**Progress in Clinical Trials**

**ARCHeR (Acculink™ for Revascularization of Carotids in High-Risk Patients)**


*Background:* In similar high-risk patient cohorts, composite endpoints of stroke, death, and myocardial infarction (MI) at one year for carotid endarterectomy (CEA) have been between 11–14%.

*Patient population:* Symptomatic patients had carotid artery stenoses ≥50%, and asymptomatic patients had stenoses ≥80%. All patients (n = 437, mean age 69.4 years, 67% male) had one or more qualifying high-risk criteria.

*Methods:* ARCHeR is a multicenter, single-arm trial that evaluated carotid artery stenting in patients with high risk for CEA. Follow-up was at 30 days and 6, 12, 18, 24, and 30 months. The primary endpoint was a composite of stroke, death, and MI at 30 days and ipsilateral stroke between 31 days and 1 year.

Patients received self-expanding nitinol stents (Acculink, Guidant Corporation), using an embolic protection system (Guidant Accunet Filter). Forty-eight hours preprocedure they received aspirin (325 mg b.i.d.) and clopidogrel (b.i.d.). They received heparin intraprocedure to maintain activated clotting time ≥250 s (but aimed at closer to 300 s), and postprocedure aspirin 325 mg daily (minimum 1 year) and clopidogrel daily (minimum of 2–4 weeks, but often 2–3 months).

*Results (30-day):* The most common high-risk entry criteria were restenosis after CEA (32.2%), ejection fractions < 30% or New York Heart Association (NYHA) class III (28.6%), or two or more diseased coronary arteries (27.5%). Accunet filter procedure success was 92.7%, and 57% had debris in filter baskets.

The 30-day stroke/death rate was 6.6%, and the stroke/death/MI rate was 7.8%. The ipsilateral stroke rate was 5.1% (0.2% contralateral), and the death rate 2.3% (one [0.7%] was stroke-related).

*Conclusion:* ARCHeR trial 30-day results demonstrate that carotid stenting with filter protection can be safely performed in high-risk surgical patients in a multicenter trial. Data compare favorably with historical CEA outcomes.

**COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation)**


*Background:* In the 25–30% of advanced heart failure patients with QRS widening, cardiac resynchronization therapy (CRT) improves contractile function and reverses remodeling. In ischemic cardiomyopathy (with and without heart failure), an implantable cardiac defibrillator (ICD) reduces mortality. No appropriately powered clinical trials have investigated these effects.

*Primary hypothesis:* In patients with advanced heart failure and QRS widening, when used in conjunction with optimal pharmacologic therapy, biventricular CRT alone decreases combined all-cause mortality and all-cause hospitalization; and biventricular CRT combined with ICD (CRT-D) decreases combined all-cause mortality and all-cause hospitalization.

*Patient population:* Included patients were in New York Heart Association class III or IV and normal sinus rhythm, and had QRS ≥120 ms, PR interval > 150 ms, left ventricular ejection fraction ≤35%, left ventricular end-diastolic diameter ≥60 mm, and were on optimal pharmacological therapy. They had histories of heart failure hospitalizations (or Rx equivalent) <12 months and >1 month prior to enrollment. Mean age was 66 years.

*Study design:* Patients were randomized 1:2:2 to either (a) optimal pharmacologic therapy (OPT), (b) OPT + CRT (CON-TAK TR%/EASYTRAK®, Guidant Corporation), or (c) OPT + CRT-D (CON-TAK TR%/EASYTRAK®).

Target time to implant was ≤2 days from randomization. The primary endpoint was time to all-cause death or all-cause hospitalization

*Results:* The Data Safety and Monitoring Board stopped the trial when prespecified endpoint boundaries had been reached. Versus OPT (67.7% event rate), for the 12-month primary endpoint of death or any hospitalization, there was an 18.6% (p = 0.015) reduction for CRT and a 19.3% (p = 0.005) reduction for CRT-D. For death or heart failure hospitalization, the OPT event rate was 46.1%, with significant (p < 0.001) reductions for both CRT (35.8%) and CRT-D (39.5%). All-cause mortality was 19.0% for OPT, with a 23.9% (NS) reduction for CRT and a 43.4% reduction for CRT-D (p = 0.002).

There were no obvious differences in mortality between ischemic and nonischemic etiologies.

*Conclusions:* Reductions in combined endpoints were due to CRT, since CRT and CRT-D resulted in similar effect sizes. The addition of an ICD to CRT produced a highly significant 43% decrease in mortality.

**DELIVER**


*Background:* The RX Achieve™ (Cook, Inc.) drug-coated coronary stent is coated with 3 mcg/mm² paclitaxel, but unlike drug-eluting stents in the TAXUS (Paclitaxel- [Taxol™, Boston Scientific Corporation] Eluting Stent study) and RAVEL (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with...
de novo Native Coronary Artery Lesions)/SIRIUS (see page 298) trials, it has no polymer coating.

