AMERICAN HEALTH CONSULTANTS® A Medical Economics Company

CLINICAL CARDIOLOGY ALERT®

A monthly update of developments in cardiovascular disease

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

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

Late-Breaking Clinical Trials: American College of Cardiology Scientific Sessions

CONFERENCE COVERAGE

Source: American College of Cardiology Annual Scientific Sessions, March 8-10, 1999, New Orleans, LA.

THE MERIT-HEART FAILURE TRIAL

Preliminary results of the merit-heart failure study were announced at the annual American Heart Association meeting in November 1998. A more complete report was given by Dr. Sidney Goldstein at the recent American College of Cardiology Late-Breaking Clinical Trials session. Approximately 4000 patients from Europe and the United States with class II-III congestive heart failure were randomized to long-acting metoprolol (Toprol XL) or placebo. Up-titration of the beta-blocker dose occurred weekly to achieve a target of 100-200 mg daily; the average dosage achieved was 159 mg daily. Forty-one percent of the cohort was NYHA class II and 55% NYHA class III. Left ventricular (LV) ejection fraction averaged 28%. Two-thirds of the patients had coronary artery disease, one-half had a prior myocardial infarction, and one-fourth had diabetes. Ninety percent of the patients were on an ACE inhibitor and 7% were on an angiotensin-II blocker.

The primary end point was all-cause mortality. The trial began in early 1997 and was scheduled to end in 2000; however, in late 1998 the study was stopped prematurely at an interim analysis because of a significant reduction in mortality. The beta-blocker patients had a decrease in one-year all-cause mortality of 34% (11% placebo, 7.2% metoprolol; P = 0.006) as well as a 41% reduction of sudden death and a 49% reduction in heart failure mortality. The response was similar in all NYHA classes. Heart failure etiology and LV ejection fraction strata were not factors in the outcomes.

COMMENT BY JONATHAN ABRAMS, MD

This is more convincing evidence that beta-blockers should become part and parcel of the treatment of symptomatic patients with heart fail-

INSIDE

ure with depressed systolic function. A variety of carvedilol studies and the recent CIBIS-2 (bisoprolol) trial demonstrated comparable reductions in mortality that are robust and consistent. The issue of whether a beta-one selective agent is more or less desirable than a nonselective beta-blocker remains unresolved. The COMET trial is comparing metoprolol to carvedilol, but the study has not been completed. Only 4% of the Merit-HF patients were in NYHA class IV, although a recent publication using carvedilol in such patients has been reported. In general, use of beta-blockers in very sick patients with heart failure is not indicated except by heart failure clinics or by individuals extremely experienced in the care of patients with severe heart failure. On the other hand, all class II-III patients should be given a beta-blocker unless there is a significant contradiction. Starting with very low doses with slow up-titration is essential, as such patients frequently become more symptomatic with initiation of this therapy. However, long-term data confirm reverse remodeling, with improved LV function (data not provided by the Merit-HF investigators), as well as symptomatic relief and improved clinical status.

The beta-blocker heart failure trials have all been with patients on ACE inhibitors; these drugs remain the first line of therapy for patients with decreased systolic function. In individuals who have normal to high blood pressure, no overt bradycardia, or AV conduction disturbance, a beta-blocker (either selective or nonselective) should be conventional therapy. Very low doses of metoprolol are difficult to administer given the current availability of only 100-mg strength Toprol CL and 50 mg of regular metoprolol. In this respect, carvedilol has an advantage because of the easier initiation with very low doses. ❖

