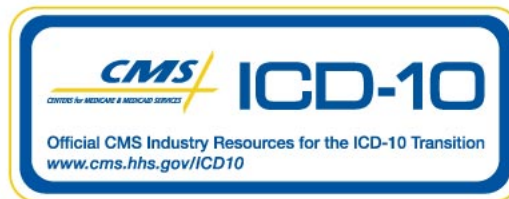


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*JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY*



## LATE-BREAKING CLINICAL TRIALS

# Results From Late-Breaking Clinical Trial Sessions at the American College of Cardiology 51st Annual Scientific Session

Eric S. Williams, MD, FACC, John M. Miller, MD, FACC

Indianapolis, Indiana

### LATE-BREAKING CLINICAL TRIALS IN INTERVENTIONAL CARDIOLOGY

*Effect of Stent Design and Strut Thickness on Long-Term Outcome of Coronary Stent Placement: Results From the ISAR-STEREO-2 Trial*

HELMUT SCHÜHLEN, MD, FACC

GERMAN HEART CENTER, MUNICH, GERMANY

**Background.** The long-term results after coronary stent placement are limited by in-stent restenosis. There is growing evidence that the characteristics of coronary stents may have a significant impact on the development of restenosis. In the ISAR-STEREO-1 trial, previously published in *Circulation*, we have found that the use of stents with thinner struts is associated with a significant reduction in restenosis. This was observed in a randomized comparison of two stents with very similar design but different strut thickness (Guidant ACS RX MultiLink stent [strut thickness, 50  $\mu\text{m}$ ] vs. MultiLink RX Duet [strut thickness, 140  $\mu\text{m}$ ]). The purpose of ISAR-STEREO-2 was to assess whether the impact of strut thickness is also evident with stents of different design. **Methods.** In this multicenter trial, 611 patients with lesions in native coronary arteries  $>2.8$  mm in diameter were randomly assigned to either the “thin-strut” Guidant ACS RX MultiLink stent (strut thickness, 50  $\mu\text{m}$ ;  $n = 309$ ) or the “thick-strut” Cordis BX Velocity stent (strut thickness, 140  $\mu\text{m}$ ;  $n = 302$ ). These two stents also differ with respect to strut configuration and design. The primary end point was angiographic restenosis at follow-up angiography. Secondary end points were target-vessel revascularization (TVR) and the combined rate of death and myocardial infarction (MI) at one year. **Results.** At baseline, there were no relevant differences in clinical or angiographic baseline characteristics between the two groups. Procedural success rates were similar in both groups (99.4% vs. 99.0%), whereas device success (i.e., procedural success with the randomly assigned device) was significantly lower with thin-strut stents (87.1% vs. 99.0%;  $p < 0.001$ ). Short-term quantitative angiographic results were almost identical in the two groups. At six-month angiography, however, late luminal loss was significantly

lower in the thin-strut group (0.93 mm vs. 1.19 mm;  $p < 0.001$ ), as was the loss index (0.51 vs. 0.65;  $p < 0.001$ ). This translated into a significant difference in the primary end point, the angiographic restenosis rate (17.9% vs. 31.4%;  $p = 0.001$ ). At one year, the rate of TVR was significantly lower with thin-strut stents (12.3% vs. 21.9%;  $p = 0.002$ ); no difference was observed in the combined rate of death and MI at one year (4.9% vs. 6.3%;  $p = 0.67$ ). **Conclusions.** Strut thickness of coronary stents has a significant impact on long-term outcome because thinner-strut stents are associated with a significantly lower restenosis rate. The ISAR-STEREO-1 trial had shown this effect in a comparison of two stents of similar design; ISAR-STEREO-2 suggests that this effect is also true for stents of different design. The findings could have an important impact on today's practice and the future development of coronary stents. The trial underscores the value of an unselected study population and a stringent follow-up of at least six months, as well as the limited value of data on short-term procedural success and early results.

### COMMENTARY

This multicenter trial has significant implications for the practice of interventional cardiology. We have grown up with the concept of “equivalence” trials as companies and investigators have evaluated new generations of stents. In the majority of stent-to-stent comparison trials from the late 1990s, different stents were found to be equivalent or at least non-inferior to the initially approved Johnson & Johnson Palmaz-Schatz coronary stent. The ISAR investigators previously found, in ISAR-STEREO-1, that not all stents are equal.

This study, ISAR-STEREO-2, builds on that question of equivalence and compares the performance of two different stents—one arguably among the most widely used in the world and the other no longer even available, at least in the U.S. Differences in stent design included stent configuration and thickness. The findings were very interesting—device success was less satisfactory with the thin-strut stents, but procedural success was the same and for both, at  $\geq 99\%$ . The most important finding was that, although short-term quantitative coronary angiographic results were almost identical, the late loss index was significantly lower with the

From the Indiana University School of Medicine, Krannert Institute of Cardiology, Indianapolis, Indiana.

thin-strut stent, resulting in significantly lower restenosis rates at 17.9% versus 31.4%, respectively; and with the thin-strut stent, accordingly, the rate of TVR was also lower.

Several unanswered questions remain, such as what is the optimal deployment pressure and the appropriate balloon size at that pressure. Answers to these will be forthcoming. The important message is that form and substance continue to matter and must be taken into consideration for future stent design and study development. To paraphrase George Orwell: All stents are equal—some are more equal than others.

DAVID R. HOLMES, JR, MD, FACC

*Acute Myocardial Infarction Study of Adenosine (AMISTAD II)*

ALLAN M. ROSS, MD, FACC

GEORGE WASHINGTON UNIVERSITY MEDICAL CENTER,  
WASHINGTON, DC

**Background.** A previous study (AMISTAD I) of adenosine given with fibrinolytic therapy to patients with acute myocardial infarction (MI) suggested that it reduced infarct size. Characteristics of adenosine that may contribute to this benefit include involvement in high-energy phosphate metabolism, an antiplatelet effect, and suppression of free-radical formation and neutrophil activation. **Methods.** To further evaluate the possible benefits of adenosine for myocardial protection in acute MI, a randomized, double-blind, placebo-controlled trial was performed with 2,118 patients at 248 clinical sites in 13 countries. A 263-patient substudy was performed at 62 sites in four countries, using technetium-99m sestamibi single photon emission computed tomography (SPECT) 120 to 216 h after randomization for assessment of final infarct size. Eligible patients with evolving anterolateral MI were randomized to receive a 3-h infusion of adenosine at 50  $\mu\text{g}/\text{kg}/\text{min}$ , at 70  $\mu\text{g}/\text{kg}/\text{min}$ , or placebo within 15 min of the start of fibrinolytic therapy or within 15 min prior to infarct-artery angioplasty. Patients were followed up until hospital discharge and for the next six months. The primary efficacy end point was time from randomization to the first occurrence of congestive heart failure (CHF) in-hospital but  $>24$  h after randomization, the first rehospitalization for CHF during follow-up, or death from any cause. The secondary efficacy end points were all-cause mortality, cardiovascular mortality, and infarct size as measured by SPECT imaging. **Results.** Adenosine was well tolerated at both dosages and in comparison with placebo. On an intention-to-treat basis, the risk for the primary clinical end point was reduced by 11% over six months for patients in the two adenosine dosage groups combined. The reduction did not reach statistical significance. However, the corresponding risk reduction did reach significance ( $p = 0.043$ ) for the subgroup that achieved successful reperfusion and received adenosine. Infarct size by SPECT was not significantly different in the pooled adenosine group and the control group. Among the group

that received adenosine at the higher dosage, however, SPECT infarct size was significantly reduced by 27% ( $p < 0.028$ ). The median infarct size was 43% among patients experiencing death, heart failure, or both and 17% among patients without such events. Infarct size and such clinical events were significantly correlated ( $p < 0.01$ ) by the Spearman rank test. **Conclusions.** We conclude that among patients who underwent reperfusion therapy: 1) there was a trend toward reduced clinical events among those who received adenosine at either dosage; 2) adenosine at 70  $\mu\text{g}/\text{kg}/\text{min}$  was associated with a statistically significant reduction in SPECT infarct size compared with placebo; 3) there was a significant correlation between infarct size and clinical events; and 4) the benefits of adenosine were amplified when reperfusion therapy, given early in the course of infarction, successfully achieved infarct-artery patency. Adenosine infusion as an adjunctive approach to limit infarct size deserves close consideration because its use has proved to be more encouraging than the vast array of previous similar efforts.

## COMMENTARY

This large multicenter trial examined adjunctive adenosine combined with reperfusion therapy for acute MI. The primary end point was time from randomization to the first occurrence of CHF. Two adenosine doses were compared with the placebo. The primary end point was reduced by 11% in the adenosine therapy groups, which was not significant statistically. The primary end point was noted to be significant for the subgroup that received adenosine and was also reperfused. Secondary end points included a substudy using SPECT thallium to measure infarct size. Infarct size was decreased by more than one-quarter only in patients who received high-dose adenosine but not in those who received low-dose adenosine.

Previous efforts to improve infarct therapy outcomes using adjunctive therapy such as magnesium have initially appeared promising and then failed to achieve efficacy in mega-trials. The results of therapy with adenosine seem somewhat encouraging in this trial but have yet to achieve the results necessary to establish this therapy as routine practice. Adenosine as an adjunct remains attractive because of its simplicity and relative lack of toxicity.

A fundamental problem in adjunctive pharmacotherapy for reperfusion is the finding in early animal studies, with agents such as beta-blockers and calcium-channel-blocking agents, that therapy is most efficacious when initiated before the onset of coronary occlusion. Initiating therapy before the onset of infarction is rarely possible. The bar that adjunctive therapies such as adenosine have to clear remains high.

TED E. FELDMAN, MD, FACC

*Coronary Artery Stenting: A 1,000-Patient Prospective Randomized Controlled Trial Comparing a Predilation With a No-Predilation Strategy*

KEITH D. DAWKINS, MD

WESSEX CARDIAC UNIT, SOUTHAMPTON, UNITED KINGDOM

**Background.** The Tetra Randomised European Direct Stenting Study (TRENDS), a 1,000-patient randomized controlled trial, evaluated the ACS MultiLink TETRA™ coronary stent system for the treatment of patients with both de novo and restenotic native coronary artery lesions.

**Methods.** The trial, conducted at 46 centers in Europe and Brazil, compared a predilation strategy (n = 499) versus a no-predilation (direct) approach (n = 501) for elective stent implantation. Inclusion criteria included angina, planned stenting of single de novo or restenotic lesions in native coronaries (multivessel procedures, one lesion per vessel, were allowed; >90% of patients had single-vessel disease), a target-vessel diameter of 2.75 to 4.25 mm and length of up to 18 mm by visual analysis, and target lesions of at least 70% stenosis. Excluded were patients with acute myocardial infarction (MI) within the previous 24 h and those with unprotected left main lesions, lesions involving a significant side branch, severe calcification, periprocedural intravascular ultrasound, or total occlusions. The primary end point was major adverse cardiac events (MACE) at 30 days: a composite of death, MI (with or without ST-segment elevation), and target-vessel revascularization. Intention-to-treat secondary analyses included number of stents used, total procedure time, fluoroscopy time, contrast volume, hospitalization time, six-month MACE, and binary restenosis rate at six months. **Results.** Procedurally, there was a significantly greater prevalence of lesion-site thrombus and moderately severe target-site calcification in the direct-stenting group (p = 0.03). Dilation pressures, the need for postdilation or additional stents, fluoroscopy time, contrast volume, and hospitalization time were all similar in the two groups. Predilation was performed in 31 of the 541 stents deployed in the direct-stenting group (5.7%) because the stent could not otherwise cross the lesion. There were no significant differences at 30 days in the rates of MACE or of any type of event making up the composite end point. **Conclusions.** Direct stenting is technically feasible in most electively stented patients in everyday practice. This study provided no evidence that direct stenting is associated with an increase in MACE at 30 days. Failure of the direct-stenting strategy is uncommon, in this study occurring in only 5.7% of attempts.