**Objective:** The objective of the DELIVER trial was to assess the safety and effectiveness of the Achieve stent in the treatment of de novo lesions in native coronary arteries measuring 2.5–4.0 mm in diameter. It was compared with the bare metal ML Penta™ (Guidant Corporation) coronary stent.

**Patient population:** DELIVER included 1,043 patients (average age 60 years) with target lesions ≤ 25 mm. Reference vessel diameters were significantly larger in the Achieve arm (2.85 vs. 2.77 mm, p = 0.0016) than in the Penta arm. Mean lesion lengths were 11.7 mm and 11.1 mm, respectively, significantly longer in the Achieve than in the Penta arm.

**Methods:** Investigators treated up to two native vessels, one target and one nontarget, with only one de novo lesion per vessel. DELIVER patients at 67 sites received aspirin (325 mg and clopidogrel ≤300 mg, Plavix™, Bristol-Myers Squibb/Sanofi Synthelabo) ≤ 24 h before or immediately after the procedure. During the procedure they received heparin (therapeutic level per activated clotting time) and GPIIb/IIIa inhibitors at the discretion of the operator. They were administered in ~64% of both arms. Post procedure, patients received aspirin 325 mg/day for a minimum of 365 days and clopidogrel 75 mg/day for a minimum of 90 days. The primary endpoint was 270-day target vessel failure (TVF), defined as a composite of death, myocardial infarction (MI) (Q-wave or non-Q-wave MI [total CK > 3 × ULN, CK-MB > 0]), target vessel revascularization (TVR), or TLR (treatment of the same lesion).

**Results:** While acute gain was identical in both arms (1.91 ± 0.81 mm vs. 0.98). There was a significant decrease in in-stent intimal hyperplasia, but binary angiographic restenosis failed to achieve significance (16.7% Achieve, 22.4% Penta, p = 0.149). Target vessel failure, the primary endpoint, was not significantly lower in the Achieve arm (11.9 vs. 14.5%, p = 0.128). Vessel size < 2.5 mm, diabetes, and use of GPIIb/IIIa inhibitors predicted angiographic binary restenosis. Principal clinical events at up to 270 days were similar between groups.

**Conclusion:** The paclitaxel-coated Achieve stent is safe. Research on this device with a more optimal dose would be useful.

**EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival Trial)**

**Presenter:** Bertram Pitt, M.D., at the American College of Cardiology 52nd Annual Scientific Session, Chicago, Illinois, 2003.

**Background:** The treatment of choice for post-myocardial infarction (MI) patients with symptoms of heart failure includes angiotensin-converting enzyme inhibitors and beta blockers. Mortality and morbidity for this population, however, remains high. Aldosterone blockade has been shown to reduce mortality and morbidity in patients with systolic left ventricular dysfunction.

**Patient population:** EPHESUS included 6,200 post-MI (3–14 days) patients with symptoms of heart failure (left ventricular ejection fraction ≤40% and rales) receiving standard therapy.

**Study design:** Included patients were randomized to eplerenone (Inspra™, Pharmacia and Upjohn) 25 mg once daily (increased to 50 mg at 4 weeks if serum potassium was < 5.0 mEq/l) or placebo. The primary endpoint was all-cause mortality.

**Results:** Mean daily eplerenone dose was 43 mg. After ~31 months of follow-up, the primary endpoint was significantly (p = 0.008) reduced 15% with eplerenone, and a second primary endpoint of cardiovascular mortality plus cardiovascular hospitalizations was reduced significantly by 13% (p = 0.002). Further secondary endpoints of sudden cardiac death (reduced 21%, p = 0.03) and nonfatal heart failure hospitalizations (both total episodes and total patients) were significantly lowered with eplerenone. Benefits were relatively consistent across predefined subsets.

The agent was generally well tolerated. Serious hyperkalemia (potassium ≥6.0 mEq/l) occurred in 5.5% of eplerenone patients (3.9% for placebo), primarily in patients with baseline creatinine clearance below 50 ml/min. Hypokalemia was found significantly less often with eplerenone than with placebo.

**Conclusions:** EPHESUS results confirm the effectiveness of aldosterone blockade in patients with systolic left ventricular dysfunction.

**Comment (Bertram Pitt, M.D.):** “In contrast with spironolactone, there was no excess of gynecomastia or impotence, which attests to the selectivity of the compound.”

**FACT II (Folate After Coronary Intervention)**

**Presenter:** Helmut Lange, M.D., at the American College of Cardiology 52nd Annual Scientific Session, Chicago, Illinois, 2003.