MUSTT

The Multicenter Unsustained Ventricular Tachycardia Trial (MUSTT) was presented by Dr. Alfred Buxton, the principal investigator. It tested the hypothesis that antiarrhythmic therapy, guided by electrophysiologic testing (EPT), would decrease cardiac deaths in patients with coronary artery disease, systolic dysfunction (EF < 40%), and nonsustained ventricular tachycardia (VT). EPT was done to detect inducible sustained VT. If none was found, the patient went into a registry. If they had inducible VT, they were randomized to an ACE inhibitor plus beta-blocker or antiarrhythmic therapy. Antiarrhythmic therapy was EPT guided: round 1, propafenone or sotalol; round 2, type IA and mexilitine or implanted cardioverter/defibrillator (ICD); round 3, amiodarone, ICD, or another round of 1 or 2 agents. The primary end point was arrhythmia death or cardiac arrest; secondary end points were all-cause mortality and cardiac death. A total of 2202 patients were enrolled; 35% had a positive EPT and 92% of these were randomized: 351 to antiarrhythmic therapy and 352 to conservative therapy. Patient characteristics were well matched between the groups: EF averaged 30%, two-thirds were NYHA class II-III, 95% had a prior MI, and 56% had a prior CABG. In the conservative group, 70% were on an ACE inhibitor and 45% on a beta-blocker; in the aggressive group, 46% had an ICD and 45% were on antiarrhythmic drugs. The median follow-up was 39 months (up to 5 years maximum).

Event-free survival was significantly better in the EPT-guided therapy group: the primary end point at 24 months was 12% vs. 18% and 25% vs. 32% at 60 months. The hazard ratio was 0.73 for EPT. Total mortality was less in the EPT group (HR = 0.8; P = 0.06). Subgroup analysis showed that patients with ICD did the best, with 92% alive at 60 months. The investigators concluded that in patients with asymptomatic nonsustained VT, CAD, reduced LVEF, and inducible sustained VT at EPT, ICD therapy reduces arrhythmic deaths. Antiarrhythmic therapy without ICD was not better than conservative therapy of ACE inhibitor and beta-blocker.

COMMENT BY MICHAEL H. CRAWFORD, MD

These results are not surprising and confirm the results of MADIT, which showed that mortality was reduced in

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

VICE PRESIDENT/GROUP PUBLISHER:

Donald R. Johnston.

EXECUTIVE EDITOR: Glen Harris.

ASSISTANT MANAGING EDITOR: Robin Mason.

COPY EDITORS: Michelle Moran, Neill Larmore, Holland Johnson.

MARKETING PRODUCT MANAGER:

Schandale Kornegay.
GST Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Clinical Cardiology Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Back issues: $17. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.
This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

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

Subscription Prices

United States
$199 per year (Student/Resident rate: $100).
Multiple Copies
1-9 additional copies: $100 each. 10 or more copies: $60 each.
Canada
$243 per year including GST
(Student/Resident rate: $110 including GST).
Elsewhere
$229 per year (Student/Resident rate: $110).

Accreditation

American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor CME for physicians. American Health Consultants designates this CME activity for 20 credit hours of Category 1 of the Physician's Recognition Award of the AMA. This CME activity was planned and produced in accordance with the ACCME Essentials. **For CME credit, add $50.**

Questions & Comments

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

Statement of Financial Disclosure

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

post-MI patients with LV dysfunction using an ICD vs. conservative therapy. The major issues with both studies are the resources required to study patients with CAD and LV dysfunction by EPT and treat appropriate ones with ICD and expensive antiarrhythmic drugs. It is dubious whether the health care system can afford this. Thus, further analysis of these trials and future, more focused studies are required to be selective in applying this expensive approach. Nonetheless, the mortality reductions are impressive and hard to ignore. ❖

Clinical Prediction of Inducible Sustained Ventricular Tachycardia

ABSTRACT & COMMENTARY

Synopsis: *Clinical factors have limited ability to accurately predict induction of sustained VT in patients with coronary artery disease and low ejection fractions.*

Source: Buxton AE, et al, for the Multicenter Unsustained Tachycardia Trial (MUSTT) Investigators. *Circulation* 1999;99:1843-1850.

