Best of the ACC Scientific Session 2004

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In conjunction with the 2004 Scientific Session of the American College of Cardiology (ACC), abstracts were published reporting significant findings in every major area of cardiovascular medicine. Here, our editorial board members report on selected findings of particular importance.

Heart Failure: New Analyses of the COMET Study

New analyses from the landmark Carvedilol or Metoprolol European Trial (COMET) were presented at this year's ACC. These reports assessed whether dosage levels affected survival benefit for heart failure patients taking carvedilol versus those taking metoprolol, as well as discussing whether differences in heart rate and blood pressure could account for the mortality reduction observed with carvedilol in COMET.

COMET was initiated in 1996, with 3,029 patients from 15 European countries and 317 centers enrolled in a multi-center, double-blind, and randomized parallel group trial. In the study, 1,511 patients with chronic heart failure were assigned to receive carvedilol and 1,518 to receive metoprolol tartrate. Inclusion criteria included chronic heart failure, a previous hospital admission for a cardiovascular reason, an ejection fraction of less than or equal to 35%, and optimal treatment with diuretics and angiotensin-converting enzyme (ACE) inhibitors, unless not tolerated. The co-primary endpoints were all-cause mortality and the composite endpoint of all-cause mortality or all-cause hospital admission. All patients were followed up for more than 45

months (175,447 patient months of follow-up) and the trial accumulated over 1,000 deaths. COMET demonstrated that carvedilol provided a significant (17%) survival benefit (P = .0017) compared with metoprolol tartrate.[1]

Dosage Levels

Research indicates that ß-blockers are often prescribed in clinical practice at lower doses than are typically studied in clinical trials. Therefore, it is important to determine whether the differences in outcomes between carvedilol and metoprolol tartrate may be influenced by the dose administered. An oral presentation by Professor Marco Metra[2] of the University of Brescia, Brescia, Italy, revealed that the greater survival benefits of carvedilol compared to metoprolol tartrate in heart failure patients were maintained independently from the dose administered. The reduction in death rate achieved with carvedilol was similar in patients on target doses (25.4% on carvedilol vs 32.4% on metoprolol tartrate; relative risk (RR) 0.75; 95% confidence interval (CI) 0.64-0.89; P = .0008) and in patients on low dose (36.9% on carvedilol vs 45.6% on metoprolol tartrate; RR 0.76; 95% CI 0.60-0.98; P = .032).

Blood Pressure and Heart Rate Effects

The influence of heart rate and blood pressure on survival in heart failure patients was not well explored prior to the COMET trial. In a presentation by Professor Christian Torp-Pedersen[3] of the Gentofte University Hospital, Copenhagen, Denmark, no correlation was found between the effect on mortality of carvedilol compared to metoprolol tartrate and change in systolic blood pressure (SBP). The new analyses showed a reduction in mortality with carvedilol compared to metoprolol tartrate in both heart failure patients with a decrease in SBP greater than or equal to 3 mm Hg (28% vs. 36%; RR 0.76; 95% CI 0.62-0.92; P = .0049) and in the remaining patient population, which did not experience the same change in SBP (28% vs 34%; RR 0.79; 95% CI 0.65-0.97; P = .0229).

Additional analyses presented by Professor Metra[4] did not demonstrate a correlation between the effect on mortality of carvedilol compared to metoprolol tartrate and early changes in heart rate resulting from the 2 courses of therapy. This revealed that mortality was reduced with carvedilol compared to metoprolol tartrate, both in patients with a decrease in heart rate greater than or equal to 12 bpm (28% vs 35%; RR 0.77; 95% CI 0.64-0.94; P = .0086) and in patients with decreases less than 12 bpm (28% vs 34%; RR 0.79; 95% CI 0.65-0.97; P = .0229).

The differences in outcomes in COMET cannot be explained by differences in the dose given, effects on heart rate, or blood pressure.

These new analyses reinforce the fact that not all ß-blockers provide the same therapeutic benefits and that comprehensive adrenergic blockade with carvedilol is a more optimal treatment for heart failure patients when compared to metoprolol tartrate. The differences in outcomes in COMET cannot be explained by differences in the dose given, effects on heart rate, or blood pressure.

Rimonabant for Obesity and Smoking Cessation

According to the Centers for Disease Control, obesity and smoking are the 2 leading causes of preventable death in the U.S., together accounting for 700,000 deaths a year. An estimated 40 million Americans are obese, 50 million Americans have metabolic syndrome, and 47 million Americans are current smokers.[5]

Cannabis smokers are known to experience extreme hunger pangs, which are commonly referred to as "the munchies." If cannabinoids stimulate appetite, blocking cannabinoid receptors in the brain has the potential to reduce appetite. The central cannabinoid (CB1) receptors are believed to play a role in controlling food consumption and the phenomena of dependence/habituation. To develop suitable drugs against this target, the human cannabinoid receptor was first cloned and then compounds with potential inhibitory activity against this receptor were screened for inhibitory activity. Rimonabant emerged from this screening process as a potent CB1 receptor antagonist.[6] Preclinical animal studies subsequently showed that rimonabant could reduce consumption of fats and sugars, which contribute to weight gain. Two studies of rimonabant were presented at a late-breaking trial session at this year's ACC. Both were conducted by Drs. Robert M. Anthenelli of the University of Cincinnati College of Medicine in Cincinnati, OH, and Jean-Pierre Despres of Laval University, Quebec City, Canada.

RIO-LIPID Trial

In the RIO (Rimonabant in Obesity) Lipids study, 1036 overweight or obese patients were randomized to placebo, 5-mg rimonabant, or 20-mg rimonabant for 1 year. Patients were placed on a diet and exercise regimen during placebo run-in and then placed on 1 of the 3 medication regimens.

Patients in the 20-mg group lost

a remarkable 15 lbs more than patients on placebo over 1 year. These patients also experienced significant positive changes in waist circumference, high density lipoprotein (HDL) level, triglyceride levels, low density lipoprotein (LDL) particle size, adiponectin and leptin levels, insulin sensitivity, and presence of metabolic syndrome (Table 1). The levels of C-reactive protein (hs-CRP) fell from 3.7 mg/L at baseline to 2.7 mg/L at follow-up in the 20 mg rimonabant-treated patients.

Table 1
Improvement in Risk Factors in Rimonabant-Treated Patients in the RIO-LIPID Trial

Endpoint	20-mg rimonabant	*P* value
Weight	-15 lb	< .001
Waist circumference	-9.1 cm	< .001
HDL	+23%	< .001
Triglycerides	-15%	< .001
CRP	-16%	< .001

CRP, C-reactive protein; HDL, high-density lipoprotein.

Of subjects taking rimonabant for 1 year, 44% lost more than 10% of their body weight, compared with only 16.3% of those taking 5-mg rimonabant and 10.3% of placebo-treated subjects. Importantly, patients taking rimonabant 20 mg daily experienced a 52.9% reduction in criteria fulfillment for the Adult Treatment Panel III definition of metabolic syndrome, compared with 25.8% of placebo patients. In addition, there was a 51.9% reduction in the incidence of type 2 diabetes among patients treated with the high dose of rimonabant versus a 41% reduction among placebo patients.

Rimonabant treatment was more effective than placebo in reducing weight, decreasing abdominal circumference, increasing HDL, decreasing triglycerides, improving insulin sensitivity, decreasing incidence of metabolic syndrome, and decreasing CRP levels.

STATUS-US Trial

The second rimonabant trial, STATUS-US (Smoking Cessation in Smokers Motivated to Quit) studied 787 smokers who had failed to quit on an average of 4 previous occasions. Patients were randomized to rimonabant, 20 mg daily, versus placebo. Smoking cessation was assessed by breath carbon monoxide and urinary cotinine measurements. After 10 weeks of treatment, including a 2-week run-in period when subjects were allowed to continue to smoke and a final 4-week period when smoking abstinence was assessed, smokers randomized to rimonabant therapy were twice as likely to quit as subjects randomized to placebo. Among patients receiving 20 mg of rimonabant daily, 27.6% were able to stop smoking, compared to 15.6% of those taking the 5 mg dose and 16.1% of those taking placebo ($P = 0.004$, HR 2.2).

Subjects taking 20-mg rimonabant lost about 0.5 lb, whereas subjects who quit smoking while taking placebo gained almost 2.5 lbs. Among patients who were not obese at baseline (body mass index less than 30 kg/m^2) there was a 77% reduction in post-cessation weight gain compared to placebo. Weight loss occurred in overweight or obese subjects on 20-mg rimonabant.

Rimonabant was generally well tolerated, with a withdrawal rate only slightly higher than placebo. In both studies, side effects were relatively mild and transient, the most commonly cited being nausea and dizziness. Adverse events occurred in 4.2% of placebo patients, 6.1% of those taking the lower rimonabant dose, and 6.9% of those taking the 20 mg dose. In addition, rimonabant had no significant impact on blood pressure, heart rate, or QT interval. Depression and anxiety measures were also similar between the rimonabant- and placebo-treated patients.

Rimonabant treatment was more effective than placebo in reducing weight, decreasing abdominal circumference, increasing HDL, decreasing triglycerides, improving insulin sensitivity, decreasing incidence of metabolic syndrome, and decreasing CRP levels. This agent was also effective in promoting smoking cessation without significant weight gain.

Results of these trials indicate that physicians may finally have a new tool to treat common, major risk factors for cardiovascular disease that are currently treated in isolation, including obesity, dyslipidemia, and smoking. However, it is not yet clear whether the improvements in metabolic and lipid profiles are entirely secondary to weight loss or due in part to a primary effect of CB1 blockade. Many smokers fear that quitting will lead to weight gain or experi-

ence recidivism due to weight gain. Rimonabant may have a distinctive dual effect that could prove to be critical in helping patients to quit smoking while reducing the likelihood of weight gain.
[Gregg C. Fonarow, MD, FACC, FACP]

Trials in Electrophysiology

At a late-breaking trial session on Monday, March 8, three randomized, clinical trials were presented: SCD-HeFT by Dr. Gust H. Bardy; DINAMIT by Dr. Stefan H. Hohnloser; PAVE by Dr. Rahul Doshi.

SCD-HeFT

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was presented by Dr. Gust Bardy of the University of Washington Medical Center in Seattle, WA, on behalf of the trial investigators. Patients with New York Heart Association (NYHA) Class II or III heart failure, either ischemic or nonischemic cardiomyopathy, and a left ventricular ejection fraction (LVEF) of 35% or less were eligible for enrollment. Patients were randomized to best medical therapy, best medical therapy plus amiodarone, or best medical therapy plus the insertion of an implantable cardioverter defibrillator (ICD). There were 2,521 patients enrolled in 148 centers in North America and New Zealand. The primary outcome of the trial demonstrated that ICD implantation reduces all-cause mortality when compared with placebo, whereas amiodarone did not improve mortality. The 3-year rates of all-cause mortality for the ICD, amiodarone, and placebo were 17.1%, 24.0%, and 22.3%, respectively; 5-year all-cause mortality was 28.9%, 34.1%, and 35.8%, respectively.

Importantly, all patients received up-to-date medical therapy. The baseline use of ACE inhibitors was 85%, 96% if angiotensin receptor blockers were included. ß-Blockers were prescribed in 69% of patients at baseline and this improved to 78% at last follow-up identification.

As with all large, randomized, controlled trials, a variety of subgroup analyses were presented. Comparisons for relative risk of all-cause mortality for ICD versus placebo therapy showed hazard ratios of 0.54 for NYHA Class II and 1.16 for NYHA Class III patients; ischemic etiology at 0.79; nonischemic etiology, 0.73; LVEF less than or equal to 30%, 0.73; LVEF greater than 30%, 1.08; QRS duration less than 120 msec, 0.84; and QRS duration 120 msec or greater, 0.67.

How does one interpret the subgroup analyses data? First and foremost, one should not apply subgroup analyses to the clinical care of patients. The key finding of this study was that patients who meet entry criteria for SCD-HeFT are candidates for an ICD. Subgroup analysis can be a valuable process to provide clues for new areas of investigation, but in and of itself does not provide adequate information to make a clinical decision. Thus, whereas the hazard ratio demonstrates the value of ICD use in NYHA Class II patients, the lack of such value of an ICD in patients with NYHA Class III cannot be determined from this study. In fact, other trials have clearly shown benefit from an ICD in patients with NYHA Class III heart failure.

Another important observation is that both ischemic and nonischemic cardiomyopathy patients benefited from ICD therapy. Whereas other trial data are available to support the use of an ICD in patients with ischemic cardiomyopathy, this is the first clear-cut demonstration of a survival benefit from an ICD in high-risk patients with a nonischemic cardiomyopathy.

In summary, the results of SCD-HeFT give direction to the clinician on how to approach patients with nonischemic cardiomyopathy, LVEF less than or equal to 35%, and NYHA Class II or III heart failure symptoms. It is hoped that regulators and payers will move quickly to provide reimbursement for an ICD in this situation. Amiodarone has no apparent survival advantage to such individuals.

Whereas other trial data are available to support the use of an ICD in patients with ischemic cardiomyopathy, this is the first clear-cut demonstration of a survival benefit from an ICD in high-risk patients with a nonischemic cardiomyopathy.

DINAMIT Study

Doctor Stefan Hohnloser of the JW Goethe-University College, Frankfurt, Germany, presented data from the Defibrillator in AMI (DINAMIT) Study. In DINAMIT, patients were randomized to optimal medical therapy compared with optimal medical therapy plus an ICD implanted within 40 days after acute myocardial infarction. More than 80% of patients were receiving a ß-blocker and approximately 90% were taking an ACE inhibitor. The ventricular back-up pacing rate was set at 40 to 45 beats per minute for those patients who received an ICD. All-cause mortality was the primary endpoint for DINAMIT, and secondary endpoints included quality of life issues and arrhythmic death. There were 332 patients who received an ICD compared with 342 control patients.

