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INSIDE

Prevention of Atrial Fibrillation After Cardioversion

ABSTRACT & COMMENTARY

THE PREVENTION OF ATRIAL FIBRILLATION AFTER CARDIOVERSION (PAFAC) Trial was a placebo-controlled study comparing sotalol and a quinidine/verapamil combination in patients with persistent atrial fibrillation after cardioversion. Patients between 18 and 80 years of age with documented persistent atrial fibrillation and a clinical indication for direct current cardioversion were eligible for inclusion. Patients were anticoagulated for at least 3 weeks prior to attempted cardioversion. Patients with implanted pacemakers or defibrillators, recent myocardial infarctions or cardiac surgery, uncontrolled valvular disease, QTc prolongation at baseline, or recurrent hypokalemia were excluded. Eligible patients were brought in to the hospital and cardioverted electrically. Patients who maintained sinus rhythm after cardioversion for at least 2 hours were then eligible for randomization. Patients were randomized to either sotalol (80 mg 3× daily for 1 day, then 160 mg 2× daily), a fixed combination of quinidine plus verapamil (160 mg quinidine plus 80 mg verapamil 2× daily for 1 day, then 3× daily thereafter), or placebo. The approximate desired randomization ratio was 4:4:1.

Patients were kept in-hospital for at least the first 3-4 days after drug initiation. After discharge, each patient was given a credit card sized ECG recorder and instructed to record and transmit at least 1 ECG every day independent of symptoms. This type of recorder stores 1 minute of a single lead electrocardiogram which can subsequently be transmitted to a monitoring center over any regular telephone. At the time of the transmission, the patient was asked if they were experiencing any symptoms. The transmitted ECGs were analyzed by trained staff at the monitoring center. When atrial fibrillation was detected on the 1 minute recording, the study site was notified to contact the patient for further ECG documentation and clinical correlation.

The primary outcome parameter was the time to first recurrence of any type of atrial fibrillation or death. Secondary outcome measures included the occurrence of, and time to, persistent atrial fibrillation, the number of occurrences, and time to symptoms.

The study was conducted in Germany and the Czech Republic. In

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68 trial centers, 1182 patients were enrolled. Of these, 848 patients were successfully cardioverted and randomized. There were 88 patients assigned to placebo, 383 patients to sotalol, and 377 patients to quinidine/verapamil. There were no significant differences in baseline demographic data between the 3 groups. For the entire group, the mean age was 63 ± 9 years, and 66% were male. Atrial fibrillation had been present for a median time of 365 days. Only 11% of the patients had previously undergone a direct current cardioversion. Coronary artery disease was seen in only 21%, and 61% of the patients were New York Heart Association functional class I. The prevalence of hypertension was not specified.

During follow-up, 572 of the 848 patients developed an ECG documented recurrence of atrial fibrillation. The 1 year actuarial recurrence rate was 83% in the placebo group, 67% in the sotalol group, and 65% in the quinidine plus verapamil group. The probability of remaining free of persistent AF was, however, considerably better. After 1 year, persistent AF had recurred in 38% in the quinidine/verapamil group, 51% in the sotalol group, and 77% in the placebo group. Fetsch and colleagues noted that in 70% of all documented recurrences, the patients did not report associated symptoms. The proportion of symptomatic vs asymptomatic episodes of AF were similar between the 3 groups.

There were 11 deaths in the study; 6 on sotalol, 5 on quinidine/verapamil, and none on placebo. Torsades de pointes ventricular tachycardia was seen only in patients on sotalol (9/383, 2.3%). Bradycardia was more common in patients treated with sotalol, whereas QT interval prolongation, diarrhea, and peripheral edema were more common in patients treated with quinidine and verapamil. All 3 documented lethal episodes of ventricular fibrillation, as well as 6 of 9 episodes of torsades de pointes ventricular tachycardia and 4 of 8 episodes of ventricular tachycardia of greater than 10 beats in duration, occurred during the first 4 days of in-hospital therapy.