In this study, buxton and colleagues report on clinical features that were associated with inducible sustained ventricular tachycardia (VT) in the Multicenter Unsustained Tachycardia Trial (MUSST). MUSST recruited patients with known coronary artery disease (CAD), a left ventricular ejection fraction (LVEF) less than 0.40, and asymptomatic nonsustained VT. The design of the study included a baseline electrophysiologic (EP) study that used a standard protocol for programmed ventricular stimulation. The end point for the stimulation protocol was initiation of either sustained monomorphic VT at any point or sustained polymorphic VT or ventricular fibrillation with one or two extra stimuli. After their EP study, patients without an inducible sustained arrhythmia were followed on routine therapy while those with an inducible arrhythmia were randomized between therapy guided by serial EP studies and no specific antiarrhythmic therapy.

Data from 1721 patients who underwent the baseline EP study were analyzed in this report. Sustained monomorphic VT was inducible in 549 patients (32%) and an additional 63 patients had inducible polymorphic tachycardias. Variables most strongly associated with induction of monomorphic VT by univariate analysis included the following: male gender, more fixed thallium defects, clinical history of myocardial infarction (MI), absence of other cardiac disease, beta-blocker therapy at enrollment, areas of dyskinesis, congestive heart failure or sustained VT or VF at the time of MI, and longer duration from last MI (all $P < 0.01$). Patients with prior coronary artery bypass were less likely to have an inducible arrhythmia. These univariate predictors were then included in several models that combined multiple variables. Receiver operating curves (ROC) were used to quantify the ability of these models to predict who would have inducible VT. An ROC area near 1.0 would signify perfect prediction, while an area of 0.5 correlates with no predictive value. The three models tested yielded ROC areas between 0.647 and 0.692. Buxton et al conclude that clinical factors have limited ability to accurately predict induction of sustained VT in patients with CAD and low EFs.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Several years ago, the Multicenter Automatic Defibrillator Implantation Trial (MADIT—*N Engl J Med* 1996;335:1933-1940) reported that implantable cardioverter defibrillator (ICD) implantation reduced mortality by 75% in patients with prior MI, low LVEF, nonsustained clinical VT, and inducible sustained VT. On the basis of this trial, induction of VT at EP study became an acceptable class I indication for ICD implantation. MADIT, however, did not systematically collect data on patients who had negative EP studies. Therefore, it has been difficult to characterize the population from which the MADIT subjects were drawn. In MUSST, data from patients both with and without inducible VT were collected. This study shows that clinical factors only add minor additional information to the basic findings of a low EF and documented nonsustained VT. Previously, the MUSST investigators had also reported that electrocardiographic characteristics of the nonsustained VT did not predict inducibility (Buxton AE, et al. *Ann Int Med* 1996;125:35-39).

Should these data be taken to imply that all patients with CAD, an LVEF less than 40, and nonsustained VT should undergo an EP study? The data from MADIT and the poor ability to use clinical features to select patients with inducible VT shown in this study would support that approach. However, in further data reported from MUSST at the recent North American Society for Pacing and Electrophysiology meeting, patients without inducible VT were compared to those patients with inducible VT who were not treated. Although a statistically significant higher mortality was shown among those with inducible VT, the increment of risk was not great. Both groups had relatively high mortality rates.

The conclusion to be reached from these data is that we have great difficulty further separating out ultra-high risk groups if we start with patients who already have severely depressed EFs. Rather, we should probably consider all these patients to be high risk and proceed accordingly. ❖

Cost-Effectiveness of Therapy in Nonvalvular Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *Cardioversion alone should be the initial therapy of nonvalvular atrial fibrillation, with amiodarone reserved for relapses.*

Source: Catherwood E, et al. *Ann Intern Med* 1999; 130:625-636.

