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The Metabolic Syndrome and Cardiovascular Mortality

ABSTRACT & COMMENTARY

THE METABOLIC SYNDROME (TMS), ALSO KNOWN AS THE DEADLY quartet, Reaven's syndrome, the insulin resistance syndrome, etc, has attracted considerable attention over the past few years, as it has been suspected that individuals with TMS are at increased risk for vascular disease, as well as the development of type 2 diabetes. Major concern has been raised by the increasing prevalence of TMS, which accompanies obesity and sedentary lifestyle in many individuals. As the world population is becoming more overweight and obese, the potential public health implications of TMS are enormous. This report is of considerable importance, as it clearly documents the increased burden of all-cause and cardiovascular mortality in men with TMS who have no overt coronary artery disease (CAD) at baseline. Mortality increases of 2- to 3-fold are documented during long-term follow-up using 2 different definitions of TMS.

The Kuopio Ischemic Heart Disease Risk Factor study is a prospective observational report of a random sample of 2700 men from Eastern Finland, who were entered into the protocol at age 42-60 years, between 1984 and 1989. Of the entire cohort, 1123 were excluded because of a history of cardiovascular disease, cancer, or diabetes; others were excluded because of absence of certain study lab tests. Thus, a population of 1209 men was available for a subsequent analysis. Major components of TMS included blood pressure, body mass index, waist circumference, waist-hip ratio, fasting blood glucose, LDL and HDL cholesterol, and white blood cell count. Two definitions of TMS were used: the National Cholesterol Education Program (NCEP)—ATP III version—and a World Health Organization (WHO) definition emphasing hyperinsulinema, elevated fasting glycemia, and at least 2 additional factors, including abdominal obesity, dyslipidemia, or hypertension. Insulin resistance (IR) was calculated; a hyperinsulinemic group was defined, which represented the upper quartile of baseline IR. Impaired glycemia was defined as a blood glucose of 101-109 mg/dL, with diabetes defined as a blood glucose of > 110 mg/dL. Thus, the WHO criteria excluded many patients who would be considered to have TMS by the NCEP criteria.

All deaths were accounted for over the follow-up period ending

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December 1998. Sophisticated statistical analyses were carried out, including several proportionate hazard regression models, a factor analysis of various components of TMS, and a technique called principle component analysis. Men in the highest quartile of any variety of the components of TMS were likely to have TMS. Cardiovascular and all-cause death were treated as dependent variables.

The median follow-up was 11.6 years (range, 9.1-13.7). There were 109 deaths, of which 46 were cardiovascular disease and 27 CAD. Univariate analyses indicated that blood pressure, BMI, waist circumference, smoking, blood glucose, and serum insulin levels were associated with cardiovascular and all-cause mortality. Overall, Kaplan-Meier survival at 13.7 years for men with TMS vs those without was 79% vs 90%, using the NCEP waist measurement of 40 inches or more; 83% vs 90% for NCEP criteria with waist size of > 35 inches; and 84% vs. 90% for WHO based on waist-hip ratio or waist circumference. Age-adjusted Cox proportional hazard regression models indicated that TMS was associated with a 2.4- to 3.4-fold higher mortality from CAD, which rose to a 2.9- to 4.2-fold increase when LDL cholesterol, smoking, or family history were taken into account. Cardiovascular death was 2.5-2.8 times greater in individuals with TMS using WHO criteria, but was not significant using the NCEP criteria. In general, the risk ratios for the WHO definition of TMS appeared to be higher than those for the NCEP definitions. All-cause mortality was increased by 2-fold using the WHO TMS definition but was not significant using NCEP definition. In men who had no impaired glycemia at baseline, comparable results were noted. Total mortality was also related to metabolic syndrome, but less strongly than CAD mortality.

Lakka and colleagues concluded, "This is the first prospective population-based cohort study reporting the association of the metabolic syndrome using recently proposed definitions with cardiovascular and overall mortality; the mortality was independent of other important factors, such as smoking, alcohol intake, and LDL cholesterol." In the Finnish Study, the overall prevalence of TMS at baseline was low at 9-14% and far less than the approximate 30% prevalence of TMS in the United States estimated by the NHANES III survey. However, Lakka et al point out that with increasing obesity and overall abdominal adiposity, TnMS will be more frequent as will be vascular disease burden and diabetes. Most of the risk of TMS in this study was modulated through CAD mortality (3- to 4.3-fold), which comprised the bulk of cardiovascular disease mortality and overall mortality. Nevertheless, overall mortality was substantially increased even in the absence of cardiovascular deaths. Lakka et al stress that this analysis excluded individuals with diabetes or known CV disease, and thus it represents an earlier stage of TMS. Waist circumference was a particularly important factor, with increased mortality in individuals with the waist cutoff of > 40 inches. WHO criteria using waist-hip ratio appear to be more sensitive in detecting individuals who will develop diabetes; the NCEP definition readily defined individuals with an increased risk for all-cause and CVD mortality. Finally, Lakka et al stress that 2 major published diabetes prevention studies, one from Finland and one from the United States, have indicated that relatively modest lifestyle interventions can have a major positive effect on decreasing risk of subsequent diabetes in TMS individuals. Thus, weight loss, diet, and physical activity favorably alter many of the components of TMS, at least in the short term; the Kuopio group has previously shown that men engaged in regular moderate to vigorous physical activity are less likely to develop TMS. Lakka et al suggest an increased emphasis on "early identification, treatment, and prevention of the metabolic syndrome" as a means of decreasing cardiovascular and overall mortality as well as diabetes and cardiovascular disease (Lakka HM, et al. *JAMA*. 2002;288:2709-2716).

