Best of the AHA Scientific Sessions 2002

Highlights from the American Heart Association Scientific Sessions
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Key words: ASSENT III Plus Trial • Atrial fibrillation • ß-blockers • Bivalirudin • CARDINAL Trial • Cardiovascular disease • Carotid artery disease • Chronic kidney disease • Clopidogrel • CREDO Trial • DIAL Trial • Elastase • End-stage renal disease • Endothelium • Enoxaparin • Glycoprotein IIb/IIIa antagonist • Heparin • Hepatic lipase • Hospitals • IMPACT-HF Trial • Implantable cardioverter defibrillator • ISAR-COOL Trial • Myocardial infarction • Percutaneous coronary interventions • Peripheral arterial disease • PROSPER Trial • REPLACE 2 Trial • Roxifiban • SAPPHIRE Trial • Statins • Stents • Surgery • Tenecteplase • Thrombus • Thromboatherectomy • Vascular endothelial growth factor

In conjunction with the 2002 Scientific Sessions of the American Heart Association, abstracts were published reporting significant findings in every area of cardiovascular medicine. Here, our editorial board members have selected the presentations they find most worthy of review.

SAPPHIRE Trial

The treatment of carotid artery disease will be profoundly affected by the results of the SAPPHIRE Trial (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy).

Carotid arterial disease affects a large number of patients; some patients have asymptomatic stenosis, whereas others have recurrent reversible events with transient ischemic attacks or completed strokes, resulting in substantial morbidity and mortality. Approximately 730,000 strokes are reported each year in the United States, and death occurs as a result of these strokes in approximately 150,000.[1] The treatment options in the past have been either medical therapy with antiplatelet or anticoagulant agents, or surgical treatment with carotid endarterectomy (CEA). The latter procedure has been performed with increasing frequency since the publication of landmark randomized, clinical trials documenting improved outcome with surgical treatment, compared with medical treatment alone (North American Symptomatic Carotid Endarterectomy Trial [NASCET][2]

Table 1
The SAPPHIRE Trial: 30-Day MACE (Death, Any Stroke, or MI) Overall and in Symptomatic and Asymptomatic Patients

	Carotid Stenting (%)	Carotid Endarterectomy (%)	*P*
Group			
Overall	5.8	12.6	.047
Symptomatic patients	4.2	15.4	.13
Asymptomatic patients	6.7	11.2	.33
Complications			
Transient ischemic attack	3.8	2.0	.50
Major bleeding	8.3	10.6	.56
Cranial nerve injury	0.0	5.3	< .01

MACE, major adverse cardiac events; MI, myocardial infarction.

and the Asymptomatic Carotid Atherosclerosis Study [ACAS]).[3] It is estimated that up to 200,000 CEA procedures will be performed in 2002.

Over the past several years, the field has changed with the introduction of percutaneous interventional procedures, either percutaneous transluminal angioplasty or stent implantation, for treatment of these patients. There has been intense controversy regarding the relative merits of surgery (the traditional approach) or a catheter-based approach. Both safety and efficiency issues have been raised. These considerations led to the design and then subsequent completion of the SAPPHIRE Trial, which was presented at this year's AHA by Dr. Jay S. Yadav from the Department of Cardiology at the Cleveland Clinic Foundation.

The SAPPHIRE Trial compared stent implantation with a distal protection device with standard CEA for the treatment of high-risk patients with carotid arterial disease. Those high-risk features included at least one of the following; age greater than 80 years, presence of congestive heart failure, severe chronic obstructive lung disease, prior CEA with restenosis, prior neck radiation therapy or radical neck surgery, or lesions proximal or distal to the typical cervical position. These patients were either asymptomatic with a severe stenosis by ultrasound or symptomatic with ≥ 50% stenosis. The primary endpoint presented at the AHA meeting was the 30-day composite endpoint of death, stroke, or myocardial infarction.

The trial was designed to objectively answer the issues mentioned above. As such, the study protocol was that eligible patients were screened by a team that included a vascular surgeon, an interventionalist, and a neurologist, and consensus was required before randomization. Both surgeons and interventionalists participating in the trial had to meet preset volume and outcome parameters, and all were excellent. After review of each patient by the team and after patients provided informed consent, patients could be included in one of three categories: 1) they could be randomized; 2) if they were believed to be too high-risk for surgery, they could be treated in a registry by stent implantation and distal protection; 3) if they were believed to be too high-risk for stent placement, they could be treated in a registry by surgical CEA. The registry totaled 416 patients, of whom 409 were treated by stent implantation and distal protection because they were believed to be too high-risk for surgery, whereas only 7 were treated by a surgical approach because they were believed to be too high-risk for stenting.

The randomized study included 307 patients: 156 were treated with carotid stenting plus distal protection and 151 by CEA. The trial was stopped prematurely because of slowing enrollment related, according to the authors, to increasing numbers of patients becoming resistant to the concept of revascularization. In the stent limb, the distal protection device could be placed in 98% of patients and the stent in 91%. Material was removed from the filter in approximately 60% of patients. Thirty-day event rates were concordant irrespective of whether a composite endpoint was considered or just a single endpoint (Table 1). The primary endpoint of major adverse cardiac events (MACE) was 5.8% in the stenting plus distal protection limb, compared with 12.6% in the CEA limb (P = .047). Even in the patients in the stent registry who had been believed to be too high-risk to undergo surgical procedures, the 30-day MACE rate was only 7.8%,

Patients will benefit greatly from the applications of this percutaneous approach to the treatment of carotid artery disease.

less than the surgical MACE in the randomized trial.

This trial, the first multicenter, randomized, clinical trial of its kind, fundamentally changes the landscape by documenting that in these high-risk patients, carotid stenting with distal protection is superior to conventional CEA as a treatment approach. The trial does not answer all questions. First, it involves only one type of distal protection device and one type of stent. Second, it was performed by very experienced surgeons and interventionalists, and it only involved high-risk patients. Whether these results will be generalizable to all distal protection devices, or all stents performed by a variety of surgeons and interventional cardiologists in different subsets of patients, remains to be determined by subsequent studies and evaluations.

Having said that, the field will never be the same, and patients will benefit greatly from the applications of this percutaneous approach to the treatment of carotid artery disease. [David R. Holmes, Jr, MD]

Heart Failure

Randomized Trial of Telephone Intervention in Heart Failure Demonstrates Reduction in Hospitalizations: The DIAL Trial

There is a very high rate of noncompliance with medical therapy and dietary restrictions among heart failure patients. A number of studies of multidisciplinary disease management programs for heart failure have demonstrated improved use of evidence-based medications, improved patient education, improved functional status, improved quality of life, and a significant reduction in hospitalizations, when compared with conventional care. The questions of which components of the interventions are most important in improving outcomes and whether this management could be provided over the telephone have not been well studied previously.

In the DIAL trial (Randomized Trial of Telephone Intervention in Heart Failure), three nurses working from a single surveillance center followed patients with chronic heart failure who were treated at 52 medical centers across Argentina. There were 760 patients assigned to telephone intervention and 758 to usual care. Patients were followed for an average of 457 days. The nurses in the telephone intervention arm provided education and counseling to patients, covering six key areas: symptoms, adherence to therapy, daily weight control, dietary compliance, usual daily activity, and walking recommendations. According to the evaluation, the nurses could change the frequency of calls and adjust diuretic doses. A computer program analyzed the data and provided daily call lists that prompted the nurses to contact specific patients both routinely and more often if their answers during previous phone calls indicated a need. Throughout the process, nurses and physicians oversaw the recording of answers by patients and reviewed the data.

The results, presented by Dr. Daniel Nul (for GESICA, the Heart Failure Study Group of Argentina), showed that there was a 20% relative risk reduction of the primary endpoint, which was the combination of all-cause mortality or heart failure admission. There were 26.3% of the patients with primary endpoints among those in the telephone intervention group, compared with 31% in those who received usual care ($P = .026$). Admissions for heart failure were significantly reduced in the telephone intervention group, with only 16.8% being admitted to the hospital compared with 22.3% of those receiving usual care, a relative risk reduction of 28% ($P = .005$). There was no difference between the groups in all-cause mortality (15.3% vs 16.1%, $P = .69$). The telephone intervention appeared to have similar benefits in patients with milder (New York Heart Association [NYHA] Class I and II) heart failure and those with more severe (NYHA Class III and IV) heart failure. It also was effective in those patients with preserved ventricular function and those with systolic dysfunction.

These results translate into 18 patients needing to receive telephone intervention to prevent one heart failure hospitalization. Telephone heart failure management would appear to be a cost-effective intervention that could be applied to patients who do not have access to multidisciplinary heart failure disease management or specialty care for heart failure. Further research is needed to determine what actually accounted for the differences in hospital admissions between the groups.

Starting ß-Blocker Therapy Before Discharge in Patients Hospitalized for Heart Failure Increases Usage: IMPACT-HF

Beta-blockers have been shown to improve survival and reduce the need for hospitalization by 35% in several large-scale, prospective, randomized clinical trials in heart failure. Despite these beneficial effects, it is estimated that nationally only 30%–40% of eligible patients receive β-blocker therapy. Such low usage led the researchers to initiate a trial to determine whether starting β-blocker therapy in the hospital setting would improve usage.

The Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) trial was designed to test the value of in-hospital initiation of β-blocker therapy for heart

failure. For the trial, the researchers randomized 363 hospitalized heart failure patients at 40 U.S. sites to one of two groups: one received at least one dose of the β-blocker carvedilol prior to hospital discharge, whereas the other group could receive a β-blocker at their physician's discretion, but it could not be started until at least 2 weeks after discharge, according to current standard practice. Patients were eligible for randomization as long as they had not received a β-blocker within 30 days and had no contraindications to β-blockade, such as cardiogenic shock, decompensated heart failure requiring inotropic therapy, severe sinus bradycardia or high-degree heart block, bronchospasm, or symptomatic hypotension.