All-cause mortality was not differ-

ent between groups. Importantly, and surprisingly, there was a highly significant reduction in arrhythmic deaths in patients who received an ICD, but this apparent gain in survival was offset by an increase in nonarrhythmic deaths. Deaths occurred in 62 patients with an ICD versus 58 in the control group. On the other hand, only 12 patients had an arrhythmic death in the ICD group compared with 29 in the control group, yielding a hazard ratio of 0.42, which was highly significant. Quixotically, there were 50 nonarrhythmic deaths in the ICD group compared with only 29 in the control group, yielding a hazard ratio of 1.75, also significant. This trade-off of modes of death for the ICD group led to a neutral study result.

The ICD deaths apparently were not due to specific complications from ICD implantation; therefore, one has to hypothesize that something about an ICD lead across the tricuspid valve would lead to relatively early mortality.

It is difficult to explain the results of this study. The ICD deaths apparently were not due to specific complications from ICD implantation; therefore, one has to hypothesize that something about an ICD lead across the tricuspid valve would lead to relatively early mortality. There could be some tricuspid regurgitation, but it is unlikely to have been severe enough to increase mortality. If there were a significant mortality risk from an ICD lead placed across the tricuspid valve, it would have been recognized over the many years that these leads have been used in patients even sicker than the group presented here. There is no obvious reason why nonarrhythmic deaths were increased in the ICD group.

In summary, whereas ICD implantation reduced arrhythmic deaths in high-risk patients post-MI, the offsetting increase in nonarrhythmic deaths made this particular study neutral in its comparative outcome. At present it would seem prudent to treat post-MI patients in accordance with the results from the Multicenter Unsustained Tachycardia Trial (MUSTT) and the Multicenter Automatic Defibrillator Implantation Trial (MADIT). Both of these study populations yielded a benefit from the ICD but entry criteria were different. For example, patients had to be at least 4 days post-MI in MUSTT and 3 and 4 weeks in MADIT I and MADIT II, respectively. Further, in MUSTT and MADIT I, spontaneous nonsustained ventricular tachycardia and inducible sustained ventricular tachycardia were requisites for inclusion in the trials. In MADIT II, patients had to have an ejection fraction of 30% or less. Until we have more clarification regarding the issues involved with DINAMIT, patients should be risk-stratified according to the entry criteria and study design of MUSTT, MADIT I, and MADIT II.

PAVE Trial

The Left Ventricular-Based Cardiac Stimulation Post AV Nodal Ablation Evaluation (PAVE) Trial did not evaluate mortality rates, but did compare patients' performance on a 6-minute walk as the primary endpoint. Patients were entered into the trial if they had atrial fibrillation that required ablation of the AV junction with implantation of a permanent pacemaker. Traditionally, a right ventricular (RV) pacemaker is given for such patients. This trial randomized patients to receive an RV pacemaker or cardiac resynchronization therapy (CRT) using bi-ventricular pacing.

Dr. Rahul Doshi of the Sunrise Hospital and Medical Center in Las Vegas, NV, presented these data. Of the 102 patients randomized, those who received CRT increased their 6-minute walk test to 82 meters compared with only 56 meters in the patients who received RV pacing, a statistically significant difference. Further, patients with CRT had a significant improvement in peak VO2 max at 6 months whereas those who received RV pacing did not. In summary, the PAVE trial in this group of patients suggested that CRT is preferred over RV pacing for the parameters investigated.

The endpoints of this trial are rather soft, and do not necessarily imply that all patients requiring permanent ventricular pacing due to heart block should receive a bi-ventricular pacemaker. This conclusion will require much more data. On the other hand, data are mounting that certain subgroups of patients may do better with CRT compared with RV pacing only, even when heart failure has not been demonstrated. These include those with left ventricular dysfunction or substantial mitral regurgitation. For now, clinicians should be selective in their use of CRT, and follow the literature on this ever-moving target.

[Eric N. Prystowsky, MD]

Percutaneous Coronary Interventions

ON-TIME Trial

In a late-breaking trials session, results of the ON-TIME (Ongoing Tirofiban in Myocardial Infarction) Trial were presented by Dr. Meno Jan de Boer of the Isala Klinieken in Zwolle, the Netherlands. The trial evaluated the efficacy of early initiation of treatment with the glycopro-

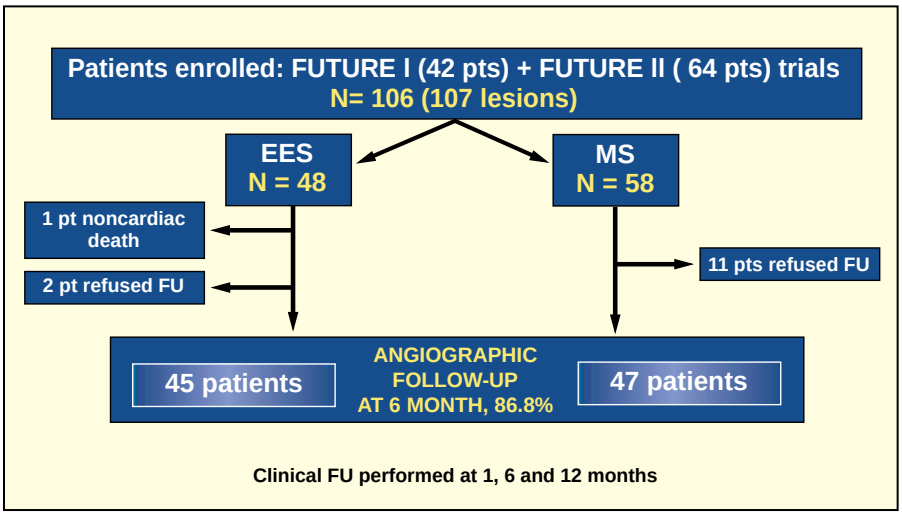


Figure 1. *Angiographic follow-up in the FUTURE I and II Trials. EES, everolimus-eluting stent; FU, follow-up; MS, metal stent.*

tein (GP) IIb/IIIa inhibitor tirofiban in patients presenting with acute myocardial infarction (MI), who were to undergo a percutaneous coronary intervention (PCI). Ambulance patients (n = 209) and patients from referral centers (n = 258) were randomized to receive placebo or tirofiban at an infusion rate of 0.15 µg/kg/min while awaiting angiography and continuing for 24 hours following PCI. The primary endpoint of TIMI III flow at initial coronary angiography actually trended worse in the tirofiban group (19% vs 15%, *P* = ns).

The ADMIRAL trial, which compared the early initiation of abciximab treatment versus placebo in patients presenting with acute MI, who were subsequently treated with primary PCI, did show a significant reduction in clinical events and infarct vessel patency in the abciximab group.[7] Prior to revascularization, TIMI grade III flow was present in 16.8% of patients receiving abciximab versus 5.4% receiving placebo, *P* = .01. This event reduction was most prominent in the population of patients who received the drug in the precatheterization-laboratory phase of their presentation, either in the ambulance or emergency department. In this group, a reduction in the composite endpoint of 30-day major adverse cardiac events (MACE), from 21.1% to 2.5%, occurred in patients receiving abciximab. Although this was not a direct comparison trial between a small-molecule GP IIb/IIIa inhibitor and abciximab, abciximab is nonetheless the only GP IIb/IIIa inhibitor that has shown benefit in patients treated with primary PCI for acute MI. Based on current clinical data, it should be a part of overall revascularization strategy, with additional benefit observed with upstream initiation.

FUTURE I and II Trials

Pooled results of a multicenter evaluation of everolimus-eluting stents for the inhibition of neointimal hyperplasia (FUTURE I and II) trials were presented by Dr. Ricardo Costa[8] of the Cardiovascular Research Foundation, New York, NY. Everolimus is a sirolimus analog that has antiproliferative and immunosuppressive properties, causing cell cycle arrest in the late G1 stage. The FUTURE I trial was a single-center safety and feasibility study comparing the everolimus-eluting stent (EES) with a metallic stent (MS) in 42 patients. The FUTURE II trial was a multicenter trial that assessed efficacy of the EES versus the MS in 64 patients.

Dr. Costa presented a pooled analysis of data from both trials, with angiographic endpoints of in-stent late loss and binary restenosis assessed at 6 months follow-up (Figure 1). The stent sizes used were 2.5 mm, 3.0 mm, 3.5 mm, and 4.0 mm in diameter, and 14 and 18 mm in length. Procedural success was defined as a final residual stenosis less than 50% and freedom from MACE postprocedure prior to hospital discharge. MACE was defined as cardiac death, myocardial infarction, coronary artery bypass graft surgery involving the target vessel, or a repeat PCI of the target lesion. The stent deployed was the investigational Challenge™ EES (Biosensors International, Singapore), which is coated with everolimus using a bioabsorbable polymer matrix.

The final minimum lumen diameter was 2.98 mm in the EES group vs. 2.88 mm in the MS group (*P* = ns). At follow-up, the minimum lumen diameter was 2.86 mm in the EES group versus 2.04 mm in the MS group (*P* < .0001). The percent diameter stenosis was also significantly lower at follow-up in the patients receiving the EES compared with the control group (2.8% vs 29.8%, *P* < .0001). Late loss was 0.12 mm versus 0.85 mm in the everolimus and control groups, respectively (*P* < .0001), corresponding to an 86% reduction in late loss among patients treated with the EES (Figure 2).

For the in-stent analysis, no patients receiving the EES (0/46) experienced binary restenosis compared with 17.0% (8/47) of patients receiving the MS (*P* = .006). In terms of in-segment analysis, 4.3% (2/46) of patients receiving the EES and 27.7% (13/47)

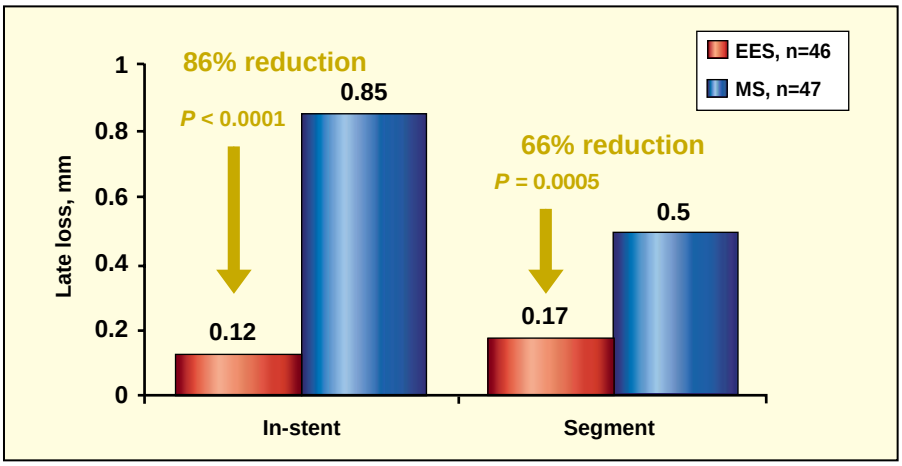


Figure 2. *Pooled analysis of late loss, at 6-month follow-up, in the FUTURE I and II Trials. EES, everolimus-eluting stent; MS, metal stent.*

receiving the MS experienced binary restenosis (P = .002). There was no occurrence of acute, subacute, or late thrombosis or aneurysm formation in either group. The rate of MACE was not significantly different between the 2 groups, at 6.4% in patients treated with EES and 15.1% in the control group.

These results with the EES utilizing a bioabsorbable polymer await confirmation in the FUTURE III (outside the United States) and FUTURE IV (within the United States) studies with the Champion™ everolimus-eluting stent (Guidant Corporation, Indianapolis, IN).

SES-SMART Trial

The randomized comparison of a Sirolimus-Eluting and an Uncoated Stent in the Prevention of Restenosis in Small Coronary Arteries Study (SES-SMART) was presented in a late-breaking clinical trial session by Dr. Diego Ardissino of the Università Degli Studi di Parma, Parma, Italy, and evaluated the ability of the Cypher™ sirolimus-eluting stent (Cordis Corp., Miami Lakes, FL) to prevent restenosis in small coronary arteries. Patients with non-ST-elevation acute coronary syndrome, chronic stable angina, or silent ischemia with de novo lesions in coronary arteries less than or equal to 2.75 mm in diameter with a lesion length that could be covered with a 33 mm stent were studied (n = 257). Patients were randomized to either the sirolimus-eluting Cypher™ stent or an uncoated Bx Velocity stent. The primary endpoint of the study was 8-month angiographic in-segment binary restenosis. The characteristics of the study population include a mean age of 65 years, 25% incidence of diabetes mellitus, and 42% of patients presenting with a non-ST segment elevation MI. The mean reference vessel diameter was 2.2 mm with average lesion length of 11.8 mm (13.0 mm in the sirolimus-eluting stent [SES] group and 10.7 in the bare metal stent group).

The binary restenosis rate in the SES group was 9.8% versus 53% in the MS group and a significant reduction of late luminal loss and loss index was shown with the SES. There was also a significant benefit to the SES when compared to the MS in terms of reduction of cumulative MACE over the 8-month follow-up period. The composite of death, myocardial infarction, target lesion revascularization, and stroke was lower in the SES group than the MS (9.3% vs 31.1%, P < .001) and there was a reduction in rates of MI (1.6% vs 7.8%, P = .0372). There was no significant difference in the rate of stent thrombosis, with 0.8% in the SES group and 3.1% in the MS group.

