Best of the AHA Scientific Sessions 2004

Highlights from the American Heart Association Scientific Sessions
November 7-10, 2004, New Orleans, LA

[*Rev Cardiovasc Med.* 2005;6(1):33-46]

© 2005 MedReviews, LLC

Key words: Cardiac support devices • CAMELOT • CARP • CREATE-ECLA • Delipidation • Diabetes • ESCAPE • Heart failure • High-Density Lipoprotein • Hypertension • Obesity • Percutaneous coronary intervention • Perioperative complications • PPAR-δ agonists • PRINCESS • Statins • STEMI

The 2004 American Heart Association (AHA) Scientific Sessions provided a forum for the presentation and discussion of important research advances in every area of cardiovascular medicine. Here our board members report on some of the most important and exciting new findings announced in New Orleans.

β-Blockers and Perioperative Complications in Diabetics

The Diabetic Postoperative Mortality and Morbidity (DIPOM) Trial[1] evaluated whether peri-operative β-blocker administration is associated with a reduction in cardiac events in diabetic patients undergoing non-cardiac surgery. Patients were randomized to either placebo (n = 459) or metoprolol (n = 462). Study drug was administered the evening prior to surgery (50 mg) and was continued during the hospitalization for up to 7 days (100 mg/day). The mean duration of drug therapy was 4.6 days in the metoprolol group and 4.9 days in the placebo group. The majority of patients in the trial underwent either orthopedic or intra-abdominal surgery. Heart rate was significantly lower in the metoprolol group compared with placebo (75 vs 84 beats per minute, respectively, $P < .001$). There was no difference by treatment group in the primary endpoint of death, acute MI, unstable angina, or congestive heart failure at follow-up (21% for metoprolol vs 20% for placebo, $P = 0.66$). Even after adjustment for age, gender, history of coronary heart disease, and malignant disease, no difference was observed (HR 1.10, $P = 0.53$). There was also no difference in the endpoint of all-cause mortality at follow-up (16% in both groups, $P = 0.88$). Serious adverse events occurred in 7.1% of the metoprolol group and 5.2% of the placebo group (P = ns). Among diabetic patients undergoing non-cardiac surgery, treatment with the β-blocker metoprolol

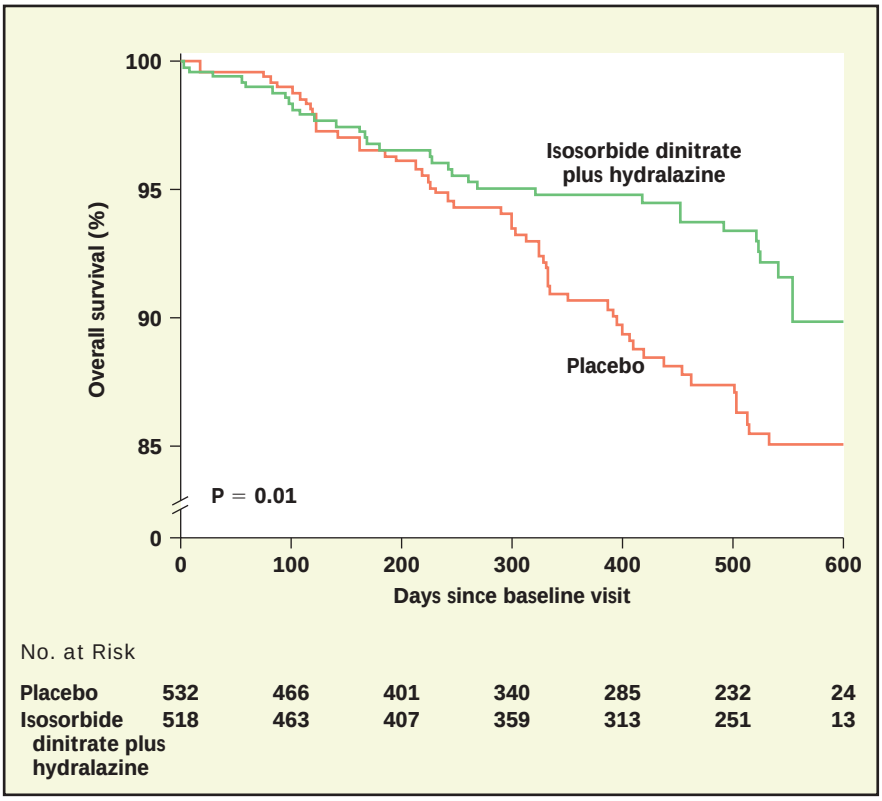
was not associated with a reduction in the primary composite endpoint or in all-cause mortality, when compared with placebo. Current guidelines recommend perioperative β-blocker use in patients with diabetes and those with established cardiovascular disease undergoing noncardiac surgery. Clearly, additional large-scale trials are needed to evaluate this practice.

Before generalizing these results to clinical practice, it should be considered that the noncardiac surgeries were relatively low-risk and relatively uncomplicated. The incidence of in-hospital cardiovascular events was low (1%), and the 10% long-term event rate corresponded to the rate in patients with a highly uncomplicated course. The drug dose was low. When orally administered, metoprolol succinate has a highly variable plasma level in ambulatory patients, which is further complicated postsurgery, when patients typically have significant gastrointestinal dysfunction for days. In addition, 33% of patients received either no metoprolol or only 50 mg of oral metoprolol postoperatively on day 1, 50% received it on day 2, and almost two thirds of patients received it on day 3, most likely yielding low plasma levels. Future trials should consider including higher-risk populations undergoing higher-risk surgery and more intensive and aggressive β-blockade (administered intravenously, perioperatively and for several days thereafter, and orally afterward).

African Americans with Heart Failure

The African American Heart Failure Trial (A-HeFT)[2] evaluated treatment with a fixed dose of isosorbide dinitrate plus hydralazine, compared with placebo, among black patients with primarily class III systolic heart failure. Subjects were randomized to a fixed dose of isosorbide dinitrate plus hydralazine (n = 518) or placebo (n = 532). Randomization was stratified by baseline use of β-blocker therapy. Initial dose was 20 mg of isosorbide dinitrate and 37.5 mg of hydralazine. Dosing was increased to a total daily dose of 120 mg of isosorbide dinitrate and 225 mg of hydralazine. The baseline therapy in subjects included: diuretics (90%), angiotensin-converting enzyme (ACE) inhibitors (69%), angiotensin receptor blockers (ARBs) (17%), and β-blockers (74%). There were more females (44.2% vs 36.1%, respectively) and more diabetics (44.8% vs 37.0%, respectively) in the isosorbide dinitrate plus hydralazine group, when compared to placebo. The etiology of heart failure was ischemic heart disease in 23% of patients, hypertension in 38% of patients, and of idiopathic origin in 26% of patients. These statistics are unique among trials in systolic heart failure primarily in Caucasians, where, generally, 2/3 have ischemic and 1/3 have nonischemic cardiomyopathy. The study was terminated after 1,050 of the planned 1,100 patients had been randomized, due to a demonstrated mortality benefit in the active treatment arm. Mortality was significantly lower in the combination therapy group (6.2% vs 10.2%, hazard ratio 0.57, $P = .01$). The survival differences were delayed until 6 months after randomization and continued to diverge through follow-up, which is unusual for drug therapy in heart failure (Figure 1). Individual components of the primary endpoint composite score were also significantly improved in the combination therapy group, including

Figure 1. *Survival rates in the African American Heart Failure Trial (A-HeFT). Reproduced with permission from Taylor et al.*[2]



death (data above), first hospitalization for heart failure (16.4% vs 24.4% in the placebo arm, $P = .001$), and change in quality of life score at 6 months (-5.6 ± 20.6 vs -2.7 ± 21.2, with lower scores representing better quality; $P = .02$). Target dose was given in 68.0% of patients in the combination therapy group and 88.9% of patients in the placebo group ($P < .001$). Blood pressure was lower in the combination therapy group compared with placebo (systolic blood pressure [SBP] averaged 3.1 mmHg lower with active treatment, $P = .02$). The major adverse effects in the combination therapy group were headache (47.5% vs 19.2% in the placebo group, $P < .001$) and dizziness (29.3% vs 12.3% for placebo, $P < .001$). The authors have credited the biologic effects of nitric oxide donation from 120 mg of isosorbide dinitrate and oxidase inhibition from 225 mg of hydralazine for the outcome. However, the mean 3.1 mmHg difference in SBP is in the range to affect cardiovascular mortality. Additional results need to be calculated, including the relative benefits relating to baseline medication and severity of initial systolic dysfunction. It is likely that at least some of the treatment effect is due to blood pressure lowering; some due to random chance, given the unusual survival curves for heart failure treatment; and some due to the unique biologic effects of this fixed dose combination of commercially available agents.

