Best of the ACC Scientific Session 2002

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Key words: Acute coronary syndrome • Acute myocardial infarction • Adenosine • AFFIRM • Aldosterone • AMIGO • AMISTAD II • Atenolol • Atherosclerosis • AZACS • Azithromycin • BNP • B-type natriuretic peptide • COAST • Congestive heart failure • DANAMI-2 • ENABLE • Enalapril • Endothelial receptor antagonists • Enoxaparin • Eplerenone • Eptifibatide • Fibrinolysis • First in Man trial • Hypertension • ICDs • INTERACT • ISAR-STEREO • Left ventricular hypertrophy • LIFE • LIPS • Losartan • MADIT II • OVERTURE • Paclitaxel • Patent foramen ovale • PCI • RAVEL • Reperfusion • Sirolimus • Statins • Stents • Stroke • Tacrolimus • Vasopeptidase inhibition • WIZARD

Leading off this comprehensive review of the 2002 Scientific Session of the American College of Cardiology (ACC) is a report on a day-long symposium on the drug-eluting stent "revolution." Following this, our Medical and Contributing Editors report on many of the late-breaking trials and other presentations of interest from this year's meeting.

Symposium Review: Enter the Drug-Eluting Stent Revolution: A Critical Appraisal

A full-day symposium, "Enter the Drug-Eluting Stent Revolution: A Critical Appraisal," was directed by Gregg W. Stone, MD and Martin B. Leon, MD of the Cardiovascular Research Foundation. This event provided a comprehensive review of the state of the art of drug-eluting stents.

Dr. Robert Schwartz of the Mayo Clinic evaluated the potential cellular and molecular targets within the coronary artery for anti-restenosis therapy. These potential sites include the endothelium, media, adventitia, plaque, and inflammatory cells. Brachytherapy, by virtue of the penetration of the radioactive energy, treats the entire vessel thickness, whereas drug therapy can be targeted to specific zones, such as the intima, thereby maximizing the benefit and minimizing long-term, adverse events. Brachytherapy is associated with neointimal thickness reduction, inhibition of smooth muscle cell proliferation, reduced re-endothelialization, prominent fibrin deposition, and increased inflammation relative to "plain old stents." Drug-eluting stents seem to be associated with better re-endothelialization (dose dependent), less fibrin deposition, less inflammation, and more prevention of smooth muscle cell proliferation than brachytherapy.

A variety of compounds are being assessed for their abilities to prevent restenosis. This list includes sirolimus,

paclitaxel, tacrolimus, taxol/taxanes, actinomycin D, antisense compounds, tranilast, angiopeptin, dexamethasone, batimastat, and halofuginone.

Stent Design, Delivery Vehicles, and Drug Selection

Dr. Campbell Rogers of the Brigham & Women's Hospital gave a presentation on the impact of stent design, delivery vehicles, and drug selection on the safety and efficacy of drug-eluting stents. There are many issues that need to be taken into account when attempting to develop the ultimate stent. One must ensure that a therapeutic level is delivered, avoiding subtherapeutic and toxic levels. Stent design, delivery vehicle, and drug selection play important roles in the efficacy and safety of drug-delivery systems. The dose, duration of action, mechanism of action, and physiochemical properties of the drug to be delivered will determine its effectiveness. Characteristics of the blood vessel, including curvature, symmetry of plaque, ostial and side branch location, side-branch location, and in-stent restenosis need to be taken into account when selecting a drug-delivery system.

Stent design is critical to maximize delivery of drug to the entire circumference of the vessel on curved segments. Differences between the "closed" and "open" cell design impact the amount of stent apposition along the vessel wall and hence the surface area available for drug delivery. A variety of polymer coatings have now been developed that appear to be safe. These coatings control the rate of drug release (rapid versus sustained) and can have anti-restenotic properties themselves.

Characteristics of the drug to be delivered are important vis-à-vis their ability to be effective. Hydrophobic drugs diffuse much more poorly than hydrophilic agents. The dose and pace of release will impact the ability of a drug to be effective and safe. Too high a dose released too quickly may induce death of endothelial cells, thus preventing re-endothelialization and predisposin to late stent thrombosis. Dr. Rogers describes the ideal drug-eluting stent as having anti-thrombotic, anti-inflammatory, anti-proliferative, and non-toxic properties, allowing for arterial healing, complete endothelialization, no late intimal "catch-up," and no late thrombosis.

Pathobiology

Dr. Andrew Farb of the Armed Forces Institute of Pathology presented a comparative biologies of drug-eluting stents with insights into effectiveness and toxicity from the animal lab. A clear dose response in the reduction of restenosis with paclitaxel was shown when stents were loaded with doses ranging from 1.5 μg to 42 μg. Local toxicity, defined as neointimal hemorrhage associated with the stent struts, was more common in the higher dose ranges. In addition, a more robust strut-associated inflammatory response was seen with the higher doses of paclitaxel. Other potential local toxic effects of paclitaxel-eluting stents include medial necrosis and persistent fibrin deposition. After 90 days, the intimal surfaces were fully healed, with full surface endothelialized with the paclitaxel-eluting stents; however, there was no reduction of neointimal growth. This remains a pharmacokinetic challenge, because as the level of drug is reduced with time, the "brake" for neointimal growth is released, and late neointimal proliferation ("catch-up") can occur, causing late restenosis.

Stent design is critical to maximize delivery of drug to the entire circumference of the vessel on curved segments.

The lack of long-term benefits of drug-eluting stents can be due to poor retention of the drug in the surrounding vascular tissues and to too rapid a release of the drug from the stent. Persistent fibrin deposition stimulates smooth muscle cell migration and proliferation and is a marker for late neointimal "catch-up." A combination of a drug-eluting stent with a systemically delivered "booster" may be what is needed to deal with these issues.

Sirolimus

Sirolimus is a naturally occurring antibiotic found on Easter Island that was developed and marketed for prevention of renal transplant rejection. It is a selective inhibitor of cellular proliferation. In the response to injury of a coronary artery by a coronary intervention, the inflammatory response and presence of thrombus result in the accumulation of growth factors and cytokines that activate receptors, inducing smooth muscle cell proliferation. By blocking the cell cycle, sirolimus blocks smooth muscle cell proliferation that would otherwise lead to their migration to the intima and matrix secretion resulting in restenosis.

First in Man. A variety of presentations were made regarding the use of sirolimus as a drug-delivery agent. Dr J. Eduardo Soussa of the Institute Dante Pazzanese of Cardiology presented the long-term (2-year) outcomes from the First in Man (FIM) trial, comparing the slow and fast release of sirolimus in 30 patients on a Bx-velocity stent, and then compared the FIM results to the fast-delivery

system in the RAVEL (Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de novo Native Coronary Artery Lesions) trial at 6 months.

In the FIM trial, intravascular ultrasound at 2 years showed the slow-delivery system to be associated with better lumen volumes, lower neointimal volumes (2.2% at 12 months and 3.3% at 24 month), and less stent obstruction. Event-free survival at 2 years was 93%, with a 2.3% incidence of Q-wave myocardial infarction and 2.3% incidence of target vessel revascularization. No aneurysms, pseudoaneurysms, perforations or other systemic disorders were observed in this small (n = 45) trial.

The restenosis rate in the RAVEL trial was 0% with no significant late loss or edge effect seen in the drug-eluting stent group.

RAVEL. Dr. Marie-Claude Morice of the Institut Cardiovasculaire Paris presented 6-month data from the RAVEL trial. The restenosis rate was 0% with no significant late loss or edge effect seen in the drug-eluting stent group.

Coated versus non-coated stents. Dr. Jeff Moses of the Cardiovascular Research Foundation presented the early safety data from the U.S. Multicenter, Randomized, Double-Blind Study of the Sirolimus-Eluting Stent in Coronary Lesions trial, comparing the coated and non-coated Bx velocity stent. Unblinded data at 30 days shows a 6.7% major adverse cardiovascular event rate and a 6.5% rate of myocardial infarction. A low rate of subacute thrombosis has been observed so far.

PCI versus CABG in diabetics. Dr. Valentin Fuster of the Mount Sinai Medical Center presented the rationale and design of a diabetic percutaneous coronary intervention (PCI) (sirolimus-eluting stent) versus coronary artery bypass graft (CABG) trial. Diabetic patients in the post–"internal mammary artery era" have higher rates of revascularization when undergoing percutaneous transluminal coronary angioplasty versus CABG, though event-free survival from death, myocardial infarction (MI), and cerebrovascular accident was similar between patients. If the drug-eluting stents are able to nullify the revascularization rate advantage of CABG in diabetics and maintain the equivalent rates of major complications, the treatment of diabetics with multivessel disease will be approached more commonly in the catheterization laboratory. The Future Revascularization Evaluation in Patients with Diabetes Mellitus Optimal Management of Multivessel Disease Trial (FREEDOM) will address this important issue.

Other sirolimus studies. Dr. Alexander Abizaid of the Institute Dante Pazzanese of Cardiology presented the Brazilian registry of treating in-stent restenosis with the sirolimus-coated Cypher stent. The late lumen loss seen in this registry was superior to what was observed in brachytherapy trials. He concluded that the implantation of a drug-eluting stent was a safe, feasible, and effective treatment for in-stent restenosis. Dr. Vincent Oliva of the Hospital Notre Dame presented the results of the Clinical Investigation of the Sirolimus Coated Cordis SMART Nitinol Self-Expandable Stent for the Treatment of Obstructive Superficial Femoral Artery Disease (SIROCCO) trial. This trial randomized 36 patients to either a 1.25-mg sirolimus-coated stent or a control, non-coated stent. At 6 months, there was a trend toward less in-stent restenosis in the drug-treated group (23% vs 31%, $P = .29$).

