Meeting Highlights
Highlights of the 49th Scientific Sessions of the American College of Cardiology

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The following studies were presented at the 49th Scientific Sessions of the American College of Cardiology, March 12–15, 2000, in Anaheim, Calif.

Acute Coronary Syndromes

The Trial: SYMPHONY II
Presenter: Kristin Newby, Duke University Medical Center, Durham, NC.

The study: A randomized trial of sibrafiban (an oral glycoprotein [GP] IIb/IIIa antagonist) in patients with acute coronary syndromes. The study was originally designed to include 8400 patients, but it was terminated prematurely by the sponsor (unilaterally) after the negative results of SYMPHONY. At the time the trial was terminated, a total of 6671 patients had been enrolled. To qualify, patients had to present within 7 days with an acute coronary syndrome and be stabilized. They were then randomized to receive aspirin (80 mg every 12 hours), sibrafiban (high dose), or sibrafiban (low dose) plus aspirin (80 mg every 12 hours). The primary end point was the composite of death, myocardial infarction (MI), or severe recurrent ischemia. Secondary end points included the incidence of coronary ischemic events, reversible coronary ischemia, coronary revascularization, rehospitalization, stroke, and bleeding. Sibrafiban dosing was performed according to patient weight and renal function.

The results: No significant differences existed in the primary composite end point of death, MI, or severe recurrent ischemia in the 3 treatment arms (aspirin, 9.3%; low-dose sibrafiban, 9.2%; high-dose sibrafiban, 10.5%). In the high-dose sibrafiban arm, a statistically significant excess in the composite of death and MI existed (8.6% versus 6.8% and 6.1% in the low-dose sibrafiban and aspirin alone groups, respectively; \( P<0.05 \) versus aspirin) and in death alone (2.4% versus 1.7% and 1.3% in the low-dose sibrafiban and aspirin groups, respectively; \( P<0.05 \)). Patients in both sibrafiban groups had more repeat hospitalizations compared with those receiving aspirin (high-dose sibrafiban, 25.8%; low-dose sibrafiban, 25.1%; aspirin, 21.5%; \( P<0.05 \)) and double the number of bleeding events.

Summary: The combination of aspirin and low-dose sibrafiban did not improve 90-day outcomes relative to aspirin alone and did result in significantly more bleeding events. High-dose sibrafiban alone was associated with no net clinical benefit and an excess of deaths and MIs. The excess of mortality is a consistent finding in OPUS, EXCITE, SYMPHONY, and SYMPHONY II.

The Trial: HART-II
Presenter: Allan Ross, George Washington University Medical Center, Washington, DC.

The study: A randomized trial comparing enoxaparin (a low-molecular-weight heparin) and unfractionated heparin (UFH), administered as an adjunct to fibrinolytic therapy in the setting of acute ST-elevation MI. A total of 400 patients presenting within 12 hours of the onset of an acute ST-elevation MI were treated with 100 mg of tissue-type plasminogen activator (t-PA) and aspirin and then randomized to receive either UFH (bolus of 5000 U, or 4000 U if weight \( \leq 67 \) kg, followed by 15 U \( \cdot \) kg\(^{-1}\) \cdot h\(^{-1}\) for up to 72 hours, adjusted to an activated partial thromboplastin time of 2 to 3× control) or enoxaparin (first dose, 30 mg IV, followed 15 minutes later by a dose of 1 mg/kg SC every 12 hours for up to 72 hours). Coronary angiography was performed at 90 minutes and repeated 5 to 7 days later. The primary end point of the study was infarct-related artery (IRA) patency at 90 minutes. Secondary end points included reocclusion at 5 to 7 days and safety parameters. The study was powered to determine equivalence of effect between the 2 therapies.

The results: Patient populations were well matched. IRA patency (TIMI grade 2 or 3 flow) tended to be higher in the enoxaparin group (80.1% versus 75.1%), which was driven mainly by a difference in TIMI grade 3 flow (52.9% versus 47.6% with UFH). Reocclusion rates within 1 week also favored enoxaparin (5.9% versus 9.8%). Two intracranial hemorrhages occurred in both groups. The need for blood transfusions was higher with UFH (7.1% versus 5.6%).
Overall, in-hospital and 30-day fatality rates were 4% to 5% in both groups. No differences existed in the need for urgent subsequent coronary intervention between the 2 groups.

Summary: IRA patency rates with enoxaparin are equivalent to those with UFH, and a trend toward lower reocclusion rates existed with enoxaparin. Adverse effects occurred with similar frequency in both groups.

The Trial: The PENTALYSE Study
Presenter: Patrick K. Coussement, University Hospital of Gasthuisberg, Leuven, Belgium.

The study: A randomized trial comparing SR9010A/ORG31540 (a synthetic pentasaccharide that selectively inhibits factor Xa) to unfractionated heparin (UFH), administered as an adjunct with recombinant t-PA and aspirin in the setting of ST-elevation MI. A total of 333 patients were treated with aspirin and recombinant t-PA (≤100 mg) and then randomized to receive conventional therapy with 48 to 72 hours of UFH (n=86) or 1 of the following 3 doses of pentasaccharide given subcutaneously: 4 mg (n=84), 8 mg (n=80), or 12 mg (n=83). The first dose of pentasaccharide was administered intravenously, and the drug was continued for 5±1 days. Angiography was performed 90 minutes after recombinant t-PA administration and on day 6±1. The primary end point was the combined incidence of intracranial hemorrhage and transfusions at 30 days. Secondary end points included TIMI 3 flow at 90 minutes and at 6 days and clinical events at 30 days.

