Providing Evidence-based Clinical Information for 21 Years

CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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

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

Treating In-Hospital Cardiac Arrest with an Automatic External Cardioverter Defibrillator

ABSTRACT & COMMENTARY

In this study, a European consortium of investigators evaluated the ability of an automatic external cardioverter defibrillator (AECD) to detect and treat arrhythmias in the in-hospital setting. The AECD used was the Powerheart model manufactured by Cardiac Science Inc, in Irving, Calif. The device uses self-adhesive electrodes placed on the thorax. The AECD continuously monitors, analyzes, and classifies the ECG rhythm of attached patients. The device can function in either an automatic mode in which it treats arrhythmias without operator intervention or in an advisory mode in which an operator is required to press a button to deliver a shock. The device is not committed to shock since it reanalyzes the rhythm again after charging. The device is currently approved by the Food and Drug Administration for in-hospital use. In this study, 117 patients were monitored. Fifty-one of the patients were in intensive care or telemetry units, and 66 patients were monitored during either electrophysiologic studies or implantable cardioverter defibrillator (ICD) implantations. Eleven of the patients were in persistent atrial fibrillation.

Data from a total of 125 hours of monitoring during invasive procedures and 1115 hours of monitoring in the ward settings were analyzed. During invasive procedures, there were a total of 34, 5, and 16 episodes of monomorphic and polymorphic VT and VF, respectively. On the monitored wards, there were 10 episodes of monomorphic VT, 2 episodes of polymorphic VT, and 17 episodes of VF documented. During monitoring, there were 1454 true-negatives, 499 true-positives, 35 false-positives, and no false-negatives. This resulted in a sensitivity of 100% and a specificity of 97.6%. Most of the false-positives resulted from T-wave oversensing during ventricular pacing. In standard clinical use, ventricular pacing is a contraindication to use of the AECD, but patients with pacemakers could be included in this trial if their devices were only in the advisory mode. Inappropriate therapy was never delivered. Movement artifact caused initial arrhythmia detections in 3 patients on 5 occasions, but reanalysis quickly classified this as artifact within 2-4 seconds. Thir-

VOLUME 22 • NUMBER 4 • APRIL 2003 • PAGES 25-32

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

ty-five episodes were treated with shock therapy. All converted to normal rhythms with a response time of 14 ± 4 seconds.

Martinez-Rubio and colleagues concluded that early automatic defibrillation of patients who suffer an in-hospital cardiac arrest is now feasible with an external device that is fast, safe, and effective for detecting and classifying arrhythmias (Martinez-Rubio A, et al. *J Am Coll Cardiol*. 2003;41:627-632).

COMMENT BY JOHN DiMARCO, MD, PhD

In-hospital cardiac arrest is still associated with a significant mortality. On unmonitored wards, survival rates are quite low, particularly if the arrest occurs during nocturnal hours. Even in monitored settings, response times are usually measured in minutes rather than in seconds, and this delay may have an adverse effect on survival.

The AECD discussed here provides a temporary alternative to an implantable device in high-risk patients. However, it remains to be seen how these devices may be integrated into patient care. In the intensive care unit setting, the improvement in time to shock delivery is relatively small, and I doubt that the cost involved in AECD use can be justified. In the ward setting, the event rates are quite low, and it would be difficult to devise a strategy that would justify widespread use of these devices on unmonitored wards. Even on telemetry wards, the event rates are quite low, and devising a cost-effective strategy for their use would be difficult. It should also be recognized that there is a wearable automatic external defibrillator made by Life-Cor, in Pittsburgh, Penn. This device is worn externally as a vest and actually can be used either in or outside the hospital.

I anticipate that the major use of an AECD might be during the transport of patients who have significant risk for life-threatening ventricular arrhythmias. These patients are usually transported on a monitor, with a skilled nurse. Use of the AECD might allow them to be transported through the hospital for various procedures with just transport personnel. Sudden onset arrhythmias could still be effectively managed by the device in an automatic mode. ■

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

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Glen Harris.
MANAGING EDITOR: Robin Mason.
ASSISTANT MANAGING EDITOR: Robert Kimball.
SENIOR COPY EDITOR: Christie Messina.
MARKETING PRODUCT MANAGER: Schandale Kornegay.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

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

Back issues: $40. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcpub.com
Editorial E-Mail: christie.messina@ahcpub.com

Subscription Prices

United States
1 year *with* Free AMA Category 1 credits: $287
(Student/Resident rate: $145).

Multiple Copies
2-9 additional copies: $213 each. 10 or more copies: $190 each.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

This CME activity was planned and produced in accordance with the ACCME Essentials.

