The following studies were presented at the 72nd Scientific Sessions of the American Heart Association, November 7–10, 1999 in Atlanta, Georgia.

Congestive Heart Failure

ELITE II (Evaluation of Losartan in the Elderly)

Presenters: Bertram Pitt, University of Michigan, Ann Arbor, Mich; Philip Poole-Wilson, National Heart & Lung Institute, London, England, UK.

The study: A large-scale multicenter (289 clinical sites in 46 countries) randomized, controlled trial of Losartan (an angiotensin receptor blocker) in patients with heart failure. A total of 3152 patients with class II to IV heart failure and an EF ≤40% were randomized to captopril (50 mg TID, n=1574) or Losartan (50 mg/d, n=1578). To qualify for the study, patients could not have been on prior ACE inhibitor therapy for ≥7 days. Patients were subsequently followed for a mean of 558 days. The primary endpoint of the study was all-cause mortality.

The results: There was no significant difference in all-cause mortality in the 2 groups (captopril 15.9%; losartan 17.7%). Mortality in both groups was approximately 11%/year. Sudden death tended to be slightly lower (but not significantly) in the captopril group. In analyses of various clinical subsets, patients on β-blockers and patients with an EF >32% showed more benefit with captopril. There were also no significant differences between group in the composite of sudden death and resuscitated cardiac arrest, in hospitalization rates, and the composite of all cause mortality and hospitalization. Captopril patients were significantly more likely to withdraw from therapy (14.5% versus 9.4% with Losartan).

Summary: In contrast to the previous ELITE trial, the larger scale ELITE II trial showed no mortality advantage for the ARB losartan. ACE-inhibit therapy remains the therapy of choice in patients with heart failure. ARBs may be considered if ACE inhibitors are not tolerated.

IMPRESS

Presenter: Jean Rouleau, Toronto Hospital, Canada.

The study: A multicenter, randomized, controlled trial of omapatrilat (a novel vasopeptidase inhibitor that blocks both neutral endopeptidase and angiotensin converting enzyme, and thus enhances the activity of vasodilator peptides (natriuretic peptides, bradykinin, and adrenomedullin) and reduces angiotensin II levels in patients with A total of 573 patients with class II to IV CHF were randomized to 24 weeks of therapy with omapatrilat (target dose 40 mg qd) or lisinopril (target dose 20 mg qd). All patients were on ACE inhibitors before randomization. The primary endpoint of the study was a composite of mortality and morbidity (hospitalization for worsening heart failure or study drug discontinuation).

The results: Exercise time at 12 weeks was slightly prolonged in both groups. Omapatrilat patients with class III heart failure showed significantly more improvement in New York Heart Association CHF class (39 improved, 0 worsened versus 29 improved, 4 worsened with lisinopril). Omapatrilat patients showed significant improvement in the morbidity/mortality composite endpoint (16% versus 29% with lisinopril; P<0.04). Both drugs appeared well tolerated, although omapatrilat was associated with a lower overall incidence of serious adverse events and elevations of BUN/creatinine.

Summary: In patients with symptomatic CHF, the vasopeptidase inhibitor omapatrilat was associated with improved symptoms and morbidity/mortality in comparison with lisinopril. Larger scale confirmatory efficacy trials are warranted.

BEST (Beta Blocker Evaluation of Survival Study)

Presenters: Michael Domanski, National Heart, Lung, and Blood Institute, Bethesda, Md; Eric Eichhorn, University of Texas-Southwestern, Dallas, Tex.

The study: A multicenter, randomized, placebo-controlled trial of bucindolol (a nonselective B1 and B2 blocker with weak α1 blocking capabilities) added to standard therapy (including ACE inhibitors) in patients with heart failure. The trial was jointly sponsored by the National Heart, Lung, and Blood Institute and the Veterans Affairs Cooperative Studies Program. A total of 2708 patients with class III/IV heart failure, and an EF ≥35% were randomized to bucindolol (3 mg initially, gradually titrated up to 50 mg BID [or 100 mg BID if ≥75 kg] over 6 to 8 weeks) or placebo. The primary endpoint of the trial was all-cause mortality. The study was originally designed to follow patients for approximately 3 years. The study was terminated prematurely because the
“totality of evidence from other trials and BEST” led the DSMB to stop the trial after 2 years of follow-up.