The results were presented at an AHA Satellite Symposium by Mihai Gheorghiade, MD, of Northwestern University and Wendy Gattis, PharmD, of Duke University. After 60 days, 91% of patients who were started on carvedilol prior to hospital discharge were still taking a β-blocker, whereas 73% of the physician-discretion group were taking them ($P < .001$). In addition, patients initiated on carvedilol before discharge were closer to reaching the target β-blocker dose at 60 days, as compared with the patients in the post-discharge, physician-discretion arm, a finding that was also statistically significant. The trial also demonstrated that early carvedilol treatment was safe. The patients initiated on carvedilol prior to discharge did not have a higher rate of serious adverse events, including worsening heart failure, hypotension, or bradycardia, as compared with the patients initiated post-discharge. Worsening of heart failure was seen in 9% with pre-discharge initiation of carvedilol and 14% with physician-discretion, post-discharge β-blocker therapy. Other important clinical events, such as death or rehospitalizations, were also less frequent at 60 days in the early treatment group, but, because of small patient numbers and the short duration of follow-up, did not reach statistical significance. Remarkably, length of stay tended to be shorter in those patients randomized to receive carvedilol prior to hospital discharge: 5.9 days versus 6.6 days for conventional care.

In-hospital initiation of ß-blockers for heart failure has now been demonstrated to be an effective method to increase the overall use of ß-blockers in this population and as a result reduce heart failure mortality.

Effective strategies to improve use of evidence-based, life-saving therapies are extremely important, as the death and disability of this group of heart failure patients continues to be alarmingly high. This trial demonstrated that beginning β-blocker therapy in-hospital can achieve a 91% usage rate 60 days after discharge and be done so safely. These new data should help encourage physicians to change long-held prescribing habits and routinely initiate β-blockers prior to discharge in stabilized heart failure patients without contraindications. Just as with in-hospital initiation of statins for coronary heart disease, in-hospital initiation of β-blockers for heart failure has now been demonstrated to be an effective method to increase the overall use of β-blockers in this population and, as a result, reduce heart failure mortality.

OPTIMIZE-HF

A new program, OPTIMIZE-HF (Organized Program To Initiate Life Saving Treatments in Hospitalized Patients with Heart Failure) is a hospital-based performance improvement system and web-based registry program that hopes to enroll up to 50,000 heart failure patients at approximately 500 hospitals across the United States. The goal of this initiative is to improve the management of heart failure patients by implementing process-of-care improvement based on current trial evidence and guidelines. OPTIMIZE-HF will allow physicians and nurses to take advantage of the latest findings from clinical trials and incorporate them into routine patient care.

[Gregg C. Fonarow, MD]

Arrhythmia Update

Secondary Prevention of Sudden Death

An important update from the Canadian Implantable Defibrillator Study (CIDS) was presented by Bokhari and colleagues.[4] The initial data from CIDS were reported in *Circulation* in 2000.[5] This study randomized 659 patients with resuscitated ventricular fibrillation, ventricular tachycardia, or unmonitored syncope to receive an implantable cardioverter defibrillator (ICD) or amiodarone. A nonsignificant reduction in the risk of death was seen with the ICD. In contrast, the Antiarrhythmics vs Implantable Defibrillator (AVID) study demonstrated a significant reduction in mortality in patients receiving an ICD compared with amiodarone. The study presented at the AHA was from a single center that did not alter the original treatment in their CIDS patients. There were 60 patients in each group, followed from 1991 to 2002. Deaths occurred in 28 patients receiving amiodarone, compared with 16 deaths in those individuals receiving an ICD. Further, 49 patients (82%) had any side effect related to amio-

darone, and 30 (50%) required discontinuation or reduction in the amiodarone dose. The authors concluded that in their CIDS patients there was a benefit of ICD over amiodarone with time.

These are important data concerning how one should approach the initial treatment of patients with a documented, life-threatening ventricular arrhythmia. Over time, the exposure to amiodarone typically results in a need to either reduce or discontinue the drug in a substantial number of patients, and the survival benefit of an ICD progressively increases. These updated results from a subgroup of CIDS are consistent with the data from AVID and strongly suggest that the ICD should be considered first-line treatment in the secondary prevention of sudden cardiac death.

Atrial Fibrillation

There were numerous presentations on results and techniques of radiofrequency catheter ablation of atrial fibrillation (AF) as well as on new clinical observations concerning AF. Several abstracts regarding new clinical findings are presented below.

Wang and associates[6] determined the lifetime risk of AF for individuals without AF at the time of enrollment in the Framingham Heart Study. They included entry ages of 40–80 years. At age 40, the lifetime risk of AF was 25.6% for men and 22.5% for women. This lifetime risk was not different when evaluating entry ages 50, 60, 70, and 80. If one analyzed only those individuals without prior or concurrent heart failure or myocardial infarction, the risk was 16%–17%. These data demonstrate a surprisingly high risk of developing AF, approximately one in four in men and one in five in women in the population studied. With our ever-aging population, the burden of AF on society will continue to increase unless we can determine methods to prevent its occurrence.

Gilliam and coworkers presented data supporting the occurrence of silent AF.[7] They analyzed the stored electrograms from pacemakers implanted in patients without a history of AF. This is an ongoing study that plans to enroll 1000 patients, and data were presented on the initial 736 patients. The mean patient age was 74 years. In those patients with at least a 6-month follow-up, there was a 4.85% prevalence of AF.

In my opinion, with continued and longer follow-up, the prevalence of AF will become greater. Although we have several randomized, prospective trials that have conclusively shown the value of warfarin therapy in high-risk patients for stroke who have documented symptomatic AF, it is not clear whether warfarin therapy in patients with previously unrecognized AF will prevent strokes. However, my bias is to treat these patients in a similar manner as one would patients with symptomatic AF, and hopefully appropriate international normalized ratio values will prevent a stroke in this group. Clearly, further studies are needed to define anticoagulation in this patient subset.

Hayes and colleagues analyzed predisposing conditions in patients demonstrating either pure atrial flutter or AF.[8] Newly diagnosed atrial flutter was found in 76 patients, and 396 had only AF. Patients with AF were more likely to have a history of hypertension (63% vs 47%), whereas patients with atrial flutter more commonly had a history of obstructive lung disease (25% vs 12%), heart failure (28% vs 15%), and smoking (49% vs 37%). Although these two arrhythmias commonly co-exist in the same patient, it appears that in other individuals specific predisposing factors predominate. These interesting preliminary data will hopefully stimulate further investigations into the electrophysiologic–anatomic changes that predispose to these arrhythmias.

The effects of obstructive sleep apnea on AF recurrence were investigated by Kanagala and colleagues.[9] Forty-three patients had obstructive sleep apnea diagnosed by prior sleep study. In 39 of these patients, the effect of continuous positive airway pressure (CPAP) was evaluated on the recurrence of AF after cardioversion. At 12 months' follow-up, individuals appropriately treated with CPAP had a lower recurrence of AF, compared with those patients without or receiving inappropriate CPAP therapy. This interesting study suggests that sleep apnea should be evaluated in patients with AF and appropriate treatment instituted as part of the overall therapeutic plan for these individuals.

Individuals with obstructive sleep apnea appropriately treated with continuous positive airway pressure had a lower recurrence of atrial fibrillation.

[Eric N. Prystowsky, MD]

Bivalirudin Antithrombotic Therapy During Percutaneous Coronary Intervention: Results of the REPLACE 2 Trial

Heparin has been a mainstay in percutaneous coronary intervention (PCI), despite advances in platelet glycoprotein (GP) IIb/IIIa antagonist therapy. However, heparin dosing is imprecise and is often implicated as the cause of bleeding. An earlier trial in the 1990s showed that bivalirudin as compared with heparin caused less

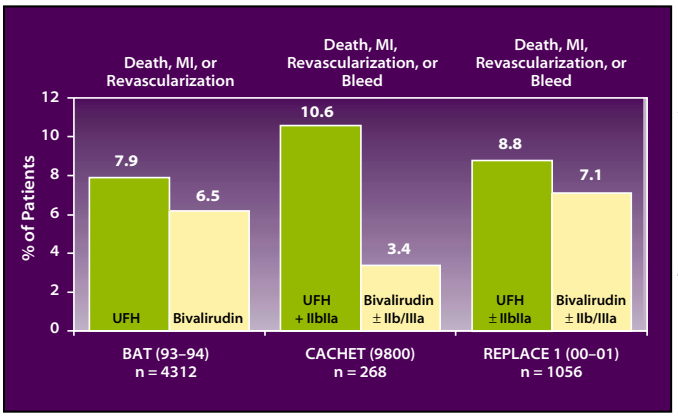

Figure 1. *Results from earlier trials of bivalirudin. BAT, Bivalirudin Angioplasty Trial; CACHET, Comparison of Abciximab Complications with Hirulog ischemic Events Trial; REPLACE, Randomized Evaluation Linking Angiomax to Reduced Clinical Events. UFH, unfractionated heparin. Source: AHA 2002 oral presentation, A. Michael Lincoff, MD.*

bleeding in patients undergoing balloon angioplasty. In the modern era of stenting with GP IIb/IIIa antagonist and heparin, it is unclear how bivalirudin can fit in. In a small study, the Comparison of Abciximab Complications with Hirulog Ischemic Events Trial (CACHET), 268 patients were randomized 2.5:1 to bivalirudin plus provisional abciximab versus heparin and abciximab (see Figure 1). The bivalirudin arm showed, not surprisingly, significantly less bleeding (less IIb/IIIa use: 24%). The MACE rate was less in the bivalirudin arm, but the sample size was too small to be conclusive. There was also no blinding as to the use of GP IIb/IIIa inhibitor.

Trial Design

The second Randomized Evaluation Linking Angiomax to Reduced Clinical Events trial (REPLACE 2) was designed to compare bivalirudin, with provisional use of glycoprotein IIb/IIIa inhibitors, versus low-dose, weight-adjusted heparin plus GP IIb/IIIa inhibition. Figure 2 outlines the trial design. The trial evaluated 6002 patients undergoing urgent or elective percutaneous coronary intervention (PCI) who were randomly allocated to receive either unfractionated heparin (UFH) 65 U/kg bolus in combination with planned platelet GP IIb/IIIa inhibitor therapy (either abciximab or eptifibatide at investigator discretion) or bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg/hour during the procedure) with provisional GP IIb/IIIa inhibition (either abciximab or eptifibatide at investigator discretion). For both randomized treatment groups, the target in-laboratory activated clotting time was ≥ 225 seconds (Hemochron). Aspirin and clopidogrel pretreatment was recommended. Exclusion criteria included primary or rescue PCI for acute MI, prior treatment with UFH (within 6 hours), low-molecular-weight heparin (within 8 hours), bivalirudin (within 24 hours), abciximab (within 7 days), or eptifibatide (within 12 hours), warfarin anticoagulation, dialysis or creatinine > 4.0 mg/dL, platelet count < 100,000/mL, active bleeding, major surgery (within 6 weeks), stroke (within 1 year or with residual neurologic deficit), and uncontrolled hypertension (> 180/110 mm Hg). Guidelines for provisional GP IIb/IIIa inhibitor therapy included abrupt coronary closure (including side branch), clinical instability, prolonged ischemia, diminished TIMI-flow, coronary dissection, new or suspected thrombus, distal embolization, and unplanned or suboptimal stent deployment.

