase (ACAT) inhibitor pactimibe to reduce the progression of coronary atherosclerosis when compared to usual care in patients with symptomatic coronary artery disease. Under conditions of excessive cholesterol accumulation in the vascular wall, ACAT is responsible for cholesterol esterification responsible for the generation of the monocyte-macrophage foam cell. Given the involvement of ACAT in the development of the atherosclerotic lesion and macrophage foam cell, inhibitors

of ACAT have been developed to block this process. Previous animal models have shown that ACAT inhibition was capable of reducing atheroma volume. The purpose of the ACTIVATE study was to test this approach to limiting atherosclerosis in human subjects.

In the ACTIVATE trial, investigators enrolled 534 patients with symptomatic coronary artery disease as documented by coronary angiography (> 20% stenosis). Baseline characteristics between the 2 study arms were similar, as patients were well treated with background therapy, with a majority of patients taking statins and an average baseline LDL cholesterol level of 95 mg/dL in both treatment arms.

Intravenous ultrasound was performed using a 40 MHz transducer and a motorized pullback at 0.5 mm/sec through a target segment greater than 30 mm in length. Patients were randomized to pactimibe 100 mg daily or placebo for 18 months of treatment. Approximately 60 patients in each study arm did not return for repeat IVUS of the target vessel. The primary efficacy parameter—change in percent atheroma volume—was no better in the pactimibe treatment group when compared to placebo, with both treatment groups showing a statistically significant progression, although the increase in percent atheroma volume was slightly greater in the pactimibe group compared with placebo ($P = 0.77$). The results of this trial show that there is no evidence for plaque regression in patients with symptomatic coronary artery disease treated with pactimibe compared to placebo.

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FIELD Study

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was a trial of 9795 type 2 diabetes patients aged 50-75 years, randomized to either 200 mg daily of micronized fenofibrate or placebo. Patients were included if their baseline total cholesterol (TC) was 115-250 mg/dL and they had either a TC/high-density lipoprotein cholesterol ratio of 4.0 or more, or they had a plasma triglyceride level of 88 mg/dL to 442 mg/dL. Of the patients studied, 22% had evidence of heart disease at baseline. An important aspect of the trial design was that patients could not be started on statin therapy at baseline but could after enrollment, at the discretion of the investigator.

After a 5-year follow-up, the primary endpoint of death from chronic heart disease(CHD)/nonfatal MI was non-significantly reduced by 11% ($P = 0.16$). Nonfatal MI was significantly reduced by 24% ($P = .010$); however, CHD death was non-significantly increased by 19% ($P = 0.22$). In terms of secondary outcomes, total cardiovascular events were significantly reduced in the fenofibrate group by 11% ($P = .035$), driven mainly by the reduction in nonfatal MI and a reduction in revascularizations. An important difference between the 2 randomized groups is that 17% of the control group was started on statins during the trial whereas only 8% of the fenofibrate group received statin therapy. After adjustment for this new lipid-lowering therapy, fenofibrate was shown to reduce the risk of CHD events by 19% ($P = .01$) and of total cardiovascular disease-related events by 15% ($P = .004$). Diabetic complications, which were prespecified tertiary endpoints, were also reduced in the fenofibrate group. The rate of progression to albuminuria was significantly reduced by fenofibrate (2.6% more patients regressing or not progressing than placebo [$P = .002$]). Similar effects of treatment were seen on urinary albumin concentration, unadjusted for urinary creatinine ($P = .001$) and reduction in laser therapy for diabetic retinopathy ($P = .001$).

In summary, this trial does not seem to be a pure evaluation of the effectiveness of fenofibrate as stand-alone therapy in diabetic patients with moderate hyperlipidemia and hyper-triglyceridemia, as it was complicated by the addition of statin therapy at the discretion of the investigator. With more subjects in the control group receiving add-on statin therapy than in the fenofibrate group, it is difficult to tease out the true efficacy of stand-alone fenofibrate therapy in this trial. Perhaps more useful information would be gleaned from a trial that compares the efficacy of statin therapy alone to statin plus fenofibrate to determine the utility of a therapy that affects primarily LDL-C reduction to one that affects both LDL-C and triglyceride reduction. The efficacy of fenofibrate therapy in reducing cardiovascular events in diabetic patients with more severe hypertriglyceridemia was not evaluated in this trial.

[Norman E. Lepor, MD, FACC, FAHA]

JELIS Trial

Dr. Mitsuhiro Yokoyama of the Kobe Graduate School of Medicine in Kobe, Japan, reported the results of

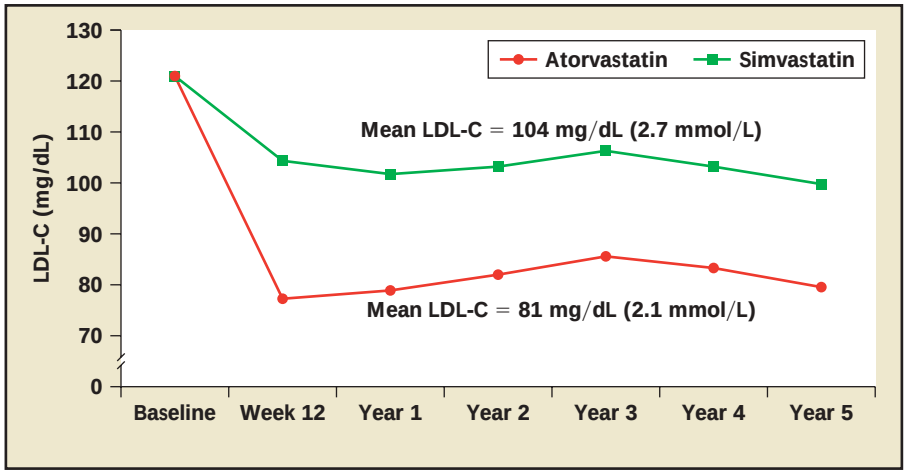


Figure 2. *Reduction in low-density lipoprotein cholesterol (LDL-C) in the IDEAL trial.*

