The following studies were presented at this year’s annual American Heart Association Scientific Sessions, which took place in Anaheim, Calif, November 11 to 14, 2001.

**Lipids and Atherosclerosis**

**The Heart Protection Study**

*Presenter:* Rory Collins, MBBS, Oxford University, Oxford, UK

*The study:* A large-scale study of HMG-CoA reductase inhibitory therapy and antioxidant vitamin supplementation in patients with a history of occlusive vascular disease or diabetes. A total of 20,536 patients were recruited in 69 hospitals in the UK between July 1994 and May 1997; those for whom their physicians considered statin therapy to be clearly indicated were excluded from the study. Participants were assigned randomly to simvastatin (40 mg QD) or placebo and further randomized to antioxidant vitamins (600 mg vitamin E, 250 mg vitamin C, 20 mg β-carotene daily) or placebo. Follow-up was planned for an average of at least 5 years and actually continued for an average of 5 1/2 years. Approximately one sixth of the placebo-treated patients subsequently had statin therapy initiated; approximately one sixth of the simvastatin-treated patients discontinued statin therapy. End points included coronary heart disease (CHD) death or myocardial infarction (MI) (total CHD events), fatal and nonfatal stroke, total CHD events plus total stroke or any revascularization (major vascular events), nonvascular mortality, and cancer.

*The results:* Vitamin supplementation did not provide any beneficial or adverse effect on vascular or nonvascular morbidity or mortality. Simvastatin therapy significantly reduced vascular mortality (7.7% versus 9.2% with placebo, *P*<0.0002) and total mortality (12.9% versus 14.6% with placebo, *P*<0.001). Nonvascular mortality was not significantly affected (5.2% versus 5.5% with placebo). The incidence of stroke also was reduced significantly (4.4% versus 6.0% with placebo, *P*<0.00001), as were overall major vascular events (19.9% versus 25.4% with placebo, *P*<0.00001). In diabetic patients without prior coronary disease, the incidence of major vascular events was also significantly reduced (13.9% versus 18.7% with placebo, *P*<0.0001). The benefits of simvastatin were present in all major clinical subgroups, in men and women, and in all age subgroups. Furthermore, there was benefit regardless of baseline LDL or total cholesterol and benefit with further LDL lowering even in patients already at target LDL levels of <100 mg/dL. Simvastatin was well tolerated. Myopathy was reported in <0.1% of participants; liver function test abnormalities (>3× upper limits of normal) were reported in 0.8% of the simvastatin group and 0.6% of the placebo group.

*Summary:* In patients at increased risk for cardiovascular disease who might not otherwise be deemed to be candidates for HMG-CoA reductase inhibitor therapy, 40 mg per day of simvastatin was associated with substantial reductions in cardiovascular events. These benefits were present regardless of initial LDL (even <100 mg/dL) and total cholesterol level, in men and women of all ages, and in patients with diabetes without preexisting coronary heart disease.

**Clinical Trial of an Educational Intervention to Achieve Recommended Cholesterol Levels Among Patients With Coronary Artery Disease (REACH)**

*Presenter:* Harlan M. Krumholz, MD, Yale University, New Haven, Conn

*The study:* A randomized study evaluating the efficacy of an educational intervention in improving adherence to National Cholesterol Education Program (NCEP) guidelines. A total of 756 patients hospitalized with coronary artery disease were randomized to usual care (n=381) or a nurse-based education program (n=375) that included monthly mailings and quarterly phone contacts and presented information about their target cholesterol goals. The primary outcome was the percentage of patients who actually met the NCEP treatment guideline of an LDL cholesterol level ≤100 mg/dL.

*The results:* At baseline, only ~5% of patients knew the correct LDL target. Of the 575 patients for whom baseline LDL levels were available, 44% of the intervention group and 41% of the usual-care group had an LDL <100 mg/dL. At 1 year, there was no significant difference in the number of patients achieving target LDL levels (70% of the intervention group and 67% of the usual-care group). At follow-up, patient knowledge of the LDL target level was significantly higher in the intervention group (20% versus 7% in the usual-care group).

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*Circulation* is available at [http://www.circulationaha.org](http://www.circulationaha.org)
Summary: This aggressive educational program did not result in any greater proportion of patients achieving NCEP target goals. The degree of knowledge about the goals improved with education but remained disappointingly low.