The results: Of the 2708 patients finally enrolled in the trial, 92% were class III and 8% were class IV. Overall, in the abbreviated trial, there was a nonsignificant trend toward lower total mortality (relative reduction of 10%) and lower cardiovascular mortality/relative reduction of 12.5% in the bucindolol group. Bucindolol patients had significantly greater improvement in ejection fraction over time and fewer heart failure-related hospitalizations. There was a somewhat heterogeneous response with less severely ill patients (class III or EF >20%) showing more benefit with bucindolol. In African-American patients, outcomes were somewhat better in the placebo group.

Summary: In the abbreviated BEST trial, overall bucindolol did not show significant mortality benefit. The totality of evidence strongly favors the use of beta blockers in congestive heart failure, although in BEST African-American and class IV patients showed no benefit.

Acute Coronary Syndromes

SHOCK (Should We Emergently Revascularize Occluded Coronary Arteries for Cardiogenic Shock?) (1 Year Results)
Presenter: Judith Hochman, Columbia University, St. Luke’s Roosevelt Hospital Center, New York, NY.

The study: A randomized, trial comparing early revascularization to initial medical stabilization in 302 patients with acute ST-segment elevation MI and cardiogenic shock in 30 clinical centers in 7 countries. Previous reports demonstrated a nonsignificant trend favoring early revascularization at 30 days (the primary endpoint of the study). Further long-term follow-up data are now available.

The results: At 30 days, mortality was 47% in the early revascularization group and 56% in the medically stabilized group (P=0.109); at 6 months, mortality was 50% in the early revascularization group and 63% in the medically stabilized group (P=0.027); at 1 year (98% complete data), mortality was 54% in the early revascularization group and 69% in the medically stabilized group (P=0.009). The primary benefit of early revascularization appeared to be in patients <75 years of age (1 year mortality 49% in the early revascularization group and 67% in the medically stabilized group; interaction P=0.029) versus those ≥75 years (1 year mortality 79% in the early revascularization group and 66% in the medically stabilized group).

Summary: In patients with ST-elevation MI complicated by cardiogenic shock, early revascularization is associated with significantly better 1-years survival, particularly in those patients <75 years. One-year mortality in patients ≥75 years of age is high regardless of treatment strategy, although the small number of elderly patients in the study (n=56) must be considered.

CHAMP (Combination Hemotherapy and Mortality Prevention)
Presenters: Louis Fiori, Boston University, Mass; Michael Ezekowtiz Yale University, New Haven, Conn.

The study: A multicenter long-term (6 years) study comparing the use of aspirin versus aspirin/warfarin therapy in survivors of an acute myocardial infarction. The study was coordinated through the Veterans Affairs Cooperative Study Program and involved 78 clinical centers. A total of 20,036 patients were screened over a 5-year period; 5059 patients (25% of those screened) were ultimately randomized in an open-label fashion to aspirin (162 mg/d; n=2537) or aspirin/warfarin (81 mg/d of aspirin, warfarin titrated to INRs of 1.5 to 2.5; n=2522). To qualify, patients had to be enrolled within 14 days of an acute MI. Median follow-up was 2.73 years (range 10 months to 6 years). The primary endpoint of the study was all-cause mortality. Secondary endpoints included nonfatal MI, nonfatal stroke, total cardiovascular mortality, and major hemorrhage.

The results: The mean age of the patients was 65 years; 99% were male; diabetes was present in 27%; 43% were smokers. Q wave MIs were present in approximately 41%. The mean ejection fraction was approximately 50%. Approximately 1/3 of patients had received thrombolytic therapy for their acute MI. Within 3 months of enrollment, approximately 15% of patients underwent PTCA, and approximately 5% of patients underwent CABG surgery. Study therapy was discontinued in 13% of the aspirin patients and 25% of the aspirin/warfarin patients. In the aspirin/warfarin group, 70% of patients had INRs >1.5; the mean INR in the group was 1.8.

All cause mortality (the primary study endpoint) was 17% in both groups; there was also no difference between groups in cardiovascular deaths (70% of the total), the incidence of nonfatal MI (14% in both groups), or nonfatal stroke (3% in both groups). Major bleeding events were approximately twice as frequent in the aspirin/warfarin group versus the aspirin group (1.25 events/100 patient years versus 0.69 events/100 patient years with aspirin). Bleeding rates increased with age in both groups. There was no increase in ICH associated with aspirin/warfarin therapy.

Summary: There is no effect on mortality of adding warfarin to aspirin in MI survivors, and combination therapy does not reduce the incidence of nonfatal MI and nonfatal stroke. Overall, the incidence of major hemorrhage is low. Adding warfarin doubles the risk of major bleeding but does not increase the risk of fatal or intracranial hemorrhage.

CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) (Preliminary Results)
Presenter: Gregg Stone, MD, Cardiology Research Foundation, Lenox Hill Hospital, New York, NY.

The study: A multicenter randomized, controlled trial comparing PTCA and stenting, with and without the use of abciximab (an intravenous platelet GP IIb/IIIa antagonist), in patients undergoing primary intervention for acute MI. A total of 2655 patients with acute MI at 76 clinical centers were entered into the study; this preliminary report focused on 1961 qualifying patients who were randomized to stenting (with or without abciximab) or PTCA. To qualify, the target lesion had to be between 2.5 to 4.5 mm in diameter and up to 70 mm in length (sufficient to be covered by 1 to 2 MultiLink
Patients with shock were excluded. All patients received aspirin (325 mg) and ticlopidine (500 mg load, 250 mg BID for 2 weeks). Ioxaglate was the contrast agent used. In patients receiving abciximab, activated clotting times (ACTs) were maintained between 200 to 300 seconds, and in placebo patients, ACTs were titrated to >350 seconds. The primary endpoint of the study is the 6-month composite incidence of death, Re-MI, and urgent intervention. This presentation reported only preliminary in-hospital safety and outcome data.

The results: The median time from symptom onset to hospital presentation was 1.9 hours. The median time from presentation to intervention was 2.0 hours. Approximately 50% of the patients had single-vessel disease. In the PTCA arms, bailout stenting (for suboptimal results) was required in 20% of the 488 placebo patients and 15% of the 494 abciximab patients. In the nonabciximab arms, bailout abciximab (for refractory thrombus or high risk anatomy) was required in 7.8% of the 488 placebo patients and 4.1% of the 487 stent patients. TIMI-3 flow was achieved slightly more frequently in the abciximab groups and slightly less frequently in the stent alone arm (95.5% versus 94.8% with placebo in the PTCA arms; 96.7% versus 92.1% with placebo in the stent arms). In the total population, inhospital clinical event rates were low: death (1.4%), stroke (0.4%), reinfarction (0.4%), and ischemia-driven target vessel revascularization (TVR) (0.9%). The incidence of mortality and stroke did not appear different between groups. There was a trend toward lower rates of reinfarction and ischemia-driven TVR in the abciximab groups and a trend toward less ischemia-driven TVR in the stent groups. There was a significant reduction in recurrent ischemia in the abciximab group: 4.5% PTCA alone, 1.4% PTCA+abciximab, 3.9% stenting alone, 1.2% stenting+abciximab. There was a slight increase in bleeding in the abciximab arms: 3.1% PTCA alone, 5.1% PTCA+abciximab, 3.5% stenting alone, 4.5% stenting+abciximab. There was no significant difference in the incidence of intracranial hemorrhage between groups.

Summary: With modern interventional techniques, primary interventional strategies result in very low in-hospital mortality and high TIMI-3 target vessel flow. Modern generation stents are safe for primary interventional therapy of acute MI. Stenting alone may be associated with slightly worse TIMI-3 flow than PTCA because of distal thromboembolic events. Use of adjunctive IIb/IIIa antagonist therapy with stenting may overcome this potential problem, and is associated with a reduction in recurrent ischemia and ischemia-driven TVR. Longer term follow-up data are necessary to adequately define the optimal invasive treatment regimen for acute MI.

HALT MI (HU23F2G Anti-Adhesion to Limit Cytotoxic Injury Following Acute MI)

Presenter: David Faxon, University of Southern California, Los Angeles, Calif.

The study: A multicenter, randomized, placebo-controlled trial of LeukArrest (Hu23F2G, an IgG monoclonal antibody directed at the CD11/CD18 leukocyte adhesion molecules) in patients undergoing primary interventional therapy for acute myocardial infarction. A total of 637 patients (at 63 US clinical centers) with acute MI were enrolled, randomized, and brought to coronary angiography. If TIMI grade II/III flow was documented, study drug was not administered (n=217). Qualifying patients (<TIMI grade II flow) were randomized to low-dose LeukArrest (0.3 mg/kg, n=128), high-dose LeukArrest (1.0 mg/kg, n=139), or placebo (n=153). After receiving study drug, patients underwent revascularization, with use of stents and IIb/IIIa antagonists at the discretion of the operator. The primary endpoint of the study was the predischARGE SPECT-determined infarct size.