Fetsch et al conclude that sotalol and quinidine plus verapamil are more effective than placebo in preventing recurrent atrial fibrillation after cardioversion in patients with persistent atrial fibrillation. It appeared that quinidine plus verapamil was slightly more effective than sotalol in preventing recurrent, persistent atrial fibrillation. Finally, Fetsch et al noted that all the episodes of torsades de pointes occurred on sotalol, and that the majority of events that might be considered proarrhythmia occurred in the first 4 days of antiarrhythmic drug therapy (Fetsch T, et al. Prevention of Atrial Fibrillation After Cardioversion: Results of the PAFAC Trial. *Eur Heart J.* 2004;25:1385-1394).

COMMENT BY JOHN P. DiMARCO, MD, PhD

The PAFAC Trial is an important study that provides interesting observations that should effect the way we treat atrial fibrillation. Perhaps the most important observation is the high frequency of asymptomatic recurrences of atrial fibrillation. These episodes could be both asymptomatic and self-terminating even in patients who had initially presented with persistent atrial fibrillation. The daily 1 minute ECG transmissions allowed this observation to be made. This high prevalence of asymptomatic atrial fibrillation in patients has obvious implications on the need for continuing anticoagulation in patients, even if they appear to be well clinically and in sinus rhythm.

The second major observation of interest is the apparent favorable interaction between quinidine and verapamil. The mechanisms responsible for this are uncertain. Although quinidine was formerly the most commonly used drug for maintenance of sinus rhythm in patients with atrial fibrillation, recent concerns about its proarrhythmic potential and its side effect profile have caused it to be less frequently prescribed. Adding verapamil has several potentially beneficial effects. Calcium channel blockers may decrease the atrial remodeling that occurs in association with atrial fibrillation. Calcium channel blockade also inhibits development of the early after depolarizations that are thought to be responsible for torsades de pointes. The opposite effects of quinidine and verapamil on GI motility

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may balance each other out, making both drugs more tolerable. Finally, verapamil and quinidine may have pharmacokinetic interactions via the cytochrome P450 system that allow more stable therapeutic plasma levels at lower doses. In PAFAC, relatively low doses of quinidine and verapamil appeared to be as successful as sotalol and relatively free of therapy-limiting side effects.

A third major observation is the temporal pattern for the occurrence of proarrhythmia. In this study, two-thirds of the proarrhythmia was seen within the first 4 days. We are unfortunately not provided much information about the clinical characteristics of those who experienced proarrhythmia. It would be important to know if patients with normal ventricular function and no ventricular hypertrophy ever developed this problem. Currently, we always hospitalize patients with left ventricular hypertrophy or congestive heart failure when starting antiarrhythmic drugs. If proarrhythmia occurred in patients without this finding, the data presented here would argue that any patients with structural heart disease should be hospitalized when drugs are begun after cardioversion of atrial fibrillation.

The PAFAC investigators should be congratulated on an excellent, well designed study. Their study confirms the relatively poor efficacy of antiarrhythmic drugs in preventing recurrent atrial fibrillation, but the careful trial design provides data helpful for designing future studies and for managing patients on a day-to-day basis. ■

Warfarin vs Aspirin for Bioprosthetic Aortic Valve Replacement

ABSTRACT & COMMENTARY

Synopsis: *Low-dose aspirin is as effective as warfarin for preventing cerebral thromboembolic events after bioprosthetic aortic valve replacement.*

Source: Gherli T, et al. *Circulation.* 2004;110:496-500.