The SES-SMART study provides important information on the treatment of small vessel disease and subacute thrombosis. The Cypher™ sirolimus-eluting stent seems to be the treatment of choice for relatively focal small vessel disease as an 82% reduction of target lesion revascularization noted. In addition, with the concern about a possible link between SES and stent thrombosis, it was comforting to see clinical data reinforcing the safety of sirolimus-eluting stents with rates of subacute thrombosis in this trial that actually trended lower than metal stents.

SECURE Trial

The Compassionate Use of SES (SECURE) trial was a multicenter study to evaluate treatment with the sirolimus-eluting Bx VELOCITY stent in patients with no acceptable alternative treatment available for bypass grafts in native vessels.[9] Results were presented by Dr. Marco Costa of the University of Florida-Shands, Jacksonville, FL. The primary endpoint was target vessel failure (TVF). SECURE included 252 patients treated at 5 U.S. sites. Compassionate use of SES was indicated in patients with serious coronary disease for whom no acceptable alternative treatment was available, including brachytherapy or coronary artery bypass graft surgery. Aspirin and clopidogrel therapy were maintained indefinitely for patients with previous brachytherapy failure. The analysis presented here includes 66 patients with 81 bypass graft lesions and 147 patients with 264 lesions who received stents in native

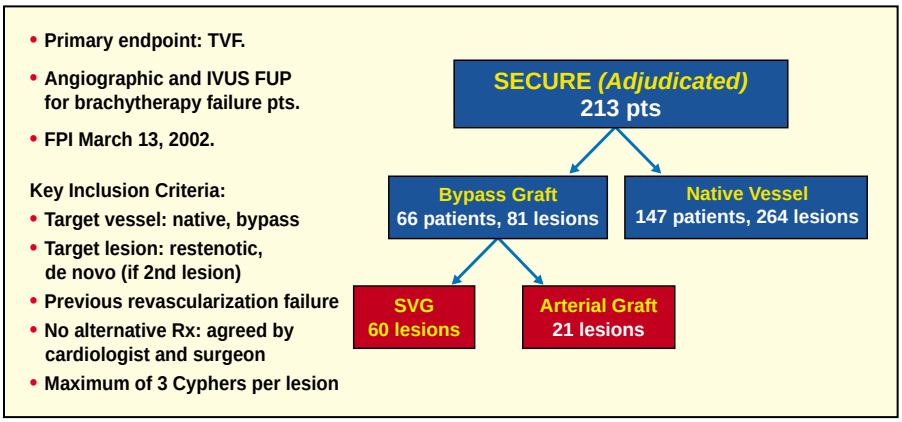


Figure 3. *Materials and methods from the SECURE trial. FUP, follow up; IVUS, intravascular ultrasound; SVG, saphenous vessel graft; TVF, target vessel failure.*

vessels only (Figure 3).

90% percent of lesions in both groups were restenotic, with 65% of coronary artery bypass graft stenoses having undergone previous brachytherapy and an average of 1.6 stents per lesion implanted. Mean total stent length was 23.5 mm in both groups, with 66% of lesions greater than 20 mm in length. The cumulative 6-month clinical outcomes provide important guidance in the care of patients who present with obstructive vein graft disease and in whom other therapies have failed (Table 2). The 21.0% rate of events at 6 months in the patients who received an SES for bypass graft disease is equivalent to that observed with native vessels and seems very favorable. Therefore, based on the results of this investigation, the SES can be considered an effective therapy to prevent neointimal proliferation and repeat revascularization in high-risk patients with recurrent bypass graft disease.

Lipid Modification

EASE Trial

The Ezetimibe Add-on to Statin for Effectiveness (EASE) trial, was presented by Thomas A. Pearson, MD, PhD, of the University of Rochester School of Medicine and Dentistry, Rochester, NY, in a late-breaking clinical trial session. EASE was undertaken to examine the effectiveness and safety of ezetimibe, 10 mg, compared with placebo, added to any statin brand and dose in patients who were not at their National Cholesterol Education Program Advanced Treatment Panel-III (NCEP ATP-III) low-density lipoprotein (LDL) cholesterol goal, despite statin monotherapy (Figure 4). The endpoints of EASE were the percent reduction in LDL cholesterol from baseline and the percentage of patients who achieved their NCEP ATP-III goal at follow-up. EASE included 3030 patients on a stable dose of any statin who were not at their NCEP ATP-III LDL cholesterol goal. Patients were randomized in a 2:1 ratio to either ongoing statin plus ezetimibe, 10 mg daily, or ongoing statin plus placebo for 6 weeks. Patients were excluded if they were on a lipid-lowering agent other than a statin, had glycosylated hemoglobin levels higher than 9%, or had alanine aminotransferase, aspartate aminotransferase, or creatine kinase (CK) levels greater than or equal to 1.5 times the upper limit of normal.

Among the total cohort, LDL cholesterol reduction was 25.8% in those randomized to ezetimibe and 2.7% among those randomized to placebo ($P < .001$). This difference between groups was consistent and

Table 2
Six-Month Clinical Outcomes in the SECURE Trial

Cumulative events up to 180 days	All native vessels (N = 133), n (%)	At least one graft (N = 60), n (%)	*P* value
MACE (death, MI, emergent CABG, TLR)	28 (21.1%)	12 (20%)	0.87
TVF (cardiac death, MI, TVR)	25 (18.8%)	12 (20%)	0.84
Death	2 (1.5%)	2 (3.3%)	0.59
Cardiac death	1 (0.8%)	2 (3.3%)	0.23
Myocardial infarction	5 (3.8%)	2 (3.3%)	1.0
Q wave MI	2 (1.5%)	1 (1.7%)	1.0
Non-Q wave MI	3 (2.3%)	1 (1.7%)	1.0
TVR	24 (18.1%)	10 (16.7%)	0.82
TLR	23 (17.3%)	10 (16.7%)	0.91
Late stent thrombosis	3 (2.3%)	1 (1.7%)	1.0
Total occlusion	3 (2.3%)	3 (5%)	0.38

CABG, coronary artery bypass graft; MACE, major adverse coronary events; MI, myocardial infarction; TLR, total lesion revascularization; TVF, total vessel failure; TVR, total vessel revascularization.

significant in all NCEP coronary heart disease (CHD) risk categories. Ezetimibe reduced LDL cholesterol from statin baseline by an additional 23% compared with placebo (Figure 5). This reduction in LDL cholesterol compares favorably with the 6% to 8% reduction in LDL cholesterol usually achieved by doubling the dose of statin. The safety of this approach was observed as there were no differences in the incidence of liver function abnormalities or elevations of CPK in either group. The addition of ezetimibe to statin therapy should be considered in patients who have not attained their NCEP ATP III LDL cholesterol goal on statin therapy alone and may be a reasonable add-on to initial treatment with a statin to accelerate the attainment of LDL cholesterol reduction goals.

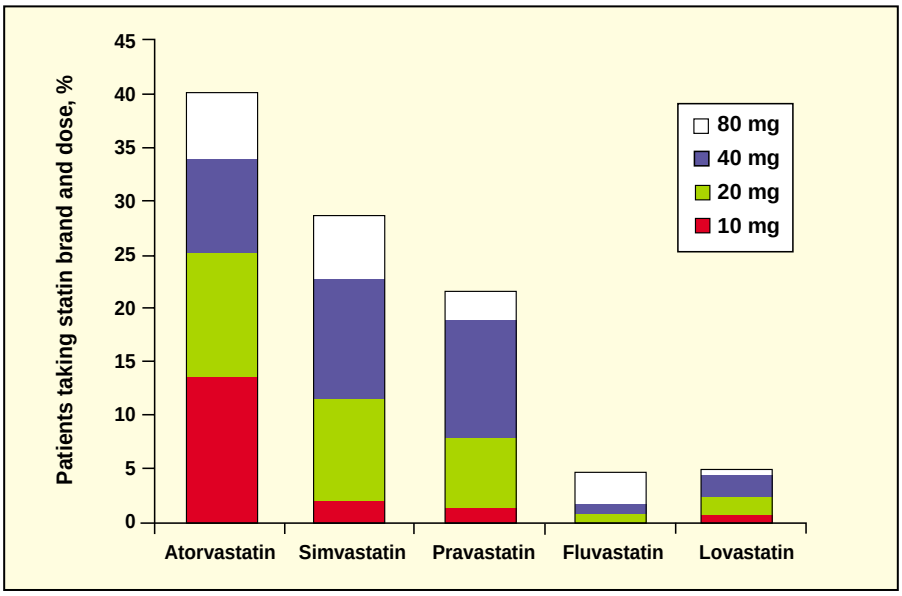


Figure 4. *Class use of statins as shown in terms of drug and drug dosage.*

Dose Titration in Lipid-Lowering Therapy

Dr. Masoor Kamalesh[11] from the Indiana University Medical Center and Veterans Affairs Medical Center, Indianapolis, IN, presented the abstract "Delay in Dose Titration of Lipid-Lowering Therapy Leads to Adverse Cardiovascular Outcomes."

The investigators conclude that the delay in titration of lipid-lowering drugs is associated with increased adverse cardiovascular events and that choice of therapy should be optimized at the start to achieve goal LDL-lowering.

The investigators attempted to identify how quickly statins are titrated and what effect any delay in titration may have on cardiovascular outcomes. They performed a retrospective chart review of 213 patients on 80 mg of simvastatin. Of those studied, 45% met the definition of the metabolic syndrome, 83% were hypertensive, 45% were diabetic, and 67% had documented coronary artery disease. Overall, only 66% of patients met NCEP LDL-cholesterol goals and 34% were short of goal. Of patients with CHD or CHD equivalents, 35% missed their LDL cholesterol goal by 20% and the 38% of patients at intermediate risk (2 or more risk factors, 10 year risk < 20%) missed their LDL cholesterol goal by over 9%.

In terms of defining efficiency in reaching the 80 mg dose of simvastatin, 40% of patients required 2 dose titrations, 18% required 3 titrations, 6% required 4 or more (up to 8) titrations. Over 67% of patients required over 1 year to achieve the 80 mg dose with the majority of these patients taking over 2 years to achieve the target dose. Patients with CHD or CHD equivalent required a mean of 2.7 years to get to this dose of simvastatin. During the titration phase, 47 patients had 80 adverse cardiovascular events with 40 episodes of hospitalization for worsening of anginal symptoms, 30 episodes of coronary intervention, 5 strokes, and 5 myocardial infarctions. Of interest is the fact that the average titration period for patients having a cardiovascular event was 3.5 years versus 2.1 years for those patients without a cardiac event.

The investigators conclude that the delay in titration of lipid-lowering drugs is associated with increased adverse cardiovascular events and that choice of therapy should be optimized at the start to achieve goal LDL-lowering. The CHD or CHD equivalent patients needed 2.7 years to reach the goal 80 mg dose of simvastatin and still missed the LDL cholesterol goals by 20%. The delay in getting to goal LDL cholesterol seems to expose the higher risk patients to excess cardiovascular risk. Based on the EASE study results discussed previously, as well as the results of this investigation, it would seem reasonable to take a combination therapeutic (statin + ezetimibe/or

resin) approach to initiation of LDL-lowering therapy whether in the hospital immediately following a cardiovascular event or when the patient at risk is identified in the clinic setting, rather than taking a primary titration approach.

Dr. Mateen Akhtar[12] of the University of California, San Diego, in La Jolla, CA, presented an abstract "Initial Response to Statin Therapy Predicts Response to Dose Titration" attempting to identify a group of patients with coronary artery disease who are resistant to lipid reduction with statins. The study was conducted retrospectively in 74 patients who met ATP III criteria for lipid therapy and were treated with an initial dose of statins followed by dose titration. Patients were divided into good responders (GR) or poor responders (PR) based on changes of LDL from baseline levels. At baseline, PR had lower total cholesterol levels, (227 vs 257 mg/dl) and lower LDL cholesterol levels (149 vs 173 mg/dl) than GR. The initial response to statin therapy resulted in a 31% reduction of LDL cholesterol in the GR and an 8% reduction in the PR ($P < .01$). Dose titration led to a 15% reduction of LDL cholesterol in the GR group and only 8% in the PR group. After dose titration, only 18% of the PR group and 71% of the GR cohort reached ATP-III LDL cholesterol goals ($P < .001$). The investigators concluded that, based on the initial response to LDL cholesterol reduction to initiation of statin therapy, a poor responder would be less likely to respond well to a dose titration and may therefore benefit more from a combination treatment strategy.