Catherwood and colleagues performed a cost-effectiveness analysis of treatment strategies in patients with nonvalvular atrial fibrillation. Catherwood et al expanded a previously published Markov decision analysis (Disch DL, et al. *Ann Intern Med* 1994;120:449-457), which favored cardioversion plus amiodarone by including health-related costs of the treatments and outcomes in the analysis. Eight different potential strategies were considered. These included rate control with either metoprolol or diltiazem, initial cardioversion followed by aspirin or warfarin at the time of relapse, initial cardioversion followed by quinidine or amiodarone at relapse, and quinidine or amiodarone along with cardioversion at presentation. The Markov model was based on a population of 70-year-old patients of both genders with nonvalvular atrial fibrillation. Patients were assumed to be hemodynamically stable with acceptable symptoms with only rate control. Probabilities of various outcomes for each strategy were estimated from data in the literature. Outcomes and costs were recalculated at three-month intervals over a five-year period. Results are reported as expected costs, increase in quality-adjusted life-years, and incremental cost-effectiveness.

Strategies involving initial cardioversion alone were most effective and less costly than those not involving this option. The cost-effectiveness of the various options after initial cardioversion could be predicted by the patient's risk of stroke. Among high- and moderate-risk patients, initial cardioversion followed by amiodarone and repeat cardioversion upon relapse were the preferred strategies. Costs were estimated to be $9300 and $18,900 per quality-adjusted life-year increments in these two cohorts, respectively. Among patients thought to be at low risk for stroke since they had no risk factors other than age, cardioversion followed by aspirin therapy on relapse was most cost effective. Sensitivity analysis showed that baseline risk for stroke, estimated stroke rate in sinus rhythm, efficacy of warfarin, and costs of warfarin and amiodarone were the major factors influencing the analysis. Catherwood et al conclude that cardioversion alone should be the initial therapy of nonvalvular atrial fibrillation, with amiodarone reserved for relapses.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Atrial fibrillation is the most commonly encountered sustained arrhythmia at the present time. Catherwood et al present an analysis of the cost-effectiveness of various treatment strategies for patients presenting with new onset persistent atrial fibrillation. Although their model is very complex, it still does not take into account several important factors that may influence clinical decision making. Catherwood et al assumed that their hypothetical patients were asymptomatic and hemodynamically stable in atrial fibrillation on rate-controlling agents only. This is probably the case for those patients in whom atrial fibrillation is discovered by chance but frequently is not the case in patients who present with new onset arrhythmia. Evaluating the efficacy of rate control and the subtle effects of atrial fibrillation on quality of life can be difficult and these problems were not considered here. Problems with chronic warfarin anticoagulation are also frequent. The event rates used here are derived from large, randomized trials but these trials excluded up to one-third of the patients they screened because of real or perceived contraindications to long-term warfarin. Finally, only a minority of atrial fibrillation patients present with persistent atrial fibrillation without any other history of arrhythmia or heart disease. A careful clinical analysis to detect prior episodes of self-terminating episodes of arrhythmia, evidence for associated sinus node dysfunction, or structural heart disease can be helpful for predicting an individual's risk of arrhythmia recurrence.

The analysis here, therefore, strictly applies to only a narrow subset of atrial fibrillation patients. However, the clinician can use these data as a guideline when he or she is deciding on care for an individual patient.

Considerations of symptoms, risk of therapy, and estimates of recurrence rate should be used in making the final clinical decision. ❖

Cost-Effectiveness of Diagnostic Testing for Coronary Artery Disease

ABSTRACTS & COMMENTARY

Synopsis: *For most patients with typical or atypical angina (but not nonspecific chest pain), a noninvasive diagnostic test is a reasonable use of health care resources.*

Sources: Kuntz KM, et al. *Ann Intern Med* 1999; 130:709-718; Garber AM, Solomon NA. *Ann Intern Med* 1999;130:719-728.

