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CLINICAL CARDIOLOGY ALERT

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Late-Breaking Trials from the ACC Scientific Sessions in New Orleans

CONFERENCE COVERAGE

SYNERGY

THE SUPERIOR YIELD OF THE NEW STRATEGY OF ENOXAPARIN, Revascularization, and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trial was presented by Dr. Kenneth Mahaffey and colleagues. The objectives of the study were to assess the use of enoxaparin in high-risk acute coronary syndrome patients and determine its safety in the cardiac catheterization laboratory. Two of the following 3 inclusion criteria had to be met to enter the study: age older than 60 years; ECG ST changes; or positive biomarkers. Of the > 10,000 patients entered, 45% met all 3 criteria. The primary end point was all-cause death and myocardial infarction at 30 days. The patients entered were randomized to enoxaparin vs unfractionated heparin (UHep). Almost all of the patients underwent cardiac catheterization (90%), 60% were also on clopidogrel, and 50% were given IIb/IIIa agents. The incidence of the primary end point was 14% and not different between the 2 treatments. Death occurred in 3% and MI in 12%; neither were significantly different in the 2 groups. Major bleeding was higher in the enoxaparin group (9.1 vs 7.6%; $P = .008$). There was no difference in other cardiac catheterization adverse events, and there were no major subgroup findings. Mahaffey et al concluded that in high-risk early invasive strategy acute coronary syndrome patients there was no difference in the efficacy of enoxaparin vs Uhep, but major bleeding was more frequent on enoxaparin.

COMMENT BY MICHAEL H. CRAWFORD, MD

Mahaffey et al pointed out that there are several limitations to the study that temper the conclusions. First, patients who were given one of the study drugs prior to randomization but did have their drug switched per the protocol were not excluded. Whether this switching of drugs produced adverse effects is unknown, as is whether any effects favored one group over another. Of interest, the ESSENCE

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trial, which showed benefit of enoxaparin over Uhep, didn't allow prerandomization treatment with the study drugs. However, this was also a lower-risk group in which such a stipulation was easier to uphold. Second, Mahaffey et al did not control postrandomization management, which resulted in a noteworthy incidence of crossovers. This was especially the case in patients who underwent revascularization after randomization, since many were switched from enoxaparin to Uhep. Third, the excess bleeding was mainly seen in the patients undergoing revascularization where the exact level of enoxaparin's effect may be more difficult to determine and may be added to if Uhep is also given. Despite these caveats, this study is not good news for enoxaparin. It will be interpreted that the invasive cardiologists and surgeons' reluctance to use this drug is well founded. The presenters emphasized that a special noninferiority analysis showed no inferiority of enoxaparin vs Uhep, but this seems like blowing smoke. What it does mean is that if there are reasons to use enoxaparin instead of Uhep, the results should be the same overall. However, in those patients undergoing revascularization, there is going to persist unease about the bleeding risks of an agent that has a prolonged duration of action and no good way of determining its level of effectiveness at any one time. Since determining who is going to need revascularization early may not always be easy, this is going to put a damper on the use of this agent in higher-risk patients more likely to undergo revascularization. ■

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WATCH

The warfarin and antiplatelet trial in chronic Heart failure (WATCH) was presented by Barry Massie, MD, from San Francisco. This was a VA cooperative study that tested the hypotheses: 1) Warfarin is superior to antiplatelet drugs; and 2) Aspirin has adverse effects in patients on angiotensin-converting enzyme inhibitors (ACEI) in heart failure patients. Inclusion criteria included NYHA class II-IV heart failure, left ventricular ejection fraction < 35%, and baseline ACEI therapy. Exclusions included high bleeding risk, atrial fibrillation, and unstable patients. The patients were randomized to 3 groups: warfarin to an INR of 2.5-3.0, aspirin 162 mg/d, and clopidogrel 75 mg/d. Follow-up was for 2-5 years. The primary end point was all-cause mortality, myocardial infarction, and stroke. Secondary end points included the above plus hospitalization for heart failure, unstable angina, and peripheral emboli. There were also safety and economic analyses. Enrollment was 40% of expected so the primary and secondary end points were combined to increase the power of the study. In January 2002 the trial was stopped because of low enrollment, not the results of the study. In all, 1587 patients were enrolled and followed for a mean of 23 months. ACEI use was 88%, and angiotensin receptor blocker use was 11% (99% combined). Beta-blockers were used in 70%. Mean INR was 2.6, with only 31% in the target 2.5-3.0 range, but 70% in the 2.0-3.5 range. There was an overall 93% adherence to the prescribed drug therapy. Three-quarters of the patients had ischemic cardiomyopathy, 56% were class II-IV, and mean EF was 24%.