The results: No differences existed in 90-minute TIMI 3 flow between the UFH and the pentasaccharide groups (68% versus 64%; P=0.595). At day 6±1 for 250 evaluable patients the patency rates were similarly improved in both groups (86% versus 79% with UFH; P=0.177). No significant difference was seen in the combined end point or in clinical events at 30 days. However, a trend existed toward fewer urgent revascularizations in the pentasaccharide group (38.6% versus 51.2%; P=0.054). The primary composite end point of intracranial hemorrhage and transfusions was reached in 6.3% of the pentasaccharide group and in 7.1% of the UFH group (P=0.7).

Summary: The adjunctive administration of SR9010A/ORG31540 to standard fibrinolytic therapy in acute ST-elevation MI seems to be safe, with no excess of bleeding; it resulted in similar rates of TIMI 3 flow at 90 minutes and at 6 days when compared with UFH, with a trend toward a lower incidence of reocclusion and urgent revascularization.

The Trial: PARAGON B
Presenter: Robert Harrington, Duke Clinical Research Institute, Durham, NC.

The study: A randomized, placebo-controlled trial of optimally dosed lamifiban (adjusted to renal function) in patients with acute coronary syndromes. A total of 5225 patients were randomized to receive either lamifiban (500-μg bolus followed by a 72-hour infusion, the dose of which was adjusted according to renal function) or placebo. All patients received aspirin and heparin (either unfractionated or low molecular weight). The primary end point of the study was the composite of death, MI, and severe recurrent ischemia at 30 days; a secondary end point was the composite of death and MI at 30 days. The study also examined safety end points of stroke (hemorrhagic and nonhemorrhagic), bleeding, requirement for transfusions, and thrombocytopenia. The study was powered at 96% to detect a 25% reduction in the primary composite end point at P=0.05 and at 82% to detect a 25% reduction in the composite of death/MI at P=0.05.

The results: No significant differences existed in the baseline characteristics between the 2 groups. Diabetes was present in 25% of patients, and nearly 60% of the study cohort had an MI at enrollment. All patients were on aspirin, and almost 90% received heparin in some form for ≈72 hours. Low-molecular-weight heparin was used in >33% of patients. The primary composite end point was reached in 12.8% of the placebo group and 11.8% of the lamifiban group (P=0.329). No differences existed in the composite of death/MI between the 2 groups (placebo, 11.5%; lamifiban, 10.6%; P=0.320). At 6 months, the survival curves did not show any divergence, and no survival benefit was demonstrated. An excess of intermediate bleeding occurred with lamifiban (14% versus 11.5%; P=0.002), but the incidence of major or life-threatening bleeding events was not significantly higher in the treated patients. Lamifiban seemed to have a significant impact on the primary end point in patients undergoing early intervention (lamifiban, 11.6%; placebo, 18.5%) and in those who were troponin-positive (11% versus 19%; P=0.018).

Summary: Dose-adjusted lamifiban did not significantly improve the primary end point compared with placebo. Intermediate bleeding was increased with lamifiban, but there was no increase in intracranial hemorrhage.

The Trial: The Post-Infarct PTCA Study of the ALKK Trial
Presenter: Uwe Zeymer, Klinikum Kassel, Kassel, Germany.

The study: A prospective, randomized comparison of medical therapy and percutaneous transluminal coronary angioplasty (PTCA) in stable, asymptomatic survivors of acute MI. A total of 300 patients were randomized. One-year follow-up was available in all patients, and extended follow-up (up to 66 months) in 96%. The primary end point of the study was event-free survival at 1 year. Secondary end points included death, reinfarction, repeat PTCA, coronary artery bypass grafting (CABG), and hospitalization for angina. The study was designed to have 90% statistical power to show a 40% reduction in events at 1 year.

The results: The peak creatine kinase level was ≈900 U/L in both groups. More patients in the PTCA arm received thrombolytics for their infarcts (63% versus 50%, P=0.03), and there were more hypertensives in the medical therapy arm (46% versus 32%; P=0.02). PTCA or recanalization was successful in 86% of patients, and coronary stents were used in <20% of patients. At 1-year, there was a trend toward improvement in event-free survival in the PTCA arm (90% versus 82%) and a
statistically significant reduction in the need for subsequent PTCA in the PTCA arm (8% versus 29%; \( P=0.03 \)). At 4.5 years of follow-up, there was a trend toward a lower death rate in the PTCA arm (5% versus 10%).

**Summary:** In asymptomatic survivors of acute MI, PTCA of the IRA is associated with a trend toward a reduction of events and improved survival.

### Congestive Heart Failure

**The Trial:** PRAISE-2  
**Presenter:** Milton Packer, Columbia University College of Physicians and Surgeons, New York, NY.

The study: A randomized, double-blind, placebo-controlled trial of amlopidine in patients with nonischemic cardiomyopathy on maximal medical therapy. A total of 1652 patients were randomized to receive either amlopidine (initially 5 mg/d, then increased to 10 mg/d after 2 weeks) or placebo. The primary end point of the study was all-cause mortality. The study was powered at 90% to detect a 25% difference in mortality between the treatment arms.