COMMENT BY JONATHAN ABRAMS, MD

This important observational study serves as a "smoking gun" with respect to the serious risks of the phenome-

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non of the metabolic syndrome and insulin resistance. The interrelationships between glycemic control, insulin sensitivity, inflammation, cytokine activation, hypertension, and dyslipidemia are complex, plus TMS probably has a genetic basis as well. The recently published Botnia study[1] indicates that high-risk TMS individuals are those with a family history of diabetes or who have known vascular disease; the present report underscores the risk for men with TMS at earlier stages, which represent a large and increasing percentage of the population. The Diabetes Prevention Program, a randomized trial comparing healthy lifestyle of diet and regular exercise to usual care, demonstrated that the development of diabetes could be substantially reduced over a relatively short period. In addition to dietary changes as well as regular physical activity, there is increasing evidence that agents activating nuclear transcription factors may also improve the metabolic syndrome. No randomized clinical trials are available to show a decrease in clinical events or increased survival in TMS, but it is likely that the substantial increase in mortality found in the Kuopio study can be abrogated with vigorous lifestyle interventions. It behooves the practicing physician-cardiologist, internist, or family practitioners to focus on the concatenation of abdominal or visceral (male pattern) obesity, hypertension, dyslipidemia, and/or elevated plasma glucose not yet in the diabetic range; these factors represent a particularly lethal phenomenon, deserving of aggressive and vigorous risk factor and lifestyle changes. The recent recognition that more than 50% of Americans are overweight or obese underscores the need for urgency in the recognition of the metabolic syndrome, as well as an aggressive therapeutic strategy of lifestyle and even pharmacologic therapy for these individuals. ■

Reference

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IIb/IIIa Inhibition for PCI of Bypass Grafts

ABSTRACT & COMMENTARY

Synopsis: *GP IIb-IIIa inhibitors do not improve outcomes in bypass graft intervention as performed in trials.*

Source: Roffi M, et al. *Circulation*. 2002;106: 3063-3067.

THE LONG-TERM SUCCESS OF REVASCULARIZATION BY coronary artery bypass graft (CABG) surgery is not infrequently limited by degeneration, and ultimately failure, of venous conduits. As the population of patients with vein grafts older than 10 or even 20 years old continues to grow, so does the frequency of their referral for repeat revascularization and particularly percutaneous revascularization. While, for the referring physician and patient, the concept of simply "popping a stent" into a diseased vein graft has considerable appeal, the interventionalist is keenly aware that these cases, even in the best of hands, carry with them considerable risk of adverse events, most notably periprocedural MI. Glycoprotein (GP) IIb-IIIa inhibitors have been shown to be highly effective in preventing adverse ischemic events and even death in many patients undergoing percutaneous coronary intervention (PCI), particularly among high-risk subgroups. Therefore, many interventionalists would not choose to perform vein graft PCI without the GP IIb-IIIa inhibitor "safety net."

But paradoxically, even though they are high risk, bypass graft interventions are one subgroup that, despite initially promising data for distal embolization, has never been shown to derive clinical benefit from GP IIb-IIIa inhibition. Unfortunately, until now, data concerning outcomes with GP IIb-IIIa inhibition in bypass graft PCI have been limited to reports of relatively small groups of patients from single centers, from subgroup analyses of individual studies, or from pooled data from early clinical trials. To better address this issue, Roffi and colleagues conducted a meta-analysis of data from 13,785 patients who underwent PCI in 5 previously published GP IIb-IIIa receptor inhibitor trials: EPIC, EPILOG, EPISTENT, IMPACT II, and PURSUIT. The first 3 of these trials evaluated abciximab and the latter 2 evaluated eptifibatide. Baseline characteristics were summarized and 30-day outcomes were subjected to logistic regression analysis. Six-month and 1-year outcomes were evaluated using Cox proportional hazard models.

