Best of the ACC Scientific Session 2003

Highlights from the American College of Cardiology 52nd Annual Scientific Session, March 30–April 2, 2003, Chicago, IL

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Key words: ADHERE • ALLHAT • ANBP2 • Angiogenesis • ARCHER • ASCOT • Atrial fibrillation • CADILLAC • Calcium-channel blockers • COMPANION • CONTRAST • Coronary artery calcification • DELIVER • Drug-eluting stents • EPHESUS • FACIT • FIRE • INVEST • ISAR-REACT • Myoblasts • Natriuretic peptides • Nesiritide • Percutaneous coronary intervention • Radiocontrast nephropathy • RAVE • RAVEL • Saphenous vein graft • SIRIUS • SPORTIF III • TAXUS II • TRAFFIC • Transesophageal echo • Thienopyridines • Vascular endothelial growth factor

This year's ACC meeting provided a forum for presentations on late-breaking trials and other important developments relating to every aspect of cardiology. Here, our editors provide reports on the latest news in each of their respective areas of expertise.

Heart Failure and Atrial Fibrillation

The American College of Cardiology (ACC) 52nd Annual Scientific Session included a number of clinical trials and late-breaking developments in heart failure and atrial fibrillation research that have important clinical implications.

EPHESUS Trial

The Eplerenone Post-AMI Heart Failure Efficacy and Survival Trial (EPHESUS) tested the hypothesis that selective aldosterone receptor blockade would reduce mortality when given in addition to standard therapy in patients with acute myocardial infarction (AMI) complicated by left ventricular systolic dysfunction and heart failure. Angiotensin-converting enzyme (ACE) inhibitors and ß-blockers have previously been demonstrated to prevent remodeling after AMI and to reduce morbidity and mortality in patients with left ventricular systolic dysfunction after MI. However, even with these medications, morbidity and mortality remain relatively high in patients with left ventricular systolic dysfunction after MI. Aldosterone receptor blockade has also been shown to prevent ventricular remodeling and collagen deposition in patients with left ventricular dysfunction after AMI. Previously, the Randomized Aldactone Evaluation Study (RALES) demonstrated that aldosterone recep-

tor blockade with spironolactone, when added to treatment that includes an ACE inhibitor, could reduce mortality in patients with severe heart failure.[1] In the RALES trial, only 10%–11% of patients were taking a ß-blocker.

Eplerenone (Inspra®, Pfizer, Inc., New York) is a selective aldosterone receptor antagonist that blocks the mineralocorticoid receptor but not glucocorticoid, progesterone, or androgen receptors. Results from EPHESUS were presented by Dr. Bertram Pitt (University of Michigan, Ann Arbor) at the late-breaking clinical trial plenary session on March 31, 2003 and were simultaneously published in the *New England Journal of Medicine*.[2]

In this trial, a total of 6632 AMI patients with left ventricular ejection fraction (LVEF) ≤ 40% and rales on physical examination were randomized to receive eplerenone or placebo. Patients with diabetes required only an LVEF of ≤ 40%. Patients were excluded if they had serum creatinine > 2.5 mg/dL or serum potassium > 5.0 mmol/L. Eplerenone was administered at a starting dose of 25 mg and titrated to a maximum of 50 mg per day, if tolerated. The mean dose of eplerenone was 43 mg/day. Therapy was initiated an average of 7 days after the onset of AMI (range, 3–14 days). The trial was continued until 1012 deaths had occurred. Subjects had a mean age of 64 years, mean LVEF of 33%, baseline creatinine of 1.1 mg/dL, and mean blood pressure of 119/72 mm Hg. Background medical treatment included ACE inhibition or angiotensin receptor blocker (ARB) therapy in 86%, ß-blockade in 75%, aspirin in 88%, statin therapy in 47%, and use of revascularization in 45% of patients. Patients were followed for an average of 16 months.

This trial demonstrated that eplerenone significantly reduced all-cause mortality (Table 1). The mortality rate was decreased from 16.7% with placebo to 14.4% with eplerenone (relative risk [RR] 0.85, 95% confidence interval [CI] 0.75-0.96, *P* = .008). There was also a significant reduction in the endpoint of death from cardiovascular causes or hospitalization for cardiovascular events. Additional secondary endpoints were also reduced by eplerenone treatment, including sudden cardiac death (RR 0.79, 95% CI 0.64-0.97, *P* = .03).

Table 1
Results from Eplerenone Post-AMI Heart Failure Efficacy and Survival (EPHESUS) Trial

Endpoint	Eplerenone n (%)	Placebo n (%)	Relative risk (95% CI)	*P*
Mortality	478 (14.4)	554 (16.7)	0.85 (0.75-0.96)	.008
Cardiovascular mortality	407 (12.3)	483 (14.6)	0.83 (0.72-0.94)	.005
CV mortality or hospitalization for CV events	885 (26.7)	993 (30.0)	0.87 (0.79-0.95)	.002

Subgroup analysis showed a relatively uniform effect of eplerenone treatment. Patients receiving optimal therapy, defined as treatment with ACE/ARB, a ß-blocker, aspirin, statin, and reperfusion therapy, had a 26% reduction in all-cause mortality with eplerenone. There was a significantly increased incidence of hyperkalemia with eplerenone (1.6% absolute increase), and patients with decreased creatinine clearance (< 50 mL/min) at baseline were at higher risk for hyperkalemia. This finding emphasizes the need to very closely monitor serum potassium and adjust eplerenone dosing as necessary. The risk for serious hypokalemia was reduced by eplerenone treatment.

The EPHESUS trial convincingly demonstrates that the addition of eplerenone to optimal medical therapy results in an improvement in survival and a reduction in hospitalization rates among patients with AMI complicated by left ventricular dysfunction and heart failure. The number needed to treat is 50 to save one life in 1 year and the number needed to treat is 33 to prevent one death from cardiovascular causes or one hospitalization for a cardiovascular event in 1 year. The benefits of aldosterone antagonism, first demonstrated in severe heart failure, have now been demonstrated to apply to patients with mild-to-moderate heart failure after MI. This represents an important therapeutic advance that will allow for additional mortality reductions in this large and important patient population.

COMPANION

Results from the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure Trial (COMPANION) were also presented at the ACC late-breaking clinical trial plenary session on March 31, 2003. Previous research has demonstrated that 25%–30% of heart failure patients have QRS widening (ventricular dyssynchrony), which is associated with increased risk of disease progression and mortality. Cardiac resynchronization therapy (CRT) (biventricular pacing)

has been developed as a means to restore synchronization of ventricular contraction. In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE), the use of CRT (InSync model 8040, Medtronic, Minneapolis, MN) in patients with moderate-to-severe heart failure was demonstrated to significantly reduce heart failure symptoms, improve exercise capacity, and improve LVEF.[3] CRT also resulted in a reduction in heart failure hospitalizations, from 15% to 8%. This led to U.S. Food and Drug Administration approval of this form of therapy in 2002. The impact of CRT on mortality had, however, not previously been determined, and this remained a significant impediment to widespread use of CRT.

COMPANION was a parallel, randomized clinical trial that sought to answer two questions: 1) whether CRT with biventricular pacing alone decreases combined all-cause mortality and all-cause hospitalization and 2) whether CRT with implantable cardioverter defibrillator (ICD) therapy reduces combined all-cause mortality and all-cause hospitalization. The trial enrolled 1634 patients with moderate or severe heart failure with QRS ≥ 120 msec and LVEF ≤ 35%.[4] Entry criteria required patients to have been hospitalized at least once in the past year for heart failure management, to have had an outpatient visit in which inotropes or a vasoactive infusion was administered, or an emergency room visit of at least 12 hours during which intravenous heart failure medications were administered. Patients were randomized in a 1:2:2 fashion to optimal medical therapy (ACE inhibitors or ARBs, ß-blockers, spironolactone, digoxin, and diuretics), optimal medical therapy plus CRT (CONTAK TR, Guidant, Indianapolis, IN), or optimal therapy plus CRT with an implantable cardioverter defibrillator (ICD) (CONTAK CD, Guidant).

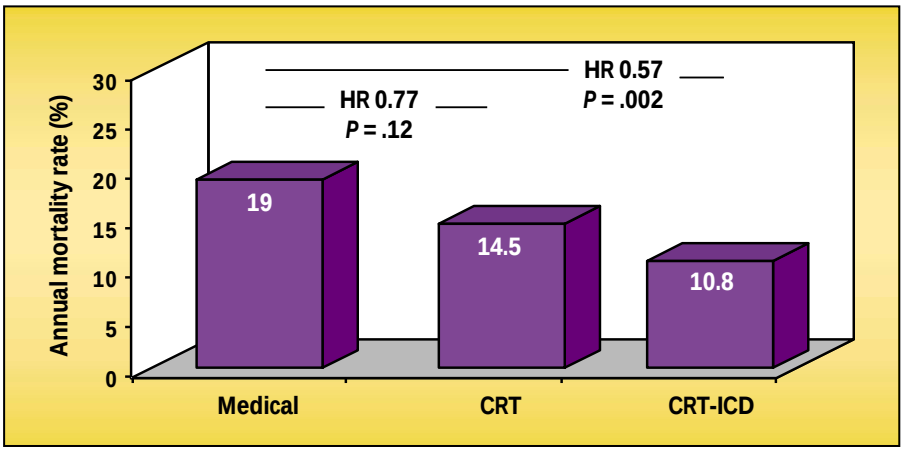


Figure 1. *Preliminary results of the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. HR, hazard ratio; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.*

At baseline, mean age of patients was 67 years, mean LVEF 22.8%, and mean QRS 156 msec; 82% were New York Heart Association (NYHA) class III. Background medical therapy was ACE inhibitor/ARB in 89%, ß-blocker in 66%, and spironolactone in 55%. CRT implants were successful in 90% and occurred within 2 days of randomization. The median implant time was 3 hours, and there were only 4 deaths related to device implants, all occurring early in the trial. Dr. Michael Bristow (University of Colorado Health Sciences Center, Denver) presented the results of this trial, which were described as "preliminary" because reported events have not been fully adjudicated.

The primary endpoint of the study, a combination of all-cause death and all-cause hospitalizations over 12 months, was significantly reduced, by 18.6% for the CRT and by 19.3% for the CRT-ICD arms of the study. The 1-year mortality rate with optimal medical therapy was 19.0%, 14.5% with CRT alone, and 10.8% with CRT-ICD (Figure 1). Thus, CRT-ICD therapy resulted in a remarkable 43.4% reduction in all-cause mortality (P = .002). CRT alone was also associated with a nonsignificant trend toward a 23.9% reduction in all-cause mortality (P = .12). There were no significant differences in treatment effects between patients with ischemic and nonischemic cardiomyopathy, or in other subgroups.

Compared with optimal medical treatment, biventricular cardiac resynchronization therapy with or without an ICD can reduce all-cause death and all-cause hospitalizations in patients with moderate or severe heart failure. The number needed to treat with CRT-ICD therapy is 12 patients to reduce a death within 1 year of treatment. This is the first therapy developed specifically for heart failure patients to result in improved survival. The mortality relative risk reduction with CRT-ICD is larger than has previously been demonstrated in heart failure and is all the more impressive because the benefit was in addition to that of optimal medical therapy. This represents a major therapeutic advance in heart failure therapy.

Cellular Transplantation for Heart Failure

Reports on progress with cellular transplantation that uses skeletal

myoblasts or peripheral stem cells generated much discussion and interest at the ACC Scientific Sessions. The studies presented, although from small and uncontrolled safety studies, have shown that it is feasible to perform cellular transplantation. Evidence of improved ventricular function was presented, but because these patients also underwent revascularization and there were no control groups, no firm conclusions can be drawn. Larger clinical trials of cellular transplantation as a treatment for heart failure are under way.

There were a number of presentations regarding the clinical utility of measuring B-type natriuretic peptide (BNP) in patients with heart failure. Beyond this assay's role in facilitating the diagnosis of heart failure, a number of studies presented demonstrated that this assay provides independent prognostic information. The effects of various heart failure treatments on BNP levels were also the topic of a number of abstracts. There was significant interest in an observational study from University of California, Los Angeles, investigators, which showed that statin treatment was associated with a significant reduction in mortality in patients with advanced heart failure due to ischemic and nonischemic cardiomyopathy, irrespective of baseline cholesterol levels. This interesting result needs to be confirmed in prospective randomized clinical trials.

SPORTIF III Trial

Exciting results were reported from a randomized, prospective trial that evaluated a new oral direct thrombin inhibitor, ximelagatran, with warfarin therapy for the prevention of stroke and systemic embolic events in patients with atrial fibrillation. The third Stroke Prophylaxis Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF III) trial results and those of SPORTIF V, which, it is hoped, will hopefully be presented before the end of this year, have tremendous implications for the treatment of patients with atrial fibrillation who are at risk of stroke. Currently, the standard for these patients is warfarin therapy guided by international normalized ratio (INR) values, which is a difficult process for both patient and physician. The use of a fixed oral dose without drug titration, as was done with ximelagatran, could clearly simplify this process and was the impetus for this trial.

Results of SPORTIF III are exciting and encouraging news for those of us who treat patients with atrial fibrillation who require long-term anticoagulation therapy.

The SPORTIF III trial was designed as a noninferiority study of ximelagatran compared with warfarin. The primary analysis evaluated combined rates of all strokes and systemic embolic events between treatment groups. Eligible patients included those with nonvalvular atrial fibrillation with at least one additional risk factor for stroke. There were 3407 patients enrolled and randomized in an open-label fashion to receive adjusted-dose warfarin with an INR target of 2–3 or a fixed dose of 36 mg b.i.d. of ximelagatran. According to Dr. Jonathan Halperin of The Mount Sinai Medical Center, New York, NY, the principal investigator of SPORTIF III, the INR values were within the therapeutic range for 66% of the entire duration of exposure. Evaluating the intention-to-treat analysis, stroke and systemic embolic events were 2.3% per year for warfarin, compared with 1.6% per year for ximelagatran, which demonstrates no significant difference between treatments. Of note, the on-treatment analysis demonstrated events at 2.2% per year for warfarin, compared with only 1.3% with ximelagatran, a significant reduction in events in the ximelagatran group.

Regarding adverse events, there was no significant difference between treatment groups in intracerebral hemorrhage or major bleeding. However, there was a significantly higher incidence of liver enzyme transaminase elevations with ximelagatran compared with warfarin. Elevations three times the upper limit of normal were seen in 6.5% of patients receiving ximelagatran, compared with 0.7% of those who received warfarin.

Results of SPORTIF III are exciting and encouraging news for those of us who treat patients with atrial fibrillation who require long-term anticoagulation therapy. It is a difficult journey for physician and patient alike when they are trying to maintain INR values. Even under optimal conditions, patients often vacillate between too-high and too-low INR values. The results of SPORTIF III suggest an alternative to long-term warfarin therapy, the thrombin inhibitor ximelagatran, especially if the results of SPORTIF V support the conclusions demonstrated in SPORTIF III. The downside seems to be an increase in liver enzymes that occurs in approximately in 6%–7% of patients. Methods to evaluate for this in patients receiving ximelagatran will be needed.

Low-Molecular-Weight Heparin Compared with Intravenous Heparin in Patients with Atrial Fibrillation

Dr. Uwe Nixdorff and colleagues of

the Friedrich-Alexander-Universitat, Erlangen, Germany, evaluated the safety and efficacy of anticoagulation with enoxaparin compared with unfractionated heparin along with phenprocoumon for cardioversion of patients with nonvalvular atrial fibrillation. Patients had nonvalvular atrial fibrillation lasting 48 hours to 1 year and were evaluated with transesophageal echocardiography to guide cardioversion timing. There were two study groups: 216 patients received enoxaparin, and 212 received heparin plus oral anticoagulation. The combined primary efficacy and safety endpoint for this trial was stroke, transient ischemic attack, systemic embolism, death, and major bleeding events. The primary endpoint was 3.2% for patients receiving enoxaparin, compared with 5.6% for those receiving heparin and anticoagulation, which demonstrated that enoxaparin showed efficacy and safety noninferior to the combination of heparin and oral anticoagulants in the cardioversion of atrial fibrillation.

