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Early ACEI-Aspirin Interaction in Acute Myocardial Infarction

ABSTRACTS & COMMENTARY

Synopsis: *The effects of ACEI on all the clinical end points were not influenced by ASA and "the benefits of ASA and ACEI are approximately independent of each other, in which case the greater benefit will be obtained by using both treatments."*

Sources: Latini R, et al. *J Am Coll Cardiol* 2000;35:1801-1807; Hall D. *J Am Coll Cardiol* 2000;35:1808-1812.

There is a lingering controversy regarding the question as to whether use of aspirin with angiotensin-converting enzyme inhibitor (ACEI) therapy attenuates the beneficial effects of the latter drugs in patients with heart failure. An unpublished analysis of the Studies of Left Ventricular Dysfunction (SOLVD) treatment and prevention trials suggested that use of aspirin is associated with a decreased benefit of enalapril in patients with symptomatic or asymptomatic left ventricular (LV) systolic dysfunction. Other data are suggestive that a negative interaction exists, but conclusive proof has yet to be established. Because the majority of heart failure patients have underlying coronary artery disease (CAD), this is a question of great importance, given the mandate to use both aspirin and an ACEI in patients with CAD and impaired LV function, respectively. Latini and colleagues pooled individual patient data from four trials using ACEI during the acute phase of acute myocardial infarction (MI), continued short-term for no more than six weeks to examine the issue of whether use of aspirin attenuated the benefits derived from ACEI in these studies. The concomitant primary analysis was the effect of ACEI on total mortality at 30 days; secondary end points included mortality within the first week and a variety of adverse clinical outcomes. The studies examined included CONSENSUS II, GISSI-3, ISIS-4, and Chinese Cardiac Study (CCS), with an aggregate of 96,712 subjects for whom adequate data were available. Of these, the vast majority (86,484) received antiplatelet therapy, almost always aspirin; just more than 10% did not receive aspirin. The latter individuals were slightly older, more women, and, importantly, had a greater likelihood of having early heart failure (26% vs 17%), and were less likely to

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have received thrombolytic therapy (40% vs 66%). Thus, nonaspirin users appeared to represent a higher risk group than the majority. Aspirin use at entry ranged from 75% to 94%, and averaged 89%. The primary end point of 30-day mortality in these trials favored ACEI, as previously published, by an absolute value of 0.5%, or 7.1% vs. 7.6%. Aspirin use did not significantly attenuate the effects of ACEI; the 30-day mortality was 6% in those taking ACEI and aspirin, and 10% in those who were on ACEI alone (P = NS). Early seven-day mortality was 7% with aspirin and 15% in the absence of aspirin use (P = NS). Analysis of clinical events indicated that ACEI increased the likelihood of hypotension and elevation of serum creatinine and decreased the incidence of nonfatal heart failure. Aspirin did not significantly affect these end points, nor did it alter the 30-day MI or stroke rate. Latini et al conclude that the effects of ACEI on all the clinical end points were not influenced by ASA, and that "the benefits of ASA and ACEI are approximately independent of each other, in which case the greater benefit will be obtained by using both treatments." Aspirin did not appear to modify the safety profile of early ACEI, although there was a greater proportion of renal dysfunction in patients taking both drugs. Latini et al state that guidelines suggesting a possible negative interaction between these two agents in acute MI patients should be reconsidered.

In an accompanying editorial, Hall of the German Heart Center in Munich outlines a cogent conflicting opinion. His lengthy editorial comment essentially refutes the argument that aspirin does not attenuate the efficacy of ACEI, as suggested by careful analysis of the heart failure literature. He emphasizes that in congestive heart failure, aspirin use does ameliorate the survival benefits of ACEI. He stresses that in the Latini et al meta-analysis, the individuals who did not receive aspirin had double the 30-day mortality, suggesting that there are clearly two different patient groups, with aspirin nonusers being significantly sicker. Hall notes that the reduction in heart failure in the four studies in the Latini et al analysis was 50% less in patients who received concomitant aspirin and ACEI (3.3% vs 8.8%). In the Consensus II trial, as noted by Latini et al, there was a trend toward a less favorable outcome in patients receiving enalapril and aspirin, which in the meta-analysis of Latini et al was neutralized by the more favorable outcomes with combined therapy in GISSI-3, ISIS-4, and the Chinese study. Hall discusses the various mechanisms of the interaction, emphasizing the role of aspirin and prostaglandins in helping understand the controversy.

