AMERICAN HEALTH CONSULTANTS® A Medical Economics Company

Providing the Highest Quality Clinical Information for 19 Years

CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

New vs. Old Drugs for Hypertension

ABSTRACT & COMMENTARY

Synopsis: *New and old antihypertensive agents were similarly effective in preventing cardiovascular events and death in elderly patients.*

Source: Hansson L, et al. *Lancet* 1999;354:1751-1756.

Concern has been raised about the efficacy of newer antihypertensive agents for the prevention of cardiovascular morbidity and mortality in elderly patients. Thus, the results of the Swedish Trial in Older Patients with Hypertension-2 (STOP-HTN-2) study are of interest. From 312 centers in Sweden, 6614 elderly patients with hypertension (HTN) were randomized to conventional drugs (diuretics, beta blockers) or angiotensin-converting enzyme inhibitors (ACE1) or calcium antagonists. All the patients were older than 70 years of age (average 76) and two-thirds were women. Criteria for HTN were systolic blood pressure greater than 180 or diastolic greater than 105 mmHg or both. End points included stroke, myocardial infarction (MI), and cardiovascular death on an intention-to-treat basis. Blood pressure lowering was similar for the three groups, with an average 35/17 mmHg difference. Compliance at the last visit (24 months) was about 60% for all three groups and 46% were receiving more than one drug. Total adverse events were similar on the three treatments, with about one-quarter of patients experiencing at least one event. The most common side effect of conventional treatment was dyspnea (12%); ACE1 was cough (30%) and calcium antagonist was edema (26%). Cardiovascular death rates were similar in the three groups, as was the combined end point of stroke, MI, or cardiac death. However, fatal or nonfatal MIs were significantly less on ACE1 as compared to the calcium blocker group, as was congestive heart failure. Also, the results in diabetics were similar in the three groups. Hansson and colleagues conclude that new and old antihypertensive agents were similarly effective in preventing cardiovascular events and death in elderly patients.

COMMENT BY MICHAEL H. CRAWFORD, MD

After concerns were raised about the safety of calcium antago-

INSIDE

nists, this trial is reassuring that mortality was not higher in the calcium blocker group. That ACE1 would prevent heart failure more than calcium blockers is not surprising, given the action of the two drug classes. That ACE1 prevented MI more than calcium blockers is somewhat of a surprise, but consistent with the recently released HOPE study results. Interestingly, ACE1 did not perform better in diabetics despite theoretic advantages in such patients. Thus, ACE1 seems to hold a slight edge over calcium blockers, but only in the prevention of MI, not total mortality.

There has also been concern about the relative lack of efficacy of conventional therapy vs. newer agents in the prevention of cardiovascular events (both being effective for stroke prevention). However, this study shows equivalent efficacy. One reason for this may be that STOP-HTN-2 included patients with isolated systolic and diastolic HTN; newer drugs may be more effective for the former and conventional drugs for the latter, and cardiovascular events are more closely related to systolic HTN. Thus, on balance, the new and old drugs are equivalent, but a breakdown of the data along the lines indicated above would have been of interest. Also, combinations of drugs from the different classes were permitted to achieve blood pressure control, further complicating the analysis of drug classes and emphasizing the dominant role of adequate blood pressure control. The major message of this study is that blood pressure control is more important for preventing cardiovascular events in the elderly than how it is achieved. ❖

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

VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.
EXECUTIVE EDITOR: Glen Harris.
ASSOCIATE MANAGING EDITOR: Robin Mason.
COPY EDITORS: Michelle Moran, Neill Larmore, Holland Johnson.
MARKETING PRODUCT MANAGER: Schandale Kornegay.

GST Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.