The primary endpoint of the trial was the composite of clinical events including death, MI, urgent revascularization (UR), and major (in-hospital) hemorrhage through 30 days. The key secondary endpoint was the composite occurrence of death, MI, and UR through 30 days. Major hemorrhage was defined as intracranial, retroperitoneal, requiring transfusion ≥ 2 units packed cells or whole blood, observed hemorrhage with hemoglobin decline of ≥ 3 g/dL, or non-observed hemorrhage with hemoglobin decline of ≥ 4 gm/dL (hemoglobin was adjusted by 1 g/unit transfused using Landefeld Index). MI was defined as new Q-waves in 2 or more electrocardiogram leads, creatine kinase (CK)-MB (or CK) more than three times the upper limit of normal (ULN) within 48 hours of PCI, CK-MB more than five times ULN within 48 hours of coronary bypass surgery, or CK-MB (or CK) more than two times ULN unassociated with revascularization.

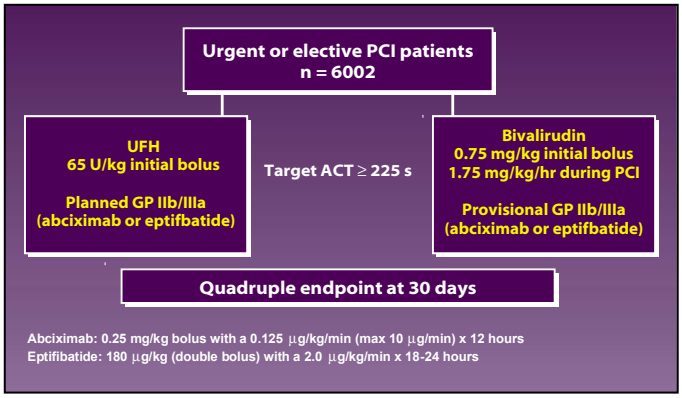

Figure 2. *Design of the REPLACE 2 trial. PCI, percutaneous coronary intervention; UFH, unfractionated heparin; GP, glycoprotein; ACT, activated clotting time. Source: AHA 2002 oral presentation. A. Michael Lincolff, MD.*

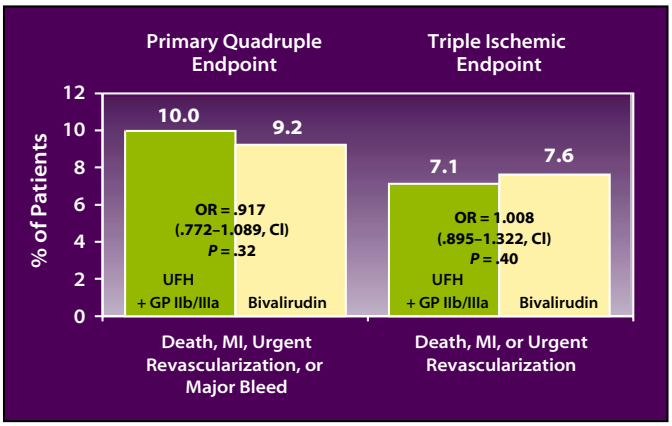

Figure 3. *Primary and secondary endpoints of the REPLACE 2 trial. GP, glycoprotein; MI, myocardial infarction; UFH, unfractionated heparin. Source: AHA 2002 oral presentation, A. Michael Lincoff, MD.*

Results

Dr. A. Michael Lincoff presented the results of REPLACE 2. Patient demographics were similar between the 3008 patients receiving UFH with planned GP IIb/IIIa inhibition (43% abciximab, 57% eptifibatide) and the 2994 patients who received bivalirudin with provisional (7.2%) GP IIb/IIIa inhibition (3.5% abciximab, 3.7% eptifibatide). There were no differences in the indication for PCI, type of PCI (stent vs balloon vs atherectomy), and number of vessels having PCI or bypass graft PCI between treatment groups. The primary (quadruple) endpoint occurred in 10% of UFH plus GP IIb/IIIa–treated and 9.2% of bivalirudin-treated patients (Figure 3). The secondary (triple) endpoint occurred in 7.1% of UFH plus GP IIb/IIIa–treated and 7.6% of bivalirudin-treated patients. Individual endpoints in UFH plus GP IIb/IIIa–treated and bivalirudin-treated patients, respectively, were death (0.4% vs 0.2%), MI (6.2% vs 7.0%), UR (1.4% vs 1.2%), and major bleeding (4.1% vs 2.4%; $P < .001$) (Figure 4).

A slight increase in the incidence of periprocedural biochemical (non-Q-wave) MI (5.8% UFH vs 6.6% bivalirudin) and a significant reduction in major bleeding were observed in the bivalirudin-treated patients. Minor bleeding events were also increased in patients treated with UFH plus GP IIb/IIIa (25.7%) compared with bivalirudin-treated patients (13.4%; $P < .001$). Interestingly, although those patients who received abciximab faired somewhat better (relative to bivalirudin) than those receiving eptifibatide (relative to bivalirudin), the choice of GP IIb/IIIa agent was not randomized, and further risk adjustment/propensity scoring analysis is ongoing.

In summary, the REPLACE 2 trial demonstrated that bivalirudin (with provisional GP IIb/IIIa blockade in 7% of patients) was equivalent to UFH plus GP IIb/IIIa blockade with respect to the occurrence of periprocedural ischemic events (death, MI, UR) and superior with respect to major bleeding events.

Discussion

What do the results of REPLACE 2 mean, and how should they be applied to our practice of PCI? First, the common theme apparent across multiple randomized trials of bivalirudin compared with UFH, which is observed again in REPLACE 2, is the relative safety (reduction of major bleeding events). This consistent observation may reflect both the thrombin specificity and short pharmacologic half-life of bivalirudin. Second, the occurrence of periprocedural ischemic events (acknowledging the increment in non–Q-wave MI in the bivalirudin group) appears comparable to UFH plus GP IIb/IIIa and superior to UFH alone. This may, in part, reflect the absence of platelet activation and aggregation with bivalirudin compared to UFH. Indeed, bivalirudin directly binds the most potent source (thrombin) of PCI-induced platelet activation. Third, the longer-term benefit of improved survival observed after abciximab (vs placebo) therapy should not be ignored. This survival advantage has been most evident in those patients with the highest degree of clinical risk. Although clinical risk profiles have failed to predict benefit for shorter-term (30-day), platelet-mediated ischemic events (death, MI, UR) from adjunctive abciximab (or eptifibatide) therapy, a clinical risk model has been developed that predicts survival to 3 years

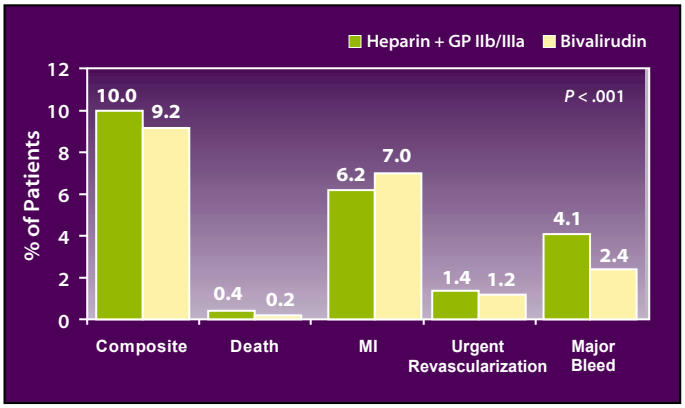

Figure 4. *Components of primary quadruple endpoints through 30 days in the REPLACE 2 trial. GP, glycoprotein; MI, myocardial infarction. Source: AHA 2002 oral presentation, A. Michael Lincoff, MD.*

after abciximab therapy. Furthermore, patients with diabetes, an established clinical predictor of risk, appear to derive differential (increased) benefit from abciximab therapy.

A plausible clinical extrapolation for the results of REPLACE 2 would be to administer abciximab during PCI to those patients who have clinical demographic high-risk predictors (particularly in diabetes). Patients with a lower clinical risk profile may be administered bivalirudin with provisional GP IIb/IIIa blockade, particularly in the context of aspirin and clopidogrel pretreatment. The potential for additional short-term (30-day reduction in periprocedural non–Q-wave MI) and long-term (survival) benefit of bivalirudin administered in combination with abciximab requires further evaluation.

[Dean J. Kereiakes, MD, FACC, Norman E. Lepor, MD, FACC, FAHA, Alan C. Yeung, MD]

The CREDO Trial

The Clopidogrel for the Reduction of Events During Observation (CREDO) Trial, provides further support for the concept of using combined clopidogrel–aspirin antiplatelet therapy in high-risk cardiovascular patients. Indeed, this study appears to amplify the results of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) Trial, which previously showed the clinical endpoints benefits of this combination therapy in patients who had experienced acute coronary syndromes.

The CREDO trial was based on patients undergoing PCI and explored two separate questions: first, whether a loading dose of clopidogrel prior to PCI would confer clinical benefits during the 4-week period following the procedure; and second, whether combined clopidogrel–aspirin treatment during the subsequent 11-month period would provide longer-term clinical benefits when compared with aspirin alone.

The Short-Term Study

A total of 2116 patients were randomized to receive a loading dose of clopidogrel (300 mg) or placebo at least 3 hours prior to the PCI. During the 28 days following the PCI, all patients—regardless of whether they had received the clopidogrel loading dose or placebo—were given combination treatment with aspirin (81–325 mg daily) and clopidogrel (75 mg daily). Part of the rationale for this across-the-board combination therapy came from the CURE trial, in which such therapy in at-risk patients was shown to be superior to single-agent treatment in providing cardioprotection.