COMMENT BY JONATHAN ABRAMS, MD

Both of these reports make points that are valid. There are, however, major differences in the databases being examined, and the clinician must be aware of this. Latini et al evaluate only the short-term, nonselective use of ACEI in acute MI, where the drugs are initiated as soon as possible after admission and continued for no more than 5-6 weeks. GISSI-3 and ISIS-4 confirmed that early nitrate administration produced only a trend for improved outcome, but that early ACEI administration did result in a modest 7% reduction in short-term mortality, as confirmed in the new meta-analysis. However, it is clear that the 10-12% of individuals in this assessment who did not receive aspirin had a number of clinical risk parameters, and the fact that aspirin itself was not administered may have also played somewhat of a negative role, in that this drug has been shown conclusively to improve morbidity and mortality in acute MI when administered upon admission. The meta-analysis data do not directly reflect subjects with congestive heart failure or LV systolic dysfunction. The strategy that ACEI should be given only to high-risk patients, as in Survival and Ventricular Enlargement (SAVE), AIRE, and Trandolapril Cardiac Evaluation (TRACE), is not addressed by Latini et al. The large majority of patients in the Latini et al analysis had relatively preserved LV function, as the ACEI was given to "all comers," irrespective of clinical status. The SOLVD data, as well as the detailed

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analysis of a variety of major heart failure trials by Hall, wave a red flag as to a negative interaction between the two drugs. For instance, several trials (such as AIRE and SAVE) found that the use of aspirin and ACEI demonstrated a lesser reduction in cardiovascular end point mortality; in CONSENSUS II and SOLVD there also appeared to be a somewhat worse outcome in those individuals receiving aspirin. In the Latini et al meta-analysis, at both seven-day and 30-day outcomes the nonuse of aspirin was favored.

How does one make sense out of these data? Two major clinical issues are critical to this discussion: 1) whether a study is long term, lasting several years; and 2) whether congestive heart failure or significant LV dysfunction was an enrollment marker for ACEI. Other data confirm that the use of nonsteroidal anti-inflammatory drugs increases the likelihood of congestive heart failure, and the use of aspirin, by interfering with prostaglandin synthesis through the cyclo-oxygenase pathway, may thus attenuate the effects of ACEI. It is difficult to recommend not using aspirin in individuals with CAD, irrespective of their LV systolic function. The HOPE trial showed that ramipril had a favorable effect in large numbers of individuals with preserved LV function and no heart failure who ordinarily might not receive an ACEI. This study should stimulate an increased use of these highly effective drugs in CAD patients, particularly those individuals with acute MI who have good LV function and no heart failure, as was the case in three of the four studies in the meta-analysis. Whether concomitant aspirin use with an ACE inhibitor in these short-term trials would ultimately have shown a greater disparity in outcomes between ACE with or without aspirin is not known. Other data emphasized by Hall suggest this might be the case. There was a trend in the Latini et al analysis favoring ACEI alone, although statistical significance was not achieved. This is important, as this is a large database.

In summary, I suggest that clinicians rethink the issue. In patients with acute MI or unstable angina who are on or will receive an ACEI, aspirin clearly appears to be safe and effective and does not appear to have an adverse effect on outcomes. However, in individuals with chronic LV dysfunction, particularly with symptomatic heart failure, the use of aspirin (or nonsteroidal anti-inflammatory drugs) must be carefully considered. In patients who have systolic heart failure, antiplatelet agents probably should be precluded. In individuals with CAD who are clinically stable with no history of heart failure, even with a depressed ejection fraction, one can go in either direction. This controversy will more than likely linger for years to come. ❖

Is a Routine Stent Strategy Superior to POBA?