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

Back issues: $35. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcpub.com
Editorial E-Mail: michelle.moran@medec.com

Subscription Prices

United States
$209 per year (Student/Resident rate: $105).
Multiple Copies
1-9 additional copies: $188 each. 10 or more copies: $167 each.
Canada
Add GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 20 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials. **For CME credit, add $50.**

Questions & Comments

Please call **Robin Mason,** Associate Managing Editor, at (404) 262-5517, or **Michelle Moran**, Copy Editor, at (404) 262-5589 or e-mail at michelle.moran@medec.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

American Health Consultants does not receive material commercial support for any of its continuing medical education publications. In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Abrams serves on the speaker's bureau for Merck, Novartis, and SmithKline Beecham.

The Best Approach to Women with Chest Pain

ABSTRACT & COMMENTARY

Synopsis: *In women with stable chest pain consistent with angina pectoris, stress myocardial perfusion imaging followed by coronary angiography in selected patients is more cost effective in the near term than a cardiac catheterization first strategy.*

Source: Shaw LJ, et al. *J Nucl Cardiol* 1999;6:559-569.

Because of perceived diagnostic inaccuracies with various forms of stress testing for coronary artery disease (CAD) in women, there has been interest in the direct coronary angiography approach. However, this approach has high initial costs. Thus, Shaw and colleagues undertook a multicentered study of 4638 women being evaluated for stable chest pain consistent with angina pectoris. Of these women, 1263 were referred for noninvasive testing first and 3375 for coronary angiography first. Noninvasive testing was exercise or dipyridamole stress SPECT myocardial perfusion imaging. The baseline clinical characteristics, including pretest likelihood of CAD, were not statistically different between the two approaches despite the absence of randomization. The incidence of at least one vessel with greater than 70% diameter stenosis in the angiography first group was 13% of low likelihood patients, 29% of intermediate, and 52% of high likelihood of CAD patients. The incidence of at least one myocardial perfusion defect in the stress test first group was 23% in low-likelihood patients, 27% in intermediate, and 34% in high-likelihood patients. When those with a positive perfusion underwent catheterization, 50%, 55%, and 76%, respectively, had significant coronary lesions. Follow-up for an average of 2.5 years (minimum 6 months from testing) showed death rates from 0.5% to 2.2%, depending on pretest risk, and did not differ between the two approaches. The estimated direct costs per patient for diagnostic testing and follow-up medical care over 2.5 years ranged from $2490 (low likelihood) to $3687 (high likelihood) in the angiography first group and from $1587 to $2585 for the stress testing first group ($P < 0.01$). Thus, Shaw et al conclude that in women with stable chest pain consistent with angina pectoris, stress myocardial perfusion imaging followed by coronary

angiography in selected patients is more cost effective in the near term than a cardiac catheterization first strategy, regardless of pretest likelihood of disease.

COMMENT BY MICHAEL H. CRAWFORD, MD

This observational study suggests that the cost of a noninvasive approach is 30% less than an invasive approach to evaluating women with stable chest pain syndromes consistent with angina, regardless of the clinically estimated likelihood of disease, and that there was no difference in outcome over an average of 2.5 years with either approach. The reasons for this difference include the fact that the invasive approach yielded two times the number of normal coronary angiogram patients as compared to the stress testing first group and the invasive group was more likely to undergo revascularization. Shaw et al argue that this study is strong evidence to pursue stress testing first in women with stable chest pain syndromes.

There are several limitations to this study. The most obvious limitation is the lack of randomization to the two testing strategies. As expected, almost two-thirds of the women were referred for catheterization first, based on current perceptions about the adequacy of noninvasive stress testing in women. Initial clinical characteristics between the two groups showed more high-risk patients and fewer intermediate and low-risk patients in the catheterization first group, although these differences were not statistically significant. One could argue that since outcomes (death and MI) were almost identical between the two groups, they must have been well matched. But remember that more of the catheterization first patients underwent revascularization, which may have improved their outcome. Also, patients with known or almost certain coronary disease were included, as evidenced by fixed perfusion defects in about one-quarter of the patients. Including such patients is known to improve the results of perfusion imaging for predicting who has significant coronary lesions.