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

Questions & Comments

Please call **Robin Mason,** Managing Editor, at (404) 262-5517, or **Christie Messina**, Senior Copy Editor, at (404) 262-5416 or e-mail at christie.messina@ahcpub.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

THOMSON
AMERICAN HEALTH CONSULTANTS

Statement of Financial Disclosure

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, Pfizer, and Parke-Davis. Dr. DiMarco is a consultant for Bayer and Novartis, is on the speaker's bureau for Medtronic and Guidant, and does research for Medtronic and Guidant. Drs. Crawford and Vernon report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Cardiac Resynchronization for Heart Failure

ABSTRACT & COMMENTARY

Synopsis: *Cardiac resynchronization reduces the mortality of progressive heart failure in patients with symptomatic left ventricular dysfunction and dyssynchrony.*

Source: Bradley DJ, et al. *JAMA*. 2003;289:730-740.

In this paper, Bradley and associates present the results of a meta-analysis of randomized trials using cardiac resynchronization. They searched the literature for randomized clinical trials of resynchronization therapy. For inclusion, the studies had to report data on death, hospitalization for heart failure, and ventricular arrhythmias as outcomes. Crossover studies were excluded if the duration of the first crossover phase was less than 3 months. Data included in the meta-analysis were obtained from 11 reports from 4 randomized clinical trials. The clinical trials included were: CONTAK CD, INSYNC ICD, MIRACLE, and MUSTIC. The first 3 trials randomized approximately 500 patients each, whereas only 54 patients were randomized in MUSTIC. Clinical characteristics were similar in all 4 trials with a mean age of about 65 and a mean left ventricular ejection fraction (LVEF) of 0.21-0.23. CONTAK CD and INSYNC ICD included patients with New York Heart Association functional classes II and III, whereas MIRACLE and MUSTIC required patients to be at least New York Heart Association functional class III. The mean QRS duration ranged from 158 to 176 msec. Patients in CONTAK CD and INSYNC ICD had conventional indications for ICD

therapy. Patients with bradycardia indications for pacing were excluded from all trials. Patients with atrial arrhythmias were also excluded. Beta blockers were used in just over half of the patients included in the meta-analysis. ACE inhibitors or angiotensin receptor blocking drugs were used in approximately 90%.

All patients received an ICD or a pacemaker capable of cardiac resynchronization and were randomized to either resynchronization on or resynchronization off. Follow-up durations in the randomized phase of each trial ranged from 3 to 6 months. In each of the 3 larger trials, there was a statistically nonsignificant trend toward death from progressive heart failure in the patients treated with cardiac resynchronization. There were no heart failure deaths in the much-smaller MUSTIC trial.

Data from all 4 randomized trials were pooled for the meta-analysis. Cardiac resynchronization was associated with statistically significant 51% reduction in death from progressive heart failure relative to control (odds ratio [OR], 0.49; 95% CI, 0.25-0.93). Pooled absolute rates of progressive heart failure mortality during 3-6 months of follow-up were 1.7% in patients treated with cardiac resynchronization and 3.5% in controls. Inclusion of cardiac transplantations with death from progressive heart failure as an end point produced similar results. Cardiac resynchronization was not associated with a statistically significant effect on mortality not related to heart failure. Pooled absolute rates of other mortality over 3-6 months of follow-up were 3.2% in patients treated with cardiac resynchronization and 2.8% in controls. When heart failure and other deaths were combined, there was a trend toward reduced all-cause mortality. The OR was 0.77 with a confidence interval of 0.51-1.8. The pooled absolute rates of all-cause mortality of 3-6 months were 4.9% in patients treated with cardiac resynchronization and 6.3% in controls. In the ICD trials, the cardiac resynchronization was not associated with a statistically significant reduction in patients who experienced ventricular tachycardia or ventricular fibrillation. The event rates for treated arrhythmias were 17.2% in those treated with resynchronization vs 18.4% in controls. Sensitivity analysis shows that these parameters were stable over a wide range of assumptions.

Bradley et al concluded that cardiac resynchronization reduces the mortality of progressive heart failure in patients with symptomatic left ventricular dysfunction and dyssynchrony.

COMMENT BY JOHN DiMARCO, MD, PhD

Cardiac resynchronization is now an accepted therapy for patients with a QRS duration of greater than 130 msec, New York Heart Association functional class III or IV congestive heart failure, left ventricular dilatation, and systolic dysfunction. End points in the studies that established this indication were changes in New York Heart Association functional class, hemodynamic measures, and exercise tests parameters. By themselves, none of the studies showed a significant decrease in mortality with resynchronization therapy. However, the studies were not powered to test mortality, and they were of relatively short follow-up.

It should be noted that all of these studies implanted a resynchronization device in every patient before randomization. Therefore, this is not a true intention-to-treat analysis starting from baseline. The studies reported here ignore any morbidity or mortality that might be associated with the procedure. However, there is another trial, which has only been reported in a news release, the COMPANION Trial, in which significant reductions in total mortality were seen with resynchronization compared to an untreated control group using an intention-to-treat analysis. An even greater reduction in mortality was seen with the addition of ICD therapy.