Results

For the primary end point, there was no statistically significant difference between aspirin and warfarin, but there was a trend for fewer strokes on warfarin. Heart failure admissions were increased on aspirin ($P < .001$). The number of hospitalizations/100 patent-years was reduced 31% on warfarin vs aspirin. There were no differences in the primary end point between aspirin and clopidogrel, but there was a trend for more hospitalizations on aspirin. Bleeding complications were increased on warfarin. The investigators concluded that warfarin use in heart failure patients with systolic dysfunction is no better than antiplatelet therapy for preventing death and adverse cardiovascular events including emboli. However, as compared to clopidogrel and warfarin therapy, aspirin increased hospitalizations for heart failure.

COMMENT BY MICHAEL H. CRAWFORD, MD

Despite the fact that this is the largest trial of anticoagulants in heart failure to date, it was underpowered to detect differences in the treatments concerning the primary end point. Power was estimated at 40-60% depending on which end point was examined. Consequently, there is no mandate for warfarin in heart failure patients due to systolic dysfunction, unless other indications are present. Definitive answers will have to await the WARCEF trial, which is ongoing. The only finding of statistical significance in this study was the increase in hospitalizations for heart failure in the aspirin group. This finding is consistent with other studies, which have suggested a negative interaction between aspirin and ACEI. However, the investigators cautioned that this is a secondary end point in an underpowered trial and has to be viewed with some skepticism. On the other hand, in the question-and-answer period after the presentation, Dr. Massie stated that he has changed his practice in 3 ways based upon these results: 1) He no longer uses aspirin in nonischemic cardiomyopathy; 2) He stops aspirin if the patient has refractory heart failure; and 3) He does not use aspirin if they have other indications for either warfarin or plavix.

Mortality in Acute Coronary Syndromes

ABSTRACT & COMMENTARY

Synopsis: *The use of combination evidence-based pharmacologic therapy was associated with lower 6-month mortality in patients with ACS.*

Source: Mukherjee D, et al. *Circulation*. 2004;109: 745-749.

Several recent multicentered trials have exhibited the advantage of specific adjunctive medical therapy in acute coronary syndromes (ACS) for reducing major adverse cardiac events. The group from the University of Michigan sought to determine the impact on mortality of combining these agents in patients with unstable angina or acute myocardial infarction (MI). The patients were identified based upon discharge diagnoses and their charts reviewed to screen for entry criteria and document their therapy. Six-month mortality data were obtained by record review and phone calls. Based upon Class I recommendations of the ACC/AHA clinical practice guidelines, a medication appropriateness algorithm was developed for lipid-lowering, beta-blocker, ACE inhibitor, and antiplatelet therapy, which ranged from 0 for no indicated medications used to IV for all 4 indicated medications used. A total of 1358 patients were studied: 55% with non-ST segment elevation MI, 30% with unstable angina, and 15% with ST segment elevation MI. Coronary angiography was performed in two-thirds, and almost half had either percutaneous or surgical revascularization. Overall use of antiplatelet medications was 95%, beta-blockers 82%, lipid-lowering 84%, and ACE inhibitors 60%. When appropriate medications used at levels II-IV were compared to level 0, statistically significant reductions in mortality were noted. Level I vs 0 was not significant. Age and ejection fraction were also powerful predictors of mortality at 6 months ($P < .0001$), as was biomarker positively ($P = .007$) and heart failure on admission ($P = .004$). Mukherjee and associates concluded that the use of combination evidence-based pharmacologic therapy was associated with lower 6-month mortality in patients with ACS.

COMMENT BY MICHAEL H. CRAWFORD, MD

Although each of these 4 pharmacologic therapies has been shown individually to decrease subsequent events in patients with ACS, this is the first study to show their synergistic benefit in combination. Six-month mortality rates were decreased an impressive 72-87%, depending on how many drugs were combined, as compared to none of these drugs being used. One drug showed a beneficial trend but was not statistically significant ($P = .08$). These are important data since most of these drugs are generic, inexpensive, and well tolerated. Given that such secondary prevention therapies are often underutilized, these data underscore the value of efforts such as Guidelines Applied to Practice and Get With The Guidelines (ACC and AHA programs, respectively).