The results of the loading phase of the CREDO study were particularly interesting. Overall, the patients pretreated with clopidogrel had an 18.5% relative risk reduction in the composite endpoint of death, myocardial infarction, or urgent target vessel revascularization, when compared with aspirin alone. Although this reduction was not significant, the investigators reported that those patients who were treated with the clopidogrel loading dose more than 6 hours before the PCI procedure had a 38.6% relative risk reduction in these events (an absolute risk reduction from 9.4% to 5.8%), which was significant ($P = .05$).

It is interesting to conjecture as to the mechanisms by which a loading dose of clopidogrel, 6–24 hours before the PCI, could have provided benefits that were still in evidence 28 days after the procedure. It seems unlikely that the enhanced inhibition of platelet aggregation produced by combination therapy could fully explain this sustained benefit of a single dose; rather, it is more probable that powerful inhibition of platelet activation—with resulting decreases in cytokines and other inflammatory and thrombotic factors—provided more optimal benefits during the trauma of the PCI and fundamentally altered the characteristics of the vascular wall responses during the subsequent 4 weeks.

It is interesting to conjecture as to the mechanisms by which a loading dose of clopidogrel, 6–24 hours before the PCI, could have provided benefits that were still in evidence 28 days after the procedure.

The Long-Term Study

Following the initial 4-week treatment period after the PCI, those patients who had previously received the clopidogrel loading dose were now retreated with clopidogrel (75 mg daily) in addition to their aspirin dose during the subsequent 11 months of the study. The other group of patients simply received placebo and aspirin.

The results of this long-term study are of particular importance, because in all likelihood they address the value of combination antiplatelet therapy in high-risk patients during a time when residual effects of the PCI were probably of only modest impact. For the full 1-year period, the combined outcome of death, myocardial infarction, and stroke was reduced by almost 27% ($P = .02$) by the combination treatment when compared with aspirin alone. When the effects of the first 28 days were subtracted from this total and only the last 11 months were considered, there was still a significant, 37%,

relative risk reduction (absolute risk reduction from 4.6% to 2.9%) by the combined treatment (P = .04). Each of the components of composite endpoint trended in the same direction as the total, though there was not sufficient power to statistically test these events as individual endpoints.

These long-term data suggest that there may be true benefits from combination treatment with clopidogrel and aspirin in patients at high cardiovascular risk, perhaps independent of their initial PCI procedures. It is interesting that following the original CURE study, a major clinical trial, The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial, was initiated to compare combination clopidogrel–aspirin treatment with aspirin alone in patients with previous histories of heart disease, stroke, and other evidence for high cardiovascular risk. The data from CREDO suggest that this ongoing clinical trial in high-risk patients could finish early in view of the significant benefits observed during just 1 year of treatment in the relatively small number of patients participating in CREDO.

In summary, the clear benefits of a loading dose of clopidogrel prior to PCI, provided it was given at least 6 hours before the procedure, and the benefits of administering clopidogrel (in addition to aspirin) in these patients during a 12-month follow-up, confer clear benefits that are not easy to explain. For example, the values of the combination therapy were just as great in patients who received a glycoprotein IIb/IIIa inhibitor as in those who did not, at the time of the PCI, suggesting that mechanisms other than antithrombotic actions might have been important. Anti-inflammatory actions most certainly play a part in the benefits of combined therapy, though precise mechanisms have yet to be defined. Interpreting these results and putting them into routine clinical practice, other than for patients undergoing PCI, may not be easy. In particular, we will require further clinical trials—and hopefully CHARISMA will help us to do that—to determine whether the advantages of combination clopidogrel–aspirin therapy persist during chronic therapy and should be used more widely in patients regarded to be at high risk of cardiovascular events.

[Michael A. Weber, MD]

Assessment of the Value of Cooling-off Strategy in Patients with Unstable Coronary Syndromes Treated Invasively: The ISAR-COOL Trial

The syndrome of unstable angina and myocardial infarction without ST segment elevation accounts for approximately 1.4 million hospital admissions annually in the United States and over 2 million worldwide. In the past, initial treatment focused on medical stabilization with anti-angina and antithrombotic agents. More recent trials, such as TACTICS and FRISC 2, have taught us that for patients with acute coronary syndromes, an early invasive strategy is associated with a significant reduction in the incidence of major cardiac events. However, in this setting, PCI may be complicated by periprocedural ischemic events that are mainly due to platelet-dependent processes resulting in thrombosis at the site of mechanical plaque disruption and distal embolization of platelet thrombi into the coronary microcirculation. What has been unclear is whether more prolonged antithrombotic treatment with intense antiplatelet therapy would decrease the risk of the procedure. Indeed, the recent observations that "active" or "acute" coronary artery disease is associated with evidence of inflammation both systemically and at the level of the arterial wall give additional credence to this hypothesis.

The Intracoronary Stenting with Antithrombotic Regimen Cooling-off (ISAR-COOL) Trial, a prospective, randomized, multicenter study, tested the hypothesis that "cooling-off" compared with early intervention would improve the outcome of PCI for patients with acute coronary syndromes. Accordingly, 410 patients with a clinical diagnosis of unstable angina or non-ST segment elevation myocardial infarction in addition to a positive troponin T or ST segment depression were randomly assigned to antithrombotic pretreatment for 72–120 hours or less than 6 hours prior to PCI. The primary endpoint of the trial was a composite of death and nonfatal myocardial infarction within 30 days, and the trial was sized based on the assumption of a 7% incidence of the primary endpoint with cooling-off that would represent a 60% relative risk reduction compared with immediate intervention. All patients were treated with heparin, tirofiban continued for 24 hours, clopidogrel for 4 weeks, and aspirin indefinitely.

As expected, at baseline, the study groups were well matched. Between study entry and PCI there were 13 events in the cooling-off group and one event in the early intervention group (P = .002), whereas after PCI, 10 events occurred in both groups. The primary endpoint was reached in 11.6% (three deaths, 21 nonfatal infarctions) of the cooling off group and 5.9% (no deaths, 12 myocardial infarctions) of the early intervention group (RR 2.0, 95% CI 1.01–3.94, P = .04). Of note, bleeding requiring transfusion occurred more frequently in the cooling-off group as compared with the early intervention group (3.4% vs 1.0%), although there were

no significant differences in noncardiac complications. It was concluded that, in patients with acute coronary syndromes, deferral of intervention for extensive antithrombotic pretreatment (cooling-off) does not improve outcome, compared with immediate intervention under the now-standard antiplatelet coverage.

Discussion

This multicenter clinical trial testing conventional wisdom and clinical practice calculated sample size in standard fashion, although it is noteworthy that few therapies achieve a 60% reduction in relative risk. In fact, contrary to the hypothesis, prolonged antithrombotic therapy was associated with a significantly higher incidence of the primary endpoint at 30 days that appeared to be driven by the incidence of myocardial infarction. It should also be noted that the difference in preprocedural ischemic events between groups was due, in part, to ascertainment bias, with a much longer period of observation in the cooling-off group. Furthermore, the conclusion of the study is supported by the data, although the stability of the point estimate is not robust with the wide confidence intervals.

The ISAR-COOL investigators have completed yet another study that will contribute to our understanding and influence management of patients with acute coronary syndromes undergoing PCI. The results of the trial can indeed be applied to the population of moderate to high-risk patients with unstable coronary syndromes. The prevalence of risk factors, female gender, and multivessel disease is similar to large-scale registries of patients undergoing PCI. Although the benefit of cooling-off prior to undergoing coronary angiography, with its implications for less urgent access to a catheterization lab has not been realized, this study supports the current clinical practice of urgent PCI in similar patients with acute coronary syndromes.

Contrary to the hypothesis, prolonged antithrombotic therapy was associated with a significantly higher incidence of the primary endpoint at 30 days.

X-TRACT Trial

Numerous clinical trials and database analyses have reported that percutaneous coronary intervention (PCI) for lesions containing thrombus is associated with an increased incidence of periprocedural complications. Hence pharmacologic and mechanical strategies that decrease thrombus burden during PCI are under active investigation. One such device, the X-SIZER, was evaluated at 75 sites in the United States in 797 patients undergoing PCI with stent implantation of one or more lesions in diseased saphenous vein grafts (72%) or native coronary arteries (28%) containing thrombus.

Patients were prospectively randomized to standard PCI or thromboatherectomy using the X-SIZER. The principal investigator, Dr. Gregg Stone, reported that baseline clinical and angiographic features were evenly distributed between the two groups of patients, except that patients in the X-SIZER group were more likely to have thrombus present (70% vs 58%; $P < .001$) and a slightly greater initial diameter of stenosis (70% vs 67%; $P < .05$). Of note is that platelet glycoprotein IIb/IIIa receptor inhibitors were administered in 78% of each group. Interestingly, there was no difference between groups in final Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow; no reflow, distal emboli, any MI, or Q-wave MI, or the composite end point of death, MI, or target vessel revascularization at 30 days.

However, large non–Q-wave MI, defined as muscle-brain isoenzyme fraction above 8 times more than normal occurred significantly more often in standard PCI in comparison to X-SIZER patients (8.3% vs 4.5%; $P = .03$). Among patients not receiving platelet glycoprotein IIb/IIIa receptor inhibitors just prior to the procedure, bail-out use was required in fewer patients treated with the X-SIZER compared to standard PCI (2.1% vs 10.3%; $P = .02$). Multivariate analysis, adjusting for the difference in baseline thrombus and lesion severity, revealed use of the X-SIZER to be an independent predictor of freedom from large MI (odds ratio 0.35; $P = .002$) and death or large MI (odds ratio 0.43; $P = .006$).

The authors concluded that thromboatherectomy with the X-SIZER prior to stent implantation in diseased saphenous vein grafts or thrombotic native coronary lesions reduces procedural complications, as evidenced by reduced need for bail-out platelet glycoprotein IIb/IIIa receptor inhibitors, and enhances 30-day survival free from large MI. The overall similar rate of major adverse cardiac events for patients treated with and without the X-SIZER

Pharmacologic and mechanical strategies that decrease thrombus burden during PCI are under active investigation.

