Results From Late-Breaking Clinical Trials Sessions at ACCIS 2000 and ACC 2000

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LATE-BREAKING CLINICAL TRIALS IN INTERVENTIONAL CARDIOLOGY

One-Year Follow-Up of Patients With Refractory Angina Randomized to Percutaneous Transmyocardial Revascularization Versus Medical Therapy
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Percutaneous transmyocardial revascularization (PTMR) has previously been reported to be safe and to improve angina and exercise tolerance. However, controlled comparisons with longer follow-up times are needed if PTMR is to be a viable treatment. Of 325 patients with New York Heart Association (NYHA) class III–IV angina who were poor candidates for percutaneous or surgical revascularization, 163 were randomized to undergo PTMR with a fiberoptic holmium-laser system, and 162 were randomized to receive solely medical management. Enrolled patients were required to have a left ventricular ejection fraction of at least 30% and a myocardial wall thickness of at least 9 mm by echocardiography in the PTMR target region.

Seven percent of the medically managed patients crossed over to the PTMR group. The six- and 12-month analyses were performed on an intention-to-treat basis. An average of 19 myocardial channels per patient in the PTMR group were created with the laser; their mean hospital length of stay was 1.8 days. Major adverse events associated with PTMR developed in 4.3% of cases and included one death, one Q-wave myocardial infarction (MI), one cerebrovascular event, and six instances of tamponade.

At 12 months, 37% of the PTMR group and 18% of the medically managed patients had improved by two or more NYHA classes (p < 0.001). Fifty-five percent of PTMR-treated patients and 31% of patients in the medical group were in NYHA class II or better at 12 months (p < 0.001). The primary end point of the study was treadmill exercise tolerance. In the PTMR group, mean time increased from 433 s at baseline to 534 s at 12 months, an improvement of 101 s versus a decrease of 16 s in the medically managed group. At both the six- and 12-month follow-ups, patients who had undergone PTMR were able to exercise significantly longer compared with baseline than were medically managed patients (p < 0.001 at six months and p < 0.001 at 12 months). The two groups had statistically similar 12-month rates of death, Q-wave and non–Q-wave MI, and rehospitalization.

Commentary. As the population ages, an increasing proportion of patients with coronary artery disease (CAD) will be found to have few or no options for improving coronary blood flow through epicardial conduit vessels. The current study demonstrates that PTMR can be applied safely in a severely ill population of patients. The findings of the current study are noteworthy because of their internal consistency and because of the robust treatment effect observed in the setting of a randomized trial. For the sake of comparison, it is worth noting that, in the Angioplasty Compared to Medicine (ACME) study of patients undergoing single-vessel angioplasty, there was an increase in exercise time of only 2.1 min for patients (with mild CAD) undergoing percutaneous transluminal coronary angioplasty, compared with those receiving medical therapy only.

By contrast, the current study does not close the book on PTMR. It must be remembered that, although the current study is randomized, it is not blinded—a limitation that becomes particularly important when evaluating subjective end points such as exercise time and anginal class. However, the consistency of the findings within this study strongly suggests that further investigation of PTMR is indicated and that modifications of the technique, perhaps in combination with endocardial mapping or with angiogenic growth factors, or using alternative forms of energy. In addition, the statistical issues with missing values are complex, and not enough cardiac events occurred in either the intervention or control populations to ensure the safety of the procedure for broad populations over the long term.

Phase II, Multicenter, Double-Blind, Placebo-Controlled, Dose-Finding Study for Safety, Pharmacokinetics, and Efficacy of Recombinant Fibroblast Growth Factor (rFGF-2) in Subjects With Coronary Artery Disease (CAD): FGF-2 Initiating Revascularization Support Trial (FIRST)
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A phase I clinical trial preliminarily suggested that an intracoronary (IC) 36 μg/kg infusion of rFGF-2, a heparin-binding growth factor that may induce angiogenesis, im-
proved indirect measures of myocardial ischemia in patients with CAD. In a phase II safety, pharmacokinetic, and efficacy study, 337 patients with CAD who were poor candidates for surgical or percutaneous revascularization were randomized to receive IC rFGF-2 at one of three dosages, or placebo. The patients were required to have a left ventricular ejection fraction >30% and reversible myocardial perfusion defects at exercise thallium/sestamibi scintigraphy.

Patients received two 10-min infusions of 10 mL of active therapy or placebo in two vessels supplying the largest viable myocardial vascular beds observed at perfusion imaging. Active therapy was administered to 82 patients at 0.3 μg/kg, to 84 patients at 3.0 μg/kg, and to 85 patients at 30.0 μg/kg; 86 patients received placebo. The mean change in treadmill exercise time from baseline to 90 days, the primary efficacy end point, was 65 s for patients receiving rFGF-2 and 45 s for patients receiving placebo (p = 0.64). However, among patients older than the median age of 63 years, the mean changes in exercise time were 80 s and 41 s, respectively (p = 0.025). No significant differences between actively treated patients and controls were observed at 90 days in other exercise-test variables or in mean stress, rest perfusion, or reversibility scores at exercise perfusion imaging. Patients who received rFGF-2 had significantly reduced angina frequency at 90 days (a prospectively defined secondary end point) as determined by the Seattle Angina Questionnaire (p = 0.057). Infusions of rFGF-2 appeared to be safe. Post-hoc analysis suggested that patients who were older, were more symptomatic, and had greater levels of myocardial ischemia at baseline tended to gain more benefit from rFGF-2 than did other actively treated patients.

Commentary. It is notable that two of the large trials presented in this session examined novel therapies for treatment of patients with end-stage CAD and refractory symptoms. A good deal of attention has been focused on angiogenic growth factors. Although much is known about experimental models of angiogenesis, little is known about its clinical application. Do atherosclerotic human vessels behave similarly to those of nonatherosclerotic pigs? Is it more reasonable to divide a dose of a growth factor among different areas of the coronary circulation or to target a single coronary artery? Is it more rational to administer a growth factor into a vessel that should supply collaterals or into one that should receive them? What is the clinical importance of collateral vessels in a patient whose epicardial vessels are too diseased to deliver blood to the new circulation? Perhaps an apt comparison is that of Martian exploration—man has been able to send crude spacecraft to the red planet but is not even close to sending living human beings.

At 90 days, the improvement in exercise capacity was similar to that seen in actively treated patients in the percutaneous transmyocardial revascularization (PTMR) trial, while placebo-treated patients in this trial had a 45-s increase in exercise tolerance compared with a 16-s decrease in the PTMR trial. Why the difference? Perhaps the timing of the assessment played an important role, or perhaps it was the ability to blind a pharmacologic but not a device study. Nonetheless, the current study, like the prior VEGF in Ischemia for Vascular Angiogenesis (VIVA) trial of vascular endothelial growth factor, does appear to contain some signal along with the noise—improvement in anginal class as measured using a validated instrument, and a greater effect in patients with more evidence of ischemia. Clearly, there is much to be learned about growing new blood vessels; FIRST appears to be an early step in that direction.

Late Clinical and Angiographic Outcomes After Use of 90Sr/90Y Beta Radiation for the Treatment of In-Stent Restenosis: Results From the 90Sr Treatment of Angiographic Restenosis (START) Trial

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Vascular brachytherapy using gamma radiation has significantly reduced angiographic and clinical recurrence rates after balloon angioplasty for in-stent restenosis in three randomized, controlled trials. Brachytherapy using the beta emitter 90Sr may provide the additional advantages of shorter treatment times and reduced operator radiation exposure. In the START trial, 476 patients with in-stent coronary restenotic lesions <20 mm in length were randomized to treatment with the Beta-Cath vascular brachytherapy system or to a placebo brachytherapy procedure. The prescribed radiation dose was calculated at 2 mm from the center of the source, which consisted of an array of 90Sr pellets. The radiation dosages were 16 Gy for target lesions with reference-segment diameters 2.7 mm to 3.3 mm and 20 Gy for lesions with reference-segment diameters 3.0 mm to 4.0 mm. Antiplatelet therapy initially consisted of ticlopidine for 14 days, which was later changed to ticlopidine or clopidogrel for 60 days.

The active-therapy and placebo groups were similar with respect to mean reference-segment diameter and target-lesion length. Only 21% of the patients received a new stent for treatment of in-stent restenosis. Clinical and angiographic follow-ups were available for 92% and 82% of the patients, respectively. Angiographic restenosis was defined as a >50% diameter stenosis at follow-up. Angiographic eight-month restenosis rates were assessed in several ways: 1) within the stented coronary segment (mean length: 22 cm), the restenosis rates were 42% for the control group and 14% for the irradiated group (p < 0.001); 2) within injured vessel segment (mean length: 25 mm), the restenosis rates were 45% and 18.2%, respectively (p < 0.001); 3) within the irradiated vessel segment (mean length: 30 mm), the restenosis rates were 45.9% and 24.4%, respectively (p < 0.001); and 4) within a prespecified analysis segment that encompassed 5 mm distal and 5 mm proximal to the...
irradiated segment (mean length: 40 mm), the restenosis rates were 45.2% and 28.8%, respectively (p = 0.001).

The rate of target-vessel revascularization at eight months, the trial’s primary end point, was 24.1% in the control group and 16% in the irradiated group, representing a 34% reduction with active therapy (p = 0.008). The rates of major adverse cardiac events, which included target-vessel failure, death, or nonfatal myocardial infarction, were 25.9% and 18%, respectively (p = 0.039). After one early case of in-stent thrombosis in the control group, no further instances were observed in either group over a follow-up extending to day 271.