Current guidelines recommend warfarin anticoagulation for the first 3 months after biprosthetic aortic valve replacement. However, because of the risk of bleeding, some surgeons are comfortable with aspirin only during this period. Thus, Gherli and colleagues from Parma, Italy performed an observational study of patients undergoing bioprosthetic aortic valve replacement at 1 institution. Patients with atrial fibrillation at any time, multiple valve replacement, and any potential indication for warfarin therapy were excluded. Of the 9 senior surgeons, 5 gave aspirin and 4 gave warfarin, so patient assignment to therapy depended on who was operating the day of surgery. All patients got low molecular weight heparin on the first postoperative day, and 100 mg aspirin or warfarin was started on day 2. Those getting warfarin had the heparin continued until INRs between 2-3 were achieved. Warfarin was continued for 3 months, and then aspirin was substituted. In those with concomitant coronary artery bypass surgery, aspirin was withheld until warfarin was discontinued. The primary endpoints were cerebral ischemic events, bleeding, and survival. There were 3 cerebral ischemic events in the 141 patients (2.1%) receiving aspirin and 5 in the 108 patients (4.6%) on warfarin. After 3 months, and up to 16 months of follow-up, there was 1 additional cerebral ischemic event in the aspirin group (0.7%) and 3 in the warfarin group (2.8%). There was no statistically, significant difference in cerebral ischemic events between the 2 groups. Major bleeding occurred in 3 patients in the aspirin group (2.1%), all were gastrointestinal bleeding, and 4 in the warfarin group (3.7%). In all cases of bleeding with warfarin, the INR was > 3.0 on readmission to the hospital. Perioperative survival was > 98% and long-term > 95%. There was no difference in survival or stroke-free survival between the 2 groups. Gherli et al concluded that low-dose aspirin is as effective as warfarin for preventing cerebral thromboembolic events after bioprosthetic aortic valve replacement.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

Despite the recommendations by the ACC/AHA guidelines, there has been a move by cardiac surgeons away from 3 months of warfarin after bioprosthetic aortic valve replacement because of observational data and their own experience with the bleeding complications of warfarin, especially during the first 30 days post-operatively. Although this study did not show a statistically significant difference in bleeding complications, the type of bleeding with each therapy is instructive. All 3 patients in the aspirin group had gastrointestinal bleeding that abated with conservative therapy. The 4 episodes on warfarin were: 1 vein harvest site bleeding; 2 mediastinal bleeding; and 1 patient with an intracranial bleed who died. You can see why surgeons are not too keen on warfarin.

This prospective observational study may be biased since the referring physicians could have directed cases, where they preferred 1 therapy over another, to a day when the right surgeon was operating. The 2 groups were well matched, except that the warfarin group was slightly older (73 vs 70 years, $P = .007$) and their preoperative risk score was higher (6.9 vs 6.1; $P = .015$). It is difficult to know if this influenced the results. Of more concern is the fact that this was a low-risk group. Patients with any possible confounder were eliminated, including patients with peripheral vascular disease or previous anticoagulation therapy. The

paper does not reveal how many patients were excluded.

Since there was no difference between the 2 groups in the major outcomes, one could establish a protocol or pick the therapy thought best for each patient. Unless there is another indication for warfarin such as atrial fibrillation, few would probably select warfarin given the inconvenience of taking it. However, when newer anticoagulants, that are less affected by food and other medications and do not require periodic blood tests, become available, the pendulum could swing the other way. ■

Public-Access Defibrillation

ABSTRACT & COMMENTARY

Synopsis: *The use of AEDs by trained volunteers is safe and effective, particularly in public locations where there is at least a moderate likelihood that an out-of-hospital cardiac arrest will be witnessed.*

Source: Hallstrom AP, et al. *N Engl J Med*. 2004;351: 637-646.

THE PUBLIC-ACCESS DEFIBRILLATION TRIAL TESTED THE hypothesis that use of automatic external defibrillators (AEDs) by lay volunteers trained in standard cardiopulmonary resuscitation (CPR) would increase the number of survivors to hospital discharge after out-of-hospital cardiac arrest. The study was performed at 24 centers in the United States and Canada. Each center recruited a sample of community facilities (eg, shopping malls, recreational centers, hotels, apartment complexes, etc). In each facility, a pool of potential volunteer responders was identified. Eligible community units were randomly assigned to a CPR-only response system or to a CPR plus AED response system. The volunteer responders were trained according to current AHA guidelines, either in standard or in CPR plus AED use. The prespecified primary outcome was the number of survivors of definite out-of-hospital cardiac arrest.