Two recent studies use highly sophisticated cost-effectiveness analysis and Markov decision analysis modeling to assess the cost-effectiveness of a variety of diagnostic techniques for coronary artery disease (CAD). Interpretation of these papers is aided by some familiarity with the concepts of quality-adjusted life-years (QALY) and decision-making analysis. The first publication, by Kuntz and associates, examines the existing data in this field and created decision-analytic models from the perspective of health care policy, which takes into account diagnostic test accuracy and cost, possibility of significant coronary disease, and the cost of subsequent treatment as well as projected clinical events. Long-term risks were estimated based on the need for angiography and revascularization procedures. Health-related quality of life was estimated for a variety of diagnostic strategies. Chest pain patient cohorts were stratified by typical, atypical, or nonspecific chest pain; gender; and age. Kuntz et al, as well as Garber and Solomon, emphasize that the preferred diagnostic strategy will in part depend on how much society is willing to spend for additional QALYs. This study assessed no test, routine exercise testing, exercise echocardiography, and exercise single-photon emission computed tomography (SPECT) in cohorts of individuals with mild to severe chest pain of various ages and sexes with typical and atypical features of angina.

The only group that had a reasonable cost-effectiveness ratio for direct coronary angiography without stress testing were men with a high likelihood of having CAD, such as middle age or older males with classic angina pectoris. In individuals with atypical angina, stress echo was considerably more expensive per QALY then exercise electrocardiography. Cost-effectiveness ratios were high for all test strategies in individuals with a low to moderate pretest probability of CAD, such as women and younger men with nonspecific chest pain. Exercise echocardiography had "… a reasonable cost-effectiveness ratio for patients at moderate risk of coronary artery disease." The discussion emphasizes that individual institutions may have differing quality performance among their noninvasive testing modalities. Although this data analysis was based on extensive literature review, some hospitals will have higher quality (increased specificity and sensitivity) with nuclear techniques as opposed to echo and vice versa.

Kuntz et al emphasize that there is a trade-off between improved diagnostic performance of a test and the burden on health care budgets. Thus, only in subgroups with a high probability of CAD was direct angiography cost effective. In subjects with a low probability of coronary disease, all testing strategies were expensive. Exercise echo appeared to be most reasonable for individuals with moderate risk for CAD, with a cost-effective use of resource ratio comparable to generally accepted medical procedures, such as bypass surgery or cholesterol lowering in a man with severe hyperlipidemia. They also conclude that "for most patients with typical or atypical angina (but not nonspecific chest pain), a noninvasive diagnostic test is a reasonable use of health care resources."

The companion article by Garber and Solomon assessed the use of exercise ECG, planar thallium, stress echo, SPECT nuclear testing, and positron emission tomography (PET) in a decision analysis model that sought to assess long-term health care outcomes and costs developing from different strategies. All five strategies were compared to an initial approach of coronary angiography. The analysis was directed at individuals with symptoms and risk factors placing them at intermediate (25-75%) risk or pretest probability of having CAD, such as middle age or older women with typical angina as well as middle age or older men with atypical angina. As in the article by Kuntz et al, sophisticated data analyses were carried out regarding health outcome measures, such as life expectancy and QALY. A management algorithm testing the various strategies was used, and costs were based on projected long-term outcomes. The study concluded that PET was highly sensitive (comparable to SPECT) for significant CAD, but its cost-effectiveness ratio was too high to be recommended. All of the imaging techniques performed better than routine stress electrocardiograms with respect to not missing individuals with severe CAD. Garber and Solomon point out that the testing strategies were all rel-

atively similar with respect to QALY outcomes but that variations in test sensitivity clearly can result in variation in health outcomes.