Cardiac resynchronization therapy is still technically difficult in approximately a third of patients. Further progress in the design of devices for resynchronization should be forthcoming. In addition, better methods to assess patients who are likely to respond will help physicians who are considering this option for their patients. ■

Acetylcysteine for Prevention of Acute Renal Dysfunction after Coronary Angiography

ABSTRACT & COMMENTARY

Synopsis: *While the clinical benefit of oral N-acetylcysteine on reducing rates of contrast nephropathy for a given patient is unproven, it should be considered for all patients with abnormal renal function referred for elective coronary angiography.*

Source: Kay J, et al. *JAMA*. 2003;289:553-558.

Contrast-induced nephropathy (CIN) is a recognized complication of any imaging procedure using intravascular contrast such as coronary angiography. Data are accumulating suggesting that this compli-

cation is associated with increased risk of other serious adverse outcomes including permanent renal dysfunction, prolonged hospitalization, and even death. Patients at particular risk for CIN include those with baseline renal dysfunction, diabetes, and poor left ventricular function, all of whom are being referred with increasing frequency to the cardiac catheterization laboratory.

Previous studies have demonstrated that preprocedural volume loading (avoidance of dehydration), the use of low-osmolality contrast, and minimization of contrast volume can reduce the risk of CIN. More recently, a randomized clinical trial demonstrated that oral administration of the anti-oxidant N-acetylcysteine (Mucomyst®) before and after contrast administration in patients with renal insufficiency undergoing contrast-enhanced CT scanning reduced the risk of postprocedural creatinine elevation.[1] For patients undergoing coronary angiography or intervention, several smaller studies, abstracts, and reports from nonrandomized registries have yielded conflicting results in terms of the effect of N-acetylcysteine on rates of CIN.

Kay and colleagues from the University of Hong Kong sought to determine whether oral N-acetylcysteine reduced the rates of CIN in patients with chronic renal insufficiency (baseline creatinine [Cr] > 1.2, creatinine clearance [CrCl] < 60 mL/min) who were referred for coronary angiography. Of note, patients with overt congestive heart failure or LVEF < 0.35 were excluded from the study. Patients were randomized to receive 600-mg oral acetylcysteine or placebo twice daily for 3 doses prior to angiography and 1 dose after angiography. All patients were volume loaded with normal saline (0.5%) 1 mL/kg body weight for 12 hours before and 6 hours after the procedure. All angiography was performed using the nonionic, low-osmolality contrast agent iopamidol. Serum creatinine was measured before the procedure, and 24 hours, 48 hours, and 7 days postprocedure. Twenty-four-hour urine creatinine collections were made preprocedure and at 48 hours and 7 days postprocedure. The primary end points were acute reduction in renal function (rise in serum Cr > 25%) and change in CrCl and serum Cr. Secondary end points were pulmonary edema, need for dialysis, and length of hospitalization.

Two hundred patients were randomized, and there were no significant differences between the acetylcysteine and placebo groups with respect to baseline clinical or procedural characteristics. The median volume of contrast administered was 130 mL in the acetylcysteine group and 120 mL in the control group ($P = 0.29$). Twelve control patients (12%) and 4 acetylcysteine patients (4%) developed a rise in Cr > 25% at 48 hours ($P = 0.03$). Serum Cr was significantly lower in the acetylcysteine group. In addition, acetylcysteine administration was associated with a significant rise in CrCL, while placebo was not. The length of hospitalization was marginally, but significantly, shorter in patients receiving acetylcysteine. There were no adverse effects associated with the use of acetylcysteine.

COMMENT BY SARAH M. VERNON, MD

Based on previously available data, many cardiac catheterization laboratories in the United States have already adopted the use of oral acetylcysteine (in this country available only as Mucomyst® solution) in hopes of preventing CIN. In our laboratory, we have been administering Mucomyst® 600 mg b.i.d. the day before and the day of/after elective coronary angiography to all patients with estimated CrCl < 50 mL/min. In addition, we have protocols in place to ensure optimal volume status pre-procedure (with a low threshold for measuring PCWP in patients with poor LV function or otherwise tenuous volume status). We perform biplane angiography with low-osmolality contrast (with an eye toward total contrast volumes less than 50 cc, which has been easily achievable) in all patients with significant renal dysfunction referred to our laboratory.

Despite its limitations, the report by Kay et al adds credence to this approach. This regimen was not completely protective against CIN and does not delineate the optimal dosing regimen or mechanism by which acetylcysteine exerts its renal-protective effects. Importantly, this study excluded patients with LVEF < 0.35, a high-risk population that we seem to encounter daily, and sometimes without prior warning, in our laboratory. However, as Curham points out in his excellent accompanying editorial,[2] while the "absolute clinical benefit" of this regimen for a given patient remains unproven, it is simple, inexpensive, and safe, and, therefore, should be considered for all patients with abnormal renal function referred for elective coronary angiography (even though, as our patients tell us, it tastes pretty bad). ■

References

1. Tepel M, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med*. 2000;343:180-184.
2. Curhan GC. Prevention of contrast nephropathy. *JAMA*. 2003;289:606-608.