the Japan EPA Lipid Intervention Study (JELIS), which randomized 18,645 adults with a mean low-density lipoprotein (LDL-C) cholesterol level of 182 mg/dL to 1800 mg of fish oil versus placebo on top of background therapy of either pravastatin, 10 mg, or simvastatin, 5 mg, daily.[5] The fish oil was associated with a 19% relative risk reduction in major cardiac events. This trial complements prior large scale clinical trials and supports the position of the American Heart Association on fish oil (omega-3 and omega-6 fatty acids) as a preventive therapy. The JELIS trial demonstrated that fish oil is complementary to statin utilization and should be a first-line approach for patients at high risk for cardiovascular disease.

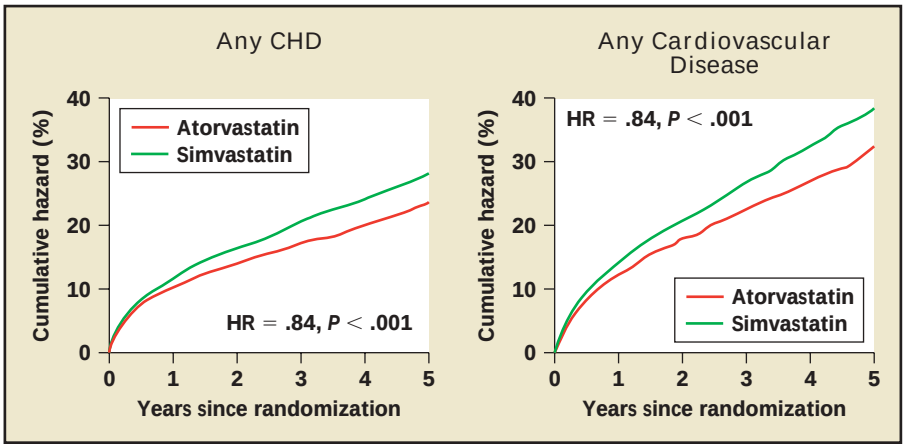
IDEAL Trial

Trials in both primary prevention and acute coronary syndromes support fixed, highest-dose statin therapy (atorvastatin 80 mg, qd) over less intensive lipid-lowering approaches.[6] The Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial randomized 8,888 patients with established coronary heart disease (CHD) to atorvastatin, 80 mg daily, versus simvastatin 20 mg, titrated to a maximum dose of 40 mg daily, in a multicenter, open-label trial.[7,8] The average baseline LDL-C level was 122 mg/dL and 75% of patients were on statins at baseline, before going through the washout and randomization. The mean LDL-C levels were lowered to 81 mg/dL and 104 mg/dL for the atorvastatin and simvastatin groups, respectively (Figure 2). This translated to a 16% relative risk reduction, in the atorvastatin group, in any CHD and any CVD event over 5 years (Figure 3). These data strongly support the use of atorvastatin, 80 mg daily, in patients with established CHD and suggests that lesser doses are inferior in this application.

REPAIR-AMI Trial

The Intracoronary Infusion of Bone Marrow-Derived Progenitor Cells in AMI: A Randomized, Double-blind, Placebo-Controlled Multicenter Trial (REPAIR-AMI) was one of the largest trials to date of the use of bone-marrow derived stem cells for the treatment of ST-segment elevation myocardial infarction (STEMI).[9] Results were reported by Dr. Volker Schachinger of the J. W. Goethe University in Frankfurt, Germany. A total of 204 patients with STEMI were randomized after percutaneous coronary intervention and stenting to active treatment with intracoronary injection of stem cells versus placebo. All patients went through the bone-marrow-aspiration protocol (Figure 4), which is a testament to their commitment to this well-controlled trial. Those who received the stem cell treatment had a modest improvement in ejection fraction

Figure 3. *Endpoint reductions with atorvastatin, 80 mg daily, versus simvastatin, 20-40 mg daily, over 5 years in the IDEAL trial. CHD, chronic heart disease.*