ABSTRACT & COMMENTARY

Synopsis: *Due to the ability of a stent to provide a large lumen diameter and a lower rate of restenosis, it is the preferred approach for patients who met the criteria in this study.*

Source: Weaver WD, et al. *Lancet* 2000;355:2199-2203.

The opus i trial asks the question whether a policy of routine stenting in large, noncomplex lesions in stable coronary disease achieves better results than balloon angioplasty (POBA) with the option of provisional or conditional stenting if POBA is thought to be less optimal. This is a practical study attempting to simulate daily clinical practice. Experienced interventionalists representing 44 centers in the United States and Canada conducted this study. Study design is straightforward. Subjects with a single coronary lesion with more than 70% stenosis, no more than 20 mm in length, and a minimal coronary artery diameter of 3.0 mm were eligible. Exclusion criteria included calcification, more than 45% vessel angle, or ostial stenosis. Multiple stents and abciximab were allowed at the investigator's discretion, as were most decisions of therapy. All patients were treated with ticlodipine for four weeks as well as aspirin. High-pressure balloon inflations were mandated by protocol for stent placement. The angiographic end point was residual target vessel diameter of stenosis of less than 10%. In the POBA-provisional stent cohort, less than a 20-30% residual was required; otherwise, a stent was used. The original protocol sought to enroll almost 2200 patients; however, enrollment was discontinued after only 19 months after 479 patients were entered due to funding restrictions and a low recruitment rate.

Patient criteria included the following: average age was 60 years, and 75% were male. Half had elevated cholesterol or hypertension, and almost 20% had diabetes. Forty percent had a history of myocardial infarction (MI), half of which were recent. There was a low rate of prior revascularization. Most patients presented with unstable angina. Left ventricular function was well preserved. Sixty-five to 70% of the overall cohort had single-vessel disease, and 20% had double-vessel disease.

Weaver and colleagues were encouraged to use the Palmaz-Schatz stent (77% overall). In the routine stent

strategy, individuals received an average of 1.2 stents compared to 0.5 in the optimum POBA group. The initial coronary lesions had a mean 90% stenosis, a reference diameter of 3.3 mm, and a lesion length ranging between 7-15 mm. The primary end point of the study was a composite of MI, target vessel revascularization, bypass surgery, or death within six months. A variety of secondary end points, including cost assessment, were included, as well as a quality-of-life survey. The results demonstrated that routine stenting was superior, resulting in fewer subsequent procedures, and comparable and even slightly lower outpatient and hospital costs at six months, although there were no obvious clinical differences between the two groups at six months. Initial hospital length of stay was comparable between the two groups; initial hospital costs were essentially $1000 greater for routine stenting, but at six months, stent costs were equal to POBA with provisional stenting. Thirty-seven percent of the POBA group received provisional stenting because of coronary dissection or failure to achieve optimal stenosis reductions. Readmission rates were twice greater in the optimum POBA group. However, functional status was similar, without differences in physical limitations, angina frequency, or treatment satisfaction at six months. Nevertheless, the subjects who had a subsequent revascularization procedure had more symptoms and a lower quality of life. Weaver et al conclude that due to the ability of a stent to provide a large lumen diameter and a lower rate of restenosis, it is the preferred approach for patients who meet the criteria in this study.

Weaver et al discuss the difference between their trial and one other published trial, in which 14% of the POBA patients crossed over to stent placement; however, that trial used a postprocedure 30-minute angiogram, whereas in OPUS I, any technique was available to the investigators, of which few were used to assess angiographic outcome other than at the time of the procedure. Weaver et al stress that OPUS I was an effectiveness trial, which deliberately encouraged clinical judgment, giving interventionalists a wide range of options for stent deployment and assessment of results. IVUS, quantitative angiography, or Doppler flow wires were allowed. The latter procedures lengthened the study by an average of 36 minutes. Weaver et al conclude that OPUS I supports the use of routine stenting during POBA, given large vessels, stable patients, the absence of complex arteries, or calcium. Multivessel angioplasty and stenting were not investigated in this trial, nor was the use of IIb/IIIa inhibitors or heparin. Weaver et al recognize that complications from stenting that might accrue after six months would not have been found in this study. Weaver et al believe that OPUS I results are concordant with the widespread use of stenting in the United States for similar patients, which probably approaches 60-70%.