Of the patients included in this analysis, 13,158 underwent PCI of a native coronary artery and 627 underwent PCI of a bypass graft. With respect to baseline characteristics, the patients undergoing bypass graft PCI represented a higher-risk population. They were older, had significantly higher prevalence of all cardiovascular risk factors, including diabetes, and had significantly higher rates of history of cardiovascular disease including heart failure, prior MI, stroke, and unstable angina. As expected, patients undergoing bypass graft PCI had significantly worse outcomes at 30 days and 6 months with respect to MI, urgent revascularization, death, and the composite end point. Most notable was a doubling of mortality at 30 days (2.1% vs 1.0%, $P = 0.006$) and at 6 months (4.7% vs 2.0%, $P < 0.001$) for patients undergoing bypass graft intervention when compared with patients undergoing native coronary intervention. In addition, PCI of a bypass

graft was found to be an independent and highly significant predictor of death, MI, or urgent revascularization at 6 months (OR 1.40; 95% CI 1.11-1.79; $P = 0.006$).

Roffi et al then evaluated outcomes for 605 patients who underwent bypass graft intervention for whom complete follow-up data were available, comparing the 389 who were randomized to receive GP IIb-IIIa inhibitors (abciximab in 51%, eptifibatide in 49%) with 216 who received placebo. These groups were well matched with respect to baseline clinical characteristics except that patients receiving GP IIb-IIIa inhibitors were more likely to have a history of heart failure (15% vs 6%, $P = 0.002$) and somewhat less likely to have a history of unstable angina (70% vs 78%, $P = 0.048$). Among patients undergoing bypass graft PCI, there were no significant differences between the groups receiving GP IIb-IIIa inhibitors or placebo with respect to death, MI, urgent revascularization, or any combined end point. At 6 months, there was no difference in the composite of death, MI, or revascularization, with a trend toward more adverse events in patients receiving GP IIb-IIIa inhibition (39.4% vs 32.7%, $P = 0.07$). This lack of benefit for GP IIb-IIIa inhibition was consistent across all 5 trials included in this analysis. In addition, from a safety perspective, rates of major bleeding (6.8% vs 1.4%, $P = 0.004$) and minor bleeding (14.9% vs 8.1%, $P = 0.016$) were higher in the graft PCI patients receiving GP IIb-IIIa inhibitors.

Roffi et al conclude that GP IIb-IIIa inhibitors do not improve outcomes in bypass graft intervention as performed in the trials included in their analysis. They postulate that in graft PCI, the amount or composition of plaque embolization may render the GP IIb-IIIa inhibitors ineffective. Importantly, Roffi et al point out that, in this analysis, more than half of the ischemic events in patients undergoing graft PCI occurred late—not in the immediate periprocedural period, but beyond 30 days of follow-up. Therefore, they suggest it is likely that additional preventive strategies will be necessary if we are to improve long-term clinical outcomes in these patients.

They acknowledge the limitations inherent in pooled data analysis due to differences in inclusion criteria, drugs, and dosages used, and differences in end points collected in the group of trials included. They state that the vast majority of PCIs included in this analysis were performed on vein grafts, but that graft type was not specified in all of the trials. The strength of this method is that it allowed Roffi et al to evaluate a large randomized patient population and conclude that GP IIb-IIIa inhibition does not confer benefit in the setting of bypass graft PCI.

COMMENT BY SARAH M. VERNON, MD

This report from Roffi et al further delineates the magnitude of increased risk associated with bypass graft intervention in a large group of patients suggested in previous observations and further clarifies the lack of benefit of GP IIb-IIIa inhibitors when given in conjunction with conventional bypass graft PCI. We have known for some time that bypass graft atherosclerosis is a different "animal," and, as such, behaves much differently than disease encountered when instrumenting native coronary arteries. As Kereiakas outlines in his accompanying editorial,[1] graft atherosclerosis is bulky, friable, and prone to distal embolization of both large and small particulate matter, which contributes to mechanical obstruction as well as distal microvascular spasm and thrombosis, all of which contribute to the angiographic phenomenon of "no-reflow" and to clinically apparent ischemic complications. As Roffi et al point out, given the complexity of the pathobiology, it is likely that alternative mechanical strategies to prevent distal embolization, or perhaps a combination of mechanical and pharmacologic strategies, will be necessary to prevent the cascade of adverse events that result in ischemic complications. There is promise in this arena in the form of the recently published SAFER trial,[2] which demonstrated a significant 42% relative risk reduction in 1-month major adverse complications when the GuardWire distal protection device was used in vein graft PCI. While the GuardWire is the only FDA-approved distal protection device currently available for clinical use, there are others in the pipeline, some of which are in clinical trials, which use alternative strategies to capture or even prevent distal embolization of debris. It is unclear whether adjunctive GP IIb-IIIa inhibitor administration might ultimately prove to confer benefit when used in combination with a mechanical distal protection device. ■

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Rate Control vs Rhythm Control In Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *There was no overall benefit to a rhythm control strategy. Therefore, rate control should be considered a primary therapeutic option, and rhythm control, if elected, may be abandoned early if not fully satisfactory.*

Source: Wyse DG. *N Engl J Med*. 2002;347:1825-1833.