There are other interesting data in the paper. Early revascularization showed a strong trend toward lowered 6-month mortality (RR, .24; 95% CI, .05-1.24; $P = .08$). These data are consistent with the results of FRISC II, which showed improved survival with early revascularization at 2 years of follow-up. Some might be surprised by a 60% overall ACE inhibitor use at an academic medical center, but remember the Class I indications for ACE are heart failure due to systolic dysfunction, reduced LV ejection fraction, and hypertension in patients with ACS. Although there are compelling data to treat all patients with CAD with ACE inhibitors, they are not as robust as these Class I indications. Also, general surveys have shown that ACE use in ACS is usually 50%.

There are limitations to this study. It is based upon

retrospective chart review, so information about previous use of the study drugs and reactions to them may not always be charted. Thus, some seeming drug omissions may be appropriate. Also, ARB substitution for ACE is not considered since this is not a Class I indication for ARB. In addition, newer therapies are not considered such as clopidogrel, enoxaparin, and platelet 11b/111a inhibitors. All 3 have demonstrated value in at least selected ACS patients. Finally, the impact of other strategies such as smoking cessation, folate, fish oils, weight loss, and exercise are not considered. However, despite these flaws, this is a powerful study for supporting the use of well-documented secondary preventive measures in ACS. A similar approach will be the subject of the next quality initiative on my cardiology inpatient service. ■

Women Really are Different! Gender Differences in Manifestations of CAD

ABSTRACTS & COMMENTARY

Synopsis: *Metabolic syndrome, but not obesity alone, was associated with a higher risk of cardiovascular events. The presence of MS in individuals with angiographic CAD at study entry substantially increased the likelihood of death and MACE.*

Sources: Kip KE, et al. *Circulation*. 2004;109:706-713; Marroquin OC, et al. *Circulation*. 2004;109:714-721.

The women's ischemic syndrome evaluation, or WISE program, co-chaired by Noel Bairey-Merz and Robert Bonow, has been making significant contributions to our understanding of differences in ischemia presentation, as well as pathophysiology of chest discomfort in women who may or may not have obstructive coronary artery disease (CAD). In the February 17, 2004, issue of *Circulation*, 4 WISE studies were published, as well as the conference proceedings from a recent AHA/NHLBI workshop (available on the WISE web site and *Circulation* electronic pages). Two of these studies are briefly reviewed. One is an examination of the importance of obesity vs the metabolic syndrome (MS) in women relating to cardiovascular risk. In this cohort of 744 women evaluated for suspected myocardial ischemia, it was determined that MS was a much better predictor of CV risk than obesity as assessed by BMI. This was a 3-year follow-up study (range, 2.8-4.7 years) of 83% of the entire WISE study population, representing all women referred for coronary angiography at 4 WISE study sites to evaluate possible myocardial ischemia. There were some interesting differences between obese and normal-weight women (obese women smoked less, had higher triglycerides, were on more antihypertension medications, and were less likely to be white than normal BMI women). They also had higher markers of inflammation (CRP and IL-6). About 30% of women with a normal BMI met MS criteria, 55% of overweight women (BMI 25-30) had MS, and 76% of obese women (BMI > 30) had MS. Confirmation of obstructive coronary artery disease (> 50% lesion) in the absence of MS was 30% in normal-weight women, 25% in overweight women, and 17% in obese women. However, women in the same weight categories who had MS, 56%, 52%, and 42%, respectfully, had CAD, representing a 2- to 3-fold increased likelihood of significant CAD. When survival and major adverse cardiovascular events (MACE) during follow-up were tabulated, normal metabolic women had a 3-year event-free rate > 96%, even in the obese women. These event-free rates were markedly higher compared to those with a dysmetabolic state, with event-free rates of 87%, 92%, and 92%, respectively, for the 3 weight groups. When BMI alone was evaluated for the relationship to cardiovascular events, there was no association for risk of death or MACE; MS was related to death and MACE with a 2-fold adjusted risk. Thus, MS, but not obesity alone, was associated with a higher risk of cardiovascular events.

Kip and associates' discussion underlines the findings that obesity, in the absence of MS characteristics, was not associated with adverse outcomes, whereas adverse metabolic status was clearly related to death and cardiovascular events. Women with diabetes were included in this cohort and were classified as dysmetabolic. Of importance, normal-weight women with MS were at increased risk, whereas overweight and obese women with normal metabolism had a relatively low cardiovascular risk. CRP and markers of inflammation appear to be more closely related to metabolic status than body weight. Thus, in women with suspected myocardial ischemia, MS is an adverse prognostic factor for subsequent risk, including death and MACE, whereas high BMI alone without dysmetabolic state does not confer increased risk.

