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INSIDE

Late-Breaking Clinical Trials

From the November 7-10, 2004, American Heart Association Scientific Sessions

ABSTRACT & COMMENTARY

ARGUABLY THE MOST IMPORTANT NEW TRIAL TO BE REPORTED in New Orleans was the African-American Heart Failure Trial (A-HeFT); the use of a combination of isosorbide dinitrate (ISDN) and hydralazine in African-Americans with congestive heart failure (HF). This trial demonstrated a robust decrease in mortality of 43% with active treatment vs placebo ($P = 0.01$). In addition, the combo pill reduced first hospitalizations for HF by 33% ($P = 0.001$). Quality of life was improved more in the active treatment group than placebo (P = 0.02). The study medications consisted of 75 mg of hydralazine and 40 mg of ISDN 3 times daily. The genesis of the A-HeFT trial was an analysis of V-HeFT I published in 1986 (*N Engl J Med.* 1986;314:1597), which indicated that ISDN-hydralazine had a beneficial effect on mortality when compared to placebo and prazosin in HF patients. In a subsequent retrospective analysis, it was observed that African-Americans had a major improvement in survival when compared to placebo, but this was not found in the Caucasian population (*J Card Fail.* 1999;5:178).

A-HeFT was based on the hypothesis that African-Americans demonstrate differences in prevalence and causation of HF that may be related to decreased activation of the rennin angiotensin aldosterone system (RAAS); in addition there have been suggestions of lower bioavailability of nitric oxide in blacks than whites. A-HEFT randomized 1040 African-American HF subjects to the drug combination or placebo. The trial was stopped by the data safety monitoring board because of a "significantly higher mortality rate in the placebo group." At the time of trial discontinuation, 10.2% of the placebo patients and 6.2% of drug therapy individuals had died, with a hazard ratio of 0.57, $P = 0.01$. The mean duration of follow-up was only 10 months, with survival differences emerging at 6 months, and widening progressively. A composite score of multiple end points, including death, hospitalization, and quality of life, was favorable for the drug combination. Virtually all patients were NYHA class III, although placebo morality at 1 year was approximately 10%, perhaps lower than expected. The use of concomitant drugs with

VOLUME 23 • NUMBER 12 • DECEMBER 2004 • PAGES 89-96

proven benefit in HF was excellent, 70% were on ACEI, 17% on ARB, 74% on beta blockers, 60% on digoxin, and 40% were on spironolactone.

COMMENT BY JONATHAN ABRAMS, MD

This remarkable result garnered national attention, as well as criticism of an emphasis that highlights ethnic differences in pathophysiology and therapy. A-HeFT was based on a V-HeFT I analysis favoring better results with ISDN-hydralazine in blacks with HF, and data suggesting that blacks have decreased activity of the RAAS, as well as race specific differences in endothelial function that suggest nitric oxide deficiency. The latter is but a hypothesis, yet fits well into the unique targeted therapy proposed by Dr. Jay Cohn. It has been known for some years that hydralazine is a natural antioxidant. It also has been documented that nitrate administration can induce oxidative stress, resulting in conversion of the nitric oxide donor (in this case ISDN) to peroxynitrate, a free radical. Thus, vasoconstriction and nitrate tolerance are potential sequelae with sustained nitrate administration. The hypothesis in A-HeFT, although not stated in the primary paper, is that hydralazine would act as free radical scavenger, thus enabling the nitric oxide donor ISDN to have a more potent and longer lasting effectiveness.

It has been well established that nitrates are beneficial in advanced congestive heart failure, as assessed by hemodynamic monitoring. Left ventricular filling pressure and both pulmonary artery and right atrial pressures decrease, typically with no change or even a small increase in cardiac input. These changes are due to the venous capacitance affects of nitrates, which are more potent venodilators than any other agent. The problem of nitrate tolerance has made these drugs unattractive to many physicians. Nevertheless, even without hydralazine, adjunctive therapy with nitrates is effective in class III-IV congestive HF. Intravenous nitroglycerin or nitroprusside are standard bailout agents for sick HF individuals. The pill used in this study is branded as BiDil, fabricated by NitroMed. An interesting Perspective article accompanying the A-HeFT manuscript discusses "race therapeutics" and the process of development to obtain FDA approval for race specific strategies. This commentary raises a number of issues regarding the use of race as a differentiating feature in selecting therapies (Bloche MG, N Engl J Med. 2004;351:2035). However, an overview of hypertension therapy in blacks confirms racial differences in response to anti-hypertensive drugs (*Ann Int Med*. 2004;141:614-627).