There were 993 community units enrolled in the study. Eighty-four percent of the units were public facilities, including recreational facilities, shopping centers, entertainment complexes, or community centers. The other 16% were multi-unit residential facilities. Over 20,000 volunteers were trained at the 993 community units. The mean age of the volunteers was 40, with 55% being male and 69% having a high school education or greater. During the course of the trial, there were a total of 526 presumed out-of-hospital cardiac arrests. In 231 of these cases, the patient was considered to be dead on arrival and no EMS treatment was delivered. In 56 cases, the arrest was considered to be from a noncardiac cause. The study group therefore consisted of 239 subjects with definite or probable treated arrests of cardiac cause. In this latter group, the mean age was 69.8, 67% were men. Seventy percent of the treated arrests occurred in a public location, and in 72%, the collapse was witnessed. There were no inappropriate AED shocks during the entire course of the study. One hundred and twenty-eight patients with an arrest of cardiac cause were treated with CPR plus an AED, and 30 survived. In contrast, among 107 patients treated with CPR only, only 15 survived. Virtually all of the survivors in both groups were in public facilities; only 2 survivors were in residential complexes. Among survivors, there was no difference between the groups in functional performance at the time of hospital discharge. Hallstrom and colleagues conclude that the use of AEDs by trained volunteers is safe and effective, particularly in public locations where there is at least a moderate likelihood that an out-of-hospital cardiac arrest will be witnessed.

■ COMMENTS BY JOHN P. DiMARCO, MD, PhD

Survival for victims with out-of-hospital cardiac arrest remains dismal. Even in communities with well organized emergency medical response systems, the probability of survival after out-of-hospital cardiac arrest is under 10%. Early defibrillation has been identified as one of the keys to survival. This usually means that the event has to be witnessed or the victim found very quickly and that the capacity for defibrillation can be made readily available. In high-risk patients, implantable cardioverter defibrillators are increasingly used for both primary prevention of sudden cardiac death and for secondary prophylaxis in survivors of prior episodes. However, more than half of the out-of-hospital cardiac arrests occur in those who are thought to be in relatively low-risk groups, and the invasive nature and cost of implantable defibrillators make them inappropriate except in high-risk populations. Further complicating the problem is the fact that most sudden deaths occur at home and are frequently unwitnessed.

The last 20 years have seen tremendous advances in AED technology. These devices now are small, portable, and both sensitive and specific for detecting ventricular fibrillation or disorganized ventricular arrhythmias. AED models developed for lay use have simple instructions and their use is easily learned with minimal instruction. Therefore, it has become a goal of the American Heart Association and most Emergency Medical Services to extend the concept of early AED use to community facilities and beyond.

This paper illustrates both the potential and the problems of public-access defibrillation. Survival after out-of-hospital cardiac arrest is dependent on a number of critical factors. It is key that the arrest be witnessed, that a trained or at least knowledgeable potential rescuer be available

and that this rescuer have access to an AED. If all 3 are present, an improved survival rate can be demonstrated; but as shown here, even if the event is witnessed and resuscitation is started, only 25% of all patients with cardiac arrests will survive.

Recently, the FDA reviewed an application from an AED manufacturer to sell AEDs to the public without prescriptions. The hope is that by making these devices more available, more lives will be saved. The emerging paradigm is that the AED is a safety device that can be made available within a short and critical time window. An AED will never be as effective as an implantable defibrillator for an individual, but greater distribution will allow them to reach a much greater population.

The NIH is currently sponsoring another trial called the Home AED Trial. This trial will focus on moderate risk patients with anterior myocardial infarctions, and will try to determine if AEDs save lives when used in the home. One could envision a future in which AEDs are regarded more as a standard safety device, similar to a fire extinguisher, rather than a piece of esoteric medical equipment. If costs can be lowered and this concept becomes fully developed, it is hoped that many families and individuals will likely elect to place an AED in their homes. ■

Relationship Between Calcium Scans and Stress Myocardial Perfusion

ABSTRACT & COMMENTARY

Synopsis: *A calcium score < 100 eliminates the need for MPS, but patients with a negative MPS often have coronary calcium. These findings imply a potential role for applying CAC screening after MPS among patients manifesting normal MPS.*

Source: Berman DS, et al. *J Am Coll Cardiol*. 2004;44: 923-930.