**Background:** High homocysteine levels have been associated with more coronary events and higher coronary artery risks. These risks are thought to be mediated by homocysteine’s promotion of smooth muscle cell proliferation, collagen deposition, platelet activation, thrombus formation, lipid peroxidation, endothelial damage, and dysfunction. Whether vitamin cocktails with folate, B6, and B12, known to lower plasma homocysteine levels, correlate with incidence of restenosis after coronary angioplasty has been in debate because of conflicting data.

**Study design:** FACT II evaluated 636 patients who had undergone successful elective coronary stent implantation, randomizing them to an intravenous bolus postprocedure of folate 1 mg, B6 5 mg, B12 1 mg, followed by oral folate (1.2 mg), B6 (48 mg), and B12 (0.06 mg) daily, or placebo, for 6 months. The primary endpoint was minimum lumen diameter (MLD) at 6-month angiography.

**Results:** At 4 weeks, folate therapy brought about a 30% drop in homocysteine levels (homocysteine levels had been elevated in both groups at baseline). While acute gain was similar in both groups, at follow-up, patients receiving folate had greater late loss than did controls (0.90 vs. 0.76 mm, p = 0.001). Also, diameter restenosis was higher in the vitamin
group (34.5 vs. 26.5%, p = 0.047). At follow-up, MLD was 1.59 mm for the folate group and 1.74 mm for controls (p < 0.01). Also, the restenosis rate in folate-treated patients was significantly higher than in controls (35 vs. 27%, p < 0.05).

At 250 days, target vessel revascularization (TLR [same lesion treated], 15.8 vs. 10.6% controls) and total major adverse coronary events (MACE, 16.8 vs. 10.9%, p = 0.03) were also negatively influenced by folate administration. While there was a trend toward folate as univariate predictor of restenosis, it did not attain statistical significance.

Conclusion: Folate therapy should not be used to achieve lower homocysteine levels in the setting of percutaneous coronary intervention.

Comment (Helmut Lange, M.D.): “No conclusions can be drawn regarding the potential value of folate for the primary or secondary prevention of coronary artery disease events.”

SIRIUS (Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de novo Coronary Artery Lesions) Cost-Effectiveness


Background: Ongoing analysis of SIRIUS, a trial of the Cypher® (Cordis Corporation) sirolimus-eluting stent in a large (1,058 patients) heterogeneous population including many with high cardiac risk, is showing reductions in need for target vessel revascularization (TLR [same lesion treated]) and other key endpoints across subgroups.

Objective: SIRIUS examined the impact of reduced clinical restenosis on long-term costs of care in contemporary practice.

Methods: SIRIUS compared in-hospital and long-term costs of percutaneous coronary intervention with the sirolimus-eluting stent and conventional bare metal stents. Sirolimus-eluting stent (SES) cost was estimated at $3,000 per stent (versus $1,000 for control stents) in the intention-to-treat analysis. The primary endpoints were 1-year total medical care costs and disease-specific incremental cost-effectiveness ratio (cost per quality-of-life year gained is well below the $50,000 threshold established for interventions in the US health care system. Availability of longer stents and improved implantation techniques should further enhance the cost-effectiveness of the SES technology in the immediate future.

SPORTIF-III (Stroke Prevention Using the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Nonvalvular Atrial Fibrillation)


Background: While warfarin reduces stroke risk 60–70%, it entails bleeding risk and requires monitoring. As a result, only 55% of those eligible actually receive warfarin. Ximelagatran (Exanta™, AstraZeneca Pharmaceutical), a direct thrombin inhibitor, is an oral anticoagulant with potential advantages over warfarin for stroke prevention in patients with atrial fibrillation (AF). It has a wider therapeutic margin than warfarin, low potential for food and drug interactions, and needs neither dose adjustments nor monitoring.

Study design: SPORTIF III is a 23-nation open-label trial comparing adjusted-dose warfarin (INR 2–3) versus fixed-dose ximelagatran (36 mg b.i.d.) in 3,407 patients with nonvalvular AF and risk factors for stroke. The primary analysis is of prevention of all strokes and embolic events.

Results: After 12–26 months of exposure to the agents, 56 events (2.3%) occurred in the warfarin group and 40 events in the ximelagatran group, a significant 41% relative risk reduction (p = 0.018) for ximelagatran. Other adverse events (congestive heart failure, myocardial infarction, all-cause mortality), were similar for both agents. While major bleeding was similar in the two treatment groups (1.3% ximelagatran, 1.8% warfarin), combined minor and major bleeding was significantly lower for ximelagatran (25.5 vs. 29.5%, p = 0.007).

Increases in liver enzyme elevation were significant in the ximelagatran group (alamine aminotransferase >3× ULN), occurring in 6.5% of patients versus 0.7% for warfarin (p < 0.001). The transaminase increases typically occurred between 2 and 6 months into the treatment phase and returned to normal in all cases when medication was discontinued.

Conclusions: In high-risk patients with AF, ximelagatran proved as effective as well-controlled warfarin in preventing stroke and systemic embolic events, but caused less bleeding. It offered fixed oral dosing without coagulation monitoring.