The study provides information of interest regarding the perception that stress testing is not particularly accurate in women. Shaw et al acknowledge this perception, but claim that technological advances such as the use of sestimibi in 80% of their patients have largely eliminated this problem. Other technical issues such as prone imaging (avoids breast attenuation) are not discussed. However, the results of stress perfusion imaging in this study are sobering. Of those with a positive study referred for angiography, 33% had normal coronary arteries. A one-third false-positive rate is not reassuring and when stratified for pretest likelihood of disease, specificity ranged from 50-76%. It does not appear that technological improvements in the tertiary care centers participating in this study have improved the false-positive problem in women.

The major difference in the costs are the initial diagnostic testing costs in all risk groups and the higher cost of follow-up care in the high-risk patients undergoing catheterization because of the higher use of revascularization in these patients. However, these are direct costs only. We don't know about indirect costs such as time lost from work, etc. Also, there was no analysis of quality of life with the two strategies. It is conceivable that quality-adjusted life-years would be better with an invasive approach. In addition, this was a costly, noninvasive approach with nuclear imaging performed in all patients, including low-risk ones. The AHCPR guidelines would not even stress most such patients and many physicians employ ECG stress tests in low-risk women with normal resting ECGs. It is hard to fault the latter strategy since the false-positive rate with ECG couldn't be much worse than the 50% incidence observed with perfusion imaging in low-risk women in this study. Thus, I remain to be convinced that stress nuclear perfusion imaging for all women with anginal syndromes is the best approach. I'm still going with physician judgment in each individual. ❖

Cyclical Breathing in Heart Failure Patients

ABSTRACT & COMMENTARY

Synopsis: *Cyclical breathing in CHF patients is associated with autonomic dysfunction and a poor prognosis, and modulation of peripheral chemosensitivity may have beneficial effects.*

Source: Ponikowski P, et al. *Circulation* 1999;100: 2418-2424.

Ventilatory rate acceleration and deceleration with apnea or Cheyne-Stokes respiration (CSR) are common during sleep in congestive heart failure (CHF) patients, and ventilatory oscillation without apnea or periodic breathing (PB) can be seen in awake patients. However, the clinical significance of cyclical breathing (CSR or PB) in CHF patients is not fully understood. Thus, Ponikowski and colleagues studied 74 stable CHF patients in sinus rhythm by observing breathing patterns, analyzing heart rate variability and baroreflex sensitivity, and assessing the response to peripheral chemoreceptor suppression. Cyclical respiration was exhibited by 66% of the patients

with approximately equal numbers displaying CSR and PB. Cyclical breathing was associated with more advanced CHF symptoms, impaired autonomic balance, and increased peripheral chemosensitivity. Also, cyclical breathing was associated with nonsustained ventricular tachycardia on ambulatory ECG monitoring (more than 50% of cyclical patients vs 10% of normal breathing patients; $P < 0.01$). In addition, mortality was higher over an average 524 days follow-up on cyclical compared to normal breathers (37% vs 12%) and cyclical breathing was independent of peak oxygen (O_2) consumption and NYHA class. Finally, hyperoxia abolished cyclical breathing in seven of eight patients tested and dyhydrocodeine reduced peripheral chemosensitivity, abolishing PB in four patients and converting CSR to PB in two. Ponikowski et al conclude that cyclical breathing in CHF patients is associated with autonomic dysfunction and a poor prognosis, and that modulation of peripheral chemosensitivity may have beneficial effects in CHF patients.

COMMENT BY MICHAEL H. CRAWFORD, MD

Cheyne-Stokes respiration (CSR) is well described in CHF patients and has been related to the severity of hemodynamic abnormalities in other studies. In fact, an inverse relationship between cardiac output and the total cycle length of a CSR cycle has been proposed. Also, the poor prognosis of CSR and its relationship to ventricular tachyarrhythmias has been reported. CSR is usually observed during sleep. This study shows that the more common awake breathing abnormality is periodic breathing without apnea (PB). Also, this study shows that CSR and PB are a continuum and have the same implications and should be considered one entity—cyclical breathing. Although there are no hemodynamic measurements in this study, cyclical breathing was related to NYHA class, ventricular tachycardia, and reduced survival, supporting their hypothesis that CSR and PB are different manifestations of the same phenomenon.