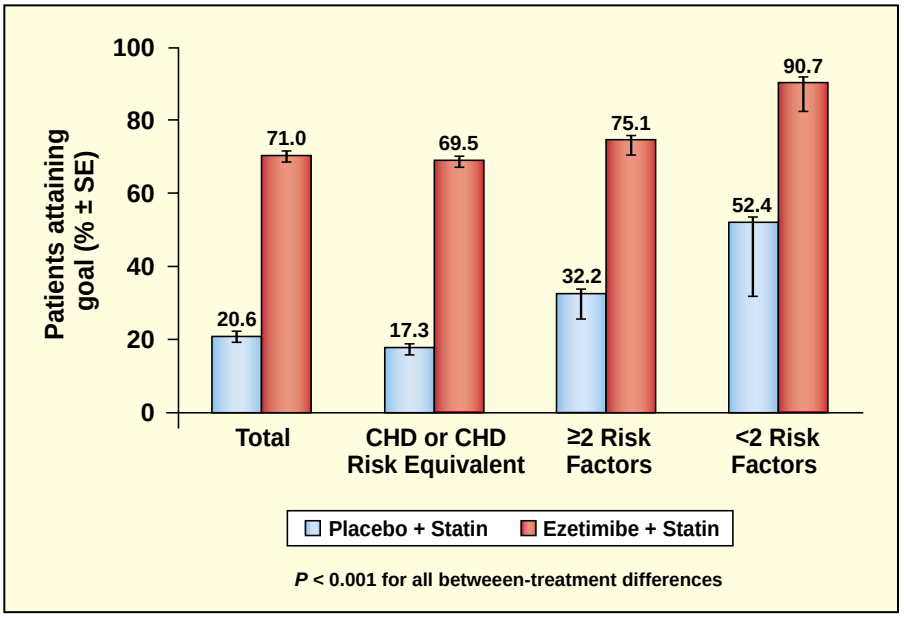


Figure 5. *Percent of patients attaining National Cholesterol Education Program Advanced Treatment Panel-III goals in the EASE Trial, for low-density lipid cholesterol levels, overall and by risk factor, based on patients not at goal at baseline.*

Diabetes

A number of abstracts were presented on issues relevant to the care of diabetic patients. Gaudiani and associates[13] presented an abstract titled "Efficacy and Safety of Ezetimibe Coadministered with Simvastatin Versus Simvastatin Alone in Thiazolidinedione-Treated Patients With Type 2 Diabetes Mellitus." As we learn more about the pleiotropic vascular benefits of the thiazolidinediones (TZDs) in the treatment of diabetes, we are seeing these agents used more commonly in association with statins and other cholesterol lowering agents such as ezetimibe. The investigators compared the lipid-lowering effects of adding ezetimibe to a dose of simvastatin versus a doubling of the simvastatin dose in a multicenter, randomized, parallel design trial. Patients included were diabetics with glycosylated hemoglobin levels ≤ 9% with LDL cholesterol levels greater than or equal to 100 mg/dL, stabilized on a TZD (rosiglitazone or pioglitazone) dose for greater than or equal to 3 months. After 6 weeks of open label simvastatin, patients were randomized to receive 10 mg of ezetimibe or another 20 mg of simvastatin. After 24 weeks of treatment, LDL cholesterol was reduced by 21% when ezetimibe was added to the regimen and only 0.3% when the dose of simvastatin was doubled to 40 mg per day ($P < .001$). In addition, levels of non-high-density lipoprotein cholesterol, very-low-density lipoprotein and apo-B were reduced by 20%, 16%, and 14% respectively. There were no significant differences between the 2 groups in terms of safety parameters. The combination of ezetimibe with a statin provided a more effective method for LDL reduction than statin titration and was achieved safely in diabetics treated with TZDs.

Ko and associates[14] presented an abstract "Preventive Effects of Rosiglitazone on Restenosis After Coronary Stent Implantation in Patients with Type 2 Diabetes Mellitus." They conducted a prospective, case-control study involving 95 patients who were treated with rosiglitazone, 4 mg daily, or placebo. Six-month coronary angiography was performed and revealed a lower

restenosis rate in the rosiglitazone group (18% vs 38%, P = .03), less diameter stenosis (24% vs 43%, P = 0.001) and lower loss index (0.49 vs 0.27, P = .008). This was achieved despite no differences in lipid, glucose, or insulin levels at 6-month follow-up. This benefit was felt to have been achieved as a result of the pleiotropic effects of the TZD agents.

Brunzell and coworkers[15] presented the abstract "Rosiglitazone Reduces Novel Biomarkers of Cardiovascular Disease in Subjects with Type 2 Diabetes Mellitus Already on Statin Therapy." Diabetic subjects (N = 72) on a prescribed diet/exercise regimen or metformin monotherapy were stabilized with statin therapy for at least 8 weeks, after which they were randomized to placebo or 4 mg or 8 mg of rosiglitazone daily. By the end of the study, at week 12, 24% and 36% of patients had converted from small LDL particles to larger "buoyant" particles in the 4 mg and 8 mg groups, respectively. The change in the 8 mg group was statistically significant. Significant reductions in C-reactive protein levels and plasminogen-activator inhibitor antigen and activity levels were observed in the 8 mg rosiglitazone group. These results confirm outcomes from other investigations, showing that the impact of the TZDs extends past their ability to lower serum glucose levels, further including positive effects on lipids, inflammation, and coagulation. Data continue to accumulate showing that the TZDs, as well as metformin, have important vascular protective effects and therefore should be used as primary therapies for diabetes, perhaps reserving the insulin secretagogues for patients with refractory hyperglycemia.

Heart Failure

WATCH

The purpose of the Warfarin and Antiplatelet Therapy in Chronic Heart Failure Trial (WATCH) was to determine the optimal antithrombotic treatment regimen for patients with chronic heart failure (CHF), with regard to clinical outcomes, safety, and cost. In view of the perceived need to reduce embolic potential, a comparison was made between aspirin and warfarin use. Because of a potential negative effect of aspirin on ACE inhibitor efficacy in CHF patients, the use of an alternative antiplatelet agent, clopidogrel, was also compared to aspirin.

Dr. Barry Massie of the San Francisco Veterans Administration Medical Center and the University of California, San Francisco, CA, presented the results of the WATCH trial, which was designed with 3 arms, each with 1500 patients: a) warfarin, open label with goal international normalized ratio [INR] 2.5-3.0; b) aspirin, 162 mg daily, blinded; and c) clopidogrel, 75 mg daily, blinded. Follow-up was planned for between 2 and 5 years with a primary endpoint of all-cause mortality, non-fatal myocardial infarction, and nonfatal stroke. The planned secondary endpoint was all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, hospitalization for congestive heart failure exacerbation, unstable angina, and embolic events. Unfortunately, enrollment was slow and the study was closed after enrolling only 40% of the expected number of patients (N = 1587), nonetheless yielding 3086 patients-years of experience and important clinical data.

In terms of compliance, 93% of patients adhered to the aspirin and clopidogrel regimen, with 31% of patients in the goal INR range of 2.5-3.0 and 70% in the "acceptable" range of 2.0-3.5. Final results showed 20% of patients with INR levels below 2.0 and 10% with INRs above 3.5. Baseline demographics revealed a mean age of 63 years, with 73% experiencing ischemic cardiomyopathy. African Americans made up 12% and 50% had hypertension. There was a significantly greater population of diabetics in the warfarin group (38%) than in the clopidogrel group (31%). These patients were well-treated at baseline and represented a relatively high acuity population, as 88% were receiving ACE inhibitors, 11% angiotensin-receptor blockers, 80% ß-blockers, and 30% aldosterone antagonists. NYHA Class III and IV heart failure made up 56%, with a mean ejection fraction of 24%.

The results showed no difference in the primary endpoint between the aspirin, warfarin, and clopidogrel groups (20.5%, 19.8%, and 21.8%, respectively) or the secondary endpoint (36.3%, 33%, and 36.6%, respectively). There was a significant reduction in heart failure hospitalizations in patients receiving warfarin compared to aspirin (16.1% vs 22.7%, P = .01). Surprisingly, the frequency of embolic events was very low, less than 1%, in all 3 groups. Bleeding complications were more common in the warfarin group compared to aspirin and clopidogrel (30 events, 19 events, 13 events, respectively, P = .012).

In summary, in this well-treated, relatively high acuity CHF population, there was no clinical benefit to clopidogrel over aspirin therapy or Coumadin over aspirin. This somewhat dispels the notion of a negative effect of aspirin therapy on the efficacy of ACE inhibitors in the CHF population, as well as the perceived benefit of the anticoagulant Coumadin over the antiplatelet agent, aspirin. What was sobering, despite the aggressive medical treatment regimen patients received in this trial, were mortality rates in the 18% range, showing the overall limitations of medical therapy. [Norman E. Lepor, MD, FACC, FAHA]

PROVE-IT-TIMI 22

Background

Several large, randomized trials have demonstrated that cholesterol-lowering therapy utilizing 3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitors (statins) reduces the risk of death or cardiovascular events across a wide range of cholesterol levels, in patients with and without a history of coronary artery disease. Although the dose of statins used in these trials reduced low-density lipoprotein (LDL) levels by 25% to 35% and current guidelines recommend a target cholesterol level of less than 100 mg/dL for patients with established coronary artery disease or diabetes, it is unclear whether further lipid lowering would increase benefit. Dr. Christopher P. Cannon of the Brigham and Women's Hospital in Boston, MA, presented results of The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT-TIMI 22) trial,[16] comparing the standard degree of LDL (lipid) lowering (to approximately 100 mg/dL) through the administration of 40 mg daily of pravastatin, versus more intensive lipid lowering (to approximately 70 mg/dL) with the use of 80 mg daily of atorvastatin, to measure reduction of death or major cardiovascular complications in patients with acute coronary syndromes (ACS).

Table 3
PROVE-IT: Primary Composite Endpoint

Primary endpoint	Pravastatin 40 mg (n=1973)	Atorvastatin 80 mg (n=2003)	Relative risk reduction, %	*P* value
All-cause mortality/MI/unstable angina/revascularization/stroke (%)	26.3	22.4	16	0.005

Methods

Patients who had been hospitalized for an ACS within the preceding 10 days (N = 4162) were enrolled at 349 sites in 12 countries. Patients were randomized to pravastatin, 40 mg daily (standard therapy), or atorvastatin, 80 mg daily, (intensive therapy) using a double-blind, double-dummy design. Patients were required to be in stable condition and to have total cholesterol of 240 mg/dL or lower. Those who had been receiving long-term lipid-lowering therapy prior to their index ACS were required to have total cholesterol levels of less than or equal to 200 mg/dL at the time of screening. Patients were to be enrolled after a percutaneous intervention if one was planned and were to receive standard medical therapy for their ACS. The primary endpoint at the time of design was the time from randomization to one of the following component end-points: death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. The study was designed to establish the noninferiority of pravastatin with the definition of inferiority being arrived at through a consideration of the 2-year event rates.

The benefit of intensive therapy was consistent across prespecified subgroups including men and women, patients with unstable angina, those with myocardial infarction, and those with and without diabetes mellitus.

The average age of subjects was 58.3 years, 78% were male, 17.5% were diabetic, and 37% were current smokers. There were similar proportions of unstable angina, ST segment elevation MI (STEMI) patients, and non-STEMI patients in each arm of the trial. Early invasive management with revascularization took place in 69% of patients. Most patients were concomitantly administered aspirin (93%), beta blockers (85%), clopidogrel/ticlopidine (72%), and ACE inhibitors (69%).

Results

Follow-up ranged from 18 to 36 months (mean 24 months). The median LDL cholesterol level achieved during treatment was 95 mg/dL in the standard-dose, pravastatin group and 62 mg/dL in the high-dose atorvastatin group ($P < .001$). Kaplan–Meier estimates of the rates of the primary end point at 2 years were 26.3% in the pravastatin group and 22.4% in the atorvastatin group, reflecting a 16% reduction in the hazard ratio in favor of atorvastatin ($P = .005$; 95% CI, 5%–26%) (Table 3). Thus, the study did not meet the prespecified criterion for equivalence but did identify the superiority of the more intensive regimen.

Among the individual components of the primary endpoint (Table 4), there was a consistent pattern of benefit favoring intensive therapy that included a significant (14%) reduction in the need for revascularization ($P = .04$), a 29% reduction in the risk of recurrent unstable angina ($P = .02$), and non-significant reductions in the rates of death from any

Table 4
PROVE-IT: Secondary Endpoints

Secondary endpoints	Pravastatin 40 mg (n=1973)	Atorvastatin 80 mg (n=2003)	Relative risk reduction, %	*P* value
CHD death, nonfatal MI, or revascularization (%)	22.3	19.7	14	0.029
All-cause mortality (%)	3.2	2.2	28	0.07
Death/nonfatal MI (%)	10.0	8.3	18	0.06
Unstable angina (%)	5.1	3.8	29	0.02
Revascularization (%)	18.8	16.3	14	0.04

CHD, coronary heart disease; MI, myocardial infarction.

cause (28%, $P = .07$), and of death or myocardial infarction (18%, $P = .06$). Stroke was infrequent and the rates did not differ between groups.

The benefit of intensive therapy was consistent across prespecified subgroups including men and women, patients with unstable angina, those with myocardial infarction, and those with and without diabetes mellitus. The effect appeared to be greater among patients at baseline LDL levels of at least 125 mg/dL, with a 34% reduction in the hazard ratio, as compared with a 7% reduction among patients with a baseline LDL cholesterol below 125 mg/dL (P for interaction = .02).

Rates of discontinuation of treatment because of adverse events or patient preference were 21.4% in the pravastatin group and 22.8% in the atorvastatin group ($P = .30$) and 33.0% and 30.4% respectively at 2 years ($P = .11$). The percentages of patients who had elevations in alanine aminotransferase levels that were more than 3 times the upper limit of normal were 1.1% in the pravastatin and 3.3% in the atorvastatin groups. Medication was discontinued because of reported myalgias or muscle aches in 2.7% of the pravastatin- and 3.3% of atorvastatin-treated patients.

Comments

This study demonstrates that among patients who have recently experienced an ACS, an intensive lipid-lowering regimen provides greater protection against death or major cardiovascular events than does standard therapy. These patients benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels. The study is not truly a comparison of drugs because different doses were used, nor of dosage, as different drugs were employed. It does, however, support the concept of more aggressive lipid lowering in this subset of patients.

This study demonstrates that among patients who have recently experienced an ACS, an intensive lipid-lowering regimen provides greater protection against death or major cardiovascular events than does standard therapy.