## COMMENTARY

The TRENDS trial addresses a clinically relevant question: Is there any disadvantage to the frequently practiced technique of routine direct stenting of non-total coronary lesions without severe calcification or major branch involvement. In

this randomized trial of 1,000 patients, the lesions assigned to the primary stent group were more likely to be calcified and contain thrombus than were traditionally dilated lesions. Despite this apparent chance adverse selection, there were no differences in 30-day MACE for the two groups, with only 5.8% of the direct stent group requiring predilation.

Short-term (1-month) results were not adversely affected by the more rapid and cost-saving strategy, particularly when additional post-stent dilation was not required. Ultimately, as shown in other studies, six-month results will be important in confirming that direct stenting is also not associated with an increased risk of restenosis.

GEORGE W. VETROVEC, MD, FACC

*Heparin-Coated Stents in Small Coronary Arteries: Results of the COAST Trial*

MICHAEL HAUDE, MD

UNIVERSITY OF ESSEN, ESSEN, GERMANY

**Background.** The role of stenting, compared with balloon angioplasty, for the treatment of symptomatic coronary artery stenoses in small vessels, where both techniques are less successful than in larger vessels, remains unclear. Also, the value of heparin-coated stents in small coronary arteries has not been documented. Heparin-coated stents were developed to limit the risk of thrombotic complications associated with coronary stenting, but their use has been little studied since the widespread use of recently introduced antiplatelet agents. **Methods.** A total of 605 patients at 21 centers with native coronary stenoses in vessels <2.6 mm in diameter were randomized to three treatment arms: balloon angioplasty or implantation with either a noncoated JOSTENT FLEX (ST) or a heparin-coated JOSTENT FLEX (H-ST). Inclusion criteria included current stable or unstable angina, a target-lesion reference luminal diameter of 2.0 to 2.6 mm by quantitative angiography. Excluded were patients with acute myocardial infarction within the last 24 h, severe heart failure or cardiogenic shock, or lesions longer than 30 mm. The primary end point was minimal luminal diameter (MLD) at six months; secondary end points included technical success rate and restenosis rate, event-free survival, and clinical events in-hospital and at 30 days, 250 days, and one year. All three groups received aspirin 100 mg/day; the two stent groups also received ticlopidine or clopidogrel for four weeks. **Results.** In the balloon angioplasty group, 27% required crossover to stenting because of recoil or flow-limiting dissections or threatened closure. There were no significant differences among the groups in rates of individual clinical events (Table 1). **Conclusions.** Larger post-interventional MLD and short-term gain were found in the two stent groups; at follow-up, there was a borderline statistically significant MLD and net gain difference in favor of the stent groups with surprisingly similar late loss compared with the balloon-angioplasty group; the findings did not indicate statistically different

**Table 1.** COAST Trial Outcomes

Results	Balloon Angioplasty	ST	H-ST	p Value
Follow-up available (N)	195	196	197	
Mean MLD postprocedure (mm)	2.05	2.17	2.18	0.005
Acute gain (mm)	1.24	1.41	1.42	< 0.0001
Mean MLD follow-up (mm)	1.34	1.47	1.45	0.049 NS*
Mean % stenosis follow-up	42	36	38	0.038
Mean net gain (mm)	0.55	0.72	0.69	0.012 NS*
Binary restenosis rate (%)	32	25	30	NS
Event-free survival 250 days (%)	84	88	88	NS

\*ST vs. H-ST.

H-ST = heparin-coated JOSTENT FLEX; MLD = minimal lumen diameter; ST = noncoated JOSTENT FLEX.

restenosis rates among the three groups, although the study was underpowered to detect such differences; angiographic results for balloon angioplasty were surprisingly good, even with a 27% crossover rate; interestingly, short- and long-term event-free survival was similar for all three groups; and the heparin-coated stent did not show any angiographic or clinically relevant benefit compared with the uncoated stent.

## COMMENTARY

Despite the widespread acceptance of stenting for most coronary lesion subsets, the routine use of stenting in small vessels is less clearly established. The COAST trial compares the use of balloon angioplasty in small vessels (2.0 to 2.6 mm diameter by quantitative coronary angiography) with coronary stenting using either a heparin-coated stent or an uncoated stent. The study involved 21 centers in Europe and enrolled 605 patients into the three treatment arms. As expected, the mean post-procedure MLD and short-term luminal gain were significantly greater in both stent-treated groups. At follow-up, the primary end point parameter of six-month MLD was greater in both stent arms compared with balloon angioplasty, although the difference was of borderline significance ( $p = 0.049$ ). Mean percent stenosis at follow-up and mean net luminal gain were also significantly better with stenting. However, binary restenosis was not different among the treatment groups, and clinical outcomes were similar in all three groups. Although 27% of balloon angioplasty patients required crossover to stenting due to dissection or a suboptimal result, the overall results with balloon angioplasty of 32% binary restenosis and 84% event-free survival were quite good and were comparable to the results in both stent groups. In addition, the heparin-coated stent conferred no advantage for early or late clinical outcome or angiographic results compared with the uncoated stent in these small vessels.

It is perhaps not surprising that passive coating of a stent with an antithrombotic agent such as heparin would have no effect in prevention of restenosis. However, it does appear that there is still a role for balloon angioplasty alone in the

treatment of small vessels, with use of provisional stenting when needed for a suboptimal result.

MICHAEL J. COWLEY, MD, FACC

*Atherectomy Before MULTI-LINK® Improves Luminal Gain and Clinical Outcomes (AMIGO): A Comparison of Coronary Stenting With or Without Adjunctive Directional Coronary Atherectomy*

ANTONIO COLOMBO, MD, FACC,  
ON BEHALF OF THE AMIGO INVESTIGATORS  
CENTRO CUORE COLUMBUS AND  
SAN RAFFAELE HOSPITAL, MILAN, ITALY

**Background.** Previous studies have shown that acute angiographic minimal luminal diameter (MLD) and residual stenosis are strong determinants of a favorable outcome after coronary intervention. When stenting alone is applied to complex lesions, results may not be as favorable as results are with noncomplex lesions due to large plaque burden. The addition of directional coronary atherectomy (DCA) to stenting may reduce the involved plaque volume and thereby increase luminal gain and lower the subsequent clinical event and angiographic restenosis rates. **Methods.** We randomized 753 patients with de novo and restenotic native coronary lesions to stenting (single-vessel only) with ( $n = 381$ ) or without ( $n = 372$ ) adjunctive DCA and followed them up for 12 months. The two groups did not differ with respect to baseline and preprocedure angiographic characteristics. **Results.** The DCA/stent patients had a mean post-DCA residual stenosis of 32.0%; only 21.5% of the patients had a post-DCA residual stenosis <20% (optimal DCA). Mean postprocedure residual stenosis was 1.2% in the DCA/stent group and 4.9% in the stent-only group ( $p < 0.0001$ ). The 30-day composite rate of death, Q-wave infarction, or target-lesion revascularization for DCA/stent was 1.6% versus 1.1% for stent only (NS). Follow-up angiographic binary restenosis rates were not significantly different (24.1% for DCA/stent vs. 19.6% for stent only). At two participating centers where optimal DCA was more consistently practiced, the binary restenosis rates were 14%

for DCA/stent (50 lesions) versus 32% for stent only (47 lesions). This led us to analyze the data by separating patients with optimal from those with suboptimal DCA. Among patients at all trial centers, the binary restenosis rates were 16.2% for optimal DCA/stent and 31.8% for suboptimal DCA/stent ( $p = 0.01$ ). Suboptimal DCA/stent emerged as a significant risk factor for binary restenosis in multivariate analysis when compared with either optimal DCA/stent or stent only ( $p = 0.01$ ). **Conclusions.** There were no significant differences between DCA/stent and stent only in clinical-event or angiographic restenosis rates; this trial failed to show superiority of DCA/stent over stent only. The stent-only binary restenosis rate of 19.6%, compared with a hypothesis assumption of 30%, suggests that the lesions were too favorable. Optimal DCA was achieved in about one-fifth of lesions. At centers that more consistently achieved optimal DCA and where complex target lesions were more prevalent, DCA/stent appeared superior to stenting alone. Therefore, we continue to perform DCA with stenting for selected lesions.

## COMMENTARY

The potential role of coronary debulking using DCA to improve outcomes with coronary intervention has been the subject of a number of clinical trials. Earlier studies of DCA compared with balloon angioplasty alone were unable to show improved follow-up clinical outcomes despite better initial angiographic results. Subsequent studies comparing "optimal" DCA with balloon angioplasty were associated with improvement in certain follow-up parameters, such as angiographic restenosis, but without clear benefit in clinical outcomes.

The AMIGO trial was designed to show the superiority of DCA followed by stenting over coronary stenting alone. The study enrolled 753 patients who were randomized to receive DCA or no DCA followed by treatment with a MULTI-LINK® stent at 43 U.S. and European centers. Patients were evenly matched for baseline characteristics. Reference vessel size was approximately 3 mm, and nearly 60% of lesions were considered complex (American Heart Association/American College of Cardiology lesion class B2 or C). In this trial, the final angiographic percent stenosis was significantly less with DCA (1% vs. 5%), and the 30-day complication rates were similar and low (1.6% vs. 1.1%) in both groups. The primary end point of binary angiographic restenosis at follow-up was not significantly different (24% vs. 19.6%). Clinical event rates were also comparable.

Review of DCA results in the study showed that "optimal" DCA (defined as  $\leq 20\%$  residual stenosis prior to stenting) was achieved in only 21.5% of patients. In a subgroup analysis involving approximately 100 lesions from two centers in which optimal DCA was more consistently achieved, the binary restenosis rate was lower in the DCA group. However, in the overall study population, the occur-

rence of suboptimal DCA followed by stenting was a significant predictor of higher angiographic restenosis rates than stenting alone ( $p = 0.01$ ). Although subgroup analyses should be viewed with caution, it appeared that suboptimal DCA was associated with a negative effect on the restenosis rate compared with both optimal DCA and no DCA.

The concept of coronary plaque debulking as a method to improve outcomes with coronary intervention has been an attractive premise that has been difficult to validate in clinical practice. The AMIGO trial does not strengthen the case for routine debulking in this era of nearly universal coronary stenting.