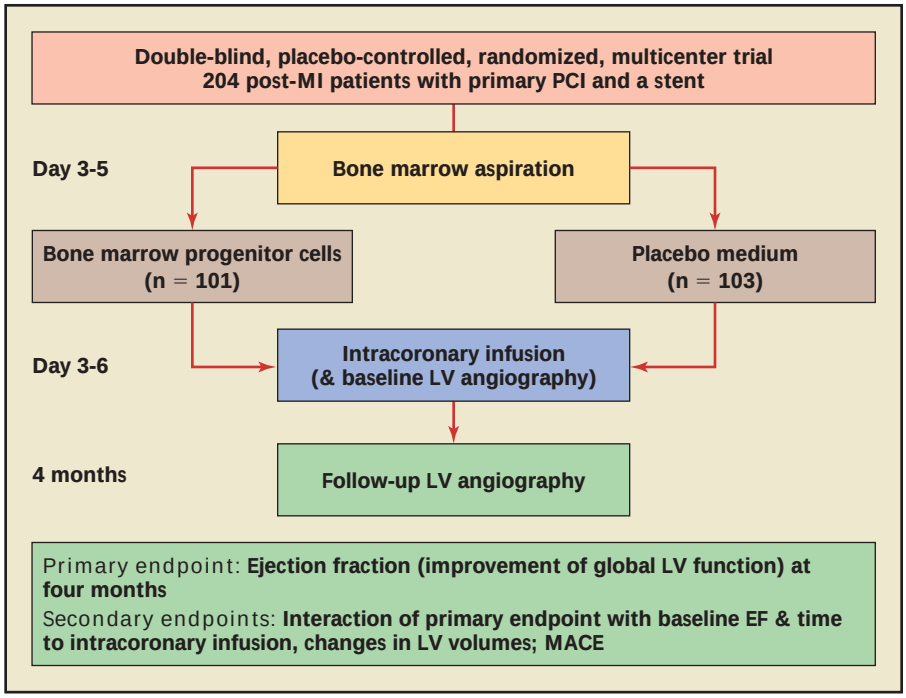


Figure 4. *Design of the REPAIR-AMI trial. MI, myocardial infarction; PCI, percutaneous coronary intervention; LV, left ventricular; EF, ejection fraction; MACE, major adverse coronary events.*

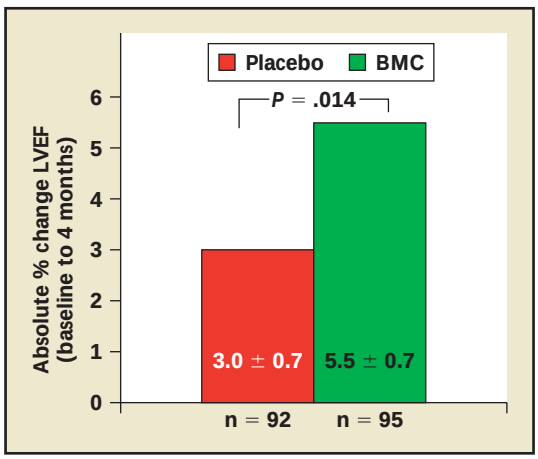
(Figure 5). These data are encouraging, in that they provide hope of some form of bone-marrow-derived cellular treatment to enhance myocardial repair as a future treatment. However, it is likely that peripheral harvesting or use of bone-marrow-stimulating proteins will become the favored approach over bone marrow aspiration.

Erythrocyte-Stimulating Proteins as Cardiovascular Therapies

It is known that erythrocyte-stimulating proteins (ESPs) stimulate not only hematoblasts and red cell production but also endothelial progenitor cells (EPCs).[10] Furthermore, these proteins have been shown to be angiogenic factors in basic models. Lipsic and colleagues tested a very simple approach with a single bolus of darbepoetin, a genetically engineered form of erythropoietin, in patients presenting with ST-elevation myocardial infarction (STEMI), with the aim of increasing measurable levels of EPCs.[11] A total of 22 STEMI patients were randomized to a 300 μg bolus (> 6 times the standard subcutaneous dose used for anemia treatment) of darbepoetin versus placebo before primary angioplasty was performed. The number of measurable circulating EPCs was more than doubled with darbepoetin at 72 hours. The trial was too small to evaluate any meaningful impact on infarction size or ejection fraction. However, this study demonstrates that ESPs can be used to boost EPCs in the setting of STEMI, without any adverse safety signal, using very high doses of the EPC. Future studies along this line are promising, given the logistical difficulties in harvesting and re-infusing EPCs in patients with STEMI.

[Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA]

Figure 5. *Results from the REPAIR-AMI trial. BMC, bone marrow cells; LVEF, left ventricular ejection fraction.*



EASY Study

Early Discharge After Transradial Stenting of Coronary Arteries

Percutaneous coronary intervention (PCI) has traditionally been performed as an inpatient procedure, in order to maintain access to emergency treatment if required and because the procedure is associated with a small but significant risk of serious complications. However, the increased use of stents and adjunctive pharmacologic therapy have decreased procedural complication rates and increased procedural cost. Therefore, a new strategy of outpatient PCI is beginning to emerge. In

fact, in a recent membership survey performed by the Society of Cardiovascular Angiography and Interventions, 28% of respondents noted that they had performed PCI in the outpatient setting.[12]

The Early Discharge After Transradial Stenting of Coronary Arteries (EASY) study was designed to test the hypothesis that discharge from the hospital on the same day following PCI is feasible and safe in selected patients. Accordingly, 1005 patients undergoing a successful PCI procedure with an adjunctive bolus dose of abciximab were then randomly assigned to same-day discharge or the addition of a 12-hour abciximab infusion and discharge on the following day. Those patients who experienced a suboptimal angiographic result were not randomized and were followed in a parallel registry. The primary endpoint of the study was a composite of death, myocardial infarction (MI), urgent revascularization, repeat hospitalization, severe thrombocytopenia, access site complications, and major bleeding at 30 days. Secondary endpoints included death, MI and target vessel revascularization at 30 days and at 6 months. The sample size was based on a non-inferiority design with a reference rate of 23% and an upper margin of 8% (placing a statistical limit on how much inferiority same-day discharge may exhibit compared with standard discharge the following day while still being considered to exhibit similar effectiveness). Of note, radial artery access was obtained in all patients and over 90% of patients received clopidogrel for a minimum of 12 hours prior to the procedure.