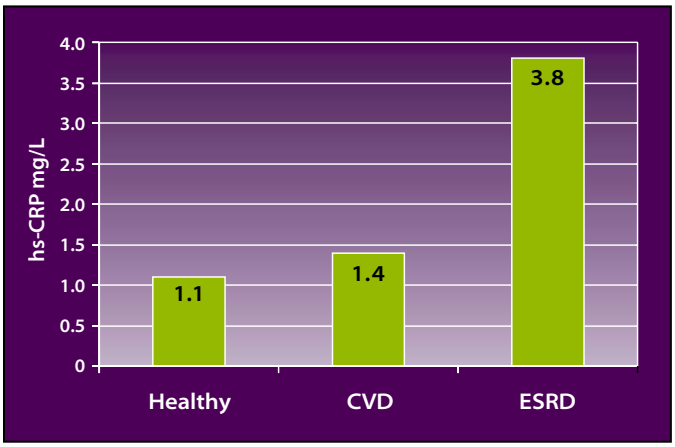

Figure 5. *Geometric mean and median high-sensitivity C-reactive protein (hs-CRP) values among healthy physicians, those who developed cardiovascular disease, and incident dialysis patients. CVD, cardiovascular disease; ESRD, end-stage renal disease. Data from Chew et al[10] and Ridker et al.[12]*

notwithstanding, thromboatherectomy with this device probably reduces the extent of periprocedural myonecrosis.

Discussion

Although the overall X-TRACT Trial results are somewhat disappointing based upon the similar 30-day outcomes for patients undergoing PCI of thrombotic lesions with and without use of the X-SIZER, this device does reduce large (and likely significant in terms of prognosis) periprocedural MI. The place it will take among other similar mechanical strategies as well as new pharmacologic agents will ultimately be decided by comparative efficacy, ease of use, and additional procedural cost.

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

Cardiorenal Update

This year's meeting of the AHA provided more analyses implicating chronic kidney disease (CKD) as a risk factor for incident cardiac events and higher complication rates after cardiovascular procedures. This risk may be mediated, in part, by the impressive hyperinflammatory state associated with CKD. Although there are no targeted randomized trials of cardioprotective therapy in patients with acute coronary syndromes and CKD, analyses from this meeting are increasingly supportive of the use of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, direct thrombin inhibitors, and glycoprotein IIb/IIIa receptor antagonists. Patients benefit either equally or to a greater extent with the use of these therapies. Community-based studies continue to show reduced rates of these agents in CKD, and hence, quality improvement efforts are needed to ensure that this at-risk population is adequately treated in the setting of a cardiac event. The risk of acute renal failure remains an issue with revascularization in patients with CKD. Unfortunately, additional trials reported at this meeting indicate that, outside of pre- and postprocedural hydration, little can be done to prevent this potentially catastrophic event.

Chronic Kidney Disease and Cardiovascular Risk

In a study titled, "Defining the Optimal Threshold for Renal Impairment in PCI," Dr. Derek Chew and coworkers carried out an analysis to identify the optimal threshold in terms of estimated glomerular filtration rate (eGFR; creatinine clearance [CrCl] in mL/min) for bleeding complications, death, and myocardial infarction after percutaneous coronary intervention (PCI).[10] Among 759 patients undergoing PCI, the optimum cutpoint was 60 mL/min. Below this cutpoint, there was an approximately fourfold increased risk of adverse events. Patients who had a CrCl < 60 mL/min accounted for 60% of all adverse events. Interestingly, above and below this cutpoint were significant differences in mean high-sensitivity C-reactive protein levels (hs-CRP), suggesting the role of inflammation in CKD as a potential driver of increased event rates.[10] It is interesting that a variety of analyses published within the last year have all found that at an eGFR ≤ 60 mL/min/1.73 m^2, there is increased cardiovascular risk. This level of renal function represents Stage III CKD and is not part of the normative aging process. This suggests that a host of factors are operative at this level, including inflammatory factors, oxidative stress, and other factors that reduce endothelial function and promote atherosclerotic plaque instability.

In support of the inflammatory hypothesis of CKD, Coresh and coworkers measured hs-CRP in 810 incident dialysis patients within the first 4 months of starting dialysis.[11] They found hs-CRP to be markedly elevated: 25th percentile 1.6 mg/L, 50th percentile 3.8 mg/L, and 75th percentile 9.5 mg/L. These values are all well above a hs-CRP value of 1.4 mg/L, which was the mean level in healthy physicians who subsequently had a cardiovascular event in the Physicians' Health Study (Figure 5).[12] Although the debate continues regarding small differences in low levels of hs-CRP due to effect modification with aspirin and confounding with lipid lowering agents, exercise, and a variety of factors, there can be little debate that the nearly fourfold increase in hs-CRP in dialysis patients is a signal of the markedly proinflammatory state of

CKD. Miles and coworkers presented a comparative analysis of dialysis patients, 13.7% of whom were taking statins; again the population median hs-CRP was 3.8 mg/L, but unexpectedly, there was no difference between those taking and not taking statins (3.8 vs 3.8 mg/L, $P = .86$, n = 575).[13] This study suggests that the inflammatory state of end-stage renal disease (ESRD) on dialysis may not be suppressible with statins as it is in the general population. In another paper, Qiao and coworkers, further supporting the inflammatory hypothesis in CKD, reported on 48 patients with predialysis CKD (mean creatinine 3.1 mg/dL) and 48 matched controls.[14] They demonstrated a more than twofold increase in serum homocysteine (23.4 vs 9.4 µmol/L, $P < .01$). Markers of inflammation and subclinical atherosclerosis, including intercellular adhesion molecule, vascular cell adhesion molecule, E-selectin, and carotid intimal medial thickness, were all elevated in patients with CKD. These data taken together support the notion that CKD is a unique, markedly proinflammatory atherosclerotic state.

Chronic Kidney Disease and Cardiovascular Risk

Drs. William Keane (Merck, Inc., West Point, PA) and William McClellan (Georgia Medical Care Foundation, Atlanta, GA), both nephrologists, moderated a session titled, "Cardiovascular Risk in Chronic Renal Disease: Is Renal Disease a Cause or Consequence of Cardiovascular Disease?"[15] This session reviewed the common, treatable cardiovascular risk factors in CKD and summarized the growing body of data to support that chronic anemia is a factor related to abnormal cardiac remodeling and heart failure. Dr. Keane summarized the results of major trials of angiotensin II receptor antagonists in type II diabetic nephropathy, which in aggregate demonstrated a reduction in ESRD and death. Importantly, some of these trials showed a modest reduction in cardiovascular events, predominantly heart failure. Lastly, Dr. Harold Feldman presented the rationale and design of the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Prospective Cohort Study of Chronic Renal Insufficiency: The Renal Framingham Study. This large, prospective study of CKD patients and cardiovascular risk factors will attempt to identify the leading pathophysiologic abnormalities that lead to accelerated atherosclerosis in this population.

A small rise in creatinine with a cardiovascular procedure is a marker for higher rates of myocardial infarction and cardiovascular death during long-term follow-up.

In a cardiovascular seminar titled, "Renal Insufficiency and Coronary Artery Disease," Dr. Gregg W. Stone (The Cardiovascular Research Foundation and Lenox Hill Hospital, New York, NY) moderated four presentations concerning outcomes in patients undergoing revascularization.[16] There were four important points summarized from these lectures: 1) an eGFR < 60 mL/min/1.73 m^2 or microalbuminuria (albumin: creatinine ratio > 30 mg/g) identifies renal risk in cardiac patients; 2) a small rise in creatinine with a cardiovascular procedure is a marker for higher rates of myocardial infarction and cardiovascular death during long-term follow-up; 3) among diabetics, renal function is the dominant predictor of cardiovascular disease events, suggesting that the risk for all diabetics is not the same; and 4) patients with CKD appear to benefit at least as much and probably more than the general population in the setting of ACS with the use of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, direct thrombin inhibitors, and glycoprotein IIb/IIIa receptor blockers. This gives a rationale for expanded use of these agents in the CKD population to reduce periprocedural morbidity and mortality.

Prevention of Acute Renal Injury

This meeting provided additional information regarding the use of N-acetylcysteine (NAC) in the prevention of radiocontrast-induced nephropathy (RCN). Boccalandro and colleagues presented a consecutive series of 73 patients who received NAC and 106 who received hydration alone prior to angiography and PCI.[17] All patients had a baseline CrCl < 50 mL/min and received approximately 130 mL of iodinated contrast. The rates of RCN were 13% and 12% for the NAC and hydration groups, respectively ($P = .86$). In a small (n = 51), randomized, prospective trial by Kahlon and coworkers, NAC failed to prevent RCN (> 0.5 mg/dL rise in serum creatinine over 96 hours), with RCN rates of 21.7% and 15.8% in the NAC and control groups, respectively ($P = .48$).[18] This study is the seventh trial of NAC in which the results of this compound have been mixed. As of this writing, it is not known whether NAC offers any benefit in RCN protection among at-risk patients undergoing PCI. The larger question is this: Can renal protection prevent the biochemical surrogate rise in serum creatinine, and hence, translate into long-term clinical benefit after revascularization? Un-

fortunately, we are still far away from answering this important clinical question.

Commentary

The 2002 Scientific Sessions of the AHA witnessed continued growth in cardiorenal research, with some of the first data by which treatment recommendations can be made. In addition, this growing body of literature is setting the stage for future randomized trials in patients with CKD presenting with cardiac events. [Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA]

Interventional Cardiology: Late-Breaking Trials

A number of important late-breaking trials were presented this year in the area of interventional cardiology. Although drug-eluting stents remained the focus of many abstract sessions, the late-breaking trials provided new information that is likely to change clinical practice.

Assessment of the Safety and Efficacy of a New Thrombolytic Regimen in the Pre-Hospital Setting (ASSENT III Plus)

Lars Wallentin, MD of Uppsala University Hospital, Uppsala, Sweden, presented the results of this study, which evaluated the efficacy and safety of enoxaparin compared with UFH added to tenecteplase (TNK) given to patients with ST elevation myocardial infarction in the pre-hospital setting. The study is an extension of the previously published ASSENT III trial, which compared the same agents in the in-hospital setting. A total of 1639 patients were enrolled at 88 sites, primarily in Europe. The study was open-labeled and used a fixed bolus dose of enoxaparin and a weight-adjusted dose of UFH. The primary endpoint was 30-day mortality, refractory ischemia, and reinfarction. In addition, bleeding events were measured.