Comment (Jonathan Halperin, M.D.): The frequency and duration of monitoring will become clear when results of SPORTIF V provide more information on the magnitude of the elevated liver enzyme problem.

TAXUS II (Paclitaxel-Eluting Stent 12-Month Follow-up)

**Background:** TAXUS II six-month intravascular ultrasound follow-up showed highly significant reductions in the primary endpoint of percent net volume obstruction at 7.85% for both slow-release (SR) and moderate-release (MR) formulations of the paclitaxel-eluting stent compared with 21.89% for bare metal stent controls. Three clinical endpoints significantly favored the paclitaxel-eluting stent at six months: major adverse cardiac events (MACE), target vessel revascularization (TVR), and TLR (treatment of the same lesion). Rate of MACE was 8.5% for SR and 7.8% for MR compared with 10.8% for combined controls. Also, TLR was 4.6% for SR, 3.1% for MR, and 13.3% for combined controls. Overall, TVR was 7.7 and 6.2% for SR and MR, respectively, and 16.0% for bare metal stent controls.

**Objective:** TAXUS II was designed to assess the safety and efficacy of Boston Scientific Corporation’s paclitaxel-eluting coronary stent implanted for reducing restenosis in de novo lesions up to 12 mm in length. The purpose of this analysis was to see whether results held up at 12 months after discontinuation of antiplatelet therapy with clopidogrel at 6 months.

**Study design:** The stent employed, a 15-mm polymer-coated NIRx™ Conformer Stent, delivers 1 µg/mm² of paclitaxel. Patients (n = 536) were randomized in two cohorts (four arms) to the SR group or bare metal stent controls, or the MR group or controls. Controls were combined in analyses.

**Results:** Analysis showed continuing significant benefits for the paclitaxel-eluting stent, with MACE at 10.9 and 9.9% for SR and MR, respectively, and at 21.7% for controls. The other benefits, mostly significant, were in TVR overall at 10.1% (NS) and 6.9 versus 17.5% for bare metal controls, and in TLR at 4.7 and 3.8% for SR and MR, respectively, compared with 14.4% for controls. No deaths were reported in patients receiving drug-eluting stents (two deaths occurred among controls).

**Conclusion:** The sustained beneficial effects on MACE-free survival at 12 months suggest that TAXUS stents prevent rather than delay in-stent restenosis.

**TWA in CHF (T-Wave Alternans in Congestive Heart Failure)**

**Presenter:** Daniel M. Bloomfield, M.D., at the American College of Cardiology 52nd Annual Scientific Session, Chicago, Illinois, 2003.

**Background:** Microvolt level T-wave alternans (TWA) is associated with development of ventricular arrhythmias, and its measurement during exercise is a potent predictor of arrhythmic events.

**Hypothesis and aims:** TWA will be associated with increased risk of arrhythmic events in patients with left ventricular dysfunction, independent of ischemic or nonischemic etiology.

This presentation offers preliminary all-cause mortality results, with an emphasis on patients with coronary artery disease and ejection fractions (EFs) ≤ 0.30.

**Patient population:** Included patients (n = 542) were ≥ 18 years old and in sinus rhythm with EF ≤ 0.40. Enrolled patients had mean EF of 25%; 71% were male. Thirty percent had diabetes, 43% documented prior myocardial infarction, 26% prior coronary artery bypass graft surgery and 59% had at least one prior hospital admission for heart failure. Most (52%) were in New York Heart Association functional class II.

**Methods:** Tests were deemed positive with sustained TWA ≥ 1.9 µV with an onset heart rate ≤ 110 beats/min, and negative with a maximum negative heart rate ≥ 105 beats/min. All others were considered indeterminate. Endpoints were arrhythmic events (arrhythmic death and nonfatal cardiac arrest) and all-cause mortality.

**Results:** Thirty percent of patients were TWA positive, 34% were negative, and 36% indeterminate. Mean follow-up was 12.2 months. There were 20 deaths, with 2-year survival at 93%. Two-year mortality among patients with negative TWA was extremely low (1%), compared with 11% in patients with positive TWA.

In 164 patients meeting MADIT (Multicenter Automatic Defibrillator Implantation Trial) II criteria, 2-year mortality was 15% for TWA-positive patients and 0% for TWA-negative patients.

**Conclusions:** TWA was a strong predictor of mortality in patients with left ventricular dysfunction, independent of EF and etiology. TWA identifies a high-risk group requiring therapy to prevent sudden cardiac death, and a low-risk group that can be managed conservatively.

**Comment (Daniel M. Bloomfield, M.D.):** The MADIT II analysis suggests that TWA-positive patients will obtain greater mortality benefit from an implantable cardiac defibrillator than would be observed in an unstratified MADIT II cohort.