**Commentary.** In-stent restenosis remains a significant problem in patients who have undergone percutaneous coronary intervention; conventional and mechanical debulking treatments have thus far been unrewarding. Although intracoronary radiation seems quite promising, a debate is raging over the benefits of gamma versus beta radiation sources. The START trial, the largest trial to date of a beta-emitting source, illustrates the benefits and pitfalls of intracoronary brachytherapy. Beta irradiation led to a meaningful reduction in both angiographic and clinical restenosis, but the effect was most pronounced directly within the full-dose irradiated area. Narrowing at the edges of the radiation zone lessened this benefit; yet restenosis rates incorporating the edges were still lower than in the control group. Thus, the START trial serves as both a proof of principle and an illustration of the challenges that remain. Another important contribution of the START trial was the observation that subacute thrombosis rates, previously reported to be approximately 10%, became quite low after thienopyridine therapy was extended from two weeks to two months. This important observation, coupled with the admonition to avoid placing a new stent at the time of brachytherapy, suggests that previously observed rates of late vessel closure following brachytherapy (approximately 10%) may be improved by prolonged therapy with thienopyridines.

**First Clinical Investigation of a Tissue-Factor Inhibitor Administered During Percutaneous Coronary Revascularization: A Randomized, Double-Blinded, Dose-Escalation Trial—Assessing Safety and Efficacy of FFR-VIIa in Percutaneous Transluminal Coronary Angioplasty (ASIS) Trial**

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The use of modified recombinant human activated factor VII (FFR-VIIa, “active-site-inhibited 7” or ASIS), which competitively inhibits the prothrombotic action of native factor VIIa, was tested in a phase II study as an antithrombin agent for potential use with percutaneous interventions. A total of 491 patients undergoing elective or urgent coronary stenting or balloon angioplasty, not for acute myocardial infarction (MI) or unstable angina, were randomized to receive either: 1) adjuvant heparin only or 2) adjuvant FFR-VIIa at one of six escalating dosage levels with supplemental heparin at gradually diminishing dosages. Seven groups were to receive FFR-VIIa plus heparin in varying proportions, with an additional group receiving heparin (100 U/kg) plus a placebo. The dosage escalation arms included FFR-VIIa at 50 μ/kg to 400 μ/kg and heparin (with the lowest FFR-VIIa dosage) at 4,000 U/kg or (in the other arms) 40 U/kg to 70 U/kg. Dosages of FFR-VIIa could be reduced, and heparin dosages increased, at the discretion of the steering committee.

An excess of thrombotic complications with FFR-VIIa at the 50 μ/kg and 100 μ/kg levels, despite co-administration of heparin, led to accelerated escalation of the FFR-VIIa dosage. For the primary end point—a composite of death, MI, urgent revascularization, abrupt vessel closure, or bailout using a glycoprotein IIb/IIIa receptor blocker or heparin by day 7 or by discharge—the rates were 20% in the control group and 5.5% to 38.9% in the combined heparin-FFR-VIIa groups (NS). No differences were observed in the rates of major or minor bleeding complications; however, the risk of “insignificant bleeding” (primarily access-site hematomas) was significantly increased in all FFR-VIIa groups compared with control. Combined analysis of the 210 patients who received FFR-VIIa at the highest dosage of 400 μ/kg showed a nonsignificant trend toward a reduction in the primary end point compared with the control group, 21.6% versus 11.9% (p = 0.073).

**Commentary.** Heparin is the drug we love to hate. Unfortunately, our therapeutic armamentarium contains few agents to interfere with thrombin-mediated clot formation. A broad variety of new anticoagulants have been developed to replace heparin. However, with the exception of the low–molecular-weight derivatives of heparin, success thus far has been limited to modest success for direct thrombin antagonists in acute coronary syndromes and during the first few days after percutaneous coronary interventions. The ASIS trial represents one of the first attempts to move “upstream” in the coagulation cascade (i.e., to block the generation of thrombin rather than its activity). Factor VIIa complexes with tissue factor, leading penultimately to the formation of factor Xa and ultimately to the generation of thrombin. As demonstrated by ASIS, the therapeutic road upstream is also likely to travel uphill. Although this dose-finding study was not designed to test the efficacy of FFR-VIIa regimens, the preliminary findings contain some disturbing as well as some encouraging information. Adjuvant heparin in combination with FFR-VIIa was required to prevent vascular thrombosis, so the regimens could not be described as “heparin-sparing.” At low doses of FFR-VIIa, vascular thrombosis was observed, suggesting either that there was incomplete blockade of the heparin generation pathway or that the picomolar quantities of thrombin that are generated independent of the TF-VIIa pathway may be sufficient to cause periprocedural ischemia.
in the absence of sufficient blockade of thrombin activity. By contrast, whatever quantity of thrombin “escaped” the blockade of TF-VIIa was not sufficient to prevent access-site bleeding. Although these findings should not by any means quench the movement to study antagonists of thrombin generation, they should indicate that such investigations need to be undertaken cautiously and that careful measurements of thrombin generation and activity are likely to be needed as adjuncts while such therapies are being refined.

Intracoronary Stenting or Angioplasty for Restenosis Reduction in Small Arteries (ISAR-SMART) Trial

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Randomized clinical trials that have shown improved outcomes with coronary stenting compared with balloon angioplasty included target vessels with reference-segment diameters no smaller than 3 mm. It is unknown whether rates of restenosis and other outcomes with stents are superior to those of balloons in arteries with smaller reference diameters. In general, small-vessel percutaneous interventions have been associated with increased risk of complications.

In the ISAR-SMART trial, 404 patients with symptomatic coronary disease, excluding acute myocardial infarction (MI), and target coronary lesions amenable to intervention with reference-segment diameters of 2 mm to 2.8 mm were randomized to treatment with either stenting or with balloon angioplasty alone. The 204 stent recipients and 200 patients treated by balloon-only received adjuvant ticlopidine (for four weeks with stents and for two weeks with balloon-only). The mean target-vessel reference-segment diameter was 2.4 mm in both groups. Stenting was performed for intimal dissection in 16.5% of patients in the balloon-only group. The mean maximal dilation pressure was significantly higher in the stent group (13.5 atm versus 12.0 atm for balloon-only patients) ($p < 0.001$). The mean residual stenosis severity was 7% in the stented group and 18.8% in the balloon-only group ($p < 0.001$).

Thirty-day rates of death and nonfatal MI were low in both groups and not significantly different. The rates of survival free of MI at seven months were 96.6% and 97%, respectively. Quantitative angiography at six months, available for 82% of the patients, indicated restenosis rates of 35.7% and 37.5% for stented and balloon-only patients, respectively, when restenosis was defined as a target-site recurrent lesion of at least 50% severity. The restenosis rates were 22.2% and 18.8%, respectively, when restenosis was defined as a recurrence of at least 70% severity. The six-month rates of target-lesion revascularization were 20.1% and 16.5%, respectively. None of the differences in six-month angiographic or clinical measures of restenosis was significant, suggesting that stenting does not reduce restenosis rates compared with standard balloon angioplasty with provisional stenting in small coronary vessels.

Commentary. Despite advances in technical and pharmacologic aspects of percutaneous coronary intervention, small coronary arteries continue to pose a challenge for the interventionalist. Approximately one third of coronary interventions are now performed in vessels <3.0 mm in diameter; as the population ages and the incidence of diabetes increases, this proportion is likely to increase. Because smaller vessels leave little margin for error, the rates of both procedural complications and restenosis are higher in small vessels. The issue of whether or not to place intracoronary stents in small vessels continues to vex interventional operators. Two randomized studies presented at the Annual Scientific Session, BESMART and ISAR-SMART, have arrived at opposite conclusions on the same issue. Although the trials are similar in many aspects, several important differences do exist and may have some bearing on explaining the trials’ divergent findings. Among these differences are the differential rates of angiographic follow-up (81% for ISAR-SMART and 91% for BE SMART), the differing definition of “restenosis” (70% for ISAR-SMART and 50% for BESMART), and the routine use of the glycoprotein IIb/IIIa antagonist abciximab in ISAR-SMART. It is interesting that the proportion of stented patients with recurrent stenoses is very similar between the two trials; however, it appears that a substantial number of patients treated with conventional balloon angioplasty had recurrent stenoses between 50% and 70% of the vessel diameter. However, there is no ready explanation for the differential rates in target-lesion revascularization—more than one-third lower in stented patients treated in BESMART and half again higher in BESMART patients treated with balloon angioplasty alone. Part of the explanation may reside in stent selection; stents composed of narrower filaments may be particularly advantageous in vessels with small lumina. Although the question of whether or not to stent small vessels still remains unanswered, it is nevertheless clear that the rheology of small vessels needs to be thought about differently from that of large vessels.