Coronary artery calcium detected by fast x-ray computed tomography (CT) or electron beam CT is associated with the presence of coronary atherosclerosis. Stress myocardial perfusion scans (MPS) can identify intermediate-risk patients likely to have coronary artery disease (CAD). The potential predictive relationship between coronary calcium and the likelihood of stress-induced myocardial ischemia is not well understood. Thus, Berman and colleagues studied 1195 patients referred for MPS on clinical grounds who also had CT for coronary calcium done. Exercise stress was used in 88%; the remainder had adenosine. Rest thallium-201 images were compared to post stress technetium-99 images. MPS and CT were done within 7 days on average. No patient had known CAD, and 51% were asymptomatic.

Results: The 76 patients with a stress MPS positive for ischemia exhibited more CAD risk factors, more abnormalities on stress testing, and higher calcium scores compared to those with a normal MPS. There was a crude relationship between calcium score and a positive MPS: calcium score < 100, positive MPS < 2%; calcium > 1000, positive MPS 20%. The age and gender adjusted calcium percentile score was also related to a positive MPS: < 50th percentile, positive MPS < 2%; > 50th percentile the incidence of a positive MPS increased, but did not exceed 11% even at the 90th percentile. Many of the 1119 normal MPS patients had positive CT scans: 78% of those with a > zero calcium score; 56% of those with > 100; 31% of those with > 400. Multivariate analysis showed that the log calcium score was the most potent predictor of a positive MPS vs other clinical variables (OR 3.4, CI 2.13-5.29, $P < .0001$). Berman et al concluded that: 1) an ischemic MPS is associated with a positive calcium scan, but rarely with a calcium score < 100; 2) a calcium score < 100 eliminates the need for a stress test; 3) normal MPS patients frequently have coronary calcium, suggesting a role for coronary calcium scanning in patients with a normal MPS if their risk for CAD is unclear.

COMMENT BY MICHAEL H. CRAWFORD, MD

Despite the fact that few insurance companies reimburse for it, the use of fast CT to detect coronary calcium is increasing. Most of the increase has been from patient demand, as its acceptance by professional organizations has been lukewarm. This study by a group that has not been one of the advocates for fast CT, nor involved in its commercial exploitation, makes several important points for those of us who are confronted with patients bearing fast CT test results. First, the raw score has more predictive value than the age-sex adjusted calcium percentile score. Unfortunately, the patients are focused on the percentile score because it is usually high (> 50%), even if their raw score is relatively low, and percent numbers seem more understandable, even though they don't mean that you have an X% chance of having a heart attack as soon as they believe. The percentile score does correlate with long-term risk and may help commit the patient to primary prevention measures for life. Second, there seems to be a threshold phenomenon with raw calcium scores. If they are < 100, almost no one has an ischemic MPS and it is not worth doing even if the percentile score is high. If it is > 400, there is a reasonable chance of getting a positive MPS even in asymptomatic patients. Scores between 100

and 400 are the grey zone where clinical judgment must be exercised. Asymptomatic patients in this range are less likely to have an ischemic MPS and could reasonably be managed conservatively. Third, stress testing does not reliably identify subclinical CAD. In this study, 88% of those with a negative MPS had detectable coronary calcium. Even with calcium scores > 1000, the majority had a negative MPS. This emphasizes the point that has been made before that screening stress tests in asymptomatic patients are low yield and may give a false sense of security. Fast CT does detect subclinical disease and seems to be of incremental value over other traditional risk factors. Obviously, costs and logistics preclude the widespread use of CT screening, but in selected patients it can be of use. I find it particularly useful in asymptomatic patients with bad family histories to reassure or motivate them, depending on the results. ■

Cardiovascular Disease Trends: United States and Worldwide

ABSTRACTS & COMMENTARY

Synopsis: *The developing world is experiencing an epidemic of CAD "which expects to continue to increase in the foreseeable future."*

Sources: Ergin, et al. *Am J Med*. 2004;117:219-227.; Arciero, et al. *Am J Med*. 2004;117:228-233.; Okrainec, et al. *Am Heart J*. 2004;148:7-15.; Yusuf, et al. *Am Heart J*. 2004;148:7-15.