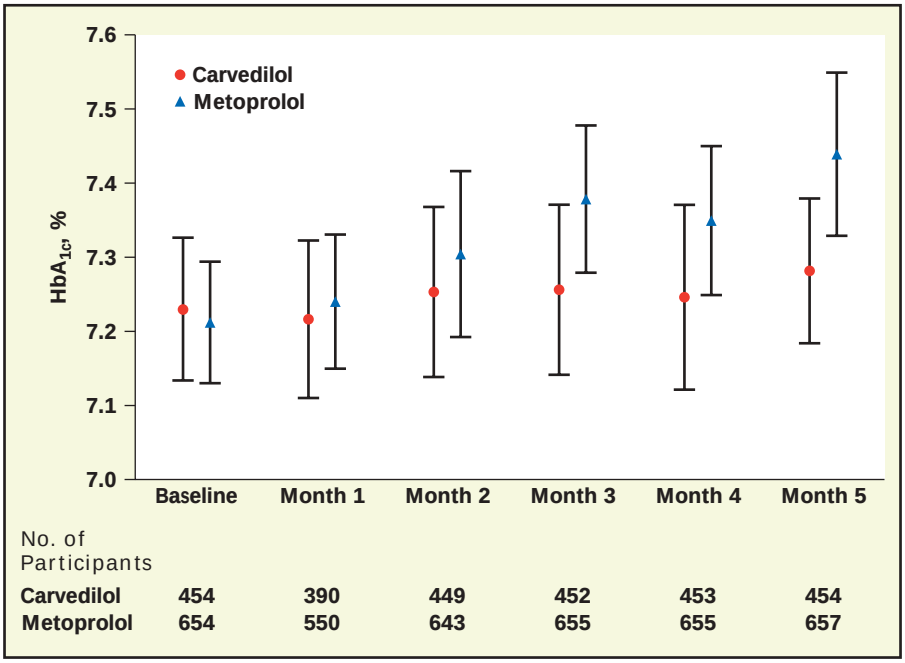


Figure 2. *Glycosylated Hemoglobin (HbA_{1c}) levels over time in the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial. The change from baseline to maintenance month 5 (primary outcome) was significant (mean difference [SD], 0.13% [0.05%]; 95% confidence interval, –0.22% to –0.04%; P = .004). Error bars indicate standard deviation from mean. Reproduced with permission from Bakris et al.*[3]

Glycemic Control in Type 2 Diabetics With Hypertension Treated With β-blockers

The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) Trial[3] evaluated the effect of 2 different β-blockers, carvedilol and metoprolol titrate, on glycemic control in patients with hypertension and type 2 diabetes. Subjects were randomized 2:3 to carvedilol (6.25 to 25 mg dose, twice daily) (n = 498) or metoprolol tartrate (50 to 200 mg dose, twice daily) (n = 737). If needed, open-label hydrochlorothiazide and a calcium antagonist were used to achieve target blood pressure. Subjects had type 2 diabetes as a result of obesity, with a mean body mass index at baseline of 34, and HbA_{1c} levels averaging 7.2%. Multiple antidiabetic medications were used in 55% of patients and 8% of patients were insulin-dependent. In addition to 99% of patients taking ACE inhibitors or ARBs at baseline, 45% were taking a statin. The primary endpoint of mean change in HbA_{1c} from baseline differed significantly by treatment group (0.12%, $P = .006$), with no change in the carvedilol group (0.02%, $P = .65$) and an increase in the metoprolol group (0.15%, $P < .001$). However, glycemic control was in a relatively tight range for both groups over time (Figure 2). Study drug discontinuation due to worsening glycemic control was higher in the metoprolol group (2.2% vs 0.6% for carvedilol, $P = .04$). Insulin resistance derived from fasting glucose and insulin levels (homeostasis model assessment insulin resistance) was reduced from baseline in the carvedilol group (-9.1%, $P = .004$) but did not differ in the metoprolol group (-2.0%, $P = 0.48$) for a significant difference between groups (-7.2%, $P = .004$). Triglycerides were increased from baseline in the metoprolol group (13.2%) but did not differ in the carvedilol group (2.2%), resulting in a significant difference between groups ($P < .001$). There was no treatment difference in terms of

change in low-density lipoprotein (LDL) or high-density lipoprotein (HDL) levels, but total cholesterol decreased more in the carvedilol group (−3.3% vs −0.4%, $P = .001$ for between-group difference). Blood pressure was similar for the groups over the study period. The albumin/creatinine ratio decreased more in the carvedilol group (−14.0% vs +2.5%, $P = .003$ for between-group difference). The frequency of most adverse events was similar between treatment groups, with the exception of a higher rate of bradycardia in the metoprolol group (4.1% vs 1.4% for carvedilol, $P = .007$).

As the long-term goal in these patients is to reduce cardiovascular and renal events with multiple blood pressure and diabetes medications, the issue of compliance needs to be measured against differences between carvedilol and metoprolol seen over 5 months in this study. Single-pill combination therapy and once-daily agents in evidence-based therapeutic classes, which result in higher compliance in achieving blood pressure and glycohemoglobin targets, should be the primary concern for practitioners. Large scale outcomes trials would be needed to demonstrate that the metabolic benefits of carvedilol translate into meaningful overall differences in event rates in the diabetic, hypertensive patient.

Endocannabinoid Receptor Blockade, Weight Loss, and Cardiovascular Risk Reduction

The Rimonabant on Weight Reduction and Weight Maintenance: RIO-NORTH AMERICA (RIO-NA) trial evaluated the efficacy and safety of rimonabant, the first selective cannabinoid type 1 (CB1) receptor antagonist, compared with placebo for weight reduction out to 2 years.[4] Nondiabetic, obese subjects (body mass index [BMI] ≥ 30 kg/m2 or BMI > 27 with dyslipidemia or hypertension) were randomized in a 2:2:1 manner to a fixed daily dose of rimonabant 5 mg, rimonabant 20 mg, or placebo. After 1 year of treatment, patients originally randomized to the rimonabant 5 mg and 20 mg were re-randomized to either the same dose of rimonabant or placebo for an additional year. The goal of the re-randomization was to evaluate whether weight loss in the rimonabant arms could be maintained following cessation of the drug. Patients in all groups were instructed to reduce caloric intake by 600 calories, and physical activity was encouraged.

Weight loss at 1 year was greater in the rimonabant 20 mg group (8.7 kg) and the rimonabant 5 mg group (4.4 kg) than the placebo group (2.8 kg; $P < .001$ for 20 mg comparison, $P = .001$ for 5 mg comparison). Additionally, waist circumference reduction was greater in the rimonabant 20 mg compared with placebo (8.2 cm for the 20 mg dose and 4.7 cm for the 5 mg dose vs 3.9 cm for placebo; $P = .001$ for 20 mg vs placebo). The proportion of subjects with the metabolic syndrome was reduced in the 20 mg rimonabant group from 34.8% at baseline to 21.1% at 1 year. Weight loss at 2 years was greatest in patients who were randomized to rimonabant 20 mg for the full 2 years (−7.4 kg vs −2.3 kg for placebo, $P < .001$).