Although the mechanism of benefit cannot be determined from this study, the effect is similar to that observed with a similar reduction in LDL cholesterol in placebo-controlled studies. Of note, the reduction in clinical events in the intensive-therapy group was present as early as 30 days after initiation of treatment, consistent with other trials of patients with acute ischemia. In contrast, studies of patients with chronic atherosclerosis have shown a lag of 1 to 2 years before a demonstrable effect was noted, suggesting that patients with ACS with 1 or multiple vulnerable plaques can derive particular benefit from early and intensive intervention.

One of the most fascinating aspects of the PROVE-IT Trial was the complement of its findings to those of A Prospective, Randomized, Double Blind, Multicenter Study Comparing the Effects of Atorvastatin vs. Pravastatin on the Progression of Coronary Atherosclerotic Lesions as Measured by Intravascular Ultrasound (REVERSAL) trial that was presented last November at the Scientific Sessions of the American Heart Association. That trial also compared regimens of pravastatin, 40 mg daily, versus atorvastatin, 80 mg daily. The patients in REVERSAL were slightly different; they were required to have evidence for coronary disease, but, unlike those in the PROVE-IT trial, they had no recent experience of ACS. Another point of difference was that the baseline LDL-cholesterol levels in REVERSAL were somewhat higher than those in PROVE-IT, thereby affecting on-treatment values accordingly. The chief finding in REVERSAL, as in PROVE-IT, favored atorvastatin.

REVERSAL was not, strictly speaking, a clinical endpoint trial, but used the surrogate of percent change in atheroma volume measured by intravascular ultrasound before and during treatment in the same coronary artery segment in each patient. The investigators reported that

although there was modest progression of relative atheroma volume within the coronary walls during pravastatin therapy, there was, on average, no change in patients receiving high-dose atorvastatin. In fact, the REVERSAL investigators pointed out that a number of patients receiving atorvastatin actually appeared to have decreases in the size of their lesions, suggesting that regression might have occurred.

When presenting their results, the REVERSAL investigators acknowledged that their study was not a true outcomes trial, and cautioned against over-interpretation of their data. In addition, the REVERSAL team knew about the still-ongoing PROVE-IT Trial and had some doubts about it. As part of their presentation, they pointed out that a trial adequately powered to explore clinical outcomes differences between these 2 treatments would require approximately 8,000 patients to be followed for 4 or 5 years. Based on these criteria, they obviously had reservations about whether the PROVE-IT study, with just over 4000 patients followed for only 2 years, could provide an adequate test. When the results of PROVE-IT were announced, they must have come as something of a surprise—presumably a pleasant one—to the REVERSAL group, providing them with strong confirmation that their findings were valid and clinically important.

Like all good studies, PROVE-IT has created some new questions. Patients who have just experienced an ACS are at high risk for further events or fatal outcomes during a relatively short subsequent time period. Can the findings of PROVE-IT, which showed benefits of reducing LDL cholesterol down into the range of 60 mg/dL, now be extrapolated to provide guidelines for patients with less acute forms of coronary disease? The investigators were prudent in their conclusions, suggesting that this more aggressive approach should only be considered in people with recently experienced ACS.

Further, was the apparent superiority of atorvastatin due entirely to its greater effects on LDL cholesterol, or does it also have additional advantageous properties? In the original presentation of the REVERSAL trial, the investigators pointed out that atorvastatin might be more effective than pravastatin in reducing C-reactive protein, perhaps providing a partial explanation for its apparent beneficial effects in the coronary wall. Again, the PROVE-IT investigators have been rightly cautious in their interpretation, focusing mainly on the differences in achieved LDL cholesterol levels as the principal explanation for atorvastatin's clinical advantage.

Finally, if we accept atorvastatin, 80 mg daily, as the appropriate therapy for the large number of people with recently experienced ACS, can we administer this type of therapy safely to all of them, even the elderly or those who, for any reason, may be frail? It may be helpful to remember that, by and large, statins lower LDL cholesterol at relatively low doses, thus reducing the likelihood of rhabdomyolysis or liver-function abnormalities. Some clinicians routinely use this low-dose strategy, adding agents such as cholesterol-absorption inhibitors, if necessary, to achieve optimal LDL cholesterol levels.

Based on these studies and speculations, more aggressive lipid lowering may be beneficial in acute and chronic coronary artery disease and serious questions arise about current guidelines for lipid-lowering therapy. Additional studies will be necessary to confirm these findings and the question of "how low is too low" remains, but, clearly, thinking on this subject has changed. In addition, the value of this type of study should be apparent to all. However, sources of further funding may prove problematic as many companies may hesitate to sponsor future studies at the risk of suggesting that their product may be "non-equivalent."

[Arthur E. Weyman, MD, Michael A. Weber, MD, Karol E. Watson, MD, PhD]

SYNERGY Trial

Is Enoxaparin Beneficial in the Early Invasive Treatment of ACS?

One of the major late-breaking clinical trials presented at this year's ACC Scientific Session was the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, presented by Dr. Kenneth W. Mahaffey of Duke University, Durham, NC.[17,18] SYNERGY demonstrated enoxaparin to be equally as effective as unfractionated heparin (UFH) in the early invasive management of acute coronary syndrome (ACS) patients, but low-molecular-weight heparin (LMWH) was associated with increased bleeding.[17]

Several previous randomized trials have demonstrated greater clinical benefit of enoxaparin versus UFH in the treatment of ACS and as the designated anticoagulant therapy in patients undergoing percutaneous coronary intervention (PCI).[19-24] In this context, the 2002 practice guideline recommendations from the American College of Cardiology/American Heart Association (ACC/AHA) designate enoxaparin a Class IIa recommendation, "preferable" to UFH as anticoagulant therapy in patients with non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina (UA).[25] Several of these trials were conducted, however, prior to the routine practice of early invasive cardiac catheterization and PCI. The key issues to be addressed in the

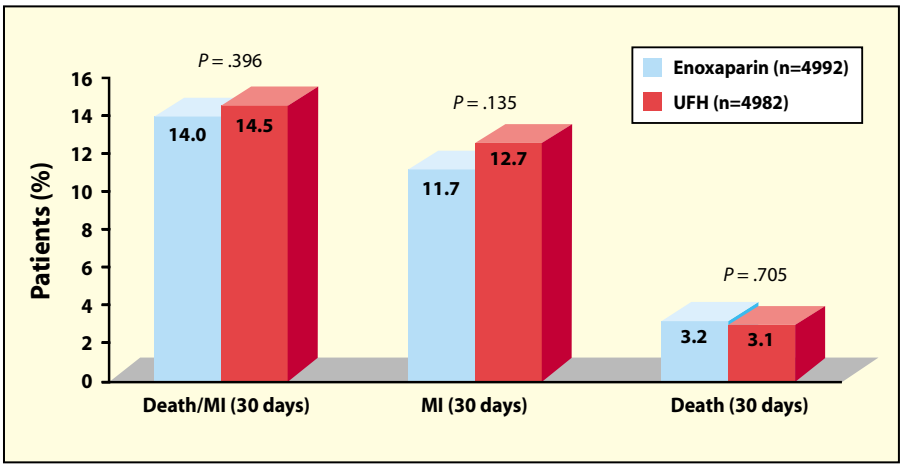


Figure 6. *Primary efficacy endpoints to 30 days after randomization in the SYNERGY trial. MI, myocardial infarction; UFH, unfractionated heparin. Reproduced with permission from Mahaffey et al.*[17]

SYNERGY trial were the definition of both the role of enoxaparin in high-risk UA/NSTEMI ACS patients managed with an early invasive treatment strategy and the safety of bringing patients rapidly to the catheterization laboratory while receiving subcutaneous enoxaparin.

SYNERGY was designed as a prospective, randomized, open-label, multicenter investigation of enoxaparin compared with UFH in patients at high risk with UA/NSTEMI ACS, treated with an early invasive strategy.[18] Patients were required to have 2 of 3 risk predictors (age > 60 years; + biomarkers; ST-segment depression) for enrollment. The primary endpoint of the study was the composite occurrence of death or nonfatal MI to 30 days after randomization. The primary safety endpoint was the composite incidence of major bleeding or stroke, with the severity of bleeding assessed by both the TIMI and GUSTO criteria. Key secondary endpoints included the combined incidence of all-cause mortality, nonfatal MI, stroke, or recurrent ischemia requiring revascularization, as well as the individual components of this composite at 14 days and 30 days after enrollment; the incidence of death or nonfatal MI at 14 days and 6 months; and mortality at 1 year. If enoxaparin failed to show superiority to UFH, a prespecified non-inferiority analysis was defined.[18]

The trial initially planned to enroll 8000 patients, but due to treatment crossover at randomization, the trial size was increased to 10,000 patients with a final enrollment of 10,027.[17] Patients were randomized to enoxaparin (1 mg/kg sc, every 12 hours) or UFH (60 U/kg bolus followed by 12 U/kg/hour, adjusted to an aPTT of 50-70 seconds). Median age in the study population was 68 (older than in previous trials), and 34% of patients were women. More than 90% of patients went to the cardiac catheterization laboratory early (median 21 hours from randomization); 47% underwent PCI, and 19% had bypass surgery; 57% received a GP IIb/IIIa inhibitor, and 63% received clopidogrel.

Results

The primary efficacy endpoint (death/MI at 30 days) was not significantly different between the 2 randomly assigned groups (Figure 6).[17] There was also no difference in death alone, MI alone, or in stroke rates. One of the major questions to be addressed by the trial was whether or not subcutaneous enoxaparin provided effective anticoagulation in those patients undergoing early PCI. SYNERGY showed no difference in unsuccessful procedures, abrupt vessel closures, or emergency CABG between the enoxaparin and UFH groups (Table 5).[17] While GUSTO severe bleeding (bleeding leading to hemodynamic compromise or intracranial hemorrhage [ICH]) or red blood cell transfusion were not different between the 2 treatment groups, an increase in TIMI major bleeding was observed with enoxaparin (Table 6).[17] The concomitant use of clopidogrel, GP IIb/IIIa inhibitors, or coronary revascularization had no impact on either efficacy or bleeding results.

The results of the SYNERGY trial are complicated by the fact that many patients crossed over from their randomly assigned treatment

Table 5
Complications in PCI Patients in the SYNERGY Trial

	Enoxaparin (n = 2321)	UFH (n = 2364)
Unsuccessful PCI, %	3.6	3.4
Threatened abrupt closure, %	1.1	1.0
Abrupt closure, %	1.3	1.7
Emergency CABG, %	0.3	0.3

P = NS
CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.
Data from Mahaffey et al.[17]

Table 6
Bleeding Events in the SYNERGY Trial

	Enoxaparin (n = 4993)	UFH (n = 4985)	*P* value
GUSTO severe, %	2.9	2.4	0.106
Any RBC transfusion, %	17.0	16.0	0.155
TIMI: major (total), %	9.1	7.6	0.008
TIMI: CABG-related, %	6.8	5.9	0.081
TIMI: non-CABG-related, %	2.4	1.7	0.025
ICH, %	< 0.1	< 0.1	NS

Number of patients needed to treat with enoxaparin to observe 1 additional non-CABG-related major bleed (TIMI criteria) estimated to be 200 patients.
CABG, coronary artery bypass graft; ICH, intracranial hemorrhage; RBC, red blood cell; TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin.
Data from Mahaffey et al.[17]

(enoxaparin to UFH or vice versa). Indeed, approximately 75% of patients were started on 1 of these medications in the emergency room and then were switched at the time of randomization. In addition, some investigators switched patients in the catheterization laboratory as they deemed necessary. Switching therapy from 1 anticoagulant to the other appeared to be associated with worse outcomes, in terms of both efficacy and bleeding. Investigators speculated that crossover patients, in receiving both agents, experienced additive effects that resulted in increased bleeding with no extra clinical benefit. In the 25% that received no antithrombotic treatment prior to randomization, enoxaparin demonstrated a strong trend toward reduction in the primary composite endpoint of death/MI, but both GUSTO severe and TIMI major bleeding trends were increased as well.

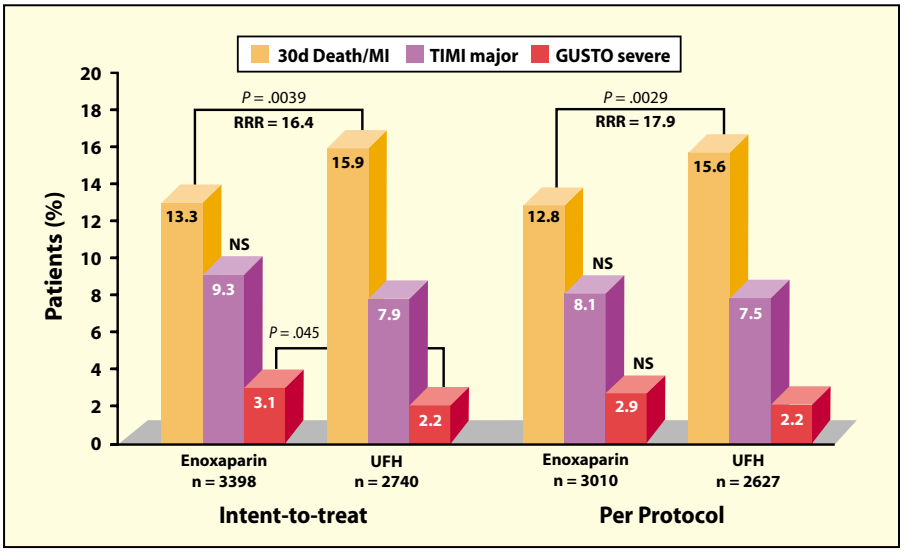
Similarly, those patients who received the same treatment throughout the study (intent-to-treat) demonstrated a reduction in death/MI at 30 days but with an increased risk of bleeding (Figure 7).[17] However, analysis of 5,637 patients with consistent therapy (per protocol) demonstrated a reduction in death/MI at 30 days with no significant difference in bleeding events (Figure 7).[17] Overall, investigators agreed that switching antithrombotic therapy from enoxaparin to UFH, or vice versa, increased the risk of bleeding without clinical benefit and should be avoided.