Paclitaxel

Paclitaxel is another agent being studied to prevent restenosis. Paclitaxel alters the microtubule dynamic and also interrupts other cellular and molecular pathways leading to restenosis. Its dosing range provides a wide safety margin, and its lipophilic properties enhance tissue uptake and sustained effects.

The TAXUS trials. Dr. Gregg Stone of the Cardiovascular Research Foundation presented the results of trials with a polymer-based paclitaxel (Taxol) delivery system (TAXUS I–VII). The Boston Scientific TAXUS program used an inert polymer carrier and EXPRESS stent platform. The polymer allows for more consistent dosing, controlled release kinetics, and structural integrity. Up to 40% of drug is lost on stent expansion without a carrier. It is thought that the small burst of drug release within the first 24 hours blunts the injury response, with the sustained, low-level release permitting healing. In TAXUS I, 6-month angiographic data showed a 27% diameter stenosis and restenosis rate of 10% in the control group and a 14% diameter stenosis and 0% restenosis in the drug-treatment group. A 32% reduction of the neointimal volume index was observed with drug treatment. TAXUS II was an efficacy study randomizing 537 patients to either a slow-rate release group or a moderate-rate release group. Blinded 30-day data shows a 3.4% and 1.9% MI rate, 0.7% and 0% subacute thrombosis rate, and 4.1% and 1.9% major adverse cardiovascular event rate (MACE) in the slow- and moderated-rate release groups, respectively. TAXUS III is a single reg-

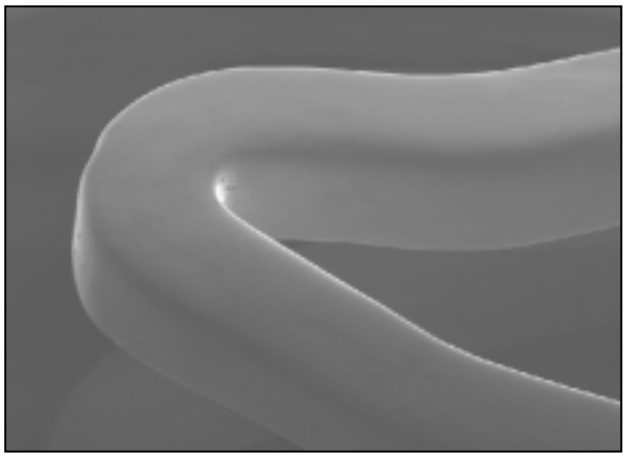

Figure 1. *Stent with nanoporous ceramic coating.*

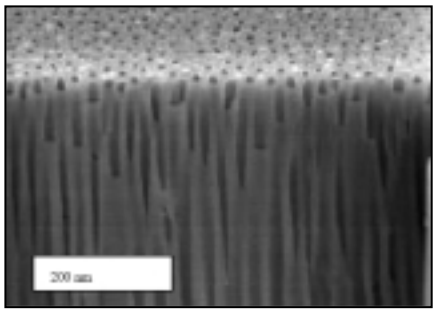

Figure 2. *Close-up of nanoporous ceramic coating.*

istry of 30 patients, with early 30-day data showing a 3.4% non-Q MI rate, 3.4% target vessel revascularization, and 6.9% MACE. TAXUS IV is a pivotal trial evaluating 1172 patients in the United States using a slow-release delivery system, with enrollment expected to begin in 2002. TAXUS VII will be a pivotal trial comparing the paclitaxel-impregnated, polymer-coated stent with brachytherapy.

ELUTES. The results from the ELUTES trial comparing four different doses of paclitaxel to an uncoated stent were presented by Dr. Bernard Chevalier of the Centre Cardiologie de Nord. The device used is the V-Flex Plus (Cook, Bloomington, IN) coated with paclitaxel, adhered to the abluminal surface using a proprietary process with no polymer. The 6-month angiographic results showed a dose–response effect with a 34% diameter stenosis and 21% binary restenosis rate in the control stent, 33% diameter stenosis and 20% binary restenosis rate in the lowest-dose group (0.2 $\mu g/mm^2$) and 14% stenosis and 3.7% restenosis in the highest-dose group (2.7 $\mu g/mm^2$). Safety data at 1 month showed safety across the different drug concentrations. In diabetic patients, the rate of restenosis in the highest-dose group was about 33% versus near 0% in nondiabetics. Across all drug doses in diabetics, paclitaxel was able to reduce restenosis from about 65% to between 25% and 33% but did not achieve the 0%–18% rates seen in the nondiabetic patients. Binary restenosis was observed to be lowest in larger vessels (>3.0 mm) compared to smaller vessels (<2.5 mm) among all patients.

Tacrolimus

Dr. Stone presented the in vitro studies and clinical trials with the JOMED (Helsingborg, Sweden) tacrolimus-eluting ceramic and polytetrafluorethylene (PTFE) stents. Tacrolimus is an immunosuppressive macrolide that suppresses T-cell proliferation and inhibits release of pro-inflammatory cytokines. Compared to rapamycin, tacrolimus has much more selectivity against the smooth muscle cells, thus sparing endothelial cells. (Paclitaxel selectivity is intermediate to the other two agents.)

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PRESENT. The Preliminary Safety Evaluation of Nanoporous Tacrolimus-eluting stents (PRESENT) study assessed the safety of the JOMED FlexMaster stent with a nanoporous ceramic coating (Figures 1 and 2), both with and without tacrolimus, in patients, using angiographic follow-up at 6 months and clinical follow-up at 2 weeks, 1, 6, and 12 months. This ceramic coating is a layer of aluminum oxide that has good tissue compatibility and intrinsic anti-restenotic properties and has been shown to reduce both macrophage and lymphocyte activity. Thirty patients received ceramic-coated stents, and 30 received the ceramic-coated stent including 60 μg of tacrolimus. Two patients receiving the drug-coated stent experienced adverse coronary events requiring target lesion revascularization at 67 days and another at 59 days.

EVIDENT. The Endovascular Investigation Determining the Safety of New Tacroliomus-eluting stent grafts (EVIDENT) trial evaluated the effectiveness of the PTFE platform in vein grafts. The stent used a higher dose (352 μg) of tacrolimus. In 15 patients who received the coated stent graft, no adverse events were observed early in the follow-up.

The conclusion of Dr. Stone, who presented these early phase I results, was that the ceramic coating as a

coating platform for drug delivery is a promising, antirestenotic coating with a 30-day major cardiac event rate of "0."

Other Trials

DELIVER. The important DELIVER trial design was presented by Dr. William O'Neill of the William Beaumont Hospital. This study, sponsored by Guidant Inc. (Indianapolis, IN), evaluated the safety and effectiveness of the ACHIEVE drug-eluting (paclitaxel) coronary stent system in the treatment of 1042 patients with de novo native coronary artery lesions (Figure 3). The dose of paclitaxel used in DELIVER is similar to that used in the ELUTES trial, which achieved a 3% restenosis rate using a non–polymer-based delivery system on a PENTA stent. This trial has just completed enrollment, with results expected to be released soon.

Figure 3. *The ACHIEVE Delivery System. Image courtesy of Guidant Corporation.*

The advent of drug-eluting stents will require that interventional cardiologists have a much clearer understanding of stent design, carrier properties, and pharmacokinetics.

Angiographic follow-up will be obtained at 8 months.

STRIDE. The BiodivYsio dexamethasone stent has a polymer coating that is non-thrombogenic and non-inflammatory. The Study of Anti-Restenosis with BiodivYsio Dexamethasone Eluting Stent (STRIDE) trial results were presented. At a dose of 0.5 $\mu g/mm^2$, dexamethasone was able to achieve 6-month restenosis rates of 15%.

AVAIL. Dr. Nicholas Kipshidzie of the Cardiovascular Research Foundation presented data relating to the local delivery of a third-generation c-myc antisense oligonucleotide. C-myc, as an early expression gene, is an important proliferative protein that is elevated after vessel injury and results in cellular proliferation. Resten-NG is an antisense oligonucleotide that inhibits the cell cycle at multiple points, making it effective regardless of what stage of cell growth the drug may find the cell in. Resten-NG has more impact on new DNA synthesis of smooth muscle cells than endothelial cells. This selective effect, sparing the endothelial cells, allows for the maintenance of proper endothelial function. The phase II study evaluating intramural delivery of resten-NG in patients with focal de novo stenosis or in-stent restenosis, The AVAIL trial, is currently evaluating this agent.

Summary

There is no question that the advent of drug-eluting stents represents a quantum leap in our ability to effectively prevent and treat restenosis. However, unlike "plain old stenting" (POS) this new pharmaco-mechanical approach will require that interventional cardiologists have a much clearer understanding of stent design, carrier properties, and pharmacokinetics, to maximize the advantages of placing these expensive devices, than was the case during the "good old days" of POS. [Norman E. Lepor, MD, FACC, FAHA, Alan C. Yeung, MD]

A Randomized Comparison of the MULTI-LINK Stent with or without Adjunctive Directional Coronary Atherectomy in Coronary Artery Lesion: The AMIGO Trial

There has been continuous debate in the interventional community as to whether proper debulking before stenting can reduce restenosis rates. Many avid directional coronary atherectomy (DCA) operators hold this notion dear to their hearts.