**LATE-BREAKING CLINICAL TRIALS I**

The Beta-Blocker Length of Stay Study (BLOSS) Trial: A Randomized, Placebo-Controlled Trial of Beta-Blocker Treatment for Reduction of Hospitalization After Cardiac Surgery

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Although the atrial fibrillation (AF) that occurs in about one third of patients undergoing cardiac surgery is generally well tolerated and easily controlled, it is also associated with prolonged hospitalization. However, it is unknown whether...
prevention of the arrhythmia, often accomplished with beta blockers, will lead to earlier discharge. One thousand patients were randomized in a double-blind fashion to receive either metoprolol or placebo beginning 12 h after cardiac surgery and continuing for 14 days or until discharge; patients were enrolled preoperatively and randomized postoperatively. Oral metoprolol was initially given at 50 mg bid, but later in the trial the dosage was increased to 50 mg tid for patients without depressed left ventricular function. An episode of postoperative AF lasting at least 1 min developed in 31% of the 500 patients randomized to metoprolol and in 39% of the 500 control patients, a significant difference (p = 0.0098). The mean intensive care unit length of stay was 39 h for metoprolol recipients and 31 h for patients given placebo, a nonsignificant difference. The mean total hospitalization time, the study’s primary end point, was also nonsignificantly higher in the actively treated group: 155 h versus 152 h for controls. Post-hoc analysis indicated the length of hospital stay was increased 9% among patients who received the beta blocker at the lower dosage compared with the control group; it was decreased by 2% among those who received metoprolol at the higher dosage. Significant predictors of postoperative AF included advanced age, a history of preoperative AF, and valve surgery as opposed to coronary artery bypass surgery. There were no deaths and no differences in rates of other postoperative complications. The authors concluded that beta-blocker prophylaxis reduces the likelihood of AF after cardiac surgery but that this benefit does not translate into reduced hospital length of stay.

**Commentary.** This study emphasizes the consequences of a preventive strategy in terms of clinical outcomes. We often assume that prevention of a complication will save resources. In this case, it did not. Fortunately, in this situation, there are many other reasons to give beta blockers before cardiac surgery, but saving money by preventing AF is not one of them.

*The Estrogen Replacement and Atherosclerosis (ERA) Trial*

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Whether estrogen replacement therapy (ERT) can reduce the risk of coronary artery disease (CAD) in postmenopausal women remains highly controversial. A long history of epidemiologic and observational studies suggesting a positive effect was not supported by the only large, randomized trial to study the effect of ERT on clinical cardiovascular outcomes in this population. The effect of ERT on angiographic end points was examined in a trial in which 309 postmenopausal women with at least one documented coronary stenosis >30% in severity were randomized double-blind to receive either opposed or unopposed ERT or placebo and were followed for a mean of 3.2 years. Treatment consisted of 0.625 mg/day conjugated equine estrogen with (n = 104) or without (n = 100) 2.5 mg/day medroxyprogesterone acetate, or placebo (n = 105). The average rate of treatment compliance was significantly lower (74.5%) in the unopposed-ERT group than in the opposed-ERT or control groups (84% and 85.8%, respectively) (p = 0.03). At follow-up, levels of low-density-lipoprotein cholesterol were significantly reduced, and levels of high-density-lipoprotein cholesterol were significantly increased in the two active-therapy arms compared with the placebo arm. Angiographic follow-up was available in 248 patients, or 80%, of those randomized. The primary outcome measure, change in mean minimum luminal diameter (MLD) of the 10 standardized coronary segments from baseline to follow-up quantitative angiography, showed no significant differences among the three groups. Stratification of patients according to baseline CAD severity also failed to disclose any significant differences in MLD change among the three treatment arms; nor were there any differences in rates of clinical events, although the trial was not designed to compare clinical outcomes.

**Commentary.** The more we learn about hormone replacement therapy (HRT), the more we realize how little we know. This study provides negative evidence about the impact of estrogen on vascular wall thickening and, in concert with the results of the Heart and Estrogen-Progestin Replacement Study (HERS) trial and the Women’s Health Initiative, casts a pall on the use of hormones to prevent coronary heart disease events. The HERS trial showed an excess of venous and arterial thrombotic events in the first year after treatment with estrogen and progestin in postmenopausal women without a uterus. After the first year, the trends favored HRT, leaving a neutral trial result in the end. The Women’s Health Initiative, which is testing HRT in primary prevention, recently announced a similar excess of thrombotic events, but the announcement stated that the excess was not enough to stop the ongoing trial. The clinical outcome results will be intriguing, as long-term follow-up is accumulated in the Women’s Health Initiative. These uncertain clinical trial results are surprising, considering that literally dozens of observational studies have observed an association between HRT use and better cardiovascular outcomes. Perhaps there is an important lesson here about the necessity for large outcome trials for common problems.

*In-Hospital Results and Six-Month Clinical and Angiographic Follow-Up of Coronary Stenting in Small Coronary Arteries: Final Results of the BEstent in SMall ARteries (BESMART) Study*

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Current recommendations do not support the use of coronary stents for lesions in small arteries, those with reference-segment diameters <3 mm, because of the increased risk of complications seen in observational studies. Several ran-
domized trials demonstrated a superiority of stenting over balloon angioplasty alone in larger vessel targets, but it remains unknown whether the advantage also applies to small vessels. In the multicenter BESMART trial, 381 patients with documented myocardial ischemia and a de novo lesion ≤15 mm in length in a native coronary artery with a reference-vascular diameter <3 mm (mean: 2.2 mm) were randomized to revascularization using either a stent or balloon angioplasty alone. All patients received aspirin and ticlopidine for one month, and aspirin thereafter. The two treatment groups were similar with respect to baseline demographic, angiographic, and clinical history, with the exceptions that significantly more of the 192 stented patients were diabetic, 22% versus 12% of the 189 patients treated with a balloon only (p = 0.008), and more were hypertensive, 51% versus 40% (p = 0.034). In both treatment groups, the mean maximal inflation pressures were similar, and 2.5-mm balloons were used almost exclusively. The rate of treatment crossover from balloon to stenting because of poor balloon angiographic outcome was 24%. Angiographic outcomes were significantly better in the stented patients. The rates of restenosis (recurrence of at least 50% severity) by quantitative angiography at six months on an intention-to-treat basis, the primary end point (available for 91% of patients), were 22.7% for stented patients. The rates of restenosis (recurrence of at least 50% severity) by quantitative angiography at six months disclosed rates of restenosis, defined as recurrent target-vascular revascularization at six months were 13% and 25%, respectively (p = 0.016). No other differences in clinical end points were observed either in-hospital or at six months.

Commentary. Despite advances in technical and pharmacologic advances in percutaneous coronary intervention, small coronary arteries continue to pose a challenge for the interventionalist. Approximately one third of coronary interventionalists are now performed in vessels <3.0 mm in diameter; as the population ages and the incidence of diabetes increases, this proportion is likely to increase. Because smaller vessels leave little margin for error, the rates of both procedural complications and restenosis are higher in small vessels. The issue of whether or not to place intracoronary stents in small vessels continues to vex interventional operators. Two randomized studies presented at the Annual Scientific Session, this one and the ISAR-SMART trial, have arrived at opposite conclusions on the same issue. Although the trials are similar in many aspects, several important differences do exist and may have some bearing on explaining the trials’ divergent findings. Among these differences are the differential rates of angiographic follow-up (81% for ISAR-SMART and 91% for BESMART), the differing definition of “restenosis” (70% for ISAR-SMART and 50% for BESMART), and the routine use of the glycoprotein IIb/IIIa antagonist abciximab in ISAR-SMART. It is interesting that the proportion of stented patients with recurrent stenoses is very similar between the two trials; however, it appears that a substantial number of patients treated with conventional balloon angioplasty had recurrent stenoses between 50% and 70% of the vessel diameter. However, there is no ready explanation for the differential rates in target-lesion revascularization—more than one-third lower in stented patients treated in BESMART and half again higher in BESMART patients treated with balloon angioplasty alone. Part of the explanation may reside in stent selection; stents composed of narrower filaments may be particularly advantageous in vessels with small lumina. Although the question of whether or not to stent small vessels still remains unanswered, it is nevertheless clear that the rheology of small vessels needs to be thought about differently from that of large vessels.

Intracoronary Gamma Radiation for Diffuse In-Stent Restenosis: A Two-Center Randomized Clinical Study—The Washington Radiation for In-Stent Restenosis Trial for Long Lesions (LONG WRIST)
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Three randomized trials have shown that vascular brachytherapy using gamma radiation for the percutaneous treatment of in-stent restenosis can reduce the risk of recurrence, but those trials did not include long, diffuse target lesions, which remain a special challenge to percutaneous interventions. The investigators of this study evenly randomized 120 symptomatic patients with diffuse in-stent restenotic lesions 36 mm to 80 mm (mean stent length: 70 mm) with coronary reference-segment diameters of 3 mm to 5 mm, to receive either a ribbon bearing 192Ir seeds or placebo seeds delivered to the target site via a noncentered, closed-lumen catheter. The radiation dosage consisted of 14 Gy to 15 Gy to a 2-mm distance from the center of the source. The mean dwell time was 19 min. Debulking of the target lesion had been carried out using rotational atherectomy in approximately two thirds of the patients in each group. Patients were treated with either ticlopidine or clopidogrel for 30 days. Twenty-eight patients in the control group crossed over to receive active therapy. Quantitative angiography at six months disclosed rates of restenosis, defined as recurrent lesions >50% of the reference-segment luminal diameter, of 32% in the irradiated group and 71% in the control group within the stented segment only (p = 0.0002). Rates of restenosis considering only the segment containing the lesion were 46% and 78%, respectively (p = 0.03). The six-month rates of major adverse cardiac events (death, nonfatal Q-wave or non-Q-wave myocardial infarction, target-lesion revascularization [TLR]) were 38.3% and 61.7%, respectively (p = 0.01), with most of the significant difference accounted for by the TLR component, the rates for which were 30% and 60%, respectively (p = 0.001). The combined rate of total target-vessel occlusion or late thrombosis at any time during the follow-up was 15% of irradiated patients and 6.7% of controls. The investigators concluded that vascular brachytherapy using gamma radiation for
diffuse in-stent restenosis lesions significantly reduces the risk of recurrence at six months.