Patients originally randomized to rimonabant in the first year but re-randomized to placebo the second year regained a considerable amount of weight but were still slightly better off than placebo (−3.2 kg vs −2.3 kg, respectively). Waist circumference reduction at 2 years was greater in patients who were randomized to rimonabant 20 mg for the full 2 years compared with placebo (8 cm for 20 mg and 4.9 cm for 5 mg vs 3.8 cm for placebo; $P < .001$ for 20 mg vs placebo). Loss of 5% or more of initial body weight was more frequent in patients randomized to rimonabant 20 mg for 2 years compared with placebo (62.5% for 20 mg vs 33.2% for placebo, $P < .001$). Similar results were reported for loss of 10% or more of initial body weight (32.8% for 20 mg vs 16.4% for placebo, $P < .001$).

At 2 years, HDL increases were greatest in patients who were randomized to rimonabant 20 mg for the full 2 years (24.5% in the 20 mg rimonabant group vs 13.8% in the placebo group, $P > .001$). Triglycerides were reduced in patients who were randomized to rimonabant 20 mg for the full 2 years compared with placebo (−9.9% for 20 mg vs +1.6% for placebo). The frequency of the metabolic syndrome was reduced to 22.5% at the end of 2 years of treatment in patients randomized to rimonabant 20 mg for the full 2 years. Dropout rates due to adverse events by 1 year were higher in the rimonabant 20 mg group (12.8% vs 7.2% in the placebo group). However, rates during year 2 of treatment among patients re-randomized to the same groups were similar (6.0% in the 20 mg rimonabant group and 6.7% in the placebo group).

The 1-year data in this trial are similar to the results reported in the RIO-EUROPE and RIO-LIPIDS trials, which also showed a greater weight reduction with rimonabant 20 mg compared with placebo. The present study is the first of the RIO trials to report data through 2 years. Although weight loss was maintained through 2 years in patients who were randomized to rimonabant 20 mg for the full 2 years, it was clear the drug was needed to maintain that loss. The overall study discontinuation rates in all arms were

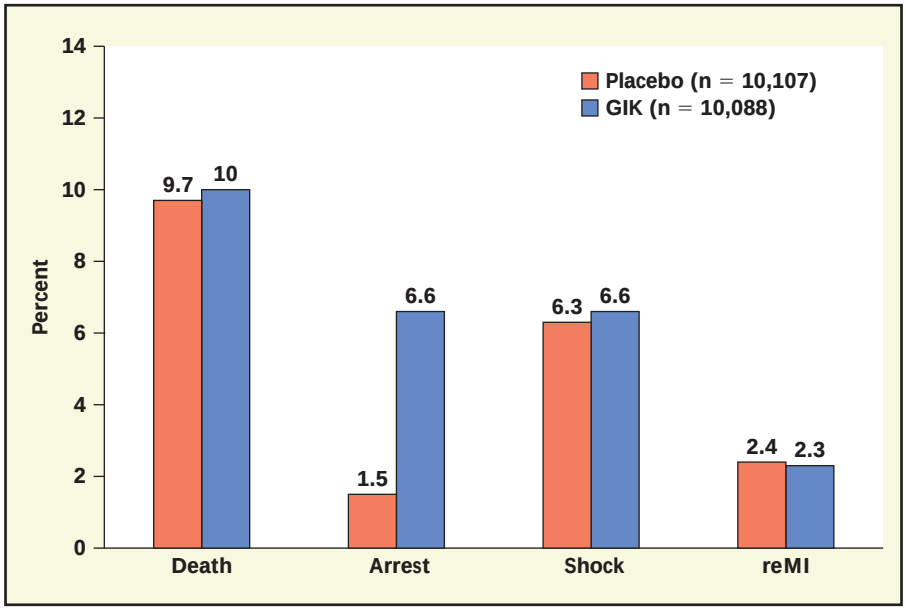


Figure 3. *Secondary endpoint measures at 7 days in the Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiologicos Latinoamerica (CREATE-ECLA) trial. reMI, repeat myocardial infarction.*

approximately 50%, which is usual for weight loss studies. Presumably these patients regained all of their weight; however, they were not weighed or reported on in the presentation. It is clear that this drug will be most effective in conjunction with an aggressive diet and exercise approach because the majority of patients whom clinicians would consider for this therapy are at least 30 lbs overweight.

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

The CREATE-ECLA Trial

The Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiologicos Latinoamerica (CREATE-ECLA) was a multinational, double-blinded trial that tested the benefit of glucose-insulin-potassium (GIK) infusion and reviparin, a low molecular weight heparin, in patients with acute ST segment elevation myocardial infarction (STEMI). Using a multifactorial design, 20,201 patients with STEMI or new left branch bundle block, presenting within the previous 12 hours, were enrolled. They received aspirin and standard care, including thrombolysis or angioplasty. All patients were randomized to GIK or placebo and the 15,500 patients enrolled in India and China were also randomized to reviparin or placebo.

The main trial of GIK compared an infusion of 25% glucose, 50 units/L of insulin, and 80 mEq/L of potassium chloride, delivered at 1.5 ml/Kg/hour for 24 hours, versus placebo. The primary endpoint was all-cause mortality at 30 days. The study group was younger than usually seen in US trials (average age was 58 years) and presented an average of 4.6 hours after the onset of chest pain. A lytic agent was administered to 74% and 9% underwent primary angioplasty. The GIK group received more than 1 liter more of fluid than the control group but did not have a higher incidence of CHF or pulmonary edema. The GIK group, however, did have a higher incidence of hyperkalemia (4.3% versus 1.6% for the placebo group, $P = .0001$). The primary endpoint was not significantly different between groups (hazard ratio [HR] = 1.03). The secondary endpoints of death, cardiac arrest, cardiogenic shock, and reinfarction were also similar (Figure 3). Only recurrent ischemia at 7 days was lower in the GIK group (HR = 0.85, $P = .004$). Even in prespecified subgroups such as elderly patients, diabetics, and those receiving a lytic agent or primary angioplasty, no difference was seen.

The second component of this trial was equally interesting. The primary endpoint of the comparison of reviparin and placebo was the composite of death, reinfarction, or stroke at 7 days. The patients' demographics were similar to the main trial. The primary endpoint, however, was significantly lower in the reviparin group compared to placebo (9.6% versus 11%; HR = 0.87, $P = .0048$). When ischemia with echocardiogram changes was added to the primary endpoint, the differences persisted (Figure 4). The benefit of reviparin was seen at 30 days as well. Of the endpoint components, however, only death and reinfarction were significantly different. Major and life-threatening bleeding were more frequent in the reviparin group (0.9% versus 0.4%, $P = 0.001$) but despite 7 days of reviparin, total stroke and hemorrhagic stroke were not increased.