Congestive Heart Failure
Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure (REMATCH)

Presenter: Eric A Rose, MD, Columbia University College of Physicians and Surgeons, New York, NY

The study: A nonblinded trial comparing the use of the HeartMate left ventricular assist device (LVAD) (Thoratec) with medical management in 129 patients (from 22 US centers) with end-stage class IV CHF who were not eligible for cardiac transplantation. To qualify, patients had to have an ejection fraction \( \leq 25\% \), cardiac index \( \leq 2.2 \text{L/m}^2 \), pulmonary capillary wedge pressure \( \geq 18 \text{mm Hg} \), and a peak oxygen consumption \( \leq 14 \). The primary end point was mortality.

The results: The trial was halted prematurely because of excess benefit in the LVAD group. Overall, mortality was reduced by 48% with the LVAD. Mortality in the LVAD group was 48% at 1 year and 77% at 2 years, compared with a mortality in the medical group of 75% at 1 year and 92% at 2 years. Assessment of quality-of-life parameters demonstrated significantly better physical function in the LVAD group. However, patients in the LVAD group were \( \geq 2\times \) as likely to have an adverse event, most frequently infection (28% within 3 months of implantation in the LVAD group). The most frequent cause of death in the medical group was heart failure (50 of 54 deaths), whereas in the LVAD group, the most common causes of death were sepsis (17 patients), LVAD failure (7 patients), and other miscellaneous noncardiovascular causes (5 patients).

Summary: LVADs can prolong life and enhance quality of life in patients with end-stage CHF who are not candidates for cardiac transplantation. This benefit comes at a cost of a higher incidence of device-related complications.

Acute Coronary Syndromes
Prevention of RESTenosis with Tranilast and its Outcomes (PRESTO)

Presenter: David Holmes, MD, Mayo Clinic, Rochester, Minn

The study: A large-scale study of tranilast (an oral medication with several effects that reduce cellular proliferation; currently used as an antikeloid drug in Japan) for the potential prevention of restenosis after coronary intervention. After successful percutaneous coronary intervention (PCI) of at least 1 vessel, a total of 11,500 patients were randomized to receive either placebo or 1 of 4 tranilast treatment regimens (300 mg BID for 1 month or 3 months, or 450 mg BID for 1 month or 3 months). Therapy was begun 4 to 8 hours after the procedure. The primary end point was a composite of death, MI, or ischemia-driven target vessel revascularization at 9 months.

The results: There was no benefit whatsoever in any of the tranilast treatment groups. There were no clinical subsets identified in which there was any differential benefit.

Summary: In a large, broadly distributed cohort of patients undergoing PCI, tranilast has no effect on adverse clinical events of death, MI, or ischemia-driven target vessel revascularization. Further detailed analysis of the extensive PRESTO database (including angiographic and intravascular ultrasound [IVUS] subsets) may provide insight into other aspects of modern-day coronary intervention.

Double-Blind Dose-Ranging Study of Fondaparinux (Pentasaccharide) in Unstable Angina (PENTUA)

Presenter: Maarten L. Simoons, MD, Thoraxcentrum, Rotterdam, the Netherlands

The study: A randomized, active control dose-ranging study of fondaparinux (pentasaccharide, a selective Factor Xa inhibitor) in patients with acute coronary syndromes. A total of 1147 unstable angina patients (from 66 hospitals in 5 European countries) were enrolled and randomized (n = 1134) to receive either enoxaparin (a low–molecular weight heparin; 1 mg/kg sq BID) or 1 of 4 doses of fondaparinux (2.5 mg, 4 mg, 8 mg, or 12 mg QD). The primary end point was the composite incidence of death, MI, and recurrent ischemia at day 9. Per-protocol analysis (n = 929) mandated collection of continuous ECG monitoring data over 48 hours. All patients received aspirin; only 3.4% received GP IIb/IIIa antagonists; 18.5% received a thienopyridine (usually in conjunction with coronary intervention). Patients were treated for a minimum of 3 to 8 days (mean, 5 days).

The results: Overall, there was no significant difference between composite events in the enoxaparin group (40.2%) and the 4 fondaparinux groups combined (37%). No dose-response was noted; the lowest-dose fondaparinux group (2.5 mg QD) did have significantly fewer composite events. Bleeding events did not differ significantly among groups but did trend lower in the low-dose fondaparinux group. Plasma concentrations of fondaparinux did increase with increasing doses, and best clinical outcomes were observed at the lowest drug levels.

Summary: In this cohort of patients with acute coronary syndromes, fondaparinux seemed to be as effective as enoxaparin, with similar bleeding risks. No dose-response of fondaparinux was observed for efficacy or bleeding; in fact, the lowest-dose group appeared to do the best.