THREE RECENT PUBLICATIONS HAVE FOCUSED ON the worldwide state of cardiovascular disease (CVD), including coronary disease and stroke. Two articles assess the United States experience, while the third focuses on multiple countries around the world. Ergin and colleagues analyzed the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHANES) which compared 2 cohorts, 1971-1982 and 1982-1992.[1] The data were based on medical history questionnaires and follow-up interviews, as well as hospital records and death certificate documentation. Other surveys estimate a 60% decrease in coronary disease (CAD) and stroke between 1970 and 2000. The NHANES analysis suggests an estimated 31% decline in CVD mortality, a 33% decrease in CAD mortality, and a 37% decrease in myocardial infarction (MI) mortality. Stroke mortality declined by 38%. All of these reductions were highly, statistically significant. CAD incidence declined only in whites. Acute MI decreased a little, and actually increased 21% in white women. The incidence of stroke declined overall except in black males. One month hospital fatality rates fell by 27-38% for all end points, particularly striking in black subjects. Ergin et al conclude that the decline in CV disease mortality was associated with a 3% decrease in CV disease incidence, as well as improvements in both short term and long term survival. The data suggest "that the decrease in mortality from cardiovascular disease was likely due to a combination of primary prevention, which reduced cardiovascular disease incidence, and secondary prevention and treatment, which reduced short- and long-term case fatality rates." There was a robust fall in age adjusted mortality from CAD and MI, but the incidence of MI remained stable among white and black men and women, but was increased somewhat in white women. This was also true for recurrent MI. In spite of relatively stable rates of MI incidence, 1 month and long term survival improved significantly. Ergin et al point out that their analysis is consonant with other community surveillance studies and national vital statistics. Ergin et al attribute the ". . . substantial decline in stroke incidence" to "a large reduction in mean blood pressure levels and improvement in detection, treatment, and control of hypertension." However, no data to confirm this are provided. Analysis of both the earlier and later cohort surveys indicates a narrowing of the difference in CV mortality rates between blacks and whites. Ergin et al conclude that the decrease in CV mortality from the 1970s to the mid 1990s "can be explained by a decline in both cardiovascular disease incidence and case fatality rates." They emphasize that while CV disease remains the U.S. leading cause of death, vigorous primary and secondary prevention efforts, as well as improved treatment must continue to be emphasized.

In a similar article assessing the Olmsted County, Minnesota, population between 1979-1998, Arciero and colleagues confirmed a modest decline in coronary disease incidence and conclude CV mortality decreases are explained both by primary and secondary prevention.[2] Arciero et al emphasized the rate of increasingly early detection of CAD. In the Olmstead County data, CAD incidence was relativity stable but mortality decreased, as in other data bases. This study, part of the Rochester Epidemio-