This study is of importance for a number of reasons. First, it was a very large trial enrolling over 20,000 patients from every continent in the world. It also enrolled a large number of patients from developing nations without pharmaceutical industry support. Despite these challenges, the quality of the data is extraordinary. The scientific questions that were answered will likely change clinical

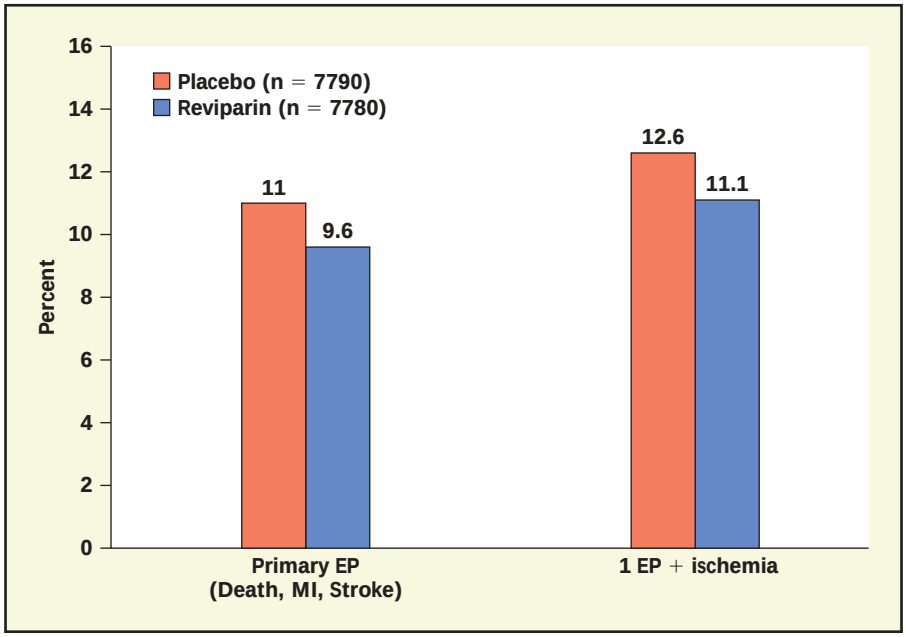


Figure 4. *Endpoint results at 7days in the reviparin substudy of the Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiologicos Latinoamerica (CREATE-ECLA) trial. EP, endpoint; MI, myocardial infarction.*

practice. GIK was proposed as a treatment for patients with STEMI by Sodi-Polaris more than 40 years ago. In an unpublished meta-analysis of 16 clinical trials of GIK by Dr. Salim Yusuf of McMaster University and Hamilton Civic Hospitals Research Center in Hamilton, Ontario, Canada, overall benefit was seen with a calculated HR of 0.85. However, only 5,000 patients were studied and most of the studies predated modern therapy for STEMI, including primary angioplasty. Though the results of this trial may close the book on GIK, this does not minimize the importance of tight glycemic control. In contrast, the findings of a survival advantage for reviparin could change the use of heparin in STEMI. To date, no clinical trial has shown a mortality advantage for heparin. This trial did differ from previous studies in that the drug was given for 7 days and the prolonged administration may be important in the newly favorable outcome. Clearly, further trials are needed to determine the duration of treatment and the type of heparin most advantageous. [David P. Faxon, MD]

The ESCAPE Trial

The Swan-Ganz pulmonary artery catheter (PAC) has long been used at medical centers to assess treatment options in heart failure patients by measuring hemodynamic response, despite controversy as to whether the technique increases risk of complication without necessarily contributing to clinical management. Observational studies had suggested there may be harm in the use of PACs but randomized trial data have not been available.[5,6]

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE),[7] sponsored by the National Heart, Lung, and Blood Institute (NHBLI), randomized 433 patients who were hospitalized at 26 institutions with a left ventricular ejection fraction (LVEF) less than 30%, systolic blood pressure (SBP) of 125 mmHg or less, and heart failure symptoms for at least the preceding 3 months. Patients received acute management with or without PAC-guided therapy. In the clinical arm, the goal was resolution of signs and symptoms of congestion. In the PAC arm, the goal was resolution of congestion, pulmonary capillary wedge pressure (PCWP) of 15 mmHg or less, and right atrial pressure (RAP) of 8 mmHg or less.

The patients enrolled in ESCAPE were of mean age 56, 74% male, 55% ischemic in etiology, and with a mean LVEF of 19%, SBP of 106 mm Hg, serum sodium of 137 mEq/L, blood urea nitrogen (BUN) of 34 mg/dL, serum creatinine of 1.5 mg/dL, b-type natriuretic peptide (BNP) of 974 pg/mL, and peak oxygen consumption on cardiopulmonary exercise testing of 10.2 mL/kg/min. The study's patients were in worse clinical condition as assessed by baseline characteristics than those in any other randomized heart failure drug trials.

The PAC was implanted for a median of 1.9 days. In the PAC cohort, the baseline PCWP was reduced from 25 to 17 mmHg, baseline RAP reduced from 14 to 10 mmHg, and baseline cardiac index increased from 1.9 to 2.1 L/min/M^2. Net diuresis was 4.0 Kg in the PAC arm and 3.2 Kg in the clinical arm. Use of angiotensin-converting enzyme (ACE) inhibitor and β-blocker therapies at discharge were similar. Of patients randomized to the PAC arm, 92% received a PAC; 18% randomized to clinical care alone crossed over.

The trial results were presented by Dr. Lynne Warner Stevenson (Brigham and Women's Hospital, Boston MA) at a late-breaking clinical trial session of the 2004 AHA meeting. For the primary endpoint of days out-of-hospital alive, there was no significant difference

Table 1
Clinical Outcomes in the ESCAPE Trial

6-month endpoints	PAC, n = 215	Clinical, n = 218
Days dead or hospitalized (mean)	38	36
Mortality (%)	20.9	17.4
Rehospitalizations/patient (mean)	2.1	2.1
Days in hospital (median)	11	11

ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; PAC, pulmonary artery catheter.

between the 2 treatment arms. The 30-day mortalities were similar at 4.7% for the PAC group and 5.0% for the clinically managed group. A comparison of endpoints can be seen in Table 1. There were trends for better quality of life and improved peak oxygen consumption on cardiopulmonary exercise testing with the PAC but these did not reach statistical significance.

Rates of complications, adverse events, and clinical outcomes were also not significantly different at 6 months between the PAC intervention and control groups (Table 2). Predictors of mortality in this patient population were PCWP, SBP, BUN, and 6-minute walk test, but not use of a PAC.

This important clinical trial has demonstrated that for patients hospitalized with heart failure, therapy guided by Swan-Ganz hemodynamic monitoring is just as safe as treatment based on clinical signs alone; however there are no improvements in clinical outcomes. A separate meta-analysis of 12 randomized PAC trials completed since the 1980s, most in surgical or ICU patients, showed that the results of ESCAPE are consistent across the board with other trials of the PAC. There was a neutral effect of PAC usage in terms of all-cause mortality. The clinical implications of this trial are that initial use of a PAC to guide care should be reserved for heart failure patients with cardiogenic shock, patients undergoing orthotopic heart transplantation evaluation, or patients who remain refractory to clinically guided therapy.

A Cardiac Restraint Device as Heart Failure Therapy

Heart failure is characterized by progressive left ventricular (LV) remodeling. LV dilatation has been shown to be a strong predictor of mortality in heart failure.[8] Experimental studies suggested that mechanical constraint of the myocardium attenuates remodeling.[9] A mesh wrap surgically implanted and designed to reduce wall stress was beneficial in 3 different animal studies.[6]

The ACORN multicenter prospective trial was designed to test the CorCap (Acorn Cardiovascular Inc., Minneapolis, MN)[10] cardiac support device (CSD). This clinical trial enrolled 300 patients with New York Heart Association (NYHA) functional class III-IV heart failure and dilated cardiomyopathy, the majority of whom were Class III (81%). Of the patients, 193 underwent mitral valve repair/replacement (MVR) and were randomized to MVR alone (n = 102) or MVR plus CSD (n = 91). The remaining 107 patients were randomized to either continuing optimal medical therapy alone (n = 50) or with the CSD (n = 57). The primary endpoint of the trial was a clinical composite, with patients classified as improved, the same, or worse, based on the occurrence of death, a major cardiac procedure indicative of heart failure progression, or a change in NYHA class.[6]

Table 2
In-Hospital Complications and Adverse Events in the ESCAPE Trial

Complications/adverse events	PAC, n = 215 (%)	Clinical, n = 218 (%)
Bleeding	1.0	0
VT > 30 sec or VF	0.5	0
PAC infection	1.9	0
Pulmonary infarction/hemorrhage	0.9	0
Cardiogenic shock	2.8	0.9
Myocardial infarction	0	0.5
Pulmonary embolism	0.5	0
Cardiac arrest	4.2	2.3
Antibiotic-requiring infection	13	9.2

ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 3
Major Cardiac Procedures Performed in the ACORN Trial

Major cardiac procedures	Control group	CSD group
Transplant	16	7
Left-ventricular assist device	8	3
Biventricular pacing	14	10
MVR	3	1

CSD, cardiac support device; MVR, mitral valve replacement.