The results: No significant differences existed in all-cause mortality between the 2 arms (placebo, 31.7%; amlopidine, 33.7%; hazard ratio, 1.09; log-rank \( P=0.32 \)). A pooled analysis of the PRAISE-1 and PRAISE-2 trials showed no significant affect of amlopidine on mortality (placebo, 34%; amlopidine, 33.4%; hazard ratio, 0.98; log-rank \( P=0.81 \)).

**Summary:** Despite the fact that in PRAISE-1 a survival benefit was noted with amlopidine in patients with nonischemic cardiomyopathy, no such difference was noted in PRAISE-2 or when PRAISE-1 and PRAISE-2 were combined. Long-term treatment with amlopidine does not seem to be of benefit in patients with severe, chronic heart failure.

**The Trial:** OPTIME-CHF  
**Presenter:** Mihai Gheorghiade, Northwestern University, Chicago, Ill.

The study: A prospective, randomized, double-blind, placebo-controlled trial evaluating the effect of intravenous milrinone on hospital stay in hemodynamically stable patients with congestive heart failure (CHF) on maximal medical therapy. A total of 951 patients in 78 US centers were randomized within 48 hours of admission to receive either intravenous milrinone (0.5 µg·kg\(^{-1}\)·min\(^{-1}\) without a bolus dose; \( n=477 \)) or placebo (\( n=472 \)) for 48 hours. Patients were followed for 60 days. The primary end point was number of days of hospitalization for cardiovascular events within 60 days following treatment. Secondary end points included subjective clinical improvement, length of initial hospitalization, treatment failures within the first 48 hours, the proportion of patients reaching and time to reach the target dose of the angiotensin-converting enzyme (ACE) inhibitor, mortality, and adverse events. Analysis was by intention-to-treat.

The results: The mean time from admission to randomization was 15 hours. CHF was equally due to ischemic (=50%) and nonischemic (=50%) causes. Most patients were New York Heart Association class III and IV. The mean ejection fraction was 23%. Medical regimens were similar in the 2 groups; >70% were on ACE inhibitors and digoxin, 90% were taking diuretics, and \( \approx20\% \) were on \( \beta \)-blockers. No significant differences existed in the primary end point of days of hospitalization for cardiovascular events within 60 days between the groups (milrinone, 12.3 days; placebo, 12.5 days; \( P=0.714 \)). Similarly, no significant differences existed in the proportion of patients achieving target ACE inhibitor dose at 48 hours and at discharge, in subjective improvement, in length of stay, or in reduction in treatment failure or progression of CHF. The milrinone group had a higher number of complications. This was driven by a higher incidence of new atrial fibrillation (4.6% versus 1.5%; \( P=0.004 \)) and sustained hypotension (10.7% versus 3.2%; \( P<0.001 \)). There was also a trend toward more MIs and ventricular tachyarrhythmias in the milrinone arm. Total mortality rates and rehospitalization rates, however, were not significantly different between the 2 groups (\( \approx35\% \) for both groups) at 60 days. A secondary subgroup analysis suggested a trend favoring milrinone in the patients with nonischemic heart failure or patients with hyponatremia.

**Summary:** Patients who are admitted for exacerbation of CHF but do not otherwise require inotropic support do not derive any additional benefit from milrinone therapy. The observation that milrinone may be beneficial in nonischemic heart failure needs further investigation.

### Interventional Cardiology

**The Trial:** ESPRIT  
**Presenter:** James Tcheng, Duke University Medical Center, Durham, NC.

The study: A randomized, double-blind, multicenter, placebo-controlled trial (in which crossover was permitted) comparing high-dose eptifibatide and placebo in patients undergoing planned stenting of a native coronary artery and in whom a GP IIb/IIIa antagonist was not otherwise indicated. The study was originally planned to include 2400 patients, who were randomized to receive either high-dose eptifibatide or placebo, which was started immediately before percutaneous coronary intervention (PCI). Eptifibatide was administered as a 180-µg/kg bolus immediately before percutaneous coronary intervention and then a second bolus of 180 µg/kg after 10 minutes. The drug infusion was continued for 18 to 24 hours. All patients received aspirin and a thienopyridine the day of the procedure. Heparin was administered as a 60-U/kg bolus in both arms (target activated clotting time, 200 to 300). The primary end point of the study was the 48-hour composite of death, MI (2 values of creatine kinase-MB \( \ge3\times \) upper limit of normal), urgent revascularization, or thrombotic GP IIb/IIIa bailout in the catheterization laboratory. A secondary end point was the combination of death, MI, or urgent target vessel revascularization (TVR) at 30 days. On February 4, 2000, the Data and Safety Monitoring Committee recommended early termination of the study on the basis of a significant reduction of death or...
MI at 48 hours, with persistence of the efficacy at 30 days in those patients for whom data were available. The current presentation included 48-hour outcome data on the 2064 patients enrolled at the time the trial was terminated.