Commentary. Few findings are more disappointing to the interventionalist than the discovery, upon restudy of a patient who has received an intracoronary stent, that the lumen has become narrowed in a diffuse pattern. Although this disease is frequently referred to as in-stent "restenosis," in many cases the recurrent stenosis is worse than the original narrowing. The LONG WRIST study was performed by a group that had previously reported that a second in-stent restenosis occurred after repeat intervention in approximately 75% of patients who exhibited a diffuse pattern of renarrowing. Debunking techniques initially appeared to offer some promise of reducing this rate; however, current findings also suggest that they are less than successful. The LONG WRIST study appears to offer some hope that gamma irradiation may help improve this dismal situation, but this improvement must be noted with two caveats. First, even with gamma irradiation, nearly half the lesions treated had evidence of a second restenosis, and more than one third required a third intervention. Second, the rates of total occlusion and late thrombosis were surprisingly high, especially in the irradiated group. Thus, the findings of the LONG WRIST study should be viewed as an improvement, rather than a cure, for a particularly vexing disease process.

Pharmacokinetics (PKs) and Pharmacodynamics (PDs) of Sotalol in a Pediatric Population: Results of the First Controlled PK/PD Study of an Antiarrhythmic Agent in Children

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Heretofore, no PK or PD studies of d,l-sotalol, a class III antiarrhythmic agent with beta adrenergic–blocking properties, had been conducted in children. The investigators enrolled a total of 59 patients age ≤12 years with supraventricular or ventricular tachycardia to follow one of two protocols. In the first, a pure PK study, a single sotalol dose of 30 mg/m² (selected as being one third of an initial adult daily dose) was administered to 34 patients and followed by the taking of 10 blood samples over 36 h. In the second protocol, a mixed PK/PD study, ascending doses of 10 mg/m², 30 mg/m², and 70 mg/m² were given to 25 patients every 8 h (based on some prior anecdotal data and contrasting with the adult dosing interval of every 12 h) for three days. Blood sotalol level sampling and electrocardiography were performed at baseline and during the 8-h interval following each of the third, sixth, and ninth doses. Patients were stratified by age group: 1) neonates, birth to 30 days; 2) infants and toddlers, ages >30 days to 24 months; 3) young children, ages 2 to 6 years; and 4) older children, ages 7 to 12 years. Their weights ranged from 2 kg to 54 kg, their heights ranged from 46 cm to 146 cm, and their body surface areas (BSAs) ranged from 0.17 m² to 1.5 m². Absolute creatinine clearance ranged from 2 mL/min to 135 mL/min. Both the clearance of sotalol and the volume of sotalol distribution were linearly correlated with BSA (r² = 0.89 and 0.86). Creatinine clearance adjusted for BSA was markedly and consistently lower in the neonate group than in the older age groups, consistent with the reduced maturation of renal function in the first months of life. However, clearances of sotalol and creatinine were linearly correlated to a highly significant degree in all age groups (r² = 0.87). The degree of QTc prolongation, a measure of the agent’s class III properties, was significantly increased among patients with a BSA <0.33 m², compared with larger patients (p < 0.05). Changes in relative risk interval, an indicator of the drug’s beta-blocking effect, were also increased in the smallest patients, but significantly only at the lowest-dose level of 10 mg/m². The mean terminal sotalol half-life over all patients in the PK study, 9.5 h, was lower than the adult range of 10 h to 17 h, prompting the use of every-8-h dosing in the PK/PD study. It was concluded that sotalol should be administered every 8 h at a dosage based on BSA in children age ≤12 years who have normal renal function. Extra caution should be observed when determining an initial dosage for neonates and other children of very small body size, in whom maximum blood concentrations of the drug and clinical effects are enhanced.

Commentary. The term “therapeutic orphan” was coined to describe the pediatric population. More than 75% of prescriptions for children are written for non–Food and Drug Administration (FDA)-approved indications for medications, and very few PK or PD studies have been done in children. The market has been literally “too small” to attract the attention of the industry, and the result has been that pediatricians have had to use pharmaceuticals at their own, and their patients’, risk. This study underscores an urgent need for additional research of this kind. Many pediatricians have been using the wrong dose of sotalol, not because of professional lassitude but because the correct dose had not been determined. The FDA Modernization Act created a six-month patent extension several years ago for companies that do reasonable studies in children; the result has been an explosion of pediatric trials. This is one of the first important results to come from this far-reaching public policy initiative.

Roxithromycin for Prevention of Restenosis After Stenting
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Inflammatory processes associated with Chlamydia pneumoniae infection may modulate the prothrombotic properties of coronary plaques and promote neointimal prolifera-
tion after percutaneous intervention. The authors hypothesized that eradication of *C. pneumoniae* by antibiotic therapy might influence angiographic and clinical measures of restenosis after coronary stenting. Of 1,010 patients undergoing coronary stenting, 506 were randomized also to receive roxithromycin 300 mg once daily for 28 days, and 504 were randomized to a placebo. All patients received aspirin and ticlopidine. About one half of the patients were experiencing an acute coronary syndrome at randomization. Coronary stenting was performed at inflation pressures of 14 atm to 15 atm; the mean acute residual stenosis severity was <6%. Angiographic restenosis was defined as 50% diameter stenosis. The restenosis rate by quantitative angiography at six months, the primary end point, was 31.5% in the actively treated group and 29.3% in the control group (p = 0.45). The rates of target-vessel revascularization (TVR) at six months were 21% and 18.9%, respectively (p = 0.41). The six-month late-loss index was nearly the same in the two groups, 1.20 ± 0.41 in the actively treated group and 2.8% in the placebo group (p = 0.72). The combined rates of death or nonfatal MI were 2.6% and 2.4%, respectively (p = 0.85).

Eight-month curves for survival free of Q-wave MI suggested a disadvantage among actively treated patients, but the difference was not significant. The findings do not support a major role for *C. pneumoniae* in the pathogenesis of thrombosis or restenosis after coronary stenting.

**Commentary.** Once associated primarily with sexual activity and cigarette smoking, *Chlamydia* infection has received new prominence in the world of cardiology as the role of inflammation in ischemic heart disease becomes recognized. After finding elevated anti-chlamydial titers in the blood of patients with atherosclerosis and in coronary atherectomy specimens, it seems natural that the role of chlamydial infection in patients with ischemic complications of intracoronary stenting should be investigated. Unfortunately, the appropriate antibiotic dosing has not been established. There are no reports on whether conventional doses of tetracycline derivatives achieve tissue levels adequate to eradicate infection in the walls of atherosclerotic blood vessels, nor has the necessary duration of therapy been established. This picture is further clouded by the fact that no one has satisfied Koch’s postulates to establish a causative role for chlamydial infection in unstable coronary syndromes. Nonetheless, ROXIS is a well-designed attempt to answer whether the current state of knowledge allows us to select a dose of roxithromycin to eliminate putatively mediated effects of *C. pneumoniae* on complications following intracoronary stent placement. Considering the trend toward benefit for clinical events at eight months in this trial, the WIZAARD Trial, which is evaluating roxithromycin in chronic coronary heart disease, will be an important complementary effort.

**LATE-BREAKING CLINICAL TRIALS II**

SR90107A/ORG31540, a New Synthetic Pentasaccharide (SP), as Adjunct to Fibrinolysis in ST-Elevation Acute Myocardial Infarction (AMI): The Pentalyse Study

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The disadvantages of unfractionated heparin (UFH) when given as an adjunct to fibrinolytic therapy in AMI have led to studies of potential alternatives. The investigators randomized 333 patients with ST-elevation AMI, who were treated within 6 h of chest-pain onset with a front-loaded infusion of 500 mg t-PA, to receive one of two adjunctive antithrombotic regimens: 1) UFH, given as an intravenous bolus of 5,000 U, followed by an infusion of 1,000 U/h for up to 72 h (n = 86) or 2) SP in one of three dosages (4 mg [n = 84], 8 mg [n = 80], or 12 mg [n = 83]) given daily for 5 ± 1 days. The SP is a highly selective antithrombin III–mediated inhibitor of activated factor X that does not directly inhibit thrombin activity. Of the patients randomized, 326 received at least one dose of study medication and became subjects of the analysis. Coronary angiography was performed at 90 min in 321 patients and at an average of five days in 250 patients. The 90-min rates of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow in the infarct artery were 68% in the UFH control group and 65%, 68%, and 59% for patients in the 4 mg, 8 mg, and 12 mg SP groups, respectively. The rates of TIMI grade 2 + 3 flow were 82%, 79%, 85%, and 73%, respectively. None of these differences was statistically significant. However, at late angiography, a trend toward a higher and dose-related increase in coronary artery patency was observed in patients treated with SP. The TIMI 3 flow rates at a mean of five days were 79% in the UFH control arm and 82%, 85%, and 90% for patients receiving 4 mg, 8 mg, or 12 mg SP, respectively (p = NS). In patients with TIMI 3 flow at 90 min, the rate of TIMI 3 flow on the second angiogram was 92% in all SP groups combined and 81% in the UFH control group (p = 0.6). Clinical event rates did not differ significantly at 30 days. Patients who received SP showed a trend toward reduced need for urgent revascularization; the 30-day incidence of this end point was 51% in the UFH control arm and 37%, 39%, and 40% in the 4 mg, 8 mg, and 12 mg SP arms, respectively (p = NS). The combined incidence of blood transfusion and intracranial hemorrhage, the study’s primary safety end point, was 6.3% in all SP groups combined and 7.1% in the UFH control arm (p = NS). The trial’s only instance of intracranial hemorrhage occurred in the 4 mg SP arm. When transfusions related to coronary artery bypass graft surgery were excluded, a trend toward a lower transfusion rate was observed with SP, compared with UFH control (3.3% vs. 7.1%; p = NS). The results of this study supported the hypothesis that inhibition of thrombin itself is not required during and after fibrinolytic therapy with t-PA as long as thrombin formation is inhibited.
Commentary. The PENTALYSE trial represents another attempt to move “upstream” in the realm of anticoagulation for syndromes of acute coronary injury. Heparin consists of a mixture of complex polysaccharides. A basic pentasaccharide sequence contained within the mixture is responsible for catalyzing the coagulation of antithrombin (AT) to factor Xa, while an 18-saccharide sequence leads to the interaction of AT with factor IIa (thrombin). The SP studied in PENTALYSE is a modified form of the naturally occurring pentasaccharide that provides specific inhibition of factor Xa. The SP did not provide statistically significant improvements in early TIMI-3 flow. However, some encouraging statistically significant trends are present, particularly with regard to reduction of late reocclusion.