COMMENT BY JONATHAN ABRAMS, MD

This small trial is disappointing in part because of the short duration and the marked reduction in the scheduled enrollment. Nevertheless, the outcomes would appear to speak for themselves, indicating a modest benefit with stenting with respect to repeat procedures. It is odd that the clinical satisfaction ratings were not different between the two groups. At six months, the total number of study end points were 6.1% in the routine stent strategy group (229 patients) and 14.9% in the optimum POBA/provisional stent strategy. The bulk of the differences were related to target vessel revascularization and subsequent revascularization procedures, which were threefold higher in the provisional stent cohort. The effect that both Weaver et al and the patients knew the enrollment strategy had is uncertain, but may have contributed to the benign view that the POBA/provisional stenting patients had regarding their clinical status. Furthermore, there was no subsequent functional testing, although a positive stress test or a recent MI was necessary for entry into this trial. Use of various medications was not provided, and there may be important differences in antianginal use between the cohorts that are important. A comparable French study has just been reported (STENTIM-2) that randomized 211 patients with acute MI to primary POBA with or without Wiktor stent placement. Six-month outcomes, including target lesion revascularization and restenosis rates, were better with routine stent use. One-year eventfree survival and revascularization rates were also improved with stenting (Maillard L, et al. *J Am Coll Cardiol* 2000;35:1729-1736).

Thus, it seems that the stent is out of the barn, so to speak, in that interventionalists in the United States, as well as in Europe, are now using stents for the majority of angioplasty procedures. Nevertheless, a policy of provisional or conditional stenting does not appear to be unattractive; OPUS I does not provide strong support to abandon this policy among experienced interventionalists who believe that visual angiographic, Doppler, or IVUS assessment of POBA results in the catherization laboratory are sufficient. While the costs of routine stenting at six months were comparable to POBA, it would be of interest to know whether there is an increasing use of IIb/IIIa platelet inhibitors, both at the time of the first intervention and in 37% of individuals in POBA who had subsequent intervention. ❖

Diuretics in Diastolic Heart Failure Patients

ABSTRACT & COMMENTARY

Synopsis: *Furosemide withdrawal is almost always successful and is associated with improved diastolic filling and improved blood pressure homeostasis.*

Source: van Kraaij DJ, et al. *Am J Cardiol* 2000; 85:1461-1466.

There is controversy regarding the role of diuretics in heart failure due to diastolic dysfunction. Although reducing pulmonary or systemic congestion, if present, may be desirable, reducing preload could lower cardiac output and exacerbate symptoms of fatigue or cause orthostatic intolerance. Thus, van Kraaij and associates hypothesized that in stable patients with heart failure and normal systolic function, withdrawal of furosemide therapy would be safe and have positive effects on functional and hemodynamic status. To test this hypothesis, they performed a placebo-controlled trial of furosemide withdrawal in 32 elderly patients (mean age, 75 years) with a history of congestive heart failure (CHF) on furosemide (20-80 mg/d) but currently without evidence of congestion; and an ejection fraction of more than 40% (mean, 60%). Evaluations of the patients were done three months after withdrawal of furosemide. Recurrent CHF occurred in two of the 21 patients in the withdrawal group (10%) and in one of the 11 patients in the continued furosemide group (9%). Two patients in the withdrawal group restarted furosemide for ankle edema and one because of hypertension. Symptom scores, blood pressure, six-minute walk test, and quality of life were not different at three months between the two groups. In those successfully withdrawn, Doppler E/A ratio increased from 0.68 to 0.79 ($P < 0.01$) and the decrease in standing systolic blood pressure changed from -8 to +5 mmHg ($P < 0.05$). Van Kraaij et al conclude that furosemide withdrawal is almost always successful and is associated with improved diastolic filling and improved blood pressure homeostasis.