Rheumatoid Arthritis: A New CAD Risk Factor

ABSTRACT & COMMENTARY

Synopsis: *Rheumatoid arthritis should be recognized as a marker of increased risk for myocardial infarction.*

Source: Solomon DH, et al. *Circulation*. 2003;107: 1303-1307.

IT IS WELL KNOWN THAT THERE IS INCREASED MORBIDITY and mortality in individuals with rheumatoid arthritis (RA), the most common systemic autoimmune disease, affecting 2 million Americans, most of whom are women. Recently, several studies have suggested increased rates of cardiovascular disease in these patients, potentially contributing to the reduced longevity in RA. In that atherothrombosis is an inflammatory process, it is a rational hypothesis that the chronic inflammation in RA may adversely affect blood vessels. Furthermore, it is well known that inflammatory markers, such as C reactive protein (CRP) and other cytokines, are elevated in RA.

This observational investigation from the the Nurses' Health Study (NHS), sought to assess whether RA was associated with increased cardiovascular events. In the NHS, women were enrolled in 1976 between the ages of 30 and 55 years and underwent questionnaire follow-up every 2 years. A total of 141,342 women remained after baseline exclusion of RA, CV disease, and cancer, of which 7786 women reported RA on at least 1 biannual questionnaire between 1978 and 1996. Solomon and colleagues pursued the RA diagnosis by a connective tissue disease screening questionnaire, followed up by careful review of medical records in the 2170 women with symptoms on the questionnaire suggestive of RA. The cardiovascular end points were myocardial infarction and stroke, both fatal and nonfatal, all verified by medical review. Associated confounding risk factors were adjusted for, including all potential major coronary artery disease (CAD) risk factors, as well as physical activity, BMI, folate, omega-3, and vitamin intake. Use of corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) was examined for possible associations. (The data on corticosteroids are available only since 1994 and for NSAIDs, 1990). The primary analysis examined the age-specific incidence rates of stroke and myocardial infarction. The duration of follow-up was calculated as the interval between the 1976 questionnaire and the first diagnosis of myocardial infarction, stroke, or death, or conclusion of the study in mid-1996. Relative risks were computed for individuals with and without RA who had cardiovascular end points. A pooled logistic regression technique was used to adjust for multiple potential confounders, including a wide variety of risk factors. Several other analyses were used, all of which produced the same results as the main analysis.

Based upon medical record reviews, 527 women developed RA during the follow-up out of the 114,000 women in the observational study, representing more than 2 million years of follow-up. There were 2296 myocardial infarctions and 1326 strokes. The women with RA were similar to those without RA with respect to CAD risk factors, with some variation. Three percent of the RA patients reported corticosteriod use since the data were documented beginning with the 1994 survey. The age-adjusted risk of myocardial infarction was 2-fold for patients with RA compared to those without (RR 2.07). After adjustment for multiple confounders, the relative risk was identical at 2.0, roughly comparable for fatal and nonfatal infarction. These risk ratios were highly significant. However, adjusted stroke rates did not achieve significance, although there was a trend approaching 50% more stroke in the RA women. Duration of disease seemed to be important; women with less than 10 years of known RA had an adjusted relative risk of 1.16 (NS), while those with > 10 years of exposure to RA had a risk of myocardial infarction of 3.1. Solomon et al point out that the relative increased risk of RA of 2- to 3-fold is comparable to that suggested in smaller studies in the literature. They emphasize that the risk association remained after adjustment for known CAD risk factors. Laboratory analyses and markers of inflammation are not available from the NHS. Solomon et al point out, however, that, "many of the cells comprising the inflammatory infiltrate in the joint lining are likewise found in atherosclerotic plaque." CRP and other cytokine markers of inflammation are known to be elevated in RA. Furthermore, one recent study reported a decrease of cardiovascular mortality in patients treated with methotrexate, suggesting that immunosuppressive therapy was beneficial for the vascular wall. Solomon et al point out that there may be inadvertent confounders, such as reduced physical activity, the various medications taken for RA, and perhaps differential use of cardiovascular prevention medications. They emphasize that medications used for RA have the potential for both inducing and protecting from thrombotic events and atherogenesis. Efforts to control for use of corticosteriods and NSAIDs were carried out, with the risk of MI persisting. Solomon et al concluded, "RA should be rec-

ognized as a marker of increased risk for myocardial infarction." They believe that treatment medications for RA and perhaps less-than-adequate CAD prevention therapy may contribute to the increased risk in these women. They concluded, "It would be prudent to consider aggressive cardiac prevention measures in patients with RA to address established coronary heart disease risk factors."