The pre-hospital administration resulted in a saving of 41 minutes in chest-pain-to-needle time. The study did not demonstrate a significant difference between the groups in the primary endpoint, with an incidence of 14.2% in the enoxaparin group and 17.4% in the UFH group. Likewise, when safety endpoints were included, the results were also negative. However, the in-hospital reinfarction and refractory ischemia were significantly lower in the enoxaparin group, consistent with the ASSENT III trial. When viewed in combination with the larger ASSENT III trial, the evidence would support the superiority of the combination of TNK with enoxaparin over heparin.

The primary hypothesis was that the use of prolonged antithrombotic and anticoagulant therapy would stabilize the ulcerated plaque, reduce complications, and improve short-term outcome.

The most surprising and important observation of the study was the high incidence of intracranial bleeding that occurred in the enoxaparin group (2.2% vs 0.97%). This was not observed in the ASSENT III study, in which the rates were 0.9% in both groups. This high incidence of intracranial stroke, however, was largely confined to elderly patients (older than 75 years), for whom both the risk of bleeding and stroke were excessive. In reviewing the ASSENT III data, the authors found that there was a trend toward an increased risk of bleeding and intracranial hemorrhage in the original inpatient study as well.

In summary, the study failed to demonstrate superiority for the combination of TNK and enoxaparin in the pre-hospital phase. The absolute and relative differences between groups are similar to that shown in the larger ASSENT III trial, which randomized more than 6000 patients. Taken together, it is clear that this combination does have advantages over TNK and UFH. There are other ongoing, larger trials, such as EXTRACT TIMI 25, ADVANCE MI, and OASIS 4 and 5, that will help to further refine the optimal combination of antithrombotic and lytic agents.

The most surprising and important observation of the ASSENT III Plus study was the high incidence of intracranial bleeding that occurred in the enoxaparin group.

The most important observation is the increased risk of stroke and bleeding in elderly patients. It is likely that the significantly increased risk in this study is related to the differences in the patient population between the two studies. In the ASSENT III Plus trial there were a higher percentage of women and elderly patients enrolled, and because of the rapidity of their enrollment in the field, careful evaluation for risk factors for stroke may not have been possible to the same degree as with the patients admitted to the hospital. In addition, all patients used a fixed dose of enoxaparin, namely 30 mg, and full-dose TNK, whereas unfractionated heparin was weight adjusted.

This difference may also make a difference in the risk of intracranial bleeding. The ADVANCE MI study will be using a lower dose of enoxaparin and TNK for this reason.

The ASSENT III Plus study also evaluated the benefits of pre-hospital administration and demonstrated a 45-minute saving of time when the drugs are administered in the field rather than at the hospital. However, the endpoints failed to reach statistical significance when they were compared in a nonrandomized manner to the ASSENT III trial. Again, this is not surprising, given the fact that the ASSENT III Plus group was older, had more women, and was clearly a different patient population from that enrolled in the in-patient study. It is very difficult to perform randomized, clinical trials of inpatient and outpatient thrombolysis; thus, we can only extrapolate from many other studies that the earlier reperfusion results in greater benefit. In a meta-analysis by Morrison and colleagues in the Journal of the American Medical Association in 2000, six well-conducted randomized trials were analyzed.[19] Overall, there was an 18% reduction in in-hospital mortality with an average of 60 minutes in saving when drugs were administered in the pre-hospital phase rather than in the hospital.

There are a number of unanswered questions, however. The most important is whether pre-hospital thrombolysis is superior to primary angioplasty, because primary angioplasty is currently more commonly performed in the United States than thrombolysis. In addition, we know from studies such as the DAMANI II trial that patients with acute myocardial infarction, when transferred to a hospital with PCI do not result in any increased risk to the patient. Thus, an ideal study would be a comparison of pre-hospital thrombolysis to PCI with or without transfer to a referral hospital. Further studies are clearly necessary for us to better understand the role of these agents in elderly patients, and the findings from ASSENT III Plus emphasize the necessity for randomized trials to include a sizable number of patients older than 75 for further definition of optimal therapy.

[David P. Faxon, MD, FACC, FAHA]

Peripheral Arterial Disease

Bone Marrow Mononuclear Cells to Treat Critical Limb Ischemia

Basic investigations have found that administration of bone marrow mononuclear cells improves the development of collateral blood vessels in ischemic limbs. A study by Masaki and colleagues of Kansai Medical University, Osaka, Japan examined the potential efficacy as well as the safety of autologous implantation of bone marrow mononuclear cells to patients with critical limb ischemia.[20] Bone marrow mononuclear cells include endothelial progenitor cells (ie, stem cells). Forty-five patients with ischemic limbs participated in this study. Bone marrow mononuclear cells were injected into the gastrocnemius muscle. In 20 patients with bilateral limb ischemia, bone marrow mononuclear cells were injected into one limb and, as a control, peripheral blood-derived mononuclear cells were injected into the contralateral limb.

In patients who received bone marrow mononuclear cells, angiography demonstrated new collateral vessels in 27 limbs, rest pain diminished in 39 of 45 patients, ischemic ulcers healed in 21 of 28 limbs, and the ankle/brachial index increased more than 0.1 in 31 of 45 patients. Limbs that received peripheral blood-derived mononuclear cells had less evidence of collateral blood vessel development or resolution of limb ischemia. There were no major adverse effects. This study provides initial evidence that autologous administration of bone marrow mononuclear cells, including endothelial progenitor cells, may promote angiogenesis and ameliorate limb ischemia in patients with peripheral arterial disease (PAD). It will be necessary to determine whether the efficacy and safety of this strategy can be duplicated in larger, placebo-controlled, blinded trials.

In patients who received bone marrow mononuclear cells, rest pain diminished in 39 of 45 patients.

Lipid-Lowering with a Statin for Intermittent Claudication

Lipid-lowering therapy is indicated in patients with coronary artery disease to reduce the risk of myocardial infarction and vascular death. Recently, the Heart Protection Study extended these observations, finding that lipid-lowering therapy with a statin reduces the risk of adverse cardiovascular events, including myocardial infarction, stroke, and vascular death not only in patients with coronary artery disease, but also in patients with other manifestations of atherosclerosis, such as cerebrovascular disease and PAD. Lipid-lowering therapy has also been shown to reduce angiographic progression of peripheral atherosclerosis. A study by Mohler and colleagues is the first to prospectively evaluate the effect of statin therapy on symptoms of claudication in patients with PAD.[21]

A total of 354 patients with inter-

mittent claudication were randomized either to placebo or to atorvastatin dosed at either 10 mg or 80 mg daily. Patients were treated for 12 months. The time to onset of claudication and the maximal walking time were determined by treadmill testing. Other endpoints included the ankle/brachial index and the scores of quality-of-life questionnaires. All of these measures were assessed at baseline and at 3, 6, and 12 months after randomization.

After 12 months of treatment, the maximal walking time increased by 50 seconds in patients treated with placebo and by 90 seconds in patients treated with 10 mg/d as well as in those treated with 80 mg/d doses of atorvastatin (P = NS). Time to the onset of claudication was increased by 39 seconds in patients treated with placebo, by 74 seconds in patients treated with atorvastatin 10 mg/d, and by 81 seconds in patients treated with atorvastatin 80 mg/d. The difference in the increase in time to onset of claudication in patients receiving 80 mg/d of atorvastatin was statistically greater than that in patients treated with placebo (P = .03). Consistent with the improvement in the time to onset of claudication was an increase in the score of the Community-based Physical Activity Questionnaire. There was no improvement in score on the Walking Impairment Questionnaire. The ankle/brachial index did not change in the placebo or atorvastatin treatment groups. Thus, this study found that atorvastatin significantly improves the time to the onset of claudication in patients with PAD. Although there appeared to be a trend in improvement in maximal walking time, this did not achieve statistical significance.

The mechanism whereby atorvastatin may improve claudication symptoms is not addressed in this study. Possibilities include improvement in endothelial function, microcirculatory blood flow, collateral development, or skeletal muscle metabolism. Based on the absence of change in ankle/brachial index, it is unlikely that cholesterol-lowering therapy significantly affected the severity of peripheral arterial stenoses. Taken together with the Heart Protection Study, this study supports the notion that statin therapy may confer functional improvement, as well as reducing the risk of adverse cardiovascular events, in patients with PAD.

After 12 months of treatment, the time to the onset of claudication increased by 39 seconds in patients treated with placebo, by 74 seconds in patients treated with 10 mg daily atorvastatin, and by 81 seconds in those treated with 80 mg daily of atorvastatin.

Roxifiban Trial in Patients with PAD

Antiplatelet drugs, particularly aspirin and clopidogrel, reduce the risk of adverse cardiovascular events in patients with atherosclerosis, including PAD. Intravenous glycoprotein IIb/IIIa receptor antagonists reduce the risk of coronary events in patients undergoing percutaneous coronary interventions and those with acute coronary syndromes. However, oral glycoprotein IIb/IIIa receptor antagonists have not been beneficial when administered long term to patients with coronary artery disease. The focus of a study by Hiatt and colleagues was to determine whether roxifiban, a potent oral glycoprotein IIb/IIIa receptor antagonist, reduces the risk of death, myocardial infarction, or stroke in patients with severe PAD, the latter defined as an ankle/brachial index < .60.[22]

This was a parallel-design, blinded, placebo-controlled trial. During the first 6 months of the trial, 355 patients had been randomized. At that time, the trial was stopped because of excess bleeding in the roxifiban treatment group. Thus, the study did not reach the targeted enrollment goal to ensure sufficient statistical power for the primary endpoint. Death or myocardial infarction occurred in 2.8% of patients treated with placebo and 3.9% of patients treated with roxifiban. No patient experienced stroke. Major bleeding occurred in 1.1% of patients randomized to placebo and in 5.7% of patients randomized to roxifiban. Thus, the incidence of severe bleeding was deemed to be excessive and greater than that previously observed in trials with aspirin, clopidogrel, or other glycoprotein IIb/IIIa receptor antagonists. It was concluded that the risk of bleeding with oral roxifiban was too great, and the likely benefit too small, to justify continuation of this trial.