The atrial fibrillation follow-up investigation of Rhythm Management (AFFIRM) trial was

designed to test the hypothesis that attempts to maintain sinus rhythm with antiarrhythmic drug therapy are beneficial in patients with atrial fibrillation who, because of age or other risk factors, are at risk for stroke or death. The study enrolled 4060 patients with a mean age of 69.7 years. Sixty-one percent were male. Hypertension was primary cardiac diagnosis in 51% of the patients and was reported as a contributing illness by 71%. Twenty-three percent had a history of congestive heart failure. In order to be eligible for the study, patients had to have had at least 6 hours of atrial fibrillation documented within the preceding 6 months. Patients could be in sinus rhythm at the time of randomization because they had either spontaneously reverted to sinus rhythm or had been cardioverted before randomization. In 69% of the patients, the qualifying episode of atrial fibrillation had lasted for 2 days or longer. In 35% of the patients, the qualifying episode was the first documented episode of atrial fibrillation. Most of the patients had normal left ventricular systolic function with 74% of the patients reported to have a normal left ventricular ejection fraction.

After enrollment, patients were randomized either to a strategy that involved AV nodal blocking agents to control rates during either persistent or recurrent atrial fibrillation or antiarrhythmic drugs to restore and/or maintain sinus rhythm. Any available antiarrhythmic could be chosen by the investigator. Chronic warfarin anticoagulation was required in the rate control group. In the rhythm control group, continuing warfarin therapy was recommended, but anticoagulation could be discontinued at the discretion of the investigator if sinus rhythm was maintained by drug therapy. Rate control was assessed at both rest and during activity. The goal was a heart rate no higher than 80 bpm at rest and no higher than 110 bpm during a 6-minute walk test. The major end point of the trial was overall mortality. Secondary end points evaluated included disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest.

In the rate control group, digoxin, beta-blockers, and calcium channel blockers, alone or in combination, could be used for rate control and this was successful in most patients. During the course of the study, only 5.2% of the patients in the rate control group had to undergo atrioventricular junctional ablation. A total of 248 patients crossed over from the rate control to the rhythm control group but one-third of these failed to maintain sinus rhythm and reverted to a rate control strategy by the end of the study. In the rhythm control group, more than two-thirds of the patients were treated with either amiodarone or sotalol. By the end of the study, almost two-thirds of the patients had undergone at least 1 trial with amiodarone. Rhythm maintenance was assessed at periodic intervals. At the 1-, 3-, and 5-year follow-up visits, 82.4%, 73.3%, and 62.6% of the patients were in sinus rhythm, respectively. Electrical cardioversion was required once in 368 patients, twice in 214 patients, and 3 or more times in 187 patients. By the end of the trial, 594 patients assigned to the rhythm control group had crossed over the rate control group. Anticoagulation was well maintained in the rate control group with more than 85% of the patients on warfarin at each follow-up visit. In the rhythm control group, approximately 70% of the patients remained on warfarin throughout the course of the trial.

There was a slight but not statistically significant increase in mortality in the rhythm control group. By the end of the trial, there had been 352 deaths among the 2033 rhythm control patients vs 306 deaths among the 2027 rate control patients. The average duration of follow-up was 3.5 years. There was no difference in the rates of the composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest. The prevalence of ischemic stroke was similar between the 2 groups within an annual rate of approximately 1% per year. Most of these events occurred in patients in whom warfarin had been stopped or in whom the INR was subtherapeutic. Quality of life measurements were similar between the 2 groups. Subgroup analysis did not identify any group that showed a significant benefit from a rhythm control strategy.

Wyse and colleagues conclude that there was no overall benefit to a rhythm control strategy. Therefore, rate control should be considered a primary therapeutic option, and rhythm control, if elected, may be abandoned early if not fully satisfactory. They also concluded that continuous anticoagulation is warranted in all patients with atrial fibrillation and risk factors for stroke even when sinus rhythm appears to be restored and maintained.

COMMENT BY JOHN DiMARCO, MD, PhD

Atrial fibrillation is the most common sustained rhythm encountered by clinicians. It is estimated that more than 2 million patients in the United States have paroxysmal or persistent atrial fibrillation. It had long been assumed that a strategy to maintain sinus rhythm should be the preferred approach for the patients. The data presented in the AFFIRM trial, however, do not support this assumption. If patients can either present with minimal symptoms or their symptoms can be made tolerable with rate control strategy, there seems to be no advantage to the rest of the attempts to maintain sinus rhythm. In particular, it appears that even when sinus rhythm is apparently maintained, patients' risk for stroke remains high if they are not anticoagulated. Therefore, Wyse et al's conclusion that either rate control or rhythm control strategy is acceptable as long as antico-

agulation is continued seems fully justified.