The above concepts suggest that cyclical breathing is a consequence of CHF and poor cardiac output, which would delay transmission of signals related to O_2 and CO_2 levels to the brain because of reduced circulation time. However, Ponikowski et al hypothesize that enhanced peripheral sensitivity to O_2 and CO_2 may be the dominant mechanism and demonstrate that two therapies (oxygen and dihydroxodeine) that reduce chemosensitivity improve cyclic breathing. If cyclical breathing is the real culprit leading to periods of hypoxia, increased sympathetic drive, ventricular arrhythmias, and sudden death (as in sleep apnea), then therapies to reduce it could decrease mortality in CHF. This is a novel concept that their study supports, but it also raises further questions. What is the best therapy for cyclical breathing? Is specific therapy better than just intensifying standard CHF care? Is reduced cyclical breathing associated with reduced arrhythmias and death? Further experimentation along these lines seems justified and is in concert with the current approach to treating CHF; blocking every adverse neurohormonal effect with a designer drug. Until gene therapy for CHF emerges, improving the modulation of peripheral chemosensitivity may be a worthy goal for the pharmaceutical industry. ❖

Higher Energy External Cardioversion for Refractory Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *A limited number of high-energy shocks can cardiovert many patients resistant to standard approaches with a low risk of complications. This is an alternative to intra-atrial cardioversion.*

Source: Saliba W, et al. *J Am Coll Cardiol* 1999;34: 2031-2034.

Saliba and colleagues report a new technique for cardioversion of patients resistant to transthoracic cardioversion using standard approaches of up to 360 joules (J). Saliba et al linked two external defibrillators together so they could be synchronized to the patient's electrocardiogram. Patches from each defibrillator were then placed in adjoining anteroposterior positions on the patient's chest. Once it was seen that the defibrillators were synchronizing to the same portion of the electrocardiographic wave (QRS) complex, a single operator depressed the energy delivery button, simultaneously delivering a 720-J shock.

Over a three-year period, 55 patients at Saliba et al's institution underwent a 720-J cardioversion attempt. The group included patients both with and without structural heart disease, but 85% were male. Only 12 of the patients had continuously been in atrial fibrillation for more than one year. All patients were anticoagulated with either warfarin (INR > 2) or heparin. Forty-eight (87%) patients were taking antiarrhythmic medications at the time of cardioversion. The antiarrhythmic medications included: amiodarone (41%), sotalol (20%), flecainide (20%), procainamide (4%), and disopyramide (2%).

Sinus rhythm was achieved in 46 of the 55 patients

(84%). However, atrial fibrillation recurred in 28 of these patients, with 27 of the recurrences noted within 90 days.

There were no acute hemodynamic complications associated with the procedure. One patient developed transient post-shock bradycardia. Another patient developed right bundle branch block and later that night had an episode of torsades de pointe.

Saliba et al conclude that a limited number of high-energy shocks can cardiovert many patients resistant to standard approaches with a low risk of complications. They offer this as an alternative to intra-atrial cardioversion, a procedure that requires placement of intracardiac electrodes and may be hazardous in an anticoagulated patient.

COMMENT BY JOHN P. DiMARCO, MD, PhD

About 15% of patients undergoing elective transthoracic cardioversion of atrial fibrillation are not restored to sinus rhythm using a protocol with energy levels between 200-360 J. This paper describes an approach that may be effective without the necessity for an invasive procedure.

The major reason why high-energy shocks have not been advocated is the potential risk of myocardial damage and arrhythmias associated with these shocks. In animal models, repeated high-energy shocks produce myocardial dysfunction and cellular damage. In humans, shocks well above the defibrillation threshold may cause excess bradycardia. However, failure to cardiovert atrial fibrillation is usually due to a high transthoracic impedance that prevents an adequate current from reaching the heart. This high impedance may be due to patient size, anatomical features, or electrode characteristics. Therefore, use of higher energy after an initial failure with standard settings is less likely to have severe consequences. If large surface area electrodes are carefully applied, skin irritation should also be minimized.