The results: Stent implantation was performed in >96% of the patients. The median duration of eptifibatide infusion was 18 hours. The primary composite end point was reduced by 37% in the eptifibatide arm (placebo, 10.5%; eptifibatide, 6.6%; \( P = 0.0015 \)). A similar reduction favoring eptifibatide occurred across the components of the primary end point: death/MI was reduced by 40% (5.4% versus 9.2% in placebo; \( P = 0.0013 \)), death/large MI (defined as a creatine kinase-MB ≥ 5× the upper limit of normal) by 33% (3.4% versus 5.1% in placebo; \( P = 0.053 \)), MI by 40% (5.4% versus 9% in placebo; \( P = 0.0015 \)), urgent TVR by 40% (\( P = \text{NS} \)), and thrombotic bailout by 52% (1% versus 2.1% in placebo; \( P = 0.03 \)). The overall 48-hour mortality rate was low in both groups (0.1% versus 0.2% in eptifibatide versus placebo groups; \( P = \text{NS} \)). A slight excess in bleeding occurred in the eptifibatide group, most of which occurred at the groin access site. No significant excess of intracranial hemorrhage or thrombocytopenia occurred with eptifibatide.

Summary: In a population of lower risk patients undergoing stenting in whom a GP IIb/IIIa blocker was not otherwise indicated, this higher-dose regimen of eptifibatide significantly reduced postprocedural events. Additional longer follow-up data will be necessary to evaluate the durability of this benefit. This study may help substantially expand the application of GP IIb/IIIa blocker therapy for these patients.

The Trial: The GOLD Study
Presenter: Steven Steinhubl, Wilford Hall Medical Center, San Antonio, Tex.

The study: A prospective, multicenter study correlating the degree of platelet inhibition achieved with standard GP IIb/IIIa dosing with subsequent clinical outcomes after percutaneous intervention. A total of 500 patients undergoing PCI and elective GP IIb/IIIa inhibitor use underwent assessment of platelet function (with the rapid platelet function assay from Accumetrics, Ultegra). Measurements were obtained at baseline, 10 minutes, and at 1, 8, and 24 hours. Patients were then monitored for subsequent major adverse cardiac events (MACE) during the hospital stay; these included death, MI, or urgent revascularization.

The results: The mean percent inhibition at 10 minutes, 1 hour, 8 hours, and 24 hours was 95%, 95%, 89%, and 72%, respectively. The percent of patients with <80% inhibition at those time points was 2%, 4%, 11%, and 54%, respectively. Achieving <95% inhibition at 10 minutes was associated with elevated MACE (14.4% versus 6.4%; \( P = 0.006 \)). Similarly, achieving <70% inhibition at 8 hours was also associated with elevated MACE (25% versus 8.1%; \( P = 0.006 \)).

Summary: The degree of platelet inhibition achieved with standard dosing of GP IIb/IIIa inhibitors can easily be measured, and it correlates with outcomes after PCI. Whether titration of GP IIb/IIIa antagonist therapy based on monitoring of platelet inhibition results in improved clinical outcomes remains to be evaluated.

The Trial: LONG WRIST
Presenter: Ron Waksman, Washington Hospital Center, Washington, DC.

The study: A 2-center, randomized, clinical trial of catheter-based γ-radiation on long, diffuse, in-stent restenosis (ISR). A total of 120 patients with diffuse ISR were randomized to receive either placebo or γ-radiation with Ir-192. The radiation doses delivered were 14 to 15 Gy at 2 mm from the center of the source in vessels <4.0 mm and 15 Gy at 2.4 mm in vessels >4.0 mm in diameter. Successful treatment with angioplasty or ablation (rotational or laser) or restenting to a residual stenosis <30% was a prerequisite before brachytherapy could be administered. The primary end points were 6-month MACE and repeat target lesion revascularization (TLR). Angiographic end points included binary restenosis (<50% at follow-up), late lumen loss, and late loss index at 6 month follow-up.

The results: The mean stent lengths in the Ir-192 and placebo groups were 45.9 mm and 46 mm, respectively (\( P = \text{NS} \)). The mean lesion length was 31 mm, and the reference vessel size was 2.5 mm in both arms. At 6 months, the ISR rate was significantly less in the Ir-192 arm (32% versus 71%; \( P = 0.0002 \)). This was driven by significantly reduced late loss in the stent group (Ir-192, 0.65 mm; placebo, 1 mm; \( P = 0.03 \)). In-lesion restenosis rates were also significantly improved in the Ir-192 arm (46% versus 78%; \( P = 0.001 \)), which was also driven by significantly less in-lesion late loss in the Ir-192 arm (0.6 mm versus 0.85 mm; \( P = 0.05 \)). MACE were significantly reduced in the Ir-192 arm (38.3% versus 61.7%; \( P = 0.01 \)), as were repeat PTCA (from 55% to 26%; \( P = 0.001 \)), TLR (from 60% to 30%; \( P = 0.001 \)), and TVR (from 60.7% to 33.3%; \( P = 0.003 \)). An “edge effect” of restenosis at the stent margins was seen more often in the Ir-192 arm than with placebo (13.1% versus 6.6%; \( P = \text{NS} \)). There was also a trend toward more Q-wave MI (8.3% versus 6.6%; \( P = 0.053 \)), subacute thrombosis (4.6% versus 1.7%), and late thrombotic events (11.7% versus 5%) in the Ir-192 group, which resulted in a late total occlusion rate of 15% in the Ir-192 arm and 6.7% in the placebo arm. No differences were seen in the rates of death or CABG.