A different trial, by Dr. Francois Phillippon and coworkers, randomized patients to receive outpatient dalteparin administration to inpatient heparin to initiate anticoagulation for atrial fibrillation. The authors concluded that the use of dalteparin for the initiation of anticoagulation in patients with atrial fibrillation was a safe alternative to the conventional approach using intravenous heparin.

The above studies add data to support the concept of using a low-molecular-weight heparin as an alternative to heparin in patients with nonvalvular atrial fibrillation who undergo cardioversion. Use of this approach in selected patients provides the advantage of preventing the several-day hospitalization needed for administration of intravenous heparin.

[Gregg C. Fonarow, MD, and Eric N. Prystowsky, MD]

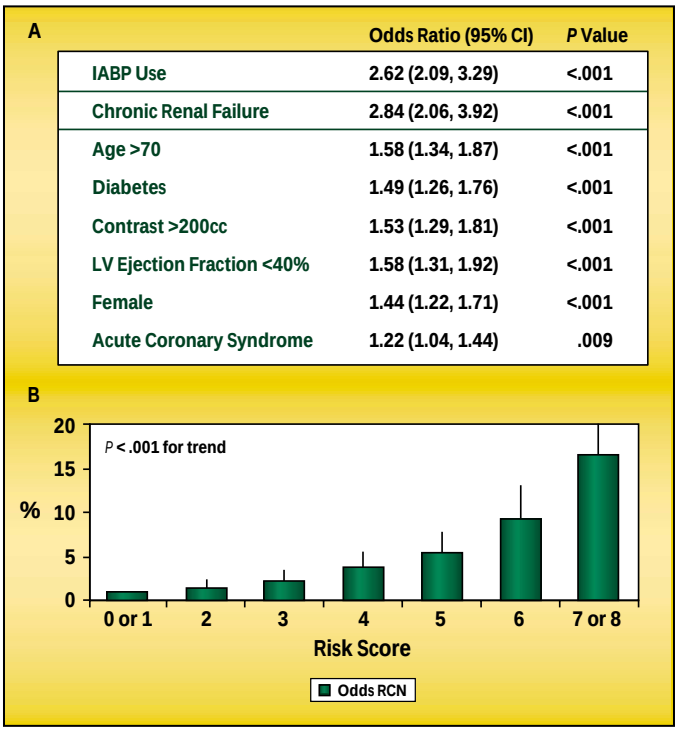


Figure 2. *Multivariate risk score for the development of radiocontrast nephropathy.* **(A)** *Components of the risk score.* **(B)** *Application of the risk score. CI, confidence interval; IABP, intra-aortic balloon pump; LV, left ventricular. Adapted from Mehran et al.*[5]

Cardiorenal Update

This year's meeting of the ACC had a large focus on renal function and its relationship to cardiovascular outcomes. Numerous abstracts dealt with the difficult problem of contrast nephropathy—unfortunately with more mixed results on prevention strategies. Additionally, a growing number of abstracts covered the topic of natriuretic peptides as a central communication system between the heart and the kidneys, which is being leveraged as both a diagnostic and therapeutic breakthrough.

Contrast Nephropathy

Eleven abstracts covered the prediction and prevention of radiocontrast nephropathy (RCN). Mehran and colleagues[5] presented a multifactorial risk score from a database of 9726 patients undergoing percutaneous coronary intervention (PCI). Subjects with 7 or 8 risk factors had an odds ratio > 15, or absolute risk > 50%, of developing RCN (Figure 2), indicating that this score will contribute to the current practice of RCN risk assessment.

Data from multiple RCN prevention trials were presented, the largest of which was CONTRAST (A Prospective, Randomized Placebo-Controlled Multicenter Trial Evaluating Fenoldopam Mesylate for the Prevention of Contrast-Induced Nephropathy). CONTRAST, which was conducted at 28 centers, randomized 315 patients with creatinine clearance < 60 mL/min to fenoldopam (0.1 µg/kg/min for 12 hours) or placebo after PCI.[6] In this study, fenoldopam did not provide a protective effect (Figure 3). In a smaller

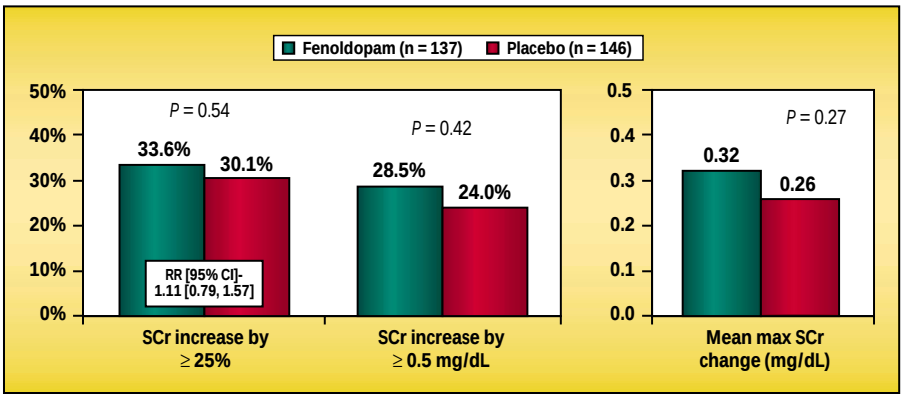


Figure 3. *Primary endpoints in the CONTRAST Trial (A Prospective, Randomized Placebo-Controlled Multicenter Trial Evaluating Fenoldopam Mesylate for the Prevention of Contrast Induced Nephropathy), which failed to find a protective benefit with fenoldopam in radiocontrast nephropathy. Serum creatinine (SCr) levels at both baseline and during the 96° post–drug-administration period were available and analyzed at the central laboratory for 283 of 315 randomized patients (90%). RR, relative risk; CI, confidence interval. Adapted from Stone et al.[6]*

trial (n = 68), Loutrianakis and colleagues[7] found no protective benefit of either fenoldopam or N-acetylcysteine (NAC) over hydration alone. However, the RAPPID study (Rapid Protocol for the Prevention of Contrast-Induced Renal Dysfunction), which randomized 80 patients at risk for RCN to intravenous NAC (150 mg/kg over 30 minutes before PCI and 50 mg/kg over 4 hours after PCI) or matching placebo, had different results.[8] In this study, which evaluated only 10 endpoints, the risk of RCN was reduced with NAC therapy (5% vs 21%, *P* = .05). Briguori and colleagues[9] extended their experience with NAC in a randomized trial of 116 patients. Results showed a protective effect of NAC 1200 mg (compared with 600 mg) given orally twice per day pre- and post-PCI (1.6% vs 12.5%, *P* = .03), again with few (8) endpoints to evaluate. This trial was counterbalanced by a randomized trial by Goldenberg and colleagues,[10] who used NAC 600 mg p.o. t.i.d. pre- and post-PCI in 80 patients with 11 endpoints and found no benefit with NAC (10% vs 8%, *P* = .5). Unfortunately, this meeting represents a microcosm of all the published trials of NAC in RCN prevention, results of which are at a state of complete equipoise. It appears that we do not know the correct dose, route of administration, or timing of administration to create a consistent beneficial effect. A large-scale trial, similar to CONTRAST, is needed for NAC to put this issue to rest.

Natriuretic Peptides: A Key Cardiorenal Communication System

There were 48 abstracts this year concerning the natriuretic peptides. Most of these papers reported on various applications of the two approved peptides for diagnostic use: B-type natriuretic peptide (BNP) and its inactive cleavage fragment, N-terminal pro-BNP (NT-proBNP). The results of the Breathing Not Properly Multinational Study regarding renal function were presented and published in the March 2003 issue of the *American Journal of Kidney Disease*.[11,12] At a creatinine clearance < 60 mL/min/1.73 m^2, BNP was increased in those with and without heart failure. The correlation between BNP and renal function was .21. This suggested that a BNP cutoff of approximately 200 pg/mL was more appropriate for patients with impaired renal function. A report from Hartmann and colleagues[13] stated that the correlation between NT-proBNP and serum creatinine was 0.35 in the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) Study. This meant nearly a doubling of the NT-proBNP levels in heart failure patients with creatinine > 1.4 mg/dL. These and other data suggest that BNP will likely be the preferred test, over the NT-proBNP assay, in heart failure patients who have multiple comorbidities, including renal dysfunction.

St. Francis Heart Study

The St. Francis Heart Study reported the results of electron beam computed tomography (EBCT) for coronary artery calcification (CAC) in 5585 subjects aged 50–70 years followed for 4.3 years.[14] The prediction of cardiac events was clearly related to the CAC score (Figure 4). The relationship between renal dysfunction and vascular calcification is clear; however, it remains unknown how much CAC deposition is related to subtle abnormalities of calcium phosphorus balance versus conventional blood factors, such as lipids. Clearly, EBCT adds to risk assessment with conventional Framingham risk factors. Compounds, such as Renagel®, are currently available that have been proven to reduce the rate of coronary calcium formation. It will be of great interest to see if treatment aimed specifically at preventing coronary artery calcium formation has an impact on the incidence of ischemic events.

The 2003 Scientific Session witnessed continued growth in cardiorenal research, unfortunately with some negative news on the prevention of RCN. However, it seems that the natriuretic peptides will be of value in patients with combined heart and kidney disease.

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

Heart Failure and Cardiovascular Disease

At the satellite symposium "Improving Heart Failure Care: Emerging Strategies for Congested Patients," Dr. James B. Young, of The Cleveland Clinic Foundation, made a general presentation on the challenges that cardiologists must face in treating heart failure patients. He enumerated the following important questions for the practicing clinician.

1) What are the goals in managing hospitalized patients with advanced heart failure and what are the optimal management strategies?
2) What endpoints are important (reduction in pulmonary capillary wedge pressure [PCWP], higher cardiac index, increased relief from symptoms, longer-term morbidity/mortality)?
3) What are the long-term implications of short-term treatments?

Dr. John C. Burnett, of the Mayo Clinic and Foundation in Rochester, MN, presented data on the physiology and pathophysiology of natriuretic peptides in cardiovascular disease. The close and important relationship between the kidney and heart in maintaining optimal cardiovascular health is illustrated in Figure 5. The natriuretic peptides (ANP, BNP, and CNP) have natriuretic, diuretic, vasodilating, renin and aldosterone inhibiting, and anti-fibrotic effects that counter the detrimental effects of the renin-angiotensin-aldosterone system. It is these properties that most likely account for natriuretic peptides' ability to positively affect clinical endpoints of dyspnea and reduction of PCWP, seen relative to the effects of intravenous nitroglycerin, in the VMAC trial (Figure 6).

Dr. Inder Arnad, of the VA Medical Center in Minneapolis, reported on the "Relationship of Natriuretic Peptide Measurements to Prognosis: Do They Have a Role as Inclusion Criteria and Endpoints in Clinical Trials?" BNP measurements have been accepted as an ideal surrogate endpoint for heart failure. Data from the Valsartan Heart Failure Trial (Val-HeFT) have confirmed what was suspected of changes in BNP levels over time: that they are associated with changes in mortality (Figure 7). The author concludes that "BNP levels and LV structure and ejection fraction are robust surrogate endpoints to demonstrate effects of therapies in patients with heart failure. These measures should, therefore, be included as endpoints in all future

Figure 4. *Prediction of future cardiac events according to coronary artery calcium score from the St. Francis Heart Study. Adapted from Arad et al.*[14]

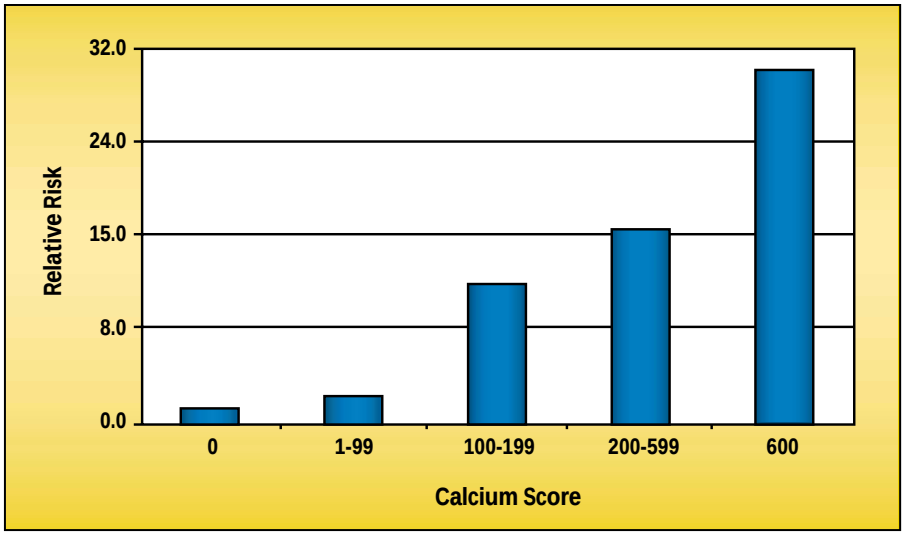
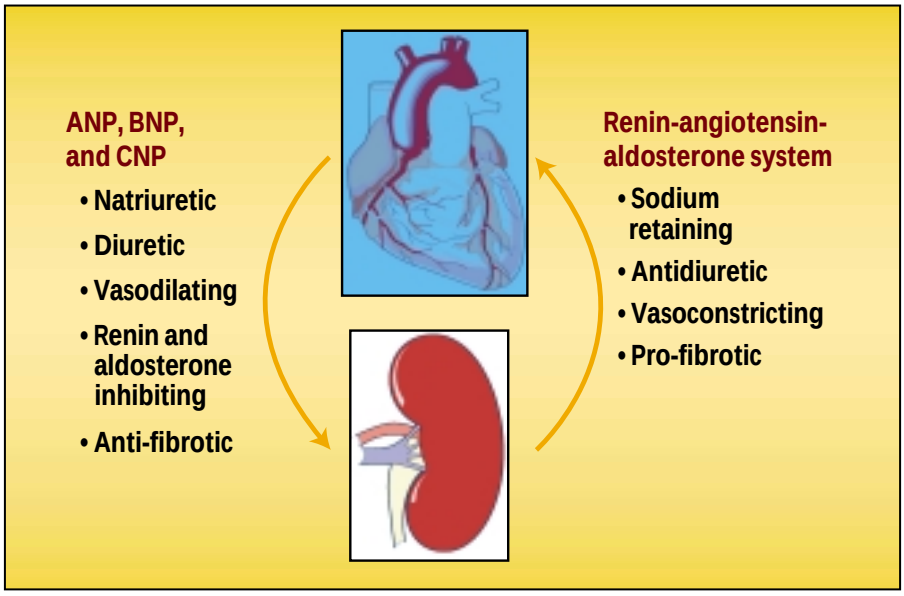


Figure 5. *Illustration of the cardiorenal axis, showing opposing actions of the natriuretic peptides and the renin-angiotensin-aldosterone system. ANP, BNP, CNP: A-, B-, and C-type natriuretic peptide.*



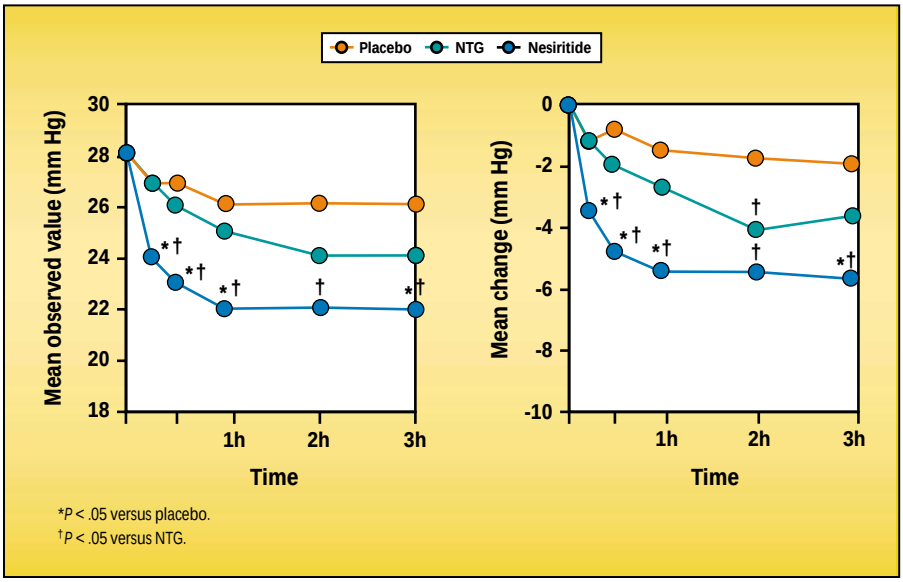


Figure 6. *Summary of primary endpoint data for the VMAC (Vasodilation in the Management of Acute CHF) Trial, showing comparative effects of nesiritide vs intravenous nitroglycerin on pulmonary capillary wedge pressure. NTG, nitroglycerin.*

heart failure clinical trials."