MICHAEL J. COWLEY, MD, FACC

### *Safety and Feasibility of a Tacrolimus-Coated Drug-Eluting Stent: Short- and Mid-Term Results of Both the PRESENT and EVIDENT Trials*

EBERHARD GRUBE, MD, PhD, FACC

HEART CENTRE SIEGBURG, SIEGBURG, GERMANY

**Background.** Local delivery of immunosuppressive or anti-proliferative agents using a drug-eluting stent can inhibit in-stent restenosis, providing both a biological and mechanical solution to an old problem. Animal trials have shown that tacrolimus (FK 506), an immunosuppressive and anti-inflammatory macrolide, specifically reduces the reactive smooth-muscle-cell proliferation frequently associated with coronary interventions but does not noticeably affect endothelial cell proliferation. The prolonged in vivo kinetics of FK 506 is caused by the agent's lipophilicity and tissue-binding effects. A tacrolimus-eluting stent is available as a nanoporous ceramic-coated coronary stent (drug dosage, 3.75  $\mu\text{g}/\text{mm}$  of length) as well as a polytetrafluoroethylene-covered stent graft for use in saphenous vein grafts (22  $\mu\text{g}/\text{mm}$  of length). **Methods.** We enrolled patients in two separate nonrandomized single-dose phase-I safety studies with similar protocols. The Preliminary Safety Evaluation of Nanoporous Tacrolimus Eluting Stents (PRESENT) trial included patients with single, de novo native-vessel target lesions, 30 of whom received the tacrolimus-eluting coronary stent and 30 of whom received the same ceramic stent without active drug. In the Endovascular Investigation Determining the Safety of New Tacrolimus-Eluting Stent Grafts (EVIDENT) trial, 15 patients with single, de novo vein-graft lesions received the tacrolimus-eluting coronary stent graft. Stent implantation was guided by intravascular ultrasound in both studies. All patients received either clopidogrel or ticlopidine for six months and aspirin for 12 months; glycoprotein IIb/IIIa receptor inhibitors were used only if clinically indicated. **Results.** Safety was defined as freedom from the primary end point of major adverse cardiac events (MACE) at 30 days, a goal reached by all of the four EVIDENT and the 18 PRESENT patients whose data were available for analysis.

## COMMENTARY

Dr. Grube and colleagues report preliminary data on tacrolimus (FK 506), an agent that in animal studies reduces smooth-muscle-cell proliferation without effect on the endothelial cell proliferation. The EVIDENT and PRESENT trials are separate, single-dose, nonrandomized studies of two types of tacrolimus-coated stents (a ceramic-coated stent in the PRESENT trial; a PTFE-covered stent in the EVIDENT trial). These trials enrolled limited numbers of patients. The 30-day follow-up reported in the abstract showed no MACE; during the presentation at the American College of Cardiology 51st Annual Scientific Session, it was noted that two patients in the PRESENT study had subsequently returned with restenosis. Whether this is a dose-dependent effect is unknown. Longer follow-up of the complete data set will be necessary to establish the safety and restenosis rates when using this agent and these stent designs.

GEORGE W. VETROVEC, MD, FACC

## LATE-BREAKING CLINICAL TRIALS I

*Survival in Patients Presenting With Atrial Fibrillation: The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM)*

D. GEORGE WYSE, MD, PhD, FACC,  
AND THE AFFIRM INVESTIGATORS  
UNIVERSITY OF CALGARY, ALBERTA, CANADA

**Background.** Atrial fibrillation (AF) is a common arrhythmia associated with increased risk of stroke or death. Treatment can consist of either antiarrhythmic drugs to maintain sinus rhythm (SR) (rhythm control) or ventricular rate-controlling drugs that allow AF to persist or recur (rate control). Both strategies use anticoagulation. It has not been known whether one strategy is superior to the other.

**Methods.** The AFFIRM study compared the two treatment strategies in 4,060 anticoagulant-eligible patients who had at least 6 h of AF within the past six months, including at least one episode documented by electrocardiogram within the past 12 weeks. They were also required to have one or more risk factors for stroke or death, including age  $\geq 65$ , congestive heart failure, hypertension, poor left ventricular function, large left atrium, diabetes, or prior stroke or transient ischemic attack. Initial therapy in the rate control arm ( $n = 2,027$ ) consisted of digoxin (51%), beta-blockers (49%), and/or calcium-channel-blockers (41%), often in combinations. Initial therapy in the rhythm control arm ( $n = 2,033$ ) included amiodarone (39%), sotalol (33%), propafenone (10%), procainamide (6%), quinidine or flecainide (5% for each), or either disopyramide or moricizine in the remainder. Many drug changes occurred during follow-up, and nonpharmacologic therapies were used in only a few patients. **Results.** The prevalence of SR was 60% to 80% of patients in the rhythm control arm and

30% to 50% of patients in the rate control arm over a five-year period. The prevalence of successful rate control (defined by protocol) over a five-year period was 60% to 80% of patients in that arm. Prevalence of warfarin use was higher in the rate control arm (86% vs. 69% at 5 years). Crossover to the other management strategy occurred in more rhythm control patients than rate control patients over a five-year period ( $p < 0.0001$ ), with the crossover rate reaching 35% and 12% for the two respective groups. All-cause mortality, the primary end point, reached 24% in the rhythm control arm and 21% in the rate control arm at five years ( $p = 0.058$ ). The rates for the secondary end point of death, disabling stroke or anoxic encephalopathy, major bleeding, or cardiac arrest at five years were 29% and 28% for the two respective groups ( $p = 0.283$ ). There were no significant differences between the groups with respect to indicators of functional status (6-min walk, New York Heart Association functional class, Canadian Cardiovascular Society angina class) or quality of life. Most strokes in both groups occurred in patients not taking warfarin or with a subtherapeutic INR. Hospitalization was more common in the rhythm control group, and this has implications for cost. **Conclusions.** The AFFIRM trial has shown that rhythm control does not offer a survival benefit or an improvement in the quality of life or functional status when compared with rate control. Rate control is an acceptable primary therapy in such patients and may have some advantages. Anticoagulation should not be stopped in these patients.

## COMMENTARY

The AFFIRM trial results provide important data relevant to the management of patients with AF. Traditionally, there had been a strong bias, at least among cardiologists, toward treatment strategies aimed at restoring and maintaining SR when patients present with AF. Physicians and patients both were likely to attribute any symptoms they experienced as being due to the arrhythmia and believed that the risk of stroke and death could be minimized if SR were restored and maintained. These clinical impressions had, however, never been adequately examined in a clinical trial. The AFFIRM trial was large enough to address these questions. The study shows that, at least with currently available pharmacologic therapy, there is no distinct a priori advantage associated with a rhythm control strategy. Over a large group of patients, symptoms were equally well managed by careful rate control. Continuation of anticoagulant therapy appears to be indicated even if a rhythm control strategy is successfully implemented.

The AFFIRM trial data are likely to result in several revisions to the current guidelines for AF management. A decision on rate control or rhythm control should now be based on a patient's response to the initial therapy. Either option is an acceptable first choice. Extensive attempts to maintain SR are rarely indicated. Anticoagulation should be

continued in patients with risk factors for stroke even if SR is apparently maintained.

JOHN P. DiMARCO, MD, PHD, FACC

*The Effect of Short-Term Treatment With Azithromycin on Recurrent Ischemic Events in Patients With Acute Coronary Syndrome: The AZACS Trial*

BOJAN CERCEK, MD, FACC

CEDARS-SINAI MEDICAL CENTER, LOS ANGELES, CALIFORNIA

**Background.** There is a high rate of ischemic events within six months after an initial episode of acute coronary syndrome (ACS). In addition, vascular inflammation leading to intracoronary plaque rupture and thrombosis may in large part be due to infection by *Chlamydia pneumoniae* or other pathogens. Previous studies have suggested that treatment with azithromycin or roxithromycin, antibiotics with activity against *C. pneumoniae*, can be associated with reduced vascular inflammation and risk of ischemic events. The AZACS study tested the hypothesis that the addition of azithromycin to standard therapy shortly after presentation with ACS reduces the risk of recurrent ischemic events and death during the ensuing six months. This is the first large-scale double-blind, placebo-controlled clinical study evaluating treatment with macrolide antibiotics in patients with ACS. **Methods.** We randomized 1,439 patients with unstable angina or acute myocardial infarction (MI) at seven centers to either azithromycin (500 mg orally on the first day, followed by 250 mg daily for the following four days) (n = 716) or placebo (n = 723). The primary end points were death, cardiac arrest, nonfatal MI, or recurrent myocardial ischemia requiring revascularization over six months after discharge. There were no differences in the baseline characteristics and treatment strategies between the two groups. Six-month follow-up data were available for 702 patients in the active-therapy group and 710 patients in the control group. There were no differences in their use of anti-ischemic or other cardiac drugs. **Results.** Overall, the primary end point event rate was 12.6% in the placebo group and 12.3% in the azithromycin group (RR 0.98, 95% CI 0.74 to 1.28). The rates of the individual end points of death, nonfatal MI, or revascularization were not statistically different after six months. There was no significant difference in the secondary end point of unstable angina or congestive heart failure; nor, in subgroup analysis, were rates for these end points different for patients enrolled with acute MI or with antibodies to *C. pneumoniae*. **Conclusions.** We conclude that in patients admitted with ACS, short-term treatment with azithromycin did not reduce the subsequent occurrence of ischemic events or death over six months; and the results of treatment with azithromycin were no different in patients with or without with antibodies to *C. pneumoniae*.

## COMMENTARY

The AZACS trial, the first large antibiotic study (n = 1,412 patients) in the setting of ACS, attempted to confirm (or refute) a large apparent treatment effect of a short course of antibiotics as reported earlier in a smaller (n = 202) Argentine trial (ROXIS; Gurfinkel E, et al., *Lancet* 1997; 350:404-7). The four-day treatment regimen of azithromycin did not reduce the primary composite end point of death, nonfatal MI, or revascularization after six months (p = 0.77) in AZACS, nor were any of a number of secondary end points or subgroups benefited. A small, early separation of time-to-event curves was visually apparent, but the curves came together and then crossed two months after the four-day treatment course ended. Thus, if a role for antibiotic therapy exists and is to be established in the setting of ACS, a longer course of treatment or a different antibiotic will need to be tested (see also Commentary on WIZARD).

JEFFREY L. ANDERSON, MD, FACC

*Weekly Intervention With Zithromax for Atherosclerosis and Its Related Disorders: Preliminary Results of the WIZARD Study*

CHRISTOPHER M. O'CONNOR, MD, FACC

DUKE UNIVERSITY MEDICAL CENTER,  
DURHAM, NORTH CAROLINA

**Background.** Epidemiologic studies link antibodies to *Chlamydia pneumoniae* with coronary disease. The organism has been found in 60% of atherosclerotic plaques. Animal models suggest that infection by certain pathogens can be followed by the initiation and progression of early plaque formation. Furthermore, the pathogenesis of arterial *C. pneumoniae* infection is associated with an inflammatory condition that is consistent with atherogenesis. The clinical impact of treating arterial infection by *C. pneumoniae* can be assessed only in large clinical trials. The objective of the WIZARD trial was to determine whether therapy with the antibiotic azithromycin can prevent the recurrence of coronary heart disease in adults with a history of acute myocardial infarction (MI) longer than six weeks previously and elevated titers to *C. pneumoniae* antibodies. **Methods.** Excluded were patients with a chronic condition that requires antibiotic therapy and patients who have had a revascularization procedure within the previous six months. The patients were randomized to receive azithromycin (600 mg every day for three days, then 600 mg every week for 11 weeks) (n = 3,879) or placebo (n = 3,868). The primary end point was a composite of all-cause mortality, recurrent MI, myocardial revascularization, and hospitalization for angina. The patient groups had similar baseline demographic and clinical features, except for a greater history of coronary heart disease in the active-therapy group: 33% versus 31% in the control group (p < 0.05). They also had similar usage of cardiovascular medications at baseline.