The Atherectomy before Multilink Improves Lumen Gain Outcome (AMIGO) trial was designed to demonstrate a reduction in late lumen restenosis in patients treated with a stent with or without prior atherectomy, both in de novo and in restenotic lesion in native coronary arteries. This study was performed in six European centers with 753 patients enrolled and randomized. The study protocol's aim was to include complex lesions, such as bifurcation and ostial lesions, with length greater than 12 mm. The operators were encouraged to perform optimal DCA, aiming for a <20% residual stenosis before stenting. Only 21% of the cases achieved this atherectomy result.

The baseline characteristics were well matched between the two groups, with mean lesion length of 14.5 mm (61% of lesions were >12 mm); 16% of lesions were on bifurcations, and 10% were ostial in location. The pre-DCA stenosis was 70%, DCA reduced stenosis to 32%, and after stenting

stenosis was reduced further to 1%. Stenting alone achieved a final stenosis of 5%.

MACE at 30 days was similar between the two groups, though a trend was seen in the DCA + stent group toward a higher incident of MI (3.1% [DCA + stent] vs 1.6% [stent alone], with non-Q wave MI of 2.1% vs 1.3%). Target lesion revascularization was low in each group (1.6% vs 1.1%). Binary restenosis rate at follow-up angiography was 24.1% vs 19.6%. If optimal DCA was performed, restenosis rate was 16.8%, and in the bifurcation group restenosis was 9.8% with DCA.

Unfortunately, the AMIGO study did not achieve the optimal DCA in complex lesions it was aiming for. Thus, it still leaves the issue of atherectomy before stenting unresolved. A few observations are now certain: 1) in simple lesions (short, focal, non-bifurcation), DCA adds little benefit to stenting alone; 2) in complex bifurcation, DCA's role of preventing plaque shift remains an attractive option, with the potential added benefit of reducing restenosis; 3) optimal DCA + stenting may still be better than stenting alone, especially in bulky lesions.

[Alan C. Yeung, MD]

The BNP Multinational Study

This year's meeting of the ACC provided the usual complement of multicenter, randomized trials of treatment safety and efficacy. One trial, however, was a prospective, multicenter, blinded evaluation of the utility of a diagnostic test, B-type natriuretic peptide. This trial is important, as it not only definitively demonstrates the usefulness of a new blood test for a cardiac condition, but also has created a prototype for future pivotal trials of diagnostic tests that are expected in the upcoming era of proteonomics and genomics.

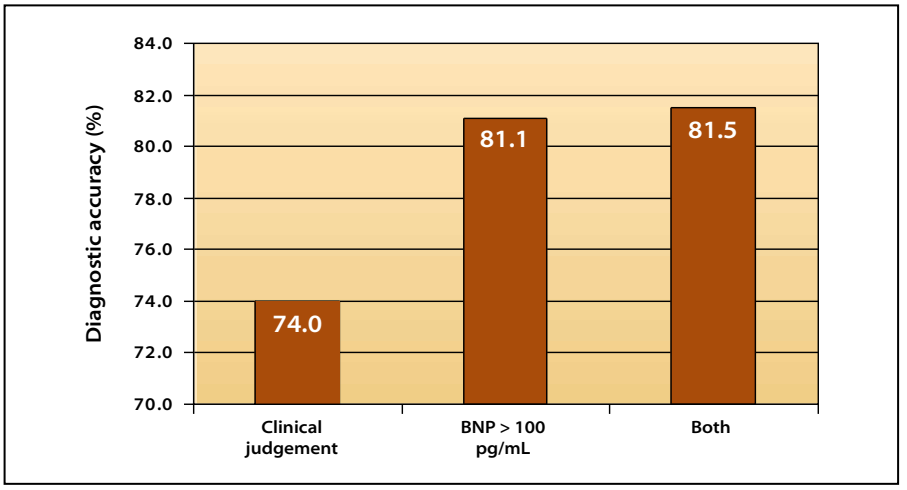

Figure 4. *Diagnostic accuracy of clinical judgment, B-type natriuretic peptide (BNP) > 100 pg/mL, and both. P < .0001 for BNP or both versus clinical judgement.*

B-Type Natriuretic Peptide

The neurohormone B-type natriuretic peptide (BNP) is released from ventricular myocytes in response to wall tension caused by ventricular volume expansion and pressure overload. Measurement of BNP has been approved by the U.S. Food and Drug Administration (FDA) as an aid to the diagnosis of congestive heart failure (CHF). In the prospective Breathing Not Properly (BNP) Multinational Study,[1] investigators sought to determine the diagnostic utility of BNP in the emergency department (ED) evaluation of dyspnea in a broad spectrum of patients.

Methods

A total of 1586 patients who presented to the ED with acute dyspnea as their primary complaint on arrival underwent measurement of BNP with a point-of-care device (Biosite Incorporated, San Diego, CA). Patients with acute myocardial infarction or renal failure as the cause of dyspnea were excluded. Emergency physicians were asked to give a blinded, pre-test probability of the diagnosis being CHF. The gold standard for CHF was adjudicated by two independent cardiologists, blinded to BNP results, who reviewed all clinical data and standardized CHF scores. The primary endpoint was diagnostic accuracy. The analysis used a Bayesian approach, which took into account the *a priori* pretest probability from the ED clinician, the BNP test converted to a likelihood ratio through the range of diagnostic values, and a post-test probability generated from these two values.

Results

The final diagnosis was CHF in 744 (46.9%), a history of CHF and left ventricular (LV) dysfunction but dyspnea due to noncardiac causes in 72 (4.5%), and not CHF in 770 (48.5%). Median level of BNP in the patients with CHF as a final diagnosis was 600 pg/mL; in those with LV dysfunction but a noncardiac cause of dyspnea, 150 pg/mL; and in patients without CHF, 50 pg/mL ($P < .0001$). Among the patients with a final diagnosis of CHF, BNP levels varied significantly as a function of New York Heart Association (NYHA) class; the median BNP values for NYHA class I (n = 18), II (n = 152), III (n = 351), and IV (n = 276) were 150, 250, 550, and 900 pg/mL, respective-

ly. At a cutoff of 100 pg/mL, BNP had a diagnostic sensitivity of 90%, a specificity of 76%, a positive predictive value of 79%, and a negative predictive value of 89%. For the primary endpoint of diagnostic accuracy, clinical judgment (with ED physicians required to be at least 80% certain of a CHF diagnosis) achieved an accuracy of 74.0%, the BNP test achieved an accuracy of 81.1%, and clinical judgment combined with the BNP test an accuracy of 81.5% ($P < .0001$) (Figure 4). In 43% of cases, the ED physician was uncertain of the final diagnosis (ED probabilities between 20% and 80%). In these cases, if BNP at a cutoff of 100 pg/mL clarified diagnosis in 75%, this left an absolute 11% of patients in whom there was diagnostic uncertainty, implying that additional testing would be warranted.

Discussion

In conclusion, BNP adds independent diagnostic information to traditional components of the CHF evaluation, including history, physical examination, and chest x-ray. Mean BNP values reflect functional class in patients with heart failure. In patients for whom the conventional ED diagnosis of heart failure is equivocal, the use of BNP at a cutoff of 100 pg/mL will correctly classify 74% of cases. The implications of this study are that BNP should be included as a component in the initial diagnostic evaluation of dyspnea, where it can play a role in confirming the clinical diagnosis and, importantly, improving diagnostic accuracy in the large proportion of cases where there is uncertainty.

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

Eplenerone and Enalapril Therapy

The renin-angiotensin-aldosterone system contributes importantly to the physiologic regulation of salt and water balance, circulatory homeostasis, and the maintenance of blood pressure. In pathologic states such as hypertension and congestive heart failure, angiotensin II and aldosterone may contribute to left ventricular hypertrophy and remodeling. Angiotensin II induces expression of multiple genes that mediate cardiac hypertrophy, including *C-fos, C-jun, C-myc*, and TGF-β1. Aldosterone may promote the growth of fibroblasts and the synthesis of type 1 and type 2 collagen. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists reduce left ventricular hypertrophy in patients with hypertension. In the Randomized Aldactone Evaluation Study (RALES), the addition of the aldosterone antagonist spironolactone, to patients with congestive heart failure already receiving an ACE inhibitor, resulted in a 30% reduction in total mortality rate compared to patients who received placebo. Addition of spironolactone was associated with reductions in death and in hospitalizations related to heart failure.

At the ACC Annual Scientific Session, Dr. Bertram Pitt and colleagues presented the results of a study that sought to determine whether aldosterone blockade favorably affected left ventricular hypertrophy in patients with hypertension.[2] They studied 202 patients with mild to moderate hypertension and left ventricular hypertrophy. Patients were randomized to one of three therapies including eplerenone, an aldosterone blocking agent (200 mg q.d.), enalapril, an ACE inhibitor (40 mg p.o. q.d.), or a combination of eplerenone (200 mg p.o. q.d.) and enalapril (10 mg q.d.). The patients were followed for 9 months. The primary endpoint was left ventricular hypertrophy assessed by magnetic resonance imaging. Left ventricular mass was reduced by 14.5 g with eplerenone ($P < .05$), by 19.7 g with enalapril ($P < .05$), and by 27.2 g with the combination of eplerenone and enalapril ($P < .05$). The combination of eplerenone and enalapril caused a greater reduction in left ventricular mass than either eplerenone or enalapril alone ($P = .007$). Eplerenone decreased systolic and diastolic blood pressure by 23.8 and 11.9 mm Hg, enalapril by 24.7 and 13.4 mm Hg, and the combination by 28.7 and 14.4 mm Hg, respectively. In addition, the urinary albumin/creatinine ratio decreased by 62% with eplerenone, compared to 45% for enalapril. The combination of eplerenone and enalapril decreased the urinary albumin/creatinine ratio by 74%.