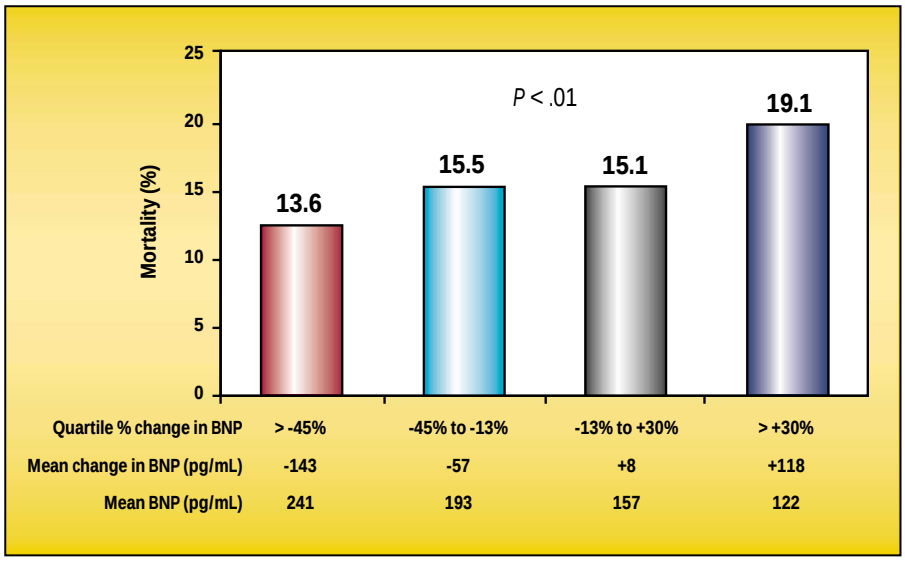
New Information on the Use of Nesiritide

Dr. J. Thomas Heywood's presentation, "Decongesting Patients, Decongesting Hospitals: Can We Do Both?" outlined the Loma Linda Medical Center experience, comparing the lengths-of-stay of patients presenting with acute decompensated heart failure (ADHF) and subsequently treated with nesiritide versus those treated without nesiritide. He found a significant reduction in length-of-stay in patients treated with nesiritide, despite the higher prevalence of comorbidities in their population, including lower ejection fraction (18% vs 24% for the non-nesiritide-treated group), lower systolic blood pressure (113 mm Hg vs 125 mm Hg), tendency toward higher baseline serum creatinine, and higher average age (see Figure 8). These findings, showing an overall average reduction in hospital stay from over four days to less than three days, may result in new accepted practices that will reduce "congestion" in cardiac intensive care units and other heart failure patient-care facilities.

Dr. James A. Hill, Medical Director of Heart Failure/Transplantation at the University of Florida, presented "Novel Approaches to Cardiac Transplant Therapy," a study containing provocative data on the negative impact of elevated pre-transplant pulmonary artery pressures on transplant outcomes. Those patients with pulmonary vascular resistance (PVR) < 2.5 Wood units had a 90-day mortality rate of 6.9% versus those patients with PVR > 2.5 at baseline, which could not be reduced with nitroprusside, who had a mortality rate of 40.6%. These patients often require long-term infusions of vasodilators as a bridge to transplant. In the case of nitroglycerin, one study showed an almost 50% rate of tolerance within a 24-hour period in these types of patients (see Figure 9).

Dr. Hill also presented an evaluation of the effect of nesiritide plus inotropes in patients with refractory pulmonary hypertension who were already undergoing treatment with milrinone and diuretics. This is a clinical situation not infrequently seen in patients awaiting transplant or those who are not transplant candidates but have refractory heart failure. In this setting, nesiritide was effective in reducing pulmonary artery pressure, PCWP, and weight, with no

Figure 7. *Results of the Valsartan Heart Failure Trial (Val-HeFT), showing corresponding rise in rates of mortality and B-type natriuretic peptide levels. BNP, B-type natriuretic peptide.*



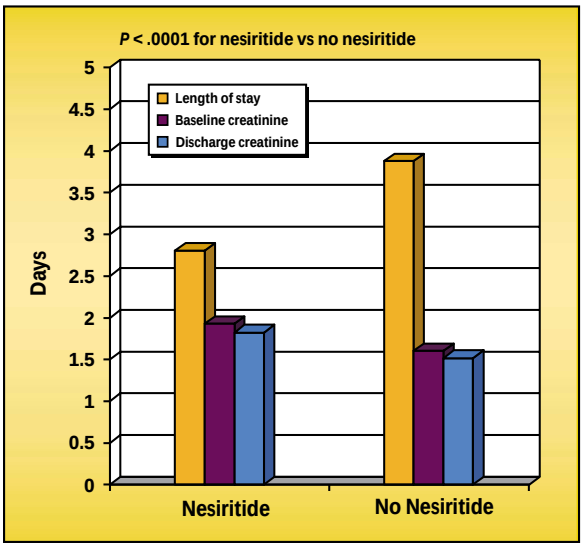


Figure 8. *Comparison of lengths of hospital stay and serum creatinine levels in heart failure patients receiving nesiritide versus controls in the Loma Linda Medical Center experience.*

change in mean blood pressure (Figure 10). Dr. Hill presented data on the use of nesiritide as an aid to bridging to transplant at the University of Florida. Seven transplant candidates with pulmonary hypertension resistant to medical therapy were treated with nesiritide for an average of 25 days. The nesiritide was well-tolerated, with only one patient requiring a dose adjustment. Patients overall showed a marked improvement in hemodynamics (see Table 2).

The ADHERE Trial

Dr. Gregg C. Fonarow, Director of the Ahmanson-UCLA Cardiomyopathy Center, provided a progress report of the Acute Decompensated Heart Failure National Registry (ADHERE). The purpose of the ADHERE registry is to investigate the processes and outcomes of care in a national sample of patients with acutely decompensated heart failure and to assist with quality-of-care improvement for patients hospitalized with ADHF. Over 43,000 patients have been enrolled in this registry at over 250 medical centers. The clinical presentations of these patients are summarized in Table 3.

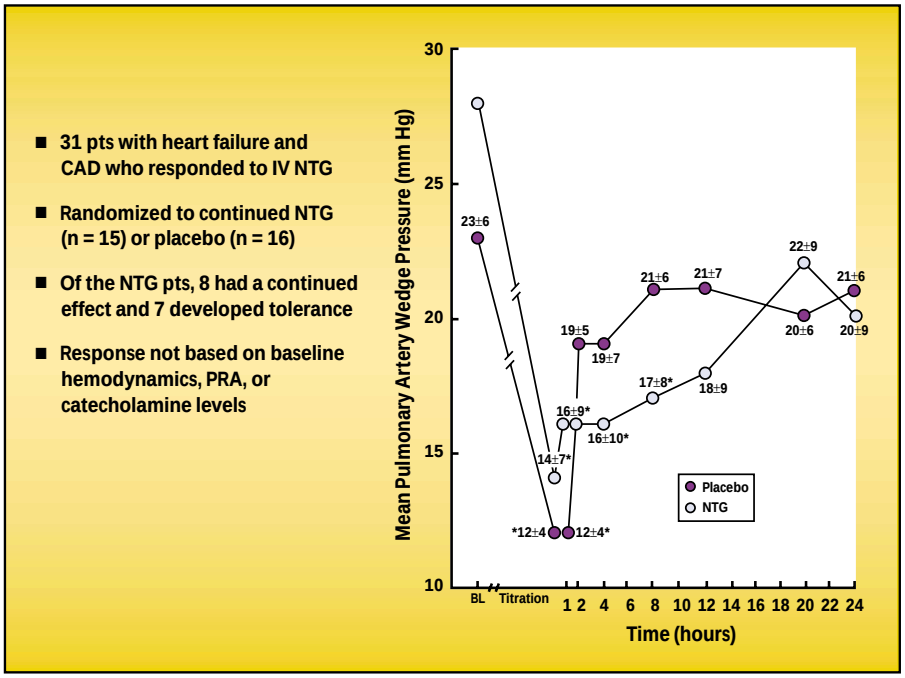
A large variance in the care of ADHF patients has been observed in this registry, as indicated by the differences in ß-blocker use and mortality between institutions. Additional variance in the use of intravenous vasoactive medications (nitroglycerin–10%, nesiritide–8%, dopamine–7%, dobutamine–6% and milrinone–3%) was also of particular interest. Ultimately, the ADHERE registry will yield a tremendous amount of clinically important information, helping to further refine and standardize the course of treatment for ADHF.

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

Anglo-Scandinavian Cardiac Outcomes Trial: Lipid-Lowering Arm

The approach to lipid-lowering therapy has evolved over the past several decades, from consisting solely of treatment of high cholesterol levels to now encompassing a comprehensive risk-reduction strategy for patients who have or are at risk for coronary heart disease (CHD). Although we have identified high-risk populations that warrant lipid-lowering therapy even in the

Figure 9. *Use and tolerance of long-term intravenous nitroglycerin in pretransplant heart failure patients. IV NTG, intravenous nitroglycerin; PRA, plasma renin activity; pts, patients. Adapted with permission from Elkayam et al., Incidence of early tolerance to hemodynamic effects of continuous infusion of nitroglycerin in patients with coronary artery disease and heart failure.* Circulation. *1987;76(3):577-584.*



Nesiritide Plus Inotropes

- 10 heart failure patients taking milrinone (≥ 0.375 μg/kg/min) and furosemide (160 mg) with resistant pulmonary hypertension had nesiritide (2 μg/kg/min bolus and 0.01 μg/kg/min) added to regimen
- Repeat hemodynamics at 24 hours
  - No change in mean blood pressure, SVR, CI, PVR
  - Significant ($P < .052$) drop in:
    - Mean PAP: **45.1 mm Hg to 37 mm Hg**
    - Mean PCWP: **32.8 mm Hg to 23.1 mm Hg**
    - Heart rate: **91 bpm to 84 bpm**
    - Weight: **83.1 kg to 81.7 kg**

Figure 10. *Scenario and results for adding nesiritide to a pre-transplant or refractory heart failure therapy regimen. CI, cardiac index; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance. From a presentation by David Smull, MD at the 2002 Annual Meeting of the Heart Failure Society of America.*

Table 2
Hemodynamic Data in Patients Treated with Nesiritide for an Average of 25 Days Prior to Transplant

	Before Nesiritide	Immediately After Nesiritide	Immediately Prior to Transplant
Pulmonary artery systolic pressure (mm Hg)	59 ± 7.3	34 ± 7.5	27.2 ± 4.2
Pulmonary artery diastolic pressure (mm Hg)	29 ± 6.1	15.6 ± 6.8	12.6 ± 2.8
Mean pulmonary artery pressure (mm Hg)	39.7 ± 6.5	22.1 ± 6.8	17.8 ± 1.8

Table 3
ADHERE Clinical Presentation

Any dyspnea (%)	90
Dyspnea at rest (%)	35
Fatigue (%)	34
Peripheral edema (%)	67
Initial ECG assessed (%)	95 (n=26,194)
A Fib (%)	20
Initial CXR assessed (%)	90 (n=24,833)
Pulmonary congestion (%)	76
Initial serum sodium assessed (%)	98 (n=26,999)
Mean serum sodium (mmol/L)	138
Initial serum creatinine assessed (%)	98 (n=27,024)
Creatinine >2.0 mg/dL (%)	20
Initial BNP assessed (%)	17 (n=4634)
Median BNP (pg/mL)	786
LVEF assessed (%)	56 (n=15,462)
LVEF < 40% or Mod/Sev (%)	49

The ADHERE Registry Third Quarter 2002 Benchmark Report. 2002:12.

absence of CHD (eg, those with diabetes), other high-risk groups have yet to be fully defined. We have known for many years that patients with hypertension are at increased risk for cardiovascular events and that blood pressure reduction decreases this risk. What needed to be determined was whether cholesterol-lowering therapy could provide an additional reduction in cardiovascular events in patients who have optimal blood pressure control and normal to mildly elevated cholesterol levels. This hypothesis was tested in the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).

ASCOT was a multicenter, international trial involving two treatment comparisons in a factorial design:[15]

1. A prospective, randomized, open-label trial comparing two antihypertensive regimes
2. A double-blind, placebo-controlled trial of a lipid-lowering agent in0 a subgroup of those hypertensive patients.

A total of 19,341 patients from Denmark, Finland, Iceland, Ireland, Norway, Sweden, and the United Kingdom were enrolled in ASCOT and randomized to one of two different antihypertensive regimens. Results of the antihypertensive trial are expected in 2004.

The lipid-lowering arm of ASCOT included patients with hypertension (blood pressu re ≥ 160/90 mm Hg treated or ≥ 140/90 mm Hg untreated) who had no known CHD but at least three cardiovascular risk factors in addition to hypertension. Participants were aged 40 to 79 years and had total cholesterol levels of 250 mg/dL or lower. A total of 10,297 subjects were randomized to atorvastatin, 10 mg/d, or placebo, and followed for the combined primary outcome of nonfatal myocardial infarction and fatal CHD. Blood pressure con-

Table 4
ASCOT Primary Endpoints

Endpoint	Atorvastatin, %	Placebo, %	Hazard Ratio	*P*
MI/fatal CHD	1.9	3.0	0.64	.0005

MI, myocardial infarction; CHD, coronary heart disease.

Table 5
ASCOT Secondary Endpoints

Endpoint	Atorvastatin, %	Placebo, %	Hazard Ratio	*P*
Total CV events/procedures	7.5	9.5	0.79	.0005
Total coronary events	3.4	4.8	0.71	.0005
All-cause mortality	3.6	4.1	0.87	.16
CV mortality	1.4	1.6	0.90	.50
Fatal/nonfatal stroke	1.7	2.4	0.73	.02
Fatal/nonfatal CHF	0.8	0.7	1.13	.58

CV, cardiovascular; CHF, congestive heart failure.

trol was achieved in both treatment groups; the average blood pressure was 136/80 mm Hg.

In September 2002, the Data and Safety Monitoring Board recommended that the lipid-lowering arm of ASCOT be prematurely terminated because the atorvastatin arm had achieved a highly significant 36% reduction in the primary endpoint (Table 4), as well as a significant reduction in stroke (Table 5), after a median follow-up of 3.3 years.[16]

The investigators calculated that if ASCOT had continued through its planned 5-year duration, atorvastatin would have reduced CHD incidence by approximately 50% in this study population. No serious adverse events were seen in either arm.

Commentary

Data from the lipid-lowering arm of ASCOT demonstrate that treating patients with well-controlled hypertension, who have normal or mildly elevated cholesterol levels, with atorvastatin results in a 36% lower risk of nonfatal myocardial infarction or fatal CHD death and a 27% lower risk of stroke. The benefits of treatment with atorvastatin were achieved above and beyond optimally treating elevated blood pressure in these patients.