There were many limitations, however, to the AFFIRM trial. Patients with the most severe symptoms in atrial fibrillation were unlikely to be enrolled in the trial. These patients probably failed attempts at symptom management with a rate control strategy and would not have been randomized. However, data from other studies suggest that these patients are also not well managed with a rhythm control strategy since it is in these sicker patients in whom sinus rhythm is the most difficult to maintain. It is also important to note that patients with both paroxysmal and persistent atrial fibrillation could be entered in the trial and that many patients had undergone cardioversion before they were randomized. This resulted in many patients, even in the rate control group, being in sinus rhythm during major portions of the follow-up period. Obviously, if these patients did not have recurrent atrial fibrillation off drugs, it would have been hard to show benefit in them with drug therapy. The study also did not carefully document if atrial fibrillation recurred and what the duration of the episodes were. Only snapshot views of rhythm maintenance were available. Finally, AFFIRM dealt with a population of patients who were either elderly or who had other risk factors for stroke or death. It, therefore, may not be appropriate to apply the results to younger patients who, although they may be at lower risk for stroke or death, may be more highly symptomatic.

The practical consequences of the AFFIRM trial data are very important to clinicians. If a patient presents with atrial fibrillation and either has few symptoms at presentation or can be made symptom-free with simple rate control strategy, then that approach is certainly acceptable. It should not be required to put many elderly patients with only minor symptoms through repeated cardioversions and drug trials that may have an unfavorable risk-benefit ratio. ■

Doppler Estimation of Pulmonary Diastolic Pressure

ABSTRACT & COMMENTARY

Synopsis: *Estimation of PADP by the new TR jet velocity method is reliable over a wide range of pressures in patients with heart failure.*

Source: Lanzarini L, et al. *Am Heart J*. 2002;144:1087.

DOPPLER ECHOCARDIOGRAPHIC TECHNIQUES FOR estimating pulmonary artery (PA) systolic pressure (SP) and diastolic pressure (DP) using tricuspid (TR) and pulmonic valve (PV) regurgitation (PR), jet velocity and estimation of right atrial pressure (RAP) usually by inspection of the size and dynamics of the inferior vena cava (IVC) have been well described. A new technique based upon the TR jet velocity alone has been studied in a small number of subjects. Lanzarini and associates sought to verify the accuracy of this approach in a larger group of patients undergoing right heart catheterization for evaluation of heart failure. In 86 stable patients who were potential heart transplant recipients, right heart catheterization and echo Doppler were performed within 24 hours of each other. PASP was estimated using the peak TR jet velocity-derived pressure difference plus estimated RAP via IVC inspection. PADP was estimated in the standard way using PR jet-derived end-diastolic pressure difference plus RAP (PADP-PR). Since PADP = RVSP at the time of PV opening, the time from the ECG QRS wave onset to the onset of PA flow can be superimposed on the continuous wave Doppler recording of the TR jet and the resulting pressure value calculated (PADP-TR). PADP-PR and PADP-TR were then compared to the invasive measure.

Catheter-measured PASP ranged from 8 to 119 mm Hg, PADP from 1 to 59 mm Hg, and RAP from -5 to 20 mm Hg. The Jin concordance correlation coefficient and Bland Altman paired differences analysis were used to determine the accuracy of each noninvasive estimate to the corresponding invasive measure. There was good agreement with PASP and PADP-TR, but agreement was poor with PADP-PR and RAP. Lanzarini et al concluded that estimation of PADP by the new TR jet velocity method is reliable over a wide range of pressures in patients with heart failure.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

The noninvasive estimation of both systolic and diastolic pulmonary pressures provides more information of value to the management of patients with heart failure and pulmonary hypertension. For example, elevated systolic pressure with normal or low diastolic pressures suggests volume overload pulmonary hypertension rather than left heart failure or pulmonary vascular disease. The derivation of both pressures largely from the TR jet velocity is advantageous since it is often obtainable even in patients with poor images, especially if contrast enhancement is used. In this study, TR jet velocity was obtainable in 87% of the patients, RAP in 77%, and PR in 76%. However, TR velocity at the time of PV opening (PADP-TR) was obtained in 93%, PASP was estimated in 84%, and PADP-PR in 89%. Thus, there is a clear acquisition advantage to TR jet-based methods.

Since PASP and PADP-PR both require estimation of RAP, which was poorly estimated, why was PASP accurate and PADP-PR not? Perhaps because RAP is numerically a larger fraction of the PADP-PR calculation. Also, PR jets are difficult to record, which may have contributed to the inaccuracy of methods based upon it. TR jets can be difficult to record also, but often the early part of the jet is better seen than the peak as was demonstrated in this study.

Interestingly, the range of the catheter RAP values was -5 to 20 mm Hg, whereas, RAP estimated by the IVC method was 5 to 25 mm Hg. Clearly, estimation of RAP continues to be a problem, especially at the low end, which explains why PASP estimates of 40 mm Hg can be observed in normal subjects. Thus, the PADP estimate from the TR jet, which does not use RAP, should have superior accuracy as was shown in this study.