The results of the trial were presented by Dr. Olivier Bertrand of the Laval Hospital, Quebec Heart-Lung Institute, Quebec City, Canada. As expected, there was no difference in baseline characteristics between groups. Approximately 20% of patients had an elevated troponin level and approximately 30% of patients had 2 or 3 lesions dilated. Of the 504 patients assigned to the outpatient procedure, 88% were discharged on the same day. The primary endpoint of the study (Table 4) occurred in 13.5% of the same-day discharge group in comparison to 10.2% of the traditional discharge group (P = NS). There was also no difference between groups in the secondary endpoint at 30 days and 6 months. Dr. Bertrand and his co-investigators concluded that 1) abciximab as a single bolus is noninferior to the standard bolus plus infusion after uncomplicated coronary stent procedures, when followed up at 30 days and 6 months; 2) the combination of transradial PCI and single bolus abciximab is safe and facilitates outpatient PCI in a wide spectrum of patients; and 3) the use of simple risk criteria permits a change of PCI practice offering significant advantages in terms of bed occupancy and cost.

The Early Discharge After Transradial Stenting of Coronary Arteries (EASY) study was designed to test the hypothesis that discharge from the hospital on the same day following PCI is feasible and safe in selected patients.

Comments

This study is both provocative and timely, suggesting that in patients undergoing uncomplicated PCI via the radial artery, who have been pretreated with a bolus of abciximab and for a minimum of 12 hours with clopidogrel, discharge on the day of the procedure is both feasible and safe. However, before the findings of the EASY study influence clinical practice, several issues will require

Table 4
Outcomes in the EASY Study

Endpoint	Abciximab Bolus (%)	Abciximab Bolus+infusion (%)	Registry (%)
30 days			
Death	0	0	-
Non-Q-wave MI	1	1.8	-
Q-wave MI	0.4	0	-
Revascularization	1	0	-
Repeat hospitalization	5	3	-
Major bleeding	0.5	0.2	-
Access site complications	4.8	4.2	-
Severe thrombopenia	0.6	0.6	-
Primary endpoint	13.5	10.2	26.8
6 months			
Secondary endpoint	5.9	5.6	20.2

MI = myocardial infarction

additional scrutiny. For example, because the event rate in the control was less than half of that anticipated, it is not clear whether the power of the study is reduced. It will be important to see the traditional 95% confidence interval around the point estimate for the outpatient group, particularly as the primary endpoint was 30% higher in this group in comparison to the standard discharge group.

In addition, it will also be important to learn the event rate at 24-48 hours, as there is a concern that discharge prior to this time precludes evaluation of bleeding, heart failure, and elevation of serum creatinine and cardiac enzymes. The 30-day endpoint seems less relevant when evaluating early discharge that is not likely to impact repeat revascularization. It is also important to note that the investigators are very experienced in the performance of radial artery access, whereas most patients undergo PCI via the femoral artery access site. In addition, it will need to be determined whether use of the radial artery during diagnostic angiography precludes its use as a conduit in patients who will require coronary artery bypass surgery rather than PCI. Finally, the impact of this strategy on cost and cost-effectiveness requires further study. In the absence of practice guidelines, the decision to discharge a patient on the day of a PCI procedure should be made by the interventional cardiologist and an informed patient.

[Alice K. Jacobs, MD, FACC, FAHA]

Percutaneous Approaches to Valvular Heart Disease

Slow but Encouraging Progress

At the 2005 AHA Scientific Session, several groups reported encouraging data regarding the safety and efficacy of percutaneous approaches to valvular repair and replacement. Led by their initial positive experience in percutaneous pulmonary valve replacement, Dr. Philipp Bonhoeffer and his colleagues from the Great Ormond Street Hospital for Children, London, UK, expanded on their prior series, presenting 109 patients who have now undergone percutaneous pulmonary valve replacements, primarily for stenosed right ventricular outflow conduits. There were no procedural deaths. Serious complications occurred in 5 patients, including homograft rupture in 2, device dislodgement in 2, and right coronary compression in 1. Figure 6 demonstrates the proximity of the right coronary artery (RCA) and the pulmonary outflow and illustrates how coronary compromise might occur. Nine cases had a second stent-in-stent placed for initial stent malfunction (4), stent fracture (3), or residual stenosis (2). Follow-up was available for up to 5 years, wherein 67.8% were free from explantation or death.

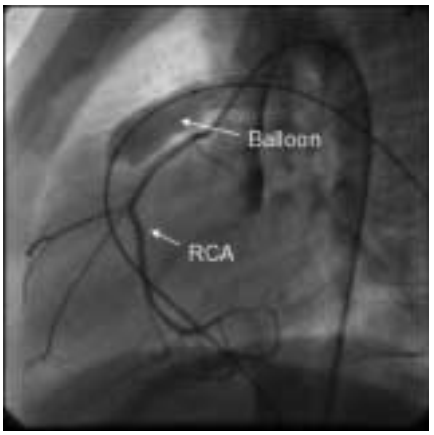


Figure 6. *Proximity of percutaneous pulmonary valve balloon and right coronary artery. Note the relationship between the right ventricular outflow/pulmonary artery balloon and the simultaneously injected right coronary artery (RCA).*

Alain Cribier, MD, from the Charles Nicolle Hospital in Rouen, France, and John Webb, MD, from St. Paul's Hospital, Vancouver, British Columbia, Canada, updated the status of percutaneous aortic valve replacement (AVR) using a balloon expandable stent with bovine leaflets (the Cribier-Edwards® bioprosthesis) and discussed two trials: the US REVIVAL trial and the European RECAST trial. The entry criteria for use of the percutaneous AVR approach still focus on extremely ill, generally non-surgical patients at high risk for cardiac events.