In a related WISE study, it was found that in women with angiographic CAD at baseline, subsequent prognosis is directly related to the presence or absence of MS. In this cohort of 755 women, 25% had MS at entry; they had a more adverse 4-year survival rate than those with a normal metabolic status (94.3% vs 97.8%; $P = .03$), and

87.8% vs 93.5% event-free survival from MACE (P = .003). Presence of CAD and MS inferred a significantly greater risk for CV events by 5-fold (P = .05). Conversely, there was no increase in 4-year cardiovascular risk in those women without significant CAD, irrespective of metabolic status. As in the first report, markers of inflammation were lower in women with normal metabolic status. The prevalence of significant CAD was 33% in women with MS compared to 22% in those without MS, and 57% in diabetics. Only 23% of the diabetics had no CAD at entry, compared to 45% and 40% of normals and MS, respectively. MS was associated with a decreased survival (94% vs 98%; P = .03) and 4-year MACE was also increased, especially in those with diabetes (survival 93.5% normal metabolic status, 88% MS, and 76% diabetes). In those women who had significant disease at entry, 4-year survival was comparable in the MS and diabetic cohorts at 86% and markedly lower than those with normal metabolic status, who had a 4-year survival of 97%. Thus, the presence of MS in individuals with angiographic CAD at study entry substantially increased the likelihood of death and MACE over 4 years. Conversely, in those women with no CAD at baseline, survival and freedom from MACE were comparable in all cohorts. MS in the presence of CAD was associated with a nearly 5-fold increased likelihood of death and MACE vs normal metabolic status. On the other hand, women without CAD at baseline had no increased risk of death, even with MS (40% increase likelihood; P = .65). CRP levels had little influence on risk in normal or MS women. Insulin resistance was higher in women with MS, as expected, but did not predict 4-year risk of death compared to the MS alone. Mortality at 4 years was as follows: normal women 2.2%, MS 7%, and diabetics 10.6%. Marroquin and colleagues conclude that angiographic CAD in women with suspected ischemia associated with metabolic status or diabetes had a substantially lower survival, as well as event-free survival, compared to women with normal metabolic status at baseline. Marroquin et al discussed supportive prior reports and concluded that risk of CAD is intermediate for MS women compared to normal metabolic status and diabetes. Marroquin et al stress that women without CAD at entry had low risk even in the presence of MS and diabetes. They also conclude that measures of insulin resistance are not as powerful predictors of prognosis as features of MS, although they believe that insulin resistance is linked to much of the increased cardiovascular risks in MS, as well as systemic inflammation and a procoagulant state. They recommend aggressive risk-factor modification to all individuals with MS.

COMMENT BY JONATHAN ABRAMS, MD

These 2 reports are of importance by documenting the powerful adverse effect of MS in women with clinical chest discomfort both before and after identification of CAD vs normal coronary arteries. It is reassuring that MS appears to be a powerful predictor of risk and that clinicians do not need to be concerned about obtaining measures of insulin resistance. Markers of inflammation were greater in obese women but appear to have relatively little relationship to clinical outcomes once CAD status was evaluated by angiography. Both reports confirm the well-known fact that diabetic women have the worst prognosis. One conclusion that seems reasonable is that all women with a clinical presentation that suggests myocardial ischemia should be aggressively evaluated for the presence or absence of CAD, as obstructive CAD appears to be a critical prognostic factor. Women with MS, obese or not, with normal angiograms had a comparable 4-year event rate to women with normal metabolic status, confirming the critical importance of significant coronary atherosclerosis.

In conclusion, women are different than men, which of course is no secret. What is surprising, however, is the increased likelihood of chest discomfort, often atypical, in women with or without angiographic CAD, as well as the adverse influence of MS in women who have coronary atherosclerosis. There are also ample data confirming ischemic symptoms in women even in the absence of CAD, which may be related to endothelial dysfunction, or "microvascular angina," a problem that appears to be much more common in females. The WISE study has made and continues to make important contributions. For those interested in cardiac disease and gender differences, these new publications are valuable resources.

The Natural History of Lone Atrial Flutter

ABSTRACT & COMMENTARY

Synopsis: *Patients with lone atrial flutter have an increased risk for thromboembolic events and use of anticoagulation is urged for all patients with atrial flutter who are older than 65.*

Source: Halligan SC, et al. *Ann Int Med*. 2004;140: 265-268.