Total cost of care in this model varied little among the alternative testing strategies. As in the prior report, exercise echo was the least expensive option for men and women of middle age without a high likelihood of CAD. Echocardiography performed better than routine exercise testing and was comparable to nuclear imaging, although the cost of stress echo is greater than routine exercise testing. PET had good outcomes, but at much greater cost than stress echo or SPECT, and was not as cost effective as immediate angiography. Garber and Solomon point out that if high cost-effectiveness ratios were acceptable, with expenses considerably greater than those generally considered to be cost effective, SPECT, angiography, and PET imaging would be reasonable choices. Doing no test at all was felt to be a poor choice, particularly since stress echo has a relatively low QALY cost. As in the previous paper, direct or initial angiography was cost-effective only in men with a high pretest likelihood of CAD. Stress echo appeared to be the most cost-effective strategy for medium- and low-risk individuals. Garber and Solomon conclude that stress "echo, SPECT, and immediate angiography are the most appropriate diagnostic tests for patients at intermediate pretest risk," with exercise testing and planar thallium resulting in poorer outcomes and greater overall costs. In the discussion of exercise echo vs. SPECT, it is emphasized that this should be an institution-dependent decision, and that physicians consider local cost and quality in using these tests.

Prognostic information from noninvasive testing was not considered in either analysis. Garber and Solomon believe that individual physicians should take into account such prognostic factors (such as CAD risk status, severity of angiographic CAD) in their choice of test selection; noninvasive testing may be favored over immediate angiography because of its ability to provide quantitative prognostic information about the future. Garber and Solomon conclude that while all of the noninvasive tests are highly sensitive for detection of severe disease (three vessel and left main), stress echo and SPECT are the most cost-effective options for general use.

COMMENT BY JONATHAN ABRAMS, MD

These two articles require time and patience for the reader; a background in the literature of cost-effectiveness and decision-making analysis is helpful. Nevertheless, the uninitiated reader can readily come away with a similar "take home" message from both studies: all available noninvasive diagnostic techniques operate with an acceptable sensitivity and specificity (except for exercise stress testing, which has a lower sensitivity than the others). The choice of a noninvasive test for a middle-aged or older male with classic angina is unimportant; direct angiography is clearly appropriate and cost effective in many such individuals. However, the large proportion of patients with chest pain evaluated by physicians have a moderate to low pretest probability of CAD, and these are the individuals who use the greatest amount of health care resources in efforts to establish a diagnosis as to whether CAD is present. Routine stress electrocardiography can be appropriately applied in many individuals, but its performance is not as high with respect to specificity as well as QALY adjusted cost-effectiveness as SPECT or stress echo. Thus, one is confronted with a tradeoff of the higher initial expense of these procedures vs. reasonable long-term health outcomes and cost. Stress echocardiography is clearly the winner in these analyses. This modality is not necessarily available in all institutions and cardiology practices; an appropriate alternative, based on the analysis of both studies, is SPECT with thallium and/or sestamibi. For those interested in health care policy, cost-effectiveness issues, as well as a broad overview of the noninvasive literature, careful reading of these publications is recommended. Both analyses conclude that stress echo and SPECT are the preferred noninvasive procedures for individuals at moderate risk for CAD. No specific test is particularly cost-effective in low-probability subjects. ❖

Coronary Angiographic Predictors of MI

ABSTRACT & COMMENTARY

Synopsis: *Quantitative analysis of coronary artery lesion morphology on angiography may provide better predictors of subsequent MI than visual inspection.*

Source: Ledru F, et al. *J Am Coll Cardiol* 1999; 33:1353-1361.

The severity of coronary artery stenoses is known to be correlated with an increased incidence of ischemic events, but predicting which artery will cause the next myocardial infarction (MI) is challenging. Thus, Ledru and colleagues evaluated the prior coronary angiograms of 84 patients with acute MI in order to determine if any lesion characteristics could predict the subsequent culprit vessel as determined by angiography within four weeks after MI. Quantitative coronary

angiography analysis was used to determine luminal diameters, plaque symmetry, and plaque angles. The results showed that culprit lesions were more symmetrical, had steeper outflow angles, smaller luminal diameters, and had larger lesions than control plaques. Stenosis severity only predicted MI within one year of angiography, whereas the symmetry index and outflow angles predicted MI at the three-year follow-up. Minimal luminal diameter and inflow plaque angles were unrelated to culprit lesion frequencies. The time between angiography and subsequent MI was related to percent stenoses and outflow angle of the lesion, whereas lesion symmetry was not related to time. Ledru et al conclude that quantitative analysis of coronary artery lesion morphology on angiography may provide better predictors of subsequent MI than visual inspection. These observations may help us understand the pathophysiologic mechanisms of plaque rupture and ultimately may help us make better decisions with regard to prophylactic angioplasty.