The combination of eplerenone and enalapril caused a greater reduction in left ventricular mass than either eplerenone or enalapril alone.

Thus, eplerenone reduced left ventricular mass to a comparable extent as enalapril in patients with hypertension. The combination of eplerenone and enalapril was more effective in reducing left ventricular mass than either agent alone. These findings lend support to a therapeutic strategy employing aldosterone antagonists in patients with hypertension and left ventricular hypertrophy.

[Mark A. Creager, MD, FACC]

LIFE Study

Clinical trials in hypertension have tended to confirm that the different classes of antihypertensive agents are closely similar to each other in

Table 1
LIFE STUDY*: Adjusted† Hazard Ratios (95% CI), Losartan vs Atenolol

	Whole Study (Losartan: n = 4605, Atenolol: n = 4588)	Diabetic Patients (Losartan: n = 586, Atenolol: n = 609)
Primary composite endpoint‡	0.87 (0.77-0.98), *P* = .021	0.76 (0.58-0.98), *P* = .031
Cardiovascular mortality	0.89 (0.73-1.07), *P* = .206	0.63 (0.41-0.95), *P* = .028
Stroke	0.75 (0.63-0.88), *P* = .001	0.79 (0.55-1.14), *P* = .204
Myocardial infarction	1.07 (0.88-1.31), *P* = .491	0.83 (0.55-1.25), *P* = .373
New onset diabetes	0.75 (0.63-0.88), *P* = .001	Not applicable

* Selected endpoints.
† For degree of left ventricular hypertrophy and Framingham risk score at baseline.
‡ Cardiovascular mortality, stroke, and myocardial infarction.

their ability to prevent major cardiovascular endpoints like strokes, heart attacks, and heart failure. For this reason, much excitement was generated by the dramatic results of the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study that was presented at the 2002 Scientific Session of the ACC. The data were published almost simultaneously in a major journal.[3] As the results of this study are further evaluated by experts in this field, it is quite possible that they will alter future guidelines for the management of hypertension.

Losartan was significantly more effective than atenolol in causing regression of left ventricular hypertrophy.

The LIFE study provided powerful insight into the potential value of using angiotensin-receptor blockers in hypertension. This double-blind randomized trial compared 4605 patients treated with losartan-based therapy to 4588 patients on atenolol-based therapy. The patients, who ranged from 55 to 80 years old (average age: 67), with left ventricular hypertrophy demonstrated by EKG, were started on 50 mg of either losartan or atenolol. To achieve blood pressure control, the doses of either drug could be increased to 100 mg and, if necessary, hydrochlorothiazide and other agents could be added. Baseline blood pressure value in the losartan group was 174/98 mm Hg, and it fell by 30/17 mm Hg by the end of the study; the baseline value in the atenolol group was 175/98 mm Hg, and it fell by 29/17 mm Hg by the end of the study.

Despite these virtually identical blood pressure effects, as shown in Table 1, there were clear differences in the effects of the drugs on major endpoints. The primary study endpoint was a composite of cardiovascular mortality, stroke and myocardial infarction, in which losartan produced a 13% relative risk reduction (*P* = .021) compared with atenolol. Although other endpoints, including cardiovascular mortality, myocardial infarction, or hospital admissions for cardiac events or revascularization procedures did not achieve significance as individual endpoints, there was a dramatic 25% reduction in stroke (*P* = .001) and a 25% reduction in new-onset diabetes (*P* = .0001). Losartan was also significantly (*P* = .001) more effective than atenolol in causing regression of left ventricular hypertrophy. Within the total cohort of 9193 patients, there were 1195 who had diabetes at baseline; 586 were randomized to losartan, and 609 to atenolol. The results in these pre-specified subgroups are also shown in Table 1. Outcomes in these patients were closely similar to those of the cohort as a whole, indicating that the cardiovascular protective effects of losartan apply to diabetic as well as non-diabetic, hypertensive patients.

One of the surprising findings from this study was that the superiority of the angiotensin-receptor blocker over the β-blocker was seen predominantly in stroke prevention. Previously, there had been a general assumption that stroke, perhaps more than any other hypertension endpoint, was primarily blood pressure dependent and that there would be no meaningful differences when comparing antihypertensive drug

classes. Some support for the possible importance of interrupting the renin–angiotensin system in preventing stroke was suggested by the Heart Outcomes Prevention Evaluation (HOPE) study,[4] in which the angiotensin-converting enzyme (ACE) inhibitor ramipril was significantly superior to placebo in reducing stroke incidence, as well as other cardiovascular endpoints, in high-risk patients. Because only a modest blood pressure difference was reported in that study between the ACE inhibitor and placebo, the investigators argued that non-hemodynamic actions of the drug could account for its beneficial effects.

Even more recently, however, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed a somewhat conflicting result.[5] In patients who had already experienced a first stroke, the ACE inhibitor perindopril alone did not significantly alter the incidence of recurrent strokes during the trial, although the combination of the ACE inhibitor and a diuretic was highly protective. Because the combination therapy reduced blood pressure quite sharply, this seems to suggest—in contrast to the HOPE study—that it was blood pressure reduction rather than blockade of the renin–angiotensin system that produced the beneficial effects on stroke. The recent LIFE study, though, appears to support the conclusions of the HOPE study that angiotensin II blockade matters, but clearly the last word on this issue has yet to be said.

Another finding from the LIFE study was the superiority of losartan in producing regression of left ventricular hypertrophy. During the trial itself this effect did not seem to produce any obvious benefits in terms of decreasing the incidence of cardiac events, although there was a reduction in hospitalization for congestive heart failure in the diabetic cohort treated with the angiotensin-receptor blocker. Also, because left ventricular hypertrophy is frequently a precursor of heart failure, particularly diastolic dysfunction, it is possible that the use of losartan over a more prolonged period of time could ultimately be shown to prevent the clinical appearance of heart failure.

With the exception of the special case of diabetic nephropathy, the LIFE study is the first major clinical trial in hypertension in which one active agent has demonstrated clear endpoint superiority over another. What is particularly tantalizing about this finding is that the comparator agent, atenolol, is a member of the β-blocker class that has been recommended as a preferred first-line therapy for the usual treatment of hypertensive patients.[6] It could now be argued quite validly that the LIFE study has propelled the angiotensin-receptor blocker class into a position where it should now be strongly considered for routine use in initiating therapy of hypertension. Losartan and the other agents in this class are not only effective at reducing blood pressure, but are very well tolerated. It will be interesting to observe how prescribing patterns in hypertension, particularly as far as angiotensin-receptor blockers are concerned, will change during the next few years.

[Michael A. Weber, MD]

The recent LIFE study appears to support the conclusions of the HOPE study that angiotensin II blockade matters.

Patent Foramen Ovale

Since the advent of transesophageal echocardiography, with its increased sensitivity for the detection of patent foramen ovale (PFO), there has been great interest in the prevalence of PFO and the potential for a causal relationship in patients with stroke or transient ischemic attack (TIA). Because PFOs are present in 27%–35% of patients in large autopsy series, the probability of finding a PFO in stroke patients is very high and proof of its role in permitting right-to-left passage of embolic material rare. More recently, percutaneous device closure of atrial septal defects and PFOs has become widely available, and many patients are undergoing these procedures based solely on capability, without data on proven efficacy. A few early studies have shown that both TIAs and stroke often recur even after device closure, and a number of complications of the devices themselves have been reported. Recent data presented at the ACC Scientific Session by Windecker and colleagues[7] from the Swiss Cardiovascular Center, Bern, Switzerland, shed some new light on the subject.

This study compares the risk of recurrence following TIA or stroke in patients undergoing percutaneous PFO closure with those treated medically. A total of 311 patients with TIA or stroke related to PFO were retrospectively included in a case-control study. Of these, 161 patients received medical treatment (oral anticoagulation: n = 80, or platelet inhibitors: n = 81), and 150 patients underwent percutaneous PFO closure.

The mean age of the study population was 50 ± 13 years. The two groups were matched for age, sex, and presence of an associated atrial septal aneurysm. The mean follow-up was 2.4 ± 1.9 years for the med-

ical treatment group and 2.2 ± 1.5 years for the device closure group. The average annual TIA and/or stroke rate was 6.6% in the medical group and 4.5% in the device closure group (P = .08). There were no recurrent major strokes in the device closure group, compared with seven recurrent events in the medically treated patients (P = .02). Patients with two or more events before enrollment were at higher risk for recurrence when treated medically (11% per year), compared to those with a device closure (5% per year; P = .01). Multivariate linear regression analysis identified arterial hypertension and more than one embolic episode at baseline as significant predictors for recurrence (odds ratio, 2.2; 95% CI, 1.1-4.9).

The study showed a nonsignificant trend toward decreased recurrence for the combined endpoint of TIA and stroke and a significant decrease in recurrent major strokes in patients with PFO and presumed paradoxal embolus undergoing percutaneous device closure when compared with medical treatment. The subgroup of patients with two or more events before enrollment had a significantly lower recurrence rate after percutaneous PFO closure compared with medical treatment.

The authors note, as have others, that TIAs are more common than major strokes following device closure. However, the follow-up periods are relatively short. Although this study clearly adds to our knowledge of this problem, it, like its predecessors, is still limited by relatively small numbers and short follow-up. The lack of understanding in this area is surprising, given that there is no shortage of patients (there are hundreds of thousands of strokes and TIAs in the United States each year), the available medical treatments are limited and certainly not experimental, and the methods of study are well established. Although device closure for PFOs and atrial septal defects is relatively new, its use is expanding rapidly despite a lack of controlled data supporting efficacy. This is clearly an area in need of far greater study, because the number of patients with strokes and/or TIA and PFO is enormous, and in the vast majority of patients causality cannot be proven, and one can only define association. Thus, as the authors suggest, confirmation of their results by a prospective randomized trial with longer follow up is badly needed.
[Arthur E. Weyman, MD]

The number of patients with strokes and/or TIA and PFO is enormous, and in the vast majority of patients causality cannot be proven.