Other alternatives for converting atrial fibrillation in resistant patients are also available. Sotalol and ibutilide may lower the atrial defibrillation threshold. Oral and colleagues recently reported a 100% success rate if patients were pretreated with ibutilide before the cardioversion attempt (Oral H, et al. *N Engl J Med* 1999;340:1849-1854). If the cardioversion is unsuccessful due to early or immediate recurrence of atrial fibrillation, any antiarrhythmia may be helpful. Biphasic defibrillation waveforms lower ventricular defibrillation thresholds and will probably be more effective for atrial defibrillation as well. New defibrillator models with biphasic waveforms are now being produced. In the future, it may be possible to analyze the atrial fibrillation waveform after subtraction of ventricular events to allow optimal timing of the shock. If these noninvasive approaches fail, intra-atrial shock delivery is still an option.

The major limitation of all these techniques is the high late recurrence rate after successful cardioversion. No strategy for maintaining sinus rhythm is uniformly safe and highly effective. In many patients, a strategy of rate control and anticoagulation will eliminate symptoms and avoid the risks and inconvenience of cardioversions and antiarrhythmic drug therapy. ❖

Prevention of Sudden Death in Patients with Coronary Artery Disease

ABSTRACT & COMMENTARY

Synopsis: *Electrophysiologically guided antiarrhythmic therapy with implantable defibrillators but not antiarrhythmic drugs is effective in patients similar to those entered in the study.*

Source: Buxton AE, et al. *N Engl J Med* 1999;341: 1882-1890.

The multicenter unsustained tachycardia Trial (MUSTT) was designed to test two hypotheses. The first was that electrophysiologic studies could be used to identify a high-risk subgroup among coronary artery disease patients with prior myocardial infarction (MI), depressed left ventricular function, and spontaneous nonsustained ventricular tachycardia. The second hypothesis was that electrophysiologically guided antiarrhythmic therapy would improve survival in patients identified to be at risk. This paper gives results relevant to the second hypothesis.

The trial enrolled patients between November 1, 1990, and October 31, 1996, at 85 study sites in the United States and Canada. The criteria for enrollment were as follows: known coronary artery disease, a left ventricular ejection fraction of 40% or less, and asymptomatic unsustained ventricular tachycardia. Patients could not have a prior history of sustained arrhythmias or syncope unless these occurred within the first 48 hours after an MI. All patients underwent an evaluation for ischemia prior to enrollment and patients with active ischemia were excluded until that had been treated. After enrollment, patients underwent an electrophysiologic study with programmed ventricular stimulation using a standard protocol. A positive study was defined as the reproducible induction of sustained monomorphic ven-

tricular tachycardia induced by any method of stimulation or of sustained polymorphic ventricular tachycardia induced by one or two extrastimuli. Patients with an inducible arrhythmia were assigned in equal numbers to either receive antiarrhythmic therapy guided by serial electrophysiologic testing or to a control group that was not prescribed specific antiarrhythmic therapy. Patients who had no inducible arrhythmia, an arrhythmia that was not reproducible, or patients who refused randomization were also followed in a large registry. The antiarrhythmic drugs to be tested were chosen at the discretion of Buxton and colleagues, with the exception that amiodarone could not be the first drug tested. Once the patient had reached steady state on the drug, programmed ventricular stimulation was repeated. Suppression of inducible ventricular tachycardia on a drug was required for the patient to continue on that therapy. If no effective drug regimen could be identified, the patient could either be discharged on a regimen that was associated with hemodynamic stability during induced tachycardia or the patient could receive an implantable cardioverter defibrillator (ICD). Guidelines for ICD implant were made more liberal after enrollment of about one-half of the study group.

The primary end point of the study was cardiac arrest or death from arrhythmia. Total mortality was a secondary end point. Events were classified by a blinded events committee. Treatment groups were compared using an intention-to-treat analysis.