**Results.** Over a follow-up of 48 months (median, 2.1 years), there was no significant difference between the two groups in the rate of the primary end point; nor was there a significant benefit from azithromycin for any of the primary end point components or for any patient subgroup by baseline cardiac risk factors such as hypertension, diabetes, or hypercholesterolemia. There was no benefit in patients who were either positive or negative for *C. pneumoniae* antibodies. **Conclusions.** We conclude that short-term azithromycin therapy was safe and well tolerated, but we found no evidence that it conferred a benefit for the primary end point, whether in the presence of *C. pneumoniae* antibodies or not. A post-hoc analysis suggested a possible early treatment benefit that was not sustained over the total observation period.

## COMMENTARY

As the first antibiotic megatrial (N = 7,747 patients) for coronary artery disease (CAD), WIZARD is of great interest. Overall, this is a negative study (hazard ratio = 0.93, p = 0.23), confirming the lack of a meaningful long-term clinical benefit of a three-month course of azithromycin in patients with stable CAD. This result is similar to that reported earlier in the smaller (N = 302) ACADEMIC trial (Muhlestein JB, et al., *Circulation* 2000; 102:1755-60) and contrary to the apparent, dramatic treatment benefit in an initial British pilot study (Gupta S, et al., *Circulation* 1997;96:404-7). However, a secondary treatment-by-time analysis of WIZARD leaves a ray of hope for antibiotic therapy: at six months, the secondary end point of death/MI was reduced by one-third (relative risk, 0.67, 95% CI 0.48 to 0.94). Thereafter, differences between treatment groups gradually diminished, suggesting a transient and cytostatic (rather than cytotoxic) effect of the three-month course of azithromycin. This secondary analysis heightens interest in Azithromycin and Coronary Events Study, which is testing one year of azithromycin, and Pravastatin or Atorvastatin Evaluation and Infection Therapy, which is testing another, potentially more cytotoxic antibiotic, gatifloxacin.

JEFFREY L. ANDERSON, MD, FACC

*The Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) Trial*

SHAUN G. GOODMAN, MD, FACC

ST. MICHAEL'S HOSPITAL, TORONTO, CANADA

**Background.** Current management of patients with high-risk non-ST-segment elevation acute coronary syndromes (NSTE ACS) generally incorporates glycoprotein IIb/IIIa inhibition. Recently, the low-molecular-weight heparin (LMWH) enoxaparin has been demonstrated to be superior to unfractionated heparin (UFH) in two large trials. The safety and efficacy of combination IIb/IIIa inhibitor and LMWH therapy has yet to be determined and was the

purpose of the INTERACT trial. The primary objective of the randomized, open-label study was to evaluate the incidence of major bleeding in this clinical setting in patients receiving either LMWH and UFH. Its secondary objectives were to assess the incidence of ischemic ST-segment shifts during continuous electrocardiographic (ECG) monitoring and of clinical ischemic events, including death and myocardial (re)infarction (MI). **Methods.** Randomized patients at 54 centers had high-risk NSTE ACS with resting angina within the past 24 h and ST-segment depression ( $\geq 0.1$  mV) or transient ( $< 20$  min) elevation ( $\geq 0.1$  mV) in  $\geq 2$  contiguous leads, or troponin rise to  $\geq 3$  times reference level or creatine kinase-MB greater than normal. All patients received aspirin and eptifibatid (180  $\mu\text{g}/\text{kg}$  bolus followed by 2.0  $\mu\text{g}/\text{kg}/\text{min}$  infusion for 48 h). They received enoxaparin 1 mg/kg SC twice daily (n = 380) or UFH 70 U/kg bolus + 15 U/kg/h continuous infusion (n = 366), titrated to an aPTT of 1.5 to 2 times control (50 to 70 s) for 48 h. All patients underwent baseline, 48, and 96 h 12-lead ECG and two consecutive 48-h 7-lead (3 channel) continuous ECG. Safety end points included major and minor bleeding events. Efficacy end points consisted of clinical ischemic events as well as the frequency of recurrent ischemia on continuous ECG in the first 48 h and in the subsequent 48 h after drug discontinuation. Thirty-day death, MI or re-MI, severe recurrent ischemia requiring urgent revascularization, and recurrent ischemia with ECG changes were also measured. **Results.** Frequency and time to angiography and revascularization were similar in the two groups. The respective rates of major non-coronary bypass-related bleeding for the enoxaparin versus UFH groups were 1.1% versus 3.8% (p = 0.014) at 48 h and 1.8% versus 4.6% (p = 0.030) at 96 h. The rates of minor bleeding at 96 h were 32.5% and 24.9%, respectively (p = 0.024). Ischemia developed by ECG within 48 h in 14% of the enoxaparin group and 25.1% of the UFH group (p = 0.0002), and from 48 to 96 h in 12.7% and 25.9%, respectively (p = 0.0001). The 30-day composite rates of death and MI or re-MI were 5% and 9% (p = 0.031); of death and MI or re-MI, or recurrent ischemia were 13.5% and 16.2% (p = 0.30); and of death, MI or re-MI or recurrent ischemia including ECG changes were 8.4% and 12.6% (p = 0.064), respectively. **Conclusions.** In summary, enoxaparin when compared with UFH in these patients, both with eptifibatid, was associated with a lower rate of major bleeding, higher rate of minor bleeding, lower rate of death or infarction, and lower rate of ischemia during and shortly after treatment. The trial, therefore, suggests that in high-risk NSTE ACS patients who receive eptifibatid, enoxaparin provides significantly better safety and efficacy than does standard UFH.

## COMMENTARY

The randomized INTERACT trial compares the use of LMWH with UFH in conjunction with the platelet glyco-

protein inhibitor eptifibatide. Low molecular weight heparin in the form of enoxaparin was given 1 mg/kg subcutaneously twice daily versus a 15 U/kg/h UFH infusion.

The primary end point of major bleeding was reduced significantly from 4.6% with UFH to 1.1% with LMWH. Minor bleeding was similar in the two groups (24.9% vs. 32.4%) at 96 h. Ischemic events at 96 h were decreased from 24.9% in the UFH group versus 12.7% in the LMWH group.

The diminution of both major bleeding and ischemic events suggests that the frequency of both under-anticoagulation and over-anticoagulation may be reduced by LMWH. In conjunction with this platelet glycoprotein inhibitor, overall ischemic events were diminished by LMWH in the INTERACT trial, and the safety of LMWH was clearly demonstrated.

TED E. FELDMAN, MD, FACC

## LATE-BREAKING CLINICAL TRIALS II

*Improved Survival With Prophylactic Implantable Cardioverter-Defibrillator Therapy in Patients With Prior Myocardial Infarction and Reduced Left Ventricular Ejection Fraction: The MADIT-II Trial*

ARTHUR J. MOSS, MD, FACC

UNIVERSITY OF ROCHESTER, ROCHESTER, NEW YORK

**Background.** The MADIT-II trial evaluated the effect of implantable cardioverter-defibrillator (ICD) therapy on survival in 1,232 patients of any age who had prior myocardial infarction (MI), had a left ventricular ejection fraction (LVEF) of  $\leq 30\%$ , and had not been required to undergo electrophysiologic testing for risk stratification. Excluded were patients in New York Heart Association (NYHA) class IV heart failure (HF) and those who had experienced an MI within the past one month or undergone coronary bypass surgery within the past three months. **Methods.** A two-sided sequential design was used, with all-cause mortality as the end point. The patients were randomized in a 3:2 ratio to receive an ICD ( $n = 742$ ) or to conventional management without an ICD ( $n = 490$ ); the groups were similar in baseline demographic and clinical characteristics. The mean LVEF in each arm of the trial was 23%. Medication usage at the last follow-up was similar in the two groups, with more than 70% in both receiving angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics. **Results.** The trial, initiated July 8, 1997, was halted on November 20, 2001, by the Data Safety and Monitoring Board because of a significant survival benefit in the ICD group. After an average of 21 months of follow-up, mortality in the ICD and conventional-therapy groups were 14.2% and 19.8%, respectively ( $p = 0.016$ ). The hazard ratio for all-cause mortality was 0.69 (95% CI, 0.51 to 0.93), indicating a 31% decrease in mortality with ICD therapy. This benefit of device therapy survival was similar in patient subgroups by age, gender, LVEF, NYHA class, QRS

duration, and other parameters. Analysis of mortality events by treatment arm showed a markedly lower rate of arrhythmic death in the ICD group: 27 events (3.6% of the total group) versus 46 events in the conventional-therapy group (9.4% of the total). **Conclusions.** This finding suggests that the reduction in all-cause mortality in the ICD group is consistent with the ICD as the protective mechanism. We conclude that in patients with prior MI and moderate to severe left ventricular (LV) dysfunction, the use of ICD prophylaxis in addition to conventional medical therapy results in a significant reduction in mortality compared with conventional medical therapy alone.

## COMMENTARY

The use of an ICD has shown to be effective in reducing risk of death in survivors of cardiac arrest (secondary prevention) as well as high-risk patients with coronary artery disease (CAD) and depressed LV function with additional markers of augmented arrhythmia risk such as nonsustained ventricular tachycardia or inducible ventricular tachycardia on electrophysiologic testing. The MADIT-II trial tested the broader extension of the use of an ICD to high-risk patients with prior MI depressed LV function ( $EF \leq 30\%$ ) but without the use of Holter monitoring or electrophysiologic testing to refine the risk of arrhythmic death.

MADIT II is a high-quality study that clearly extends the life-saving benefits of the ICD to the broader population post-MI patients with LV dysfunction but without marked HF and without a major selection for arrhythmic risk. By extending the use of ICDs to this broader population, implications for both public health and financial allocations are immense. Since not all patients with stable CAD depressed LV function die a sudden ICD-preventable arrhythmic death, we are going to need more information from the investigative community on the best ways to utilize the MADIT II results within the confines of health care budgets. Information regarding nonfatal events, such as the development of HF, recurrent MI, other hospitalizations, cost-benefit analyses, and quality of life, from MADIT-II and other ongoing studies will be needed for the optimal implementation of the important scientific advance gained from MADIT II.