Acute Coronary Syndromes

INTERACT Trial

Previous trials have demonstrated the superiority of low-molecular-weight heparin (enoxaparin) in comparison to unfractionated heparin in decreasing adverse outcomes (albeit at an increased risk of bleeding) in patients with acute coronary syndromes.[8,9] The Integrilin and Enoxaparin in Acute Coronary syndrome Treatment (INTERACT) trial[10] was designed to determine the safety and efficacy of enoxaparin in combination with the glycoprotein IIb/IIIa inhibitor eptifibatide. Accordingly, 746 patients with acute coronary syndromes (angina at rest with ST segment changes on electrocardiogram or serum markers above the upper limits of normal) in 54 hospitals across Canada treated with aspirin and eptifibatide (180 μg/kg intravenous bolus followed by 2.0 μg/kg/min infusion for 48 hours) were randomized to receive unfractionated heparin (70 U/kg followed by 15 U/kg/hr infusion or enoxaparin 1 mg/kg subcutaneous every 12 hours) for a minimum of 48 hours. Prescription of all other medications, the decision to proceed with coronary angiography, and the use of coronary revascularization was left to the discretion of the investigator. The primary endpoint of the trial was the incidence of major bleeding at 96 hours and the trial was sized based upon equivalency between groups. Secondary endpoints included clinical measures of efficacy.

Baseline characteristics were similar between the two groups, with an 80% index myocardial infarction (MI) rate overall. Coronary angiography was performed in 62%–65% of patients at an average of 100 hours, with 27%–30% of patients undergoing percutaneous coronary intervention and 12%–13% undergoing coronary bypass surgery. At 96 hours, noncoronary bypass surgery–related major bleeding was 1.8% versus 4.6%, (P = .03) in the enoxaparin and unfractionated heparin groups, respectively, although an alternative analysis using a different scale with a high threshold for bleeding revealed no difference between groups. Consistent with other trials, minor

The primary endpoint of the INTERACT trial was the incidence of major bleeding at 96 hours.

bleeding at 96 hours was observed more in the group receiving enoxaparin and occurred mostly at the local injection site. Interestingly, there was a dramatic reduction in the incidence of Holter monitor–detected ischemic episodes during the first 48 hours (14.0% vs 25.1%, $P = .0002$) and during 48–96 hours (12.7% vs 25.9%, $P < .0001$) in the enoxaparin group, compared to the unfractionated heparin group. Furthermore, at 30 days, the rate of death and nonfatal MI was 5.0% versus 9.0% ($P = .031$), and the rate of the composite endpoint of death, MI, and recurrent ischemia was 8.4% versus 12.6% ($P= .064$) in the enoxaparin and unfractionated heparin groups, respectively.

Commentary. This study suggests that for patients with acute coronary syndromes and high-risk features being treated with eptifibatide, the low-molecular-weight heparin enoxaparin improves outcomes in comparison to unfractionated heparin in terms of safety and efficacy. However, the optimal duration of therapy prior to undergoing coronary angiography and revascularization requires further study.
[Alice K. Jacobs, MD, FACC]

Percutaneous Coronary Intervention

Role of Statins Following Percutaneous Coronary Intervention

Although statins have been shown to improve outcomes in subjects with stable coronary heart disease or acute coronary syndrome, the benefit of routine use in association with percutaneous coronary intervention (PCI) has not been proven. The Lescol Intervention Prevention Study (LIPS) Trial, led by Dr. Patrick Serruys, principal investigator, enrolled 1677 patients with coronary artery disease following successful PCI.[11] Patients were randomized to 80 mg (40 mg twice daily) of fluvastatin or placebo and were followed for over 3 years. The mean age of subjects was 60 years, 83% were men, 1.4 lesions were intervened per patient, and 56% received stents. The mean initial total and low-density lipoprotein (LDL) cholesterol levels were 200 mg/dL and 132 mg/dL, respectively. On treatment, LDL cholesterol levels were 99 mg/dL and 130 mg/dL for treatment and placebo groups, respectively.

The primary endpoint was a major adverse cardiac event (MACE), such as cardiac death, nonfatal myocardial infarction (MI), repeat coronary artery bypass graft, or PCI. Fluvastatin was started at an average of 2.7 days after successful PCI and reduced MACE by 22% ($P = .019$), with a separation of the treatment curves at approximately 1.5 years. Event-free time was also significantly increased by 34% ($P = .002$), and cardiac death was reduced 47% ($P = .07$). Patients with multivessel disease had a greater primary endpoint risk reduction (34%), as did those subjects with diabetes (38%). Dr. Serruys commented that the event curve in the fluvastatin group appeared to "flatten out" at about 1 year. The results strongly support the use of statins in patients undergoing PCI, regardless of initial cholesterol level.

Results strongly support the use of statins in patients undergoing percutaneous coronary intervention, regardless of initial cholesterol level.

The findings of a prospective registry by Chan and colleagues from the Cleveland Clinic add further support to the findings of the LIPS Trial. Between 1993 and 1999, 6647 patients were enrolled in this registry, and 23.5% of these patients were on statins.[12] The statin group had a lower mortality in 30 days (1% vs 2.5%, $P = .0007$) as well as at 6 months (3.1% vs 4.9%, $P = .003$). Even after adjustment for differences in baseline characteristics between patients on statins and those not, treatment with statins at the time of PCI reduced mortality 6 months following PCI (relative risk [RR] = 0.66, $P = .017$).

Similar observations were also found in a prospective registry from eight Michigan hospitals of 16,932 patients undergoing PCI between July 1997 and September 2000.[13] A total of 9087 patients were on lipid-lowering therapy before the procedure. The in-hospital mortality was 0.5% for those on lipid-lowering therapy, as compared with 2.8% for those not on lipid-lowering therapy. After adjustment for differences in baseline characteristics, lipid-lowering therapy reduced in-hospital mortality significantly (RR = 0.31).

These three studies reinforce the findings of a large number of randomized clinical trials of lipid-lowering therapy and statin therapy in primary and secondary prevention. Collectively, these studies emphasize the need to ensure that all patients undergoing PCI are adequately evaluated for lipid abnormalities and that appropriate therapy is instituted. A number of studies have suggested that only 30% of patients undergoing PCI are currently on lipid-lowering therapy. Programs, such as the American Heart Association's *Get with the Guidelines* and the American College of Cardiology's *Guidelines Applied in Practice* programs, have been developed to insure compliance with secondary prevention guidelines for all patients hospitalized with coronary disease or acute MI. However, more needs to be done to insure adequate compliance with

current recommendations.

The results of the LIPS randomized trial and the previously reported Health Protection Study would also support the concept that all patients undergoing PCI, regardless of initial lipid levels, should be started on statin therapy. The lack of correlation between outcome and initial lipid values suggests that the non-lipid effects of statins may be more important than their lipid-lowering effects. A number of abstracts from the American College of Cardiology meeting emphasize the importance of markers in inflammation, such as C-reactive protein or interleukins, on the short- and long-term outcome of PCI. The benefits of statins may be more related to their anti-inflammatory effects than to other potential mechanisms.

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This is the first trial to demonstrate that patients undergoing PCI benefit at least as much from cholesterol lowering as stable coronary heart disease patients do. Further study is needed to determine the mechanism of benefit of statins in patients with coronary disease, but until then, more aggressive use of these agents in PCI patients is clearly warranted.

[David P. Faxon, MD, FACC, Robert A. Vogel, MD, FACC]

Electrophysiology

MADIT II Trial

The results from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) were presented at the American College of Cardiology meetings by its principal investigator, Dr. Arthur J. Moss of the University of Rochester Medical Center.[14] This was a primary prevention trial that evaluated survival benefit of an implanted cardiac defibrillator (ICD) in patients with a left ventricular ejection fraction (LVEF) of 0.30 or less who had a prior myocardial infarction (MI). The 1232 enrolled patients were randomized in a 3:2 ratio to receive an ICD or conventional medical therapy. Patient exclusion criteria included New York Heart Association functional Class IV for heart failure at enrollment; coronary revascularization within 3 months of enrollment; MI within 1 month of enrollment; and advanced cerebrovascular disease. The follow-up average was 20 months. The clinical characteristics were similar between groups. For example, for the ICD and conventional therapy group, respectively, mean age was 64 and 65 years, percent with left bundle branch block was 19% and 18%, and LVEF was 23% versus 23%. Similarly, use of angiotensin-converting enzyme inhibitors was 68% and 72%, and β-blocker use was 70% for both groups.

Results. During an average follow-up of 20 months, the mortality rate was 14.2% in the ICD group, compared with 19.8% in the conventional-therapy group, with a hazard ratio of 0.69 for risk of death from any cause in the ICD group compared with the conventional-therapy group ($P = .016$). The Kaplan-Meier survival estimates demonstrated that the survival curves began to separate at 9 months. There was a reduction in the rate of death after ICD therapy of 12% at 1 year and 28% at 2 years. Of note, there was a slightly higher incidence of new or worsened heart failure in patients who received a defibrillator.