There are more than 16 million adults in the United States who have high blood pressure, no recognized CHD, and normal to mildly elevated cholesterol levels in whom the use of statins will substantially lower the risk of cardiovascular events. The number needed to treat for the reduction of a fatal or nonfatal CV event is 294 patients treated for 1 year.

[Karol E. Watson, MD, PhD]

Time to Treatment in Percutaneous Coronary Intervention

A fundamental tenet of thrombolytic therapy is that "time is muscle." This idea has its roots in the original and seminal contributions of Reimer and Jennings. Their animal model of occlusion and reperfusion established the "wave front phenomenon" of myocardial ischemic cell death.[17] Myocardial salvage is a time-dependent phenomenon with a relatively narrow window of opportunity. The majority of the benefit in terms of mortality reduction and salvage occurs within the first 3 hours, and most of that within the first hour (see Figure 11).[18] Although late reperfusion may still be of substantial benefit, it depends on the presence and extent of ongoing ischemia and collateral circulation. In addition, the

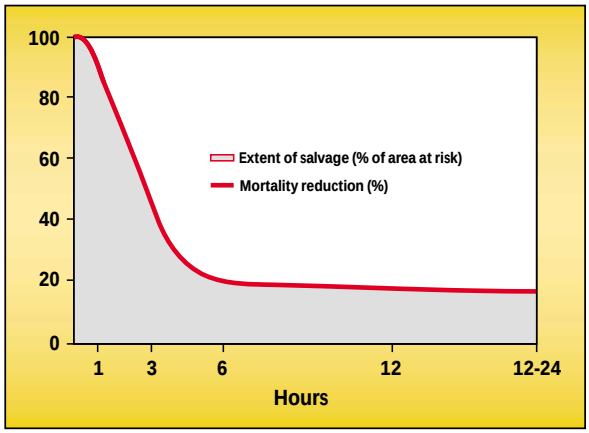


Figure 11. *Hypothetical construct illustrating the relationship between the time-to-treatment with reperfusion therapy, reduction in mortality, and myocardial salvage. The solid line depicts mortality reduction with the area below reflecting extent of salvage. The major benefit is achieved within three hours, with the first hour considered the "golden window of opportunity." In this figure, late reperfusion (12 to 24 hours after onset of symptoms) is shown to be possibly beneficial, particularly in patients with continued or stuttering pain in whom collaterals may play a role and among whom the precise timing of the onset of myocardial infarction is difficult to determine. Reproduced with permission from Gersh et al.*[18]

"late, open-artery hypothesis," in which late reperfusion of an occluded artery results in mortality reduction, independent of any effect on myocardial salvage, remains an intriguing and attractive concept currently undergoing study in randomized trials.[19,20,21]

The relationship between time to treatment and outcomes has been consistently proven in multiple trials of thrombolytic therapy.[18] Experimental evidence also exists suggesting that t-PA is superior to streptokinase in the dissolution of older clots.[22] Nonetheless, the average time to treatment in contemporary fibrinolytic trials is approximately 2.5 to 3.0 hours, and there has been no improvement over the last decade[23] (Figure 12).

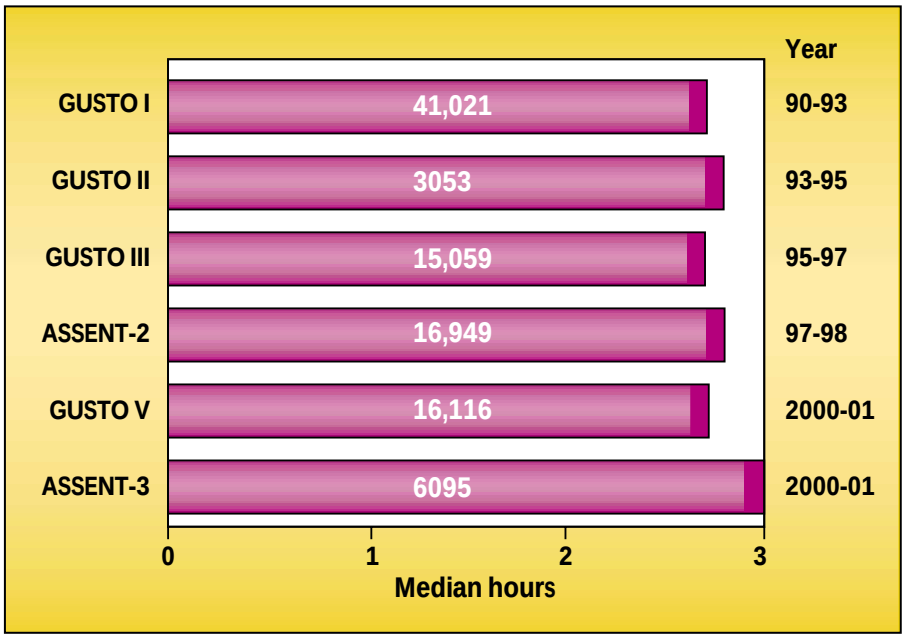


Figure 12. *The median time to treatment in contemporary fibrinolytic trials remains stalled at approximately 3 hours after the onset of symptoms. Reproduced with permission from Welsh et al.[23]*

One would expect that in patients undergoing primary percutaneous coronary intervention (PCI), the same relationship between time to treatment and outcomes would exist. Somewhat surprisingly, studies in this regard have not been consistent. In the PAMI (Primary Angioplasty and Myocardial Infarction) trial, major outcomes did not differ according to door-to-balloon and symptom-to-balloon time.[25,26] In contrast, analyses from the GUSTO-IIb trial and other studies demonstrated a strong relationship between treatment delay and mortality.[27,28]

An explanation for these discordant results was provided by an important study from Antoniucci and associates, at the Careggi Hospital in Florence, Italy. Patients undergoing primary PCI were stratified according to characterizations of either low-risk or greater than low-risk, according to the Thrombolysis in Myocardial Infarction (TIMI) Phase II trial criteria.[29,30] Seventy-one percent of patients were categorized as not low-risk and 29% as low-risk. The 6-month mortality rate was 9.3% for not low-risk patients and 1.3% for low-risk patients (Figure 13). Among patients who were not low-risk, unadjusted mortality increased from 4.8%, at a time-to-reperfusion of 2 hours, to 12.9%, with a corresponding increase in time-to-reperfusion up to six hours, whereas the mortality of the low-risk group was constant, despite an increased time-to-reperfusion. Among those at not low-risk, there was a fairly steep gradient relating mortality to time to treatment, and one has to assume that patients in other studies that did not show a relationship between time to reperfusion and outcome were at lower risk in comparison to those in GUSTO-IIb and subsequent studies.

Resolution of this controversy would be reassuring, since the traditional paradigm of "salvage as a time-dependent phenomenon" is logical, and it is difficult to conceive of an alternative explanation. It is possible, however, that in patients receiving thrombolytic drugs, the relationship between the duration of symptoms and treatment is somewhat stronger than in patients undergoing primary angioplasty, but this requires further validation.

Several abstracts presented at the recent Annual Scientific Session of the American College of Cardiology, as well as other recently published articles, address the issue of time to treatment in patients undergoing primary PCI, from a number of perspectives.

Dr. Bruce R. Brodie of the LeBauer Cardiovascular Research Foundation and the Moses Cone Heart and Vascular Center in Greensboro, NC, utilizing the large CADILLAC trial database of patients treated within 12 hours of symptom onset, demonstrated 30-day mortality rates of 0.9%, 2.3%, and 2.2.% in patients treated within 3 hours, 3 to 6, and ≥ 6 hours respectively (P = .04); 1-year mortality rates were 2.5%, 4.5%, and 4.8% respectively (P = .04); and there was a trend towards a lower rate of reinfarction in patients treated early.[31] Moreover, the same group of investigators has demon-

strated a strong relationship between the time to treatment, the extent of ST-segment resolution, and mortality, implying that the time to treatment may have an impact on myocardial perfusion and microvascular function.[32] Somewhat disconcertingly, only 28% of patients were treated within 3 hours.

Dr. Tukefumi Takahashi and colleagues from Tokushima Red Cross Hospital in Komatsuhima, Japan, demonstrated that treatment delay was associated with increased microvascular dysfunction as assessed by Doppler measurements of coronary flow reserve.[33] Dr. William J. French and associates of Harbor-UCLA Medical Center in Torrance, CA, provided additional confirmatory evidence utilizing the large National Registry of Myocardial Infarction (NRMI) database of over 30,000 patients undergoing primary PCI.[34] Overall, less than one third of "higher-risk" patients had door-to-balloon times within the recommended 90-minute window. Moreover, just over half the patients had door-to-balloon times of less than or equal to 120 minutes. Two other studies, from the United States and Holland, also demonstrated that delays in revascularization were associated with adverse outcomes.[35,36]

In the DANAMI-II trial in Denmark, 30-day rates of death, myocardial infarction, and stroke were doubled in patients receiving primary PCI 4-12 hours after the onset of symptoms in comparison to patients treated within 1.5 hours.[35] In another trial of primary PCI with and without adjunctive t-PA, a strong association between treatment delay and left ventricular dysfunction was noted.[37] Two studies from the CADILLAC database[38,40] have emphasized differences in time to treatment according to the time of day at onset, or whether the patients presented on a weekday versus the weekend (see Figure 14). Hospital arrival at night, especially in the early morning hours and on weekends, was associated with a longer time to treatment and worse outcomes, including mortality, major adverse coronary events, and reinfarction. Interestingly, patients presenting with acute myocardial infarction tend to have a higher incidence of thrombus and pre-PCI TIMI 0/1 flow late in the day and during the early morning hours, suggesting circadian variations in thrombogenicity.[41]

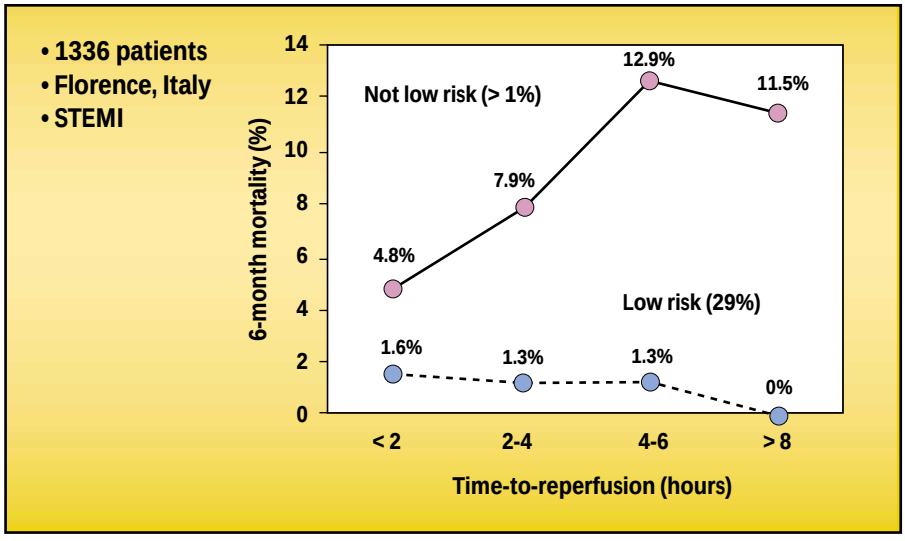
A recent study from a large North American database demonstrated that door-to-balloon times were prolonged more frequently in older patients, women, patients with contraindication to fibrinolysis, and those without chest pain on admission (Figure 15). Delay was also more common with transfer from another hospital and with presentation outside the hours of 8 a.m. and 4 p.m.[24]

It would appear that in patients undergoing primary PCI, as with lytic therapy, time is of the essence. Whether patients with a longer duration of symptoms and older thrombi benefit to a greater extent with primary PCI versus thrombolytic therapy is unproven, but there was the suggestion of such an effect in the GUSTO IIb Trial.

The idea that primary PCI is the best form of reperfusion therapy is well accepted, particularly in higher risk patients, but the efficacy of the former depends to a large extent upon the nature and experience of the institution and individual operators.[41] Moreover, in some centers, logistical constraints may be influenced by the time of day and the day of the week on which the patient presents. The key is for each institution to analyze its own experience and not to rely upon published experience from the randomized control trials and registry series[42] in which the majority of participants may exhibit both expertise and enthusiasm.

What is clear is that we do not treat enough patients with reperfusion ther-

Figure 13. *Six-month mortality as affected by time to reperfusion in low- and not-low-risk patients. Patients not at low risk were those age 70 years or older, those with anterior myocardial infarction, or those with a heart rate of 100 bpm or more on admission. In patients not at low risk, the mortality after successful primary percutaneous intervention is related to the delay from symptom onset to treatment. This does not appear to be a factor in patients at low risk, in whom mortality is extremely low, irrespective of time to treatment. Reproduced with permission from Cannon et al.[28]*



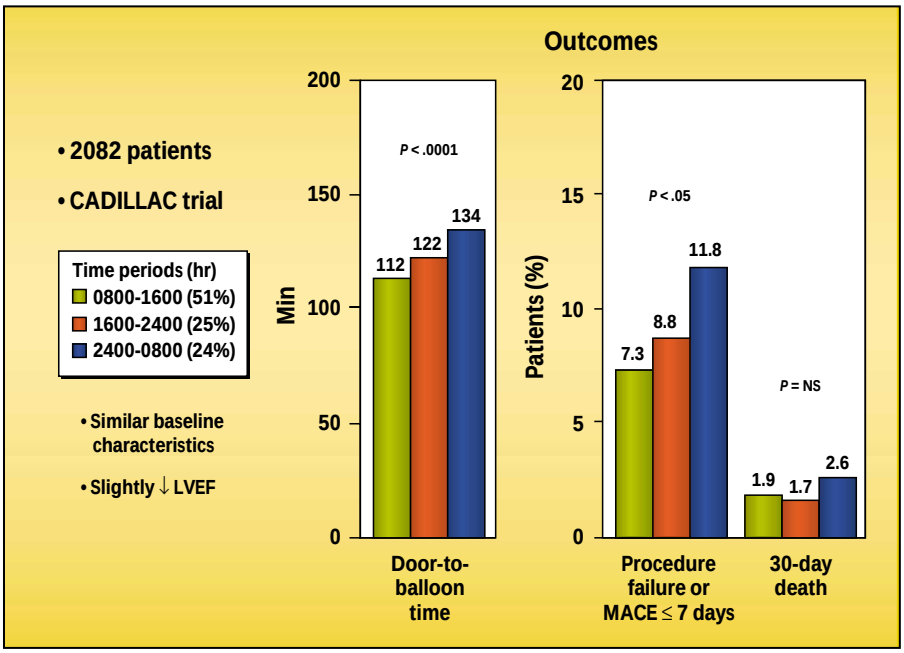


Figure 14. *Illustration of the results of primary percutaneous coronary intervention and the timing of treatment in 2082 patients in the CADILLAC trial. Fifty-one percent of patients were treated between the hours of 8 a.m. and 4 p.m. and 24% after midnight and before 8 a. m. Baseline characteristics among patients treated during the three time periods were similar other than a slightly reduced left ventricular ejection fraction in patients presenting after midnight. The graphs demonstrate door-to-balloon times in patients treated after 4 p.m., and particularly after midnight, along with a corresponding increase in procedure failure or major adverse cardiac events (MACE), but with no significant difference in mortality. Adapted with permission from Sadeghi et al.*[38]

apy and that when we do, it is done too late.[43] In the case of primary PCI, the role of this therapeutic approach in centers without on-site cardiac surgery versus facilitated primary PCI is subject to ongoing debate.[44] The proliferation of studies demonstrating that time to treatment is an important predictor of outcomes in primary PCI provides additional impetus for these discussions. It is hoped that the several trials that are under development or currently ongoing will provide us with definitive answers. Perhaps the key to reperfusion therapy in 2003 is not just the nature of the therapy, but the efficacy of its delivery.