The early period after thrombolysis is marked by intense thrombin generation. Perhaps, as occlusive intracoronary thrombus is degraded during thrombolysis, thrombin that has previously been formed is released. If so, then some antithrombin activity might be needed to inhibit thrombin-induced platelet activation and cleavage of fibrin. Beginning at 14 h within the PENTALYSE trial, thrombin-antithrombin complexes were reduced in pentasaccharide-treated patients compared with heparin-treated patients. These findings may explain the late findings of the trial. Measurement of pharmacodynamic parameters such as anti-Xa activity and measures of fibrin generation and activity would be helpful in interpreting the results of PENTALYSE and determining whether the doses selected for study provided adequate anticoagulant activity during the early procoagulant storm that accompanies thrombolytic therapy.

A Randomized Comparison of Low-Molecular-Weight Heparin and Unfractionated Heparin (UFH) Adjuvante to t-PA Thrombolysis and Aspirin (HART-II)
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Although the low–molecular-weight heparins have been thoroughly tested in many of the treatment roles traditionally occupied by UFH, they have not been systematically studied as adjuncts to fibrinolytic agents in patients with acute ST-elevation myocardial infarction (MI). As a prelude to a randomized trial comparing enoxaparin and UFH as an adjunct to recombinant t-PA, a pilot study was conducted in which 20 patients with acute ST-elevation MI were randomized to receive 100 mg t-PA over 90 min with aspirin and either enoxaparin or UFH. Enoxaparin was given to 10 patients at a 30-mg intravenous (IV) bolus followed by 1 mg/kg SC twice daily for at least 72 h. Unfractionated heparin was given to 10 patients as a weight-adjusted IV bolus followed by a weight-adjusted IV infusion with a target-adjusted partial thromboplastin time (aPTT) of 2–2.5 times control levels. Serial aPTT determinations evidenced a relatively consistent effect over time for enoxaparin, with the exception of spikes coincident with the IV bolus and the initiation of t-PA. Serial aPTT readings associated with UFH were highly variable and unpredictable. Based on the pilot study, a randomized angiographic study was initiated in which 400 patients with acute ST-segment elevation MI received the same fibrinolytic therapy used in the pilot study. The patients were randomized to adjunctive enoxaparin (same regimen as used in the pilot study, n = 200) or UFH (4,000 U IV bolus for patients ≤67 kg in weight or 5,000 U IV bolus for patients >67 kg, followed by IV to a target aPTT of at least two times control levels, n = 200). The rates of TIMI grade 2–3 flow at angiography performed 90 min after the start of the t-PA infusion, the primary end point, were 80.1% for enoxaparin and 75.1% for UFH. The relative increase among patients who received enoxaparin was attributable mostly to an increase in the rate of TIMI 3 flow (52.9% and 47.6%, respectively). Of the patients with TIMI grade 2–3 flow at 90 min, 5.9% of those who received enoxaparin and 9.8% of those who received UFH had angiographic evidence of re-occlusion at one week. Clinical event rates were similar in the two treatment groups: rates of in-hospital mortality were 5.6% and 4.5%, respectively; 30-day mortality, 5% and 5%, respectively; predischARGE emergency percutaneous revascularization, 4% and 3%, respectively; major hemorrhage, 3.6% and 3.0%, respectively; and intracerebral hemorrhage, 1% and 1%, respectively.

This study was constructed as an equivalence trial, and all comparisons were well within the equivalence range and trended strongly in favor of enoxaparin over UFH. It was concluded that enoxaparin can be substituted for UFH as an adjunct to fibrinolytic agents in patients with acute ST-elevation MI.

Commentary. Unfractionated heparins have become increasingly popular in the management of patients with acute coronary syndromes because of their established clinical efficacy and because their predictable anticoagulant effect renders them considerably easier to use than UFH. Nowhere is the theoretical need for a predictable anticoagulant response greater than in patients receiving thrombolytic therapy. In HART II, the substitution of enoxaparin for UFH led to a minor increase in early TIMI 3 flow and a halving of the rate of angiographic re-occlusion. This occurred at the cost of a small increase in major bleeding, without an observed increase in the rate of intracranial hemorrhage.

It is fairly well known that low–molecular-weight heparins possess a greater ratio of anti-Xa to anti-IIa activity than UFHs. In the case of enoxaparin, this ratio is approximately 3.6:1, compared with 1:1 for UFH. It is interesting that the results of HART II parallel the results of PENTALYSE in that there are few differences in early TIMI 3 flow but more important differences in late reocclusion. Perhaps thrombolytic therapy will ultimately involve the use of an adjunctive glycoprotein IIb/IIIa antagonist during the early course and an Xa antagonist (or low–molecular-weight heparin) after the initial course. Al-
though these results are promising, the safety aspect of combined low–molecular-weight heparin and thrombolytic therapy has not been explored in nearly as much depth as that of UFH and thrombolytic therapy. Unfortunately, the development of heparin replacement molecules is constrained by the absence of adequate proof that heparin itself is superior to placebo. Although well over 100,000 patients have been treated with UFH in fibrinolytic trials, few have been randomized to heparin or placebo. Thus, although the results of HART II are promising, it is too early to recommend routine use of low–molecular-weight heparin as adjunctive therapy with fibrinolytic drugs.

Optimal Dosing of a Platelet Glycoprotein (GP) IIb/IIIa Antagonist, Lamifiban, Using Renal–Based Algorithms, in Patients With Acute Coronary Syndromes (ACS): Results From the PARAGON B Study

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Treatment with platelet glycoprotein (GP) IIb/IIIa receptor blockers can reduce the risk of death or acute myocardial infarction (MI) when given to patients with ACS not associated with persistent ST-segment elevation. Studies heretofore have used weight-adjusted dosages of these agents. Evidence suggests that lamifiban, a nonpeptide GP IIb/IIIa blocker with a renal mechanism of clearance from the circulation, might be more suited to renal-based dosing methods. The PARAGON B study enrolled 5,225 high-risk patients with ischemic chest pain within the previous 12 h and either ST-segment or T-wave changes or cardiac enzyme or troponin readings suggestive of acute ischemic syndromes. Patients were randomized to receive either placebo or lamifiban as a 500-mg intravenous bolus followed by an infusion of 1.0, 1.5, or 2.0 mg/min based on calculated creatinine clearance over 72 h, to a maximum of 120 h following any percutaneous intervention. All patients received aspirin and either unfractionated or low–molecular-weight heparin. Sixty percent of patients underwent cardiac catheterization, 27% underwent percutaneous interventions, and 15% underwent coronary artery bypass surgery, with no significant differences among randomization groups. The composite rates of all-cause death, acute MI, or severe recurrent ischemia, the trial’s primary end point, were 12.8% in the 2,597 patients randomized to placebo and 11.8% for the 2,628 patients randomized to lamifiban (p = 0.329). Death and MI constituted most of the events making up the primary end point; the 30-day rates of death or MI were 11.5% in the placebo group and 10.6% in the lamifiban group (p = 0.320). There was no significant difference between randomization groups with respect to rate of hemorrhagic stroke. There was an excess of moderate bleeding (blood transfusion or ≥5 g/dl drop in Hgb) with lamifiban compared with placebo (14.0% vs. 11.5%, p = 0.002). In a substudy encompassing 1,160 of the randomized patients who underwent serial assessments of cardiac troponin T, among those who were troponin-positive, the primary 30-day rates of death or MI were 19% or 11%, respectively (p = 0.018).

Commentary. Much attention has recently been paid to the variability of individual patients’ responses to GP IIb/IIIa antagonists. Although experimental data suggest that blockade of approximately 80% of platelet surface GP IIb/IIIa receptors represents the threshold necessary to interfere with platelet participation in thrombosis, clinical data to confirm this concept are scant. Notably, when two different doses of lamifiban were studied in the first PARAGON trial, both ischemic coronary events and bleeding were more common among patients assigned to receive the higher dose. The PARAGON B study was subsequently designed to test an observation from the first PARAGON trial. In that trial, separation of patients according to blood levels of lamifiban revealed that event rates were approximately 50% lower in patients whose blood levels were between 20 and 40 ng/mL. Because of lamifiban’s binding-affinity for GP IIb/IIIa, these levels represent an intermediate level of receptor blockade.