Reference

1. Taylor AL, et al. *N Engl J Med*. 2004;351:2049.

ARBITER 2

A Double-Blind, Placebo-Controlled Study of Long-Acting Niacin on Atherosclerosis Progression in Secondary Prevention Patients Treated with Statins (ARBITER-2) assessed the potency of HDL elevation with long acting niacin preparations in patients with CAD on a statin. Taylor and colleagues used carotid intimal-medial thickness (CMT) as an indicator of atherosclerosis in subjects with stable coronary artery disease on a statin with good lipid control, but an HDL-C < 45 mg/dL. This randomized, double-blind trial lasted for 3 years; 149 patients completed the protocol at 1 year, which consisted of baseline statin therapy plus 1000 mg sustained release niacin vs placebo. The primary end point was the change in carotid intimal-medial thickness (CMT) of the common carotid artery. The cohort was mostly male, mean age 74, 60% hypertensive, and 50% with metabolic syndrome. All had documented CAD. The baseline CMT was 0.88 mm, comparable to other studies of individuals with vascular disease. Statin therapy was not regulated; 80% of patients were on beta-blockers, 60% on ACEI, 85% on aspirin, and 20% on antioxidants.

Results: Lipid profile demonstrated an increase in

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Clinical Cardiology Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.
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United States
1 year *with* Free AMA Category 1 credits: $319
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HDL of approximately 20% and a decrease in triglycerides with niacin, and no change in C-reactive protein. The primary end point of CMT demonstrated progression in the placebo cohort, compared to virtually no change in the niacin patients (68% slowing of progression). The CMT increase at 1 year with niacin was 0.01 mm (NS) and 0.04 mm with placebo ($P = 0.001$). Thus, the progression rate with niacin-statin was nil. Patients on placebo demonstrated an increase in CMT, and there was a trend towards more clinical end points in the placebo treated patients. Adherence was good, with only minimal hyperglycemia. Taylor et al concluded that niacin was effective and safe and slowed progression of carotid disease in subjects with CAD and low HDL on a statin (available as e-publication in *Circulation*, publish date Dec 7, 2004).

REACT

The rescue angioplasty vs conservative therapy, or repeat thrombolysis (REACT) trial for failed reperfusion in acute myocardial infarction, was presented by Dr. Anthony Gershlick. He explained that rescue angioplasty is an accepted practice, but there is not much data to support it. Consequently, this study was undertaken to establish its benefit. The entry criterion was an ECG 90 minutes following thombolytic therapy that showed less than 50% ST segment decrease. The patients were randomized to conservative treatment vs percutaneous coronary intervention (PCI), or repeat trombolysis. Exclusion criteria included severe heart failure and shock. The primary end point was death, myocardial infarction, stroke, or severe heart failure. The study end point was powered for 150 patients per group, but it was stopped early due to poor recruitment over 4 years. The safety end point was major and minor bleeding. The 3 groups were well matched. Of interest, 14% were diabetics, 50% were smokers, 60% received streptokinase, and 70% received stents. Average onset of symptoms to thrombolytic therapy was 4 hours, with a door to needle time averaging 27 minutes.

The results at 6 months showed that the primary end point was achieved in 31% of those treated conservatively, 30% of those treated with repeat thrombolysis, and 15% of those treated with PCI. The difference between the 3rd group and the other two was $P < .001$. All components of the composite primary end point were equally decreased by PCI. The hazard ratio comparing PCI to repeat thrombolysis was .45 in favor of PCI, and the hazard ratio for conservative therapy was .47 favoring PCI. Subgroup analysis did not affect the outcome. The secondary outcome of freedom from revascularization at 6 months was 80% in the conservative group, 77% in the repeat thrombolysis group, and 87% in the PCI group. Major bleeding was increased by PCI, but most were sheath complications, and there were no deaths. Minor bleeding was not significantly affected. Gershlick and colleagues concluded that rescue PCI is beneficial compared to conservative therapy or repeat thrombolytic therapy.