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

Drug-Eluting Stents

This year's ACC Scientific Sessions included a number of clinical trial results that add to our knowledge about the safety and efficacy of drug-eluting stents (DES). At present, sirolimus and paclitaxel are among the most promising agents for stent-based elution.

First-In-Man: 3-Year Follow-Up

The first safety/feasibility study of DES was a single-center experience, the First-In-Man (FIM) Study, addressing the use of two different formulations (slow-release and fast-release) of the sirolimus-coated Bx Velocity stent (Cypher®, Cordis Corporation, Brussels, Belgium) in patients undergoing elective percutaneous coronary intervention (PCI).[45] All patients received the sirolimus-eluting stent (SES) in *de novo* lesions < 18 mm in length, in vessels 3.0-3.5 mm in diameter. At 4 months, intravascular ultrasound (IVUS) demonstrated minimal neointimal hyperplasia in both the slow-release and fast-release Cypher® groups and quantitative coronary angiography (QCA) demonstrated an in-stent late loss of 0.09 ± 0.3 mm and -0.02 ± 0.3 mm for the slow and fast-release groups respectively. Binary in-stent restenosis (≥ 50%) was not observed, and no major adverse cardiac events (MACE) occurred up to 8 months follow-up. In the previously reported 2-year follow-up results, diameter stenosis for the slow-release formulation was 1.4 %, while the fast-release was 14.6% (see Figure 16).[46,47] Percent obstruction measurements of neointimal hyperplasia within the stented segment in 28 patients remained minimal after 2 years (9.90 ± 9 mm^3 fast-release; 10.35 ± 9.3 mm^3 slow-release). Analysis of plaque volume at proximal and distal edges also demonstrated no "edge effect" over time. Evaluation of 2-year clinical outcomes revealed no deaths, 1 non-ST segment elevation myocardial infarction, a non-target ostial circumflex artery progression and 1 target vessel revascularization (TVR) for target lesion progression. Follow-up extended to 39 months and demonstrated that no new events had occurred in the intervening year. Event-free (death, myocardial infarction [MI], coronary artery bypass graft [CABG], repeat percutaneous coronary intervention [Re-PCI]) survival at 36 months for FIM patients remained at 90.1%. Eduardo Sousa, MD, Institute Pazzanese, São Paulo, Brazil, who presented the 3 year results concluded "early clinical benefits observed after implantation of the sirolimus Bx Velocity stent appear durable at late follow-up of 3 years…concern about potential late complications such as late occlusion, thrombosis, aneurysm, late restenosis, or rebound hyperplasia has not been confirmed."

Two-Year RAVEL Results

The RAVEL trial randomized 238

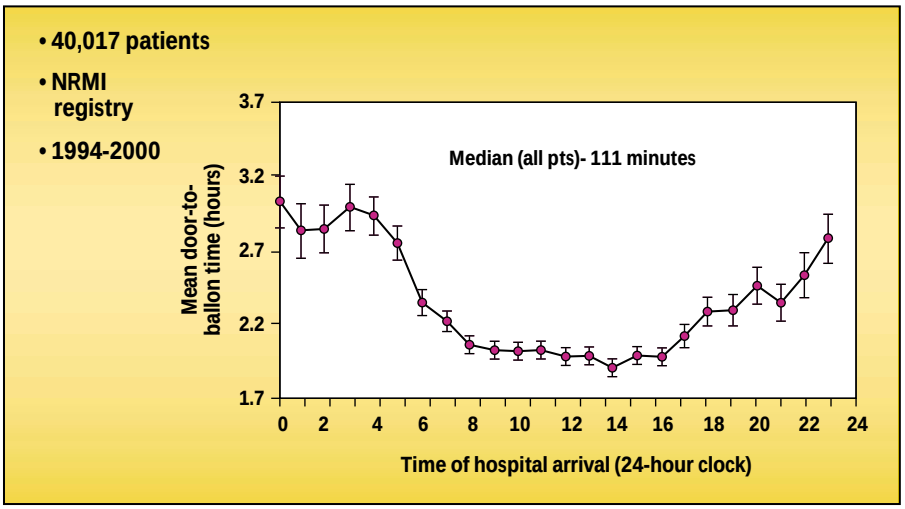


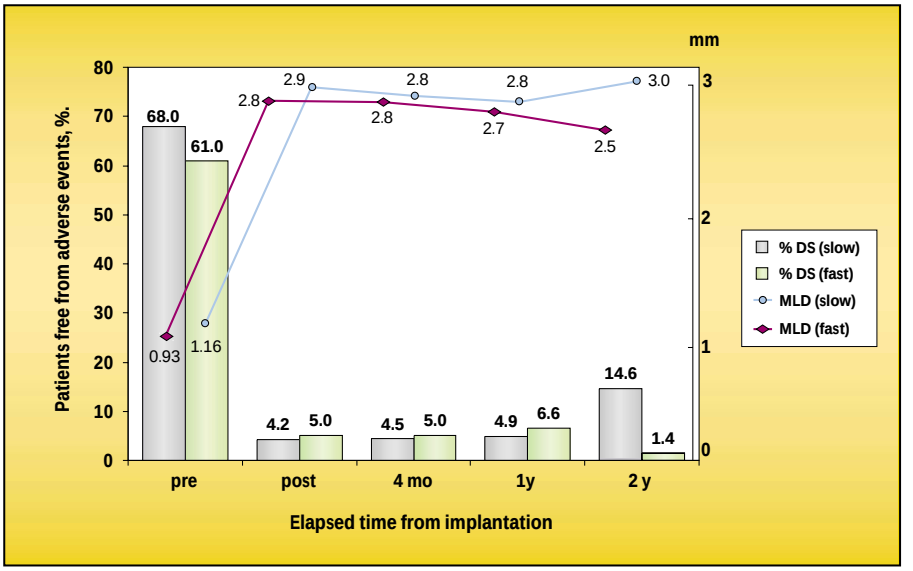
Figure 15. *Time of day and variation in door-to-balloon time. Time of day (24-hour clock) is plotted on the x-axis and the mean delay in hours is plotted on the y-axis. Point estimates indicate the mean door-to-balloon times, with standard deviation indicated above and below as horizontal lines. Delay was more common with transfer from another hospital and with presentation outside the hours of 8 a.m. to 4 p.m. Reproduced with permission from Angeja et al.*[24]

patients undergoing revascularization of single *de novo* lesions in native coronary arteries (vessel diameter 2.5-3.5 mm; lesion length < 18 mm) to either an uncoated Bx Velocity stent, or a sirolimus-eluting Bx Velocity (Cypher®) stent.[48] At 6 months, neointimal proliferation was markedly suppressed in the Cypher® stent group, as evidenced by a mean late luminal loss on QCA of -0.01 ± 0.33 mm (vs 0.80 ± 0.53 mm in the bare stent group; $P < .001$). None of the patients in the Cypher® group, compared with 26.6% in controls, had binary (≥ 50%) angiographic restenosis ($P < .001$) at 6 months. Major cardiac events to one year were composed predominantly of target vessel revascularization (5.8% Cypher® vs 28.8% control; $P < .001$). No stent thromboses were reported. Edge effect (promotion of neointimal hyperplasia) at the stent edges was not observed. Incomplete stent apposition (malapposition) by IVUS was more common in Cypher® patients (21%) than in controls (4%; $P < .05$) at late follow-up.[49] Follow-up to 2 years in the RAVEL trial reveals sustained clinical and angiographic benefit according to Marie-Claude Morice, MD, Institut Cardiovasculaire Paris Sud, Paris, France. At 1-year follow-up, repeat PCI of the target lesion was not observed for the Cypher® patients (n = 120) as compared with 13.6% of controls (16/118). At 720 days, there were no cardiac deaths and event-free (death, MI, CABG, Re-PCI) survival was 90.0% for the Cypher® patients versus 80.5% for controls. Target lesion revascularization was low at 2.5% and no stent thromboses were observed in Cypher® patients. Dr. Morice concluded that "the early favorable results of RAVEL were sustained at 2 years...one can say now that the revolution has become reality."

Update on the SIRIUS Trial

In the SIRIUS trial, 1101 patients with de novo lesions were randomized to either the Cypher® or uncoated Bx Velocity stent.[50] A total of 850 patients were included in the angiographic substudy. Whereas the suppression of binary (≥ 50%) in-stent restenosis was striking (3.2% Cypher® vs 35.4% control; $P < .001$), the reduction of in-segment (includes 5 mm margins proximal and distal to the stent edges) restenosis was slightly less impressive (8.9% vs 36.3% respectively; $P < .001$). The primary endpoint, target vessel failure (death, MI, or TVR) at 9 months, occurred in 46 Cypher® patients (8.6%) and in 110

Figure 16. *Two-year follow-up results from First-In-Man (FIM) trial of the Cypher™ stent. DS, diameter stenosis; MLD, minimal lumen diameter.*



controls (21.0%; $P < .001$). Similar to the RAVEL trial, an IVUS analysis of 181 patients enrolled in the SIRIUS trial demonstrated an increased incidence of late-stent malapposition at 8 months in the Cypher® group (19% vs 9% controls; $P < .05$). See figure 17. Both European (E-SIRIUS, n=352) and Canadian (C-SIRIUS, n=100) versions of the SIRIUS trial are ongoing and the preliminary results of C-SIRIUS were presented by Erick Schampaert, MD, Sacred Heart Hospital, Montreal, Quebec, Canada. The purpose of C-SIRIUS was to assess safety and effectiveness of Cypher® (vs uncoated Bx Velocity stent) for maintaining in-stent minimal lumen diameter (MLD) at 8 months post-deployment (primary endpoint) in *de novo* native coronary lesions. One hundred patients (mean age 60.5 years) with target lesion length ≥ 15 mm and ≤ 32 mm in target vessels of 2.0-3.0 mm in diameter were randomized. At 8 months, angiographic follow-up was complete in 88% of patients and the in-stent MLD for Cypher® patients was 2.46 mm compared with 1.50 mm for the bare stent controls. Late loss (.09 mm for Cypher® vs 1.01 mm for controls), and restenosis (0% for Cypher® vs 41.9% for controls), were significantly ($P < .001$) reduced by the study device. In-lesion measurements showed similar advantages for the Cypher® stent (MLD 2.16 mm vs 1.41 mm in controls; late loss 0.10 mm vs 0.76 mm in controls; restenosis 2.3% vs 44.2% in controls). Regarding the relatively high angiographic and clinical restenosis rates in the control group, Dr. Schampaert stated, "patients with long lesions in small vessels are at very high risk for angiographic and clinical restenosis…the positive results of the RAVEL and SIRIUS trials can now be extended to patients with long lesions in smaller vessels."

12-Month TAXUS-II Results

Both polymer-based and non-polymer-based elution strategies have been employed with the drug paclitaxel. The TAXUS trials have utilized a polymer-based strategy for paclitaxel elution. TAXUS I was a pilot trial that randomized 61 patients with de novo coronary lesions to either the paclitaxel-eluting polymer-coated NIRx (Boston Scientific Corporation, Natick, MA) stent or the non-paclitaxel eluting polymer coated NIRx.[51] The mean percent diameter stenosis at 6 months was 13% in the paclitaxel-eluting (TAXUS) stent and 27% in the non-paclitaxel controls ($P < .001$). Binary angiographic restenosis rates were 0% and 10% respectively ($P < .001$). Two different release strategies (moderate or slow) for paclitaxel were compared to the non-eluting NIRx stent in the TAXUS II trial. TAXUS II enrolled 537 patients with short lesions (< 12 mm length) in large vessels (3.0-3.5 mm diameter).[52] The primary endpoint was percent in-stent net volume obstruction as assessed by IVUS at 6 months. In the moderate-release (MR, 2-week elution) arm, in-stent net volume obstruction was 7.8% in the TAXUS stent group versus 20.5% in controls ($P < .001$). The in-segment restenosis rate was 8.6% and 23.8%, respectively ($P < .001$), and the TVR rates were 6.2% and 17.7%, respectively ($P < .007$). Similar results were observed in the slow-release (SR, 4 week elution) arm, with in-stent net volume obstruction of 7.8% in the TAXUS stent group and 23.2% in controls ($P < .001$). The in-segment restenosis rates were 5.5% and 20.1%, respectively, and TVR was reduced (7.7% TAXUS vs 14.3% controls). The purpose of the 12-month analysis (presented by Antonio Colombo, MD, EMO Centro Cuoro Columbus, Milan, Italy), was to determine if the benefit present at 6 months was maintained to 12 months following discontinuation of clopidogrel. Continued benefit was indeed observed for the TAXUS stent, which demonstrated a cumulative incidence of MACE of 10.9% and 9.9% for SR and MR respectively, versus 21.7% for controls. Other benefits observed for TAXUS stents included TVR rates of 10.1% and 6.9% (SR and MR, respectively) versus 17.5% for controls, and target lesion revascularization rates of 4.7% and 3.8% (SR and MR, respectively) compared with 14.4% for controls. With regard to the sustained beneficial effects on MACE-free survival at 12 months, Dr. Colombo concluded, "…TAXUS stents prevent rather than delay in-stent restenosis." Ongoing trials with the TAXUS stent (TAXUS IV, V, VI) will evaluate a wider variety of coronary lesions (diameter 2.5-3.5 mm, lengths up to 40 mm) and provide more valuable clinical data regarding the benefits of this drug-eluting stent.

The issue of subacute stent thrombosis with the Cypher™ stent in the community setting has been raised. Whether the incidence of thrombosis is greater than that observed in clinical trials is not clear. Drug-eluting stent implantation therefore should follow manufacturer's recommendations.

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

DELIVER Trial

On the heels of previous reports touting the benefits of both sirolimus and paclitaxel drug-eluting stents in the prevention of restenosis, "A Randomized Comparison of Paclitaxel-Coated Versus Metallic Stents for the Treatment of Coronary Lesions" (DELIVER) was presented by Dr. William O'Neill at the William Beaumont Hospital, Royal Oak, MI. The aim of the study was to

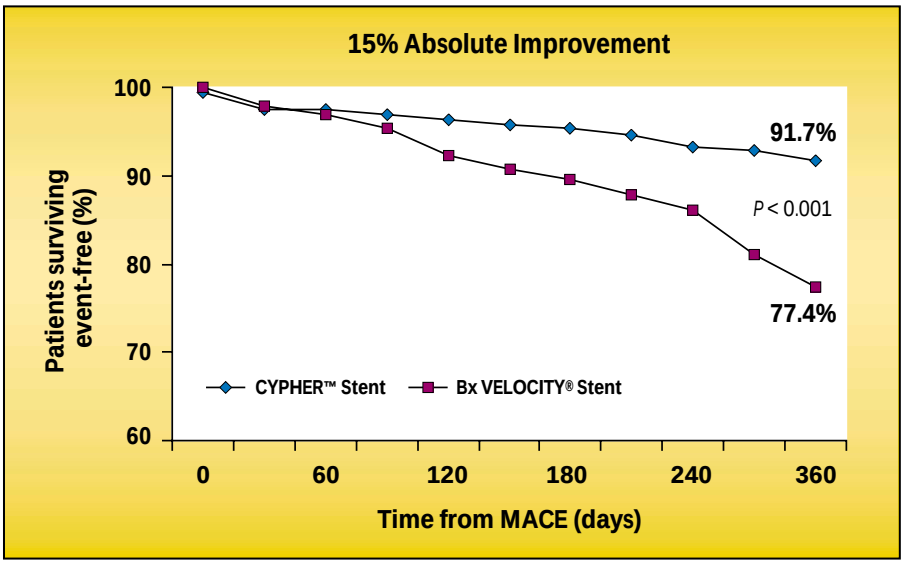


Figure 17. *Event-free survival (EFS) from major adverse cardiac events (MACE) to 12 months in the SIRIUS trial.*

assess the safety and efficacy of the rapid-exchange ACHIEVE drug-coated stent in the treatment of *de novo* lesions in native coronary arteries (2.5-4.0 mm in diameter, lesion length ≤ 25 mm) in comparison to the Multi-Link PENTA™ stent (both stents, Guidant Corporation, Indianapolis, IN). Accordingly, 1043 patients undergoing percutaneous coronary intervention (PCI) were randomly assigned to receive the ACHIEVE or the PENTA stent. Up to two native vessels were treated in each patient, one target and one non-target lesion, with only one de novo lesion per vessel. Peri-procedure, all patients received aspirin, clopidogrel, and heparin in standard fashion and 64% of patients in both arms of the trial were treated with glycoprotein IIb/IIIa platelet-receptor inhibitors. The primary endpoint of the study was target vessel failure at 270 days, defined as the composite of death, myocardial infarction, target lesion revascularization, and target vessel revascularization (non-target lesion). The secondary endpoint was in-stent angiographic binary restenosis at 240 days, defined as diameter stenosis ≥ 50%. As expected, baseline demographic and angiographic characteristics were similar between groups, with the exception of a larger reference-vessel diameter and a longer lesion length in the ACHIEVE stent group.