COMMENT BY MICHAEL H. CRAWFORD, MD

A decade ago, Dr. William Little and associates surprised the medical community by debunking the myth that the tightest lesion angiographically measured by percent stenosis was the culprit lesion for the next MI. Although the data were solid and replicated by others, cardiologists still spent the last decade practicing as if they could identify plaque characteristics that do predict future events. Interestingly, good old percent stenoses did predict future culprit vessels within one year in this study, but not longer. Longer term events were better predicted by stenosis symmetry and outflow angles. Also, future culprit lesions were generally 40-70% stenoses. Lesions less than 40% were less often future culprits. What was actually predicted by these characteristics was a lack of future MI events, since the positive predictive accuracy was 50% vs. a negative predictive accuracy of 87%.

This study is also somewhat iconoclastic since the irregular ugly-looking lesions were less likely to be culprits and the smooth, symmetric ones were culprits. Although the paper provides no scientific explanation for this observation, recent atherosclerosis biology studies offer some possible explanations. It may be that irregular plaques are like extinct volcanoes and more symmetric plaques are loaded with lipid gruel and have a thin fibrous cap that allows the flow of blood to push the lipid core downstream, creating an acute outflow angle. This may also explain the observation in this study that aspirin had little effect on such future culprits.

There were limitations to this study. It was retrospective in design and had the bias of including patients with a prior catheterization done for a variety of reasons that could have affected outcomes. Also, the post-MI catheterization was done for various different reasons. In addition, only those patients presenting with ECG ST elevation who had a second catheterization were included. We do not know what plaque morphology predicts non-Q presentations. Finally, intravascular ultrasound, 3D reconstruction, and other newer techniques were not used to corroborate the quantitative angiographic findings.

The real issue is whether interventional cardiologists will be impressed enough by these results to modify their practice. This would require performing angioplasty post-MI only on symmetric 40-70% lesions with acute outflow angles and leaving others alone, especially if imaging tests failed to identify the other lesions as causing ischemia. My guess, based upon a survey of our institution's interventional cardiologists, is that they will wait and see. ❖

Anticoagulants for Aortic Debris

ABSTRACT & COMMENTARY

Synopsis: *More severe aortic atheroma are associated with high mortality and embolic events, and anticoagulant therapy is associated with a better outcome than antiplatelet therapy in such patients.*

Source: Ferrari E, et al. *J Am Coll Cardiol* 1999; 33:1317-1322.

Aortic atherosclerosis is known to be associated with higher incidences of systemic emboli, but the prognostic value of specific atheroma characteristics and appropriate treatment are not well defined. Thus, Ferrari and colleagues from Nice, France, performed a prospective observational study of patients referred for transesophageal echocardiography (TEE) in whom aortic atheroma were found. Follow-up averaged 22 months, during which time treatment was at the discretion of the patients' physicians. Independent observers identified aortic atheroma in 139 of 1116 TEEs (12%), of which 10 were lost to follow-up, resulting in a study population of 129 patients. Among those referred for embolic events or stroke, atheroma were found in about 25% and if no other etiology for the embolic event was found, about 50% had atheroma. Atheroma were classified as: grade I—1.0-3.9 mm thick; grade II— more than 4.0 mm thick; and grade III—mobile plaque (aortic debris). Of note, all but one of the plaques with a mobile component were greater than 4 mm thick. About half the patients were treated with oral antiplatelet drugs and

half with oral anticoagulants (none received both). The primary end-point of embolic event or death occurred in 23% of the patients and was directly related to the severity of atheroma. The highest mortality was observed in those with debris (24%). Patients with grade II-III atheromata had more events when treated with antiplatelets vs. anticoagulants (relative risk = 5.9). Treatment did not affect outcome in grade I patients. Ferrari et al conclude that more severe aortic atheroma are associated with high mortality and embolic events, and that anticoagulant therapy is associated with a better outcome than antiplatelet therapy in such patients.