In this paper, Halligan and colleagues identified and determined the natural history of patients with lone

atrial flutter. Halligan et al used the medical database maintained on all residents of Olmsted County, Minn, to identify patients with atrial flutter. Five hundred and sixty-seven patients were identified. Halligan et al then excluded patients with any form of cardiac disease with the exception of controlled hypertension. Patients with atrial flutter that occurred only as a consequence of an acute illness were also excluded. These patients with "lone atrial flutter" were then compared to 2 control groups: the general population of Rochester, Minn, and a second control group consisting of Olmsted County patients with no history of hypertension who received a diagnosis of lone atrial fibrillation. Survival and stroke or transient ischemic attack rates were calculated for the 3 patient cohorts. A proportional hazards model technique was used to identify variables associated with the development of atrial fibrillation and stroke or transient ischemic attack in the patients with lone atrial flutter.

Fifty-nine patients were identified who had lone atrial flutter during this 30-year period. Of these, 75% later developed recurrent episodes or persistent flutter. The average age at diagnosis was 70, with a range of 40-97 years. Of these 59 patients, 20 had controlled hypertension. Eleven had diabetes mellitus, 3 had had prior transient ischemic attacks, and 1 had a history of an ischemic stroke. Medical therapy in these patients consisted of digitalis (61%), beta-blockers (17%), calcium channel blockers (31%), and antiarrhythmic drugs (24%). Atrial flutter ablation was introduced relatively late during the period covered in this study, and only 4 patients underwent atrial flutter ablation. At the time of diagnosis, 31 patients were receiving antithrombotic or antiplatelet therapy. At latest follow-up, 41 patients were being treated with antithrombotic or antiplatelet agents. Atrial fibrillation developed in 33 of 59 patients, a mean of 5.5 ± 6 years after the initial diagnosis of atrial flutter. Significant age- and sex-adjusted predictors for developing atrial fibrillation were diabetes, hypertension, and recurrent atrial flutter. Nineteen of 59 patients (40%) experienced at least 1 cerebrovascular ischemic event during follow-up. The mean age at the time of these events was 80 ± 10 years. The mean time from atrial flutter diagnosis to cerebrovascular event was 4.3 ± 3.9 years. Six of these 19 patients had previously developed atrial fibrillation. An actuarial analysis indicated a 5-year stroke risk of 23% and a 10-year stroke risk of 35%. Patients with atrial flutter had a higher incidence of ischemic stroke or transient ischemic attack than patients with atrial fibrillation. This was true even among the atrial flutter patients without hypertension. Halligan et al concluded that patients with lone atrial flutter have an increased risk for thromboembolic events and urge use of anticoagulation for all patients older than 65 with atrial flutter.

COMMENT BY JOHN DiMARCO, MD, PhD

There are relatively few data in the literature on the management of patients with only atrial flutter. Large series have often combined patients with atrial fibrillation and atrial flutter. Although many patients, as shown in this series, have both atrial flutter and atrial fibrillation at various times during their clinical course, this is not always true. The data in this paper suggest that atrial flutter has at least the thromboembolic potential of atrial fibrillation and, therefore, guidelines for anticoagulation used for patients with atrial fibrillation should also apply to patients with atrial flutter, even in the absence of any structural heart disease.

Recently, it has been standard practice to perform ablation of the cavotricuspid isthmus early in the course of patients who present with typical atrial flutter. Recently, however, it has been shown that the recurrence rate of atrial fibrillation is high after atrial flutter ablation. It is likely that the reported recurrence rate underestimates the recurrence rate since asymptomatic episodes of atrial fibrillation may also occur. Therefore, ablation for atrial flutter should probably be regarded as a palliative, rather than a curative, procedure, especially in patients without structural heart disease.

This paper does not mention the development of other types of conduction system diseases in its cohort. This is surprising. In my experience, atrial flutter often presents in association with sinus node dysfunction. In particular, patients who present with atrial flutter and controlled ventricular rates, many of whom may be asymptomatic, often have underlying sinus node disease. The coexistence of conduction system disease and atrial flutter is another reason why ablation procedures may only be palliative in this condition. ■

ICD Therapy In Congenital Heart Disease

ABSTRACT & COMMENTARY

Synopsis: *ICD therapy is an effective management strategy in selected pediatric and congenital heart disease patients.*

Source: Alexander ME, et al. *J Cardiovasc Electrophysiol*. 2004;15:72-76.