COMMENT BY MICHAEL H. CRAWFORD, MD

This study suggests that many patients with a history of CHF and normal systolic left ventricular function are being overtreated with diuretics. It may be that diuretics were started during an episode of CHF and then just continued. In such cases, a re-examination of the need for diuretics seems appropriate and relatively safe based upon this study. Although van Kraaij et al claim that 90% did not need continuation of diuretics, if pedal edema and hypertension are included with CHF as appropriate indications for diuretics, then 75% did not need continued diuretics.

It should be pointed out that this was a highly selected, small group of patients that was studied. There were no NYHA class IV patients; no hypertensive patients; all were in sinus rhythm; none had more than mild angina; and all had negative stress tests for ischemia. Also, the follow-up interval was short (3 months). In addition, no data on left ventricular size were given. This would have been of interest since an enlarged left ventricle may be an indication for diuretics despite an ejection fraction of more than 40%, to reduce left ventricular size and hence wall stress. Finally, it is unclear how many patients were on angiotensin-converting enzyme inhibitors (ACEI) or other drugs that could affect blood pressure, left ventricular filling, and diastolic flow velocity parameters.

In addition to the failure to relapse into CHF in 90% of those with furosemide withdrawn, there were objective improvements in diastolic mitral velocity flow characteristics and orthostatic blood pressure homeostasis. However, these measured benefits did not translate into improved symptoms or exercise time. Thus, the clinical effect of withdrawing diuretics is unclear. Eliminating diuretics in 75-90% of patients should save some money and reduce the complexity of the patients' treatment regimen. Consequently, an attempt to eliminate diuretics in stabilized diastolic heart failure patients seems a reasonable thing to do. Also, I would suggest re-evaluating the need for ACEI in such patients is appropriate as well. ❖

Electrophysiologic Testing to Identify Patients at Risk for Sudden Death

ABSTRACT & COMMENTARY

Synopsis: *Electrophysiologic testing can be used to assess the prognosis of patients with coronary disease, left ventricular dysfunction, and nonsustained VT.*

Source: Buxton AE, et al. *N Engl J Med* 2000:342: 1937-1945.

This provides further information from the multicenter Unsustained Tachycardia Trial (MUSST). The primary objective of MUSST was to determine if electrophysiologically guided drug therapy improved sur-

vival in patients with coronary artery disease (CAD), prior myocardial infarction (MI), left ventricular dysfunction, and spontaneous unsustained and inducible sustained ventricular tachycardia (VT). The primary objective implicitly assumed that induction of sustained VT was a marker for high risk. A secondary objective of MUSST was to evaluate the validity of that assumption.

In MUSST, patients who met the clinical criteria listed above underwent electrophysiologic testing using a standard protocol. If sustained monomorphic VT or sustained ventricular fibrillation with a protocol limited to two extrastimuli was induced, a consenting patient was randomly assigned to either electrophysiologically guided drug or device therapy or to no antiarrhythmic therapy. If an arrhythmia was not induced, the patient was followed without antiarrhythmic therapy in a registry. A comparison between these two untreated groups provided the data to test the secondary hypothesis that the baseline electrophysiologic study could be used to define a high-risk subgroup.

This paper provides data from 353 patients with inducible VT randomly assigned to no antiarrhythmic therapy and 1397 registry patients. There were several differences between the two groups. Registry patients were more likely to be women (16% vs 10%) and to have undergone coronary bypass surgery (63% vs 56%). The patients with induced VT were more likely to have a clinical history of MI (94% vs 87%). At the time of hospital discharge, 51% of the patients with inducible VT were receiving a beta-blocker vs. only 35% of the registry patients.

At discharge, among the patients with the inducible VT, 2% were receiving an antiarrhythmic drug and 2% had received an implantable cardioverter defibrillator (ICD). The corresponding values for the registry patients were 3% and 0.2%.

The primary end point in MUSST was cardiac arrest or arrhythmic death. After two and five years, the rates for the primary end points were 12% and 24% in the registry vs. 18% and 32% in the inducible VT group (unadjusted P = 0.005). Total mortality rates after two and five years were 21% and 44% in the registry vs. 28% and 44% in the inducible VT group.