Summary: Intracoronary γ-radiation for diffuse ISR is feasible and safe, without significant adverse effects compared with placebo. TLR (50%), TVR (45%), any MACE (37%), and angiographic restenosis (54%) were all reduced with γ-radiation therapy. A higher rate of late thrombosis existed in the Ir-192 arm; this may be averted with a longer duration of intensive antiplatelet therapy.

The Trial: The BESMART Study
Presenter: Rene Koning, Rouen, France.

The study: A prospective, randomized trial to determine the benefit of coronary stenting versus balloon angioplasty in small (<3 mm) vessels. A total of 381 patients with symptomatic coronary disease and a >50% de novo lesion...
in 1 or 2 native coronary arteries that were <3 mm in diameter were treated with a single stent that was 15 mm long or with a 2.0 to 2.5 mm balloon. The primary end point of the study was the 6-month angiographic restenosis rate. Secondary end points included in-hospital MACE, angiographic results, and clinical events at 6 months.

**The results:** The stent group had more diabetics (22% versus 12%; \(P=0.038\)), hypertensives (51% versus 40%; \(P=0.034\)), and patients with 1- vessel disease (58% versus 43%; \(P=0.0035\)) but fewer with 3- vessel disease (5% versus 13%; \(P=0.010\)). The groups were well matched for other baseline characteristics. The mean reference diameter in both groups before the procedure was 2.2 mm. Procedural success was 98% in both arms, with a 24% crossover rate from balloon to stenting. Maximal inflation pressure was 10 atm in the PTCA group and 12 atm in the stent arm (\(P=NS\)). Postprocedural minimal lumen diameters were greater in the stent arm (2.08 mm versus 1.72 mm, \(P=0.0001\)). In- hospital MACE rates were not different between the stent and angioplasty groups. At 6 months, the angiographic restenosis rate was lower in the stent arm (22.7% versus 48.5%; relative risk, 0.48; \(P<0.00001\)), as was the TLR rate (13% versus 25%, \(P=0.016\)).

**Summary:** Small vessel (<3 mm) stenting is associated with improved immediate angiographic results compared with balloon angioplasty and reduced restenosis at 6 months.

**The Trial: ISAR-SMART**

**Presenter:** Adnan Kastrati, Deutsches Herzzentrum, Munich, Germany.

**The study:** A randomized clinical trial comparing the efficacy of stenting and balloon angioplasty on reducing restenosis in small vessels (2.0 to 2.8 mm). A total of 404 patients were randomized to implantation of a Multilink stent or balloon angioplasty. Patients received adjunctive aspirin, ticlopidine, and GP IIb/IIIa antagonists at the time of the procedure. The primary end point was restenosis at 6 months.

**The results:** The mean residual stenosis was 7% in the stent arm and 18.8% in the balloon angioplasty arm. There was a 16.5% crossover rate from balloon angioplasty to stenting. At 6 months, no significant differences were detected in restenosis (stent, 35.7%; balloon, 37.5%), the percent of lesions with a >70% diameter stenosis (stent, 22.2%; balloon, 18.8%), or the need for TVR (stent, 20.1%; balloon, 16.5%). Freedom from death/MI approached 97% in both groups.

**Summary:** In ISAR-SMART, a strategy of routine stenting in small vessels measuring 2.0 to 2.8 mm conveyed no benefit in 6-month restenosis rates when compared with balloon angioplasty.

**The Trial: ISAR**

**Presenter:** Franz-Josef Neumann, München, Germany.

**The study:** A randomized, double blind, placebo-controlled trial of the effect of antibiotic treatment with roxithromycin on restenosis and clinical outcomes after coronary stent implantation. A total of 1010 patients were randomized to receive either 300 mg of roxithromycin once daily or a placebo; the dose was administered after successful stenting and continued for 28 days. The primary end point was angiographic restenosis at 6 months. Secondary end points included death, MI, and TVR. The study was powered at 80% to detect a 30% reduction in restenosis.

**The results:** The mean age of the population was \(\approx 65\) years. Nearly half of the study cohort presented with an acute coronary syndrome, 15% had an acute MI, and \(\approx 70\%\) had multivessel disease. Study drug compliance exceeded 90% in both groups, and angiographic follow-up was obtained in \(>80\%\). At 30 days, no significant difference existed in MACE between the roxithromycin and placebo arms (3.2% versus 2.8% for any MACE; 2.6% versus 2.4% for death/MI). At 6 months, no significant difference existed in the angiographic restenosis (roxithromycin, 31.5%; placebo, 29.3%) or TVR rates (roxithromycin, 21%; placebo, 18.9%).

**Summary:** Adjunctive antibiotic treatment with 300 mg of roxithromycin daily for 4 weeks did not reduce early thrombotic complications, restenosis rates, TVR, or clinical outcomes after coronary stenting.

**The Trial: BARI 7-Year Outcomes**

**Presenter:** Katherine M. Detre, University of Pittsburgh, Pittsburgh, Pa.

**The study:** BARI was a large-scale, randomized trial sponsored by the National Heart, Lung, and Blood Institute comparing CABG and PTCA in patients with multivessel coronary artery disease. The previously published 5-year results demonstrated no significant difference in survival with either strategy (CABG, 89.3%; PTCA, 86.3%; \(P=0.19\)). In the diabetic subgroup; however, 5-year survival was significantly reduced with PTCA compared with CABG (65.5% versus 80.6%; \(P=0.0003\)). The current presentation described the 7-year outcomes in the BARI cohort by treatment assignment and diabetic status.