Commentary. The MADIT II study supports and extends the observations of the Multicenter Unsustained Tachycardia Trial (MUSTT) and the Multicenter Automatic Defibrillator Implantation Trial I (MADIT I). All three multicenter randomized trials clearly demonstrate that prophylactic implantation of an ICD in high-risk patients with coronary artery disease substantially reduces overall mortality. MUSTT and MADIT I enrolled patients who had coronary artery disease with LVEFs of 40% or less (MUSTT) or 35% or less (MADIT I). Furthermore, these patients required the presence of nonsustained ventricular tachycardia, and at electrophysiologic study, sustained ventricular tachyarrhythmias were induced. Patients enrolled in MADIT II required much simpler entrance criteria. They all had evidence of coronary artery disease with a LVEF of 0.30 or less, but they did not require inducible sustained ventricular tachycardia or the presence of nonsustained ventricular tachycardia for enrollment. Thus, these patients would be easy to identify in any clinician's practice by merely analyzing the ejection fraction of patients with documented coronary artery disease, likely ones with previous MI. Some estimate the prevalence of such patients in the United States at more than 100,000.

How should the clinician integrate the results of MADIT II in the treatment of their patients? The "simple" answer would be to identify all such patients and refer them to an electrophysiologist for further care. Unfortunately, there is no indication for ICD implantation in a MADIT II patient at the time of this writing. Thus, until such an indication is given, it would be wise to search out such patients and at least refer them to an electrophysiologist for potential electrophysiologic studies. Assuming an indication is given for

MADIT II patients to receive an ICD, I feel it would still be in the best interest of the patient to have an electrophysiology consultation to see if further testing is necessary, or if they are indeed the best candidates to receive an ICD. One should remember that the survival benefit in MADIT II, although significant, was less than that noted in MUSTT and MADIT I, in which patients received electrophysiologic testing. The slight yet disturbing increase in congestive heart failure in patients who received an ICD in MADIT II deserves more study, but does not preclude the use of ICD in these patients if an indication is given.

The AFFIRM Trial

D. George Wyse, MD, of the University of Calgary, Alberta, Canada presented the results from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Trial, a National Heart, Lung, and Blood Institute–funded study involving 213 U.S. and Canadian centers. The study evaluated patients with persistent atrial fibrillation randomized to either rate or rhythm control. The primary endpoint of the study was all-cause mortality. There were 4060 patients randomized, with at least 2 years of follow-up achieved for each patient. Enrollment consisted of patients who were 65 years or older, or if under 65 years they had at least one of the following risk factors: high blood pressure, diabetes, previous stroke, or poor ventricular function. All individuals were able to take anticoagulation medication. Most importantly, the enrolling physician made the judgment that long-term treatment could be appropriate using either rate or rhythm control. Drugs for rate control were digoxin, β-blockers, or calcium channel antagonists, and they were used in relatively similar proportions. Rhythm control medication included amiodarone, sotalol, and propafenone, with amiodarone and sotalol being used more frequently.

Results. At follow-up, 60% of patients who were assigned to the rhythm control group were in normal sinus rhythm, and successful rate control was present in 80% of patients assigned to the rate-control limb of the study. The primary endpoint of mortality was not different between rate and rhythm control groups. When strokes occurred, it was typically in patients who either stopped warfarin or in whom the international normalized ratio fell below 2.0.

Commentary. The outcome of AFFIRM should help physicians manage patients with atrial fibrillation. In essence, for patients in whom rate control is an acceptable form of treatment, there appears to be no mortality advantage in trying to maintain sinus rhythm. It is important to stress that the entry criteria for AFFIRM included patients in whom rate control was an acceptable form of therapy. In other words, if patients have good rate control yet continue to experience troubling symptoms, the data from AFFIRM are not applicable to them. The data from AFFRIM may not apply to the younger patients with paroxysmal atrial fibrillation, in whom rate-control therapy may not be appropriate. Thus, it is important for the clinician to avoid extrapolating the results from AFFIRM to all patients they see with atrial fibrillation, but rather to use these data as an important new finding for those individuals who have AFFIRM-like qualities.

[Eric N. Prystowsky, MD]

[Note: Dr. Prystowsky serves as a consultant for Guidant Corporation.]

Heart Failure

Vasopeptidase Inhibition in Chronic Heart Failure

Neurohumoral activation plays a key role in the initiation and progression of heart failure. Neutral endopeptidase (NEP) inhibitors are a new class of pharmaceutical agents that have been shown to increase activity of endogenous vasodilators. NEP inhibitors inhibit the activity of the enzyme neutral endopeptidase, which degrades the natriuretic peptides (atrial, B-type, and C-type natriuretic peptides), bradykinin, and adrenomedullin. These inhibitors may provide additional benefit in heart failure, because they target the imbalance between endogenous vasoconstrictors and vasodilators in heart failure more than angiotensin-converting enzyme (ACE) inhibition alone. Vasopeptidase inhibitors provide dual inhibition against NEP and ACE. Ompatrilat is a vasopeptidase inhibitor that has been shown in preliminary trials to improve functional status in patients with heart failure compared to an ACE inhibitor.

The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial was designed to evaluate this new class of therapy in patients with mild to severe heart failure. The trial enrolled 5770 patients with New York Heart Association (NYHA) Class II-IV heart failure, left ventricular ejection fraction (LVEF) ≤ 0.30, and at least one hospitalization for heart failure in the past 12 months.[15] Patients were randomized to uptitration with the ACE inhibitor enalapril to target dose 10 mg b.i.d. or omapatrilat to target dose 40 mg q.d. The primary endpoint was all-cause mortality and heart failure hospitalizations. The trial had a 98% power to detect a 15% difference in the composite endpoint. The study also pre-specified a non-inferiority comparison.

Table 2
Results of the OVERTURE Trial

Endpoint	Enalapril (n = 2884)	Omapatrilat (n = 2886)	Hazard ratio (95% CI)	*P* value
Death/CHF hospitalizations	973 (33.7%)	914 (31.6%)	0.94 (0.86-1.03)	.187
All-cause mortality	509	477	0.94 (0.83-1.07)	.339
CV death/CV hospitalization	1275	1178	0.91 (0.84-0.99)	.024
Ischemic events	578	537	0.93 (0.83-1.05)	.233

Baseline characteristics of patients included mean age of 63 years, blood pressure 124/74, mean LVEF 0.24, with 48% of patients NYHA class II and 48% class III. Baseline medication use included β-blocker therapy in 52%, spironolactone in 42%, and digoxin in 60%. The results of the study were presented by Dr. Milton Packer (Columbia University, New York). The risk of death and heart failure hospitalization were similar between enalapril-treated patients, 33.7%, and omapatrilat-treated patients, 31.6%, odds ratio (OR) 0.94 (95% confidence interval [CI] 0.86-1.03, $P = .187$). Additional results are shown in Table 2. There was no significant heterogeneity by various subgroups. Omapatrilat was associated with a higher rate of hypotension (19.5% vs 11.5%, $P < 0.001$) and dizziness (19.4% vs 13.9%, $P < .001$) compared to enalapril. There was, however, no significant difference in the incidence of angioedema (0.8% vs 0.5%).

The risk of death and heart failure hospitalization were similar between enalapril-treated patients and omapatrilat-treated patients.

This study showed that the combination of ACE and NEP inhibition with omapatrilat was equivalent to ACE inhibition with enalapril for cardiovascular morbidity and mortality in patients with heart failure. Omapatrilat use was associated with more hypotension and dizziness. These disappointing results may imply that heart failure patients are relatively resistant to natriuretic peptides, or alternately that excess hypotension negated the potential benefits of neutral endopeptidase inhibition. ACE inhibitors, β-blockers, and aldosterone antagonists remain the standard of care for heart failure due to systolic dysfunction.

Endothelial Receptor Antagonists in Chronic Heart Failure

The endothelin system is activated in patients with heart failure, and plasma endothelin-1 levels correlate with disease severity and a worse prognosis. Endothelin receptor antagonists have been developed to block this neurohumoral system. In animal models of heart failure, endothelin receptor antagonists have produced improved survival. In a prior trial, Enrasentan Cooperative Randomized Evaluation (ENCOR), when the mixed ET-A and ET-B receptor antagonist enrasentan was added to standard heart failure therapy clinical status did not improve, and clinical outcomes appeared to worsen. Bosentan is also a mixed ET-A/ET-B receptor antagonist. The Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) I and II trials were designed to determine if the addition of bosentan to standard heart failure therapy improves clinical outcomes.

The study enrolled patients with NHYA Class IIIb and IV heart failure with LVEF ≤ 0.35. Patients were randomized to bosentan 62.5 mg b.i.d. followed by up titration to 125 mg b.i.d. in 4 weeks. This represents doses that are 1/8–1/4 of doses used in prior studies. The primary endpoint was the composite of death or heart failure hospitalization. The study randomized 1613 patients with mean age 67 years, LVEF 0.25, and blood pressure 120/75. The results of this study were also presented by Dr. Milton Packer of Columbia University.[16] The rate of death or heart failure hospitalization was 39.7% with placebo and 38.8% with bosentan, OR 1.01, $P = .90$. For all cause mortality the rate was 21.4% with placebo and 19.4% with bosentan, OR 0.94, $P = .54$. There appeared to be an early increased risk of mortality with bosentan followed by the survival curves converging. An early and sustained increase in edema and increased body weight with bosentan was noted in the trial. There was also a significant increase in bosen-

tan-treated patients with abnormal liver function tests (>3 × control: 3.4% placebo and 9.6% bosentan, $P < .001$).