During the study, a total of 2202 patients were enrolled. Of these, 767 (34.8%) manifested an inducible sustained ventricular tachycardia during the baseline electrophysiologic study. Seven hundred four of these patients agreed to be randomized to either serial drug therapy or no therapy. The clinical characteristics of the group were typical for an ischemic heart failure population. The median age was 67 years, with 90% of the patients being male and 88% of the patients being Caucasian. The median ejection fraction was 30%. Patients were essentially equally distributed between New York Heart Association classes I, II, and III.

Among the 351 patients assigned to electrophysiologically guided therapy, only 158 were discharged on antiarrhythmic drugs. Twenty-six percent of the entire group received class I drugs, 10% received amiodarone, and 9% received sotalol. One hundred sixty-one of the 351 patients (46%) received defibrillators. In addition, 2% of the patients randomized to therapy died during their initial hospitalization and 7% of the patients refused antiarrhythmic drug therapy and did not receive a defibrillator. The median duration of follow-up was 39 months. Among the patients assigned to no antiarrhythmic therapy, the two-year and five-year rates of cardiac arrest or death from arrhythmia were 18% and 32%, respectively. The corresponding rates for patients assigned to electrophysiologically guided therapy were 12% and 25% (P = 0.04; RR, 0.73). Total mortality rates after two and five years were 28% and 48% for the patients assigned to no antiarrhythmic therapy compared to 22% and 42% for those assigned to electrophysiologically guided therapy (P = 0.06; RR, 0.80). A preplanned subgroup analysis comparing drug therapy and ICD therapy in the treated group showed that all of the benefit could be attributed to ICD therapy. The total mortality at five years was 24% among patients who received defibrillators and 55% among those who did not. This difference associated with ICD treatment remained significant even after a regression analysis in which adjustments for relevant clinical factors were made. Buxton et al conclude that electrophysiologically guided antiarrhythmic therapy with implantable defibrillators but not with antiarrhythmic drugs is effective in patients similar to those entered into the study.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Prevention of sudden death remains a major problem. Most cardiac arrest victims do not survive their initial event. Therefore, effective strategies for primary prevention of sudden death have long been sought. Unfortunately, trials with antiarrhythmic drugs either given empirically or when guided by Holter monitoring have been largely unsuccessful. A single trial that compared "conventional antiarrhythmic drug therapy" and ICD therapy, the Multicenter Automatic Defibrillator Implantation Trial showed benefit in the defibrillator group, but that trial was small and had no control group. The MUSST data reported here are important since they confirm that ICD therapy is superior to drug therapy in a population at high risk for sustained and life-threatening arrhythmias. However, a number of factors make it difficult to estimate from these data the magnitude of benefit that will be associated with ICD therapy. There are several reasons why the benefit of the ICD may be overestimated in this paper. First, most of the patients who received antiarrhythmic drugs were treated with class 1A agents. After the Cardiac Arrhythmia Suppression Trial showed an increased mortality with drug therapy and the Endocardial Stimulation Versus Electrocardiographic Monitoring Study showed sotalol to be superior to other agents, most electrophysiologists shifted to using class III drugs. Sotalol and amiodarone, however, were used in fewer than half of the drug-treated patients in MUSST. There was also a change in the rules for ICD implantation during the trial and device technology significantly improved during the study period. Therefore, it

seems probable that a higher proportion of patients in the latter phases of the trial received an ICD. Since treatment for heart failure and ischemia also improved during the course of the trial, some of the benefits seen with ICD therapy may be attributable to better medical therapy. Finally, the improvement in total mortality was only 6% at five years, a difference that was only of borderline significance.

The first hypothesis of the trial—that the electrophysiologic study would help identify a high-risk subset—is really not discussed in this paper. However, in preliminary reports, Buxton et al have shown that the electrophysiologic study connotes only a relatively modest increase in risk over that seen among patients who do not have inducible arrhythmias. Although, due to the large size of the trial, a positive electrophysiologic study did turn out to be a significant predictor of arrhythmic events and mortality, the control group was also a relatively high-risk population.