MARC A. PFEFFER, MD, PhD, FACC

*Effects of the Endothelin Receptor Antagonist Bosentan on Morbidity and Mortality in Patients With Chronic Heart Failure: The ENABLE 1 and 2 Trial Program*

MILTON PACKER, MD, FACC

COLUMBIA PRESBYTERIAN MEDICAL CENTER,  
NEW YORK CITY, NEW YORK

**Background.** Endothelin-1 (ET-1) is a potent endogenous vasoconstrictor capable of exerting a wide range of adverse biological and pathophysiological effects in chronic heart failure (HF). Antagonism of endothelin receptors has been

shown to favorably influence cardiac remodeling and hypertrophy and to prolong life in experimental HF. Bosentan is an oral dual endothelin (ETA/ETb) receptor antagonist that has produced favorable hemodynamic effects in patients with chronic HF and improved the clinical status of patients in early small pilot studies. However, the long-term effects of endothelin antagonism on the morbidity and mortality of patients with chronic HF have not been evaluated. The ENABLE (ENdothelin Antagonism with Bosentan for Lowering of Events) trial program consisted of two identical, double-blind, randomized, placebo-controlled, concurrent trials conducted at 150 centers in Europe, Israel, and Australia (ENABLE-1) and the U.S. and Canada (ENABLE-2). **Methods.** The two trials enrolled 1,613 patients with New York Heart Association class IIIB to IV ischemic or nonischemic HF, and a left ventricular ejection fraction (LVEF) <35%, who had been hospitalized for chronic HF within 12 months or had a 6-min walk distance <375 m. Patients were randomized to either bosentan (62.5 mg twice daily, escalated in four weeks to a target dose of 125 mg twice daily) (n = 805) or matching placebo (n = 808), both added to conventional therapy, for a mean of 18.7 months. The trials continued until the prespecified number of 600 primary morbidity/mortality events had been observed. **Results.** For the primary end point of all-cause mortality or hospitalization for chronic HF, the rates were 38.8% in the bosentan group and 39.7% in the placebo group with a hazard ratio of 1.01 (p = 0.9). For the secondary end point of all-cause mortality, the rates were 19.9% and 21.4%, respectively, hazard ratio 0.94 (p = 0.53). In subgroup analysis, bosentan was not associated with a significant benefit in either the primary or the secondary end point by age, gender, ENABLE trial (1 or 2), LVEF, functional class, etiology of HF, or use of beta-blockers at baseline. Bosentan was associated with an increased risk of worsening chronic HF in these studies, possibly the results of an unexpected increase in fluid retention: bosentan-treated patients showed early and sustained increases in body weight and peripheral edema and decreases in hemoglobin. In addition, as previously reported with higher doses of bosentan, the use of low doses in this trial was associated with an excess frequency of liver function abnormalities, manifested primarily as increases in hepatic transaminases that were rapidly reversible upon discontinuation of therapy. **Conclusions.** Long-term treatment with the endothelial antagonist bosentan did not reduce the risk of death or hospitalization or the risk of death alone in patients with chronic HF. This lack of benefit may have been related to the early and sustained development of fluid retention. Therefore, efforts to minimize fluid retention, either with much more aggressive use of adjunctive diuretics or perhaps lower doses of bosentan, may help to identify the appropriate role of endothelial antagonism in the treatment of HF.

## COMMENTARY

The ENABLE study is another contribution to the rich collection of large randomized clinical trials of medical management in the world of HF. There were certainly excellent theoretical reasons and experimental evidence to indicate that the blocking of endothelin receptors should be beneficial in HF, and smaller short-term clinical studies revealed mixed results but were generally encouraging. This definitive study, however, failed to show any improvement in the primary or secondary end points when the endothelin receptor antagonist bosentan was added to standard medical therapy for HF. Importantly, there was also a negative aspect to the study in that there was an increased incidence of worsening HF observed in the bosentan-treated patients soon after the initiation of therapy.

It is difficult to know whether more meticulous attention to management of volume status after introduction of the drug could have obviated the worsening HF that was observed. All the patients were managed at experienced HF centers in the U.S. and Europe, where excellent management would be expected. It is also difficult to know whether the dose of bosentan chosen for the study was the "optimal" dose. While the dose was, in fact, considerably lower than that used in earlier clinical trials, it is possible that even lower doses could prove beneficial without the fluid retention side effects.

For the moment, the role of endothelin receptor antagonism in the therapy of HF remains uncertain.

SHARON HUNT, MD, FACC

*Randomized Evaluation of Mechanical Assistance for Treatment of Congestive Heart Failure (REMATCH): Major Survival Benefit From Left Ventricular Assist Devices for Patients Receiving Intravenous Inotropic Therapy*

LYNNE WARNER STEVENSON, MD, FACC,  
LESLIE MILLER, MD, FACC,  
PATRICE DESVIGNE-NICKENS, MD,  
DONNA MANCINI, MD, DEBORAH ASCHEIM, MD,  
ALAN WEINBERG, MD, DALE RENLUND, MD,  
RONALD OREN, MD,  
STEVEN KRUEGER, MD, FACC,  
MARIA COSTANZO, MD, FACC,  
L. SAMUEL WANN, MD, FACC, NUALA RONAN, MD,  
LOPA GUPTA, MD, FOR THE REMATCH

CARDIOLOGISTS

BRIGHAM & WOMEN'S HOSPITAL,  
BOSTON, MASSACHUSETTS

**Background.** New therapies should be directed toward the patients most likely to benefit. Left ventricular assist devices (LVADs) as permanent therapy will have the greatest impact on survival in those patients for whom heart failure (HF) severity predicts early death during medical therapy but does not compromise the postoperative course. **Methods.** Patients in REMATCH had New York Heart Association class IV symptoms with left ventricular ejection

fraction (LVEF) <25% and were ineligible for transplantation. Severity was further defined by a peak  $\text{VO}_2$  of <12 to 14 ml/kg/min or an inability to wean intravenous inotropic agents. The entire group was randomized to undergo implantation with the HeartMate LVAD or to receive optimal medical management from experienced HF cardiologists. The latter management strategy focused on optimization of oral therapy without inotropic infusions (i.e., “survival without suffering”). **Results.** The primary hypothesis of REMATCH was that an LVAD would reduce mortality by 33% over the trial’s two-year follow-up. As previously reported, one-year survival in the LVAD arm was 51% versus 28% for optimal medical management, and the two-year survival was 28% and 10%, respectively ( $p = 0.0015$ ). In the current analysis, we attempted to identify a subgroup of patients in the REMATCH trial who derived the major survival benefit and meaningful quality of life from the LVAD as destination therapy. Of the 129 patients in REMATCH, 91 (71%) were receiving inotropic infusions at baseline. Hypotension, low cardiac output, and renal dysfunction were the most common reasons for continuing inotropic infusions. The patients receiving inotropic infusions at baseline had the same mean LVEF but more severe HF than those not receiving inotropic infusions, as indicated by lower mean systolic blood pressure (99 mm Hg vs. 107 mm Hg,  $p < 0.019$ ), lower serum sodium (134 mEq/l vs. 137 mEq/l,  $p < 0.0008$ ), and a trend for higher pulmonary wedge pressure ( $p < 0.06$ ) despite inotropic infusions. Among patients receiving intravenous inotropes at baseline, survival at six months reached 58% in the LVAD group versus 39% in the group receiving medical management, and by one year the survival rates were 49% and 22%, respectively ( $p = 0.0016$ ). By two years after randomization of the patients receiving inotropic infusions, 24% of the LVAD group were still alive, and all patients in the medical group had died. Quality-of-life measures in this group showed more favorable outcomes in the LVAD group at all time points, but because of small patient numbers in the medical group the difference did not reach significance. Among patients not receiving intravenous inotropic agents at baseline, the survival rate at six months was 61% in both the LVAD group and the group receiving optimal medical management, at one year 56% and 40%, respectively, without significant difference during the two-year period ( $p = 0.52$ ). **Conclusions.** The major benefit of the LVAD as destination therapy was observed in patients receiving inotropic therapy at the time of randomization. The immediate extension of currently successful LVAD technology to a less-sick population would not be expected to confer a benefit comparable to that shown in REMATCH. However, further improvement in outcomes is anticipated with device modifications and other management strategies such as the effective infection prophylaxis that has already decreased complication rates at programs in Salt Lake City and Minneapolis. As device complications decrease, there will be a benefit for a broader population. For the current

selection of candidates, the use of intravenous inotropic therapy alone should not be viewed as a sufficient indication for the LVAD as destination therapy; inotropic infusions are frequently used in patients who do not require them and who are frequently considered unweanable until they undergo redesign of their other medical therapy at expert centers. The urgent implications of this study are that we need to use the imminent “incubation period” before allowing multiple support devices to proliferate in order to better understand the candidate population, particularly with regard to the real and perceived need for inotropic support. Furthermore, the identification of this population mandates an increased attention to development of alternative therapies for end-stage HF for patients who are not candidates for devices. Such therapies should include better inotropic therapy for symptom palliation and enhancement of hospice therapies for those who face imminent mortality.

## COMMENTARY

It is clear that, although heart transplantation provides an excellent therapy to extend life and improve its quality for patients with HF that is truly end-stage, the limited donor supply restricts transplantation to making a quantitatively small contribution to the considerable number of patients who could benefit from it. It is clear as well that many patients with end-stage HF have contraindications to heart transplantation. Thus, there is a great need for alternatives to allotransplantation of the heart.

This subset analysis of the previously published REMATCH trial of permanent circulatory support with LVAD technology in patients with end-stage heart disease who were, mainly because of advanced age, considered ineligible for heart transplantation provides important insight into the study data. It reveals that the improved survival with LVAD use seen in this study was really confined to the 70% of the group who were truly inotrope dependent. This fact emphasizes the danger in considering the extension of the LVAD technology used in this study to a less-sick population. The survival rates in the LVAD patient group in this study are so markedly inferior to those expected after transplantation that it is difficult to view the current generation of LVAD technology as a true “alternative” to transplantation.

SHARON HUNT, MD, FACC

*A Prospective, Blinded Trial of B-Type Natriuretic Peptide as a Diagnostic Test for the Emergency Diagnosis of Heart Failure: The Breathing Not Properly (BNP) Multinational Study*

ALAN S. MAISEL, MD, FACC,  
PETER A. McCULLOUGH, MD, MPH, FACC

UNIVERSITY OF CALIFORNIA-SAN DIEGO  
SCHOOL OF MEDICINE, SAN DIEGO VETERANS AFFAIRS  
MEDICAL CENTER, SAN DIEGO, CALIFORNIA;  
UNIVERSITY OF MISSOURI-KANSAS CITY  
SCHOOL OF MEDICINE, TRUMAN MEDICAL CENTER,  
KANSAS CITY, MISSOURI

**Background.** The neurohormone B-type natriuretic peptide (BNP) is released from ventricular myocytes in response to wall tension caused by ventricular volume expansion and pressure overload. Measurement of BNP has been approved as an aid to the diagnosis of congestive heart failure (CHF). In the prospective BNP Multinational Study, we sought to determine the diagnostic utility of BNP in the emergency department (ED) evaluation of dyspnea in a broad spectrum of patients. **Methods.** A total of 1,586 patients who presented to the ED with acute dyspnea as their primary complaint upon arrival underwent measurement of BNP with a point-of-care device. Patients with acute myocardial infarction or renal failure as the cause of dyspnea were excluded. Emergency physicians were asked to give a blinded, pre-test probability of the diagnosis being CHF. The gold standard for CHF was adjudicated by two independent cardiologists, blinded to BNP results, who reviewed all clinical data and standardized CHF scores. The primary end point was diagnostic accuracy. The analysis used a Bayesian approach that took into account: 1) the a priori pre-test probability from the ED clinician; 2) the BNP test converted to a likelihood ratio through the range of diagnostic values; and 3) a post-test probability generated from these two values. The final diagnosis was CHF in 744 (46.9%), a history of CHF and left ventricular (LV) dysfunction but dyspnea due to noncardiac causes in 72 (4.5%), and not CHF in 770 (48.5%). Median levels of BNP in the patients with CHF as a final diagnosis were 600 pg/ml; in those with LV dysfunction but a noncardiac cause of dyspnea, 150 pg/ml; and in patients without CHF, 50 pg/ml ( $p < 0.0001$ ). Among the patients with a final diagnosis of CHF, BNP levels varied significantly as a function of New York Heart Association (NYHA) class; the median BNP values for NYHA class I ( $n = 18$ ), II ( $n = 152$ ), III ( $n = 351$ ), and IV ( $n = 276$ ) were 150, 250, 550, and 900 pg/ml, respectively. At a cutoff of 100 pg/ml, BNP had a diagnostic sensitivity of 90%, a specificity of 76%, a positive predictive value of 79%, and a negative predictive value of 89%. For the primary end point of diagnostic accuracy, clinical judgment (with ED physicians required to be at least 80% certain of a CHF diagnosis) achieved an accuracy of 74.0%, the BNP test achieved an accuracy of 81.1%, and clinical judgment combined with the BNP test achieved an accuracy of 81.6% ( $p < 0.0001$ ). In 43% of cases, the ED physician was uncertain of the final diagnosis (ED probabilities between 20% and 80%). In these cases, if BNP at a cutoff of 100 pg/ml, clarified 75% of those cases, leaving an absolute 11% of patients in whom there was uncertainty, implying additional testing would be warranted. **Conclusions.** The BNP test adds independent diagnostic information to the traditional components of the CHF evaluation (history, physical exam and chest X-ray). Mean BNP values reflect functional class in patients with heart failure (HF). In patients for whom the conventional ED diagnosis of HF is equivocal, the use of BNP at a cutoff of 100 pg/ml, will correctly classify 74% of cases. The

implications of this study are that BNP should be included as a component in the initial diagnostic evaluation of dyspnea, where it can play a role in confirming the clinical diagnosis and, importantly, in improving diagnostic accuracy in the large proportion of cases where there is uncertainty.