SYNERGY in Perspective

A meta-analysis of 21,000 patients in the major randomized trials of enoxaparin versus UFH in ACS, presented by the investigators, demonstrated a reduction in death/MI with enoxaparin (Figures 8 and 9).[17] Some investigators thought that lowering the dose of enoxaparin in the very elderly or those patients with reduced renal function might improve bleeding rates in subsequent investigations.

Whether the results of SYNERGY will lead to a change in clinical practice remains to be seen. SYNERGY has demonstrated the non-inferiority of enoxaparin to UFH in this patient population, and the subcutaneous route of administration appears efficacious during early PCI. Those clinicians who are currently comfortable using enoxaparin to treat ACS patients receiving PCI will view this trial as supportive of their practice. Others may view the results as demonstrating 2 comparable agents in terms of efficacy with enoxaparin adding cost and the potential for increased bleeding. Whether or not bleeding risk can be tempered by empiric enoxaparin

Figure 7. *Efficacy and safety endpoints by 'intent-to-treat' and 'per-protocol' therapy, in the SYNERGY trial. MI, myocardial infarction; RRR, relative risk reduction; UFH, unfractionated heparin. Reproduced with permission from Mahaffey et al.[17]*



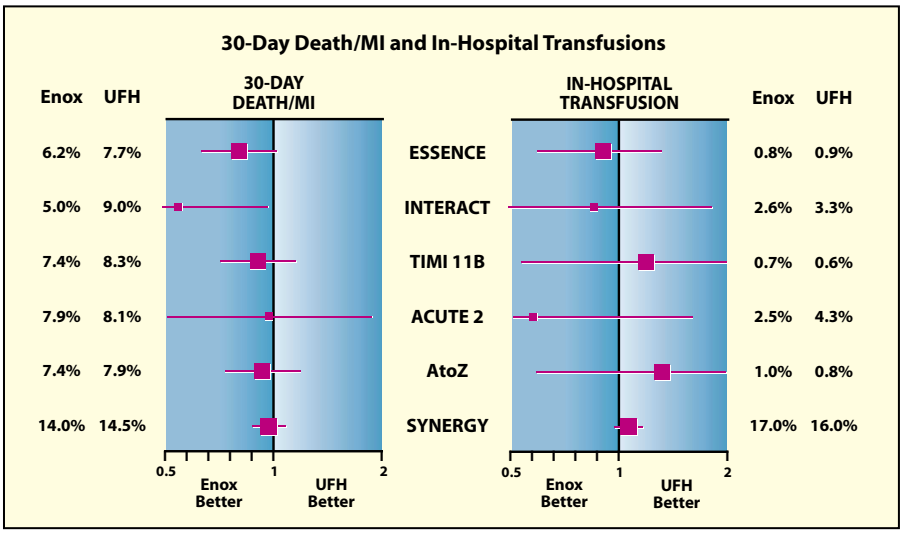


Figure 8. *Thirty day death / MI in major randomized trials of enoxaparin versus UFH in ACS in the SYNERGY trial. Enox, enoxaparin; MI, myocardial infarction; UFH, unfractionated heparin. Reproduced with permission from Mahaffey et al.*[17]

dose reduction or monitoring technology remains to be determined. What the future holds for LMWH, in the ever-evolving field of antithrombotic therapy for ACS and PCI, remains unknown.

[John J. Young, MD, FACC, Dean J. Kereiakes, MD, FACC]

Acute ST Elevation Myocardial Infarction: More May Not Be Better

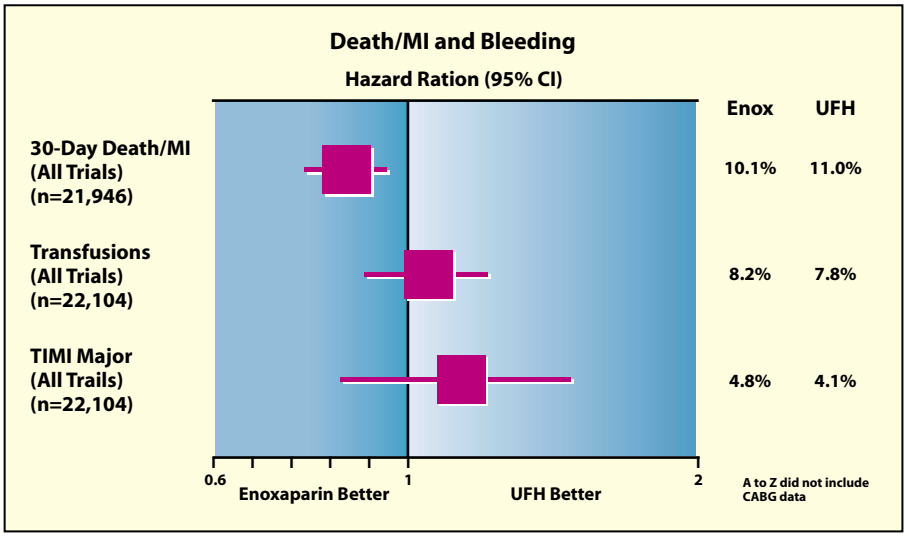
The treatment of acute ST Elevation myocardial infarction (MI) with primary angioplasty has achieved remarkably widespread use worldwide. However, efforts continue to determine whether infarct size can be reduced further, thereby improving long-term outcomes for these patients, in terms of preserved ejection fraction and mortality rates. Several studies were presented at the 2004 ACC Scientific Session that attempted to address these concerns.

The EMERALD study, presented by Dr. Bruce Brodie of the Moses Cone Heart and Vascular Center, LeBauer Cardiovascular Research Foundation, Greensboro, NC, examined the use of occlusive distal protection balloon devices to improve outcomes in ST elevation patients. ST elevation MI patients (N = 501) were treated within 6 hours of symptom onset, with PCI or PCI plus the Guardwire Plus™ device (Medtronic, Inc., Minneapolis, MN). The primary endpoint was 70% ST elevation resolution, 30 minutes after vessel opening. An additional endpoint was infarct size at day 5 to 14, as measured by sesta MIBI scan. The secondary endpoint was myocardial blush score. Plaque and thrombus were present in 76% of the retrieved blood. The final TIMI grades were 92% and 88% in the Guardwire versus non-Guardwire groups, respectively (P = ns). The endpoints of ST segment resolution, infarct size, and MACE were not different between the 2 groups.

The AMIHOT study, presented by Dr. William W. O'Neill of the William Beaumont Hospital, Royal Oak, MI, was designed to determine benefit of infusion of a supersaturated oxygen solution after the infarcted vessel is opened. Patients (N = 282) were randomized to 90-minute infusions of saline versus the treatment solution. There was no significant difference in the endpoint of major adverse coronary events at 30 days. However, ST segment elevations were lowered by 25% in the supersaturated oxygen group, in an under the curve analysis (P = 0.09).

The CASTEMI study, presented by Dr. Dan Tzivoni of Shaare Zedeck Medical Center in Jerusalem, Israel, investigated the effect of caldaret, a

Figure 9. *Meta-analysis of death / MI and bleeding of enoxaparin versus UFH in the SYNERGY trial. MI, myocardial infarction; UFH, unfractionated heparin. Reproduced with permission from Mahaffey et al.*[17]



novel inhibitor of calcium overload, which may prevent reperfusion injury. Patients undergoing PCI (N = 387) were randomized to placebo or 2 doses of caldaret infusion. A 30% reduction of infarct size was observed in the treatment groups as determined by creatine phosphokinase marker curve. A decrease in end-diastole and end-systole volumes was also observed.

The POZNAN trial, presented by Dr. Tomasz Siminiak of the University School of Medical Sciences, District Hospital, Poznan, Poland, explored the transvenous delivery of myoblasts after acute myocardial infarction. Myoblasts were delivered using a novel transvenous delivery catheter into the myocardium. The method was found to be safe with no incidence of venous thrombosis and no pericardial effusion. Class improvement was observed in 4 out of 6 patients.

These trials illustrate some of the difficulties in studying patients with acute ST-elevation MI. Many factors contribute to outcomes in these patients: the time from onset to opening of the vessel, infarct size at risk, reperfusion injury, embolization of thrombus, or vasoactive materials. However, these factors are not equal. The major determinant is the time from onset to opening of the infarct vessel. Additional therapies ranging from balloon pumping, cooling, superoxide dismutase, adenosine, and now distal protection, offer only minor benefits at best. Other therapies, including those that target myocardial protection and regeneration, still require further investigation. The current goal in clinical practice should be to shorten door-to-balloon times and to utilize adjuvant therapies to achieve early partial, if not full, reperfusion.

[Alan C. Yeung, MD]

Percutaneous Valve Replacement and Repair

Since the introduction of cardiac surgery in the 1940s, standard treatment for severe valvular heart disease has been surgical replacement or repair. Over the last several years, however, the possibility for a percutaneous approach to valvular heart disease has been demonstrated by several animal studies.[26] In an educational symposium at this year's ACC, Philipp Bonhoeffer, MD, reviewed his pioneering work on the replacement of the pulmonic valve in patients with congenital heart disease using a bovine jugular vein sutured to a vascular stent. The valve has a profile of a trileaflet pulmonic valve with excellent hemodynamics. Following glutaraldehyde preparation, it is hand crimped to a balloon catheter and inserted percutaneously.

The current goal in clinical practice should be to shorten door-to-balloon times and to utilize adjuvant therapies to achieve early partial, if not full, reperfusion.

Dr. Bonhoeffer first published a description of the technique in 2000 and performed the first human implant in September of 2000, in a 12-year-old boy with stenosis of a right ventricle-to-pulmonary-artery conduit.[27] His latest experience was presented at this year's ACC and included 44 patients, 30 of whom had tetralogy of flow and an average age of 16 years. Mean follow-up was 12.5 months and procedural success was greater than 90%.[28] Freedom from need for surgical intervention was 83.8% at 2 years. Six patients had the valve explanted, 1 due to endocarditis, 2 due to significant regurgitation, 1 due to problematically small conduit size, and 2 for stenosis.

Percutaneous aortic valve replacement was also reported by Cribier and associates in 2002.[29] Their valve consisted of 3 bovine pericardial leaflets on a tubular stent that is also crimped onto a balloon for delivery. Since the initial case, 21 patients (age 78 ± 10) have undergone the procedure. All were in NYHA Class IV, 4 were in cardiogenic shock, and none were considered surgical candidates. The procedure was performed retrograde via the femoral artery in 4 cases. Due to the large size of the catheter, the majority (14) underwent the procedure using an antegrade approach via the femoral artery in a transseptal catheterization. Of the 21 patients, 17 had successful implantation and 4 had technical failures. The complications seen in this early experience included 1 cardiac arrest, 1 right ventricular perforation, and 2 deaths (both patients were in cardiogenic shock at the time of the procedures). In the remaining patients, ejection fraction increased from an average of 42% to 55% and the final aortic valve area was 1.7 cm^2. The longest follow-up to date is less than 2 years, but the patients are doing well.[30]

Preliminary results of the EVEREST I trial were presented by Ted E. Feldman, MD.[31] EVEREST I is a feasibility study of the Evalve mitral valve clip (Evalve, Inc., Redwood City, CA). The technique is a percutaneous approach via the femoral artery with a transseptal catheterization. The device involves a metal clip, guided by transesophageal echocardiography (TEE). The clip is placed in the midportion of both the anterior and posterior mitral valve leaflets and, once adequate placement is verified by

TEE, it is secured to the leaflets, creating a double orifice mitral valve. The technique is identical to that reported by Alfieri and Maisano[32] to treat mitral regurgitation surgically. To date, the technique has been used on 10 patients with severe mitral regurgitation, with all patients evaluated as viable surgical candidates. Successful deployment occurred in 7 patients with a reduction in mitral regurgitation in 3. No major complications were encountered; however, 1 patient had prolapse of the valve with continued severe regurgitation and 1 patient had a clip detachment requiring subsequent surgery. Three patients with failed procedures underwent elective surgery without complications.

The clip is placed in the midportion of both the anterior and posterior mitral valve leaflets and, once adequate placement is verified by TEE, it is secured to the leaflets, creating a double orifice mitral valve.