The electrophysiologic findings in the registry group were analyzed to see if induced arrhythmias other than sustained monomorphic VT had prognostic significance. In the registry group, 661 patients had no VT of any type induced, 531 patients had nonsustained VT induced, and 205 patients had sustained polymorphic VT or ventricular fibrillation induced with triple extrastimuli. There were no significant differences in outcome when registry patients were subclassified based on these responses to stimulation.

Buxton and associates conclude that electrophysiologic testing can be used to assess the prognosis of patients with CAD, left ventricular dysfunction, and nonsustained VT.

COMMENT BY JOHN P. DiMARCO, MD, PhD

The results of the randomized portion of MUSST were published last year (*N Engl J Med* 1999;341:1882-1890). The two most important observations were that electrophysiologically guided therapy decreased cardiac arrest and arrhythmic death in the randomized group and that all the benefit was observed in patients who received an ICD rather than antiarrhythmic drugs.

This paper deals with the prognostic value of the electrophysiologic study performed in patients with CAD, left ventricular dysfunction, and nonsustained VT. Although Buxton et al are technically correct in their claim that electrophysiologic study results are a predictor of outcome in this patient population, the results are of only limited clinical value.

When electrophysiologic testing was first introduced for patients with ventricular arrhythmias more than 25 years ago, it was observed that a higher proportion (> 90%) of patients with recurrent, sustained monomorphic VT could have their arrhythmia replicated during an electrophysiologic study. Many of these early patients had a long history of VT, had large aneurysms or scars, and could have their VT reproduced by relatively simple stimulation protocols. Limited control data showed that monomorphic VT was a rare response to programmed stimulation among patients without a history of VT. The early hope was that induction of sustained VT by stimulation would be a sensitive and highly specific finding. When cardiac arrest survivors were tested with the same stimulation protocols, a much lower proportion, only 50-70%, had an inducible sustained arrhythmia and, in many cases, polymorphic VT or ventricular fibrillation was the arrhythmia induced. As therapy for acute MI has improved, the characteristics seen in a contemporary VT population have changed. Large discrete aneurysms are less commonly found, more aggressive stimulation protocols are required to induce VT, and the arrhythmias are often more rapid and less well tolerated. However, it was still hoped that failure to induce VT would be a good prognostic sign. In this paper, Buxton et al note that 88% of patients without inducible monomorphic VT have been free of cardiac arrest or arrhythmic death after two years. However, 82% of the untreated patients with inducible VT were also doing well. Although the proportions are statistically different due to the power conferred by the large study group, this difference is

too small to be useful for clinical decisionmaking. Rather, given the five-year mortalities of 44% and 48%, both groups should be considered to be at high risk. The electrophysiologic findings become just another risk factor of modest significance.

Prevention of CAD and early treatment of MI remain the most promising approaches for lowering the sudden death rate in the general population. Once MI has occurred and severe left ventricular dysfunction is present, the MUSST data indicate that general strategies that can be applied to all patients offer more hope than a strategy based on electrophysiologic testing. Hopefully, ongoing studies on the use of drugs and ICD therapy for patients with low ejection fractions and heart failure will provide new data that can guide clinicians dealing with these patients. ❖

Clinical Characteristics of Patients Intolerant to VVIR Pacing

ABSTRACT & COMMENTARY

Synopsis: *Intolerance to VVIR pacing is frequent in elderly patients but it is difficult to predict from baseline measurements those who will require DDDR pacing.*

Sources: Ellenbogen KA, et al. *Am J Cardiol* 2000; 86:59-63.

The pacemaker selection in the elderly (pase) trial was a single-blind, randomized comparison of ventricular pacing and dual-chamber pacing in 407 patients older than 65 years of age. Patients in PASE all received a dual-chamber pacemaker for treatment of bradycardia. Patients were required to have a stable atrial rhythm at the time of implantation. After enrollment, patients were randomized to either the DDDR mode or the VVIR mode. During the implant procedure, baseline blood pressure was measured during intrinsic rhythm and after one minute of ventricular pacing at 10 bpm faster than the intrinsic rhythm. The presence or absence of retrograde ventricular retrograde atrial conduction was also determined. Patients were followed at prescribed intervals after enrollment. Their health status was assessed with the 36-item Medical Outcomes Study Short Form general health survey (SF-36).