COMMENT BY MICHAEL H. CRAWFORD, MD

Other studies have shown no benefit of PCI, but there were major differences between the studies. In some, PCI was done later than in REACT, and there was less use of platelet 2b/3a agents and stents. Also, previous studies only compared PCI to conservative therapy, or were underpowered for major end points. Thus, the REACT study is more close to what is done today. Although it was difficult to recruit into this study, and it took 4 years to accomplish, they did show a benefit for primary angioplasty between 30 days and 6 months. This is important because 40% of thrombolysis patients demonstrate suboptimal or no return of blood flow. The REACT trial is not definitive, but it supports current clinical practice of rescue angioplasty rather than conservative therapy or repeat thrombolysis, whenever feasible.

Cardiac Support Device

Dr. Douglas Mann presented the initial results of a multi-centered randomized clinical trial for the assessment of a cardiac support device (CSD) in patients with dilated cardiomyopathy and heart failure. The device is called CORCAP®, and consists of a mesh that is surgically wrapped around the heart and results in decreased left ventricular volume and improved function in animal models. The hypothesis tested was that the CSD would decrease remodeling and increase outcomes in dilated cardiomyopathy patients. Entry criteria included an ejection fraction of < 35%, a left ventricular end diastolic dimension > 60 mm, a 6-minute walk < 450 m, and clinically stable. The primary end point was clinical, functional class and death. Secondary end points included left ventricular size, function, quality of life, and re-hospitalization for heart failure. Three hundred patients, 90% of whom had nonischemic dilated cardiomyopathy, were randomized to CSD or medical therapy. Those undergoing CSD could also have mitral valve surgery, if indicated.

Results: More patients improved their clinical functional class than worsened, with an odds ratio of 1.73 ($P = .02$) in favor of CSD. There was no affect on survival. Secondary end points showed a reduction in left

ventricular end diastolic volume by CSD (P = .01), which continued for 12 months. There were also significant, favorable changes in end systolic volume and the sphericity index (P = .026), however, ejection fraction was unchanged. Quality of life was improved (P = .05). Rehospitalization for heart failure was not significantly different. There was no evidence of cardiac constriction. Those who did not receive mitral valve surgery did not differ in their overall results. Mann and colleagues concluded that patients with progressive heart failure due primarily to dilated cardiomyopathy, on optimal medical therapy, improved with the cardiac support device, demonstrating an increase in functional state, a favorable effect on left ventricular mechanics and an improvement in quality of life.

COMMENTS BY MICHAEL H. CRAWFORD, MD

These results follow from the experience with wrapping the heart with the latissimus dorsai muscle, where improvements in clinical function were seen without any change in ejection fraction. Since the latissimus dorsae wrap seemed to constrain dilation more that it improved the contractile effort of the heart, it makes sense to use some less traumatic device to constrain dilation of the heart than the patient's thoracic musculature. What is confusing about this study is that two-thirds of the patients had mitral valve surgery. What affect this had on the results is not clear, although the absence of mitral valve surgery did not seem to result in less benefit from the cardiac support device. However, this does not establish that the cardiac support device alone is superior to mitral valve surgery alone. Constraining the heart may also be less traumatic and more effective than the Batista operation, and accomplish the same objective of improving the mechanics of the left ventricle. At this time, it is unclear whether the CSD would be a primary surgical therapy for dilated cardiomyopathy, or whether it would be an adjunctive treatment when mitral valve surgery is done. In addition, it doesn't seem that it would be feasible for patients with ischemic cardiomyopathy, who also needed coronary bypass surgery. Clearly, this is an evolving area.

PEACE

This double-blind, placebo-controlled, multicentered study Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) was presented by Dr. Marc Pfeffer (published in *N Engl J Med*. November, 2004). The hypothesis tested was that angiotensin converting enzyme inhibitors (ACEI) plus modern therapy would reduce cardiovascular mortality, myocardial infarction, and revascularization in stable coronary artery disease patients with normal or near normal left ventricular ejection fraction at low risk for cardiovascular events. Prior to randomization, patients were treated with the ACEI trandolapril during a run in period to be sure that they were tolerant of the drug. Exclusion criteria also included a creatinine > 2.0 mg/dL, and a potassium > 5.5 mmol/liter. A total of 8290 patients were randomized, 4158 to trandolapril, 4132 to placebo. The baseline characteristics of the 2 groups of patients were equivalent. The maximum target dose of trandolapril was 4 mg a day, and the patients were followed-up for 4.8 years. Greater than half of the patients were post myocardial infarction patients, and about three-quarters had had a previous revascularization. Mean ejection was 58 ± 9%, 60% were on beta-blockers, 70% on lipid lowering drugs, and almost all were on aspirin. Adherence to ACEI therapy at 1 year was 80% and 75% at 3 years. The major reason for discontinuation was cough.