Enhancing Recovery In Coronary Heart Disease patients (ENRICHD) Study

Presenters: Lisa F. Berkman, PhD, Boston, Mass; Allan Jaffe, MD, Rochester, Minn

The study: A randomized clinical trial to determine whether treating depression and low social support reduces mortality and recurrent MI after an initial MI. A total of 2481 patients who met criteria for either major or minor depression and/or low social support were recruited within 28 days of an index infarction and were randomized to usual medical care or to psychosocial intervention (consisting of a series of individual and group cognitive-behavioral therapy sessions with adjunc-
tive pharmacotherapy for depression, when indicated). Patients were followed for a mean of 2.5 years. The primary end point was the composite incidence of death or MI.

The results: Although there was significant improvement in indices of depression and social support, there was no significant difference in the composite of death or MI (24.2% with psychosocial intervention, 24.4% with usual care). There were no differences in outcomes for patients with depression only, low social support only, or both, or by major demographic subgroups.

Summary: In post-MI patients with depression and/or low social support, psychosocial intervention does not significantly affect mortality.

Interventional Cardiology

European evaLUation of paclitTaxel Eluting Stent (ELUTES)
Presenter: Anthony H. Gershlick, MD, Glenfield Hospital, University Hospitals, Leicester, UK

The study: A randomized, double-blind, controlled trial evaluating a paclitaxel-eluting coronary stent. Paclitaxel is a chemotherapeutic agent that stabilizes microtubules by shifting the dynamic equilibrium between soluble and insoluble tubulin, thus inhibiting cellular mitosis, proliferation, and migration, while cells remain viable. A total of 192 patients with de novo single lesions in a native coronary artery undergoing stenting were enrolled and randomized to either uncoated V-flex Plus stents, or 1 of 4 dose-treatment groups of paclitaxel-coated stents. Study end points included quantitative coronary angiography—measured percent diameter stenosis and late loss at 6 months and major adverse clinical events (MACE) at 1 and 6 months.

The results: The highest dose-density of paclitaxel (2.7 µg/mm² stent area) was found to be the most effective. Late loss at 6 months was 0.10 ± 0.22 mm versus 0.73 ± 0.12 mm with uncoated stents (P < 0.005); percent diameter stenosis at 6 months was 14.2 ± 4.1% versus 33.9 ± 4.1% with uncoated stents (P < 0.01). Binary restenosis was 3% versus 21% with uncoated stents. There were no significant differences in clinical events of death, MI, or stent thrombosis.

Summary: Paclitaxel-coated stents seem to be safe and effective in reducing restenosis. The highest dose-density of paclitaxel was most effective.

Canadian Antioxidant Restenosis Trial (CART) I
Presenter: Jean-Claude Tardif, MD, Montreal Heart Institute, Montreal, Canada

The study: A randomized, controlled trial of AGI 1067, a vascular protective drug with potent antioxidant properties and selective anti-inflammatory effects) in the prevention of restenosis after percutaneous intervention. A total of 305 patients undergoing PCI of one or more de novo lesions in native vessels were randomized to placebo, probucol (500 mg BID) or 1 of the 3 doses of AGI 1067 (70, 140, or 280 mg/d). Quantitative angiography and IVUS measurements were performed before and after intervention and at 6-month follow-up. Study drug therapy was initiated 2 weeks before intervention and continued for 1 month after intervention.

The results: At 6 months, IVUS-assessed lumen volume was significantly improved with probucol and higher-dose AGI1067 (control, 64.2 mm³; probucol, 80.2 mm³). In contrast to probucol, AG1067 was not associated with prolongation of the QTc.

Summary: In this preliminary study, AGI 1067 seemed to reduce the incidence of restenosis after percutaneous interventions without prolonging the QTc. Further confirming studies are needed.

Hypertension

The African-American Study of Kidney disease and hypertension (AASK)
Presenter: Janice G. Douglas, MD, Case Western Reserve University, Cleveland, Ohio

The study: A randomized, factorial design trial examining the progression of hypertensive renal disease in African Americans, comparing 3 antihypertensive regimens (initial therapy with ramipril, amlodipine, or metoprolol) and 2 levels of blood pressure control (usual mean arterial pressure [102 to 107 mm Hg; low mean arterial pressure ≤92 mm Hg]). A total of 1094 African-Americans with hypertensive renal disease (glomerular filtration rate [GFR] 20 to 65 mL/min) at 21 clinical centers were randomized and followed for 3 to 4 years. The primary end point was change in GFR.