The investigators from Rouen reported 20 patients as part of their latest ongoing RECAST trial, favoring an antegrade approach via transseptal rather than a retrograde aortic approach (Figure 7). They noted less vascular injury from the large 22-24F sheaths inserted into the femoral vein rather than the artery, and a greater success rate in their hands (84% versus 57%) with the antegrade approach. In contrast, Dr. Webb presented 20 patients who underwent percutaneous AVR via the retrograde approach and noted the procedure was initially successful in 80%. Using echocardiography, his group found the aortic valve area increased from 0.6 cm^2 to 1.6 cm^2. They had no

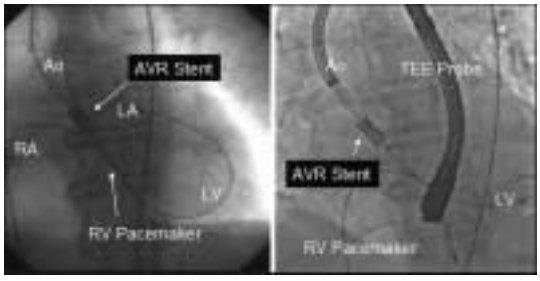


Figure 7. *Percutaneous aortic valve replacement using the Cribier-Edwards® bioprosthesis. The left panel reveals the technique using the antegrade approach via transseptal catheterization. The right panel reveals the retrograde technique. Ao, aorta; AVR, aortic valve replacement; LV, left ventricle; RA, right atrium; RV, right ventricle; TEE, transesophageal echocardiography.*

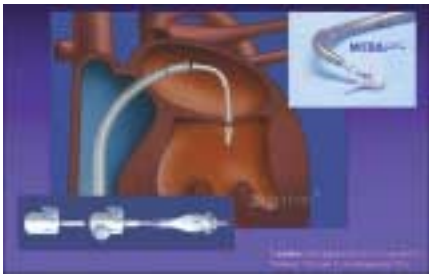
procedural deaths though there were 2 deaths at 30 days (one due to vascular complications and one due to pneumonia and compromise of the left main coronary).

The aortic valve stent had previously only been available in one size, 23 mm, and both groups felt the introduction of a 26 mm device should help reduce the incidence of paravalvular leaks, a particularly vexing problem in some patients after percutaneous AVR. A self-expanding (rather than balloon-expanding) percutaneous AVR stent from CoreValve (Irvine, CA) was also included at another session at AHA, in a presentation by Dr. John Carroll from the University of Colorado Health Sciences Center, Boulder, CO. Of the initial 13 patients, there were 10 devices deployed successfully and 4 deaths were reported.

Percutaneous approaches to mitral regurgitation continue, though there remain sparse clinical data with only a few patients being reported. One of the more complete trials, the phase I EVEREST I trial, presented originally at the American College of Cardiology in 2004 and recently published,[13] continues into its second phase (EVEREST II). This method utilizes the mitral clip device (Figure 8), and percutaneously replicates the surgical Alfieri approach to mitral repair, resulting in a double orifice mitral valve. In the surgical series,[14] concomitant mitral annuloplasty was recommended for best results. The EVEREST trial enrolled 47 patients in the phase I portion, and data from 27 who had reached a 1-year anniversary were available for analysis. Of these 27, procedural success was noted in 19 (70%), and of these 19, continuing positive results were reported in 13 (68%) at 1 year. Of the 6 poor outcomes, 1 had late surgery, 2 had increasing mitral regurgitation, and 3 had partial clip detachments. EVEREST II is currently ongoing and has a randomization scheme of 2 patients for percutaneous closure for each undergoing surgical repair. Although most patients enrolled have mitral valve prolapse, some do have mitral regurgitation related to an underlying cardiomyopathy.

Finally, Dr. John Liddicoat, from Beth Israel Deaconess Medical Center, Boston, MA, presented an overview of the current status of percutaneous mitral valve repair. Besides the percutaneous clip approach, efforts continue toward the development of coronary sinus cinching devices to reduce the mitral annular size or to attempt annuloplasty using stitches inserted into the mitral annulus from the ventricular side. Figure 9 outlines the various

Figure 8. *Percutaneous mitral clip method. Using the Mitraclip® (Evalve, Menlo Park, CA) device shown, the anterior and posterior mitral leaflets are held together to form a double orifice mitral valve.*