These 3 percutaneous techniques to repair or replace aortic and mitral valves offer new and exciting opportunities for interventional cardiologists. There is little question that these techniques are in their very earliest phase of development, and that significant problems exist with their implementation. Percutaneous pulmonic valve replacement presents issues of appropriate sizing and longevity. Aortic valve replacement presents similar problems, with significant limitations in longevity of the valve. The mitral valve clip procedure has not yet shown an acceptable rate of success. Nevertheless, each of these studies demonstrates the feasibility and possibilities of percutaneous valve repair and replacement. With continued technical advances and clinical experience, interventional treatment of aortic, pulmonary, and mitral valve disease is now a real possibility for the future. [David P. Faxon, MD, FACC, FAHA]

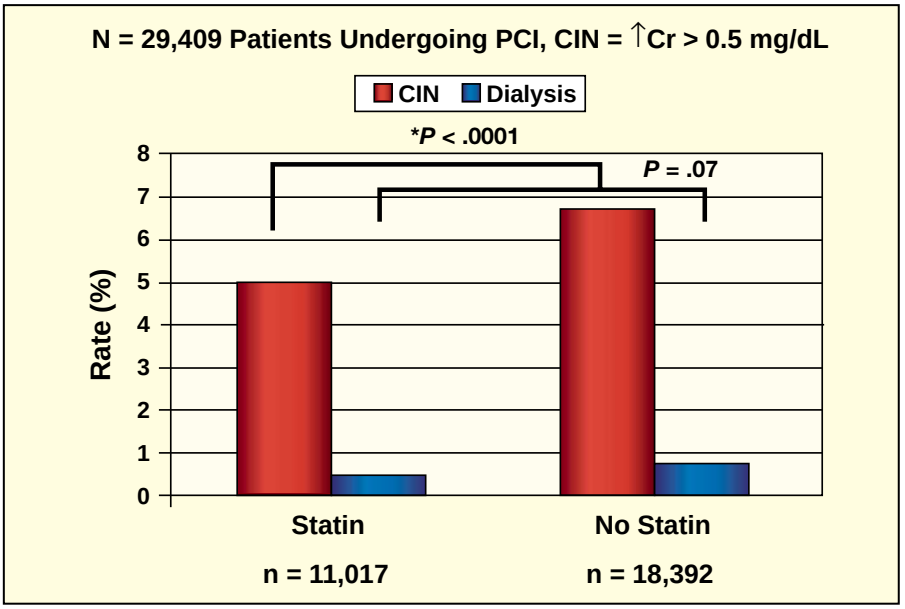
Cardiorenal Update

This year's ACC featured 36 original papers indexed to renal dysfunction as a cardiovascular risk condition, 38 papers indexed to the renin-angiotensin-aldosterone system (RAAS), and 38 papers indexed to the natriuretic peptides. Many papers presented data continuing to demonstrate the clear relationship between chronic kidney disease (CKD) and negative cardiovascular outcomes. An analysis of 29,409 patients undergoing percutaneous coronary intervention (PCI) demonstrated that baseline treatment with statins reduced the rates of contrast-induced nephropathy by 27.9% ($P < .0001$). Cystatin C, a novel marker for renal function, was found to track C-reactive protein with high sensitivity, and was independently associated with incident cardiovascular disease (CVD). Papers concerning the RAAS and natriuretic peptides continue to refine our knowledge of these respective regulatory and counter-regulatory systems. Imbalance between them appears to result in a cardiorenal syndrome manifested by higher mortality in patients with combined heart and renal failure.

Contrast Nephropathy

With the exception of adequate hydration, use of iso-osmolar contrast and possibly N-acetylcysteine, there appears to be little the cardiologist can do to prevent contrast nephropathy, which occurs in 15% of patients undergoing PCI. Khanal and coworkers[33] from the University of Michigan, Ann Arbor, MI, studied a PCI database (N = 29,409) where pre- and postprocedure serum creatinine (Cr) was measured. A total of 11,017 patients (37.5%) were taking statins at baseline. Both groups

Figure 10. *Impact of baseline statin use on rates of renal injury after percutaneous coronary intervention (PCI). CIN, contrast-induced nephropathy; Cr, creatinine. Data from Khanal et al.[33]*



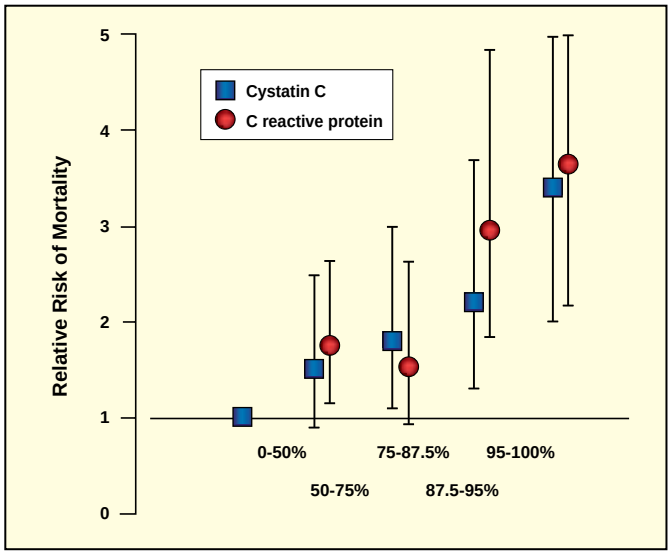


Figure 11. *Relationship among cystatin C, a marker of renal function, high-sensitivity C-reactive protein, and all-cause mortality in the PREVEND Study. Data from Hillege et al.*[34]

(statin, no-statin) had baseline Cr = 1.2 mg/dL. The rates of contrast-induced nephropathy and acute renal failure requiring dialysis were reduced in the statin group (Figure 10). Although this study could have been confounded, the baseline characteristics were well matched, and, indeed, renal protection may prove yet another indication for statin therapy.

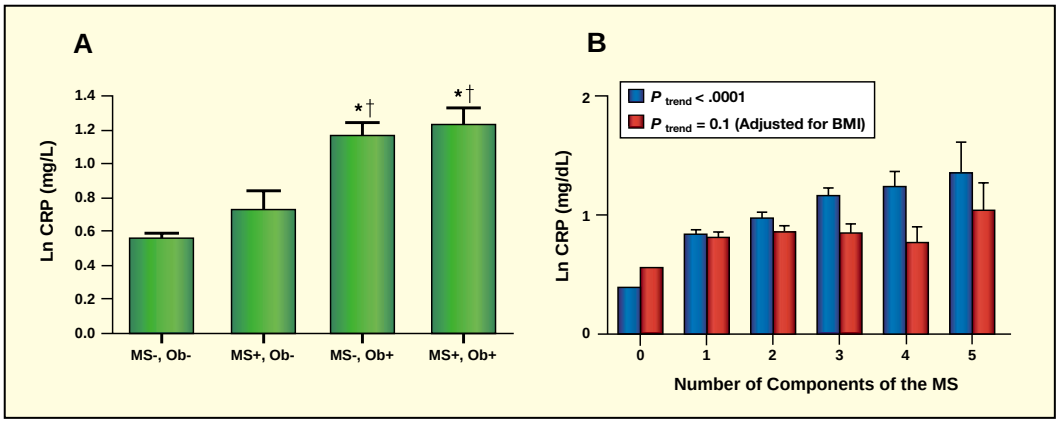
Cystatin C and Inflammation

The Prevention of Renal and Vascular End Stage Disease (PREVEND) Study, a longitudinal population-based study presented by Hillege and colleagues, University Hospital Groningen, Groningen, The Netherlands, evaluated cystatin C in 6135 participants aged 28-75 years.[34] Cystatin C is a newly discovered measure of renal filtration function that does not depend on muscle mass. Over 5.2 years, 180 participants in the study died. Both cystatin C and high sensitivity C-reactive protein were independently related to all-cause mortality (Figure 11). This study highlights the key concept that chronic kidney disease is an inflammatory state and chronic inflammation partly explains the relationship between renal insufficiency and CVD. Another study by Aronson and coworkers[35] linked high-sensitivity C-reactive protein and obesity. Although this is not a new finding, this study of 1929 healthy subjects, mean age 50 years, found that obesity, with or without the presence of the metabolic syndrome, was related to the highest levels of high-sensitivity C-reactive protein (Figure 12). We can conclude from this study that high-sensitivity C-reactive protein is heavily confounded by body mass index, and, with the expanding obesity pandemic, will most likely lose its independent predictive value in cardiovascular medicine.

Natriuretic Peptides

B-type natriuretic peptide (BNP), a hormone produced by the cardiac ventricles in response to wall tension, continued to receive considerable attention at this year's ACC. The main concept, discussed in multiple papers, is that even mildly elevated BNP, still considered in the normal range (> 20 pg/mL or equivalent), is predictive of future CVD events. This was best shown in the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial of losartan in patients with hypertension. N-terminal pro-BNP was measured in 945 patients followed for 55 months. An N-terminal pro-BNP level greater than 20.1 pmol/L predicted CVD events (stroke, myocardial infarction,

Figure 12. *Relationship among obesity (Ob), the metabolic syndrome (MS), and high-sensitivity C-reactive protein (measured as Ln CRP) in healthy subjects. *P < 0.005 compared with MS-, Ob-; †P < 0.01 compared with MS+, Ob-. BMI, body mass index. Data from Aronson et al.*[35]



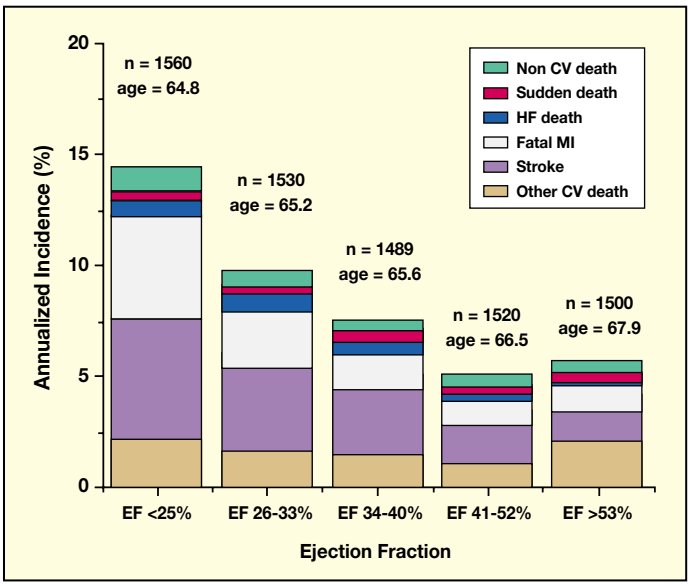


Figure 13. *Cause of death in the CHARM trial stratified by ejection fraction. Data from Solomon et al.*[37]

or cardiac death).[36] Among those patients with no prior history of CVD or diabetes, an elevated N-terminal pro-BNP level was associated with an 11.0% event rate compared with a rate of only 3.2% in those with low N-terminal pro-BNP. This relationship held after adjustment for baseline characteristics. The LIFE study is another piece of evidence supporting use of BNP to identify high-risk patients in practice. It is possible that in the future BNP will be used to select medications to best reduce the risk of CVD in individual patients.

Cardiorenal Failure

A core concept in heart failure is that as ejection fraction lowers, the rate of mortality increases. Data from the Candesartan in Heart Failure Trial (CHARM) indicates that death due to myocardial infarction and non-cardiac causes are similar across the spectrum of ejection fraction.[37] However, the proportions of death due to heart failure and sudden death increase markedly in the population with ejection fractions lower than 40 % (Figure 13). Data from the Acute Decompensated HEart failure national REgistry (ADHERE) adds considerable insight into the heart failure epidemic.[38] Data from 46,599 hospitalizations reveal that those patients with a baseline serum Cr greater than 2.0 mg/dL receiving chronic diuretics have the longest lengths-of-stay and require the greatest utilization of resources. In another study of 498 patients admitted with congestive heart failure (CHF), 21% experienced deteriorating renal function (rise in serum Cr > 0.5 mg/dL).[39] Worsening renal function was an independent predictor of 6-month mortality, RR = 2.93, $P < .0001$ (Figure 14). It appears from these papers that the key mortality determinants in CHF are ejection fraction, baseline renal function, and, for those hospitalized, worsening renal function. Future therapies that favorably impact both cardiac and renal function will likely improve outcomes in this population.

Commentary

The 2004 Scientific Session witnessed continued advances in cardiorenal research. Statins, which should be used in nearly all patients with atherosclerosis, appeared to have renal-protective effects. CKD was further defined as an inflammatory state, helping to explain its relationship to CVD. B-type natriuretic peptide, even when mildly elevated within the normal range, showed predictive value for future CVD events. Cardiorenal failure is increasingly being recognized as a syndrome and is closely related to increased resource utilization and higher mortality.

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

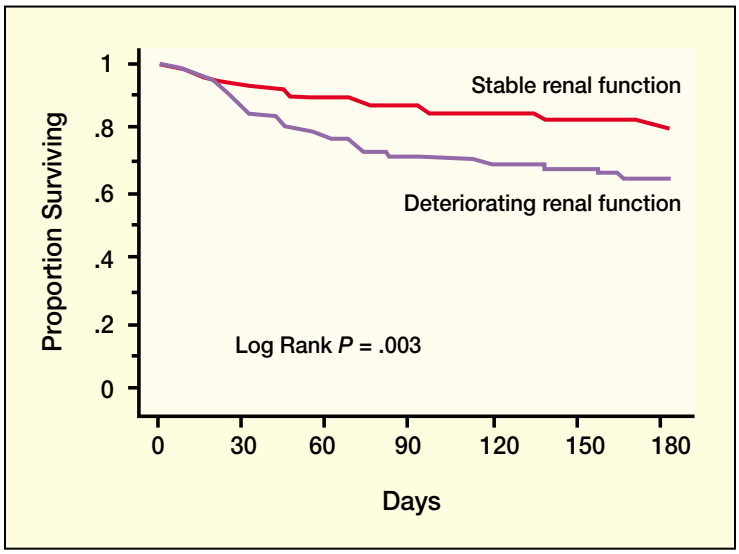


Figure 14. *Independent effect of worsening renal function on heart failure outcomes after hospitalization. Data from Aronson et al.*[39]

CAPITAL–AMI Trial

The objectives of the Combined Angioplasty and Pharmacologic Intervention versus Thrombolytics Alone in Acute Myocardial Infarction (CAPITAL-AMI) Trial were to assess the efficacy of thrombolytic therapy using weight-adjusted tenecteplase (TNK) plus routine angiography versus thrombolytic therapy alone.[40] The group treated with the former strategy (combination group) included patients who underwent intentional rescue-stenting of the infarct-related artery, in the event that lytic therapy had not achieved arterial patency. In the thrombolysis-alone group, if treatment was judged successful, patients were given standard follow-up care. If treatment failed, the option of transferral to a catheterization-equipped center for angiography, and possible intervention, was available.