Although lamifiban did not reduce ischemic event rates significantly in the PARAGON B study, the findings are very consistent with other trials of GP IIb/IIIa antagonists in ACS. There was an approximate 1% absolute reduction in the composite rate of death or MI, and the reductions were greatest in patients undergoing early percutaneous coronary intervention and those with elevated troponin levels. In both of these settings, there is objective evidence of acute arterial injury at the time when GP IIb/IIIa receptors are blocked. In a broader perspective, it seems unlikely that lamifiban will be developed as a therapeutic agent. However, these findings do lend further support to the use of GP IIb/IIIa antagonists in patients with ACS, particularly in patients who have objective evidence of ischemia.

A Randomized Comparison of Sibrafiban, an Oral Glycoprotein (GP) IIb/IIIa Receptor Antagonist, With and Without Aspirin Versus Aspirin After Acute Coronary Syndromes (ACS): Results of the Second SYMPHONY Trial

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Intravenous GP IIb/IIIa receptor blockers reduce the risk of ischemic events in patients with ACS, but a similar benefit for chronic oral GP IIb/IIIa blockers compared with aspirin alone has yet to be demonstrated. A first SYMPHONY trial found that one such oral agent, sibrafiban, given without aspirin did not reduce ischemic risk in patients with ACS compared with aspirin alone. A second SYMPHONY trial was initiated to attempt the same comparison, using sibrafiban plus aspirin. A total of 8,400 patients with stabilized ACS were expected to be randomized to receive either low-dose sibrafiban with aspirin, high-dose sibrafiban alone,
or aspirin alone for at least one year. Sibrafiban dosing was based on weight and serum creatinine, with the goal of either >25% (low-dose group) or >50% (high-dose group) steady-state inhibition of platelet aggregation. Following a negative finding in the first SYMPHONY trial, the second SYMPHONY trial was terminated by the sponsor after only 6,671 patients had been enrolled. As a result of randomization, 2,232 patients received aspirin plus low-dose sibrafiban, 2,174 patients received aspirin plus high-dose active therapy, and 2,231 received aspirin only; patients were treated for a mean of 90 days. The composite rates of death, acute myocardial infarction (MI), or severe recurrent ischemia, the primary efficacy end point, were not significantly different: 9.2%, 10.5%, and 9.3%, respectively. However, patients who received high-dose sibrafiban showed significant increases in some secondary end points compared with those randomized to aspirin only. The rates of death or MI were 6.8% in the low-dose group, 8.6% in the high-dose group, and 6.1% in the aspirin-only group (p = 0.004 for the high-dose sibrafiban group compared with the aspirin group). Mortality alone was 1.7%, 2.4%, and 1.3%, respectively (p = 0.008 for the high-dose sibrafiban group compared with the aspirin group). The MI rate alone was 5.3%, 6.9%, and 5.3%, respectively (p = 0.03 for the high-dose sibrafiban group compared with the aspirin group). The composite rates of major or minor bleeding, a primary safety end point, were 21.1% and 22.1% for the low- and high-dose sibrafiban groups, respectively—significantly higher than the 11.7% rate for aspirin-only patients. Patients who received low-dose active therapy had a 43% increase in risk of major bleeding complications compared with the aspirin group.

Commentary. The second SYMPHONY trial represents an attempt to extend the benefits of GP IIb/IIIa antagonism to secondary prevention after initial presentation with an ACS. Unfortunately, the contrast between the intravenous and the oral GP IIb/IIIa antagonists is dramatic. Although trials of the intravenous agents have almost universally indicated a 10% to 15% reduction in the composite of death or MI, the second SYMPHONY is the fourth consecutive negative trial of an oral agent. Even worse, all four trials of oral GP IIb/IIIa antagonists have shown an increase rather than a decrease in mortality.

Although it has been hoped that pharmacokinetics—specifically more avid binding of GP IIb/IIIa and more predictable bioavailability—would provide an advantage for newer oral GP IIb/IIIa antagonists, the promise has been thus far unfulfilled. Two potential reasons need to be considered: first, the efficacy of GP IIb/IIIa antagonism appears to be related to the temporal proximity of receptor blockade to the initial arterial injury. It is greatest in trials of percutaneous coronary intervention, when the antagonist is administered immediately before balloon inflation, somewhat less in trials of ACS when 12 h to 24 h have elapsed after the injury has occurred, and least in the secondary prevention trials if the oral agent is given at least 72 h after presentation. The decreased efficacy must be balanced against a more prolonged period of drug exposure and, hence, bleeding risk over the longer time period when oral GP IIb/IIIa antagonists are administered. A second reason that has been postulated for the failure thus far of the oral agents concerns other biological effects of the drugs. In addition to permitting platelet aggregation, GP IIb/IIIa may also mediate platelet activation through a process known as “outside-in-signaling.” Occupancy of the receptor may prevent aggregation from occurring but may at the same time activate the platelet, rendering it more, rather than less, likely to participate in thrombosis during trough periods between oral doses. Most recently, concerns have been raised that the oral agents induce a pro inflammatory state. The book is not yet closed, however, concerning oral GP IIb/IIIa antagonism. A second generation of agents has been developed. These newer agents bind GP IIb/IIIa with much higher affinity than the first generation and thus have the potential to avoid some of the problems associated with receptor occupancy–mediated platelet activation. For the time being, however, oral antagonists of GP IIb/IIIa are not likely to come into clinical use in the immediate future.

Randomized Comparison of Percutaneous Transluminal Coronary Angioplasty (PTCA) of the Infarct Vessel and Medical Therapy in Stable Survivors of Acute Myocardial Infarction (AMI): The Post-Infarct PTCA Study of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenbauarzte (ALKK)

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Percutaneous revascularization of a significant infarct-related artery (IRA) stenosis is often performed in stable and symptom-free patients with a recent AMI. However, there are no randomized studies to support this practice. This study randomized 300 stable patients who had experienced an AMI within the previous one to six weeks (mean: three weeks) and who had a significant IRA stenosis and no critical lesions in other coronary arteries to undergo PTCA or medical therapy. The 149 patients treated with PTCA and the 151 who were medically managed were similar at randomization with respect to stenosis severity and vessel location and whether the IRA was occluded. The rates of event-free survival at one year, the primary end point, were 90% and 82%, respectively (p = 0.066). In a follow-up extended to a mean of 53 months, available for 96% of patients, the rates of death were 5% in the intervention group and 10% in the medically managed group (p = 0.1). The rates of event-free survival were 76% and 67%, respectively (p = 0.1). Nitrate use, although similar in both groups at baseline, at one year was significantly reduced among patients who underwent intervention (38% vs. 67%, p = 0.001). Use of beta blockers and calcium-channel blockers remained comparable. The study suggests that PTCA does not significantly reduce the rate of death and reinfarction in stable survivors of AMI.
Commentary. ALKK appears to be a new trial reaffirming an old message: despite the intuitive appeal of anatomically directed revascularization, data collected in the current era do not seem to differ appreciably from those collected a decade and a half ago. ALKK differs from the oft-quoted Thrombolysis In Myocardial Infarction (TAMI I), Thrombolysis and Angioplasty In Myocardial Infarction (TIMI II), and European Cooperative Study Group trials in that patients were not required to have undergone fibrinolytic therapy and that intervention was performed somewhat later than in the previous trials. We do not know the baseline characteristics of these patients, but judging from the event rates reported, the patients appear to be at relatively low clinical risk. Similarly, technical details of the interventional procedures are not reported, but it seems fair to assume that intracoronary stents were used liberally and that GP IIb/IIIa antagonists (in Europe, abciximab) were available. Although this trial is small, its findings are concordant with data produced in a number of previous trials and still support an approach to intervention in stable, low-risk survivors of AMI involving risk-stratification rather than routine angiography.

High-Dose Eptifibatide in Elective Coronary Stenting: Results of the ESPRIT Trial
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ESPRIT was an efficacy and safety study of a new dosing regimen for the small-molecule GP IIb/IIIa inhibitor eptifibatide used as an adjunct to planned, elective coronary stenting. Approximately 2,400 patients undergoing coronary stent placement in native coronary arteries were expected to be randomized to either adjunctive eptifibatide (180 mg/kg double bolus, with boluses separated by 10 min, followed by 2.0 mg/kg/min infusion for 18 h to 24 h) or placebo in a double-blind fashion. Heparin was administered to a target activated clotting time of 200 s to 300 s. Almost all patients also received ticlopidine or clopidogrel. Enrollment was terminated in February 2000, when it was observed that active therapy was associated with a significant 43% reduction in relative risk of death or acute myocardial infarction (MI) at 48 h (4.9% in the active-therapy group vs. 8.6% in the control group, p = 0.0017). Outcomes at 48 h factor for the 1,040 patients randomized to eptifibatide and the 1,024 patients randomized to placebo are available; analysis of outcomes at 30 days, six months, and one year are planned. The 48-h rates of the primary end point—a composite of death, MI, urgent target-vessel revascularization, or (placebo arm only) bailout GP IIb/IIIa blockade—were 6.6% and 10.5%, respectively (p = 0.0015). Reductions in relative risk of all components of the composite end point were also significant. The rates of major and minor bleeding complications were statistically similar in the two treatment groups; most such complications consisted of femoral access-site bleeding. Intracranial hemorrhage occurred in two patients who received eptifibatide and one in the placebo group.