The strengths of this study include the large population with a wide range of right heart pressures. Weaknesses include the up to 24-hour time difference between the invasive and noninvasive measurements and the lack of contrast use, which may have increased the success of recording TR jet velocity. Finally, Lanzarini et al recommend that this new technique for estimating PADP be incorporated into the standard echo Doppler report. ■

The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial

ABSTRACT & COMMENTARY

Synopsis: *DDDR pacing using a right ventricular lead in patients without an indication for antibradycardia pacing is detrimental. Therefore, for patients with standard indications for ICD therapy and no standard indication for cardiac pacing, dual-chamber pacing offers no clinical advantage over ventricular back-up pacing and may be detrimental.*

Source: The DAVID Trial Investigators. *JAMA*. 2002; 288:3115-3123.

The DAVID trial was designed to see if aggressive dual chamber pacing would benefit patients with implantable cardioverter defibrillators (ICDs) even in the absence of an accepted bradycardia indication for pacing.

The trial recruited patients who had a standard indication for an implantable cardioverter defibrillator. These criteria for ICD insertion included both primary and secondary therapy for ventricular arrhythmias. Patients with known symptomatic bradycardia or secondary third-degree AV block or current or unstable atrial arrhythmias were excluded. All patients underwent implantation of an ICD with dual-chamber pacing capability. After implant, patients were randomly assigned to have the pacing function of the device initially programmed to either the VVI mode with a lower rate of 40 bpm (VVI-40) or to the DDDR mode with a lower rate of 70 bpm (DDDR-70). Supraventricular tachycardia detection enhancements could be used only in the DDDR mode. Tachyarrhythmia detection was set to 150 bpm or slower and diagnostic features were set to collect atrial and ventricular bipolar electrograms and markers during ventricular tachyarrhythmia episodes for all patients. Optimal pharmacologic therapy for left ventricular dysfunction and heart failure was recommended for all patients. Antiarrhythmic drug therapy could be used when thought necessary by the investigator. Amiodarone was the preferred agent for both supraventricular and ventricular arrhythmias. Crossover from one pacing mode to another was discouraged and required permission from the clinical trial center.

The combined primary end point was freedom from death or hospitalization from heart failure. Events were reviewed by an events committee, which made the final decision on each reported end point.

A total of 506 patients were enrolled and randomized in the trial. The mean age was 65 years and 83% were male. Approximately equal numbers of patients received their ICD for primary and secondary prevention reasons. There were no major differences in the use of various cardiac drugs between the 2 groups. The mean left ventricular ejection fraction was 27%, but only 12% of the patients were New York Heart Association functional Class III or IV. Sixty-nine percent of the patients had a QRS duration of less than 130 m/sec. Subsequent to randomization but not during the baseline hospitalization, new or worsened heart failure occurred in 4.2% of the DDDR-70 group vs 0.8% of patients in the VVI-40 group. New or worsened heart failure during the initial hospitalization was not counted as a primary end point. Recurrent ventricular arrhythmias requiring therapy during the hospitalization for ICD implantation were slightly more frequent in the DDDR-70 group (7.5%) than in the VVI-40 group (5.9%).

The trial was stopped by the Data Safety Monitoring Board after a median follow-up of 8.4 months. There were fewer deaths and hospitalizations for new or worsened heart failure in the VVI-40 group. The hazard ratio was 1.61 with a 95% confidence interval of 1.06-2.44 ($P < 0.03$). One-year survival free of the composite end point was 83.9% for the VVI-40 patients compared with

73.3% for the DDDR-70 patients. Both rates of congestive heart failure hospitalization (13.3% vs 22.6%) and death rates (6.5% vs 10.1%) were higher in the DDDR-70 group. When the percentage of right ventricular paced beats was correlated with survival, it was found that patients with a higher percentage of right ventricular pacing had worse 12-month event-free rates.

The investigators conclude that DDDR pacing using a right ventricular lead in patients without an indication for antibradycardia pacing is detrimental. Therefore, for patients with standard indications for ICD therapy and no standard indication for cardiac pacing, dual-chamber pacing offers no clinical advantage over ventricular back-up pacing and may be detrimental.

COMMENT BY JOHN DiMARCO, MD, PhD

The DAVID investigators optimistically hoped that they would be able to show an improved survival with the use of dual-chamber pacing in patients with implantable cardioverter defibrillators. I term this an optimistic hypothesis since it has been difficult to show that dual-chamber pacing benefits even those with accepted bradycardia indications for permanent pacing. For example, in the Canadian Trial of Physiologic Pacing,[1] there was no significant improvement in the rate of stroke or death due to cardiovascular causes with physiologic pacing as opposed to ventricular pacing. There was, however, a significant improvement in the development of atrial fibrillation with the addition of atrial pacing, primarily in patients with sinus node dysfunction.