## COMMENTARY

B-type natriuretic peptide is now accepted as an adjunctive diagnostic test to confirm the presence of HF. This trial represents an important step by investigators in assessing the value of plasma BNP as an aid in the diagnosis HF in the setting of the hospital ED. The value of the test lies mainly in its negative predictive value, although increased plasma BNP levels may help to identify patients with more advanced HF. Plasma BNP was more accurate than the clinical judgment of the ED physician. The Breathing Not Properly study confirms the utility of plasma BNP as an aid in the diagnosis of HF. However, the design of the study did not allow for a direct testing of whether BNP adds value to clinical judgment, which is perhaps a more important question in the "real world." Patients with HF may have intermediate plasma BNP levels when clinically stable or only mildly symptomatic. Age, gender, and diastolic function can also alter plasma BNP levels. Normal levels and very high levels are seemingly of greatest value. However, the intermediate BNP values may possibly be used to guide therapeutic decisions. There is already a suggestion that BNP-guided therapy may be more beneficial to patients than non-BNP-guided conventional therapy. However, this hypothesis needs to be tested in a randomized controlled trial.

GARY S. FRANCIS, MD, FACC

### *Heart Allograft Rejection: Detection With Breath Alkanes in Low Levels (the HARDBALL Study)*

MICHAEL PHILLIPS, MD,\*†,  
JOHN P. BOEHMER, MD, FACC,‡,  
RENEE N. CATANEO, MA,\*  
TASEER CHEEMA, MD,\*  
HOWARD J. EISEN, MD, FACC,§,  
JOHN T. FALLON, MD, PhD,||,  
PETER E. FISHER, MD,¶,  
ALAN GASS, MD, FACC,¶,  
JOEL GREENBERG, BS,\*  
JON KOBASHIGAWA, MD, FACC,#,  
DONNA MANCINI, MD,¶,  
BARRY RAYBURN, MD, FACC,\*\*,  
MARK J. ZUCKER, MD, FACC, ††

We thank Eugene Sersen, PhD, for statistical advice and review.

\*MENSANA RESEARCH INC., FORT LEE, NEW JERSEY;

†NEW YORK MEDICAL COLLEGE, VALHALLA, NEW YORK;

‡M. S. HERSHEY MEDICAL CENTER OF THE PENNSYLVANIA STATE UNIVERSITY SCHOOL OF MEDICINE, HERSHEY, PENNSYLVANIA;  
§TEMPLE UNIVERSITY HOSPITAL, PHILADELPHIA, PENNSYLVANIA;  
||MOUNT SINAI MEDICAL CENTER, NEW YORK CITY, NEW YORK;  
¶COLUMBIA PRESBYTERIAN MEDICAL CENTER, NEW YORK CITY, NEW YORK;  
#UNIVERSITY OF CALIFORNIA, LOS ANGELES MEDICAL CENTER, LOS ANGELES, CALIFORNIA;  
\*\*UNIVERSITY OF ALABAMA AT BIRMINGHAM, BIRMINGHAM, ALABAMA;  
††NEWARK BETH ISRAEL MEDICAL CENTER, NEWARK, NEW JERSEY

**Background.** Endomyocardial biopsy remains the gold standard for the detection of tissue rejection in patients with transplanted hearts. However, the procedure is costly, highly invasive, of limited accuracy, and can cause infection, arrhythmias, or other complications. A sensitive and non-invasive screening test for heart transplant rejection would represent an advance. The rejection process is accompanied by oxidative stress caused by increased mitochondrial production of reactive oxygen species. Oxidative stress degrades polyunsaturated fatty acids in membranes by lipid peroxidation, which releases alkanes and methylalkanes, volatile organic compounds (VOCs) that are excreted in the breath. **Methods.** We evaluated a breath test for oxidative stress—the breath methylated alkane contour (BMAC)—using a proprietary breath VOC collection device as a screening tool in heart transplant recipients at seven institutions prior to their scheduled endomyocardial biopsy. We also collected breath samples from healthy, age-matched normals. Collection of the 1,061 breath samples required approximately 2 min of each patient's time. A site pathologist and two reviewers independently scored biopsies for International Society for Heart and Lung Transplantation (ISHLT) rejection grade. Breath VOCs were analyzed by gas chromatography and mass spectroscopy, and the BMAC was derived from alveolar gradients (relative abundance in breath minus relative abundance in air) of C4-C20 alkanes and monomethylalkanes. The BMAC results were compared with the jointly agreed ISHLT scores, and VOC markers of rejection were identified by discriminant analysis. **Results.** The independent-reviewer biopsy results disclosed 645 patients (60.8%) with ISHLT rejection grade 0 (no rejection) and 281 (26.5%) with grade 1 (mild) rejection, 93 (8.8%) with grade 2 (moderate) rejection, and 42 (4.0%) with grade 3 (severe) rejection. Compared with the independent reviewers, a biopsy reading by a site pathologist had a sensitivity of 42.4% and specificity of 97.0% for grade 3 rejection. Breath test results revealed nine VOCs whose levels represented markers of grade 3 rejection. In a predictive model, the breath markers had a sensitivity of 78.6% and specificity of

62.4%; the cross-validated model had a sensitivity of 59.5% and specificity of 58.8%. Thus, the breath test for markers of oxidative stress was more sensitive but less specific for grade 3 heart transplant rejection than were biopsy readings by site pathologists. The negative predictive value of the breath test for grade 3 rejection was 97.3%, which was similar to that of a biopsy reading by a site pathologist (97.5%) (i.e., in a patient with a negative breath test, a biopsy contributes no additional clinical information). **Conclusions.** Based on these findings, a screening breath test could potentially reduce the number of endomyocardial biopsies for heart transplant rejection by at least one-half with no loss of diagnostic accuracy.

## COMMENTARY

The “holy grail” in the surveillance for cardiac rejection in heart transplant patients has always been the discovery of a noninvasive, inexpensive, readily available, “low-tech” alternative to the use of the endomyocardial biopsy, a technique that possesses none of these characteristics but is currently considered the gold standard. The assay described in the **HARDBALL** study is another in a long series of technologies that are candidates for replacing surveillance heart biopsies, and it is certainly one of the most unusual, basically being a breathalyzer test.

The study shows a surprising lack of consistency between biopsy interpretation by the pathologist at the transplant program site and the independent pathologist working with the authors. It also shows that, although only 9 of 42 (independent pathologist–interpreted) biopsies with grade 3 rejection were predicted by the threshold level of volatile organic compounds that the authors set for the breath sample, the negative predictive value for grade 3 rejection was 97.3%. These results are difficult to evaluate given the disparity of pathology interpretation, and adoption of the technology also awaits further investigation and correlation with the presence or absence of concurrent patient illnesses, such as hemodynamic compromise and infection, which theoretically could decrease sensitivity and specificity of anything that is a marker of oxidative stress.

SHARON HUNT, MD, FACC

## LATE-BREAKING CLINICAL TRIALS III

*Results of the InSync ICD Clinical Trial*

JAMES B. YOUNG, MD, FACC

THE CLEVELAND CLINIC FOUNDATION, CLEVELAND, OHIO

**Background.** More than one-third of patients with moderate-to-severe heart failure (HF) have ventricular dyssynchrony, which leads to poor left ventricular (LV) function, limited exercise tolerance, and impaired quality of life (QOL). The InSync ICD trial is a multicenter, double-blind controlled study evaluating the safety and effectiveness of cardiac resynchronization therapy (CRT) in patients with advanced (New York Heart Association [NYHA] class III to IV) systolic HF, LV ejection fraction  $\leq 35\%$ , ventricular

dyssynchrony, and an indication for an implantable cardioverter-defibrillator (ICD). **Methods.** A total of 362 such patients were implanted with an InSync model 7272 ICD with anti-tachycardia and biventricular pacing. Within three to seven days, 186 patients were randomized to have their implant control (their CRT unit) set to "on," and 176 patients were randomized to have their CRT units set to "off." The ICD functions were continuously activated in all patients. The primary safety end points included freedom from ICD discharges and system and LV lead-related complications. Primary effectiveness end points included were QOL, NYHA class, and 6-min hallwalk distance. Secondary end points included cardiopulmonary exercise testing (peak  $\text{VO}_2$  and exercise time), neurohormonal variables, and the HF clinical composite response (incorporates death, HF hospitalizations, NYHA class, and global self-assessment into categories of "improved," "unchanged," or "worsened" HF status). **Results.** At six months, mean QOL scores had improved by 19 points in the CRT-on group and by 10 points in the CRT-off group ( $p = 0.0098$ ); NYHA functional class improved in 63% and 47%, respectively ( $p = 0.028$ ); mean peak  $\text{VO}_2$  had improved by 1.1 ml/kg/min in CRT-on patients and had not changed in CRT-off patients ( $p = 0.05$ ); mean total exercise time had changed by +58 s and -26 s, respectively ( $p < 0.001$ ). The clinical composite end points were improved, 55% for CRT-on patients and 40% for CRT-off patients; no change, 19% and 26%; and worsened, 26% and 33% ( $p = 0.038$  for all differences between treatment groups). There were no significant six-month differences in 6-min hallwalk. **Conclusions.** In the patients with moderate-to-severe HF, cardiac resynchronization therapy improved QOL, functional capacity, and exercise tolerance and had an acceptable safety profile.

## COMMENTARY

Device therapy has many potential applications in patients with HF and LV dysfunction. Biventricular pacing may improve HF symptoms and functional status by reversing ventricular dyssynchrony. An ICD may decrease arrhythmic death and, possibly, total mortality. Since device-to-device interactions can be a source of potential problems whenever two devices are used in the same patient, it would be beneficial to have these functions combined in a single device in appropriate patients with HF. The InSync ICD trial is the first reported large trial of such a combined device. All patients in the study had an indication for ICD therapy, but their HF appears to have been somewhat less severe than was the case in previous studies on CRT. There was a consistent pattern toward improvement in HF status; but, as in the trials of biventricular pacing alone, many patients also improved even if the resynchronization was not activated. Larger studies with long follow-up trials will be needed to determine whether biventricular pacing provides better survival than ICD therapy alone. It will also be

important to determine if the benefits are maintained in the long term.