The results: Preliminary results were presented. The presence of even small amounts of proteinuria at baseline was associated with rapid progression of kidney disease. There was no difference in progression of renal disease between the levels of blood pressure control (usual versus low); both compared favorably to previous reports of the natural history of progression of untreated disease. With respect to the 3 types of medication, differences did not achieve statistical significance in all patients. Ramipril, in comparison to metoprolol, reduced the rate of decline of GFR by 25% and the rate of composite clinical events by 22% in all patients. In patients with proteinuria (urine/plasma [creatinine] >0.22) ramipril and metoprolol, in comparison to amlodipine, reduced clinical event rates by 46% and 37%, respectively.

Summary: In African-Americans with hypertensive renal disease, more aggressive blood pressure lowering does not further slow the progression of renal disease, although blood pressure lowering does seem to substantially slow progression in comparison to historical reports on the natural history of the disease. Ramipril seems to slow progression more than metoprolol, independent of the degree of baseline proteinuria. In patients with proteinuria, both ramipril and metoprolol seem to slow progression in comparison to amlodipine.

Electrophysiology and Arrhythmias

Clinical Outcomes from the Prevention of Post-operative Arrhythmia (COPPA) II
Presenter: Peter R. Kowey, MD, Lankenau Hospital and Main Line Heart Center, Wynnewood, Pa

The study: A randomized, placebo-controlled trial of propafenone in the prevention of postoperative atrial fibrillation. A total of 293 patients were randomized after uneventful coronary artery bypass surgery (CABG) to placebo, lower-dose propafenone (150 mg q 8 hours), or higher-dose propafenone (225 mg q 8h). Patients received their first oral
between 80% and 90% of patients were receiving concomitant β-blockers. The primary end point was the incidence of atrial fibrillation lasting >5 minutes. Hospital length of stay was a secondary end point.

The results: The mean hospital length of stay was not significantly different between groups. The higher-dose propafenone group had a lower incidence of atrial fibrillation (12.4% versus 22.2% with lower-dose propafenone and 22.7% with placebo) and later onset of atrial fibrillation (time to onset, 4.8±2.6 days versus 3.4±1.0 days with lower-dose propafenone and 3.7±1.1 days with placebo). Overall adverse events were similar between groups, but cardiovascular adverse events were slightly more frequent with propafenone.

Summary: Propafenone (over and above β-blockers) does reduce the incidence of postoperative atrial fibrillation after CABG; however, it does not significantly reduce hospital length of stay.

Azimilide post-Infarct surviva1 Evaluation (ALIVE)

Presenter: A. John Camm, MD, St Georges Hospital, London, UK

The study: A double-blind, randomized, placebo-controlled study of azimilide (a Vaughn-Williams class III antiarrhythmic agent that prolongs the action potential) in patients with impaired left ventricular function after MI. A total of 3717 patients from 483 clinical centers in 26 countries were randomized to placebo (n=1690) or azimilide (100 mg, n=1691); 336 patients received a reduced dose (75 mg) of azimilide and were included only in the safety (not efficacy) analyses. Patients were stratified as either “at risk” (ejection fraction 15% to 35%) or “at high risk” (ejection fraction 15% to 35% and heart rate variability ≤20 U on 24-hour holter). The primary end point was all-cause mortality.

The results: The high-risk group (n=1268) had substantially higher mortality (15% versus 9.5%, P=0.0005). There was no significant effect of azimilide on mortality for either the total population (196 deaths with placebo versus 197 deaths with azimilide) or the high-risk group (96 deaths with placebo versus 88 deaths with azimilide). No subgroups were identified in which azimilide provided any mortality benefit. There was a higher incidence of neutropenia with azimilide (n=15) than with placebo (n=4); there were more instances of torsades de Pointes with azimilide (n=5) than with placebo (n=1). Fewer patients developed atrial fibrillation with azimilide (n=8) than with placebo (n=19).

Summary: Low heart rate variability does identify a population of patients at higher risk after MI. Azimilide has no beneficial or adverse effect on mortality.