The results: Overall, interventional therapy was successful in nearly 90% of patients. Stents were used in 85% of patients; abciximab (a GP IIb/IIIa antagonist) was used in 70% of patients. There was no significant difference in SPECT-determined infarct size between groups (placebo, 16.8%; low dose, 16%; high dose, 17.2%). Post intervention corrected TIMI frame counts were also not significantly different between groups. There was a nonsignificant (P=0.2) trend toward better survival and reinfarction in the LeukArrest groups (mortality: placebo, 3.3%; low dose, 1.4%; high dose, 0.8%; reinfarction: placebo, 3.9%; low dose, 2.9%; high dose, 0.8%).

Summary: In patients undergoing primary interventional therapy for acute MI, blockade of CD11/CD18 with a monoclonal antibody was well tolerated, but did not affect infarct size, and did not significantly reduce clinical events, although encouraging trends were noted.

ERASE (Emergency Room Assessment of Sestamibi for Evaluation of Chest Pain)

Presenter: James Udelson, Tufts-New England Medical Center, Boston, Mass.

The study: A randomized, controlled trial evaluating the use of adjunctive sestamibi testing in the evaluation and triage of patients presenting to the emergency room for chest pain. The study sought to determine: 1) its potential utility in reducing the inappropriate discharge of patients with ischemia; and 2) the unnecessary admission of patients without true ischemia. A total of 2456 patients with recent (within 3 hours) symptoms consistent with ischemia and normal or nondiagnostic electrocardiograms were randomized to “usual care” (n=1246) or “usual care with adjunctive sestamibi testing” (n=1210). All admitted patients were followed in-hospital, and all discharged patients were seen again for follow-up stress testing.

The results: A final diagnosis of acute ischemia was made in 329 patients (13.4%) of those evaluated. The adjunctive use of sestamibi did not affect the admission rate both for patients with an ultimate diagnosis of acute MI (n=56) or unstable angina (n=273). In the 2127 patients in whom the diagnosis was not acute ischemia, adjunctive sestamibi testing did significantly reduce the admission rate (52% in the usual care group, 42% in the sestamibi group) and did improve the effectiveness of triage. Among all randomized patients, there was a 14% reduction in hospitalization in the sestamibi group.

Summary: In patients with recent symptoms consistent with ischemia and normal or nondiagnostic electrocardiograms, adjunctive sestamibi testing did not significantly alter the admission or discharge of patients with ischemia but did
significantly reduce the incidence of unnecessary admissions in patients without ischemia.

Arrhythmias

ASAP (Azimilide Supraventricular Arrhythmia Program)

Presenter: Edward Pritchett, Duke University Medical Center, Durham, NC.

The study: A large scale study examining the efficacy of azimilide in preventing the recurrence of symptomatic supraventricular arrhythmias. Previous studies in this program of trials have suggested a substantial prolongation of the time to recurrent events with increasing doses of azimilide. The current study expanded on this experience and randomized patients with a history of symptomatic atrial fibrillation, atrial flutter, or paroxysmal SVT to azimilide, 125 mg bid for 3 days, then 125 mg/d (n=202) or placebo (n=200). Patients had to be in sinus rhythm at the time of the first dose of study medication. Patients were stratified at the time of randomization into atrial fibrillation, atrial flutter, or paroxysmal SVT groups. The time to the first symptomatic recurrence of supraventricular tachycardia was the primary endpoint of the study. The initial 3-day loading period was not included in the analysis.

The results: The mean time to symptomatic recurrence was 27 days in the placebo group and 38 days in the azimilide group (P=not significant). Symptomatically, the azimilide group had less fatigue or dyspnea. There was one episode of torsades de pointes in the azimilide group.

Summary: In this study of patients with symptomatic supraventricular arrhythmias, azimilide did not significantly prolong the time to symptomatic recurrence. The reason for this failure, in the face of previous possible studies, remains unexplained.

Radiation Therapy

WRIST (Washington Radiation for In-stent Restenosis Trial)

Presenter: Ron Waksman, Washington Hospital Center, Washington, DC.

The study: A double-blind, randomized, placebo controlled trial of gamma coronary radiation therapy in patients with in-stent restenosis. A total of 130 patients with in-stent restenosis (100 native arteries, 30 vein grafts) underwent percutaneous therapy and were randomized to gamma radiation therapy (192-IR source, dose of 15 Gy to a 2 mm radial distance from the source) or placebo. Randomized placebo patients with restenosis at follow-up were eligible to crossover to radiation therapy (n=39). The primary endpoint of the study was the incidence of 6-month angiographic restenosis.