In this paper, Alexander and colleagues present a retrospective analysis of implantable cardioverter defibrillator (ICD) therapy from a single center, Chil-

dren's Hospital in Boston. All patients younger than 30 at implant were identified at Children's Hospital for the present analysis. The study group included 76 patients. The primary diagnosis was congenital heart disease in 32 patients, primary electrical disease in 25 patients, dilated cardiomyopathy in 6 patients, and hypertrophic cardiomyopathy in 13 patients. The mean age at the time of the initial ICD procedure was 16 ± 6 years. Only 3 patients were younger than 5, and only 6 patients were younger than 10. Eighteen patients were between the ages of 11 and 15, and 19 patients were between the ages of 16 and 20. Among the patients with congenital heart disease, 19 of 32 had tetralogy of Fallot, 5 had D-transposition of the great arteries, and 4 had aortic valve disease with left ventricular outflow tract obstruction. ICD therapy was used most frequently for secondary prevention. Sixty-one of 76 patients (80%) had a history of either cardiac arrest, syncope, or spontaneous sustained monomorphic ventricular tachycardia. Only 6 patients had no symptoms due to arrhythmia or advanced heart failure. In the 76 patients, there were 90 implants of new leads or generators. The majority (93%) of these procedures used transvenous techniques. Dual-chamber devices were used in 29 (32%) of the implants. Placement of a subcutaneous electrode array was necessary to lower defibrillation thresholds in 7 patients.

In the entire group, there was a median follow-up of 1.4 years. Overall survival was 95%. Six patients underwent cardiac transplantation. During follow-up, 28% of the patients experienced at least a single episode of appropriate therapy—shock or antitachycardia pacing. The median time to first shock was 13 months. Inappropriate therapy was observed in 25% of the patients. The reasons for inappropriate therapy were: lead failure (7 patients), sinus tachycardia (8 patients), supraventricular tachycardia (4 patients), and T-wave oversensing (2 patients). Patients with inappropriate therapy experienced a mean of 7 ± 15 inappropriate discharges. The patients with lead failure received the greatest number of inappropriate shocks. Other problems were also frequently noted. There were 11 patients (14%) who developed acute complications that extended hospital stay or required a repeat procedure. These included 2 pocket infections, 2 pocket hematomas, and single episodes of hemothorax, superior vena cava syndrome, pneumonia, electromechanical dissociation during fibrillation testing, second degree burns from external rescue shocks, and one acute lead dislodgement. In addition, there were 38 chronic complications noted in 29 patients. The most frequent chronic complication was lead failure, which was seen in 21% of the patients. Patients who were the youngest and the smallest at the time of implant and those who had the greatest growth after implant had the highest rate of lead complications.

Alexander et al conclude that ICD therapy is an effective management strategy in selected pediatric and congenital heart disease patients. Defibrillator shocks and lead failure are important problems in this population.

COMMENT BY JOHN DiMARCO, MD, PhD

ICD therapy is now a well-established option for managing life-threatening ventricular arrhythmias in adult patients with coronary artery disease and most other forms of acquired heart disease. However, there are additional factors that must be made before recommending an ICD in a child or teenager. This paper by Alexander et al reports a single-center experience with ICD therapy in children. However, the group is mixed, with 42% having congenital heart disease, 5% having some form of cardiomyopathy, and 33% having primary electrical disease. These 3 groups present somewhat different problems.

In patients with congenital heart disease, life-threatening ventricular arrhythmias often occur in association with scars related to curative surgery or as a result of ventricular dysfunction in patients who are inoperable or who have an incomplete hemodynamic response to surgery. Patients with scar-related ventricular tachycardia are very similar to those with ischemic heart disease and are well managed with an ICD if curative ablation is not possible. Patients with failure after surgery from congenital heart disease may present with a complex cardiac anatomy, and standard transvenous approaches for ICD placement may be difficult or even impossible. In addition, the defibrillation pathway in an ICD was designed with the left ventricle as the target. Since many patients with complex congenital heart disease have predominantly right ventricular involvement and enlargement, defibrillation may be more difficult. It is now almost unheard of to not have a satisfactory defibrillation threshold in an adult with coronary disease, but this study reports a relatively frequent need for subcutaneous arrays to lower defibrillation thresholds. Among patients with cardiomyopathy, there is also a difference between those with dilated cardiomyopathy and hypertrophic cardiomyopathy. The prognosis in the former group is usually determined by hemodynamic status. Many young patients with hypertrophic cardiomyopathy, however, may be relatively asymptomatic but still be at risk for arrhythmias and sudden death. In patients with hypertrophic cardiomyopathy and in primary electrical disease, implantation in young active individuals is problematic since they are often very active. This can lead to a relatively high incidence of lead failure as is reported in this series, which covered only a short follow-up period. In patients with primary electrical disease and hypertrophic cardiomyopathy, one would expect patients to

require ICD therapy for decades. As a result, these patients are likely to require multiple device procedures, and care must be used to try to preserve venous access and subcutaneous sites for device implants. When the ICD is to be placed for primary prevention, it is hard to know at what age to intervene. I prefer to wait until age 12 or so, if at all possible. When a decision to implant is made, doing the minimum necessary to provide sudden death protection rather than going for more complex initial procedures is often the best approach. ■