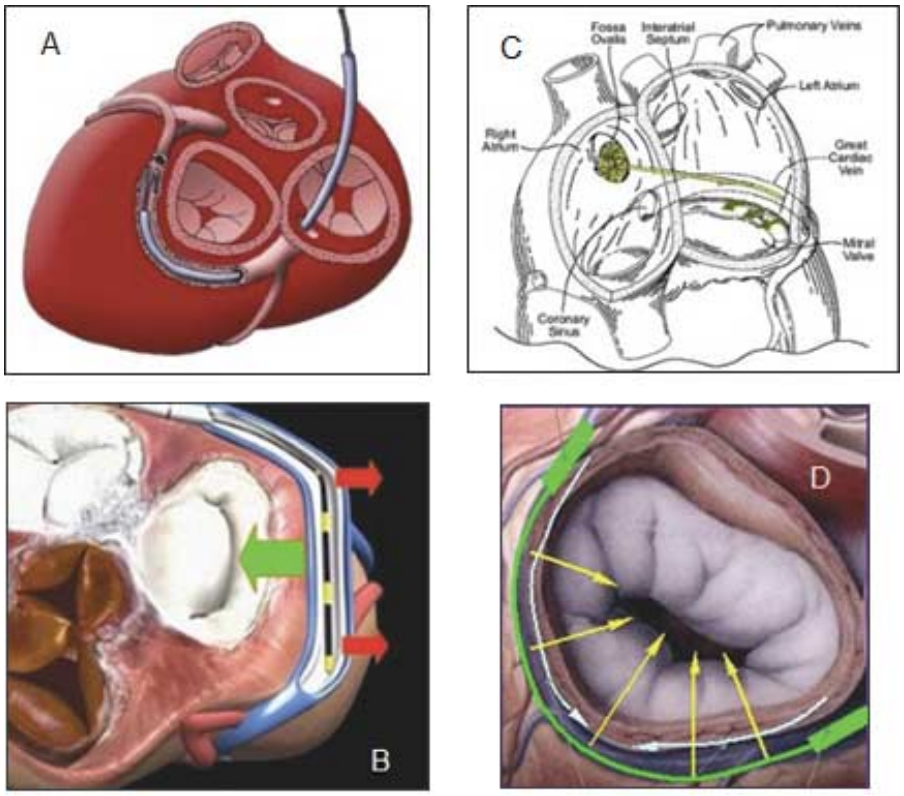


Figure 9. *Coronary sinus devices to produce percutaneous annuloplasty. The acute cinching device from Cardiac Dimensions (Kirkland, WA), known as the Carillon™ Mitral Contour System™ is shown* ***(A)****. The device is anchored on either end by stenting and the degree of closure acutely determined. The Viacor (Wilmington, MA) straightening device reduces annular size by straightening the P2 segment of the posterior mitral leaflet* ***(B)****. The Percutaneous Septal Sinus Shortening System (PS*$^{3®}$*) by Ample Medical (Foster City, CA) provides an anchor in the atrial septum* ***(C)****, much like an Amplatzer® occluder device, and a T bar anchor in the great cardiac vein. Tension between the two anchors reshapes the mitral annulus. The Edwards LifeSciences (Irvine, CA) Viking® system has a coiled nitinol wire system with material between the coils that dissolves over several days to weeks* ***(D)****. Placed straight into the coronary sinus and fixed at both ends by stents, the nitinol device contracts when the material between the coils dissolves. The mitral annulus is then narrowed due to the resultant spring-like action.*

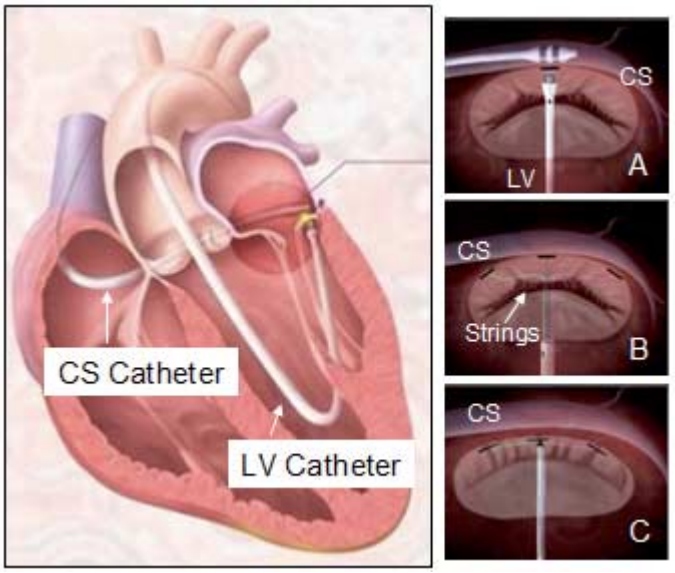


Figure 10. *The transventricular percutaneous annuloplasty method (Mitralign®) by Ample Medical (Foster City, CA). Shown on the left is the annuloplasty catheter in the left ventricle (LV) abutting the mitral annulus and a second catheter in the coronary sinus (CS). On the right* ***(A)****, the magnetic tips of the CS catheter are shown localizing the tip of the transventricular catheter. Implants are placed along the mitral annulus at various strategic positions* ***(B)****. The strings from the implants are pulled together by advancing the catheter toward the annulus, and thus reducing the annular size* ***(C)****.*

coronary sinus approaches. Though all are being tried in phase I human studies at this time, the data are very premature as to the advantage, or even the safety and efficacy, of any particular approach. In the transventricular method (Figure 10), a magnetic-tipped catheter is placed into the coronary sinus and used to locate the tip of a second catheter placed through the aortic valve into the LV and shaped to abut against the mitral annulus. Stitches are implanted into the mitral annulus at various locations identified by the 2 catheters. Each stitch site is then pulled toward the other to reduce the mitral annular size.

In summary, percutaneous approaches to valve repair and replacement remain in the early stages of development. The presentations at the AHA, though, reveal that progress is clearly being made. It is hoped that in the next few years, percutaneous options for the treatment of valvular heart disease will become a viable option for selected patients.

[Thomas M. Bashore, MD, FACC, FAHA]

PREVENT IV Trial

Efficacy and Safety of Edifoligide, an E2F Transcription Factor Decoy, for Prevention of Vein Graft Failure Following Coronary Artery Bypass Graft Surgery

Although coronary artery bypass surgery remains one of the most common coronary revascularization procedures, long-term vein graft patency is limited by the development of neointimal hyperplasia that results in accelerated atherosclerosis and thrombosis. E2F transcription factors have been implicated in the up-regulation of several genes that promote neointimal hyperplasia and may lead to premature vein graft failure. Edifoligide (Corgentech Inc., South San Francisco, CA) is a novel, double-stranded oligonucleotide decoy to E2F that has been previously demonstrated to inhibit neointimal hyperplasia in preclinical and early phase trials.