JOHN P. DiMARCO, MD, PhD, FACC

*The 4E Study: Eplerenone, Enalapril, and Eplerenone/Enalapril Combination Therapy in Patients With Left Ventricular Hypertrophy*

BERTRAM PITT, MD, FACC

UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN

**Background.** Left ventricular hypertrophy (LVH) is associated with significant increases in cardiovascular morbidity and mortality in hypertensive patients. Activation of the renin-angiotensin-aldosterone system plays an important role in the pathophysiology of LVH. Although angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-II receptor blockers and their combination fail to suppress aldosterone over the long term, this may be accomplished by aldosterone receptor blockers. These agents prevent LVH progression and cardiac fibrosis in hypertensive patients when used alone or in combination with an ACE inhibitor.

**Methods.** We conducted a double-blind, forced-titration study comparing the efficacy and tolerability of eplerenone, a selective aldosterone blocker, with the ACE inhibitor enalapril and also with their combination. Patients with diastolic blood pressure (BP) at least 90 mm Hg and  $<114$  mm Hg and systolic BP  $>140$  mm Hg and  $\leq 200$  mm Hg with echocardiographic LVH were randomized after a 14-day washout period to eplerenone only 200 mg/day ( $n = 64$ ), enalapril only 40 mg/day ( $n = 71$ ), or eplerenone 200 mg/day plus enalapril 10 mg/day ( $n = 67$ ) for nine months. After eight weeks, diuretics or amlodipine were added as necessary. The primary end point was change in left ventricular (LV) mass after nine months as assessed by magnetic resonance imaging (MRI). Secondary end points included changes in systolic and diastolic BP, urinary albumin-creatinine ratio (UACR), and safety events. **Results.** The mean change in LV mass was -14.5 g for the eplerenone-only group, -19.7 g for the enalapril-only group, and -27.2 g for the combination-therapy group ( $p = 0.007$  eplerenone-only vs. combination;  $p < 0.05$  for all three groups vs. baseline). Blood pressure reductions were statistically similar in the three groups. However, UACR was significantly reduced in the combination group (by -52.6%) as compared with the eplerenone-only group (-24.9%,  $p = 0.001$ ) and the enalapril-only group (-37.4%,  $p = 0.038$ ). Cough was significantly less common in the eplerenone-only group (3.1%) than in the enalapril-only group (14.1%,  $p = 0.05$ ); the rate of cough was 9.0% in the combination group (NS). There were no significant differences in rates of hypotension, hyperkalemia, hypokalemia, impotence, gynecomastia, menstrual abnormalities, or breast pain. Thus, eplerenone was similar to enalapril in reducing LV mass, BP, and UACR in patients with hypertension; eplerenone plus enalapril reduced LV mass and systolic BP significantly more than eplerenone alone;

the combination of eplerenone and enalapril significantly reduced UACR more than eplerenone or enalapril alone; add-on BP medication was required significantly more often in the enalapril group than in the eplerenone group; and all treatments were safe and well tolerated, although significantly more patients who received enalapril experienced cough than those who received eplerenone. **Conclusions.** Selective aldosterone blockade, with eplerenone alone or combined with ACE inhibition, is effective for organ protection and BP control in patients with essential hypertension and LVH.

## COMMENTARY

Eplerenone is a new highly selective aldosterone receptor antagonist that is currently under study for the treatment of hypertension and heart failure (HF). Eplerenone use results in less gynecomastia than spironolactone. Because it acts in part through a nuclear receptor, it is likely that it is altering transcription of a number of genes, including those responsible for the generation of nitric oxide. Preliminary studies suggest that eplerenone reduces collagen turnover and myocyte size in an experimental animal model of cardiomyopathy. In the 4E Study, eplerenone was shown to reduce LV mass as measured by MRI to nearly the same extent as enalapril. However, the combination of enalapril and eplerenone dramatically reduced LV mass over a period of nine months. Because BP reduction was similar in the three arms, the data suggest that the combination may provide benefit beyond that afforded by simple improvement in loading conditions. The results of this and other studies have produced in an increased awareness of the role of aldosterone in the pathogenesis of hypertension and HF. Eplerenone is also being studied in a large, randomized, placebo-controlled trial in which it is being evaluated in patients with acute myocardial infarction and HF. The results of this mortality study should be known in the fall of 2002.

GARY S. FRANCIS, MD, FACC

*The LIFE Trial: Cardiovascular Mortality and Morbidity in the Losartan Intervention for End Point Reduction in Hypertension Trial*

BJÖRN DAHLÖF, MD

UNIVERSITY OF GÖTEBORG AND

OSTRA UNIVERSITY HOSPITAL, GÖTEBORG, SWEDEN

**Background.** No antihypertensive agent has shown a uniquely greater benefit than any other in a primary comparison. Left ventricular hypertrophy (LVH) is a strong independent risk indicator of cardiovascular (CV) morbidity and mortality. Selective blocking of angiotensin II (A-II), an important growth factor, might confer benefits beyond blood pressure (BP) reduction. **Methods.** In the LIFE trial, 9,193 patients with essential hypertension (160 to 200 mm Hg systolic, 95 to 115 mm Hg diastolic; mean 174/98) and electrocardiographic LVH were randomized prospectively and double-blind to losartan- or atenolol-

based therapy (A-II blockade and beta-blockade, respectively) for at least four years. Patients were followed up until at least 1,040 had experienced a first primary event, which could be myocardial infarction (MI), stroke, or CV death. In this 945-center trial from northern Europe, Britain, and the U.S., the primary hypothesis was that losartan would be more effective than atenolol in reducing CV morbidity and mortality. Dosages were titrated to target pressures of <140 mm Hg systolic and <90 mm Hg diastolic: losartan to 100 mg/day and atenolol to 100 mg/day, with hydrochlorothiazide 12.5 to 25 mg/day with or without other therapies, excluding any of the randomized therapies and ACE inhibition. **Results.** The systolic target was reached by 49.5% of patients in the losartan group (n = 4,805) and 46.2% of patients in the atenolol group (n = 4,588); diastolic target was reached by 87.6% and 89.4%, respectively. Over a mean follow-up of 4.8 years, the reductions in adjusted and unadjusted risk for a first primary event for patients who received losartan as compared with those who received atenolol were 13.0% (p = 0.021) and 14.6% (p = 0.009), respectively. Significantly more patients in the atenolol group discontinued treatment due to adverse effects (p < 0.0001), which included bradycardia, cold body extremities, hypotension, and sexual dysfunction. Mean regression in LVH was significantly greater in the losartan group than in the atenolol group. In a subgroup of 1,195 patients with diabetes according to WHO criteria, the reductions in adjusted and unadjusted risk for a first primary event for patients who received losartan as compared with those who received atenolol were 24.5% (p = 0.031) and 26.7% (p = 0.017), respectively. **Conclusions.** When compared with atenolol-based therapy, losartan-based therapy in this group was associated with significant clinical benefits, including reductions in CV morbidity and mortality, stroke, new-onset diabetes, and improved LVH regression, given similar degrees of BP reduction. Among diabetics, losartan provided more pronounced protection against the primary composite end point and total mortality, and losartan was significantly better tolerated. Based on NHANES III statistics, the use of losartan instead of atenolol for 4.8 years by patients meeting LIFE trial selection criteria would result in 70,000 fewer CV morbidity and mortality end points and 54,000 fewer cases of new-onset diabetes.

## COMMENTARY

Beginning with the original Veterans Administration studies, for the last three decades we have been treated with a series of placebo-controlled trials demonstrating that the risk of death and other serious cardiovascular events can be reduced by administering BP-lowering medications to individuals with hypertension. With the availability of several distinct mechanistic classes of antihypertensive agents, there has been a wide speculation regarding possible differential influences of these therapies on clinical event rates beyond those achieved by lowering BP. The LIFE study is one of

several modern attempts to compare the relative efficacy of different antihypertensive agents by using clinical end points rather than surrogates. Higher-risk hypertensive patients with electrocardiographic LVH were targeted. The patients were randomized to initial antihypertensive control based primarily on either the angiotensin-receptor blocker, losartan, or the beta-blocker, atenolol, with hydrochlorothiazide and then other antihypertensive agents added as needed to achieve BP control. With 9,193 patients, more than four years of follow-up, and over 1,000 events, the trial was robust. Despite similar BP control, randomization to losartan was associated with a lower risk for the composite end point—CV death, stroke, and MI. Of these components, the most preferentially altered by losartan therapy was the risk of stroke. Other prespecified end points, such as hospitalization for angina, heart failure, or revascularization procedures were not differentially altered by two modes of antihypertensive therapy. Of interest, losartan treated patients were less likely to be diagnosed with new onset diabetes than atenolol treated patients.

The LIFE study is a major advance and ushers in a new era of head-to-head antihypertensive trials, where the questions are whether an agent offers additional advantages beyond the lowering of BP. Losartan was found to provide such a benefit. Other major drug comparison trials (ALLHAT—chlorthalidone, lisinopril, amlodipine, calcium-channel-blocker and VALUE—valsartan, amlodipine) are well under way. As we advance with these important fine-tuning studies comparing antihypertensive agents, we must not lose sight of the fundamental importance of BP control and the disturbingly large segment of our hypertensive population that currently remains undiagnosed or undertreated.

MARC A. PFEFFER, MD, PhD, FACC

*DANAMI-2: The Danish Multicenter Randomized Trial of Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction*

HENNING RUD ANDERSEN, MD  
SKEJBY UNIVERSITY HOSPITAL IN AARHUS,  
AARHUS, DENMARK

**Background.** Emerging data from randomized trials suggest a superior role for primary percutaneous coronary intervention (PCI) when compared with fibrinolytic therapy for patients presenting to centers that offer primary PCI. But it remains unknown whether primary PCI is also superior for patients who must be transferred to a PCI center. **Methods.** The prospective, randomized DANAMI-2 trial encompassed 24 referral hospitals and five independent angioplasty centers. The longest transport distance from referral hospitals was 150 km (95 miles). A total of 1,572 patients (including 1,129 presenting to referral centers) were randomized to treatment with front-loaded tPA (alteplase, up to 100 mg, given at the presenting center without transport) (n = 782) or early transfer for primary PCI with

stenting (n = 790). The primary end point was a composite of mortality/reinfarction/disabling stroke at 30 days. The inclusion criteria were symptoms for no longer than 12 h, ST-elevation  $\geq 4$  mm, and ability to complete transfer to a PCI center within 3 h of randomization. Cardiogenic shock and malignant arrhythmias were exclusion criteria. **Results.** The trial was stopped prematurely on October 1, 2001, according to a safety and ethical committee recommendation. The primary end point had been reached by 13.7% of patients who had received fibrinolytic therapy and 8.0% of those who had received primary PCI (p = 0.0003). Whereas component rates of death and disabling stroke were each nonsignificantly different between the two groups, the reinfarction rate was significantly higher in the fibrinolytic-therapy group: 6.3% versus 1.6% (p = 0.0001). Among the 1,129 patients randomized at referral hospitals, the primary end point rates were 14.2% for the fibrinolytic-therapy group and 8.5% for the primary-PCI group (p = 0.002). These rates for the 443 patients randomized at the PCI centers (and who were, therefore, not transported) were 12.3% and 6.7%, respectively (p = 0.048). Few adverse events developed during any transport of PCI candidates; atrial fibrillation occurred in 2.5% of such patients, ventricular tachycardia in 0.2%, ventricular fibrillation in 1.4%, and second- to third-degree atrioventricular block in 2.3%. **Conclusions.** The DANAMI-2 trial showed a relative risk reduction exceeding 40% for primary PCI versus front-loaded tPA over 30 days. The trial, therefore, confirms previous trials indicating that primary PCI is superior to fibrinolytic therapy whether or not the PCI-treated patient required transport to a PCI center, as long as transfer time does not exceed 3 h. Transfer of patients with acute myocardial infarction (MI) to PCI centers is safe.