During the study, 53 of the 203 patients initially randomly assigned to the VVIR pacing mode crossed over to the DDDR mode. Seven of 53 (13%) crossed over before hospital discharge, 16 of 53 crossed over within one month of implant, and another 17 crossed over before six months. Patients were crossed over from VVIR to DDDR pacing because of the presence of one or more symptoms including: fatigue, effort intolerance, dyspnea, and presyncope. Independent predictors of crossover were the use of beta-blockers, the presence of nonischemic cardiomyopathy, and a systolic blood pressure of less than 110 mmHg during ventricular pacing. Data from the SF-36 survey were available in 29 patients who crossed over from VVIR to DDDR pacing. Among these 29, there was an improvement in multiple factors, including physical and social function and physical and emotional roles.

Ellenbogen and associates conclude that intolerance to VVIR pacing is frequent in elderly patients but that it is difficult to predict from baseline measurements those who will require crossover.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Intolerance to ventricular pacing was first observed in patients with acute myocardial infarction (MI) who were treated with temporary ventricular pacing. At that time, it was shown that retrograde VA conduction produced cannon A waves with a marked decrease in cardiac output and blood pressure. Similar observations were soon reported in patients with permanent pacemaker systems outside of the setting of acute infarction. Dual-chamber or physiologic pacing was then introduced in hopes that this problem would be eliminated. However, controversy still exists about the magnitude of benefit that should be seen with dual-chamber and physiologic pacing systems.

The PASE trial attempted to address this hypothesis. One important feature of the study design was that all patients had a dual-chamber pacing system implanted. Even though the protocol had some barriers to prevent crossover to a dual-chamber pacing mode from VVIR pacing, a high proportion of patients in this study were crossed over for clinical reasons. Crossover only required reprogamming the device. However, it is important to recognize that crossover has been much less common in studies where a surgical procedure is required to change pacing mode. For example, in a trial of patients with sinus node dysfunction that compared AAI and VVI pacing, only 1.7% of patients were crossed over to a physiologic pacing system over an eight-year period (*Lancet* 1994;344:1523-1528). Similarly, in the Canadian Trial of Physiologic Pacing, only 4.3% of patients initially assigned to ventricular pacing were crossed over to physiologic pacing over a five-

year period (*N Engl J Med* 2000;342:1385-1391). It therefore seems likely that in studies where crossover involves merely a programming change, investigators and patients are much more likely to attribute symptoms to the mode of pacing. The desire of the physician and patient to try something relatively simple leads to reprogamming and crossover. Total elimination of investigator and patient bias toward crossover would be difficult unless both were kept blinded to the mode of pacing used.

Despite numerous studies, the magnitude of benefit over single-chamber ventricular pacing that can be expected with dual-chamber or physiologic pacing remains uncertain. The simplicity and lower cost of VVIR pacing is balanced by questions that may arise during chronic therapy about possible advantages that might be derived from a physiologic pacing system. At this point, published data don't allow us to reach firm conclusions. ❖

CME Questions

8. Aspirin may be contraindicated in:
a. acute MI.
b. unstable angina.
c. symptomatic chronic heart failure.
d. CAD with depressed ejection fraction.

9. Stent vs. balloon angioplasty alone results in:
a. lower readmission rates over six months.
b. equal costs at six months.
c. equal functional status at six months.
d. All of the above

10. What percentage of stable patients with diastolic heart failure can be successfully taken off furosemide?
a. 25%
b. 50%
c. 75%
d. 100%

11. In patients with CAD, LV dysfunction, and unsustained VT, electrophysiology testing predicts:
a. subsequent rates of cardiac arrest or arrhythmia death.
b. LV aneurysm formation.
c. which patients can benefit from VT ablation.
d. All of the above

12. DDDR vs. VVIR pacing results in:
a. fewer cardiac symptoms.
b. higher ejection fractions.
c. fewer ventricular arrhythmias.
d. less atrial fibrillation.