logic Project, determined trends and incidence of several CAD manifestations. Because of the stable population in Olmstead County (the site of the Mayo Clinics and a relatively white population isolated from urban centers), these data are felt to be valid. Arciero et al analyzed incident CAD events, including MI, sudden death, and angiographic CAD. The latter is not felt to be a reliable method of examining trends, as there was an enormous increase in coronary angiography beginning in the 1980s. Arciero et al found that the overall incidence of CAD declined modestly. Sudden death decreased. MI rates were somewhat lower between 1979 and 1998. Documentation of CAD was considerably more common than the incidence of MI and sudden death. There was a 9% decrease in CAD incidence between 1988 and 1998. Overall, the incidence of combined hospitalized MI and sudden death decreased by 17% over the 20 years. MI rates were little changed, concordant with other studies. As in the NHANES analysis, MI rates in women, and in this study, older individuals, actually increased. Arciero et al stress the early detection of CAD in this population, in part related to the widespread use of coronary angiography, and note the discrepancy between the increasing burden of CAD, as documented by angiography and the decline in CVD incidence. The age and sex related trends for all CAD parameters were comparable. Arciero et al conclude that overall, "trends in the age- adjusted incidence in coronary disease in the 1990s paralleled the trends in myocardial infarction and sudden death." They note that in Olmsted County, there has been relative shift of CAD burden to women and older persons. Arciero et al cite both primary and secondary prevention improvements to explain the modest decrease in CV mortality during the study interval. They call for an increase in prevention efforts in the aging population; the decreases in CAD incidence in younger individuals, particularly males, was noteworthy. In conjunction with the Ergin et al, Arciero et al believe that "declining CAD mortality is multifactorial, explained in part by primary prevention and secondary prevention and mediated by earlier detection."

The last study is an assessment of CAD in the developing world.[3] This is a sobering overview of CAD in multiple countries derived from an extensive review of Medline database articles from 1990 to 2002 regarding CAD prevalence in developing countries. Okrainec and colleagues conclude that there is relatively sparse, reliable data regarding CAD in the developing world, but it is clear that overall, CAD mortality rates are increasing, and are projected to double between 1990 and 2002 , almost all attributable to the developing world countries. Multiple factors, including increasing exposure to CAD risk factors (diabetes, hypercholesteremia, hypertension, smoking) and a "relative lack of prevention and control measures to decrease exposure to these risk factors in developing countries, are contributing to what appears to be a projected epidemic." Furthermore, there has been a major decline in infectious disease mortality. Thus, this "epidemiologic transition" is in part due to increased longevity, with greater exposure for CAD to manifest developing as individuals live longer due to the decline in communicable diseases. Furthermore, globalization of dietary habits and urbanization are major factors in developing countries that increase the risk of CAD by exposure to risk factors. Dietary practices, with enhanced consumption of sugar and fat and increased sedentary lifestyles are also more common than in the past. Diabetes incidence and prevalence is increasing worldwide, much attributed to the atherogenic "western diet." They note that almost half of the world's diabetic population is found in China. Smoking has increased in Africa by 40% over the past 2 decades. Higher socioeconomic class appears related to a higher prevalence of CAD in developing populations. This may relate to increased diabetes and obesity. Okrainec et al discuss prevention and control approaches, which are highly variable from region to region. The WHO global study of risk factors called INTER-HEART is evaluating risk factors for acute MI in 46 countries, so that risk factors may be isolated as to their contribution to CAD in different populations. They conclude that the developing world is experiencing an epidemic of CAD "which expects to continue to increase in the foreseeable future." Adverse dietary practices, high rates of tobacco use, urbanization, and sedentary lifestyle are all major factors. Okrainec et al estimate that current statistics underestimate the extent of the CAD epidemic, and they call for immediate prevention and control measures from the developing world, such that CAD prevalence and mortality can be reduced by primary and secondary prevention. "Thus, an opportunity before the international community to intervene in the growing threat of CAD worldwide."

COMMENT BY JONATHAN ABRAMS, MD

These articles represent somewhat difficult read-

ing for the non-epidemiologist or sophisticated expert. Nevertheless, the first 2 reflect what has been happening in the United States, which contrasts markedly to the developing world. In our country, CAD prevalence has declined somewhat, as well as myocardial infarction, but this is not as dramatic as predicted several decades ago. Clearly, the prevalence of CAD in the United States, is in part related to the aging of our population, providing far more individuals the likelihood of developing vascular disease. One conclusion that can be drawn from these data are that western countries, and in particular the United States, have benefited remarkably from policies of early detection, appropriate treatment, and prevention. The armamentarium available to physicians today is remarkable, with respect to CAD prevention and treatment, compared to just 20 years ago. As our therapies keep patients with CVD alive longer, and the population ages, there clearly will be plenty of vascular disease for American physicians to deal with for decades. The flipside is the very disturbing statistics and predications relating to CVD in developing countries. New data confirms that emotional stress is an important risk factor not adequately appreciated. An editorial by Yusuf et al4 lays out a worldwide plan for dealing with the challenge of cardiovascular disease in developing countries. However, as with the current war against HIV/AIDS, there are profound obstacles to implementation of these proposals, and it is difficult to have much optimism that the dire developing country analysis can be significantly and favorably impacted with the modern day detection and prevention strategies so available to the Western world. ■