## COMMENTARY

The DANAMI-2 trial provides support for an early invasive strategy for acute ST-elevation MI even if transfer to an interventional center is required, as long as that transportation can occur in <3 h. Using a well-planned cooperative national program involving 62% of Danish hospitals, the investigators tested the hypothesis that immediate transfer to an invasive hospital would produce equivalent or better 30-day composite outcomes of mortality, reinfarction, and disabling stroke compared with local administration of front-loaded TPA. Using this strategy, the investigators demonstrated a 40% reduction in events for the patients who underwent primary PCI. Time to mechanical reperfusion was optimized for the transfer patients by preparing the cath lab in the interventional hospitals during transfer. In fact, the total time from presentation to balloon inflation was only slightly longer for the transfer patients than for patients who initially presented to the invasive hospital. Importantly, transfer was associated with small numbers of manageable complications.

Several comments should be noted. First, the relative use

of adjunctive revascularization was remarkably low, particularly when compared with the U.S. (16% of patients had unscheduled intervention or bypass surgery within 30 days), for the transfer hospitals. Could a strategy of lytics with or without adjunctive IIB to IIIA antagonists or low-molecular-weight heparin coupled with semi-urgent transfer for possible coronary intervention have provided equivalent results? This question seems relevant because much of the benefit of early transfer with coronary intervention was not based on mortality or stroke reduction but on a reduction in reinfarction, a benefit that may have been provided equally well by intervention performed within 24 h of the MI in thrombolytic patients without the need and risk (albeit small) of urgent transfer. Such a strategy may even reduce resource utilization and ultimate cost.

In summary, DANAMI-2 broadens the role of PCI in ST-elevation MI to include patients who initially present to a hospital at which PCI facilities are not available. Even accounting for the time required to transfer the patient to a PCI-capable hospital, patient outcomes were improved compared with lytic therapy, with an acceptable risk of in-transfer complications.

GEORGE W. VETROVEC, MD, FACC

*A Randomized Trial of Fluvastatin After Successful Percutaneous Intervention in Patients With Coronary Heart Disease: The Lescol Intervention Prevention Study (LIPS)*

PATRICK W. SERRUYS, MD, PhD, FACC  
THORAXCENTER, ERASMUS UNIVERSITY HOSPITAL,  
ROTTERDAM, THE NETHERLANDS

**Background.** Statins are now well established as therapy for primary and secondary prevention of fatal and nonfatal coronary events. **Methods.** In the LIPS trial, 1,677 patients were randomized in a double-blind fashion to receive either fluvastatin (40 mg bid) or placebo after a successful first percutaneous coronary intervention (PCI) and were followed up for three to four years. The primary end point was survival free of major adverse cardiac events (MACE), which encompassed cardiac death, nonfatal myocardial infarction (MI), surgical bypass, or repeat PCI. Secondary end points included all-cause death, cardiac death, noncardiac death, death or nonfatal MI, cardiac death or nonfatal MI, lipid effects, and safety and tolerability. Patients were required not to have been on lipid-lowering therapy for the six weeks prior to randomization and to have a total cholesterol 135 to 270 mg/dl and triglycerides <400 mg/dl. A total of 1,141 lesions were treated by PCI in the fluvastatin group (mean 1.35 per patient), and 1,083 lesions were treated in the placebo group (mean 1.3 per patient). Stents were used in more than half of the patients in both groups. **Results.** The fluvastatin group showed a significantly greater rate of MACE-free survival over four years than the placebo group, with a risk reduction of 22% ( $p = 0.0127$ ). The corresponding rates excluding re-PCI in the first six months from the primary end point showed a risk

reduction of 34% with fluvastatin ( $p = 0.0002$ ). The composite MACE rates over four years were 21.4% and 26.7% for the fluvastatin and placebo groups, respectively ( $p = 0.006$ ); however, differences in none of the component end points individually reached significance. The risk ratios significantly favored fluvastatin for the subgroups of patients with multivessel disease and those with diabetes. The MACE rates also were significantly lower for fluvastatin-treated patients in these two subgroups ( $p = 0.008$  in multivessel disease and  $p = 0.022$  in diabetes). **Conclusions.** The LIPS trial supports the use of early lipid-lowering therapy with fluvastatin after PCI in patients initially having cholesterol levels in the normal range.

## COMMENTARY

This large multicenter trial substantiates what cardiologists have known, namely, that statins work not only for primary prevention but also for secondary prevention of coronary artery disease. The importance of this trial, which randomized patients with “normal cholesterol” who had undergone a successful first PCI to placebo or fluvastatin, is that it strongly emphasizes the critical nature of statin therapy in this highest-risk group of patients.

The primary end point of this trial was survival free of MACE, which included cardiac death, nonfatal MI, coronary bypass graft surgery, or repeat PCI. The composite end point was significantly reduced from 26.7% to 21.4% ( $p = 0.006$ ) with fluvastatin. If repeat PCI is excluded from the primary end point, there is an even more dramatic 34% reduction with fluvastatin ( $p = 0.0002$ ). When the authors looked at high-risk subsets of patients—for example, those with multivessel disease and those with diabetes—MACE rates were significantly lower in the patients treated with fluvastatin.

There are some issues that need to be addressed. This was an intention-to-treat trial. Although the drug was generally well tolerated, some of the fluvastatin-assigned patients were no longer taking the drug at the end of four years. Secondly, some of the patients who were originally randomized to placebo were subsequently treated with a statin. These two findings could have resulted in narrowing of the differences between the two groups. If analysis had been performed according to treatment received, we can only presume that there would have been an even more dramatic difference between the two groups.

The fundamental message of this study is the importance of statin drugs in the postprocedural care of coronary interventional patients. These drugs are as important as aspirin and thienopyridines.

DAVID R. HOLMES, JR, MD, FACC

*Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE)*

MILTON PACKER, MD, FACC  
COLUMBIA PRESBYTERIAN MEDICAL CENTER,  
NEW YORK CITY, NEW YORK

**Background.** The vasoconstrictor and vasodilator neuro-hormonal systems normally oppose each other to achieve homeostasis. But chronic heart failure (HF) is characterized by a marked increase in the influence of endogenous vasoconstrictors and a marked decrease in the influence of endogenous vasodilators. These effects are particularly great in severe chronic HF and probably contribute to the development and progression of chronic HF. Angiotensin-converting enzyme (ACE) inhibitors are the established treatment for chronic HF, but these drugs inhibit only one part of the endothelium-based peptide system that controls vascular tone. Vasopeptidase inhibitors, which inhibit not only ACE but also the co-localized enzyme neutral endopeptidase (NEP), modulate this peptide system more extensively. Combined inhibition of both enzymes not only reduces the adverse influence of endogenous vasoconstrictors (due to ACE inhibition) but also potentiates the favorable effect of endogenous vasodilators (due to NEP inhibition). In experimental chronic HF models, combined inhibition of both enzymes by a vasopeptidase inhibitor has been shown to prolong life to a greater extent than ACE inhibition alone. However, the possibility that vasopeptidase inhibitors might be superior to ACE inhibitors in reducing mortality had not been previously explored in patients with chronic HF. **Methods.** In the OVERTURE study, 5,770 patients with moderate-to-severe chronic HF were randomized to treatment with either the vasopeptidase inhibitor omapatrilat (target dosage, 40 mg/day) or the ACE inhibitor enalapril (target, 20 mg/day). Both agents were given in addition to patients' baseline chronic HF medications for 0.8 to 2.3 years. Patients had New York Heart Association (NYHA) class II to IV HF of any etiology and a left ventricular ejection fraction 30% or lower. The primary end point was all-cause mortality or HF hospitalization. Secondary end points included cardiovascular (CV) death or hospitalization; CV death; and NYHA class at eight months. The trial was designed to have >98% power to detect a 15% difference in the primary end point and 90% power to detect a 20% difference in all-cause mortality. The design allowed for discrimination of noninferiority of omapatrilat compared with enalapril and superiority of omapatrilat compared with enalapril. The two treatment groups were similar with respect to all baseline characteristics. Of note, over 50% of the patients were receiving a beta-blocker, and over 40% of the patients were receiving spironolactone at the beginning of the trial. **Results.** The primary end point rate for the 2,886 patients who received omapatrilat was 31.7% and, for the 2,884 patients who received enalapril, was 33.7% ( $p = 0.187$ ). This difference reflects a nonsignificant 6% lower risk in the omapatrilat group. CV death or hospitalization was the only secondary end point for which there was a significant difference: 40.5% and 44.2%, respectively. Angioedema

developed in 0.8% and 0.5%, respectively. **Conclusions.** Thus, OVERTURE did not demonstrate the superiority of omapatrilat over enalapril. However, the upper bound of the confidence interval was <1.09. Thus the trial fulfilled the criteria for noninferiority. Therefore, omapatrilat was shown to be an effective treatment for chronic HF and therapeutically equivalent to enalapril.

## COMMENTARY

Omapatrilat is a dual ACE inhibitor and NEP inhibitor that has been widely studied in patients with hypertension and HF. Preliminary data have suggested that the drug might be more beneficial than ACE inhibitors alone. Omapatrilat is associated with improved renal blood flow, natriuresis, and a modest diuresis. It offers the added advantage of increasing counter-regulatory natriuretic peptide activity. In fact, omapatrilat blocks the degradation of a number of peptides, including bradykinin. It has been widely recognized that omapatrilat may be associated with a higher incidence of angioedema than ACE inhibitors, particularly in African Americans.

The OVERTURE study findings fail to support the hypothesis that omapatrilat favorably alters the natural history of patients with HF beyond that of conventional therapy. The primary end point of all-cause mortality or HF hospitalization was essentially similar both in the patients treated with an ACE inhibitor and in those randomly allocated to omapatrilat. As with any large randomized controlled clinical trial, it is possible that the neutral findings were at least in part due to an inappropriate dose. However, this is speculation. Finally, in the era of modern HF trials, it may be difficult to determine a unique or an incremental beneficial effect of an investigational agent in patients already receiving several effective drugs for the same disorder. This may be particularly true if these agents share common mechanisms of action.

It is perhaps becoming more difficult to demonstrate drug superiority in the current era of polypharmacy in which so many drugs are being used. We need to re-think how we choose dose, select patients, and adjust concomitant medication in large clinical HF trials. Simply stacking numerous neurohormonal blockers on top of each other may no longer be an effective strategy to demonstrate efficacy. Finding ways to select those patients who are the most likely to respond to a specific treatment may be worth the effort.

GARY S. FRANCIS, MD, FACC

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**Reprint requests and correspondence:** Dr. Eric S. Williams, Professor of Medicine, Indiana University School of Medicine, Krannert Institute of Cardiology, 1800 N. Capitol Avenue, Indianapolis, Indiana 46202-4800. E-mail: ewillia@iupui.edu.

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**Results from late-breaking clinical trial sessions at the American College of  
Cardiology 51st Annual Scientific Session**  
*J. Am. Coll. Cardiol.* 2002;40;1-18

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