Physician Education and PAD

Recent studies such as the PARTNERS (PAD Awareness, Risk, and Treatment: New Resources for Survival) study found that the diagnosis of PAD is frequently missed by primary care physicians and that effective therapy to reduce adverse events, such as lipid-lowering therapy and antiplatelet drugs, are underutilized. A study by researchers at the University of Massachusetts Medical School utilized the database of the Worcester Heart Attack Study to assess the characteristic treatment of patients with and without PAD who had sustained an acute myocardial infarction.[23] The database comprised

2088 patients with acute myocardial infarction, of whom 11.8% had PAD. The PAD patients were generally older and more likely to have diabetes or hypertension. Prior to acute myocardial infarction, patients with PAD were less likely to receive effective therapy, such as aspirin, β-blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors, than patients without PAD. Yet, PAD independently predicted mortality for up to 2 years following the myocardial infarction. Thus, findings from the Worcester Heart Attack Study support the need for physician education and increased use of therapies known to reduce the risk of adverse cardiovascular events in patients with PAD.

Endothelial Function in PAD

A study by Silvestro and colleagues of Naples, Italy examined endothelial function in patients with PAD.[24] Flow-mediated vasodilation of the brachial artery was measured in 88 patients with PAD and compared with 30 age-matched controls. Flow-mediated vasodilation of the brachial artery is considered a useful surrogate for the biologic availability of endothelium-derived nitric oxide, an important substance synthesized and released by the endothelium. In this study, flow-mediated endothelium-dependent vasodilation was lower in patients with PAD than in the age-matched controls. Moreover, those patients with lower measurements of flow-mediated vasodilation also had lower ankle/brachial indices and higher plasma levels of c-reactive protein and fibrinogen. A multivariate analysis found that c-reactive protein, fibrinogen, and the ankle/brachial index were all independently associated with impaired flow-mediated vasodilation (ie, endothelial dysfunction). These findings tied together several important pathophysiologic mechanisms for atherosclerosis in patients with PAD.

[Mark A. Creager, MD, FACC]

Vascular Biology

Role of Src Kinase in VEGF-Induced Increased Vascular Permeability

In an elegant presentation, Dr. David Cheresh of Scripps Clinic, La Jolla, CA described the molecular mechanisms by which vascular endothelial growth factor (VEGF) increases vascular permeability. This effect of VEGF may contribute to the edema and increased infarct size following vascular occlusion in the brain and the heart. Similarly, it may contribute to some of the adverse effects of therapeutically administered VEGF. Dr. Cheresh described a series of experiments that helped define the signaling mechanisms responsible for VEGF-induced increase in vascular permeability. It turns out that VEGF interacts with its receptor, Flt-1, leading to activation of the cytoplasmic tail of the receptor, which in turn recruits Src kinase, a phosphorylating molecule that then phosphorylates a focal adhesion kinase linked to the cytoplasmic end of the integrin receptor, α5 β3. This interaction then results in the dissociation of a complex of the cytoplasmic tail of the Flt-1 receptor, VE-cadherin, and β-catenin. Dissociation of this complex results in separation of endothelial cells from each other, cells that in the basal state are kept together by the VE-cadherin, β-catenin, and cytoplasmic tail of VEGF receptor Flt-1. The permeability-increasing effect of VEGF was essentially absent in mice lacking Src gene; these mice developed smaller brain and myocardial infarct size following vascular occlusion of cerebral and coronary arteries, respectively. Similar results were observed when a synthetic inhibitor of Src was used in wild-type mice. Thus, inhibitors of Src signaling pathway could have therapeutic implications.

The permeability-increasing effect of vascular endothelial growth factor was essentially absent in mice lacking Src gene.

Role of Hepatic Lipase in Lipoprotein Metabolism and Atherosclerosis

Dr. Sylvia Santamaria-Fojos of the Molecular Branch of the National Institutes of Health, Bethesda, MD, described the role of a lipolytic enzyme, hepatic lipase (HL), in atherosclerosis during the delivery of the George Lyman Duff Lecture for 2002. She described a series of experiments showing that HL not only hydrolyses lipoproteins and phospholipid, but also acts as a ligand, increasing the cellular uptake of lipoproteins. Using bone marrow transplantation experiments, Dr. Santamaria-Fojos provided evidence that macrophage-specific expression of HL enhances atherosclerosis in apo E null mice and that bone marrow derived from HL mice reduces atherosclerosis when transplanted into apo E deficient mice with normal HL genotype, lending further support to the concept that HL is a pro-atherogenic molecule.

CARDINAL Trial: Complement and Reduction of Infarct Size After Angioplasty or Lytics: Another One Bites the Dust

Dr. Christopher Granger from Duke University presented disappointing data from a multicenter, randomized, placebo-controlled trial in which

investigators tested the hypothesis that concomitant administration of a synthetic inhibitor of complement (C5) with reperfusion therapy would reduce infarct size as measured by area under the creatinine phosphokinase time activity curve over 72 hours in patients with evolving acute myocardial infarction. Approximately 1900 patients with acute evolving myocardial infarction were randomized to placebo or treatment with a humanized chimeric anti-C5 antibody (pexelizumab) produced by Alexion Pharmaceuticals (Cheshire, CT). In one part of the trial (Complement Inhibition in Myocardial Infarction Treated with PTCA [COMMA]), reperfusion strategy was primary PCI, whereas in the other part of the trial (Complement Inhibition in Myocardial Infarction Treated with Thrombolytics [COMPLY]) the reperfusion strategy was thrombolytic therapy. The rationale for the trial was the hypothesis that complement activation after myocardial ischemia–reperfusion induces myocyte death, contributing to so-called "reperfusion injury" and increased infarct size. Unfortunately, but not surprisingly, there was no significant reduction in the infarct size with the use of the complement inhibitor, regardless of the type of reperfusion strategy used. As with several previous human trials of agents postulated to reduce the so called "reperfusion injury," this trial also failed to demonstrate benefit, most likely because the underlying premise is wrong. A large body of evidence, including the elegant experimental studies of Dr. William Ganz of Cedars-Sinai Medical Center, has challenged the very notion of reperfusion injury as a viable paradigm. It is time that our industry and investigative colleagues rethink the whole concept of the existence of reperfusion injury before launching additional expensive and time-consuming clinical trials that are bound to fail.

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Role of Elastase in Pulmonary Hypertension, Acute Myocardial Infarction, and Transplant Vasculopathy

Dr. Marlene Rabinowitch of the University of Toronto gave the Paul Dudley White Lecture. Dr. Rabinowitch described an elegant series of experiments highlighting the role of elastin degradation products produced by endogenous elastase, in the pathogenesis of fibroproliferative occlusive vascular disease involving the pulmonary circulation in pulmonary hypertension and the coronary circulation in transplant vasculopathy. By using animal models with genetic deficiency of elastase and pharmacologic inhibition of elastase with a synthetic inhibitor, elafin, Dr. Rabinowitch showed that inhibition of endogenous elastase activity not only reduced the development and progression of fibroproliferative occlusive pulmonary vascular disease, but also induced regression of pre-existing occlusive vascular disease. Similarly, in a heart transplant model, elastase inhibition was associated with a dramatic inhibition of transplant-related occlusive coronary vasculopathy. Finally, using an acute myocardial infarction model, elastase inhibition was shown to attenuate adverse ventricular remodeling. These elegant series of studies provide a potential basis for investigation of elastase inhibition as a potential therapeutic strategy in humans.

[Prediman K. Shah, MD, FACC, FACP, FCCP]

Elastase inhibition was associated with a dramatic inhibition of transplant-related occlusive coronary vasculopathy.

Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction: Facilities Without On-Site Cardiac Surgery

The 2001 American College of Cardiology/American Heart Association Guidelines recommend that primary percutaneous coronary intervention (PPCI) for patients with acute myocardial infarction (defined as ongoing chest pain and ST-segment elevation or new left bundle branch block on electrocardiogram) at hospitals without on-site cardiac surgery be restricted to facilities that can meet the following standards:

1. More than 36 cases of PPCI performed annually;
2. A proven plan for rapid access to a nearby surgical facility;
3. PPCI performed rapidly, as defined by balloon inflation within 90 ± 30 minutes; and
4. Presence of skilled operators, performing at least 75 PCI procedures per year.

Even if these standards can be met, PPCI in this setting is designated as a Class IIb indication (ie, the weight of evidence does not favor performance of this procedure).[25]

Earlier this year, a review from our group at Mayo Clinic argued that it was "time for reappraisal" of this designation.[26] A presentation from Dr. Timothy Sanborn on a report from the National Registry of Myocardial Infarction (NRMI)[27] at provided additional evidence to suggest that PPCI in qualified community hospitals may be the best approach to reperfusion therapy, at least in some centers.

Study Design

This study evaluated this issue in 26,764 eligible patients in three groups of hospitals: group A consisted of 47 hospitals with catheterization activities only (no on-site cardiac surgery); group B, 50 hospitals performing elective PCI but with no on-site cardiac surgery; and group C, 562 hospitals performing elective PCI, with on-site cardiac surgery available. Group C hospitals were larger and had a greater volume of PCI procedures, but 47% of all hospitals performed fewer than 27 PPCIs per year.

Results

Door-to-balloon times were shortest in group A hospitals: 104 minutes compared with 116 minutes and 199 minutes in groups B and C, respectively. In-hospital mortality was not significantly different among the three groups of institutions: 3.2%, 4.2%, and 4.8% in groups A, B, and C, respectively. The limitation of this study is that 4.7% of patients were transferred to another institution for unknown reason after PPCI, and their outcomes were not tracked; however, there was a trend (albeit not statistically significant) suggesting that patients in group A hospitals were at lower risk. We also do not have information on total operator experience at each institution, particularly because operators (physicians who perform the cardiac catheterization procedure) at high-volume institutions with cardiac surgical facilities may also have performed procedures at smaller hospitals in which catheterization laboratories were utilized primarily for diagnostic catheterization and which were not part of the NRMI database.

An astounding and disappointing finding was that 24.1% of all ST-segment elevation myocardial infarction patients did not receive any reperfusion strategy at all.

An astounding and disappointing finding was that 24.1% of all ST-segment elevation myocardial infarction patients did not receive any reperfusion strategy at all—data consistent with the multinational Global Registry of Acute Coronary Events.[28]

The major message of this report, however, is that prompt PCI in community hospitals without cardiac surgical facilities may be preferable to the delays involved in transfer to tertiary care hospitals. It is also noteworthy that in the smaller community hospitals it appeared that the onset-of-chest-pain-to-door intervals and door-to-balloon times were shorter.

Commentary and Literature Review

Where best to perform PPCI remains a contentious issue, but these data certainly strengthen the argument that the current guidelines warrant reappraisal—a Class IIb indication appears to be too stringent.