Commentary. As GP IIb/IIIa blockade during intervention has become more refined, the major reason most interventional operators cite for withholding its use during routine cases has been economic. The preliminary results of ESPRIT indicate that this last argument is likely to wither. The design of ESPRIT was based on pharmacokinetic and pharmacodynamic observations made in patients receiving eptifibatide during previous trials. After a 180 mg/kg bolus is given and a 2 μg/kg/min infusion is begun, levels of eptifibatide increase after the bolus and then decrease for a period of approximately 4 h before rising to a steady-state level. In ESPRIT, a second bolus of eptifibatide was given 10 min after the first dose to prevent this transient decrease in inhibition of platelet aggregation. A previous trial of eptifibatide given at a lower dose during percutaneous coronary intervention (PCI) had shown a nominal but transient reduction in ischemic events. In that trial, intracoronary stenting was performed in fewer than 4% of patients, but in ESPRIT it was performed in more than 95%. It is not known whether this difference between the two trials is the result of different dosing schedules or the fact that the procedure of stenting changes the substrate of ischemic events into one that is likely to be ameliorated by GP IIb/IIIa blockade. It is also not known whether the short-term results reported here will be robust enough to be present at the end of one year, although, if the pattern seen in the Evaluation of Platelet Inhibition with Stent study is followed, this is likely to be the case. Clinicians who plan to use eptifibatide based on the ESPRIT results should keep two important points in mind: the procedures studied were largely elective ones, and the dosing of eptifibatide used here differs from that currently labeled for either PCI or acute coronary syndromes (ACS). It is also important to note that the model used to calculate the eptifibatide doses is based on steady-state drug levels obtained with a 2 μg/kg/min infusion. Therefore, patients who have received eptifibatide for more than 3 h to 4 h for the treatment of ACS do not need to receive a further loading dose.

LATE-BREAKING CLINICAL TRIALS III

Outcomes of a Prospective Trial of Intravenous (IV) Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF)
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There have been few randomized, placebo-controlled trials to guide the management of hospitalized patients with worsening symptoms of chronic heart failure (CHF). Intra-
venous positive inotropic agents can improve hemodynamics and may aid the titration of standard oral drug therapy. This study randomized 949 patients with worsening CHF within 48 h of hospital admission to receive a 48-h infusion of either milrinone (0.5 μg/kg/min IV without a loading dose) or placebo and followed them for 60 days. Eligible patients had worsening CHF with a left ventricular ejection fraction ≤40% and did not require IV vasopressor or inotropic support. Patients with unstable angina or acute myocardial infarction within the prior three months were excluded. The CHF was ischemic in etiology in 51% of both treatment groups. The number of days of hospitalization for cardiovascular causes within 60 days after randomization, the primary end point, was a mean of 12.3 for the 477 patients who received milrinone and 12.5 for the 472 randomized to placebo (median, 6.0 and 7.0, respectively), a nonsignificant difference. Similarly, there was no significant difference in the mean number of days from initial discharge to rehospitalization (5.7 days and 5.9 days, respectively), a secondary end point. No significant differences were observed with respect to subjective measures of CHF severity. Milrinone treatment was associated with an increase in relative risk of atrial fibrillation (AF) and a 10.7% increase in relative risk for sustained hypotension, whereas placebo was associated with a 1.5% increase in relative risk for AF and a 3.2% increase in relative risk for sustained hypotension. The proportion of patients who failed to show clinical improvement was similar in both treatment groups; however, 20.4% of actively treated patients and 9.0% of controls required infusion adjustments because of an adverse effect, primarily hypotension. Mortality was 3.8% and 2.3%, respectively, in-hospital and 8.9% and 10.3%, respectively, over 60 days; neither difference was significant. Multivariate analysis indicated the following significant predictors of death within 60 days: low systolic blood pressure (BP), low serum sodium, advanced age, and New York Heart Association (NYHA) functional class. The following were significant independent correlates of increased hospitalization time over 60 days: low systolic BP, low serum sodium, male gender, an increase in NYHA functional class, and the number of hospitalizations over the previous year. When the primary end point was analyzed based on CHF etiology, patients with ischemic disease tended to have fewer hospitalization days when receiving placebo therapy, while the opposite was true for the nonischemic group. Specifically, milrinone was associated with fewer days of cardiovascular hospitalization during follow-up (10.9 vs. 12.6 days). It appears that patients with low serum sodium levels at baseline and those with nonischemic heart failure tended to do better with milrinone therapy, while the opposite was true for patients without hyponatremia and with ischemic heart failure. The OPTIME–CHF data suggest that, in patients who do not require IV inotropic therapy, routine use of IV milrinone is not recommended. This study does not evaluate whether IV milrinone is beneficial in the other subsets of patients with more severe heart failure.

Commentary. This trial is the first reasonably large randomized trial in patients with acutely decompensated heart failure. The use of inotropic agents in heart failure has been controversial because of increased mortality in trials in which patients were treated over the long term with orally active agents. Surprisingly few outcome data have been available, despite the widespread use of intravenously administered inotropic agents. Although the trial failed to demonstrate a benefit in the expanded indication of early milrinone use in decompensated heart failure, it did provide evidence of safety in patients with severe heart failure as manifested by a low serum sodium and those with a nonischemic etiology. Much more evidence is needed in this field, considering that heart failure is the most common reason for hospitalization in Medicare, that it carries a substantial mortality risk, and that almost nothing is known about which therapies are effective.

Prospective Randomized Amlodipine Survival Evaluation (PRAISE–2)

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The first PRAISE trial randomized 1,153 patients with ischemic or nonischemic New York Heart Association (NYHA) class IIIB–IV heart failure to receive amlodipine (up to 10 mg/day) for up to 33 months. No significant benefit of amlodipine therapy was observed with respect to the combined primary end point of death or cardiovascular hospitalization, although the agent demonstrated a nonsignificant trend toward improved mortality. Solely among patients with nonischemic heart failure, however, amlodipine was associated with a 45% reduction in risk of death (p = 0.001), leading the investigators to conduct a PRAISE 2 trial to explore the finding further. The study randomized 1,652 patients with nonischemic NYHA class IIIB–IV heart failure to receive amlodipine (up to 10 mg daily, n = 826) or placebo (n = 826) and followed them for 48 months for a primary end point of all-cause mortality. The protocol mirrored that of the previous trial in virtually every respect. By intention-to-treat, all-cause mortality was 33.7% in the amlodipine group and 31.7% in the placebo group (p = 0.32). In the combined analysis of outcomes data from patients in the first and second PRAISE trials, all-cause mortality was 33.4% among those who received amlodipine and 34.0% among those who received placebo (p = 0.81). The results of PRAISE 2 do not support the apparently favorable effect of amlodipine on survival for patients with nonischemic heart failure observed in the first PRAISE trial. Combined analysis of both trials suggests that amlodipine has neither a favorable nor an unfavorable effect on mortality in patients with severe chronic heart failure.
Commentary. This surprising result should sound a note of caution for anyone who accepts marginal evidence of a mortality benefit. The Evaluation of Losartan in the Elderly (ELITE) I trial similarly showed a substantial apparent benefit of losartan compared with captopril, but the larger ELITE II showed a trend in favor of captopril. Similarly, a small trial with vesnirinone was markedly positive compared with placebo, but a larger follow-up trial had to be stopped because of excessive mortality with vesnirinone. The message here is clear: we need a substantial number of deaths (perhaps 200–300) in heart failure trials before a stable estimate of the effectiveness of the treatment can be reached.

Seven-Year Outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by Treatment and Diabetic Status

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Analysis of five-year survival in the BARI trial, which has been published previously, disclosed no significant difference in survival between patients randomized to coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA). However, in the retrospectively defined subgroup of patients with diabetes mellitus, patients treated with CABG showed a significant survival advantage. The trial randomized 1,829 patients with symptomatic multivessel disease and no prior coronary revascularization to undergo either CABG or PTCA as an initial treatment strategy. Patients were required to be angiographically eligible for either procedure. Patients have been followed for an average of 7.8 years. In the analysis of outcomes at seven years, the rate of survival for the population as a whole was 84.4% for those who underwent CABG and 80.9% for those who received PTCA (p = 0.043). The subgroup of 353 patients with treated diabetes mellitus accounted for virtually all of the difference in survival. Among diabetics, the seven-year survival rates were 76.4% and 55.7%, respectively (p = 0.0011). Their rates of survival free of acute myocardial infarction (MI), a secondary end point, were 65.2% and 50.0%, respectively (p = 0.049). Among the remaining 1,476 patients without diabetes, the seven-year survival rates were almost identical at 86.4% and 86.8%, respectively (p = 0.72). The rates of MI-free survival among nondiabetics were 77.8% and 78.9%, respectively (p = 0.57). Patients randomized to CABG had a significantly lower rate of subsequent coronary revascularization than did patients who underwent PTCA: 13.1% and 59.7%, respectively (p = 0.001). It was concluded that CABG is associated with significantly improved seven-year survival compared with PTCA in the overall BARI population of patients with symptomatic multivessel disease. Improvement in the seven-year survival rate was highly significant with CABG among diabetic patients. Survival at seven years among nondiabetic patients was virtually the same with either CABG or PTCA.