The patients in the DAVID trial had an indication for an ICD but did not have bradycardia. Therefore, we would have expected improved survival only if the higher heart rate associated with DDDR pacing at 70 bpm improved their hemodynamics or their risk for arrhythmia. The study also allowed activation of supraventricular tachycardia detection enhancements based on the information provided by the atrial electrogram, but one would not have expected successful use of these enhancements to result in a mortality benefit.

Since the trial was terminated early for safety reasons, the investigators thought it important to publish data before many secondary end points could be analyzed. It will be important to see if there is a decrease of inappropriate shocks for supraventricular arrhythmias associated with the addition of the atrial lead. If this is so, it may be appropriate to implant a dual-chamber defibrillator even if the atrial lead is used only for diagnostic purposes initially.

The mechanism by which the increase in early heart failure was seen is probably related to overuse of right ventricular pacing in patients who normally had narrow QRS complexes. It has been shown in patients with myocardial dysfunction that there can be adverse hemodynamic side effects from right ventricular pacing. The DAVID trial data indicate that in many patients with significant ventricular dysfunction biventricular pacing may be preferred to just right ventricular pacing in patients who will depend on the pacemaker functions of their ICD to prevent bradycardia. ■

Reference

1. Connolly SJ, et al. *N Engl J Med*. 2000;342:1385-1391.

CME Questions

Effective with this issue, Clinical Cardiology Alert *is changing its testing procedure. You will no longer need to return a Scantron answer sheet to earn credit for the activity. Please review the text, answer the following questions, check your answers against the key on the following page, and then review the materials again regarding any questions answered incorrectly.* ***To receive credit for this activity, you must return a CE/CME evaluation at the end of the testing term.***

This testing procedure has proven to be an effective learning tool for adults. If you have any questions about the new testing method, please contact Customer Service at 1-800-688-2421.

7. Observational data suggest that the metabolic syndrome increases:

a. cardiovascular mortality.
b. coronary artery disease mortality.
c. total mortality.
d. All of the above

8. Rate control in atrial fibrillation as compared to rhythm control:

a. increases mortality.
b. increases stroke.
c. increases bleeding episodes.
d. None of the above

9. Dual-chamber pacing in patients with ICDs:

a. decreases survival.
b. decreases atrial arrhythmias.
c. decreases syncope.
d. All of the above

10. Pulmonary diastolic pressure can be estimated from Doppler:

a. pulmonary regurgitant velocity.
b. tricuspid regurgitant velocity.
c. inferior vena cava flow.
d. a or b

11. Percutaneous interventions in bypass grafts:

a. are benefitted by IIb-IIIa inhibitors.
b. increase mortality vs native arteries.
c. increase acute complications vs native arteries.
d. All of the above

Answers: 7: D; 8: D; 9: A; 10: D; 11: B

PHARMACOLOGY WATCH

FDA Issues 'Black Box' Warning Based on WHI Study

The FDA has mandated a "Black Box" warning for all estrogen and estrogen/progestin products for use by postmenopausal women. The new warnings are based on analysis of data from the Women's Health Initiative (WHI) study that was published July 2002. The box warning emphasizes that these drugs have been associated with increased risks for heart disease, heart attacks, strokes, and breast cancer and that they are not approved for heart disease prevention. Wyeth Pharmaceuticals, the manufacturer of Premarin, Prempro, and Premphase, products that were used in the WHI study, are also required to change their indications to: treatment of severe vasomotor symptoms, vulvar and vaginal atrophy associated with menopause, prevention of postmenopausal osteoporosis, and should only be used when the benefit clearly outweighs the risk. The labeling will also be required to include consideration of other therapies for the atrophy and osteoporosis indications, and to recommend use of the lowest dose for the shortest duration possible. While Wyeth's products are the focus of this initial press release and FDA action, all estrogen products will be subject to new labeling. The FDA is also recommending future research to answer questions regarding the risks of lower-dose estrogen products and if other types of estrogens and progestins are associated with lower risk of CVD and breast cancer. The complete press release can be viewed at www.fda.gov.