Patients were mean age 53, 81.3% in NYHA Class III, mean left ventricular end diastolic dimension (LVEDD) 72.1 mm, mean LVEF of 27.4%, peak oxygen consumption on cardiopulmonary exercise testing averaging 14.7 mL/kg/M^2. Medical therapy consisted of an ACE inhibitor or angiotensin receptor blocker (ARB) in 97%, β-blockers in 88%, and aldosterone antagonists in 47%.

The results of this clinical trial were presented by Dr. Douglas Mann (Baylor College of Medicine, Houston, TX) at a late-breaking clinical trial session. Compared with the control group, the CSD group had more patients "improved" (27% vs 38%, respectively) and fewer patients "worsened" (45% vs 37%), yielding an odds ratio of 1.73 ($P = 0.02$) in favor of the CSD group. The improvement in the primary endpoint was mainly driven by major cardiac procedures (19 vs 33; $P = 0.01$).

Major cardiac procedures performed in the 2 groups can be seen in Table 3. There were no significant differences between the 2 groups in mortality ($P = 0.90$) or change in NYHA class ($P = 0.12$), nor in repeat hospitalizations (307 vs 305, respectively, $P = 0.44$). Survival rates were approximately 90% at 12 months and 80% at 24 months, in both groups, with not even a trend for improved survival visible with the CSD.

The CSD group had a greater reduction in LV end diastolic ($P = 0.009$) and systolic ($P = 0.017$) volumes and a greater improvement in sphericity index ($P = 0.026$). There was, however, no change in LVEF. There was an improvement in quality-of-life measures ($P = 0.05$ for Minnesota Living with Heart Failure Index; $P = 0.015$ for change in SF-36 Health Survey). No evidence of constrictive physiology was observed in patients who received the CSD. The implant complications were minimal, except for a trend toward greater prevalence of pneumonia with CSD. In the subgroup of 107 patients who did not undergo MVR, the odds ratio improved in favor of the CSD group to 2.56 for the clinical composite endpoint ($P = 0.03$).

The use of the CorCap CSD improved the clinical composite score in patients with NYHA Class III heart failure with or without MV replacement, a result driven entirely by fewer procedures and improved quality-of-life scores. The device reduces ventricular size and appears to be safe.

This clinical trial has provided proof of the concept that mechanical restraint can reduce LV size in patients with heart failure. It must be noted that in this trial, this CSD failed to improve LVEF, reduce hospitalizations, or influence mortality. It is also notable that this trial was not double blinded and patients were aware of the group to which they were assigned, a factor that could influence the quality-of-life assessment. As a stand-alone therapy, the optimal approach would have a less invasive method of device placement and demonstrate more compelling evidence of efficacy.

[Gregg C. Fonarow, MD, FACC, FACP]

The CARP Trial

Coronary artery disease accounts for the majority of peri-operative morbid events in patients undergoing vascular surgery and is the cause of death in at least half of all such patients. The decision of whether to refer patients with stable coronary artery disease for coronary angiography and revascularization, prior to vascular surgery, has long been debated. As the options for percutaneous coronary intervention (PCI) increase, enthusiasm for routinely performing either percutaneous or surgical revascularization prior to the elective vascular procedure has grown, with the intention of decreasing peri-procedural cardiac events—this despite a lack of definitive supporting evidence.

The Coronary Artery Revascularization Prophylaxis (CARP) Trial[11] prospectively randomized 510 patients with significant but stable coronary artery disease at 18 Veterans Affairs Medical Centers in the United States scheduled to undergo elective abdominal aortic aneurysm repair (33%) or lower extremity arterial revascularization (67%), to revascularization with PCI (59%) or coronary artery bypass graft (CABG) (41%), or to optimal medical therapy. The primary endpoint of the study was long-term mortality, and the secondary endpoints were mortality at 30 days and postoperative myocardial infarction. The vascular procedure was to be performed within

Table 4
Outcomes in the CARP Trial

Outcome	Revascularization Group (n = 258)	No Revascularization Group (n = 252)	*P* Value
Primary endpoint: 2.7-y mortality (%)	22	23	0.92
30-day mortality (%)	3.1	3.4	0.87
Postoperative MI (%)	11.6	14.3	0.37

CARP, Coronary Artery Revascularization Prophylaxis.

3 months of randomization and the patients in the medical therapy group were to have their medical regimen maximized.

The average age of the study participants was 66 years. In the group assigned to coronary revascularization, the vascular surgery was delayed an average of 54 days in comparison to 18 days ($P < 0.001$) in the medical therapy group. There was no difference in mortality at either 30 days or 2.7 years and no difference in the incidence of postoperative myocardial infarction (Table 4) between groups. Dr. Edward McFalls, from the University of Minnesota, Minneapolis, MN, presented the results at a late-breaking trial session. He and his colleagues concluded that preoperative coronary revascularization among patients undergoing elective vascular surgery can be done safely but that revascularization delays, and, in some patients, prevents, vascular surgery, and does not improve outcomes. He highlighted the importance of medical therapy, in particular β-blockers, at the time of surgery.

Comment

The results of this long awaited study have the potential to significantly impact clinical practice and decrease the perceived need (and benefit) of elective coronary revascularization prior to elective vascular surgery. However, because 10 patients in the revascularization group died before vascular surgery, compared with only 1 in the medical therapy group, the extension of these results to patients undergoing other non-cardiac surgical procedures is problematic. The CARP trial does underscore the potential risk of delaying major vascular surgical procedures, but it is unclear whether PCI or CABG prior to nonvascular surgery would be of benefit.
[Alice K. Jacobs, MD, FACC, FAHA]

Novel Therapeutics Targeting High-Density Lipoprotein

Currently, many effective medications are available to raise low-density lipoprotein (LDL) levels and improve LDL function. Fewer therapies exist that target high density lipoprotein cholesterol (HDL), though many studies have shown that HDL levels are inversely related to coronary heart disease (CHD) incidence[12-14] and therapies targeting HDL have the potential to make a dramatic impact on CHD morbidity and mortality. Two presentations at the 2004 AHA meeting evaluated novel therapies aimed at altering HDL levels.