The primary endpoint of this study, target vessel failure, occurred in 11.9% versus 14.5% of the ACHIEVE and PENTA stent patients, respectively, $P = .128$. However, quantitative coronary angiographic analysis in-stent revealed a larger minimal lumen diameter (2.08 vs 1.86 mm, $P = .001$) and less late loss (0.81 vs 0.98 mm, $P = .003$) in the ACHIEVE and PENTA stent groups respectively. Angiographic binary restenosis occurred in 16.7% of patients receiving the drug-eluting stent in comparison to 22.4% of patients receiving the bare metal stent, $P = .149$. Unexpectedly, the use of IIb/IIIa platelet-receptor inhibitors was an independent predictor of angiographic restenosis (OR 2.32, 95% CI 1.24, 4.36, $P = .009$).

The authors concluded that paclitaxel coated on the abluminal surface of the Multi-Link PENTA™ stent at 3μg/mm² is safe (mortality 1%, stent thrombosis .4%, aneurysm .9%, 30-day major adverse cardiac events 1%), and that the system results in a significant decrease in fibrointimal hyperplasia. However, the magnitude of the effect was not significant enough to meet pre-specified endpoints for target vessel failure and angiographic binary restenosis. In addition, the potential drug-drug interaction with platelet glycoprotein IIb/IIIa platelet-receptor inhibitors requires additional study.

Comments

The results of this long-awaited but somewhat disappointing study reinforce the importance of trial design, particularly in terms of preliminary dose-response studies and sample size calculations. Despite angiographic follow-up in 88.2% of patients and clinical follow-up in 96% of patients, only a 17.3% reduction in target vessel failure (vs 40% hypothesized) and a 22.7% reduction in observed angiographic binary restenosis (versus 50% hypothesized) were noted. Future studies will likely be undertaken to provide a more optimal dose-response evaluation of this formulation.

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

Angiogenesis

This year, a number of important trials evaluating angiogenesis were presented at both the late-breaking trial session and during a plenary session chaired by Dr. Robert Lederman from The National Heart, Lung, and Blood Institute (NHLBI) and Dr. Doris Taylor from Duke University. During the plenary session, Dr. Stephen Epstein from the NHLBI gave an overview of angiogenesis. He reviewed the five randomized clinical trials that have been published to date: VIVA, FIRST, TRAFFIC, AGENT and VEGF. While the VIVA trial failed to show a significant difference between the group receiving angiogenesis and

placebo, the remaining trials, while also negative, demonstrated a trend toward positivity. None, however, conclusively demonstrated efficacy. There are five additional ongoing trials evaluating both vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (FGF).

A potential problem of all clinical trials to date is that they evaluate only a single angiogenic growth factor. An alternate approach, which may prove more effective, would be to target the "master switch" genes rather than the protein or gene specific to a growth factor. HIF-1α is one such gene. It is activated by severe hypoxia, and causes transcription factor activation of VEGF, angiotensin, nitric oxide endothelin, and PGK-1. Efforts to modify this master gene have shown potential benefit in endothelin models. Dr. Epstein also discussed another approach, using autologous bone marrow cells, which abundantly express cytokines and growth factors such as VEGF, FGF, and monocyte chemotactic protein (MCP-1), and could stimulate angiogenesis. He reviewed three such studies by Fucks, Yuyama, and Tse, and the report by Stam of the Top Care-AMI trial, which supports this strategy. Dr. Michael Simons, of Dartmouth Medical School, extended these comments, reviewing a variety of growth factors currently being investigated, and discussed cell-bound studies as well.

An important point that needs to be considered in designing future clinical trials is the stability of the new vasculature. In the study by Dr. Dor, of the Hebrew University-Hadassah Medical School, regression of neovascularization occurred once growth-factor stimulation was withdrawn. He suggested that extended drug delivery may be necessary in order to provide prolonged duration of effect. In addition, he discussed the difficulty of delivering genes to the myocardium, given their poor uptake. Certain techniques, however, may enhance this uptake and make delivery more efficient. He described the use of adenosine and increased arterial pressure as potential mechanisms to do so.

The Euroinject study demonstrated an improvement in angina in both the placebo and the VEGF group, with an overall reduction in Canadian Cardiovascular Class score of approximately 1.

Dr. Thomas Hennebry, from the University of Oklahoma, described cell-bound therapies for coronary disease and discussed the reports from Kocher, Hamano, Tse, and Stam concerning the use of bone marrow delivery in the coronary vasculature. Dr. Emerson Perin, from Texas Heart Institute in Houston, discussed bone marrow and stem cell delivery. Both emphasize the preliminary nature of these studies with only 5-10 patients observed in each report. They also emphasized the difficulty in obtaining a sufficient number of stem cells from bone marrow and described methods to increase their mobilization, including the administration of granulocyte-macrophage colony-stimulating factor (GM-CSF).

Dr. Brian Annex, from Duke University, presented data on peripheral vascular disease. He reviewed the results from the TRAFFIC trial of recombinant fibroblast growth factor-2 (rFGF-2) as treatment for peripheral vascular disease, recently published by Lederman in *The Lancet*. In this study, 190 patients were randomized to two doses of FGF. The primary endpoint was peak walking time at 90 days. The study demonstrated an increase in walking time in the FGF group (1.77 min and 1.54 min in the single and double dose groups respectively, vs .6 min in the control, $P < .026$). There was also a significant increase in ankle-brachial index.

Dr. Annex also presented preliminary results of the Regional Angiogenesis with Vascular Endothelial Growth Factor in Peripheral Artery Disease (RAVE) Trial, a phase II, randomized, double-blind, control trial in patients with disabling intermittent claudication. This study evaluated adVEGF-121 (bio-bypass) in patients with intermitted claudication. Two hundred and twenty-nine patients were recruited, but 105 patients were subsequently randomized to three groups: placebo, low-dose, and high-dose. The agent was injected regionally and the primary endpoint was treadmill walking time at 12 weeks following drug administration. The study demonstrated no significant difference between groups with an increase in walking time of 1.8, 1.6 and 1.5 min respectively. There was also no change in ankle-brachial indices. There was, however, a dose-dependent increase in peripheral edema with 31% of the high dose group experiencing this side effect. No other major adverse cardiac events occurred with therapy. The results were disappointing, and conflict with the previously reported TRAFFIC trial. This study, however, continues to emphasize the significant placebo effect seen in randomized clinical studies.

The Euroinject-1 trial was a gene therapy study utilizing phVEGF-A165 to treat severe ischemic heart disease. In this study, VEGF was injected intra-myocardially using the NOGA imaging system. The pri-

mary endpoint of the trial was SPECT imaging 3 months following drug administration. The study demonstrated an improvement in angina in both the placebo and the VEGF group, with an overall reduction in Canadian Cardiovascular Class score of approximately 1. However, no significant difference was seen between the groups, although there was a decrease in nitroglycerin use in the VEGF group. No major adverse cardiac events were noted.

These studies collectively demonstrate that angiogenic agents do provide slight benefit in both peripheral and coronary vascular treatment. Unfortunately, the two randomized clinical trials presented at the ACC were negative. However, researchers in the field remain optimistic that investigations of angiogenesis, either through gene therapy or bone marrow infusion, will lead to an effective therapy in the future. Current issues in this field include defining the optimal viral vector, finding a means to create a persistent and significant angiogenic effect, and the role of a cellular versus growth factor approach to angiogenesis. A number of studies are currently ongoing, and the results of these should help define the future of this field.
[David P. Faxon, MD, FACC, FAHA]

Imaging and Diagnosis

In a presentation entitled "Thromboembolic Risk Stratification Based on the SPAF Clinical Criteria in Patients with Paroxysmal Atrial Fibrillation: A Prospective Transesophageal Echocardiographic Study," Dr. Nadia Benyounes and associates of Saint Antoine University, Paris, France, examined thrombolic risk (TR) in patients with permanent versus paroxysmal atrial fibrillation and flutter (PAT). The authors note that the reported risk in patients with PAT has been lower than in those with sustained arrhythmia, although a recent longitudinal study reported similar risk. They hypothesize that the difference could be explained by differences in the transesophageal echo (TEE) risk markers in these studies. They therefore prospectively studied 145 patients within 48 hours of spontaneous cardioversion of any documented PAT (atrial fibrillation [AF] in 120 pts, Atrial flutter in 25 pts). Patients were divided into low-, moderate-, and high-risk groups, using the stroke prevention in atrial fibrillation (SPAF) risk criteria. The following parameters were evaluated: left atrial (LA) and left atrial appendage (LAA) areas, spontaneous echo contrast (SEC), LAA end-diastolic emptying velocities (Vel), LAA thrombus (Thr), and thoracic aortic atheroma (TAA). Of these parameters, only age, degree of SEC, and presence of TAA were significantly different between the groups. There was no difference in the 3 groups in LA or LAA area, Vel, or Thr. They conclude that there is a need for similar risk stratification and anticoagulation regimes in high-risk patients with PAT and permanent AF.

This paper adds to the growing evidence that patients with paradoxical atrial fibrillation and flutter should be treated in a similar manner in regard to risk. The conclusion, however, is inferential because no data is presented on the actual occurrence of embolic stroke. It is also of note that aortic atheroma were most common in the high-risk group.

In a presentation entitled "Recurrent Ischemic Cerebral Events in Patients with Different Subtypes of Arterial or Cardiac Source of Embolism: a Four- and Five-Year Follow-Up Study," Dr. Stefano DeCastro and colleagues of La Sapienza University, Rome, Italy, studied the risk of recurrent ischemic events or death in stroke patients with different subtypes of arterial or cardiac embolic sources. All patients admitted to the authors' neurology service underwent a general medical and neurologic exam, chest radiography, general blood chemistry, computed tomography (CT) scan, carotid ultrasound, and TEE. Patients were divided into 3 groups and followed for 5 years by clinical examination or telephone interview. Group I was composed of patients with a definite or probable arterial or cardiac source of embolism; group II of those with small vessel disease; and group III of those who could not be classified in either of the above groups. A total of 228 patients were studied, mean age was 55+17 years, 51% male. There were 152 patients (67%) in group I, 60 patients (26%) in group II, and 16 patients (7%) in group III. Overall, recurrent stroke or death occurred in 34 (22%), 5 (8%), and 1 (6%) patient(s), respectively, in each group. During the observation period, the recurrence rate was 43% for patients with definite, 17% for patients with probable, and 20% for patients with possible arterial or cardiac source of embolism and 21% for those with carotid artery disease. In particular, the highest recurrence rate of embolic events or death was observed in patients with complicated aortic plaque (12/27, 44%) and with atrial septal abnormalities with right-to-left shunting (12/62, 19%). The authors conclude that patients with complicated aortic plaque are at increased risk for embolic stroke and suggest a need for more aggressive anticoagulation in these patients.

This presentation emphasizes the relative frequency and importance of complex aortic atheroma as a risk factor for stroke. Despite growing literature on the subject, this problem is underappreciated and these lesions, when seen in other contexts, are often ignored. Additional data is

necessary on the predictive value of such lesions in patients without a prior stroke or transient ischemic attack (TIA).

In a presentation entitled "Short-Term Effect of Oral Anticoagulation Therapy on Documented Left Atrial Thrombi in Candidates for Percutaneous Transvenous Mitral Commissurotomy (PTMC)," Dr. Song Kwan Silaruks and associates of Khon Kaen University, Khon Kaen, Thailand, studied 687 consecutive PTMC candidates, over a 6-year period, by transthoracic echocardiography and TEE to determine the prevalence and response to therapy of LA and LAA thrombus. The question is important since LA/LAA appendage thrombus is generally considered a contraindication for PTMC. Two hundred and nineteen patients demonstrated LA/LAA thrombus (32%); 27 in the body of the left atrium (12%) and the remainder in the appendage (88%). Patients were placed on oral anticoagulation (International Normalized Ratio [INR] 2.0 to 3.0) and restudied by TEE after 6 months of therapy. Complete resolution of the thrombus was seen in 53 patients (24.2%). None of the patients with thrombi in the body of the LA had resolution. Of the patients in whom the left atrial thrombus (LAT) persisted, the size of the thrombus was reduced by a mean of 20%. By multiple logistic regression, the predictors of LAT resolution included NYHA class I or II (OR, 11.1; CI, 3.23-33.33), LAT size < 1.6 cm^2 (OR, 16.67; CI, 4.35-50.00), a fixed LAT (OR, 4.35; CI, 1.49-12.5), an LA spontaneous echo score of < 1 (OR, 3.45; CI, 1.2-10.0), and an INR of > 2.5 (OR, 19.53; CI, 3.37-113.16). They conclude that only a quarter of patients with LAT will show resolution after 6 months of anticoagulation. Better functional class, smaller, fixed thrombi, minimal LA spontaneous contrast, and an INR > 2.5 predict likelihood of resolution.

This study presents a large series of patients with a very high incidence of LAT, much higher than noted prior to percutaneous mitral valvuloplasty in our experience. The author fails to indicate the rate of AF in this population, the pre-procedure anticoagulation status of these patients, or the relationship of thrombi to mitral regurgitation. The high prevalence of pre-procedure thrombi may reflect a lack of adequate anticoagulation. However, the study emphasizes that in a large series, a significant percentage of large thrombi, once established, may fail to resolve, despite adequate anticoagulation. The likelihood of resolution further decreases when the level of anticoagulation is less than optimal.

These data are consistent with prior clinical observations that the incidence of stroke was lower in patients with combined mitral stenosis and mitral regurgitation than in those with isolated mitral stenosis.

In a presentation entitled "Effects of Mitral Regurgitation on Left Atrial Clot and Spontaneous Echo-Contrast in Patients with Severe Mitral Stenosis," Dr. Kewal Goswami and colleagues from the All India Institute of Medical Sciences, New Delhi, India, examined the hypothesis that mitral regurgitation may prevent stasis of blood and ensuing clot formation in patients with severe mitral stenosis (MS). They studied 100 patients with isolated severe MS (mitral valve area < 1.0 cm^2) and at least mild mitral regurgitation (MR), 200 patients with isolated MS, and 20 controls. All patients were studied by TEE for evaluation of LA or LAA clot, SEC, and LAA function (filling and emptying velocities and their integrals). There was no significant difference in age, duration of symptoms, or mitral valve area (MVA) in either group. Patients with MS and MR had significantly more AF, larger LA and LAA area, significantly less SEC, and fewer clots than those with isolated MS. LAA functional parameters were similar in both groups. MR grade was I-II in 40% of patients with combined MS and MR, and grade III and IV in 60%. The number of clots in the MS/MR group (8) was significantly lower than in the MS group (25) and all clots occurred in patients with grade I-II MR.

These data are consistent with prior clinical observations that the incidence of stroke was lower in patients with combined MS and MR than in those with isolated MS. It is particularly noteworthy that no thrombi were noted in the patients with grade III-IV MR. Unfortunately no data on the prevalence of stroke in this population were presented.