Results: The ACEI resulted in modest, but significant systolic and diastolic blood pressure decreases. The primary end point of death, myocardial infarction, or revascularization was unchanged. No component of this composite end point was changed. The death rate in both groups was 4%. No subgroup did any better than the overall results. The secondary end point of heart failure hospitalizations was decreased by ACE inhibitors (P = .05). Also, newly diagnosed diabetes was decreased on ACE inhibitor (P = .02). Pfeffer and colleagues concluded that in patients with stable coronary artery disease and preserved left ventricular function, there was no benefit of ACEI above standard therapy.

COMMENT BY MICHAEL H. CRAWFORD, MD

These results differ from those in HOPE and EUROPA, which showed significant reductions in cardiovascular events in patients with vascular disease, diabetes (HOPE), or stable coronary artery disease (EUROPA). However, there were significant differences in the patient populations of these studies. Patients in PEACE, vs those in HOPE and EUROPA, had lower blood pressure, more lipid therapy, more prior revascularization, and less diabetes. PEACE patients showed a lower event rate in the placebo group than either HOPE or EUROPA in the ACEI treatment groups. Thus, PEACE was a very low-risk group for cardiovascular events. An alternative explanation would be that trandolapril is just less potent than ramapril (HOPE) or perindopril (EUROPA). Thus, the clinician needs to tailor the therapy to the individual characteristics of the patient, and use drugs of proven value, rather than formulaically applying the results of these mega trials.

ESCAPE

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) was presented by Dr. Monica Shah. The hypothesis tested was that pulmonary artery catheter use improves outcome, versus clinical assessment in patients with severe heart failure. The primary end point was the number of days that the patient was not dead or in the hospital at 6 months. The secondary end points included brain natriuretic peptide levels, mitral regurgitation, quality of life, maximum oxygen consumption, and 6-minute walk test. The study was stopped early, with only 433 patients enrolled because there was no difference in the primary end point, and no subgroup benefited from pulmonary artery catheterization. Also, there were no significant differences in this secondary end points. Although there were more complications in the pulmonary artery catheter group, there were generally few complications, and no pulmonary artery catheter complication resulted in patient death. There was an 18% crossover rate from the clinical assessment group into the pulmonary artery catheter group. Length of stay was not different. Although not significant, there was a trend for a better 6-minute walk test and quality of life in the pulmonary catheter group. Shah and colleagues concluded that there was no benefit in the routine use of pulmonary artery catheters in patients with severe heart failure. There were more adverse events with pulmonary artery catheters, but no deaths attributable to its use. There was a trend towards functional improvement with pulmonary artery catheter use. Thus, patients could be managed by either method successfully.

COMMENT BY MICHAEL H. CRAWFORD, MD

Although there was no benefit from the routine use of pulmonary artery catheters, it did not seem to worsen outcomes, and may actually improve patients' symptoms subsequently. Thus, in selected patients where its use is believed to be advantageous by the physicians, there is certainly no prohibition against pulmonary catheter use, based on this study. There are several explanations for these results. One would be that the knowledge of hemodynamics does not improve outcomes, because doctors are very good at using drugs in such patients and do not need this information. However, it is interesting that there was less diuretic use in the pulmonary catheter arm and more ACE inhibitor use in this arm. This could be viewed as a positive result of hemodynamic knowledge, and may have explained the trend towards long-term clinical benefit. What is disturbing is that overall mortality was still 19% at 6 months, suggesting that the current drugs we're using for severe heart failure are not highly efficacious. Perhaps newer drug treatments will require more knowledge of hemodynamics, but this remains to be seen. One limitation to this study is that the serial use of noninvasive tests, such as echocardiography, were not tested, but may provide equally as good results or better. So at this point, what are the indications for pulmonary artery catheter use in patients with severe heart failure? 1) to diagnose the etiology of pulmonary edema if noninvasive tests are not helpful; 2) management of cardiogenic shock, which was not studied in this trial; 3) to guide treatment in selected patients; 4) to confirm the diagnosis of cardiac tamponade; 5) to assess patients for possible cardiac transplantation; and 6) the treatment of patients with severe pulmonary hypertension. Clearly, routine use in severe heart failure patients is not indicated, based on this study and others.