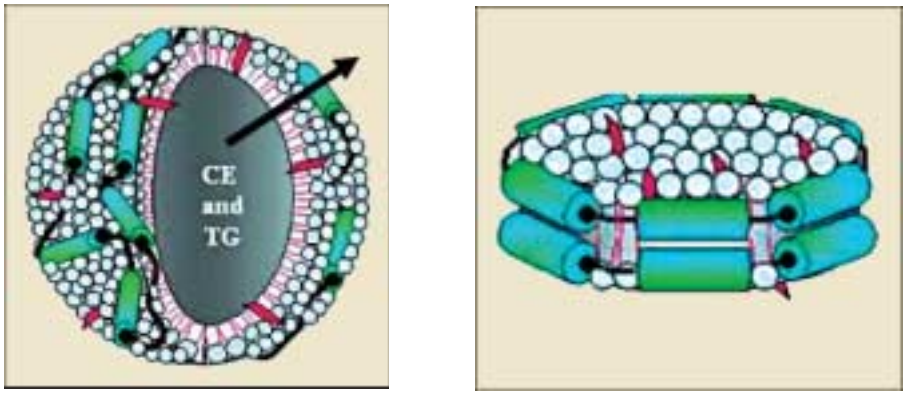
PPAR-δ Agonists

PPAR-δ agonists have been shown to raise HDL levels and reduce triglyceride levels in obese rhesus monkeys and mice but had not heretofore been tested in human subjects. Dr. Dennis Sprecher and associates[15] of GlaxoSmithKline R&D outlined the results of a clinical trial, which evaluated the effects of a PPAR-δ agonist in man. This study tested the potent PPAR-δ agonist, GW501516. This agent was administered to 18 healthy adults for 14 consecutive days at 2 different doses (2.5 mg or 10 mg daily) and the effects on lipid/lipoprotein levels were evaluated. It was found that, compared to placebo, HDLc increased by an average of 14% in patients on the 2.5 mg daily dose and by 19% in patients on the 10 mg daily dose. Concomitantly, triglycerides decreased by an average of 15% with the 2.5 mg dose and 20% with the 10 mg dose. LDL levels did not change. There were no obvious toxicities from this therapy.

This first-in-man study of the potent PPAR-δ agonist, GW501516, revealed that it is safe, well tolerated, and associated with favorable HDL and triglyceride changes. Although further studies are certainly needed with this agent, it may ultimately represent a novel therapy for HDL modification.

HDL Delipidation

Another study, presented by Dr. H. B. Brewer, Jr.,[16] of the National Institutes of Health, evaluated a unique therapy for HDL modification: the selective delipidation and reinfusion of plasma HDL. Dr. Brewer and associates assessed the effects of selective plasma HDL delipidation on HDL levels, HDL composition, and HDL function. The basis of this therapy is not to increase HDL levels (HDL levels dramatically decrease with this therapy) but rather to improve what is believed to be the main beneficial function of HDL: reverse cholesterol transport. Reverse cholesterol transport is the body's natural mechanism for removing



A B

Figure 5. *The delipidation process. Removal of cholesterol from the mature high-density lipoprotein (HDL) form* ***(A)*** *leaves the smaller, discoid, pre-beta HDL form* ***(B),*** *which acquires cholesterol from the artery wall. CE, cholesterol ester; TG, triglyceride.*

lipids from the artery wall and it is solely carried out by HDL. This therapy is intended to enhance reverse cholesterol transport through the selective delipidation of HDL. This delipidation process involves removal of cholesterol from the mature HDL form (Figure 5A), leaving the smaller, discoid, pre-beta HDL form (Figure 5B). The pre-beta HDL form acquires cholesterol from the artery wall.

The acute effect of this therapy was to decrease HDL level by an average of 76% with no change in LDL level. However, the percentage of pre-beta HDL increased by 300%. As expected, after delipidation, the HDL was 25 times more effective at reverse cholesterol transport than was native HDL. [Karol E. Watson, MD, PhD]

The CAMELOT Study

There is an ongoing need to examine drug interventions that might affect natural history and pathologic changes in patients at high risk of cardiovascular events. The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study[17] was a placebo-controlled trial designed to compare the effects of a calcium channel blocker, amlodipine, and an angiotensin-converting enzyme (ACE) inhibitor, enalapril, on major clinical endpoints in patients with documented coronary disease. Although not strictly a hypertension study, CAMELOT focused primarily on those patients with above-normal blood pressure levels, sometimes referred to as prehypertensive.

This study was originally selected for presentation as a late-breaking trial at the 2004 Scientific Session of the American Heart Association. However, due to a scheduling mischance, the publication of this trial appeared the day before its planned presentation and was thus withdrawn from the program. Even so, the findings and implications of CAMELOT became well known at the meeting, and, in fact, were frequently discussed in the interpretation of other presented trials. For this reason, it is important to consider the principal outcomes and interpretations of this work.

Background and Methods

Experts continue to debate whether antihypertensive drugs, beyond their blood pressure-lowering properties, might confer additional cardiovascular benefits in at-risk patients. CAMELOT was designed to compare 2 widely used, but clearly different, types of antihypertensive agents: a calcium channel blocker and an ACE inhibitor. To better define the effects of these drugs, the study was carried out in patients with essentially normal or only minimally increased blood pressure so that a placebo control could also be included. In this way, CAMELOT serves, interestingly if unintentionally, as an outcomes trial in the range of blood pressures described as prehypertensive.

Patients. To ensure an adequate level of risk, the study was performed in patients with angiographically demonstrated coronary artery disease; evidence of at least a 20% stenosis was required for study entry. Diastolic blood pressure (whether or not subjects were on antihypertensive therapy, which generally was continued during the study) was required to be below 100 mmHg at the start of the study. A total of 1991 patients entered the trial. In addition, 274 of these patients entered a substudy in which intravascular ultrasound (IVUS) was performed in defined coronary artery segments at baseline and at the end of the study. Coronary artery disease was documented by angiography in 1 vessel in approximately one-third of patients, in 2 vessels in approximately one-third, and in 3 vessels in approximately one-third. In addition, 38% of the patients had experienced a previous myocardial infarction and 60% had a previous history of hypertension.

CAMELOT serves, interestingly if unintentionally, as an outcomes trial in the range of blood pressures described as prehypertensive.

Table 5
Cardiovascular Events in the CAMELOT Study

	Placebo [n, (%)]	Amlodipine [n, (%)]	Enalapril [n, (%)]
Primary endpoint (multiple CV events)	151 (23.1)	110 (16.6)*	136 (20.2)
Components			
Coronary revascularization	151 (23.1)	78 (11.8)	95 (14.1)
Hospitalization for angina	103 (15.7)	51 (7.7)*†	86 (12.8)
Nonfatal MI	19 (2.9)	14 (2.1)	11 (1.6)
Stroke or TIA	12 (1.8)	6 (0.9)	8 (1.2)
CV death	2 (0.3)	5 (0.8)	5 (0.7)
Hospitalization for CHF	5 (0.8)	3 (0.5)	4 (0.6)
Resuscitated cardiac arrest	4 (0.6)	0	1 (0.1)
New-onset PAD	2 (0.3)	5 (0.8)	8 (1.2)
All-cause mortality (secondary endpoint)	6 (0.9)	7 (1.1)	8 (1.2)

*Significant vs. placebo.
†Significant vs. enalapril.
CAMELOT, Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; CHF, chronic heart failure; CV, cardiovascular; MI, myocardial infarction; PAD, peripheral arterial disease; TIA, transient ischemic attack. Adapted with permission from Nissen et al.[17]

Endpoints. The primary endpoint of the study was a composite of cardiovascular events including cardiovascular death, nonfatal myocardial infarction, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, resuscitated cardiac arrest, fatal or nonfatal stroke, and peripheral arterial disease. All-cause mortality was a secondary endpoint. The primary comparison in the study was between amlodipine and placebo, though obviously comparisons were also made between the 2 active drugs, as well as between each of them and placebo.

Treatments. In this double-blind study, patients were randomized equally to treatment with amlodipine 10mg, once daily, enalapril 20mg, once daily, or placebo. In addition, patients continued to take their previously prescribed cardiovascular drugs. Overall, 83% of patients continued on statins, 76% continued on β-blockers, 30% continued on diuretics, and 96% continued on aspirin.