The oral endothelin antagonist bosentan failed to reduce the risk of death or hospitalization in patients with chronic heart failure treated with standard therapy. There was a significant increased in fluid retention with this agent that occurred within 2 weeks and was sustained over the course of the study. The mechanisms for this deleterious effect will require further study. Endothelin antagonists with the doses and agents studied to date appear to offer no benefit and have the potential for harm in patients with chronic heart failure. Despite initially high expectations for the therapeutic role of endothelin receptor antagonists in systemic hypertension, post-myocardial infarction, and heart failure, the role of these agents may end up being confined to patients with pulmonary hypertension.
[Gregg C. Fonarow, MD]

Endothelin antagonists with the doses and agents studied to date appear to offer no benefit and have the potential for harm in patients with chronic heart failure.

WIZARD and AZACS Trials

Although inflammation clearly plays an important role in the development of atherosclerosis, the role of infection is less clear. Smaller trials have shown variable effects of antibiotics on cardiovascular events in subjects with coronary heart disease. The WIZARD trial (Michael Dunne, principal investigator) evaluated the effect of azithromycin on cardiovascular events in 7747 coronary heart disease subjects with at least 1:16 positive titers for *Chlamydia pneumoniae*, who were more than 6 weeks post-MI. Subjects had not undergone revascularization in at least 6 months. Azithromycin was given as 600 mg/day for 3 days and then weekly for another 11 weeks. Among subjects, the mean age was 62 years, and 18% were female. Statins and aspirin were used in 67% and 87% of subjects, respectively. At a 2.1-year mean follow-up, there was no significant reduction in the risk ratio of the primary composite endpoint of death, MI, revascularization, and hospitalization for angina (hazard ratio, 0.93; confidence interval, 0.83–1.05; $P = .23$), nor in any of the endpoint components. Those subjects who were male, smokers, and diabetic experienced stronger trends toward benefit, but none were statistically significant.

The Azithromycin After Acute Coronary Syndrome (AZACS) study (Bojan Cercek, principal investigator) evaluated the effect of azithromycin in subjects enrolled shortly after admission for acute coronary syndrome. A single dose of azithromycin 500 mg was followed by 4 days of 250 mg initiated 3–4 days after admission in 1439 subjects, 826 of whom had experienced an acute MI. After 6 months of follow-up, there was no difference in the composite primary endpoint of death, nonfatal MI, and revascularization (14.3% vs 14.9%, P = NS), nor in any of its components.

Clinical Message. The WIZARD and AZACS studies provide strong evidence that antibiotic azithromycin does not reduce cardiovascular risk after either acute MI or unstable angina. Although infection may play a role in the development of atherosclerosis, once the disease is present, antibiotics do not appear to be helpful.
[Robert A. Vogel, MD]

Although infection may play a role in the development of atherosclerosis, once the disease is present, antibiotics do not appear to be helpful.

Coronary Stents

ISAR-STEREO-2 Trial

Several factors, such as patient characteristics, lesion morphology, and stent implantation techniques, have been shown to influence the rate of in-stent restenosis. However, the results of the Intracoronary Stenting and Angiographic Results: Strut Thickness Effect on Restenosis Outcome-2 (ISAR-STEREO-2) trial[17] suggest that stent thickness may also play a role. In this study reported by Dr. Helmut Schuhlen of the German Heart Center in Munich, Germany, 611 patients undergoing percutaneous coronary intervention were randomly assigned to receive the first-generation Multi-Link® stent (Guidant Corporation, Indianapolis, IN) with 50-μm struts or the Bx Velocity™ stent (Cordis Corporation, Miami, FL) that has 140-μm struts. Patients with complex lesions were included in the study, and baseline characteristics were similar between groups. The primary endpoint of the trial, angiographic restenosis rate, was 17.9% in the Multi-Link stent group compared with 31.4% in the Bx Velocity stent group ($P < .001$), a 43% reduction (relative risk 0.57, 95% confidence interval, 0.42-0.78). In addition, median lumen diameter

at 6 months was significantly larger (1.96 mm) with the thin-strut stent in comparison to the thicker-strut model (1.70 mm). Target vessel revascularization was also significantly reduced in patients who received stents with thin struts (12.3% vs 21.9%). As anticipated, survival without myocardial infarction at 1 year was no different between groups (95.1% vs 93.7%). However, although procedural success was similar, device success was lower with the Multi-Link versus the Bx Velocity stent (87.1% vs 99.0%), a difference attributed to the fact that the Multi-Link stent is a first-generation device, whereas the Bx Velocity stent is a more recent design.

Target vessel revascularization was significantly reduced in patients who received stents with thin struts.

This study corroborates and extends the findings of the ISAR-STEREO-1 trial,[18] which reported that stents with similar design but different strut thickness were associated with different restenosis rates. Six months following the procedure, the stent with thinner struts (Multi-Link) was associated with a 15.0% restenosis rate, compared to 25.8% with the thicker struts (Multi-Link Duet).

Commentary. This trial demonstrates that there may be significant differences in restenosis rates based on stent thickness independent of design that should be taken into account when deciding among various stents for specific patients and lesions. Whether thinner stent struts are associated with less acute vessel injury and wall stress or facilitate more rapid re-endothelialization will require further study. However, the findings of this study have the potential to influence the results and design of future trials evaluating the influence of drug-eluting stents on the incidence of restenosis.

COAST Trial

In contrast to the promising results of several preliminary trials reporting dramatically reduced restenosis rates in patients treated with paclitaxel- and sirolimus-eluting stents, trial results with heparin-coated stents continue to be disappointing. In the Heparin-Coated Stents in Small Coronary Arteries (COAST) trial,[19] reported by Dr. Michael Haude of the University Essen in Germany, 600 patients from 21 centers in Europe with small (2.0–2.6 mm) coronary arteries were randomly assigned to treatment with balloon angioplasty, a bare stent, or a heparin-coated stent. Baseline characteristics were similar among the groups, and all patients were pretreated with aspirin and 10,000 units of heparin. Patients in the stent groups also received ticlopidine for 2–4 weeks post-procedure. The primary endpoint of the trial, restenosis at 6 months, was no different among groups (32% balloon angioplasty, 25% bare stent, 30% heparin-coated stent). Late loss was also similar among the three groups. As expected by the size of the trial, there was no difference in event-free survival.

The primary endpoint was a composite of death, reinfarction, or disabling stroke within 30 days of the initial event.

Commentary. This trial is consistent with previous studies reporting minimal efficacy in improving long-term outcomes in patients treated with heparin-coated stents and adds yet another study showing no difference in restenosis rates between balloon angioplasty and stents in patients with small coronary arteries. [Alice K. Jacobs, MD, FACC]

Percutaneous Coronary Intervention

DANAMI-2

Controversy continues to swirl around issues of the optimal reperfusion strategy for acute myocardial infarction (MI). Because of the large number of patients with the disease, and the documented benefit of two very different reperfusion strategies with different logistics and different risk/benefit ratios, large-scale studies have been required. The Danish Multicenter Randomized Trial on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) is one such study, which evaluates the strategies of care across the spectrum of patients at a range of institutions.

This study, presented by principal investigator Dr. Henning Rud Andersen of Skejby Hospital, Århus University Hospital, was performed at five percutaneous coronary intervention (PCI) centers and 24 referral centers in Denmark, which together treat approximately two thirds of the entire Danish population. It was aimed at evaluating fibrinolytic therapy with 100 mm of front-loaded tissue-type plasminogen activator versus PCI with a stent in patients with ST segment elevation MI. The study included patients with ST segment elevation MI, with the onset of symptoms within 12 hours

of randomization, in whom the transfer time from presentation at the referral hospital to the catheterization laboratory was ≤ 3 hours. Important study exclusion criteria were a contraindication to fibrinolysis, cardiogenic shock, or persistent, life-threatening, ventricular arrhythmias. The primary endpoint was a composite of death, reinfarction, or disabling stroke within 30 days of the initial event.

Based upon the study assumptions, 1900 patients were to be enrolled; the study was stopped early. Baseline demographics were similar between the two groups, with a mean age of approximately 63 years, 75% being male, and approximately 50% with anterior MI. In the five angioplasty centers, 443 patients were randomized to either PCI or fibrinolysis; in the referral hospitals, 1129 were randomized to either fibrinolysis or ambulance transfer for PCI. In the patients randomized to early- or urgent-transfer, serious events during transfer were very infrequent, with ventricular fibrillation at 1.4%, atrial fibrillation at 2.5%, and no mortality.

An important aspect of the trial was the actual treatment rate in each limb of the trial, which was very high. Of patients randomized to fibrinolytic treatment, 99% were treated with it; 99% of the PCI patients had an angiogram, and 87% of these were treated with a PCI.

The results of DANAMI-2 were dramatically positive. Of the 1572 patients randomized, there was approximately a 40% reduction (from 13.7% to 8%) in the primary endpoint of death, reinfarction, or stroke, at 30 days in patients undergoing PCI. For each of the individual components of the primary endpoint, the PCI group had improved outcome; individually, however, the only significant difference between the groups was with reinfarction (6.3% fibrinolysis vs 1.6% PCI, $P < .0001$). The primary composite endpoint was reduced, irrespective of whether the patients were seen initially at referral hospitals or at one of the five PCI centers.

When the data were broken down according to the time of treatment, the event rates were 9% and 13% in adenosine and placebo groups treated within 2 hours of symptom onset.