RIO North American Trial

This is the Phase 3 study of rimonabant, which involves 6600 patients in 4 trials in the Rimonabant In Obesity (RIO) program. The results of the North American part of the study was presented by Dr. Xavier Pi-Sunyer. This is a randomized, double-blind, placebo-controlled trial of rimonabant in 5 mg or 20 mg doses involving US and Canadian centers, which randomized 3486 patients. The study protocol consisted of a 6-week screening period, a 4-week run in phase with dietary restrictions, and then randomization to either 5 mg or 20 mg of placebo or rimonabant. After 52 weeks, there was cross over in the 2 rimonabant groups, but not in the placebo group. Study entry criteria included a BMI > 30, or > 27 with one co-morbidity, and compliance with the diet. Patients with diabetes were excluded. The primary end point was weight change at 1 year and at 2 years. Secondary end points were the number of patients who lost > 5% of their weight, 10% of their weight, change in waist circumference, and changes in parameters of the metabolic syndrome. Patient characteristics showed most were Caucasian females; average age was 45 years, mean body mass index 38, and mean waist circumference 42 inches.

Results: With 20 mg of rimonabant, the mean weight loss at 1 year was 8.7 lbs, with 5 mg of rimonabant 5.4 lbs, and with placebo plus diet 2.8 lbs. The difference between placebo and the 2 rimonabant arms was highly significant, $P = .001$. Waist circumference also significantly decreased compared to placebo; 8.2 vs 4.7 vs 3.9 inches ($P = .001$). HDL cholesterol increased significantly 16.1 vs 9.3 vs 7.2 mg/dL ($P = .001$). Tryglicerides were also significantly reduced, as was the diagnosis of

metabolic syndrome using ATP 3 criteria, which declined from 34.8% to 21.1% at 1 year in the 20 mg of rimonabant group. When the affect of weight loss on the parameters of the metabolic syndrome was considered, vs the affect of the drug, it was concluded that half the effect was attributed to drug use alone. The drop out rate on rimonabant was not different than placebo, and averaged between 45 to 49% at 1 year. Adverse events occurred in 7.2% of the placebo patients, 9.4% of the rimonabant 5 mg, and 12.8% of the rimonabant 20 mg. This was not significantly different. There were 4 deaths in the study, and they were evenly distributed between the 3 arms. The major adverse effects of rimonabant were depression, anxiety, and nausea.

The re-randomization at 1 year, with follow-up to the end of year 2, showed that the rimonbant patients that were switched to placebo gained weight back to their original values, and the patients who were continued on rimonabant showed a maintenance of weight loss at 2 years. Sixty-two percent of the rimonabant patients lost > 5% of their weight vs 33% of the placebo patients. Thirty-three percent of the rimonabant patients lost > 10% of their weight vs 16% of the placebo group. Waist circumference data paralleled that of the weight loss data, and the gains in metabolic syndrome were also maintained for 2 years. Adverse events at the end of 2 years were 6.7% for placebo, 8.3% for 5 mg of rimonabant, and 6.0% for 20 mg of rimonabant. These were not significantly different. Pi-Sunyer and colleagues concluded that rimonabant resulted in significant weight losses, improvement in the metabolic syndrome beyond that due to weight loss, and that these beneficial effects persisted for 2 years with a good safety profile.

COMMENT BY MICHAEL H. CRAWFORD, MD

This interesting study of a cannabanoid receptor-blocker is a follow-up to the results of the 1-year data that were presented at a previous meeting, and are very encouraging. What is remarkable for cardiologists is that you only need a 5 to 10% weight decrease to improve metabolic syndrome with rimonabant. Thus, the metabolic effects are more than one would expect, given the weight reduction achieved. These results seem better than the currently approved medications for weight loss, such as appetite suppressants and fat-absorption blockers. Thus, blocking the endocannabanoid system, either by rimonabant or other drugs that come along, seems to be a promising approach. The major issue will be long-term safety, and whether or not this drug will achieve FDA-approval.