Results: At 6 months, angiographic restenosis was present in 19% of the radiation group and 59% of the control group (P=0.001). Target lesion revascularization was also significantly reduced at 6 months (13.8% versus 63.1% with placebo) and 12 months (23.1% versus 63.1% with placebo). Although there were more late recurrences (between 6 and 12 months) in the radiation therapy group.

Summary: In patients with in-stent restenosis, gamma radiation therapy significantly reduces angiographic restenosis and the need for target lesion revascularization. Despite more late recurrences in the radiation group, this clinical benefit is maintained through 1 year.

PREVENT (Proliferation Reduction With Vascular Energy Trial)

Presenter: Albert Raizner, Baylor College of Medicine, Houston, Tex.

The study: A safety/feasibility study of intracoronary radiation therapy using a 32P Beta source with a centering catheter and automatic source delivery system in patients undergoing coronary intervention. A total of 72 patients were randomized to receive 16, 20, 24, or 0 (control) Gy after successful percutaneous intervention (65% de novo, 35% restenotic, 39% PTCA alone, 61% PTCA plus stent).

The results: Radiation therapy was successfully delivered in 71/72 patients (99%). In hospital adverse events (death, MI, target lesion revascularization) were 1.8% with radiation and 5.9% in the control group. At 6-month follow-up angiography, late loss was 0.15±0.5 mm with radiation versus 1.0±0.7 mm in the control group (P=0.0002). Late loss index was similarly reduced (5±27% versus 51±32% in the control group; P=0.0001). Restenosis of the target lesion was present in 6% of the radiation group and 33% of the control (P=0.015). Nine-month adverse events occurred in 16% of the radiation group and 24% of the control group (P=not significant). No late aneurysms or nonhealed dissections were noted.

Summary: Intracoronary radiation therapy with an automatically delivered Beta source appears to be effective in reducing restenosis at the lesion site after successful PTCA or stenting.

Hypertension

HBP Care

Presenter: Martha Hill, Johns Hopkins School of Nursing, Baltimore, Md

The study: An evaluation of the efficacy of comprehensive hypertension care in young urban black men. A total of 309 hypertensive black men from inner city Baltimore were randomized to less intensive care (referral to community health care resources) or intensive care follow-up program. Patients continued to be followed for 24 months.

The results: In this high risk population, the mean age was 41 years, 62% to 67% had been in prison at some point, 74% to 84% were smokers, 50% had positive urine drug screens, and 50% manifested microscopic or gross proteinuria. At the time of the 12-month follow-up, 88% returned for a follow-up visit. Deceased or incarcerated (and otherwise unavailable) subjects were excluded. Twelve-month follow-up was obtained in 93% of subjects. Both groups reduced their blood pressure significantly from entry into the study. There were no significant
differences between the more intensive follow-up group and the usual care group.

**Summary:** This study demonstrated that a high risk cohort of hypertensive young, urban black males could participate, be randomized, treated effectively, and successfully followed-up. More intense follow-up in this population was not associated with more effective therapy.

### Acute Ischemic Stroke

**Abciximab for Acute Ischemic Stroke**

**Presenter:** Harold Adams, University of Iowa, Iowa City.

**The study:** A multicenter preliminary dose-escalation study of abciximab (a chimeric antibody that inhibits platelet GP IIb/IIIa) in patients with acute ischemic stroke. Eligible patients who presented within 24 hours of an acute ischemic stroke were randomized (3:1) to 1 of the 4 doses of abciximab (0.15 mg/kg bolus, 0.20 mg/kg bolus, 0.20 mg/kg bolus plus 0.125 μg · kg⁻¹ · min⁻¹ infusion × 12 hours, 0.25 mg/kg bolus plus 0.125 μg · kg⁻¹ · min⁻¹ infusion × 12 hours) or placebo. Patients were followed subsequently for 3 months.

**The results:** At 3-month follow-up, 35% of the patients treated with any dose of abciximab had minimal or no residual disability, compared with 20% of the placebo group. With regard to function in carrying out daily activities, 50% of the abciximab groups showed improvement, compared with 40% of the placebo group. There were no instances of symptomatic ICH in the overall study group. There was 1 asymptomatic ICH in the placebo group (n=20) and 7 asymptomatic ICHs in the abciximab groups (n=54).

**Summary:** The use of abciximab in patients with recent or ongoing acute ischemic stroke was not associated with an increase in symptomatic ICH, but perhaps more frequent asymptomatic ICH. The promising efficacy results need to be confirmed in a large-scale study.
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