CME Questions

21. In women with CAD, the highest risk for subsequent cardiovascular events occurs in those:
a. who are overweight.
b. who are obese.
c. with metabolic syndrome.
d. All of the above

22. The best predictor of mortality in women with angiographic CAD was:
a. metabolic syndrome.
b. insulin resistance.
c. CRP.
d. diabetes.

23. Which is most correct concerning lone atrial flutter?
a. Stroke risk is high.
b. Anticoagulation is not indicated.
c. Atrial fibrillation rarely develops.
d. All of the above

24. The major problem with AICD placement in children is:
a. repeated shocks.
b. lead failure.
c. thromboembolism.
d. a and b

25. Mortality in acute coronary syndromes is least when:
a. 0-1 indicated drug is used.
b. 2-4 indicated drugs are used.
c. cardiac catheterization is avoided.
d. enoxaparin is used.

26. In high-risk acute coronary syndrome patients enoxaparin vs unfractionated heparin showed:
a. a survival advantage.
b. reduced composite end point.
c. less bleeding.
d. noninferiority.

27. In patients with cardiomyopathy and heart failure on ACEI:
a. warfarin reduces mortality.
b. aspirin increases hospitalization for heart failure.
c. clopidogrel reduces cardiovascular complications vs aspirin.
d. All of the above

Answers: 21(c); 22(d); 23(a); 24(d); 25(b); 26(d); 27(b)

PHARMACOLOGY WATCH

Estrogen Found to Not Affect Heart Disease, Breast Cancer

The NIH has halted the estrogen-alone wing of the Women's Health Initiative (WHI) a year before its scheduled end. The 11,000 postmenopausal women who have had a hysterectomy and were enrolled in the estrogen-alone trial recently received a letter informing them of the preliminary results of the study and asking them to stop their study medication. After nearly 7 years of follow-up it appears that estrogen alone does not affect the rates of heart disease or breast cancer (either positively or negatively), both key findings of the estrogen/progesterone wing of the study, which was halted in July 2002. The researchers did find, however, that estrogen alone led to a slightly higher incidence of stroke (8 per 10,000), similar to the rate found in the estrogen/progesterone wing. Estrogen alone was also found, however, to decrease the risk of hip fracture. The NIH statement also says that older women (65 and older) showed a trend toward increase risk of probable dementia or mild cognitive impairment with estrogen-alone treatment. All of the women in the study were taking Wyeth & Co.'s conjugated estrogen product, Premarin. The full results of the trial will be published in a major peer-reviewed journal in the next 2 months. The NIH statement concurs with the guidance from the FDA, which states that hormone use should be limited to treatment of moderate-to-severe menopausal symptoms, vulvovaginal atrophy, and prevention of osteoporosis (as a second-line drug). The NIH statement is available on its web site at www.nih.gov/news.

Antibiotics Associated With Cancer Risk

Is antibiotics use associated with an increased risk of breast cancer in women? The question, which was first raised decades ago, has been the subject of much debate, but now a new study suggests that the answer may be yes. Researchers looked at data from more than 10,000 female members of the Group Health Cooperative in Washington state and identified 2266 women with invasive breast cancer and 7953 randomly selected controls without breast cancer. The variable evaluated was cumulative days of antibiotic use over the study period from January 1993 to June 2001. Increasing cumulative days of antibiotic use was associated with increased risk of breast cancer. The categories were 0 days, 1-50, 51-100, 101-500, 501-1000, and > 1001 days. The odds ratios (95% CI) for breast cancer were, respectively, 1.00 (reference), 1.45 (1.24-1.69), 1.53 (1.28-1.83), 1.68 (1.42-2.00), 2.14 (1.60-2.88), and 2.07 (1.48-2.89) ($P < .001$ for trend). Increased risk was seen in all antibiotic classes, including women taking tetracycline or macrolides for treatment of acne or rosacea. After adjusting for age, length of enrollment, and use of postmenopausal hormones, the death rate from breast cancer also increased with cumulative days of antibiotic use. The authors conclude that use of antibiotics was associated with an increased risk of incidence of breast cancer and death from breast cancer; however, it cannot be determined