Main Findings

Hemodynamics. In accordance with the study plan to include patients with normal to prehypertensive blood pressure levels, the mean baseline blood pressure was 129/78 mmHg. During the course of the trial, it increased by 0.7/0.6 mmHg in the placebo group, but fell by 4.8/2.5 mmHg with amlodipine and by 4.9/2.4 mmHg with enalapril. These treatment-induced changes were significant when compared with placebo ($P < .001$ for both).

Outcomes. The composite primary endpoint of cardiovascular events occurred in 151 (23.1%) of placebo-treated patients, in 110 (16.6%) of amlodipine-treated patients, and in 136 (20.2%) of enalapril-treated patients. Compared with placebo, the effect of amlodipine was significant (hazard ratio [HR] 0.69; 95% CI: 0.54-0.88, $P = .003$). The effect of the enalapril was not significant (HR 0.85; 95% CI: 0.67-1.07, $P = 0.16$). The difference between amlodipine and enalapril did not quite reach significance (HR 0.81; 95% CI: 0.63-1.04, $P = 0.10$).

The major components of the composite endpoint are listed in Table 5. The most common events were coronary revascularization and hospitalization for angina. Amlodipine was significantly superior to placebo in preventing events in both of these categories and was also superior to enalapril in the angina category. The other components of the primary endpoint—major outcomes such as myocardial infarction or stroke that typically are referred to as "hard endpoints"—also trended in amlodipine's favor, though the numbers were too small to test for significance.

IVUS Data. As shown in Table 6, percent atheroma volume increased significantly in the placebo group and also increased in the enalapril group (though not quite reaching significance, $P = 0.08$). The change in the amlodipine group, however, was clearly not significant. When compared with the placebo group, there was a trend ($P = .12$) toward a lesser change with amlodipine. Interestingly, in a prespecified analysis comparing the amlodipine and placebo changes in patients whose baseline systolic blood pressures were greater than the group mean, amlodipine was superior to placebo in preventing atheroma progression ($P = 0.02$).

Comment

Quite clearly, adding a high dose of amlodipine to the regimens of high-risk coronary patients with

Table 6
Mean Percent Atheroma Volumes in the CAMELOT Study

	Placebo, n = 95	Amlodipine, n = 91	Enalapril, n = 88
Baseline (SD)	42.1 (9.3)	39.9 (10.5)	41.6 (9.8)
Follow-Up (SD)	43.4 (9.6)	40.4 (10.8)	42.4 (10.4)
Change (SD)	1.3 (4.4)	0.5 (3.9)	0.8 (3.7)
P vs baseline	.001	.31	.08

Figures based on intravascular ultrasound data. Differences between treatment groups were not significant. SD, ± standard deviation. CAMELOT, Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis. Adapted with permission from Nissen et al.[17]

only minimally elevated blood pressures provides endpoint benefits. In particular, there is a sharp reduction in symptomatic ischemic heart disease and a trend towards a reduction in some harder endpoints as well. Although it could be anticipated that a drug already indicated for the treatment of angina pectoris would confer symptomatic benefits, it is noteworthy that there was such a large reduction in the need for revascularization procedures.

One problem with the study design in CAMELOT was that the dose of enalapril was inadequate. At the very least, enalapril should have been given as 40 mg, daily, or perhaps as 20 mg, twice daily. It could be argued that the dose was not a critical factor because the 2 active drugs reduced blood pressure virtually identically. Such a claim, though, overlooks the fact that the study was really focusing on non-blood pressure effects of drugs; in the ACE inhibitor dose administered, it was not possible to determine whether a more effective interruption of the renin-angiotensin system (plus whatever other beneficial mechanisms might be provided by ACE inhibitors) could have provided greater benefits. It should also be noted that, unlike some earlier trials in high-risk patients with ACE inhibitors that appeared to show dramatic benefits, more than 80% of patients in CAMELOT were receiving statins. We cannot ignore the possibility that there might be some drug interaction between ACE inhibitors and statins that could limit them from conferring full additive cardiovascular protection when given concomitantly.

Probably the most interesting part of CAMELOT was the IVUS substudy. Over the years, studies in animal models have demonstrated that calcium channel blockers might have direct anti-atherosclerotic actions. Perhaps CAMELOT is the first study to raise the possibility that a high-dose dihydropyridine could have the ability to reduce the progression of atherosclerosis in humans. Unfortunately, the dosing issue with enalapril does not allow us to reach any conclusions as to whether ACE inhibitors or other blockers of angiotensin II might have similar effects. Although the modest changes in blood pressure during this trial might have contributed to the IVUS findings, the possibility of a non-hemodynamic effect of amlodipine upon vascular pathology is tantalizing and provides a strong incentive for further, more highly powered studies to explore this question.
[Michael A. Weber, MD]

Statins and Acute Coronary Syndromes

There is growing evidence that statins possess anti-inflammatory and antioxidative vascular characteristics that are independent of lipid lowering. In studies of experimental myocardial infarction therapy, statins have been shown to enhance endothelial nitric oxide (eNO) availability by both increasing eNO production and reducing NO inactivation; to improve endothelium-dependent, NO-mediated vasorelaxation; to mobilize endothelial progenitor cells; and to increase myocardial neovascularization in the infarct border as well as reducing infarct size following 60 minutes of ischemia/reperfusion but not following permanent coronary occlusion. Based on these results and the established, statin-related, all-cause mortality reduction in patients with chronic coronary disease, investigators are now seeking to determine whether this benefit extends to patients with acute coronary syndromes (ACS) and to determine the optimal time to begin therapy.

Several recent studies have shown that statin therapy at or following hospital discharge for acute MI reduces recurrent ischemia; however, the optimal time to begin therapy remains unclear.

Several recent studies have shown that statin therapy at or following hospital discharge for acute MI (AMI) reduces recurrent ischemia; however, the optimal time to begin therapy remains unclear. The Prevention of Ischemic Events by Early treatment with Cerivastatin (PRINCESS)[18] study

was designed to examine the effects of early statin therapy (within 48 hrs) of AMI. The study was conducted at 280 centers in Europe, Israel, Canada, and the United States. Patients with AMI (n = 3605) were randomized within 48 hours of the event to cerivastatin (0.4 mg/d, n = 1795) or placebo (n = 1810) in a double-blind manner for 4.5 months. The endpoints of the study were complex, however; using a secondary endpoint of reduction in recurrent coronary ischemia including ischemic coronary revascularizations, fatal and non-fatal re-infarction, and unstable angina, the authors showed a significant (P = .05), positive result. They concluded that statin therapy very early during hospitalization for AMI reduces recurrent coronary ischemia during short-term follow-up.

In a second study, Saab and associates[19] examined the optimal time for administration of statins in the setting of ACS. The study was designed as a prospective cohort of 1639 consecutive patients with ACS, comparing patients (not on statin therapy at presentation) who received statins within the first 24 hours after admission (n = 1639) with a second group of patients (n = 355) who received statins after the first 24 hours. The endpoints studied included death, heart failure, pulmonary edema, stroke, and recurrent infarction. Multivariate analysis was performed to adjust for baseline demographics and comorbidities in order to assess the independent benefit of early versus late administration of a statin. The