ALLHAT: Thiazide for Hypertension Treatment

Thiazide diuretics should be considered first-line therapy for hypertension, according to the authors of the ALLHAT study published in December. In a finding that surprised nearly everyone (especially the sponsors of the study) in patients with hypertension and at least one other cardiovascular risk factor, the diuretic chlorthalidone was associated with better cardiovascular outcomes at less cost and with equal tolerability compared to a calcium channel blocker or an ACE inhibitor. ALLHAT enrolled more than 33,000 patients from 623 centers in the United States, Canada, and the US Virgin Islands. Patients were randomized to the calcium channel blocker amlodipine, the angiotensin-converting enzyme inhibitor lisinopril, or chlorthalidone. Mean follow-up was 4.9 years with the primary outcome being combined fatal CHD or nonfatal MI. Secondary outcomes included all-cause mortality, stroke, combined CHD, and combined cardiovascular disease (CVD). The 6-year rate of the primary outcome and all-cause mortality was virtually identical for all 3 drugs. Chlorthalidone was superior to amlodipine in preventing heart failure (10.2% vs 7.7%, RR, 1.38, 95% CI, 1.25-1.52) and was superior to lisinopril for lowering blood pressure and in 6-year rates of combined cardiovascular disease including stroke (6.3% vs 5.6%) and heart failure (8.7% vs 7.7%). With improved cardiovas-

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cular outcomes, lower cost, and equal tolerability, the study concludes that thiazide-type diuretics are superior in preventing one or more forms of CVD and that they should be the preferred agent in antihypertensive therapy, and should be included in all multidrug regimens (*JAMA*. 2002;288:2981-2997). An accompanying editorial calls ALLHAT "one of the most important trials of antihypertensive therapy" and suggests that national guidelines should be changed to emphasize use of thiazide diuretics as initial therapy (*JAMA*. 2002;288:3039-3042).

Candesartan Effective Against Migraines

The angiotensin II receptor blocker candesartan is effective in preventing migraine headaches, according to a new study. Norwegian researchers looked at 60 patients age 18-65 with 2-6 migraines per month. Patients were randomized in a double-blind placebo-controlled crossover study with the main outcome being number of days with headache. Secondary outcomes included use of pain medications and triptans, hours with headache, headache severity, and days lost from work. During the 12-week study, the mean number of days with headache was 18.5 with placebo vs 13.6 with candesartan (P = .001) in the intention to treat analysis (n = 57). Patients were considered a candesartan responder if they noted a reduction of 50% or more of days with headache (18 of 57 patients, 31.6%) or days with migraine (23 of 57 patients, 40.4%). Although this represented a minority of patients, those who did respond benefited from effective migraine prophylaxis. Candesartan's tolerability profile was comparable with placebo (*JAMA*. 2003;289:65-69).

Cough! No Cold Relief from Echinacea

Echinacea offers no benefit in treating the common cold according to a study from the University of Wisconsin. A total of 148 college students with recent onset colds were randomized to an encapsulated mixture of unrefined Echinacea (*E purpurea* herb and root and *E angustifolia* root) 6 times a day on the first day of illness and 3 times a day on the subsequent days up to a total of 10 days. The main outcome was the severity and duration of self-reported symptoms of URI. No statistically significant differences were detected between Echinacea and placebo groups for any of the measured outcomes, which included trajectories of severity over time or mean cold duration. No significant side effects were noted with Echinacea. The study concludes that no detectable benefit or harm could be found with Echinacea treatment for the common cold (*Ann Intern Med*. 2002;137:939-946).

COX-2 Inhibitors and GI Benefits Could Be Overrated

Could the GI benefits of COX-2 inhibitors be overrated? A new study suggests that the COX-2 inhibitor celecoxib is no safer than a combination of diclofenac plus omeprazole with regard to ulcer risk in patients with a history of peptic ulcer disease and arthritis. Researchers from Hong Kong recruited patients with arthritis and NSAID-related bleeding ulcers. After their ulcers had healed, 287 patients who were negative for *Helicobacter pylori*, were randomly assigned to receive celecoxib 200 mg twice a day plus placebo, or diclofenac 75 mg twice a day plus 20 mg of omeprazole for 6 months. Recurrent bleeding ulcer occurred in 7 patients receiving celecoxib and 9 receiving diclofenac/omeprazole (4.9% vs 6.4%). Renal adverse events including hypertension, peripheral edema, and renal failure occurred in 24.3% of patients receiving celecoxib and 30.8% of those receiving diclofenac/omeprazole. The authors suggest that neither regimen offered effective protection against recurrent ulcer complications or renal adverse effects (*N Engl J Med*. 2002;347:2104- 2110).

FDA Actions

Pfizer's new anti-migraine drug, eletriptan (Relpax) has been approved by the FDA for marketing. The drug that is available in 20-mg and 40-mg tablets has been shown to be effective in aborting migraine headaches within 2 hours. The company is marketing a 80-mg tablet in Europe, but the FDA refused to approve the higher dose due to an increase in adverse events.

Montelukast (Singulair), Merck's leukotriene inhibitor, has been approved by the FDA for the treatment of seasonal allergic rhinitis. The drug has been on the market since 1998 for the treatment of asthma in adults and children. This new indication is the first for a leukotriene inhibitor, and creates a new, nonantihistamine treatment modality for this indication. Montelukast was approved for symptoms of seasonal allergic rhinitis in adults and children aged 2 years and older. It is available in 10 mg strength for adults, and a chewable 4 mg or 5 mg strength for children. ■