SCD-HeFT

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) included 2521 patients with New York Heart Association class II or greater heart failure and a left ventricular ejection fraction of less than or equal to 30%. Preliminary data reported earlier this year showed a 93% reduction in all cause mortality with ICD therapy, compared to either medical therapy or placebo. There was no difference in survival between amiodarone and placebo. In this report, the investigators describe the cost effectiv ness of ICD therapy in SCD-HeFT. Costs after 5 years were calculated using medical billing information and hospital resource utilization data expressed as costs not charges. The Medicare fee schedule for outpatient and physician cost data was used to create an empirical cost data base that included generator replacements in the ICD group, as well as the cost of late ICD complications. Cost-effectiveness of ICD therapy was calculated as the incremental life expectancy divided by incremental lifetime cost.

The 5 year cumulative cost was $49,443 for amiodarone, $43,078 for placebo, and $61,968 for ICD therapy. The cost of ICD therapy was estimated as $33,192 per life year, added with this robust benefit, demonstrated over a range of sensitivity analyses. Subgroup analyses were also reported. Cost-effectiveness data were similar for patients with ejection fractions between 30% and 35%, and those below 30%; in those with ischemic vs nonischemic heart failure etiology; and in those with wide and narrow QRS durations. There did seem to be an increase cost in those older than age 65 ($39,469) vs the cost in those younger than age 65 ($29,164). However, all of these values were below the standard of $50,000 per life year saved, often used as a measure of economic attractiveness for medical interventions.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Expansion of the indications for ICD therapy to all patients with heart failure and systolic dysfunction will have a significant impact on society's medical costs. The data presented here by the SCD-HeFT investigators indicate that the incremental cost per life year saved will be less than the $50,000 per year benchmark often used for these analyses. Physicians will still, however, have to evaluate each patient individually, since some patients with advanced heart failure or numerous, severe co-morbidities will still remain poor candidates for ICD treatment.

SEEDS

The Syncope Evaluation in the Emergency Department (SEEDS) study was reported by Dr. Win K. Shen of the Mayo Clinic. Syncope accounts for over 1 million hospital admissions each year in the United States, and medical expenses associated with syncope evaluations are enormous. In this trial, 103 patients were randomly assigned to either a specialized syncope evaluation protocol in the emergency room before hospital admission or standard care. Those with neurological conditions that were obvious at the time of the evaluation were excluded by the study design. In the syncope unit, patients were continuously monitored for up to 6 hours. In addition, 2 tests not normally performed in the emergency room—a tilt table test and carotid sinus massage—were performed in the emergency room. An electrophysiologist was available to help interpret results.

Results: In the patients in the syncope unit, a presumptive diagnosis was achieved in 67% of the cases, in contrast to only 10% of the patients in the standard care group ($P = 0.01$). As a result, only 22 of the 51 syncope unit patients, versus 51 of 52 of the standard care group patients, were admitted to the hospital. There was no difference between the groups in terms of recurrent syncope or total mortality.

Shen and colleagues argue that since many cases of syncope are due to either neurally mediated hypotension or bradycardia, that addition of the tilt table study in the emergency room greatly aids in reaching a diagnosis.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Syncope is one of the most frustrating presenting symptoms for both patients and physicians. By definition, syncope is a transient event, and the patient is typically free of symptoms by the time he presents for evaluation. In many patients, diagnostic tests that have a low yield are ordered, with little hope of defining the cause of the syncopal episode. In this study Shen et al tried to keep patients out of the hospital. Unless patients are at high risk for a ventricular arrhythmia, most episodes of syncope of unknown cause are thought to be due to hypotension with or without associated bradycardia. Adding a tilt-table evaluation and carotid massage to the emergency room protocol for syncope patient helps identify patients with these conditions. In most cases, however, the judgment can be made with reasonable accuracy after just a careful history, physical exam, and simple tests. Whether or not tilt table tests are indicated in all patients, or should only be used selectively, remains to be determined.