Trial Design and Results

The PREVENT IV Trial[15] was conducted among 107 centers in the United States. Results were presented by Dr. John H. Alexander of the Duke Clinical Research Institute in Durham, NC. Patients (N = 3014) undergoing coronary bypass surgery were randomized in a 1:1, double-blinded fashion to treatment with either placebo or edifoligide. Among patients assigned to treatment with edifoligide, each patient's harvested vein was treated ex vivo in a specially constructed pressure-mediated delivery tube for 10 minutes prior to surgical implantation. The principal inclusion criteria were planned bypass surgery with at least 2 vein graft conduits and no concomitant valvular surgery. Patients older than 80 years were excluded, in addition to those with prior bypass surgery and/or a nonatherosclerotic cause of coronary artery disease. Follow-up angiography at 12 to 18 months following revascularization was planned for the initial 2400 patients enrolled. The primary endpoint was the occurrence of death or vein graft stenosis of 75% or more, in at least one vein graft identified during follow-up angiography.

Baseline characteristics did not statistically vary between the 2 groups, although patients who underwent angiographic follow-up generally had less comorbidity than patients who did not. Among the 1920 patients undergoing surveillance angiography, the primary endpoint occurred in 436 (45.2%) patients treated with edifoligide and in 442 (46.3%) patients assigned to placebo ($P = 0.66$). The most common cause of vein graft failure was graft occlusion, which also did not significantly

differ between the 2 groups (41.8% edifoligide versus 41.7% placebo, $P = 0.97$). There was no clinically meaningful treatment effect with edifoligide among the subgroups studied.

At 1 year, there were no significant differences between treatment groups regarding the occurrence of death (3.5% edifoligide vs 2.9% placebo, $P = 0.37$) or the composite endpoint of death, myocardial infarction, or revascularization (7.6% edifoligide vs 9.1% placebo, $P = 0.16$).

Comment

Despite previous smaller trials suggesting its benefit, treatment with edifoligide had no significant effect on the primary endpoint or secondary angiographic endpoints. These negative results are similar to the recent PREVENT III trial, which did not show a benefit in improving peripheral vein bypass graft patency.[16] However, these findings do highlight clinical and angiographic outcomes among patients undergoing contemporary bypass surgery (21% off-pump surgery, 92% received an internal mammary artery graft, ~20% discharge on aspirin and thienopyridine therapy). In particular, the per-vein graft failure and occlusion rates were approximately 29% and 26%, respectively, and patients with vein graft failure had a significantly higher likelihood of adverse events. These overall negative results inform the need for further therapies intended to improve the durability of bypass surgery.

[David E. Kandzari, MD]

ASSENT-4 PCI Study

Facilitated angioplasty has the potential to utilize the advantages of lytic therapy, specifically through early administration and thus early reperfusion followed by complete reperfusion with PCI. Three small studies have compared facilitated PCI with lytic therapy alone and all have shown superiority of the facilitated approach. Of the 3 small studies comparing facilitated and primary PCI, 1 has been positive and 2 negative. The Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction (ASSENT-4 PCI) study was designed to be the largest trial to evaluate the role of facilitated PCI, as compared to primary PCI, in patients with ST elevation myocardial infarction, within 6 hours of the onset of chest pain. Thirty-day results had been previously reported at the European Society of Cardiology meeting in September. At the 2005 AHA scientific session, the final endpoint results were presented by Dr. Frans Van de Werf of the University Hospital Gasthuisberg in Leuven, Belgium.

Despite previous smaller trials suggesting its benefit, treatment with edifoligide had no significant effect on the primary endpoint or secondary angiographic endpoints.

The protocol for the facilitated group was to receive full dose tenecteplase and a bolus dose of unfractionated heparin (60 U/kg) prior to PCI. GP IIb/IIIa agents were allowed for bailout only. In the primary PCI group, a bolus dose of unfractionated heparin (70 U/kg) was given and GP IIb/IIIa agents could be given at the discretion of the operator. In the facilitated group, the delay from randomization to the lytic agent was 10 minutes and the delay to PCI was 115 minutes. In the primary PCI group, the delay to PCI was 107 minutes. In the facilitated group, 9.5% of patients received a GP IIb/IIa agent as compared to 50.4% of the primary PCI group. Stents were used in 81% to 86% but drug-eluting stents were not commonly used (19%-20%).

The study was intended to enroll 4000 patients but was stopped prematurely by the Data Safety Monitoring Board (DSMB) because of an increased mortality in the facilitated group. Thus only 1667 patients were enrolled. The primary endpoint was a combined endpoint of death, congestive heart failure, or cardiogenic shock at 90 days, which occurred in 18.8% of the facilitated group and 13.7% of the primary PCI group. The individual components were as follows for the facilitated group as compared to the primary PCI group: death, 6.7% versus 5.0%, $P = 0.141$; congestive heart failure, 12.1% versus 9.4%, $P = .078$; cardiogenic shock, 6.1% versus 4.8%, $P = 0.273$. In addition, recurrent myocardial infarction and target vessel revascularization were increased in the facilitated group. Major bleeding was low in both groups and stroke occurred in 2.65% of the facilitated group but in only 0.12% (1 patient) in the primary PCI group ($P < .0001$).

The study was conducted in a variety of settings, including community hospitals, hospitals with the ability to administer lytic agents in the ambulance, and PCI-capable hospitals. The setting made a significant difference in outcome, with the lowest mortality in both groups occurring in those who were randomized in the ambulance (3.1% versus 4.1% for the facilitated and primary PCI groups, respectively). The mortality in the PCI hospitals was the highest at 8.5% for facilitated PCI and 5.2%