COMMENT BY JONATHAN ABRAMS, MD

This is an interesting analysis, which seems not surprising given our current knowledge and the focus on inflammation and its relationship to atherothrombosis and unstable plaque. In this large, observational cohort, it is difficult to establish the effects of various potent drugs used for RA. Furthermore, the recent controversy about COX-2 inhibitors and the suggestion that nonselective NSAID may be safer point out the complexity of anti-inflammatory medications. Aspirin use was less common in the RA patients, 41.5% vs 52.2%. Hormone replacement therapy was slightly greater in RA, 33% vs 27%; as expected, NSAID use approached 67% in the RA patients vs 22% in non-RA women. Physical activity, measured in estimated mets per week, was somewhat less in the RA women but not strikingly so. No data were provided for CRP in these women, and one wonders if the banked plasma stored at the beginning of the study could be analyzed for CRP. It is clear that many to most patients with RA will have elevations of CRP and other inflammatory markers. Many believe that CRP itself may play an adverse role in the vasculature and is not just a marker of increased vascular risk. Thus, chronic elevation of cytokines in this autoimmune disease over many years may induce or exacerbate events in the vessel wall in promoting atherothrombosis and perhaps unstable plaque. I agree firmly with the conclusions of Solomon et al that aggressive CAD preventive measures should be considered in RA, and I would suggest that this approach be mandated. We are currently treating diabetes without obvious overt vascular disease as a CAD risk equivalent (ie, diabetics should be treated with the same target goals of blood pressure and lipid modification as individuals with established CAD or a previous stroke). It is logical that for the RA patient, one should aim for an LDL target of 100 mg/dL or less; aspirin should be used in all; COX-2 NSAID use should be avoided until the current controversy is resolved; blood pressure should be controlled, with a target of 130/80 or less; an optimal "heart healthy diet" is recommended; and as much physical activity as can be carried out should be. With the complexity of this illness and its treatment, it may be difficult to carry out randomized trials looking at CAD risk prevention, particularly since the major adverse vascular effects of RA are seen only after 10 or more years of exposure. Thus, RA is now added to the pantheon of conditions for which very aggressive CAD prevention approaches are warranted. In this case, it is unlikely that a "smoking gun" trial of aggressive prevention therapy vs "usual care" will be carried out. ■

Fibrinolysis For Mechanical Prosthetic Valve Thrombosis

ABSTRACTS & COMMENTARY

Synopsis: *Although fibrinolytic therapy was highly successful for thrombosis of prosthetic mechanical heart valves, a high complication rate limits its use to nonsurgical candidates.*

Sources: Roudaut R, et al. *J Am Coll Cardiol*. 2003;41:653-658; Alpert JS. *J Am Coll Cardiol*. 2003;41:659-660.

THE CURRENT ROLE OF FIBRINOLYSIS THERAPY FOR mechanical prosthetic valve thrombosis remains controversial. Thus, investigators from Pessac, France, and San Diego, Calif, retrospectively reviewed their experience with 127 episodes of prosthetic valve thrombosis in 110 patients treated with fibrinolytic agents between 1978 and 2001. They noted that the use of fibrinolytic agents has decreased over the past decade, possibly because the increased use of transesophageal echocardiography has increased the accuracy of the diagnosis and has increased the number of patients excluded because of large atrial clots. Bileaflet mitral valves were most frequently affected, and 91% of all thrombosed valves were obstructed. Almost half were documented to be on inadequate anticoagulation. About 20% of cases were heralded by systemic emboli, but most presented with symptoms of heart failure. Approximately one-third of the patients initially received 1 of 3 agents: streptokinase, urokinase, or recombinant tissue plasminogen activator (rt PA), followed by heparin. Therapy was continued until echocardiography or cinefluoroscopy became normal. Complete success was noted in 71%; seventeen percent experienced marked clinical improvement, but incomplete recovery of valve function; and in 12%, therapy failed. Success rates were higher for aortic vs mitral prostheses. One-third of patients required the use of 2 fibrinolytic agents. As a first agent either streptokinase or rt PA were superior to urokinase, and after combination therapy those given streptok-

inase first had considerably more success—86% vs 68% for rt PA first and 59% for urokinase first (P = .045). In one-quarter of patients complications were observed: major bleeding in 5%, systemic embolism in 15%, and death in 12%. The mortality was higher in patients with more severe heart failure. About 20% of patients required surgery for incomplete results. Roudaut and colleagues concluded that although fibrinolytic therapy was highly successful for thrombosis of prosthetic mechanical heart valves, a high complication rate limits its use to nonsurgical candidates.

COMMENT BY MICHAEL H. CRAWFORD, MD

The results of this observational data base study suggest that fibrinolytic therapy for thrombosed mechanical prosthetic valves is still controversial. The major competing therapy is surgical thrombectomy or valve replacement. Results from observational surgical reports suggest that the overall mortality is similar (10-20%) and higher (up to 50%) in critically ill patients. However, the rate of systemic emboli is much higher with fibrinolytic therapy. Thus, it would appear that the risk of emboli may be acceptable in critically ill patients at high risk for surgery but not in stable patients at lower risk for surgery. This conclusion is supported in the accompanying editorial by Alpert.