SHIELD

Azimilide is a new antiarrhythmic drug that is currently being evaluated for the treatment of both supraventricular arrhythmias (primarily atrial fibrillation) and ventricular arrhythmias. The Shock Inhibition Evaluation With Azimilide (SHIELD) trial was designed to test whether therapy with azimilide decreased the frequency of arrhythmias requiring therapy in ICD patients. The study involved was a double-blind, randomized, placebo-controlled trial that looked at the effects of azimilide 75 mg and 125 mg daily. Patients were eligible for the trial if they had a spontaneous clinical arrhythmia episode, with documented ventricular tachycardia or ventricular fibrillation during the 6 weeks proceeding a new ICD implant. Patients with previously implanted ICDs were also eligible, if they had experienced a recent ICD shock. The study included 633 patients randomized to either placebo (n = 214), azimilide 75 mg daily (n = 220), or azimilide 125 mg daily (n = 199). The major end point of the trial was arrhythmic events terminated by either shock therapy or antitachycardia pacing (ATP). It was interesting that similar proportions of patients in the 3 groups, placebo 58%, azimilide 75 mg 52%, and azimilide 125 mg 50% experienced at least 1 episode of VT that was terminated by antitachycardia pacing, but the total number of events was reduced by both doses of azimilide. When all-cause shocks were analyzed, the percentage of patients who experienced 1 event was similar in the 3 groups; placebo 53%, azimilide 75 mg 48%, azimilide 125 mg 46%, but again, the total number of events was decreased. This latter reduction in events, however, does not achieve statistical significance with hazard ratios of 0.72 in the azimilide 75 mg group ($P = 0.13$) and 0.83 in the azimilide 125 mg group (0.36). Adverse events were uncommon. There were 5 patients in the azimilide group and 1 patient in the placebo group who developed torsades de pointes. The incidence of patient withdrawal due to adverse effects was similar across all 3 patient groups. One patient had severe neutropenia on azimilide 75 mg that was reversible after drug discontinuation.

COMMENT BY JOHN P. DiMARCO, MD, PhD

It has previously been shown that therapy with sotalol, dofetilide, and amiodarone decreased the frequency of shocks in ICD recipients. In patients who develop recurrent episodes of arrhythmia on beta blockers, any of these drugs might be added. Since azimilide has a relatively benign toxicity profile, it may become a drug of choice. One limitation of this study, however, was that the mean ejection fraction in the group was 34%. Since most ICD recipients have ejection fractions below 30%, one should extrapolate these results to other patients with caution.

CME Questions

23. African Americans with heart failure may do better when ____ is added to standard therapy?
a. bosentan
b. atrial natriuretic peptide
c. hydralazine/nitrate
d. endothelin antagonists

24. Patients with failed thrombolysis for acute MI should receive:
a. repeat thrombolysis.
b. angioplasty.
c. bivalirudin.
d. diltiazem/nitrate.

25. Which of the following shows promise for the treatment of heart failure due to dilated cardiomyopathy?
a. Cardiac support device (constraining mesh)
b. Batista operation
c. Latissimus dorsai wrap
d. All of the above

26. Trandolapril therapy in chronic stable CAD patients decreased:
a. myocardial infarction,
b. mortality.
c. revascularization.
d. hospitalizations for heart failure.

27. A new study of the use of pulmonary artery catheters in severe heart failure showed:
a. increased catheter related deaths.
b. reduced length of stay.
c. increased complications.
d. All of the above.

28. A new cannabanoid receptor blocker rimonabant given for 2 years showed:
a. sustained weight loss.
b. decreased waist circumference.
c. less metabolic syndrome parameters.
d. All of the above.

29. The cost per life year saved of ICD therapy for cardiomyopathy patients is:
a. $10,000.
b. $30,000.
c. $60,000.
d. $100,000.

30. Emergency Department syncope units:
a. improve diagnostic yield 6-7 fold.
b. decrease hospital admissions.
c. reduce mortality.
d. A and B.

31. A promising new drug to reduce VT induced shocks in ICD patients is:
a. azimilide.
b. amiodarone.
c. sotalol.
d. dofetilide.

Answers: 23. (c); 24. (b); 25. (a); 26. (d); 27. (c); 28. (d); 29. (b); 30. (d); 31. (a)

United States Postal Service
Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Clinical Cardiology Alert	0 7 4 1 - 4 2 1 8	10/1/04
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305

Contact Person: Robin Salet
Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*
Brenda Mooney, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*
Leslie Hamlin, same as above

Managing Editor *(Name and Complete Mailing Address)*
Glen Harris, same as above

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PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: Clinical Cardiology Alert
14. Issue Date for Circulation Data Below: September 2004

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1530	1267
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	995	940
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	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	43	40
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c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			1078	1028
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	47	13
	(2)	In-County as Stated on Form 3541	2	2
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			26	25
f. Total Free Distribution *(Sum of 15d and 15e)*			75	40
g. Total Distribution *(Sum of 15c and 15f)*			1153	1068
h. Copies Not Distributed			378	199
i. Total *(Sum of 15g, and h.*			1530	1267
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			94	96

16. Publication of Statement of Ownership
Publication required. Will be printed in the December 2004 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 9/27/04

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