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from the study whether antibiotic use is causally related or whether the indication for use of antibiotics was the primary factor (*JAMA*. 2004; 291:827-835). The link between antibiotics for breast cancer is plausible since antibiotics affect intestinal microflora, thus affecting phytochemical metabolism in the gut. Phytochemicals are thought to play an inhibitory role in the carcinogenesis pathway. Antibiotics also affect immune and inflammatory responses, which may lead to mammary carcinogenesis. An accompanying editorial reviews the possible mechanisms of the antibiotic/breast cancer connection and suggests that this study provides more questions and answers but that further research is needed. In the mean time, antibiotic use in women should be scrutinized, especially when other treatment options are available (*JAMA*. 2004;291:880-881).

Topiramate Effective Against Migraine

Topiramate is an effective agent for migraine prevention, according to a new double-blind study of 483 migraine patients. The drug, which is approved for prevention of seizures, was used in maximal doses of 50, 100, or 200 mg for 18 weeks in patients aged 12-65, who had at least a 6-month history of migraine and averaged 3-12 migraines per month. Mean monthly migraine frequency decreased significantly in the 100-mg ($P = .008$) and 200-mg ($P \leq .001$) doses, and the benefit was seen within the first month of therapy. Migraine days and use of rescue medication were also significantly reduced in the 100-mg and 200-mg groups. Adverse events included paresthesia, fatigue, and nausea (*JAMA*. 2004;291:965-973). Johnson & Johnson has already received conditional approval from the FDA for topiramate for the indication of migraine prevention pending additional safety information.

Statin Therapy For Heart Failure

Statin therapy has been found to be beneficial for a number of chronic illnesses; now add 2 more to the list. Statins have been found to benefit patients with advanced ischemic and non-ischemic heart failure. Researchers from UCLA reviewed the records of 551 patients with systolic heart failure with ejection fractions of 40% or less. After risk adjustment, statin use was associated with improved survival without the necessity of urgent transplantation in both non-ischemic and ischemic heart failure patients (91% vs 72% [$P < .001$] and 81% vs 63% [$P < .001$], at 1-year follow-up, respectively) (*J Am Coll Cardiol*. 2004;43:642-648). A new, large, randomized trial shows statins may also reduce the risk of stroke. As part of the Heart Protection Study in the United Kingdom, 3280 adults with cerebrovascular disease and an additional 17,256 patients with other occlusive arterial disease or diabetes were randomized to simvastatin 40 mg per day or placebo. Over the 5-year treatment period, there was a significant 25% proportional reduction in the rate of first stroke (4.3% simvastatin vs 5.7% placebo; $P < .0001$). The entire benefit was found in reduction in ischemic stroke. There was no difference found in the rate of hemorrhagic stroke, either increase or decrease. Simvastatin also reduced the number of TIAs ($P = .02$) and requirement for carotid endarterectomy or angioplasty ($P = .0003$). Among patients with pre-existing cerebrovascular disease, there is no apparent reduction in the stroke rate, but there was a highly significant 20% reduction in the rate of any vascular event ($P = .001$). Interestingly, benefit was seen in all levels of LDL, even in patients with LDL levels less than 116 mg/dL. The authors conclude that statin therapy reduces the risk of ischemic stroke by one-quarter to one-third in these at-risk patients (*Lancet*. 2004;363:757-767).

FDA Actions

The consumer watchdog group Public Citizen is calling for the FDA to ban AstraZeneca's new statin, rosuvastatin (Crestor), because of the risk of myositis and rhabdomyolysis. The drug, which was introduced to the American market in September, has been associated with 7 cases of rhabdomyolysis, 9 cases of renal failure, and 1 death. Myositis is a class affect of statins, especially the high-potency statins like Crestor. AstraZeneca states that the drug has been used in more than 1 million patients and that its benefits outweigh the risks. The FDA banned Bayer's cerivastatin (Baycol) in 2001 because of more than 100 deaths associated with the drug due to rhabdomyolysis.

Drug Approved to Target Angiogenesis

The FDA has approved the first monoclonal antibody that targets tumor angiogenesis. Genentech's bevacizumab (Avastin) is approved for the treatment of metastatic colorectal cancer. The drug works by binding vascular endothelia growth factor, thus inhibiting the formation of new blood vessels in tumors. In clinical trials the drug was found to extend survival time in patients with metastatic colorectal cancer by several months. ■