Commentary. The news from BARI is most likely disappointing to interventional cardiologists. However, it is very consistent with earlier results of the trial, which demonstrated a nonsignificant survival trend favoring CABG five years after randomization. As in the previously reported results, the difference was nearly completely accounted for by patients with diabetes mellitus. Although it can, and should, be argued that current interventional technique, namely stenting and GP IIb/IIIa antagonism with abciximab, were not included in BARI (for obvious reasons), the advantages of these treatments must also be placed in the correct context. Abciximab has been shown to reduce the periprocedural risk of diabetics to a level similar to that of nondiabetics and perhaps reduces the rate of in-stent restenosis in patients with diabetes. Although intracoronary stenting reduces the rate of recurrent stenoses in patients with diabetes, it is not clear whether these rates are reduced to levels seen in nondiabetic patients. It should also be noted that the increased risk in patients with diabetes did not occur during hospitalization, but it accumulated gradually over the follow-up period. That the BARI investigators found the risk reduction to be confined to patients for whom the internal mammary artery was used as a surgical conduit suggests that the extent of coronary artery disease, rather than procedural factors, was responsible for the findings. Unfortunately, the investigators involved in the multiple trials of percutaneous coronary intervention versus CABG done around the world have been unable to pool their data. A systematic overview would provide the important evidence for replication that is generally required before adopting a major therapeutic strategy change. The seven-year findings should, therefore, at the very least, lead to a clear note of caution when planning percutaneous procedures in diabetic patients with multivessel disease.

Outcomes 15 Years After Valve Replacement With a Mechanical Versus a Bioprosthetic Valve: Final Report of the Veterans Administration (VA) Randomized Trial

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The VA Randomized Trial was launched in 1976 to compare the long-term outcomes of bioprosthetic and mechanical prostheses for aortic valve replacement (AVR) and mitral valve replacement (MVR). Five-year and 10-year follow-up results have been published previously. The cohort has now been followed up for 15 years. Among the 394 patients who underwent AVR, all-cause mortality at 15 years was 66% for those randomized to mechanical valves and 79% for those randomized to bioprostheses (p = 0.02). Survival curves for patients with AVR began to diverge after year 10 in such a way that the 13% absolute difference comprised an approximately 2.5% per year absolute differ-
ence in mortality from years 10 to 15. The 15-year mortality rates for valve replacement in the mitral position were 81% for patients randomized to mechanical valves and 79% for patients randomized to a bioprosthesis (p = 0.30). The rate of primary valve failure was significantly increased with the bioprosthesis at both valve locations; the rates were 0% for mechanical valves and 23% for bioprosthetic valves for AVR (p = 0.0001) and 5% and 44%, respectively, for MVR (p = 0.0002). Among patients <65 years of age, the rate of primary valve failure was also significantly increased with the bioprosthesis at both valve locations: 0% for mechanical valves and 26% for bioprosthetic valves for AVR (p = 0.001) and 4% and 44%, respectively, for MVR (p = 0.0001). Among patients ≥65 years of age, the primary valve failure rate in the aortic position was 0% for mechanical valves and 9% for bioprosthetic valves (p = 0.16). Among patients undergoing AVR, the need for repeat valve replacement was 10% for mechanical valves and 29% for bioprosthetic valves (p = 0.0004). Bleeding complications were significantly more common in patients randomized to mechanical valves: the bleeding complication rate was 51% for mechanical valves and 30% for the bioprostheses for AVR (p = 0.0001) and 53% and 31%, respectively, for MVR (p = 0.01). The rates of valve-related complications and of thromboembolism were not significantly different for valve replacement at either location. It was concluded that, 15 years after randomization, patients who underwent AVR had a significantly better survival with a mechanical valve than with a bioprosthesis, largely because of the former's primary failure rate of essentially zero. Primary valve failure was significantly more common for bioprostheses than for mechanical valves among patients <65 years. Primary valve failure rates were not significantly different after AVR among patients ≥65 years.

Commentary. The long-term follow-up from this VA study is not surprising, but it raises a number of interesting issues. The current paradigm for cardiac valve development is focused on intensive engineering standards and registries rather than randomized trials. This study demonstrates the need for methodologic development on two fronts: how to distinguish modest differences between valves in clinical outcomes without requiring randomized trials that are not affordable by the device industry and how to reliably measure long-term outcomes when we cannot wait for long-term outcomes before putting a new valve on the market.

Assessment of Cardioversion Using Transesophageal Echocardiography (TEE) Multicenter Study (ACUTE I): Clinical Outcomes at Eight Weeks

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The use of TEE to screen for the presence of left atrial thrombi in patients with atrial fibrillation (AF) has the potential for reducing the duration of anticoagulation before cardioversion. A total of 1,222 patients with either AF of >2-days duration or atrial flutter and a history of AF, and who were candidates for direct-current cardioversion (DCC), were randomized to undergo DCC using either a TEE-guided or conventional approach. Patients who required long-term anticoagulation, who were hemodynamically unstable, or who had contraindications to anticoagulation or TEE were excluded. Patients assigned to the TEE group were to undergo TEE preceded by brief anticoagulation. In the absence of thrombus, DCC was to be performed, followed by four weeks of warfarin therapy. With thrombus present, patients were instead to receive warfarin for three weeks, followed by repeat TEE; then, in the absence of thrombus, the patients were to have DCC, followed by four weeks of warfarin, or, in the presence of thrombus, they were instead to receive another four weeks of warfarin. Patients assigned to the conventional DCC strategy were to receive warfarin for three weeks, followed by DCC, then followed by another four weeks of warfarin. Of the 619 patients randomized to the TEE-guided approach, TEE was performed in 551; of the 551, 427 had DCC, which was successful in 344 patients. Of the 603 patients randomized to the conventional strategy, 367 underwent DCC, which was successful in 293 patients; spontaneous conversion was the most common reason that DCC was not performed in the remaining 236 patients. On an intention-to-treat basis, the rate of the primary composite end point of stroke, transient ischemic attack, or peripheral embolism was 0.81% in the TEE-guided DCC group and 0.50% in the conventional-strategy DCC group (p = 0.501). With respect to secondary end points, the rates of major bleeding were 0.81% and 1.50%, respectively (p = 0.261), the rates of minor bleeding were 2.30% and 4.0%, respectively (p = 0.084), and the composite rates of major or minor bleeding were 3.11% and 5.50%, respectively (p = 0.025). No significant differences were observed in rates of other secondary end points, including all-cause mortality, cardiac mortality, achievement of sinus rhythm at eight weeks, and functional capacity at eight weeks. It was concluded that the TEE-guided approach with short-term anticoagulation does not reduce the risk of embolic events over eight weeks but may decrease the risk of major or minor bleeding complications. Furthermore, the TEE-guided approach allows for earlier cardioversion of AF but does not improve the rate of sinus conversion, functional capacity, or survival at eight weeks. TEE-guided DCC of AF may be considered an alternative to the conventional approach.

Commentary. This investigator-initiated trial will generate a substantial amount of important information about cardioversion, but the low event rate with the traditional approach is already one surprising result of the study. Indeed, with event rates this low, it is difficult to envision a scenario in which TEE could lead to a clinical benefit, although the economic benefit of avoiding four additional weeks of anticoagulation could be substantial.
The ALLHAT trial has randomized 42,448 hypertensive patients with multiple cardiovascular risk factors to undergo long-term double-blind therapy with either a diuretic (chlorthalidone) or one of three alternatives: a calcium-channel blocker (amlodipine), an angiotensin-converting enzyme inhibitor (lisinopril), or an alpha-adrenergic blocker (doxazosin). The trial also includes a randomized, open-label evaluation of statin therapy in the hypercholesterolemic subset of the population. The projected duration of the trial was an average of six years. In March 2000, the doxazosin arm was terminated on the grounds that it had become futile to attempt to find a significant difference in the primary outcome (fatal coronary heart disease or non-fatal myocardial infarction) by the trial’s scheduled conclusion and, more important, to find it on the basis of a 25% increase (p < 0.00001) in the secondary end point of combined cardiovascular events (including heart failure) among patients treated with doxazosin. Although heart failure contributed the largest proportion of increased events in the doxazosin arm of the trial (other components of the secondary end point included coronary heart disease, stroke, peripheral vascular disease, vascular procedures, and angina pectoris), without the heart-failure component, a 13% increase in the combined end point (p < 0.001) remained.

No difference was observed in the primary end point, or in total cumulative mortality, between patients treated with chlorthalidone and those who received doxazosin. The effects of chlorthalidone and doxazosin on reductions in systolic and diastolic blood pressure (BP) were largely similar. It was concluded that chlorthalidone is superior to doxazosin for the treatment of high-risk hypertensive patients. Chlorthalidone, and probably diuretics as a class, should remain the drug therapy of first choice for patients with hypertension. Alpha-adrenergic blockers are not recommended as a first-line treatment for hypertension.

Commentary. The ALLHAT study brings forth one of the most crucial issues in contemporary medicine. Can we assume that therapies that affect surrogate end points in the same way will affect clinical outcomes similarly? The answer is, apparently, “no.” For years, BP has been considered a straightforward surrogate: there is a direct relationship between BP reduction and reduction in the risk of stroke in particular but also a reduction in the coronary heart disease end points in general. The ALLHAT Study points out that two agents that lower BP to the same degree may have different effects on clinical outcomes, leading to the inescapable conclusion that, when it is possible, we need to measure the impact of therapies on tangible human outcomes (death, events, and quality of life).