The DANAMI-2 trial is extremely important, and has major implications for the development of regional infarction centers. The investigators' conclusion stands by itself: with experienced centers, an initial strategy of transferring patients with ST segment elevation MI to centers for primary PCI is superior to fibrinolysis, when the transfer time is within 3 hours. [David R. Holmes, Jr., MD]

AMISTAD II Trial

The first Acute Myocardial Infarction Study of Adenosine (AMISTAD I) demonstrated a benefit on infarct size in patients with anterior MI, but not in patients with inferior infarcts. Among the latter there was an increase in bradycardia and hypotension. AMISTAD II, presented by Dr. Allan M. Ross, was confined to patients with anterior infarcts within 6 hours of symptom onset and was a much larger multicenter and multinational study, involving 2118 patients.[20] All patients underwent reperfusion therapy with primary angioplasty or fibrinolytics, and were randomized to three different treatment groups: placebo, adenosine 50 μg/kg/min for 3 hours, or adenosine 70 μg/kg/min for 3 hours. Protocol also specified that the adenosine groups would be pooled for analysis.

The primary combined endpoint was death, adjudicated congestive heart failure (CHF) on the index admission, or rehospitalization for new CHF up to 6 months after MI. Infarct size as defined by sestamibi single photon emission computed tomography at 5 days was the secondary endpoint.

Results

The primary combined endpoint results were 18%, 16%, and 15% in the placebo, pooled adenosine, and high-dose adenosine subgroups, respectively. The difference was not statistically significant, although the relative reduction versus placebo was 17% in patients receiving high-dose adenosine. Among patients in whom reperfusion was judged to be successful, the 6-month event rate was 11% versus 15% with placebo ($P = .043$), whereas in the presence of reperfusion failure, the corresponding rates were 33% and 34%, respectively (P = ns). We do not know at this stage what the definitions were for successful versus unsuccessful reperfusion.

The results of DANAMI-2 were dramatically positive.

When the data were broken down according to the time of treatment, the event rates were 9% and 13% in adenosine and placebo groups treated within 2 hours of symptom onset. Among patients treated 2 to 4 hours after symptom onset, the event rates

were 16% and 18%, and after 4 hours the trend was toward a higher event rate in the adenosine group (22% vs 20%; P = ns).

The secondary endpoint of infarct size as a percentage of the left ventricle was 26% in placebo treated patients, 23% with low-dose adenosine (P = .122), and 11% (P = .028) in the high-dose adenosine groups. Also of interest was the correlation between infarct size and clinical events. Among patients who had a clinical event at 6 months (s/CHF), the average infarct size was 43%, versus 17% in those without events (P = .001).

Comment

One of the new frontiers of reperfusion therapy is the shift "downstream" from flow in the epicardial infarct-related artery to the entity of myocardial perfusion or malperfusion.[21–23] Myocardial malperfusion is common, and in one series of patients with successful primary percutaneous coronary angioplasty, 16% of patients with Thrombolysis in Myocardial Infarction (TIMI) Grade 3 flow demonstrated the no-reflow phenomenon on myocardial contrast echocardiography.[23] Moreover, the severity of myocardial malperfusion as determined angiographically by the measurement of myocardial blush, has a major impact upon late prognosis, independent of TIMI flow grades.[22]

Several techniques for measuring myocardial perfusion are under evaluation, and although magnetic resonance imaging may be the most sensitive, it is also the most costly. The most practical technique from a clinical standpoint is the speed and extent of electrocardiographic ST-segment resolution.[24] Future developments in intravenous contrast will hopefully increase the applicability of myocardial contrast echocardiography.

Mechanisms

Microvascular dysfunction after reperfusion therapy is well documented, frequent, and clinically relevant. To what extent this is due to microvascular spasm, as opposed to obstruction secondary to thrombus, platelet aggregation, or atheroembolism, remains to be determined, and is probably multifactorial, with considerable variability among patients.[25,26] On the other hand, the concept of "lethal reperfusion injury" is much more controversial.[25] This entity probably does exist, at least in some animal models, but its clinical relevance is uncertain, as is the extent to which this can be ameliorated in the clinical setting.

Therapeutic Implications

There are many potential targets for the modification of microvascular dysfunction and reperfusion injury. Before coming back to the AMISTAD II Trial, we need to realize that although the agenda has been a large one, the results of randomized controlled trials to date have been rather unimpressive.[27,28] Agents and approaches that have shown some promise include adenosine, nicorandil, magnesium, glucose-insulin-potassium, aqueous oxygen, and hypothermia.[27,29] IIb/IIIa inhibitors appear to exert some effect in patients undergoing reperfusion therapy, suggesting that platelets and thrombo-emboli play some role. In one trial, Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up (ADMIRAL), in which many patients received IIb/IIIa inhibitors (abciximab) prior to reperfusion therapy, the results were positive, but less so in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Trial.[28]

Another problem relates to the timing of the administration of agents aimed at minimizing myocardial vascular dysfunction and/or reperfusion injury. Perhaps after 2–4 hours of symptoms it is already too late to exert an appreciable impact on the microvasculature? On the other hand, if patients were treated within 60 to 70 minutes of symptom onset, the relatively low mortality and small extent of myocardial necrosis would make it extremely difficult to demonstrate any additional effect as a result of an improvement in myocardial perfusion.

Conclusions

The AMISTAD II Trial does provide some encouragement in an area of investigation that has been characterized to date by enthusiasm based upon experimental data, only to be followed by disappointment when the agents were subjected to the more rigorous scrutiny of a clinical trial. There are several mechanistic reasons why adenosine could be beneficial as a cardioprotective agent; it is a mediator of ischemic preconditioning, reduces free radical formation, preserves energy stores, inhibits neutrophil activity, and plays a role as a local regulator of coronary blood flow through its effects on coronary vasomotor tone.[30,31]

The AMISTAD II trial is too small to provide definitive answers, and there was actually no statistically significant difference in the primary endpoint of death and CHF. Nonetheless, the trends are all in the right direction, and the reduction in infarct size with a higher dose of adenosine is quite encouraging. Clinical data also suggest that adenosine may be particularly effective in patients undergoing successful reperfusion and among those whose treatment was started early. The drug appears to be safe, and perhaps we

Main Points

- In the First in Man trial, intravascular ultrasound at 2 years showed the slow-delivery system with sirolimus to be associated with better lumen volumes, lower neointimal volumes, and less stent obstruction.
- In the TAXUS I trial, evaluating stents with a polymer-based paclitaxel delivery system, 6-month angiographic data showed a 27% diameter stenosis and restenosis rate of 10% in the control group and a 14% diameter stenosis and 0% restenosis in the drug-treatment group.
- The AMIGO trial demonstrated that in simple lesions, directional coronary atherectomy (DCA) adds little benefit to stenting alone, and that in complex lesions, such as ostial or bifurcation locations, DCA's role of preventing plaque shift remains an attractive option, with the potential added benefit of reducing restenosis.
- The results of the BNP Multinational Study imply that B-type natriuretic peptide should be included as a component in the initial diagnostic evaluation of dyspnea, where it can play a role in confirming clinical diagnosis (heart failure versus none) and improving diagnostic accuracy in the large proportion of cases where there is uncertainty.
- The results of a study that sought to determine whether aldosterone blockade favorably affected left ventricular hypertrophy in patients with hypertension demonstrated that the combination of eplerenone and enalapril was more effective in reducing left ventricular mass than either agent alone.
- The LIFE study has propelled the angiotensin-receptor blocker class into a position where it should now be strongly considered for routine use in initiating therapy of hypertension.
- A study comparing the risk of recurrence following transient ischemic attack or stroke in patients undergoing percutaneous patent foramen ovale closure with those treated medically showed a significant decrease in recurrent major strokes in patients undergoing percutaneous device closure when compared with medical treatment.
- The INTERACT study suggests that for patients with acute coronary syndromes and high-risk features being treated with eptifibatide, the low-molecular-weight heparin enoxaparin improves outcomes in comparison to unfractionated heparin in terms of safety and efficacy.
- The results of the LIPS study strongly support the use of statins in patients undergoing percutaneous coronary intervention (PCI), regardless of initial cholesterol level.
- The MADIT II study clearly demonstrated that prophylactic implantation of an implanted cardiac defibrillator in high-risk patients with coronary artery disease substantially reduces overall mortality.
- The outcome of the AFFIRM trial, which randomized patients with persistent atrial fibrillation to either rate or rhythm control, showed that for patients in whom rate control is an acceptable form of treatment, there appears to be no mortality advantage in trying to maintain sinus rhythm.
- The OVERTURE trial showed that the combination of angiotensin-converting enzyme (ACE) and neutral endopeptidase inhibition with omapatrilat was equivalent to ACE inhibition with enalapril for cardiovascular morbidity and mortality in patients with heart failure.
- In the ENABLE trial, the oral endothelin antagonist bosentan failed to reduce the risk of death or hospitalization in patients with chronic heart failure treated with standard therapy.
- The WIZARD and AZACS studies provide strong evidence that antibiotic azithromycin does not reduce cardiovascular risk after either acute myocardial infarction (MI) or unstable angina.
- The ISAR-STEREO-2 trial demonstrates that there may be significant differences in restenosis rates based on stent thickness independent of design that should be taken into account when deciding among various stents for specific patients and lesions.
- The COAST trial reports no efficacy in improving long-term outcomes in patients treated with heparin-coated stents in small arteries.
- The investigators of DANAMI-2 concluded that an initial strategy of transferring patients with ST segment elevation MI to centers for primary PCI is superior to fibrinolysis, when the transfer time is within 3 hours.

can expect further trials using the higher dose.

This is certainly a very interesting area of investigation, but to my mind, the disparity between the experimental results and clinical trials suggests that we need to understand a great deal more about mechanisms before we can expect "blockbuster" clinical trial outcomes. ■

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