In a presentation entitled "Is Surgical Closure of the Left Atrial Appendage Useful for Preventing Cardioembolic Events?," Dr. Birke Schneider and colleagues from the Klinik fur Kardiologie Stadt, Krankenhaus, Lubeck, Germany, noted that surgical closure of the atrial appendage is recommended in fibrillating patients to reduce the risk of future embolic events. In a study of 5 patients, the authors noted that there was disruption of the suture line and partial recanalization of the orifice in all patients when studied 23-45 days postoperatively. The size of the orifice of the LAA ranged from 3–20 mm, and relatively high-flow velocities were noted across the orifice (0.33-2.2 m/sec) but not in the body of the appendage. Compared

to the preoperative TEE, spontaneous contrast was much more intense, and in one patient a thrombus was present that was not noted preoperatively. One patient suffered a postoperative stroke despite adequate anticoagulation. The authors conclude that surgical closure of the LAA was incomplete, resulting in blood stagnation and an increased likelihood of clot formation. They also observe that, because of the high velocity jet, passage of the thrombus from the appendage to the atrium and systemic circulation may be facilitated.

Although the study involved only a few patients, it does make the important point that surgical closure of the LAA in patients with AF is generally incomplete. This is intentional to avoid necrosis of the appendage distal to the ligature. It is not surprising that thrombus forms in the residual appendage. However, the suggestion that this may increase the risk of embolism is difficult to support in such a small study. Many physicians believe that once the appendage has been ligated, there is no further reason to consider the appendage as a potential source of embolism. This is clearly not the case. As noted here, many, if not most, appendages that are reported as surgically ligated will continue to connect to the left atrium. Some will contain thrombus and the velocity of flow at the orifice will often be high. Thus, they should be studied by TEE before cardioversion, using similar criteria as for native LAA.

In a report entitled "Mitral Pressure Half-Time Does Not Predict the Effective Valve Area in Prosthetic Mitral Valves of All Types: A Review of 2,175 Prosthetic Mitral Valves," Dr. Gregory Scalia and associates from The Prince Charles Hospital, Brisbane, Australia, examined the value of mitral Doppler pressure half-time, a widely used measure of valve area, in assessing the area of a variety of prosthetic valves in cases of rheumatic MS. They retrospectively studied 2175 patients with prosthetic valves including ATS (547 pts), Bjork-Shiley (51 pts), Carpentier-Edwards (126 pts), Hancock (91 pts), Lilliehei-Kastor (36 pts), Mosaic (31 pts), Perimount (62 pts), St Jude (1139 pts), Starr-Edwards (47 pts), and Xenotech (45 pts). Exclusion criteria included incomplete data (n = 699) and significant (> 1/4) mitral or aortic regurgitation (n = 217). There was no relationship between mitral valve area as measured by pressure half-time and area as determined by the continuity equation (R = 0.1, *P* = NS). However, the continuity-derived MVA linearly decreased (r2 = .98) with increasing mean pressure gradient. There was no relationship between pressure half-time derived MVA and mean pressure gradient. The authors conclude that transmitral pressure half-time is of no use in assessing the area of prosthetic valves. However, the MVA calculated by the continuity equation is linearly related to the transmitral pressure gradient and may be useful in following patients post-operatively.

A number of earlier studies have shown a fair correlation between Doppler pressure half-time and prosthetic valve area in patients with prosthetic mitral valves. Not surprisingly, there has been considerable over- and underestimation. The half-time method was originally derived for rheumatic mitral stenosis, and the empiric constant 220 in the half-time equation implicitly reflects, among other factors, the geometry and discharge coefficient of this type of stenosis. Application of this general equation and the cited constant to the wide range of available prostheses, therefore, cannot be expected to yield accurate results. This large study confirms these concepts. The relationship of the continuity-equation/valve area to mean gradient is not surprising since the mean gradient or its correlate mean velocity (via the Bernoulli) equation is a component of the valve area calculation. The level of correlation and the linear relationship is surprising since cardiac output is the numerator in this equation and is obviously variable, and velocity is a function of the square root of the gradient. Despite this the continuity method is clearly the preferable approach for following the area of PMV.

[Arthur E. Weyman, MD]

FACIT Trial

Epidemiologic evidence suggests that total plasma homocysteine is an independent risk factor for cardiovascular disease, correlates with the extent of coronary artery disease, and is a predictor of mortality in patients with coronary atherosclerosis.[53-56] In addition, homocysteine has been reported to induce endothelial dysfunction and lipid peroxidation.[57-59] Reduction of homocysteine levels, with a combination of folate/vitamin B-12 and vitamin B-6, has been shown to decrease restenosis and major adverse cardiac events (MACE) following PCI.[60,61] Therefore, the adverse effect on outcomes in folate/vitamin B-12/vitamin B-6–treated patients undergoing PCI, in the Folate After Coronary Intervention Trial (FACIT), was unanticipated.

In this trial, reported by Dr. Helmut Lange from the Bremen Heart Center in Germany, 626 patients were randomly assigned to receive a combination of intravenous folate/vitamin B-6/vitamin B-12, followed by oral therapy or placebo, for 6 months following successful PCI. The primary endpoint of the trial was minimal lumen diameter measured angiographically at six months.

Although the aim of the trial was

to prove the hypothesis that folic acid therapy in combination with vitamin B-6 and vitamin B-12 reduces restenosis following PCI, in fact, the investigators found just the opposite. Despite a significant reduction (30%) in homocysteine levels in the folate-treated group and similar baseline clinical and procedural characteristics in both groups, at follow-up the minimal lumen diameter was significantly smaller in the folate-treated group than in the placebo group (1.59 mm vs 1.74 mm, $P < .01$). In addition, late loss (0.90 mm vs 0.76 mm, $P = .001$), restenosis rate (35% vs 27%, $P < .05$), target vessel revascularization (15.8% vs 10.6%), and MACE (16.8% vs 10.9%, $P = .03$) were all greater in the folate-treated group when compared to the placebo group. The authors concluded that combination folate and vitamin B therapy should not be used to achieve lower homocysteine levels in the setting of PCI.

Comment

The results of this study are quite provocative, because they contradict previously published studies reporting the use of homocysteine-lowering folate therapy in the prevention of restenosis and MACE following PCI. The reasons for these different outcomes are unclear. However, the greater use of stents, the slightly higher dose of folate and vitamin B, and the presence of fewer diabetic patients in the FACIT trial have been implicated. For now, however, it is clear that although this inexpensive treatment was thought to have little chance of causing harm, patients undergoing PCI should not receive homocysteine-lowering therapy with folate/vitamin B-6/vitamin B-12.

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

The results of this study are quite provocative, because they contradict previously published studies reporting the use of homocysteine-lowering folate therapy in the prevention of restenosis and MACE following percutaneous coronary intervention.

Distal Protection: Standard Therapy for Saphenous Vein Bypass Graft Interventions and Carotid Interventions

Percutaneous intervention (PCI) in degenerated saphenous vein grafts (SVGs) and ulcerated carotids frequently leads to distal embolization, resulting in myocardial infarction and stroke, often complicated by death. The availability of distal protection devices, in the form of a distal occlusion balloon or a filter, has made these procedures much safer. Data from two late-breaking studies are presented here.

FIRE Trial

The FilterWire during Transluminal Intervention of Saphenous Vein Graft (FIRE) trial was a prospective, randomized, multicenter trial of distal protection during SVG intervention with a filter-based catheter (Figure 18) compared with balloon occlusion and aspiration. A total of 651 patients undergoing PCI for diseased SVGs were randomized in this non-inferiority study. Patients were stratified by pre-intervention glycoprotein IIb/IIIa inhibitor use. All patients were pre-treated with acetylsalicylic acid and clopidogrel. The SVG lesion had to be 2.5 cm proximal to the distal anastomosis. The primary end point was the incidence of major adverse cardiac events—death, myocardial infarction (myocardial band enzymes of creatine phosphokinase > 3 times the upper limit of normal) or target vessel revascularization (TVR)—at 30 days. Clinical and angiographic characteristics were similar in both groups. Approximately 50% of patients received glycoprotein IIb/IIIa antagonists, and few patients required bail-out use.

Procedural time was similar in both groups, as was the final Thrombolysis in Myocardial Infarction (TIMI) flow grade and TIMI frame count. The FilterWire group had a higher fail-to-deliver rate than did the group that received the balloon occlusion system (3.9% vs 0.6%, respectively). Thirty-day MACE was 9.9% for subjects who received the FilterWire system and 11.6% for those who received the GuardWire system. There was a similar trend in the incidence of myocardial infarction and TVR. The P value was .0008 for non-inferiority. IIb/IIIa inhibitor use did not seem to influence clinical outcome.

Comment. Trials of new SVG PCI devices have been yielding improved clinical outcomes. Results of the Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial demonstrated that the balloon occlusion wire significantly lowered the incidence of MACE compared with control subjects (9.6% vs 16.5%, respectively). Use of the FilterWire has now been shown to produce similar results. Non-distal protection atherectomy trials without distal protection continue to show significantly increased rates of MACE; for example, the X-Sizer for Treatment of Thrombus and Atherosclerosis in Coronary Intervention Trial (X-TRACT) demonstrated a 20.7% incidence of 30-day MACE. It is clear that degenerated vein grafts are prone to embolization that cannot be prevented with direct stenting or atherectomy techniques.

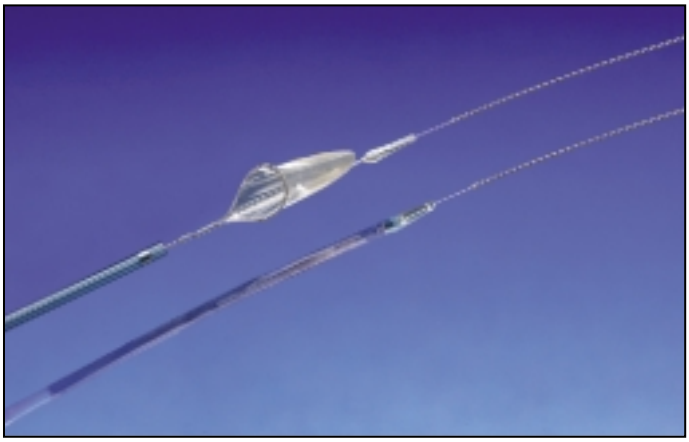


Figure 18. *The FIRE trial studied distal protection during SVG intervention with a FilterWire.*

Both the balloon occlusion system and the filter wire system are effective in preventing embolization. The disadvantage of the balloon system is that it requires total occlusion of the graft while the vessel is being treated; this can lead to significant ischemia and infarction. However, this method offers the best protection, because all materials, regardless of size, will be evacuated from the graft through a suction catheter. The filter system has the advantage of allowing blood flow to continue while the interventional work is taking place. However, the filter has a finite pore size (approximately 100 microns) and allows smaller particles and vasoactive substances to go downstream. In addition, the filter has a finite "carrying capacity" and can become blocked by a large embolization load. It is no surprise that the two systems currently produce equivalent results. However, in the upcoming years, improvements in technology and techniques will likely lead to the advancement of one system over the other.

ARCHeR Trial

The ACCULINK™ for Revascularization of Carotids in High-Risk Patients (ARCHeR) trial studied outcomes in 437 high-risk patients with moderate to high-grade carotid stenosis who underwent carotid stenting with or without distal protection provided by the ACCUNET™ Embolic Protection System. When the filter was removed after the procedure, more than 57% of the baskets had retrieved visible debris. Death, myocardial infarction, and stroke occurred in 7.8% of patients (stroke, 5.3% [major stroke, 1.6%]; death, 2.3%; myocardial infarction, 2.1%). This trial demonstrates the feasibility of carotid stenting with distal protection in this challenging patient population.

Comment. Results from the ARCHeR trial confirm the findings of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, which were presented at the 2002 Scientific Session of the American Heart Association. In the SAPPHIRE trial, patients in whom carotid stenting was performed had a 30-day MACE rate of 5.8%, compared with 12.6% in the patients who had endarterectomy ($P = .047$). It is likely that with proper technique, carotid stenting can be performed safely in both moderate and high-risk patient populations.

[Alan C. Yeung, MD]

The ISAR REACT Trial

Identification of the most appropriate adjunctive pharmacological therapy during and after percutaneous coronary intervention (PCI) has been the focus of considerable scientific investigation, as well as substantial controversy. This is the result of rapid changes in the field, including the introduction of new devices and new drugs and drug classes. The introduction and widespread use of stents has been a major catalyst in PCI therapy, as has the expansion of patient-selection criteria to include high-risk, acute coronary syndrome patients.

Stents are now used in 80%-95% of all PCI procedures. With the introduction of drug-eluting stents, it is anticipated that the frequency of stent placement will increase even further. When initially introduced, stenting procedures were complicated by a relatively high frequency of subacute closure (> 10% in some series), which resulted in Q-wave infarction or death in the majority of the patients in whom it occurred. Early attempts to prevent the problem included use of aspirin, dextran, warfarin, and 3-5 days of heparin administration, all of which led to a marked prolongation of the initial hospital stay and a significant increase in bleeding complications.

The first major advance in alleviating these complications was the introduction and testing of the thienopyridines. Ticlopidine, a thienopyridine, was compared with warfarin in 4 randomized trials, and with aspirin alone in a fifth trial.[62-66] Clopidogrel was afterward compared with ticlopidine in 3 randomized clinical trials and many registries.[67] These trials and registries documented that 1) the combination of aspirin and a thienopyridine was superior to aspirin with heparin or warfarin, 2) that clopidogrel and ticlopidine were similarly effective in decreasing subacute closure rates following stent implantation, but that the former

was much better tolerated, particularly in regard to nausea, vomiting, and diarrhea. It is also known that clopidogrel is associated with a much lower frequency of severe, life-threatening neutropenia and thrombotic thrombocytopenic purpura. These studies support the current worldwide practice pattern of prescribing a combination of aspirin and clopidogrel for patients undergoing coronary stent implantation. There are, however, many unresolved issues regarding treatment with clopidogrel, including the optimal dose, duration of therapy, and the need for and duration of pretreatment.

The second major advance in adjunctive therapy has been the introduction and widespread use of the potent IIb/IIIa antagonists. Beginning with the landmark EPIC trial with abciximab, multiple randomized trials have documented that, in patients undergoing PCI, particularly higher-risk patients such as those with positive biomarkers or diabetes mellitus, administration of IIb/IIIa antagonists improved patient outcomes. However, the importance of these improved outcomes has been somewhat controversial. In general, these agents improve early outcome, not by reducing mortality or the need for emergency surgery, but rather by decreasing post-procedural myocardial enzyme elevations. There is some evidence that abciximab may be associated with improved long-term survival; early data suggesting that these agents may reduce restenosis has not been borne out in most subsequent trials.

Table 6
ISAR REACT Treatment Regimen

Clopidogrel 600 mg at least 2 h before procedure
Aspirin p.o. or i.v. according to local standards
Heparin bolus of 70 U/kg

Abciximab group	Placebo group
• Bolus of .25 mg/kg	• Heparin bolus of 70 U/kg
• Infusion of .125 mg/kg/min for 12 h	• Placebo infusion for 12 h

Clopidogrel 2 x 75 mg/day until discharge
75 mg for at least 4 weeks
Aspirin at least 100 mg/day

Utilization rates of IIb/IIIa antagonists during PCI vary widely, and have been generally lower in Europe than in the United States. In some U.S. institutions, they are used routinely (unless there is a contraindication); in others, the utilization rate is less than 40%. This variation is largely related to individual physicians and the importance they attach to preventing creatine phosphokinase (CPK) elevation, post-PCI. Other issues, such as cost-benefit ratios, are also important. In high-risk patients with positive biomarkers and diabetes mellitus, these agents are used in the majority of cases.

Recent data indicate that with clopidogrel, a loading dose of 600 mg achieves maximal inhibitory effect on platelet aggregation within 2 hours; the dose of 300 mg that is more often used requires 6 hours to achieve peak inhibition of aggregation.