**The result:** In the overall population, survival at 7 years was superior in the CABG group (84.4% versus 80.9%; \(P=0.043\)); this difference was primarily attributable to the diabetic population. Nondiabetic patients undergoing either procedure had similar 7-year survival, but diabetic patients fared significantly better with surgical revascularization (76.4% versus 55.7%; \(P=0.0011\)). Within the diabetic subpopulation, those on oral hypoglycemic agents had improved survival with CABG (84.1% versus 67.6%) and PTCA (60.6% versus 49.4%) compared with patients requiring insulin. Overall, in the BARI cohort, no significant differences existed in Q-wave-free survival between the CABG and PTCA group. Among the diabetic patients, however, freedom from Q-wave MI was significantly lower with PTCA (50.0% versus 65.2%; \(P=0.049\)). By 7 years, with the entire BARI cohort, repeat revascularization was higher with PTCA (59.7% versus 13.1%); this difference was again more pronounced in the diabetic PTCA patients, in whom only 30% were free of subsequent revascularization compared with 42% of nondiabetics.

**Summary:** Symptomatic, multivessel coronary artery disease patients without diabetes have similar 7-year survival rates whether they are treated with PTCA or
CABG. Diabetic patients with multivessel coronary artery disease requiring revascularization benefit from CABG. For both PTCA and CABG, the outcomes are worse in insulin-requiring diabetic patients.

Arrhythmias

**The Trial: BLOSS**

*Presenter:* Stuart J. Connolly, Hamilton, Ontario, Canada.

*The study:* A randomized, placebo-controlled trial of β-blocker therapy for the reduction of hospital stay after cardiac surgery. A total of 1000 patients undergoing cardiac surgery who were not in chronic atrial fibrillation (AF) and who had no contraindications to β-blocker therapy were randomized to either placebo (n=500) or oral metoprolol (n=500) within 12 hours of arrival in the intensive care unit (ICU). Metoprolol was given at a dose of 50 mg twice a day for the first 411 patients and at 50 mg 3 times a day for the remainder; it was continued for 14 days or until discharge. The primary outcome was length of hospital stay. Secondary outcomes were occurrence of AF, ICU length of stay, and postoperative costs. The study was powered at 90% to detect a 10% decrease in length of hospital stay.

*The results:* The patients in the 2 arms were comparable in terms of age, prior history of AF, and medical regimens. No significant difference existed in length of hospital stay between the 2 groups (metoprolol, 155 hours; placebo, 152 hours). The length of ICU stay tended to be higher in the metoprolol group (39 versus 34 hours; *P*=NS). β-Blockade with metoprolol resulted in a 20% reduction in the incidence of AF lasting ≥1 minute (31% versus 39%; *P*=0.0098). This reduction was significantly more pronounced in patients receiving the higher dose of metoprolol (26% relative risk reduction). Significant preoperative predictors of postoperative AF included age (odds ratio, 2.18 per 10 years of age; *P*<0.0001), a prior history of AF (odds ratio, 7.23; *P*<0.0001), and type of surgery (odds ratio, 1.88; *P*=0.0028).

*Summary:* Metoprolol administered prophylactically significantly decreased the incidence of postoperative AF by 20%, but this reduction did not translate into a decrease in length of stay. It remains to be seen whether β-blockade impacts the hard events of stroke/embolism.

**The Trial: ACUTE 1**

*Presenter:* Allan Klein, Cleveland Clinic, Cleveland, Ohio.

*The study:* A prospective, randomized, controlled trial comparing transesophageal echocardiography (TEE)–guided therapy (with short-term anticoagulation) with conventional anticoagulation therapy for AF in 1222 patients. In the TEE-guided arm, immediate anticoagulation with heparin was initiated followed by TEE. If no left atrial thrombus was detected, immediate cardioversion followed by 4 weeks of oral anticoagulation with warfarin was undertaken. If a left atrial thrombus was seen, the patient was anticoagulated for 3 weeks with warfarin, and TEE was repeated. If no thrombus was detected on repeat study, cardioversion was performed, and the patient received 4 more weeks of oral anticoagulation.

The primary endpoint of the study was the composite of stroke, transient ischemic attack, or peripheral embolism. Secondary end points included all-cause mortality, major and minor bleeding, functional status, and success in maintaining sinus rhythm. All patients were followed-up at 8 weeks for clinical outcomes. All analyses were performed on an intention-to-treat basis.

*The results:* The estimated median duration of AF in the study was 13 days. Among the patients assigned to the TEE arm (n=619), cardioversion was eventually performed in 427 patients at a median of 1 day; it was successful in 344. Of the 603 patients assigned to conventional therapy, a total of 367 patients underwent cardioversion at a median of 30 days, which was successful in 293. The primary end point of stroke, transient ischemic attack, or peripheral embolism was not significantly different between the 2 arms (TEE arm, 0.81%; conventional therapy, 0.5%; *P*=0.501). The composite of major and minor bleeding was significantly higher in patients receiving conventional therapy (5.5% versus 2.9%; *P*=0.025). A nonsignificant trend existed toward higher all-cause mortality in the TEE arm (2.42% versus 1%; *P*=0.055), although cardiac mortality was not significantly different between the 2 groups (TEE arm, 1.29%; conventional therapy, 0.66%; *P*=0.265). At 8 weeks, no difference existed in functional status and the maintenance of sinus rhythm.