Main Points

- Results of the Diabetic Postoperative Mortality and Morbidity (DIPOM) Trial call into question current guidelines recommending peri-operative administration of β-blockers for diabetic patients undergoing surgery, as the administration of metoprolol in this study had no effect on rates of the composite endpoint of death, acute MI, unstable angina, or congestive heart failure at follow-up, when compared to placebo.
- The Rimonabant on Weight Reduction and Weight Maintenance North America (RIO-NA) study is the first of the RIO trials to report data through 2 years and although weight loss was maintained through 2 years in patients who were randomized to rimonabant 20 mg for the full time period, it was clear that the drug was needed to maintain weight loss and this drug will be most effective in conjunction with an aggressive diet and exercise approach because the majority of patients whom clinicians would consider for this therapy are at least 30 lbs overweight.
- The Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiologicos Latinoamerica (CREATE-ECLA) showed no advantage in the treatment of acute ST elevation myocardial infarction with combination glucose/insulin/potassium as an adjunct to standard therapy. However, extended (7-day) administration of the low molecular-weight heparin reviparin proved advantageous in terms of overall mortality and major adverse events.
- The ESCAPE Trial demonstrated that for patients hospitalized with heart failure, therapy guided by Swan-Ganz hemodynamic monitoring is just as safe as treatment based on clinical signs alone but there are no improvements in clinical outcomes; initial use of a pulmonary artery catheter to guide care should be reserved for heart failure patients in cardiogenic shock, patients undergoing orthotopic heart transplantation evaluation, or patients who remain refractory to clinically guided therapy.
- The ACORN Trial has provided proof of the concept that mechanical restraint can reduce left ventricle (LV) size in patients with heart failure but this particular cardiac support device failed to improve LV ejection fraction, reduce hospitalizations, or influence mortality.
- Results of the CARP Trial showed that preoperative coronary revascularization among patients undergoing elective vascular surgery can be done safely but that revascularization delays, and, in some patients, prevents, vascular surgery, and does not improve outcomes.
- New therapies are under investigation that target high-density lipoprotein (HDL) and its role in reverse cholesterol transport. They include the administration of PPAR-δ agonists, which work to raise HDL levels, and the process of HDL delipidation, which improves HDL function.
- The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study is the first to raise the possibility that a high-dose dihydropyridine could have the ability to reduce the progression of atherosclerosis in humans.
- The PRINCESS trial, combined with the results of the PROVE IT-TIMI 22 and REVERSAL trials, supports the concept of early and aggressive use of statins for both their (early) anti-inflammatory and lipid-lowering effects.

incidence of the composite endpoint of death/MI/stroke was 7% in the early (< 24 hr) group versus 10.4% in the late administration group ($P < 0.3$). Multiple logistic analysis showed that patients who received statins in the first 24 hours had less heart failure/pulmonary edema (OR 0.44, CI 0.28-0.69), and a reduction in rate of death, stroke, and reinfarction (OR 0.62, CI 0.39 −1.00; $P = 0.05$). The authors concluded that patients with ACS receiving statins within the first 24 hours of admission had lower incidences of death, stroke, reinfarction, heart failure, and pulmonary edema compared with delayed administration.

These studies, combined with the results of the PROVE IT-TIMI 22 and REVERSAL trials, support the concepts of early and aggressive use of statins for both their anti-inflammatory (early) and lipid-lowering effects. In secondary prevention, statins are often combined with other anti-ischemic therapies (β-blockade, antiplatelet therapy, angiotensin-converting enzyme inhibitors) and, although each option has been shown to be individually effective, little is known about the combined effects of multiple therapies.

In another study, Schwammenthal and colleagues[20] hypothesized that secondary preventive drugs at discharge (from 1 to 4) will independently predict mortality of ACS survivors. To address this question, 3407 patients from the Israeli ACS surveys of 2000 and 2002 were analyzed. A score from 1 to 4 was assigned to each patient based on the number of secondary prevention drugs at discharge: platelet inhibitor, β-blocker, statin, and angiotensin-converting enzyme inhibitor (or receptor blocker), irrespective of combination or dosage. The crude 1 year mortality score from 1 to 4 was 12.6%, 7.9%, 4.0%, and 2.6% respectively ($P < .0001$). There was a 60% risk reduction associated with the use of 3 or 4 versus 1 or 2 drugs (OR 0.4, CI 0.28-0.56) that was independent of age, sex, past ACS, diabetes, heart failure during hospitalization, ejection fraction, or the presence of ST elevation. The authors conclude that the use of a higher number of secondary preventative drugs at discharge is associated with incremental survival benefits.

Although many questions remain concerning timing of onset of therapy, drug dosage, and drug type, these data support the additive effects of combined therapy.

[Arthur E. Weyman, MD] ■

References

1. Juul A, for the DIPOM Investigators. Diabetic Postoperative Mortality and Morbidity Trial (DIPOM). Late Breaking Clinical Trials, American Heart Association Scientific Sessions. November 7-10, 2004. New Orleans, LA.
2. Taylor AL, Ziesche S, Yancy C, et al. African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004;351:2049-2057.
3. Bakris GL, Fonseca V, Katholi RE, et al. GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA*. 2004. 292(18):2227-2236.
4. Pi-Sunyer X, et al. Rimonabant on Weight Reduction and Weight Maintenance: RIO-NORTH AMERICA. Late Breaking Clinical Trials, American Heart Association Scientific Sessions. November 7-10, 2004. New Orleans, LA.
5. Connors AF Jr, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients: SUPPORT investigators. *JAMA*.1996;276:889-897.
6. Shah MR, O'Connor CM, Sopko G, et al. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE): design and rationale. *Am Heart J*. 2001;141:528-535.
7. Hill JA, Shah MR, Hasselblad V, et al. Pulmonary artery catheter use does not change the contribution of renal dysfunction to outcomes in patients with advanced heart failure: findings from ESCAPE. *Circulation*. 2004; 110(17): III-638 (abst. 2964).
8. Vasan RS, Larson MG, Benjamin EJ, et al. Left ventricular dilation and the risk of congestive heart failure in people without myocardial infarction. *N Engl J Med*. 1997;336:1350–1355.
9. Saavedra WF, Tunin RS, Paolocci N, et al. Reverse remodeling and enhanced adrenergic reserve from passive external support in experimental dilated heart failure. *J Am Coll Cardiol*. 2002;39:2069–2076.
10. Mann DL, Acker MA, Jessup M, et al.; ACORN Investigators and Study Coordinators. Rationale, design, and methods for a pivotal randomized clinical trial for the assessment of a cardiac support device in patients with New York Health Association class III-IV heart failure. *J Card Fail*. 2004;10:185-192.
11. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med*. 2004;351:2795-2804.
12. Franceschini G. Epidemiologic evidence for high-density lipoprotein cholesterol as a risk factor for coronary artery disease. *Am J Cardiol*. 2000; 88:9N-13N.
13. Assmann G, Schulte H, von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis* 1996;124(Suppl): S11-S20.
14. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989; 79:8-15.
15. Sprecher D, Massien C, Patterson S, et al. HDLc effects in healthy subjects administered a peroxisome proliferator activated receptor (PPAR) delta agonist. *Circulation* 2004;110(17):III-52(abst. 244).
16. Brewer HB, Alaupovic P, Kostner G, et al. Selective plasma HDL delipidation and reinfusion: A unique new approach for acute HDL therapy in the treatment of cardiovascular disease. *Circulation* 2004;110(17):III-51(abst. 241).
17. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary heart disease and normal blood pressure: The CAMELOT study: A randomized controlled trial. *JAMA*. 2004; 292:2217-2226.
18. LaBlanche JM, Wright RS, Jukema W, et al. Reduction in lipids but not inflammatory markers from early administration of statin therapy upon admission for myocardial infarction: Results of the PRINCESS Trial. *Circulation* 2004; 110 (17, Suppl III):III-448 (abst. 2110).
19. Saab F, Fang J, Kline-Rodgers E, et al. Early (within 24 hours) statin administration in patients with acute coronary syndromes is associated with better outcomes compared to delayed (after 24 hours) administration. *Circulation* 2004;110(17, Suppl III):III-498 (abst. 2338).
20. Schwammenthal E, Sandach A, Klempfner R, et al. Predicting mortality in survivors of acute coronary syndrome using the 4 Drug (4D) score: Risk stratification by discharge medication. *Circulation* 2004;110(17, Suppl III):III-500 (abst. 2345).