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Progress in Clinical Trials

ARBITER 2 (ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol)

Presenter: Allen J. Taylor, M.D., at the American Heart Association 2004 Scientific Sessions, New Orleans, Louisiana.

Background: Niacin, the most effective available agent to increase levels of high-density lipoprotein cholesterol (HDL-C), reduces coronary heart disease (CHD) outcomes as a monotherapy or in combination with statins or a bile acid sequestrant. No trial, however, has previously demonstrated the superiority for a clinical endpoint of therapy with a statin + niacin over statin therapy alone.

The Cholesterol Lowering Atherosclerosis Study (CLAS) (Hodis: *Ann Intern Med* 1998;128(4):262–269) showed that the rate of common carotid intimal media thickness (IMT) progression was directly associated with higher risk for future myocardial infarction (MI) and CHD death.

Objective: ARBITER 2 compared the effect of prescription, extended-release niacin (ERN) (Niaspan®) 1000 mg/day with placebo for the endpoint of the change in carotid IMT.

Study population: Patients (n = 167, mean age 67.5, 76% male) with known CHD receiving statin therapy with good control of low-density lipoprotein cholesterol (LDL-C) (LDL-C < 130 mg/dl and HDL-C < 45 mg/dl)were included. In the placebo group, 53% had history of MI and 34% had angina; for the ER-niacin group the respective rates were 47 and 30%.

Study design: Patients were randomized double-blind to placebo or ERN 500 mg q.h.s. × 1 month and then 1 g q.h.s. × 11 months. Intimal media thickness was assessed by B-mode ultrasound. The primary endpoint was change in mean common carotid IMT within treatment groups after 12 months.

Results: Mean statin dose (93% simvastatin) was ~35 mg. Baseline IMT was 0.868 mm in the placebo group and 0.893 mm in the ERN group (NS). Progression at 12 months was significant in the placebo group (0.44 ± .011 mm, $p < 0.001$) and nonsignificant for the ERN group (.014 ± .011, $p = .23$). Carotid IMT progression was 68% lower in the ERN group ($p = 0.08$).

An exploratory analysis of progression in patients with or without diabetes mellitus or metabolic syndrome revealed that in the latter group, found significantly lower progression in the ER niacin group than in the placebo group ($p = .026$).

Study withdrawals were identical (n = 9) in each group with fewer due to adverse effects in the niacin group (6 vs. 2). Cutaneous flushing was more common (13% placebo; 69% ERN, $p < 0.001$) in the ERN group, however.

Conclusions: Placebo-treated patients with a mean HDL-C of 40 mg/dl receiving only statin monotherapy showed significant progression of carotid IMT despite LDL-C of 86 mg/dl. Combination therapy with statin + ERN (1000 mg/day) slowed carotid IMT, showing an incremental benefit of adding ERN to existing statin therapy.

CARP (The Coronary Artery Revascularization Prophylaxis) Trial

Presenter: Edward McFalls, M.D., Ph.D., at the American Heart Association 2004 Scientific Sessions, New Orleans, Louisiana.

Background: According to American College of Cardiology/American Heart Association guidelines, indications for coronary angiography prior to vascular surgery include patients at "high risk" (acute coronary syndromes) and patients at "intermediate risk" with multiple clinical risk variables or high-risk cardiac stress imaging tests. There has been, however, no large-scale randomized study testing the benefit of such coronary artery revascularization prior to elective vascular surgery.

Hypothesis: Among stable patients with coronary artery disease amenable to either coronary artery bypass graft aurgery (CABG) or percutaneous coronary intervention (PCI), coronary artery revascularization prior to elective vascular surgery improves long-term survival.

Methodology: This 4-year multicenter, randomized controlled trial among 18 Veterans Affairs Medical Centers enrolled 680 patients undergoing aortic and infrainguinal vascular operations. They were randomized to revascularization (PCI or CABG) or no revascularization prior to vascular surgery. The primary endpoint was long-term survival.