*Summary:* Compared with conventional therapy, a TEE-guided strategy does not seem to reduce the risk of embolic events but it does reduce bleeding complications. It allows for early cardioversion and results in no significant improvement in immediate or 8-week sinus rhythm or functional capacity outcome.

Hypertension

**The Trial: ALLHAT Interim Results**

*Presenter:* Barry Davis, University of Texas at Houston, School of Public Health, Houston, Tex, and Curt Furberg, Wake Forest University, Winston-Salem, NC.

*The study:* An ongoing, practice-based, randomized, multicenter trial of >42 000 hypertensive patients with risk factors for coronary artery disease (CAD) designed to assess whether newer agents (a calcium antagonist [amlodipine], an ACE inhibitor [lisinopril], and an α-blocker [doxazosin]) reduce the incidence of CAD compared with a diuretic (chlorothalidone) and whether pravastatin therapy for hypertensive patients with moderate hypercholesterolemia is capable of reducing all-cause mortality. Patients were randomized to receive 1 of the above 4 antihypertensive agents. Those eligible for lipid lowering were further randomized to pravastatin or placebo. The primary end point of this study was the development of MI or CAD death. Secondary outcomes include all-cause mortality, stroke, combined CAD (nonfatal MI, CAD, death, revascularization, and hospitalization for angina), and combined cardiovascular disease (combined CAD, CHF, stroke, and peripheral vascular disease). Follow-up was planned for a period of 4 to 8 years. On January 24, 2000, an independent review committee recommended terminating the doxazosin arm because of futility (a low likelihood of finding a significant difference in the primary outcome with doxazosin) and a 25% higher rate of combined cardiovascular disease (a major secondary end point) in the doxazosin group.
**The results:** Baseline characteristics were comparable for the doxazosin arm (n=9067) and the chlorthalidone arm (n=15268). The magnitude of diastolic pressure reduction was similar, whereas systolic blood pressure was 2 to 3 mm Hg higher in the doxazosin arm. At 4 years, no significant difference existed in the relative risk (RR) of CAD between patients receiving doxazosin and those receiving chlorthalidone (RR, 1.03; 95% confidence interval [CI], 0.9 to 1.17). The RR of combined cardiovascular disease in the doxazosin arm compared with the chlorthalidone arm was 1.25 (95% CI, 1.17 to 1.33; P<0.0001), with the event curves diverging during the first year. This was related to a significantly increased risk of CHF in the doxazosin arm (RR, 2.04; 95% CI, 1.79 to 2.32). This increased RR of CHF was seen across sex, age, and ethnic subgroups. The risk for stroke was also increased in the doxazosin group (RR, 1.19; 95% CI, 1.01 to 1.4; P=0.04). When cardiovascular disease events were analyzed without the influence of CHF, a significant excess of events with doxazosin persisted (RR, 1.13; 95% CI, 1.06 to 1.21).

**Summary:** The α-blocker doxazosin was associated with an increased risk of developing cardiovascular disease, and it is a poor selection for primary therapy for blood pressure management in patients with risk factors for CAD.

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**Atherosclerosis**

**The Trial: ERA**

**Presenter:** David Herrington, Winston-Salem, NC.

**The study:** A randomized, double-blind, placebo controlled trial to determine the effect of unopposed estrogen or combined estrogen-progestin therapy on the progression of coronary artery disease in postmenopausal women with preexisting, documented coronary disease. A total of 309 women with ≥1 coronary stenosis >30% were randomized to receive conjugated estrogen (0.625 mg/d; n=100), combined estrogen (0.625 mg/d) and medroxyprogesterone acetate (2.5 mg/d) (n=104), or placebo (n=105). Mean follow-up was 3.2 years. The primary outcome of the study was within-subject mean minimal lumen diameter (MLD) change by quantitative coronary angiography, which was derived by averaging the MLD of 10 coronary segments for each patient at baseline and follow-up. Angiography was performed in a blinded fashion using standard techniques. Follow-up studies were performed in 80% of patients.

**The results:** The mean age of the study population was 65 years. The mean LDL level was 135 mg/dL. Patients receiving estrogen or combination therapy showed a significant decline in LDL and an increase in HDL compared with placebo. The mean MLD and change in mean MLD were not significantly different among the 3 treatment arms. No difference existed among the 3 arms in terms of stroke, transient ischemic attacks, fatal or nonfatal MI, angioplasty, or CABG. A excess of deep venous thrombosis/pulmonary embolism existed in patients receiving unopposed estrogen.

**Summary:** Estrogen replacement therapy, either unopposed or in combination with progesterone, did not affect the progression of atherosclerosis in women with established coronary disease. The effects of hormone therapy in younger women remain to be seen.

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**Valvular Heart Disease**

**The Trial: Outcomes After Valve Replacement With a Mechanical Versus Bioprosthetic Valve:**

**Final Report of the VA Randomized Trial**

**Presenter:** S.H. Rahimtoola, University of Southern California, Los Angeles, Calif, for the VA Investigators

**The study:** A randomized trial initiated in 1977 comparing the outcomes in 575 patients treated with either a mechanical (Bjork-Shiley spherical disc) or bioprosthetic (Hancock porcine heterograft) valve; 394 of these valves were placed in the aortic position and 181 in the mitral position. Complete follow-up was available in 97% of the study cohort. Among the 16 patients lost to follow-up, 10 had follow-up data until the last 1 to 2 years. The 5- and 10-year follow-up results were previously published.