The relative value of each of these adjunctive strategies—IIb/IIIa inhibitors versus pretreatment with a thienopyridine—remains uncertain. All randomized studies assessing the clinical value of IIb/IIIa inhibitors in patients undergoing PCI studied patients not routinely pretreated with a thienopyridine. In a substudy of the EPISTENT trial, Steinhubl and associates found that in patients treated with a IIb/IIIa inhibitor, pretreatment with a thienopyridine was not important.[68] However, data from the TARGET trial suggested that pretreatment was beneficial, even if a patient receives a IIb/IIIa inhibitor.[69]

Recent data [Peyrou et al, unpublished] indicates that with clopidogrel, a loading dose of 600 mg achieves maximal inhibitory effect on platelet aggregation within 2 hours while the dose of 300 mg that is more often used requires 6 hours to achieve peak inhibition of aggregation.[70]

These data form the basis for the ISAR REACT study, which randomized patients undergoing elective PCI to one of two regimens (see Table 6). Of note, all patients received 600 mg of clopidogrel at least 2 hours, and in most cases > 3 hours, before the procedure. The elective PCI patient population included some moderate-risk patients as well as low-risk patients but specifically excluded those at highest risk, with an acute coronary syndrome indicated by a positive biomarker or marked ST segment shifts, a myocardial infarction within 14 days, or insulin-dependent diabetes mellitus. Patients with thrombotic lesions were also excluded from the trial. The primary endpoint was a composite of death, myocardial infarction (defined as Q-wave or three times creatine kinase/creatine

kinase myocardial band elevation), or urgent target vessel revascularization, within 30 days of the procedure.

The preliminary results were presented as a late-breaking clinical trial of 2159 patients, of whom 1079 were randomized to receive abciximab and 1080 to receive placebo. As previously mentioned, the study excluded high-risk patients. However, 40% of the randomized patients presented with Canadian Cardiovascular Society Class 3 or 4 angina pectoris, and complex lesion characteristics (ACC/AHA class B2 or C) were present in 65% of lesions treated. As presented, the primary 30-day endpoint of death, myocardial infarction, or urgent revascularization was reached in 4.2% of the abciximab group and 4.0% of the placebo group (Figure 19) (P = .82).

There was absolutely no difference in the incidence of death (0.3% in each group), and Q-wave infarction occurred in 0.4% of patients treated with abciximab versus 0.5% treated with placebo. Non–Q-wave infarction occurred in 3.3% of patients in both groups.

ISAR REACT has important implications for the practice of interventional cardiology. The authors found that 1) a 600 mg loading dose of clopidogrel was well tolerated and no drug interactions were noted, 2) although all patients in the study received a 600 mg loading dose of clopidogrel, and thus the study does not directly address the benefit of such a regimen, pretreatment with clopidogrel is probably beneficial and is most likely to explain the low overall event rate in the trial and the lack of benefit from adding a IIb/IIIa inhibitor in this lower-risk population.

In terms of translation to clinical practice, at those institutions equipped to perform PCI within 6 hours after a 300 mg loading dose of a thienopyridine, or 2 hours after a 600 mg loading dose, IIb/IIIa agents do not need to be used routinely in low- and moderate-risk patients. If pretreatment with a thienopyridine is not an option, or patients are classified as high-risk, such as those excluded from ISAR REACT, IIb/IIIa inhibitors are likely beneficial, as has been shown in many randomized trials. Subsequent studies are planned to evaluate the need for IIb/IIIa inhibitors among high-risk patients who receive pretreatment with clopidogrel.

[David R. Holmes, Jr, MD and Peter Berger, MD]

New Studies in Hypertension

A number of studies of clinical outcomes in hypertension have been reported during the past several months. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[71] was published shortly after the American Heart Association meetings in late 2002 and the Second Australian National Blood Pressure Study (ANBP2)[72] published in the *New England Journal of Medicine* in February 2003. Most recently, the International Verapamil SR Tranolapril Study (INVEST) was presented at the 2003 meeting of the ACC.

The ALLHAT and ANBP2 Trials

The ALLHAT study compared the clinical outcome effects of chlorthalidone, a diuretic, amlodipine, a calcium channel blocker, and lisinopril, an ACE inhibitor. The study authors concluded that the diuretic showed the greatest efficacy of the three and reasoned that because it is also the least expensive, it should be regarded as the preferred first-line treatment for hypertension.[71] Unfortunately, as detailed elsewhere,[73,74] flaws in the design, interpretation, and reporting of ALLHAT have raised doubts concerning the validity of its conclusions.

The ANBP2 study seemed to contradict the findings of ALLHAT. Although the cohorts studied were somewhat different—the patients in the Australian study included a higher proportion of whites and tended to have higher blood pressure—ANBP2 showed that the composite endpoint of all-cause mortality and cardiovascular events was lower in patients receiving an ACE inhibitor than in those receiving a diuretic.[72] Accordingly, it was

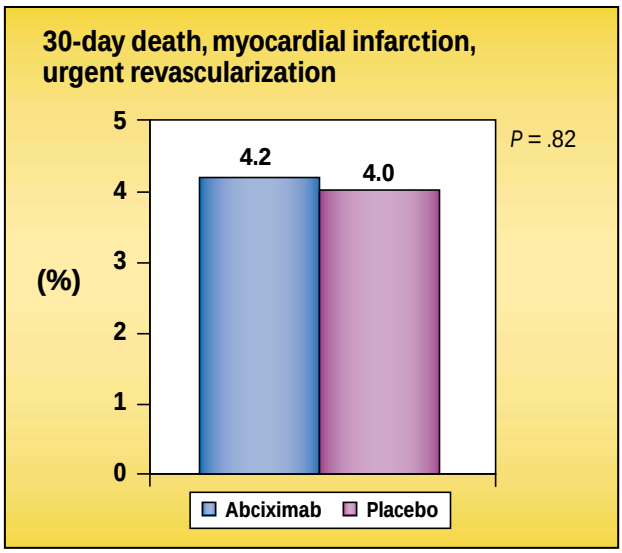


Figure 19. *Efficacy analysis results of the ISAR REACT trial. Primary endpoint was a combination of 30-day death, myocardial infarction, or urgent revascularization.*

hoped that the results of INVEST presented at ACC would reconcile these conflicting findings.

The INVEST Trial

Like ALLHAT and ANBP2, INVEST was designed to compare the clinical-outcome effects of newer antihypertensive agents (a calcium channel blocker and an ACE inhibitor) with older agents (a beta blocker and a diuretic). The study was set up with a null hypothesis, namely that the calcium–channel-based treatment and the beta-blocker–based treatment would have equivalent endpoints. The primary outcome for the study was a composite of all-cause mortality plus nonfatal stroke or nonfatal myocardial infarction. A variety of secondary endpoints, including cardiovascular death, fatal plus nonfatal stroke, and fatal plus nonfatal myocardial infarction, were also defined.

The two principal entry criteria were that patients have hypertension requiring drug therapy and a documented history of coronary heart disease. Patients who had recent myocardial infarction or other cardiovascular conditions requiring mandatory use of agents such as ACE inhibitors or beta blockers were excluded from the study. The minimum age for study entry was 50 years.

Altogether there were 22,576 patients, 76% in the United States. Slightly more than half were women. Approximately half were white, 36% Hispanic, and 13% black. There were equal numbers of patients over and under 65 years of age. Twenty-seven percent were previously diagnosed with diabetes, approximately 33% had a history of myocardial infarction, approximately 66% had classic angina, and 28% had a history of coronary artery bypass graft or angioplasty.

Treatment Strategies

INVEST was characterized by a prospective, randomized, open-label, blinded endpoints (PROBE) design. The calcium–channel-blocker group started treatment with the non-dihydropyridine agent, verapamil (in a sustained-released formulation), 240 mg daily. The following titration steps could be undertaken to achieve a goal blood pressure of < 140/90 mm Hg (or < 130/85 in patients with diabetes or renal complications). Trandolapril could be added as a second step; if necessary, the dose of calcium channel blocker could then be increased to 180 mg twice daily and, if necessary, hydrochlorothiazide, 25 mg daily, could be added. The comparative ß-blocker regimen began with atenolol, 50 mg daily. If necessary, hydrochlorothiazide, 25 mg daily, could be added. The dose of atenolol could be increased to 50 mg twice daily and as a final step, trandolapril could be added.

Treatment Progression and Outcomes

Only 16% of patients controlled blood pressure with one drug, and only 31% of patients sustained efficacy with two drugs. Fully 50% of the patients in the study required all three allowed drugs, and 40% actually received drugs in addition to those comprising the basic therapeutic regimens. Not surprisingly, most patients finished the study at the maximum doses of the required drugs.

At the time of study entry (with many of the patients previously on antihypertensive therapy), blood pressure averaged 151/88 mm Hg. The effects of the two treatment regimens were virtually identical, each reducing blood pressure by approximately 19/10 mm Hg. By the end of the 24 month period, achievement of target blood pressures of < 140/90 mm Hg (or < 130/85 mm Hg for patients with diabetes or renal dysfunction) were again equal for the two groups. The diastolic targets were reached in almost 91% of patients, whereas systolic targets were reached in 65%.

If pretreatment with a thienopyridine is not an option, or patients are classified as high-risk, such as those excluded from ISAR REACT, IIb/IIIa inhibitors are likely beneficial, as has been shown in many randomized trials.

There were no significant statistical differences between the two treatment regimens in the primary or any of the secondary endpoints of the trial. Among the 11,267 available patients in the calcium–channel-blocker group, there were 1084 first events. Among the 11,309 available patients in the ß-blocker group, there were 1112 first events. Likewise, for the secondary endpoints of death, cardiovascular death, nonfatal myocardial infarction or stroke, or cardiovascular hospitalization, there were no differences between the two groups. The data were also analyzed for a variety of pre-specified subgroups, including age stratification, men versus women, whites and non-whites, positive or negative prior history of myocardial infarction, the presence or absence of prior congestive heart failure, prior dyslipidemia, or prior diabetes. None of these comparisons yielded differences in outcomes between the two treatment groups.

The one difference that did emerge in the study was in the incidence of new-onset diabetes. In the calcium–channel-blocker group, 6.16% of patients became diabetic, whereas in the ß-blocker group,

7.29% of patients became diabetic. This difference was highly significant. A composite endpoint of death plus new-onset diabetes also significantly favored the calcium–channel-blocker group, though this was driven largely by the difference in new-onset diabetes.

Comments

This study clearly satisfied the null hypothesis on which it was based. In fact, with the exception of new-

Main Points

- The EPHESUS trial convincingly demonstrated that the addition of eplerenone to optimal medical therapy results in an improvement in survival and a reduction in hospitalization rates among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.
- The COMPANION trial showed that, compared with optimal medical treatment, biventricular cardiac resynchronization therapy with or without an implantable cardioverter defibrillator can reduce all-cause death and all-cause hospitalizations in patients with moderate or severe heart failure.
- The SPORTIF III trial evaluated a new oral direct thrombin inhibitor, ximelagatran, with warfarin therapy for the prevention of stroke and systemic embolic events in patients with atrial fibrillation; on-treatment analysis demonstrated events at 2.2% per year for warfarin, compared with only 1.3% with ximelagatran, a significant reduction in events in the ximelagatran group.
- Data from the CONTRAST trial, which randomized 315 patients with creatinine clearance < 60 mL/min to fenoldopam or placebo after percutaneous coronary intervention (PCI), showed that fenoldopam did not provide a protective effect against radiocontrast nephropathy.
- The St. Francis Heart Study, which reported the results of electron beam computed tomography for coronary artery calcification (CAC), demonstrated that the prediction of cardiac events was clearly related to CAC score.
- The use of nesiritide in the treatment of acute decompensated heart failure (ADHF) has been shown to significantly shorten lengths of hospital stay. It has also proven effective in lowering pulmonary arterial pressure in pre-transplant patients.
- The ADHERE registry continues to accumulate data and show variance in the course of therapy for patients with ADHF, particularly in the prescription of beta blockers and intravenous vasoactive medications.
- The ASCOT investigators calculated that if the trial had continued through its planned 5-year duration, atorvastatin would have reduced coronary heart disease incidence by approximately 50% in the study population targeted for lipid-lowering therapy.
- Based on information from current studies, time-to-treatment is an important factor in the efficacy of primary PCI. While patients with additional contributing risk factors are more likely to be negatively affected by delayed treatment, the goal in every instance should be immediate treatment, preferably within the first hour after onset of symptoms.
- New and follow-up studies of drug-eluting stents used in PCI have shown up to 3 years of durability of benefit and, in the case of the SIRIUS study, extend the safe and efficacious use of stents to patients with long (15-32 mm) lesions in smaller (2.0-3.0 mm diameter) vessels.
- Recent studies of angiogenic agents in peripheral and coronary vascular treatment demonstrate a slight benefit, and researchers in the field remain optimistic that continued investigations, either of gene therapy or bone marrow infusion, will lead to an effective therapy in the future.
- Patients with permanent versus paroxysmal atrial fibrillation and flutter have a similar risk profile and should be treated in a similar manner with anticoagulation.
- The FIRE trial adds to the growing body of evidence linking the use of distal protection devices in saphenous vein graft PCI and improved clinical outcomes.
- The ISAR REACT trial definitively establishes 600 mg of clopidogrel as a safe and optimal loading dose for pretreatment before PCI, as well as demonstrating a lack of need for additional IIb/IIIa inhibitor therapy in patients considered to have a lower risk of complications.
- In the INVEST trial, more than 50% of patients required three or more drugs in order to reach recognized blood pressure treatment targets.

onset diabetes, every meaningful endpoint was similar between the two treatment groups.

The reason for this result appears to lie within the design of the antihypertensive treatment regimens. At first sight, the two groups appeared to provide an interesting contrast: the new drugs, a calcium-channel blocker and an ACE inhibitor, versus the older drugs, a beta blocker and a diuretic. Had it been possible to maintain that simple and interesting contrast in therapies, the results, either positive or negative, would have been of great interest. Unfortunately, because so many patients progressed to a third and fourth step of therapy, and even beyond that, there was substantial overlap in treatment between the two groups; about half the patients in the newer drug group were receiving the diuretic and about half in the older drug group were receiving the ACE inhibitor. Moreover, about 10% of the patients in the calcium–channel-blocker group were also receiving a ß-blocker and 16% of patients in the ß-blocker group were also receiving a calcium channel blocker. Considering that drugs beyond those comprising the official therapeutic regimens were prescribed, it is difficult to state with certainty that there was any meaningful difference between the two regimens.

Nonetheless, INVEST does provide some important blood pressure information. First, more than 50% of patients required three or more drugs in order to reach recognized blood pressure treatment targets. This has been demonstrated in previous hypertension studies, but because INVEST was a large-scale study performed with an open-label design, maximizing the ability of physicians to monitor and manage hypertension, it showed more definitively that multidrug combinations are a vital part of effective blood pressure control.

The second major lesson is that, for equal blood pressure control, clinical endpoints were virtually equal. Unfortunately, the common use of drugs across the two treatment groups prevents us from reaching any valid conclusions regarding their particular benefits in protecting against clinical hypertension outcomes. This question will require further studies, several of which are already ongoing or planned. Even so, it is useful to know—as INVEST has shown us—that well-constructed treatment regimens, employing both newer and older drugs, can achieve reasonably good blood pressure control in a majority of high-risk, hypertensive patients.

The only difference to emerge from INVEST was the comparative prevalence of new-onset diabetes in patients in the beta-blocker treatment group versus those in the calcium–channel-blocker treatment group. This, again, is not a new finding. Another recent study showed an increased likelihood of new-onset diabetes in patients treated with a beta blocker,[75] whereas ALLHAT demonstrated that patients treated with a diuretic were more likely than those treated with an ACE inhibitor or a calcium channel blocker to develop new-onset diabetes. These findings add more weight to a recent recommendation by the British Hypertension Society[76] that diuretics and beta blockers not be routinely used, in combination, in the treatment of hypertensive patients at risk for diabetes. ■

[Michael A. Weber, MD]

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