Results: Among 258 patients assigned to revascularization, 141 underwent PCI, 99 underwent CABG, and 18 were not revascularized (9 refused, 8 had urgent surgery, 1 stroke). Median time to surgery was 18 days in the nonrevascularization group and 54 days in the revascularization group. Mortality among the 240 patients revascularized was 1.7%, with no stroke, loss of limb or renal dialysis. At a median time of 2.7 years following randomization, mortality was 22% in the revascularization group and 23% in the no revascularization group ($p = 0.92$). Death, MI, and 3-month left ventricular ejection fraction (LVEF) were similar between groups. Survival at 5+ years ($p = 0.92$) and causes of death were similar in both groups, as well.

Conclusions: Among patients with stable cardiac symptoms, coronary artery revascularization with either CABG or PCI prior to a major elective vascular operation can be performed safely. However, the revascularization procedure delays or, in some cases, prevents the vascular operation and does not improve either long-term survival or short-term outcome.

Comment (Edward McFalls, M.D.): This gives us more confidence in our medical therapies long term (beta blockers, statins, antiplatelet agents), whether or not you revascularize.

CREATE-ECLA (Clinical trial of metabolic modulation in ami tREATment Evaluation-Estudos Cardiológicos LatinoAmérica—Riviparin)

Presenter: Salim Yusuf, M.D., at the American Heart Association 2004 Scientific Sessions, New Orleans, Louisiana.

Background: Despite the use of reperfusion therapy, aspirin, beta blockers and angiotensin-converting enzyme (ACE) inhibitors, 30-day mortality following acute MI is in excess of 10%.

Trials of antithrombotics and GPIIb/IIIa inhibitors have failed to demonstrate a reduction in mortality and have a high rate of strokes and bleeding complications. With >75% of the global burden of acute MI occurring in low- and middle-income countries, there is a need for effective, relatively safe and simple, low-cost antithrombotic therapy that does not require monitoring.

Study design: A total of 15,570 patients with ST-segment elevation or new bundle-branch block presenting within 12 h of symptom onset were randomized to placebo or the low-molecular weight heparin reviparin (weight-adjusted, q. 12 h subcutaneous injections) for 7 days in addition to usual therapy. The primary outcome measure was combined death, reinfarction, or stroke at 7 days. The co-primary endpoint was death, reinfarction, or recurrent ischemia at 7 days.

Study population: Mean age of enroless was 59 years (77% male). Median time from symptom onset was 4.9 h for reviparin and 4.8 h for placebo, with ~61% being treated < 6 h in both groups. Similar percentages of patients were receiving thrombolytics (~73%), aspirin (~97%), thienopyridines (~55%), beta blockers (~66%), ACE inhibitors (~72.5%) and lipid-lowering agents (~67%).

Results: The primary endpoint was reported in 745 of 7,780 patients (9.6%) in the reviparin group and in 854 of 7,790 (11.0%, hazard ratio [HR] 0.87, p = 0.0048) in the placebo group. The co-primary endpoint was reported in 864 (11%) of the reviparin group and in 982 (12.6%, HR 0.87, p = 0.0039) in the placebo group. Significant differences were found for the components of death, and MI, with a strong trend (p = 0.057) for any ischemia. At 30 days, both endpoints remained similarly in favor of reviparin.

Benefits were significantly greater in patients treated < 2 h from symptom onset (30% relative risk reduction).

Major or life-threatening bleeding at 7 days was significantly higher with reviparin (71/7,780, 0.9% vs. 28/7,790, 0.4%, p < 0.001).

Conclusions: Reviparin significantly reduces mortality and reinfarction in acute MI without increasing the overall risk of strokes. There is a small increase in major and life-threatening bleeding.

Comment (Salim Yusuf, M.D.): Treating 1,000 individuals for 7 days prevents 17 deaths, MI, or strokes at a cost of 1 additional life-threatening bleed and 2 major bleeds. The benefits clearly outweigh the risks, especially in those treated within 8 h of symptom onset. Reviparin is relatively affordable even in low- and middle-income countries.

ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness)

Presenter: Lynne Stevenson, M.D., at the American Heart Association 2004 Scientific Sessions, New Orleans, Louisiana.

Background: While nonrandomized studies in critically ill patients have suggested that pulmonary artery catheter (PAC) increases morbidity and mortality, nonrandomized studies in heart failure have suggested that PAC improves symptoms and quality of life, and decreases hospitalizations.

Primary hypothesis: For patients with severe heart failure, therapy guided by PAC monitoring and clinical assessments will lead to fewer days dead or hospitalized over a 6-month period than therapy guided by clinical assessment alone.

Study population: ESCAPE included 433 patients with decompensated heart failure (mean age 56 years, 74% male, ~50% Caucasian)—that is, one sign or symptom of congestion with dyspnea, gastrointestinal symptoms, jugular venous pressure > 10 cm, hepatomegaly, edema, or rales, and history of advanced heart failure despite standard therapy (aggressive outpatient therapy for at least a month or hospitalization or urgent visit in preceding 6 months with intravenous treatment for heart failure).

Other criteria included LVEF < 30%, systolic blood pressure (SBP) ≤ 125 mmHg, symptoms of heart failure for ≥ 3 months with angiotensin-converting enzyme inhibitors and diuretics for ≥ 3 months, and cardiac transplant unlikely within ≤ 6 months.

Methods: Patients were randomized 1:1 to a clinical assessment-guided arm (CLIN) or to a PAC and clinical assessment-guided arm. The primary endpoint was number of days patients are not dead or hospitalized over 6 months.

Results: About 50% of patients had an etiology of ischemic heart failure. Mean EF was ~20% with mean SBP of 106 mmHg.

For the primary endpoint, median days dead or hospitalized was 13 in both groups (average 38 for PAC+CLIN, 36 for CLIN). Patients averaged 2.1 rehospitalizations in both groups and a median of 11 days in hospital (both groups, average 17 for PAC+CLIN and 16 for CLIN). The initial hospitalization was ~8 day in both groups.

There were trends toward greater functional improvement in treatment guided by PAC. While there were no PAC-related deaths, in-hospital PAC-related complications occurred in 4.2% of PAC group patients, with a higher adverse event rate for the PAC group (22% vs. 11%). Time from randomization to discharge and total time of initial hospitalization was similar for both groups.

Conclusions: There was no benefit or adverse impact of PAC on the primary endpoint and no adverse impact of PAC on hospital outcome.

Comment (Mariell Jessup, M.D.): A pulmonary artery catheter may give us information that will help us leave behind optimal medical therapy and to go into future therapies (e.g., transplant, assist devices, passive restraint, cellular therapies).

SCD-HeFT (Cost-Effectiveness of Implantable Cardioverter Defibrillator [ICD] Therapy in the Sudden Cardiac Death in Heart Failure Trial)

Presenter: Daniel B. Marks, M.D., M.P.H., at the American Heart Association 2004 Scientific Sessions, New Orleans, Louisiana.

Objective: Using data collected in SCD-HeFT (median follow-up 46 months), the objective of this trial to evaluate the costs of amiodarone and implantable cardioverter defibrillator (ICD) therapy and cost effectiveness of ICD for primary prevention of sudden cardiac death (SCD).

Study design: Patients at 148 sites were randomized to state-of-the-art medical therapy plus amiodarone (200–400 mg/day), single-chamber ICD (Medtronic 7223) shock only, or placebo, with follow-up of 48 months. The primary endpoint was all-cause mortality. Secondary endpoints were cost and cost-effectiveness.

Amiodarone cost analysis was based on $3.52/day for a 200-mg dose. Single chamber ICD + lead cost was $17,500.