**The results:** In the mitral valve replacement group, there were no differences in survival at 15 years between patients receiving a bioprosthetic or mechanical valve (mortality rates were ≈80% in both arms, reflecting the high-risk nature of the patient population). In the aortic valve replacement group, mortality was significantly lower in patients receiving a mechanical valve (66% versus 79% in the bioprosthetic group; P=0.02). This difference was not detected at prior 10-year follow-up. In the mitral valve replacement group, the replaced valve was deemed to be the cause of death in 57% of the patients who received a bioprosthetic valve and in 44% of the mechanical valve recipients. In the aortic valve replacement group, ≈40% of deaths were thought to be valve-related in both arms. Primary valve failure rates were negligible with mechanical valves and significantly higher with bioprosthetic valves. Primary valve failure in the mitral position began to appear at around year 5 in those with bioprosthetic valves and progressed to 44% by year 15, whereas in the aortic position, bioprosthetic valve failure appeared at around year 9 and was 23% by year 15. In patients with an aortic bioprosthesis, there was a 26% failure rate in patients <65 years of age (P<0.001 versus mechanical valves) and one of 9% in those >65 years (P=NS versus mechanical valves). No structural deterioration was noted in the mechanical valve group; the reoperation rate was higher with bioprosthetic valves. No significant differences existed between mechanical and bioprosthetic valves in terms of systemic embolism, valve thrombosis, endocarditis, or any valve-related complication.

**Summary:** In the mitral position, no differences in total mortality existed between the mechanical and bioprosthetic valves. Use of a mechanical valve in the aortic position was associated with lower mortality and no primary valve failure. Primary valve failure is fairly frequent with bioprosthetic valves in either position by year 15, but more so with mitral compared with aortic valves. Younger patients (<65 years) receiving bioprosthetic valves, particularly in the mitral position, have a much higher primary valve failure rate. The rate of primary valve failure for bioprosthetic valves in the aortic position in patients ≥65 years was not significantly different from that of mechanical valves.
### APPENDIX. Trial Name Acronyms

<table>
<thead>
<tr>
<th>Trial Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>SYMPHONY</td>
<td>Sibrafiban vs aspirin to yield maximum protection from ischemic heart disease</td>
</tr>
<tr>
<td>SYMPHONY II</td>
<td>Sibrafiban with and without aspirin after acute coronary syndromes</td>
</tr>
<tr>
<td>OPUS</td>
<td>Orbofiban in patients with unstable coronary syndromes</td>
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<tr>
<td>EXCITE</td>
<td>Evaluation of oral xemilofiban in controlling thrombotic events</td>
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<tr>
<td>HART II</td>
<td>Heparin and reperfusion therapies</td>
</tr>
<tr>
<td>PENTALYSE</td>
<td>SR9010A/ORG31540, a new synthetic pentasaccharide, as an adjunct to fibrinolysis in ST-elevation acute myocardial infarction</td>
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<tr>
<td>PARAGON B</td>
<td>Platelet IIb/IIIa antagonist for the reduction of acute coronary syndrome events in a global organization network</td>
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<tr>
<td>ALKK</td>
<td>Arbeitsgemeinschaft leitender kardiologischer krankenhaeuserze</td>
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<tr>
<td>PRAISE-2</td>
<td>Prospective randomized amlodipine survival evaluation</td>
</tr>
<tr>
<td>OPTIME-CHF</td>
<td>Outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure</td>
</tr>
<tr>
<td>ESPRIT</td>
<td>Enhanced suppression of the platelet IIb/IIIa receptor with Integrilin therapy</td>
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<tr>
<td>GOLD</td>
<td>Prospective multicenter study to determine the optimal level of platelet inhibition with GPIIb/IIIa inhibitors in patients undergoing coronary intervention</td>
</tr>
<tr>
<td>LONG-WRIST</td>
<td>Washington radiation for in-stent restenosis trial for long lesions</td>
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<tr>
<td>BESMART</td>
<td>Bestent in small arteries</td>
</tr>
<tr>
<td>ISAR-SMART</td>
<td>Intracoronary stenting or angioplasty for restenosis reduction in small arteries</td>
</tr>
<tr>
<td>ISAR</td>
<td>Intracoronary stenting and antibiotic regimen trial</td>
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<tr>
<td>BARI</td>
<td>Bypass angioplasty revascularization investigation</td>
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<tr>
<td>BLOSS</td>
<td>The β-blocker length of stay study</td>
</tr>
<tr>
<td>ACUTE 1</td>
<td>Assessment of cardioversion using transesophageal echocardiography</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Antihypertensive and lipid-lowering treatment to prevent heart attack trial</td>
</tr>
<tr>
<td>ERA</td>
<td>Estrogen replacement and atherosclerosis</td>
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Meeting Highlights: Highlights of the 49th Scientific Sessions of the American College of Cardiology
Rollo P. Villareal, Paul Kim, Hatim Mahmood, Andrew Civitello and James J. Ferguson III

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