The costs associated with ICD therapy in its present form are substantial. Several clinical trials have now indicated that the ICD is superior to antiarrhythmic drugs in different settings. We still need good studies to help identify in which groups of patients use of an ICD will be economically feasible and attractive. ❖

Improved Outcomes with Stenting in Diabetics: Controlling the Unruly Platelet

ABSTRACT & COMMENTARY

Synopsis: *A strategy of stent-abciximab was more effective in reducing the need for future revascularization in diabetic patients than stent-placebo or POBA-abciximab.*

Source: Marso SP, et al. *Circulation* 1999;100: 2477-2484.

It is well accepted that diabetics have less optimal angiographic and clinical outcomes following percutaneous intervention (PCI) than nondiabetics, particularly in individuals with multivessel disease. The first clue to an adverse outcome following PCI in diabetics came from the Bypass Angioplasty Revascularization Investigation (BARI) trial, which demonstrated improved survival rates in diabetics undergoing bypass surgery vs. plain old balloon angioplasty (POBA) (*Circulation* 1997;96:1761-1769); other studies, but not all, have supported these observations. The use of stenting in the diabetic has resulted in conflicting results as to whether outcomes are improved over POBA. While platelet IIb/IIIa receptor inhibition has not been shown to improve outcomes in diabetics treated with POBA, the question of stent placement in conjunction with platelet inhibition has not been addressed. The EPISTENT trial analyzed a subset of 491 diabetic patients who were prospectively randomized into three groups: stent-placebo, stent-abciximab, and POBA-abciximab. Most patients had stable single-vessel disease. Approximately 20% of the overall EPISTENT cohort were diabetic, with a mean age of 60 years. The diabetic patients had a greater incidence of markers of insulin resistance, including obesity and hypertension. Approximately half of the patients had a prior myocardial infarction (MI), and one out of six had a recent MI (within 7 days of PCI). The primary end point for this substudy was a composite of all-cause mortality, nonfatal MI, or target-vessel revascularization (TVR) at six months. Patients were followed up to one year. An angiographic substudy involving 900 patients, of whom 132 were diabetic, was also analyzed.

The results clearly indicated that stent-abciximab therapy in the diabetic was substantially better than stent-placebo or POBA-abciximab. The composite end-point, death, and MI rates were reduced by 50%. There was a greater than 50% reduction in six-month TVR rates; the stent-abciximab patients had a similar six-month TVR rate as nondiabetics treated with stent-abciximab, whereas stenting without platelet blockade was associated with increased TVR rates in diabetics compared to nondiabetics. There was an absolute decrease in events, and consistent benefit for all end-points in the stent-abciximab group compared to stent-placebo. One-year survival was better in these individuals (4.1% vs 1.2%; P = 0.11). Because of some discrepancies in baseline characteristics, a multivariate analysis was carried out, which confirmed the overall group observations. Stenting-abciximab in diabetics was associated with a 50% reduction in the primary end point. The results were similar when only diabetics treated with medication were analyzed. Of interest, in the entire diabetic cohort, including drug-treated diabetics, there was a reduction in six-month TVR rates for stent-abciximab patients vs. stent-placebo (9.2% vs 18.2%; P = 0.05), with a strong trend for increased survival in the stent-placebo group at one year.

The relatively small number of individuals in the angiographic cohort confirmed the larger study results, indicating an improvement in net luminal gain at six months for stent-abciximab compared to stent-placebo (0.88 vs 0.55 mm; P = 0.01). Late loss index was less for