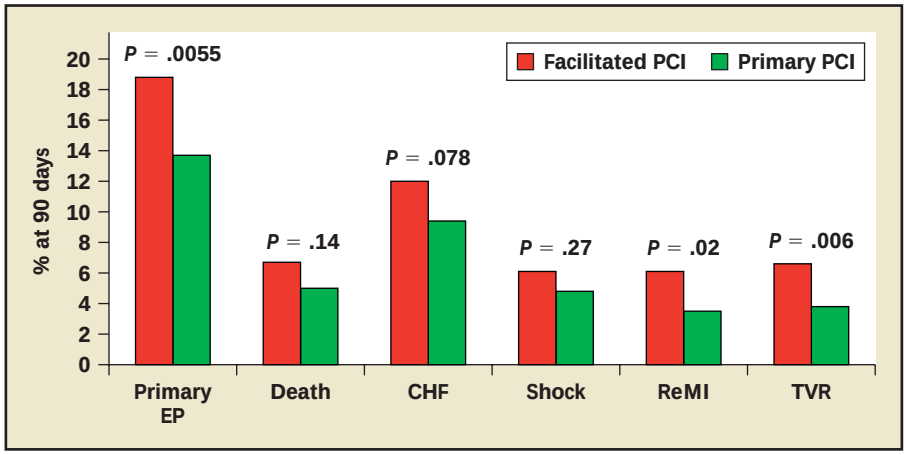


Figure 11. *Ninety-day endpoint results in the ASSENT-4 PCI Trial. CHF, chronic heart failure; EP, endpoint; PCI, percutaneous coronary intervention; ReMI, re-infarction; TVR, target vessel revascularization.*

for primary PCI. This lower mortality could be explained in part by a significantly shorter time from the onset of chest pain to randomization (105 minutes for the ambulance group versus 160 minutes for the PCI hospitals). In addition, those randomized in the ambulance had a significantly higher TIMI flow at the time of PCI in the facilitated group than those randomized in the PCI hospital or in a community hospital (55% vs 39% and 43%, respectively) (Figure 11).

The study raises a number of issues. First, in retrospect the trial may have been stopped prematurely. At the time the DSMB stopped the trial, 1320 patients were enrolled and the mortality difference between the groups was significant (6.5% versus 3.4%, $P = .01$). However, as noted above, at 90-day follow-up of all 1667 patients, differences in mortality rate were no longer significant. It is the usual convention to stop a trial for safety when the difference between groups reaches a P value of less than .001, given the uncertainty with a relatively small number of

Main Points

- The REVIVE-2 and SURVIVE-W trials, taken together, suggest that levosimendan improves symptoms in acute decompensated heart failure, with symptom relief and a mortality rate comparable to dobutamine, but also with significantly more serious adverse events and potentially increased mortality compared to placebo.
- The ERICA study demonstrated the efficacy of ranolazine in reducing the frequency of incidence in chronic angina patients. Ranolazine represents an advance through its novel mechanism of action, which reduces late inward sodium current rather than affecting blood pressure or heart rate.
- Newly reported subgroup analysis from the PROactive trial showed cardiovascular benefit of therapy with pioglitazone, an agonist of the peroxisome proliferator-activated receptor-γ, in patients with diabetes and a history of myocardial infarction.
- Experience from the IDEAL trial strongly supports the use of a maximal statin dose (atorvastatin, 80 mg daily) in patients with established coronary heart disease (CHD) and suggests that lesser doses are inferior in these patients in terms of risk reduction for CHD-related events.
- Experience from the EASY study showed that the combination of transradial percutaneous coronary intervention (PCI) and single bolus abciximab is safe and facilitates outpatient PCI procedures in a wide spectrum of patients.
- New advances in percutaneous valvular repair include positive reports from the REVIVAL and RECAST trials, focusing on aortic valve replacement, and EVEREST II, utilizing a clip device for mitral regurgitation.
- The PREVENT IV trial utilized ex vivo vein graft treatment with edifoligide in an attempt to improve outcomes and long-term patency in coronary artery bypass procedures, but found no significant improvement in primary or secondary angiographic endpoints.
- Facilitated versus primary angioplasty were compared in the ASSENT-4 PCI trial of patients with ST elevation myocardial infarction. The trial was stopped early due to increased mortality in the facilitated group but nevertheless illustrated the importance of shortening the time from onset of symptoms to treatment in these procedures.

patients. Nevertheless, the primary endpoint in ASSENT-4 was significantly different despite the reduced sample size. However, this endpoint was driven largely by the difference in congestive heart failure, although the other components were directionally in favor of the primary PCI group. The lack of a difference is contrary to the smaller GRACIA 2 trial but consistent with the BRAVE trial and the CAPTIM trial.

The primary difference between ASSENT-4 and GRACIA 2 was the rapidity with which both groups received PCI in ASSENT-4 (155 and 105 minutes) whereas in GRACIA 2 the difference was 5.89 hours versus 1.08 hours for facilitated PCI versus primary PCI. The early PCI following lytic therapy appeared to be detrimental. The reason for this is not clear but one possibility is that activation of platelets with lytic agents in the presence of a stent may have predisposed to acute closure, which occurred in 1.9% of the facilitated group and 0.1% in the primary PCI group. The higher in-hospital reinfarction and target vessel revascularization of 4% for each is of concern. The lack of continued heparin and pretreatment with clopidogrel may have contributed to these differences.

Despite these limitations, there is no refuting the main message of this trial, which is that time is critical regardless of the strategy used. Shortening the average time from onset of chest pain to treatment to 105 minutes halved mortality. Whether facilitated PCI is more reasonable when the delay to PCI is lengthened, as when patients are transported from a remote area to a PCI hospital, remains unclear. In addition, the role of GP IIb/IIIa agents is also unclear. The ongoing FINESSE trial will be evaluating facilitated PCI with 3 groups: primary PCI, facilitated PCI with abciximab, and facilitated PCI with half dose retaplase plus abciximab. The results of this study will further help define whether facilitated PCI has a role in the treatment of STEMI.

[David P. Faxon, MD, FACC, FAHA] ■

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