Several caveats are discussed by Roudaut et al. The success of fibrinolysis was higher in aortic prostheses vs mitral, which could influence decisions in difficult cases. Also, without presenting any data, they suggest that fibrinolysis should be first choice in right heart prosthetic valves, presumably because the sequelae of emboli to the lungs is less important clinically. Although Alpert agrees with this recommendation, it would have been nice to see some supportive data. In addition, Roudaut et al make much of the great value of transesophageal echocardiography in the last decade. In particular, they point to the elimination of patients for fibrinolytic therapy with large atrial clots, presumably because they are hard to dissolve and the risk for emboli may be higher. Although this makes some sense, and no one would question the overall value of this new endocardiographic technology, no supportive data are presented. Finally, Roudaut et al point to an almost 20% recurrence rate over a mean of 2 years as another reason to favor surgery. However, since the majority of prosthetic valve thromboses are caused by inadequate anticoagulation, it is not clear how surgery solves this problem. Some patients may have structural problems with the valve (pannus, etc) that could predispose to recurrent thrombus. It may be better to try to identify such patients by transesophageal echo before surgical referral. ■

Immunosuppressive Therapy for Myocarditis

ABSTRACT & COMMENTARY

Synopsis: *In patients with active lymphocytic myocarditis and persistent heart failure for greater than 6 months, those with circulating cardiac autoantibodies and no viral genomes detected on myocardial biopsy are the most likely to benefit from immunosuppressive therapy.*

Source: Frustaci A, et al. *Circulation*. 2003;107: 857-863.

THE ROLE OF IMMUNOSUPPRESSIVE THERAPY IN myocarditis is controversial due to the heterogeneity in the pathophysiology. Thus, Attilio Maseri's group from Catholic University in Rome, Italy, performed a retrospective analysis of their experience in patients with active lymphocytic myocarditis and heart failure who failed conventional supportive care and were treated with immunosuppression. Their goal was to identify the virological and immunologic characteristics that defined those who responded to this therapy. The population was derived from 652 patients who underwent myocardial biopsy for a variety of reasons. Active myocarditis was observed in 112—80 with heart failure, 28 with ventricular arrhythmias, and 4 with unexplained chest pain. Among the 80 with heart failure, 41 had lymphocytic myocarditis and NYHA class III-IV heart failure for greater than 6 months unresponsive to conventional supportive care. These 41 patients were treated for 6 months with prednisone and azathioprine and constitute the study population. At 1 and 6 months, all had repeat catheterization and biopsy. At the end of this treatment, 21 were classified as responders because they decreased at least 1 NYHA clinical class and their left ventricular ejection fraction increased at least 10% compared to baseline. Follow-up continued for 1 year. Clinical, echocardiographic, and hemodynamic data were not different between the responders and the nonresponders. By polymerase chain reaction on the biopsy material, viral genomes were detected in 17 of the nonresponders (85%) vs 3 responders, all of whom had hepatitis C identified. Serum cardiac autoantibodies were present in 19 responders (90%) and none of the nonresponders. Frustaci and associates concluded that in patients with active lymphocytic myocarditis and persistent heart failure for greater than 6 months, those with circulating cardiac autoantibodies and no viral genomes detected on myocardial biopsy are the most likely to benefit from immunosuppressive therapy.

COMMENT BY MICHAEL H. CRAWFORD, MD

The heterogeneous clinical and biopsy results of previous studies has led to a sense of therapeutic nihilism for treating patients with heart failure and suspected myocarditis with immunosuppressive agents. Current guidelines suggest that certain biopsy findings warrant a trial of immunosuppressive therapy, namely, eosinophilic, granulomatous, or giant cell myocarditis, none of which is particularly common. Also, myocarditis thought to be due to connective tissue diseases or cardiac transplant rejection responds to immunosuppressive therapy. Thus, it is not surprising that Maseri's group found that patients with circulating cardiac autoantibodies responded to immunotherapy. These 19 patients were 46% of the 41 patients with lymphocytic myocarditis and persistent heart failure, who were 51% of the 80 patients with heart failure and biopsy evidence of myocarditis, who were 17% of the 478 patients with idiopathic heart failure who underwent biopsy at their institution. Thus, 4% of patients (19 of 478) with idiopathic heart failure are potential candidates for immunotherapy. If you add other rare cases described above that may respond to immunotherapy, perhaps 5% will be candidates. Unfortunately, that is a lot of biopsies for a small, albeit important, gain. Clearly, the ability to use circulating autoantibodies to cull out potential responders is very important. Whether biopsy still needs to be done to detect viral genomes before embarking on a trial of immunosuppressives in patients with high autoantibody titers is unclear because we don't know if it is harmful, if not successful. Of interest is the fact that the responders in this trial were improved within a week. This suggests that a trial of immunosuppressives may not have to be long to assess efficacy. Another issue is whether one needs to wait 6 months to see which patients with suspected myocarditis are not within the 40% who will improve spontaneously. Perhaps autoantibodies should be sought earlier in the course.