The impressive technological advances in PCI over the last decade, which have resulted in markedly improved outcomes, when considered alongside the logistical and financial problems involved in adding additional cardiac surgical facilities to community hospitals, have created an opportune climate in which to reexamine the role of PPCI in community hospitals without on-site cardiac surgery. There are, however, several issues that need to be addressed.

PPCI versus thrombolytic therapy. More than 20 randomized, controlled trials have demonstrated that PPCI is superior to thrombolytic therapy in terms of reducing mortality, stroke, and recurrent ischemia.[29] It is generally accepted that PPCI is the optimal reperfusion strategy when performed in the right institution and by the right hands. There is evidence, however, that results are not uniform across institutions. It is essential that any institution or operator embarking upon this approach must audit their own data and not rely on published series, because the latter may reflect the experience of experts and enthusiasts. It may well be that hospital constraints and other factors in a particular institution may indicate favoring the use of thrombolytic therapy over PPCI, even in institutions in which elective angioplasty is performed with great success.[30] Nonetheless, if PPCI can be performed promptly, safely, and effectively, it is the preferred strategy.

Emergency CABG after PPCI for patients with acute myocardial infarction. Rates of emergency coronary artery bypass graft (CABG) after failed elective PCI have fallen dramatically in recent years. After failed PPCI in the setting of an acute evolving myocardial infarction, in six randomized trials of primary stenting versus percutaneous transluminal

coronary angioplasty, comprising 1953 patients, only 67 patients (6.8%) underwent CABG during the index hospital admission, and in only 4 patients (0.4%) was emergency surgery required for complications related to PCI failure.[26,31–36]

Issues related to patient transfer. Although several studies have suggested that the outcomes of PPCI are less time-dependent than is the case with thrombolytic therapy, two large studies have shown a clear relationship between longer door-to-balloon times and adverse outcomes.[37,38]

It appears that the majority of individuals performing PCI in the United States are relatively low-volume operators working out of relatively low-volume institutions.

On the other hand, several studies, including one randomized, controlled trial have demonstrated that transferring patients from community hospitals to centers with facilities for PPCI is safe and effective and may be preferable to an initial approach of lytic therapy.[39–41] In contrast, a trend toward less myocardial salvage and a higher mortality was noted in two other series.[42,43] The duration of the delay incurred by transport is likely to be a critical factor and one that is probably related to distance, mode of transport, and weather.

Studies of PPCI in facilities without cardiac surgery. Several relatively small studies, ranging from 62 to 506 patients,[44–49] and one randomized, controlled trial[50] of 453 patients have demonstrated favorable outcomes for PPCI in facilities without on-site cardiac surgery. In the Atlantic Cardiovascular Patients Outcomes Research Trial,[50] comparing PPCI with thrombolysis, the composite endpoint of death/reinfarction/stroke was 25.4% in patients receiving thrombolytic therapy, compared with 15.4% in the PPCI group ($P = .03$). To what extent these results can be applied to community hospitals and other regions and countries remains to be confirmed. This trial was carried out in 11 hospitals in which the comprehensive, logistical, and training program had been set up in advance. Moreover, it should be mentioned that no trial as yet has directly compared the strategy of PPCI in a community hospital without on-site cardiac surgery with transport to a referral center for PPCI. We can only extrapolate from trials of community-hospital PPCI versus thrombolysis to a trial comparing the two strategies directly.

Limitations and conclusion. The implications of widely expanding the availability of PPCI to the community at large are sobering. In the National Registry of Myocardial Infarction Study published in 2000,[51] 28.1% of hospitals in the United States were classified as noninvasive, 32.6% were capable of performing PCI, and only 39.2% had cardiac surgical facilities. Operator experience is an additional factor, because in the current era, the range of available technical options (eg, distal protection devices, clot aspiration techniques, adjunctive therapies including cooling, etc) may introduce challenges to an inexperienced operator. Moreover, it appears that the majority of individuals performing PCI in the United States are relatively low-volume operators working out of relatively low-volume institutions.[52] To what extent this will be an impediment to the more widespread adoption of PPCI in community hospitals without cardiac surgery remains to be determined, but the Sanborn study is encouraging in this regard.

Summary

There is now enough evidence to state with confidence that PPCI in qualified community hospitals is safe and effective and may well be the best reperfusion strategy available. To what extent this will apply to the majority of community hospitals with cardiac catheterization laboratories is unknown.

The key to reperfusion therapy is not just the nature of the therapy but the efficacy of its delivery.

To be effective, PPCI requires an integrated approach involving physicians, allied health professionals, hospital administrators, extensive logistical support, and ongoing protocol-driven training, outcomes analysis, and quality improvement.

In summary, in community hospitals without cardiac surgical facilities, PPCI may be the best treatment for some, but not all, patients with acute myocardial infarction. Moreover, we must not overlook an embarrassing statistic: 20%–30% of eligible patients get no reperfusion therapy at all.

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

Statin therapy should not be withheld from subjects at risk of a subsequent cardiovascular event because of advanced age.

Statins Before Surgery and at the End of Life

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial is the first statin trial to directly

focus on primary and secondary prevention in the elderly.[53] This study randomized 5804 men and women (52%), ages 70–82 years, to pravastatin 40 mg per day or placebo. The cholesterol range of the subjects was 155–350 mg/dL, with a mean total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol of 221, 147, and 50 mg/dL, respectively. The mean triglyceride level was 133 mg/dL. Forty-four percent of the subjects had cardiovascular disease, and the remainder had diabetes mellitus or hypertension or were smokers.

Pravastatin therapy reduced cholesterol 23%, LDL cholesterol 34%, and triglycerides 13%, and increased HDL cholesterol 5%. After a mean follow-up of 3.2 years, the pravastatin group experienced a significant (15%) reduction in the primary endpoint (coronary heart disease death, nonfatal myocardial infarction, or stroke) (14.1% vs 16.5%, $P = .014$), which was entirely due to a reduction in coronary events (19% reduction) with no effect on stroke. A significant (25%) increase in cancer was observed, which has not been observed in any other statin trial. No significant effects were observed

Main Points

- Results of the SAPPHIRE Trial indicate that carotid stenting with distal protection is superior to conventional carotid endarterectomy as a treatment approach for high-risk patients with carotid arterial disease.
- The DIAL Trial showed that telephone-based management of heart failure appears to be a cost-effective intervention that could be applied to patients who do not have access to multidisciplinary heart failure disease management or specialty care for heart failure.
- An update from the Canadian Implantable Defibrillator Study strongly suggests that in patients with resuscitated ventricular fibrillation, ventricular tachycardia, or unmonitored syncope, an implantable cardioverter defibrillator should be considered first-line treatment in the secondary prevention of sudden cardiac death.
- The REPLACE 2 trial demonstrated that bivalirudin (with provisional glycoprotein [GP] IIb/IIIa blockade) was equivalent to unfractionated heparin plus GP IIb/IIIa blockade with respect to the occurrence of periprocedural ischemic events and superior with respect to major bleeding events in percutaneous coronary intervention (PCI).
- The CREDO Trial showed clear benefits from a loading dose of clopidogrel prior to PCI, provided it was given at least 6 hours before the procedure, and from the administration of a clopidogrel–aspirin combination in these patients during a 12-month follow-up.
- The ISAR-COOL Trial concluded that, in patients with acute coronary syndromes, deferral of intervention for extensive antithrombotic pretreatment (cooling-off) does not improve outcome, compared with immediate intervention under the now-standard antiplatelet coverage.
- Data from several studies support the notion that chronic kidney disease is a unique, markedly proinflammatory atherosclerotic state.
- The ASSENT III Plus study failed to demonstrate superiority of the combination of enoxaparin and tenecteplase (vs unfractionated heparin and tenecteplase) given to patients with ST elevation myocardial infarction in the pre-hospital setting.
- In patients with peripheral arterial disease, one study provided initial evidence that autologous administration of bone marrow mononuclear cells, including endothelial progenitor cells, may promote angiogenesis and ameliorate limb ischemia. Another study found that atorvastatin significantly improved the time to the onset of claudication.
- The CARDINAL Trial, which tested the hypothesis that concomitant administration of a synthetic inhibitor of complement (C5) with reperfusion therapy (PCI or thrombolytic therapy) would reduce infarct size, showed no significant reduction in infarct size with the use of complement inhibitor, regardless of the type of reperfusion strategy used.
- A study of PCI performed at hospitals with and without on-site cardiac surgery facilities showed that prompt PCI in community hospitals without cardiac surgical facilities may be preferable to the delays involved in transfer to tertiary care hospitals.
- Two studies of statin therapy before surgery suggest that, for elective surgery, statin therapy should be begun preoperatively if scheduling permits.

in rates of congestive heart failure, revascularization, cognitive function, or all-cause mortality. The reduction in cardiovascular risk was not dependent on initial cholesterol level, age, or gender. No cases of myositis were observed, and the incidence of liver dysfunction was equal in the two groups. This study demonstrated that statin therapy should not be withheld from subjects at risk of a subsequent cardiovascular event because of advanced age.

Two studies presented at the 2002 AHA meeting suggested that statins may be of value in subjects undergoing noncardiac surgery. In a retrospective study, 26,264 subjects with at least one risk factor (age > 70 years, diabetes, angina, prior myocardial infarction or stroke, hypertension, or heart failure) undergoing noncardiac surgery during the 1990–2000 period at Erasmus University, the Netherlands were followed postoperatively for 30 days.[54] Those subjects on β-blocking agents at the time of surgery had a significant, 44% lower incidence of mortality by multivariate analysis.

A prospective, randomized trial has confirmed this benefit of statin therapy in subjects undergoing vascular surgery.[55] Ninety-eight subjects were randomized to receive either atorvastatin 20 mg per day or placebo for a mean of 30 days before vascular surgery. A significant, 68% reduction in cardiac death, nonfatal myocardial infarction, unstable angina or stroke was observed in the statin group over a 6-month follow-up period. Most of the reduction was observed during the first 2 weeks after surgery.

These two studies suggest that for elective surgery, statin therapy should be begun preoperatively if scheduling permits. Two randomized trials have also demonstrated the same for β-blocker therapy in high-risk subjects undergoing noncardiac surgery. ■

[Robert A. Vogel, MD, FACC]

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