Study population: The trial included 2,521 patients with stable congestive heart failure (CHF) (New York Heart Association [NYHA] class II or III, ejection fraction [EF] ≤ 35%) (mean age 60 years, 23% female). At baseline, mean CHF duration was 25 months, with 52% of ischemic etiology. Seventy percent of patients were in NYHA class II heart failure, and mean left ventricular EF was 25%.

Results: The hazard ratio for mortality with ICD therapy versus placebo was 0.77 ($p = 0.007$); for amiodarone versus placebo it was 1.06 ($p = 0.523$), slightly favoring placebo. Five-year costs, by intention-to-treat, for the amiodarone, ICD, and placebo arms were $49,444, $61,967, and 43,077 respectively.

Life expectancy with the ICD was 10.87 years compared with 8.41 years for placebo, giving a total of 2.455 life-years saved. Analysis reveals a cost per year of life added for ICD therapy versus placebo of $36,886.

Conclusions: Amiodarone is no more effective than placebo, but more expensive. Therapy with an ICD is both more effective and more expensive, but represents an economically attractive way to increase societal health benefits.

Comment (William Weintraub, M.D.): The analysis shows an amount less than the common willingness-to-pay threshold for society of $50,000. However, there are about a million patients potentially eligible. Even when a therapy is highly cost effective, we can still spend more money than is available to us.

SHIELD (SHock Inhibition Evaluation with azimiLiDe)

Presenter: Paul Dorian, M.D., at the American Heart Association 2004 Scientific Sessions, New Orleans, Louisiana.

Background: Implantable cardioverter defibrillators (ICDs) are superior to antiarrhythmic drug therapy in reducing mortality in patients at risk for ventricular tachycardia/ventricular fibrillation (VT/VF). However, many patients need other treatment to prevent symptomatic arrhythmias and to reduce the number of device therapies. Azimilide is an investigational antiarrhythmic drug that blocks potassium channels (I_{Kr} and I_{Ks}) and prolongs ventricular refractory periods.

Hypothesis: Azimilide will reduce the number of arrhythmia episodes in selected patients with ICDs.

Study design: Patients (n = 624, 10% female, mean age 63 years) were randomized double-blind to placebo, azimilide 75 mg, or azimilide 125 mg per day (208 patients per arm). Programming of the ICD was specified by protocol, adapted to the index arrhythmia cycle length. Duration of treatment was 1 year. The primary endpoint was all-cause shocks plus symptomatic VT or all-cause shocks.

Study population: Patients with newly implanted ICDs (implanted after spontaneous sustained VT or cardiac arrest/VF) or existing ICDs (experiencing an ICD shock triggered by spontaneous VT or VF) from 121 centers in 9 countries (North America and Europe) were enrolled. About 84% had existing ICDs. Mean ejection fraction was 35%, and ~64% had history of myocardial infarction.

Results: Analysis revealed a total of 8,986 events (6,125 asymptomatic) with triggering of 1,565 shocks. Azimilide reduced the total number of all-cause shocks plus the number of times antitachycardia pacing was used to steady symptomatic VT. Relative risk reductions were 57% ($p = 0.00055$) with the 75 mg dose and 47% ($p = 0.0053$) with the 125 mg dose. Shock reductions trended in favor of the 75-mg dose versus placebo ($p = 0.13$).

Five patients in the test group and one in the placebo group developed torsade de pointes. Overall, adverse events were similar between groups with similar withdrawals (40% placebo, 36% azimilide 75 mg, 35% azimilide 125 mg). Emergency room visits (with and without hospitalization) significantly favored azimilide 75 mg versus placebo.

Conclusions: Azimilide reduces the symptomatic arrhythmia burden from VT and shocks in patients with ICDs. There is a significant, possibly dose-dependent reduction in all VT/VF episodes.

Comment (Arthur J. Moss, M.D.): This is a highly significant and positive trial and provides some proof of the principle that antiarrhythmic agents (which, except for beta-blockers, are pro-arrhythmic for the most part) may, in fact, have a place in ICD-treated patients—because the ICD can correct the pro-arrhythmic effects of the drug.