Of interest, the 3 responders with viral genomes detected in their biopsies all had hepatitis C identified. None had hepatic or other systemic manifestations. When therapy ended, these 3 patients quickly deteriorated unlike the other responders, and they had histologic evidence of recurrent myocarditis. They improved clinically and histologically on resumption of immunosuppressive therapy. Thus, patients with hepatitis C virus-associated myocarditis may need to be on chronic immunosuppression. Other viruses detected in this study included enterovirus, Epstein-Barr, adenovirus, influenza A, and parvovirus B19. Of these, enterovirus and adenovirus alone or in combination had the worst prognosis. Patients with viruses other than hepatitis C detected on biopsy may respond to beta interferon. ■

CME Questions

Effective with this testing period, 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.

15. Which of the following are associated with a higher incidence of CAD?
a. Diabetes mellitus
b. Rheumatoid arthritis
c. Alcoholism
d. a and b

16. Fibrinolytic therapy for thrombosed mechanical heart valves is indicated for patients with:
a. large left atrial thrombis.
b. right heart valve thrombosis.
c. critically ill patients at high risk for surgery.
d. b and c

17. Immunotherapy for persistent heart failure due to lymphocytic myocarditis on biopsy is indicated if:
a. viral genomes are detected on biopsy.
b. serum cardiac autoantibodies are detected.
c. hepatitis C is found on biopsy.
d. b and c

18. Acute renal dysfunction following coronary angiography can often be prevented by:
a. volume loading.
b. low osmolality contrast agents.
c. acetylcysteine (Mucomyst®).
d. All of the above

19. In-hospital use of automatic external cardioverter-defibrillators has been shown:
a. to be 100% sensitive for VT or VF.
b. to be 100% specific for VT or VF.
c. to occasionally give inappropriate shocks.
d. All of the above

20. Cardiac resynchronization for heart failure patients:
a. reduces all-cause mortality.
b. reduces heart failure-related mortality.
c. reduces cardiac arrhythmias.
d. All of the above

Answers: 15(d); 16(d); 17(d); 18(d); 19(a); 20(b)

PHARMACOLOGY WATCH

Warfarin Effectively Prevents Venous Thromboembolism

Low intensity warfarin therapy effectively prevents recurrent venous thromboembolism, according to a recent study in the *New England Journal of Medicine*. After a median of 6.5 months of full-dose anticoagulation therapy, 508 patients with idiopathic venous thromboembolism were randomized to placebo or low intensity warfarin therapy with target INRs of 1.5 to 2.0. The study was terminated early after 4.3 years of follow-up due to a marked reduction in recurrent thromboembolism in the low intensity warfarin therapy group. Of 253 patients assigned to placebo, 37 had recurrent venous thromboembolism compared with 14 of 255 patients assigned to low intensity warfarin, a risk reduction of 64% (hazard ratio 0.36; [95% CI, 0.19-0.67]; $P < 0.001$). Major hemorrhage occurred in 2 patients assigned to placebo and in 5 assigned to low intensity warfarin ($P = 0.25$). Death occurred in 8 patients in the placebo group and 4 in the low intensity warfarin group ($P = 0.26$). The composite end point was recurrent venous thromboembolism, major hemorrhage, or death. There was a 48% reduction in the composite end point with low intensity warfarin therapy. Because of the importance of these findings, the journal published the study online more than a month prior to its publication date of April 10, 2003.

Vitamin D Reduces Osteoporotic Fractures

British researchers have reduced the rate of osteoporotic fractures in older adults by mailing low-cost vitamin D3 supplements to study subjects every 4 months. Researchers from Cambridge and Oxford universities randomized 2686 adults age 65-85 (2037 men and 649 women) to 100,000 IU vitamin D3 or placebo every 4 months for 5 years. The active medication and placebo were sent to patients by mail and compliance was tracked by completion of a form. At the end of the study period, 149 fractures were noted in the control group and 119 were noted in the vitamin D3 group (RR = 0.78). Fractures of the hip, wrist, forearm, or spine were considered osteoporotic fractures, of which 87 were noted in the control group and 60 in the vitamin D3 group (RR = 0.67). The vitamin D treatment was well tolerated and cost less than 1 pound per year. The authors suggest that vitamin D may be a good, inexpensive primary prevention strategy for the prevention of osteoporotic fractures (*BMJ*. 2003;326:469-472).

Adefovir Effective for Hepatitis B Treatment

Adefovir is an effective treatment for chronic hepatitis B, according to 2 studies published in February. The first study from Greece randomly assigned 185 patients (in a 2:1 fashion) with e antigen-negative chronic hepatitis B, to 10 mg of adefovir or placebo daily for 48 weeks. Patients in the adefovir group were significantly more likely to have improvement in histologic abnormalities as shown by liver biopsy compared to placebo (64% improvement [77 of 121] adefovir group, 33% [19 of 57] placebo group; $P < 0.001$). Patients in the treatment group also had reduced hepatitis B virus DNA levels and improved alanine aminotransferase levels compared to placebo. Resistant hepatitis B virus was not noted, and the drug was well tolerated (*N Engl J Med*. 2003;348:800-807). In a second multinational study of