CAPITAL-AMI followed 170 high-risk patients experiencing AMI within 6 hours of the onset of symptoms. Patients were randomized, and the primary endpoint was a composite measure of clinical outcomes of death, recurrent infarction, recurrent unstable ischemia, and stroke, assessed at both 30 days and 6 months after the index AMI. Secondary endpoints included the clinical outcomes as listed for the primary endpoint plus ST-segment resolution, requirement of subsequent revascularization, frequency of congestive heart failure and cardiogenic shock, Canadian Cardiovascular Society Angina Class, cost effectiveness, and quality of life.

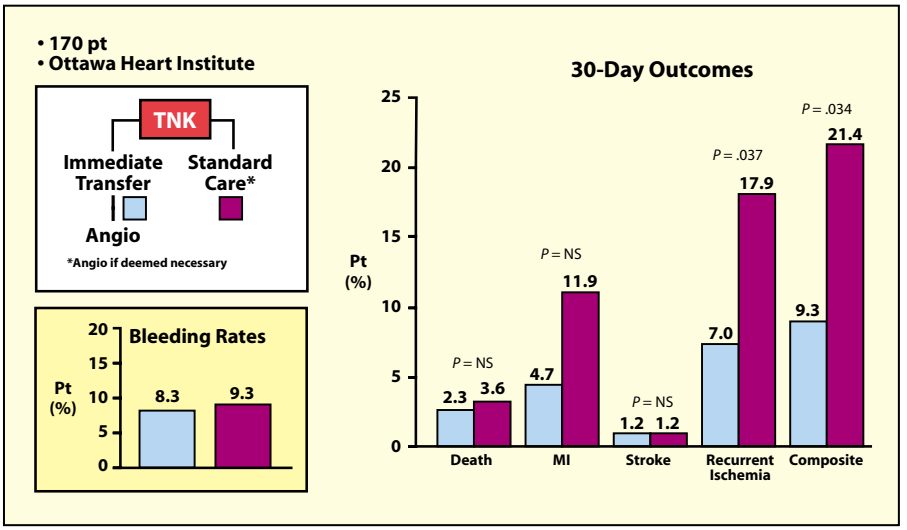


Figure 15. *Summary of 30-day outcomes and bleeding rates in the CAPITAL-AMI Trial. MI, myocardial infarction. Reproduced with permission from LeMay et al.*[40]

Results

Major efficacy results are illustrated in Figure 15. There was no significant difference in mortality, which measured 3.6% in the thrombolysis-alone versus 2.3% in the combination group (P = not significant). Neither were there any significant differences in the rates of recurrent myocardial infarction and stroke, although there appeared to be a trend in the rate of the recurrent MI, with 11.9% in the thrombolysis group higher than the 4.7% reported in the combination group. Recurrent ischemia was significantly reduced by combination therapy (7.0% vs.17.9% in the thrombolysis-only group, P = .037). This was the main factor driving the composite primary endpoint results (21.4% in the thrombolysis alone group vs. 9.3% in the combination group, P = .034). There was no significant difference in bleeding rates, which were 8.3% in the thrombolysis-alone group versus 9.3% with combination therapy. In his presentation, Dr. LeMay also reported a trend towards a reduced incidence of heart failure and shock in the combination group and a reduction in hospital stay of 1 day.

Comment

It is generally accepted that, in centers with requisite facilities and logistic capabilities, primary PCI is superior to fibrinolytic drug therapy in patients with evolving ST-segment elevation myocardial infarction.[41] Among patients presenting in community hospitals without percutaneous coronary intervention (PCI) and/or coronary bypass surgery capability, varying therapeutic options are currently the subject of considerable interest, debate, and, occasionally, emotion. These include (a) fibrinolytic drugs followed by either routine angiography or a policy of "watchful waiting" based upon recurrent symptoms of ischemia; (b) immediate transfer to primary PCI centers, or (c) the strategy of facilitated PCI.[42] The latter strategy is composed of an initial administration of fibrinolytics, either full-dose or reduced-dose and in combination with platelet inhibitors, followed by transfer for early angiography.

Fibrinolytics. One approach is to treat all patients in community hospitals with a fibrinolytic regimen, particularly patients seen within 3 hours of symptom onset, followed by a course of watchful waiting or transfer for routine PCI, performed either as an emergency procedure or electively within 24 hours. The logistics to transfer for "rescue angioplasty" should be in place.[43] In many parts of

the world, one can make a very strong case for the pre-hospital administration of thrombolytic drugs.[44] Among patients presenting after 3 hours or those considered at high risk for intracranial hemorrhage, a good alternative is transfer for primary percutaneous coronary intervention without preceding lytic therapy.[45]

Among patients presenting in community hospitals without percutaneous coronary intervention and/or coronary bypass surgery capability, varying therapeutic options are currently the subject of considerable interest, debate, and, occasionally, emotion.

Several trials performed during the 1980s, which reflected the "learning curve" for PCI procedures, suggested that "routine" early angiography after thrombolytic therapy was not beneficial, and in several studies appear to be deleterious.[46-51] This has been readdressed in the modern era of PCI by the GRACIA 1 Pilot Trial which demonstrated the safety and efficacy of routine angiography within 24 hours of fibrinolytic administration,[52] and the Southwestern German Interventional Study in Acute Myocardial Infarction (SIAM III).[53] In this trial, patients treated with thrombolytics were randomized to angiography, including stenting, within 6 hours of fibrinolytic therapy as opposed to 2 weeks after thrombolysis. At 6 months, the combined endpoint of death, ischemic events, reinfarction, and target lesion revascularization occurred in 25.6% of patients in the early (6-hour group) versus 50.6% in the delayed angiography group (P = .001). Major bleeding occurred in 9.8% and 7.4%, respectively.

The CAPITAL-AMI Trial addresses the same issue from a different perspective and basically compares the strategy of facilitated PCI to thrombolytic therapy alone. As was the case, however, in GRACIA 1, the CAPTURE-MI Trial demonstrated the safety of early angiography after a course of full-dose thrombolytics. This is certainly reassuring, given the negative results and high rates of bleeding engendered by such an approach in trials carried out 10-15 years ago. The advent of improved percutaneous catheter interventional technology, the use of weight-adjusted dosing of fibrinolytics and heparin, stents, and high-resolution imaging has certainly altered the interventional landscape, promoting increased efficacy and safety.[54]

Transfer for PCI with no preceding thrombolytic therapy. Several trials and a meta-analysis suggest that transfer for primary PCI is a better strategy than the administration of fibrinolytics.[45] These trials have generated considerable enthusiasm in favor of immediate transfer, and in certain regions of the world, "a state of transfer mania exists." The results of the trials are quite persuasive but require further scrutiny, and certain aspects are open to criticism.

Despite some data to the contrary, there is good evidence that time-to-treatment is of great importance in patients receiving primary PCI, as well as in the case of fibrinolytics, but this is particularly relevant to patients treated early.

Despite some data to the contrary, there is good evidence that time-to-treatment is of great importance in patients receiving primary PCI, as well as in the case of fibrinolytics, but this is particularly relevant to patients treated early (within 1 to 3 hours of symptom onset).[55-57] In this situation, the delays incurred by transfer, as opposed to immediate administration of fibrinolytics, could be detrimental. This is borne out by the results of the CAPTIM Trial, in which patients treated within 2 hours of symptoms had better outcomes with fibrinolytics.[44] A trend in the other direction occurred in patients treated after 2 hours. Similarly, the benefits of primary PCI in the PRAGUE 2 Trial were only noted in patients treated after 3 hours of symptoms.[58]

In summary, fibrinolytic therapy is extremely effective in patients treated early (1-2 hours, or perhaps within 3 hours, of symptom onset).[57] In this setting, time-to-treatment is critical and delays may be harmful; however, later in the course of the myocardial infarction, clots may become more resistant to lytics and outcomes are less time dependent. At this juncture, the main priority is to open the infarct-related artery, and the rapidity of therapeutic delivery is less of a concern.[57] In this situation, primary PCI is superior to fibrinolytics, and it should be emphasized that the majority of trials, which have demonstrated the superiority of patient transfer for primary PCI to lytic therapy, enrolled many patients 2.0 to 2.5 hours after symptom onset.[46] Regrettably, the majority of patients still present to the hospital relatively late after symptom onset and outside the window of opportunity.

Facilitated PCI. The concept of facilitated PCI is an attractive one

given the delays related to transfer and the benefits of an "open artery" at the time of the initial angiogram. The downside is the risk of bleeding complications related to the administration of lytics prior to PCI. Prior pilot studies have had mixed results[47,59] and the recent BRAVE Trial was completely negative in regard to final infarct size, despite higher initial rates of TIMI 3 flow in the group treated with a combination of half-dose lytics plus abciximab versus abciximab alone.[60]

Two large randomized trials (ASSENT 4 and FINESSE) are currently addressing the role of facilitated PCI in approximately 7000 patients presenting within 6 hours of symptom onset. Answers should be available within the next 2 years. The positive results of the CAPITAL-AMI trial should, however, serve as a boost to the recruitment of patients into these trials because the safety of early angiography has been convincingly demonstrated and concerns raised by trials performed approximately 10 years ago can perhaps be assuaged.

For the present, the message is clear. As we focus on new strategies, it is sobering to realize that many eligible patients receive no reperfusion therapy at all.[59] The ultimate goal should be to treat all eligible patients as quickly as possible—the underlying efficacy of delivery may still be more important than the nature of the therapy. ■

[Bernard J. Gersh, MB, ChB, DPhil, FRCP]

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Main Points

- New analyses of the COMET trial data reinforce the fact that not all ß-blockers provide the same therapeutic benefits and that comprehensive adrenergic blockade with carvedilol is a more optimal treatment for heart failure patients when compared to metoprolol tartrate. The differences in outcomes in COMET are not mitigated by variations in the dose given, effects on heart rate, or blood pressure.
- Rimonabant is a potent cannabinoid-receptor antagonist that could potentially aid physicians in treating the common cardiovascular risk factors of obesity and cigarette smoking. More research is required to determine whether its positive effect on metabolic and lipid profiles may be a primary effect of CB1 blockade or secondary to its weight loss-promoting properties.
- Results of the SCD-HeFT trial demonstrated that internal cardioverter-defibrillator implantation, in conjunction with standard medical therapy, reduces all-cause mortality in patients with NYHA Class II or III heart failure, when compared with placebo, whereas amiodarone therapy did not have any effect.
- The PAVE study showed significant improvement in 6-minute walking test for biventricular pacing over traditional right ventricular pacing in patients with atrial fibrillation that required ablation of the AV junction with the implantation of a permanent pacemaker.
- Abciximab is the only GP IIb/IIIa inhibitor that has shown benefit in patients treated with primary PCI for acute MI and therefore should be part of an overall revascularization strategy, with additional benefit observed from early initiation.
- Data continue to accumulate showing that the thiazolidinediones, as well as metformin, have important vascular protective effects and therefore should be used as primary therapies for diabetes, perhaps reserving the insulin secretagogues for patients with refractory hyperglycemia.
- The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT-TIMI 22) trial compared the standard degree of LDL-lowering therapy with pravastatin to more intensive lipid lowering with atorvastatin, to measure reduction of death or major cardiovascular complications in patients with acute coronary syndromes (ACS). The benefit of intensive therapy was consistent across subgroups including men and women, patients with unstable angina, those with myocardial infarction, and those with and without diabetes mellitus, and results did not meet the prespecified criterion for non-inferiority of pravastatin therapy.
- The SYNERGY trial illustrated the non-inferiority of enoxaparin versus unfractionated heparin as an anticoagulant in patients undergoing invasive procedures for acute coronary syndromes, with equal efficacy in major outcomes and non-significant differences in the incidence of major bleeding. The investigators did observe that switching antithrombotic therapy from enoxaparin to unfractionated heparin, or vice versa, in the midst of treatment, increased the risk of bleeding without clinical benefit and should be avoided.
- Various trials studying patients with acute ST-elevation MI have shown that, in lieu of shortening door-to-balloon time, current invasive therapies have minor benefit at best. Other therapies, including those that target myocardial protection and regeneration, still require further investigation.
- Three new percutaneous techniques to repair or replace aortic and mitral valves are in the earliest phase of development. Percutaneous pulmonic valve replacement and aortic valve replacement present issues of appropriate sizing and longevity whereas the mitral valve clip procedure has not yet shown an acceptable rate of success. Nonetheless, feasibility of these techniques as viable future therapies, with continued technological refinement and advances, has been demonstrated.
- Advances in cardiorenal research include a possible indication for statins as a renal protective agent, the definition of chronic kidney disease as an inflammatory state, and further refinement of the role of BNP as a predictor of cardiovascular events.
- The CAPITAL-AMI trial offers further evidence in the debate over fibrinolytic therapy versus immediate transfer for percutaneous coronary intervention (PCI), in patients with acute myocardial infarction. Although some improved efficacy is shown in the use of combination therapy or "facilitated" PCI versus thrombolytic monotherapy, overall evidence continues to support the idea that time-to-treatment is a more important factor than the means of therapy.

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