abciximab patients, and the restenosis rate at six months was almost half that in the stent-placebo group. Restenosis rates for POBA-abciximab were 20%, compared to 7.8% and 14.2% for stent-abciximab and stent-placebo groups, respectively. Diabetics with markers of insulin resistance (hypertension and obesity) had an improvement in clinical outcomes with stenting and IIb/IIIa platelet inhibition. These clinical markers of insulin resistance were significant predictors of increased TVR rates in multivariate analysis; procedural outcomes were improved with stent-abciximab, and contributed greatly to the favorable six-month outcomes in this group. These patients had a decreased six-month rate of death, MI, and need for repeat revascularization. Marso and colleagues conclude that a treatment strategy with stent-abciximab "both improved safety profile for stenting and decreased the need for future revascularization procedures in diabetic patients." They provide a detailed discussion of potential mechanisms and suggest that enhanced platelet activation in the diabetic is an important adverse factor, and that IIb/IIIa platelet receptor inhibition decreases restenosis in diabetics who receive a stent. This may be due to a less intimal neoproliferation and mural thrombis following balloon or stent coronary arterial injury. Abciximab binds not only to the platelet IIb/IIIa receptor but also to the vitronectin receptor on endothelial and smooth muscle cells, which may also be important in decreasing restenosis and intimal proliferation. In EPISTENT, abciximab was not effective in reducing restenosis after POBA.

COMMENT BY JONATHAN ABRAMS, MD

The conundrum of the diabetic with obstructive coronary disease has been the focus of increasing attention over the past several years. Many individuals, including William O'Neil and the BARI investigators, have suggested that bypass surgery is the preferred revascularization strategy for the diabetic with multivessel disease. Results of EPISTENT indicate that diabetics who receive a stent fare better than those who have POBA, but all reported studies have not reached the same conclusion. The advent of IIb/IIIa platelet receptor inhibitors has provided evidence that short- and long-term outcomes are improved in individuals who receive a PCI, particularly when they have high-risk features. This study strongly suggests that abciximab also may play an important role in decreasing morbidity and mortality in diabetic patients undergoing angioplasty with stenting. The data from the EPISTENT trial suggest that the use of abciximab and a stent moves the diabetic undergoing PCI closer to the nondiabetic with respect to morbidity and mortality, although not completely so. This is similar to recent hypertension and statin trials, which are concordant with a major risk reduction in the diabetic with effective therapies that favorably alter clinical outcomes and eliminate much of, but not all, the risk associated with diabetes. This single study should not completely change our therapy, but the results of this trial are not surprising and are concordant regarding all end points. Thus, the interventionalist treating the diabetic should strongly consider the use of stenting as well as a platelet IIb/IIIa inhibitor. Given the present state of knowledge, it does not seem presumptuous to use such an approach until more data are available. The provocative suggestion that insulin resistant features contribute to less favorable PCI outcomes suggests that such patients may also benefit from the same approach. This clearly requires confirmation in future studies. ❖

CME Questions

8. Diabetics undergoing percutaneous coronary interventions show the lowest total mortality, MI, and target vessel revascularization with:
a. balloon angioplasty.
b. balloon angioplasty plus abciximab.
c. stent.
d. stent plus abciximab.

9. Patients with CAD, reduced LVEF, and nonsustained ventricular tachycardia had the lowest cardiac death rate with:
a. electrophysiology testing guided drug therapy.
b. holter-monitor-guided drug therapy.
c. no specific antiarrhythmic therapy.
d. an internal cardioverter defibrillator.

10. Which of the following is most *correct* concerning a stress test first vs. a catheterization first approach in women with chest pain consistent with angina?
a. It is clearly superior in high-risk patients.
b. Direct costs are less.
c. The absolute number of normal coronary angiograms is more.
d. Outcomes are superior.

11. The frequency of converting atrial fibrillation to sinus rhythm may be increased by:
a. antiarrhythmic drugs.
b. higher energy shocks.
c. biphasic defibrillators.
d. All of the above

12. Cyclical breathing in heart failure is associated with:
a. higher mortality.
b. more symptoms.
c. ventricular arrhythmias.
d. All of the above

13. Compared to older drugs (diuretics/beta blockers), newer drugs (ACE inhibitors/calcium antagonists) for treating hypertension:
a. are less well tolerated.
b. increase total mortality.
c. reduce stroke rates.
d. are similar for preventing cardiovascular events.