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

e antigen-positive chronic hepatitis B, 515 patients were randomized to adefovir 10 mg/d, adefovir 30 mg/d, or placebo for 48 weeks. The primary end point was histologic improvement, which was noted in 53% of the 10 mg group, 59% of the 30 mg group, and 25% of the placebo group ($P < 0.001$ for both dose schedules). Once again, evidence of hepatitis B virus was markedly reduced, and there was significant normalization of alanine aminotransferase levels in both treatment groups. The safety profile of 10 mg/d adefovir was similar to placebo; however, there was a higher frequency of adverse events and renal laboratory abnormalities in the 30 mg/d group. Again no hepatitis B virus mutations were noted in the treatment groups. The authors conclude that 10 mg/d adefovir is a favorable risk benefit profile for long-term treatment of e antigen-positive chronic hepatitis B (*N Engl J Med*. 2003;348:808-816). An accompanying editorial states "we appear to be at the dawn of the new era" in the treatment of hepatitis B (*N Engl J Med*. 2003;348:848-850).

Ibuprofen/Aspirin Study Revisited

Another study suggests that ibuprofen blocks the cardioprotective effects of aspirin. In 2001, researchers showed that ibuprofen may block the COX-1 receptor on platelets, keeping aspirin from binding to the receptor (*N Engl J Med*. 2001;345:1807-1817). Now a new study suggests that ibuprofen may reduce the cardioprotective effect of aspirin. Researchers in the United Kingdom reviewed the records of more than 7000 patients who were admitted for MI, angina, stroke, TIA, or peripheral vascular disease and were given aspirin at discharge.

All survived at least 1 month post discharge. In addition to aspirin, 187 patients were also prescribed ibuprofen and 206 were prescribed diclofenac. The patients who took the aspirin/ibuprofen combination were associated with significantly higher all-cause mortality (hazard ratio, 1.93 [$P = 0.011$]) and higher cardiovascular mortality (hazard ratio, 1.73 [$P = 0.0305$]) compared to patients who took aspirin alone. There was no adverse effect noted with aspirin/diclofenac (*Lancet*. 2003;361:573-574). An accompanying editorial suggests that the lack of effect of diclofenac may be due to its relative COX-2 selectivity. The author also suggests that because of the wide availability of over-the-counter ibuprofen, physicians need to be vigilant and explain this potential drug-drug interaction to patients on aspirin cardioprotection (*Lancet*. 2003;361:542-544).

ACE Inhibitors Favored in Cardiovascular Care

A head-to-head study of ACE inhibitors vs diuretics for the treatment of hypertension suggests that ACE inhibitors are better at reducing cardiovascular events. The Second Australian National Blood Pressure Study (ANBP2) compared ACE inhibitors to diuretics and a perspective, randomized, open-label study with blinded assessment of end points. More than 6000 hypertensive men and women age 65-84 were followed for a median of 4.1 years. The drug treatment was titrated to a similar level of blood pressure lowering (a decrease of 26/12 mm Hg). The end point was the total number of cardiovascular events in the 2 treatment groups. There were 695 events in the ACE inhibitor group (56.1/1000 patient years) and 736 events in the diuretic group (59.8/1000 patient years). The hazard ratio for the ACE inhibitor group was 0.89 (95% CI, 0.79-1.00 [P = 0.05]). The hazard ratio for male patients was 0.83 and for female patients was 1.00. The authors conclude that treatment of hypertension with ACE inhibitors leads to better cardiovascular outcomes than treatment with diuretics, particularly in older men (*N Engl J Med*. 2003;348:583-592). The results of this study seem to contradict the recently published ALLHAT study which showed better outcomes with diuretics (*JAMA*. 2002;288:2981-2997).

Digoxin Dosing and Heart Failure

If digoxin is to be used in men with heart failure, serum digoxin concentrations (SDC) are optimal between 0.5 to 0.8 ng/dL, according to further analysis of the Digitalis Investigation Group (DIG) trial. The initial reports of DIG reported that digoxin provided no overall mortality benefit and only modest reduction in hospitalizations among patients with heart failure and depressed left ventricular function. This new study looked at outcomes in 1171 men based on SDC of 0.5-0.8 ng/mL, 0.9-1.1 ng/mL, and greater than or equal to 1.2 ng/mL, compared to 2611 men randomly assigned to receive placebo. The main outcome was all-cause mortality of follow-up of 37 months. The highest SDC were associated with higher all-cause mortality. Patients in the lowest SDC range(0.5-0.8ng/mL) had a 6.3% lower mortality rate compared with patients receiving placebo (95% CI, 2.1-10.5). Patients in the midrange SDC (0.9-1.1 ng/mL) had no reduction mortality, while patients with the SDCs above 1.2 ng/mL had 11.8% higher mortality rate than those receiving placebo (95% CI, 5.7-18%). The authors conclude that higher serum digoxin concentrations were associated with increased mortality and that the optimal SDC for men with heart failure is 0.5-0.8 ng/mL, and the authors suggest this for the new optimal therapeutic range (*JAMA*. 2003;289:871-878). ■