COMMENT BY MICHAEL H. CRAWFORD, MD

TEE is frequently ordered to "rule out embolic source" even though this is not a reimbursable indication by the Health Care Financing Administration (HCFA). However, many such patients studied have aortic atheroma. This study confirms that such atheroma, especially if more severe, are a likely cause of embolic events and suggests that anticoagulant therapy is superior to antiplatelet therapy. Even though this was not a randomized treatment trial, the data for oral anticoagulation therapy are persuasive. The patients on oral anticoagulants more frequently had atrial fibrillation and left ventricular dysfunction, which should have made their prognosis worse. However, we do not know how many very sick patients were not put on anticoagulants and contributed to the event rate of the antiplatelet group. On the other hand, most of the patients treated with antiplatelet agents had mild atheroma.

Another interesting aspect of this observational study was that the majority of events were death vs. emboli (17 vs 12). This suggests that aortic atheroma are a marker for severe vascular disease that frequently involves the coronary and cerebral vasculature. Other reports have suggested benefits for such patients of oral anticoagulation therapy. Thus, it may be that patients with advanced generalized atherosclerosis do better with anticoagulants vs. antiplatelet drugs.

The major limitation of this study is that the patients had some event that occasioned a TEE. Thus, the results are only applicable to such patients and do not suggest that more widespread use of TEE is justified. In fact, one could argue from these data that all patients with embolic events should be treated with anticoagulants, at least for three months. Perhaps HCFA is correct and endocardiography is not indicated for embolic events unless other clinical information supports a cardiac etiology. These data and others would suggest that if an echocardiogram is considered appropriate, it should be a TEE, since many of the potential cardiac etiologies for embolic events are best identified by TEE (e.g., atrial septal aneurysms, aortic atheroma, left atrial thrombi). On the other hand, most cardiac etiologies for systemic emboli would be treated with anticoagulants anyway, so the debate will go on.

I can't help remembering a 40-year-old woman referred for an echocardiogram for a stroke. I scoffed to my fellow that this would be a normal (read, unnecessary) study. The patient had a left atrial myxoma, so I asked the internist why he ordered the echo. He said because the patient had no risk factors for stroke and he suspected something unusual. Again, there is no substitute for astute clinical judgment. It's too bad the HCFA doesn't think we have any of this. ❖

CME Questions

32. Recent heart failure trials suggest that beta blocker therapy is indicated for:
a. class I patients.
b. class II-III patients.
c. class IV patients.
d. all classes of patients.

33. In patients with CAD, systolic dysfunction, and inducible sustained VT on electrophysiologic testing, total mortality is reduced by:
a. implantable cardioverter-defibrillator.
b. antiarrhythmic therapy.
c. ACE inhibitors.
d. beta blockers.

34. Cost-effectiveness in the management of nonvalvular atrial fibrillation is enhanced by:
a. initial cardioversion.
b. chronic warfarin therapy.
c. initial amiodarone therapy.
d. None of the above

35. A strategy of immediate coronary angiography was cost-effective for which patient group?
a. Women with intermediate pretest likelihood of CAD
b. Patients with low probability of CAD
c. Men older than age 55 with classic angina
d. Patients with atypical chest pain

36. Angiographic features that predict future culprit lesions include which of the following?
a. Percent stenosis
b. Plaque symmetry
c. Plaque outflow angle
d. All of the above

37. Severe aortic atherosclerosis is best managed by:
a. watchful waiting.
b. risk factor control.
c. aspirin.
d. warfarin.