Cardiovascular Surgery

PR0ject of Ex-vivo Vein graft Engineering via Transfection (PREVENT) II trial

Presenter: Eberhard Grube, MD, Heart Center Sieburg, Sieburg, Germany

The study: A randomized, placebo-controlled, double-blind study of E2F decoy therapy in patients undergoing CABG. E2F decoy (Corgentech Inc, Palo Alto, Calif) is an oligodeoxynucleotide (a short strand of DNA) that is transferred into cells in the wall of the vein graft and interferes with cell proliferation. A total of 200 CABG patients were randomized to either nondistending pressure-mediated transfection with E2F decoy (6 psi for 10 minutes) or placebo. Follow-up quantitative angiography and IVUS were performed at 12 months in 136 patients.

The results: At angiography, graft failure (percent diameter stenosis >75%) was present in 27% of E2F decoy patients and 39% of placebo patients (P=0.03). If grafts with initial intraoperative poor flow were excluded, graft failure was present in 18% of E2F decoy patients and 30% of placebo patients (P=0.03). IVUS-assessed intimal volume was 78.6±45.6 mm³ with E2F decoy, versus 114.8±78.3 mm³ with placebo (P=0.03). No adverse clinical sequelae of the gene therapy treatment were reported.

Summary: In patients undergoing CABG, E2F decoy therapy was safe and was associated with a reduction in vein graft failure and lower intimal volumes.

Stable Angina

Combination Assessment of Ranolazine In Stable Angina (CARISA)

Presenter: Bernard Chaitman, MD, St Louis Medical Center, St Louis, Mo

The study: A double-blind, randomized, placebo-controlled trial of ranolazine (a PFOX inhibitor that inhibits fatty acid oxidation and favors glucose metabolism, resulting in lower lactic acid production and less intracellular acidosis). A total of 823 patients from 15 countries, who had stable angina and limited exercise tolerance, underwent baseline exercise testing and were randomized to ranolazine 750 mg BID (n=279), ranolazine 1000 mg BID (n=275), or placebo (n=269); 791 completed an exercise test (at peak and trough drug levels) at 2 weeks, and 743 completed exercise testing at 12 weeks. Patients were stratified by background anti-anginal therapy. The primary end point was exercise duration at trough drug levels.

The results: Exercise times at both trough and peak drug levels increased significantly in both ranolazine groups; this benefit was similar across the different background anti-anginal therapies. The time to angina onset also was increased at both peak and trough drug levels in the ranolazine groups; the exercise time to 1-mm ST-segment elevation was prolonged at peak drug levels in the ranolazine group. Ranolazine treatment was also associated with a decrease in the number of angina episodes at home. There were no differences between groups in the incidence of serious adverse events.

Summary: Ranolazine, a new class of anti-anginal therapy that modifies fatty acid oxidation, is associated with significant improvement in exercise capacity, in the time to onset of exercise-related anginal symptoms, and in the time to ECG-documented ischemia in response to exercise.

Impact Of Nicorandil in Angina (IONA)

Presenter: Henry Dargie, University of Glasgow, Glasgow, Scotland

The study: A randomized, placebo-controlled study evaluating the effect of nicorandil (a K-channel opener that acts
as an arterial and venous vasodilator and has been shown to be cardioprotective and enhances ischemic preconditioning) when added to existing therapy in patients with stable angina. A total of 5126 patients with previous MI or CABG or coronary artery disease with high-risk features were recruited in the UK; in order to qualify, patients had to not be actively considered for revascularization. Patients were randomized to placebo (n=2561) or nicorandil (10 mg BID, increased to 20 mg BID after 2 weeks; n=2565) and followed for up to 3 years; mean follow-up was 1.6 years. The primary end point of the study was the composite incidence of CHD death, nonfatal MI, and unplanned hospitalization for chest pain. A secondary end point was the composite of CHD death and nonfatal MI.

**The results:** Primary outcome events were significantly lower with nicorandil (13.1% versus 15.5% with placebo, heart rate 0.83, \( P=0.014 \)). The curves separated rapidly. The composite of death/MI was slightly, but not significantly, lower with nicorandil (4.2% versus 5.2% with placebo, heart rate 0.79, \( P=0.068 \)). Mortality also tended to be slightly lower with nicorandil (4.3% versus 5.0% with placebo, heart rate 0.87, \( P=0.27 \)). Total cardiovascular events were slightly reduced with nicorandil (14.7% versus 17.0% with placebo, hazard ratio 0.85, \( P=0.025 \)).

**Summary:** In the first large-scale trial assessing clinical outcome in primary effect angina, nicorandil significantly reduced major cardiovascular events, when added to existing therapy.
Meeting Highlights: American Heart Association Scientific Sessions 2001
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