CME Questions

13. Better outcomes are achieved with which agent after bioprosthetic aortic valve replacement?
a. Aspirin
b. Warfarin
c. Either
d. Neither

14. Which of the following is most correct concerning the relationship between CT coronary calcium score and myocardial perfusion scanning?
a. Calcium score < 100, MPS almost always negative
b. MPS negative, calcium score usually negative
c. Calcium percentile score > 50%, MPS usually positive
d. Calcium score > 400, MPS almost always positive
e. Constrictive pericarditis is associated with myocardial thickening

15. Epidemiologic studies in the United States have shown that:
a. stroke rates have decreased substantially.
b. MI rates have decreased substantially.
c. cardiovascular mortality has decreased substantially.
d. a and c

16. Which of the following is most correct concerning automatic external defibrillators?
a. They are most effective in public places
b. Inappropriate shocks are common
c. Survival rates approach 80%
d. All of the above

17. Which is most correct concerning antiarrhymic therapy for atrial fibrillation recurrences after cardioversion?
a. Asymptomatic intermittent recurrences are common
b. Recurrent persistent AF is reduced by antiarrhythmic therapy
c. Most proarrhythmic events occurred in the first 4 days of therapy
d. all of the above

Answers: 13. (c); 14. (a); 15. (d); 16. (a); 17. (d);

Correction

Issues July, August, and September 2004 were printed as Volume 21. They should read Volume 23.

Binders

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PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Linking COX-2 Inhibitors and Cardiovascular Event Risk

A new, and as of yet unpublished study, has raised increased concern about the relationship between rofecoxib (Vioxx), Merck's blockbuster COX-2 inhibitor, and cardiovascular events. The study, which was presented at a meeting in Bordeaux France, was financed by the FDA in collaboration with California's HMO giant Kaiser Permanente. The study was designed to determine if celecoxib, rofecoxib, ibuprofen, naproxen, or other NSAIDs increase the risk of acute myocardial infarction (AMI) or sudden cardiac death (SCD). Utilizing the 6-million member California database for Kaiser Permanente, all patients ages 18-84 who had taken a COX-2 inhibitor or nonselective NSAIDs between January 1999 and December 2001 were entered into the cohort. Controls were a risk-set match 4:1 on event date, birth year, gender, and health plan region. There were 8199 acute cardiac events within the study cohort (6675 AMI, 1524 SCD). The data revealed that rofecoxib use at > 25 mg per day increased the risk of acute cardiac events 3.15 fold (OR, 3.15 [1.14-8.75]). Rofecoxib at a dose < 25 mg resulted in an odds ratio of 1.29 (0.93-1.79), which was not statistically significant. When comparing low-dose rofecoxib to celecoxib (Celebrex), the risk of AMI and SCD was higher with rofecoxib (P= 0.04). Other NSAIDs, including naproxen, indomethacin, and possibly diclofenac, also increased the risk of AMI and SCD. These data will be presented in this country in October at the American College of Rheumatology. Concern about the relationship between rofecoxib and cardiac events was first raised with the publication of the VIGOR trial (*N Engl J Med.* 2000;343:1520-1528) which showed a relative risk of cardiac events associated with rofecoxib of 2.38 (95% CI, 1.39-4.00; P= .002). Dr. Eric Topol and colleagues from the Cleveland clinic subsequently reevaluated these data along with data from other studies and raised the concern of prothrombotic potential of COX-2 inhibitors, especially rofecoxib (*JAMA.* 2001;286:954-959). Their concern centered on the tendency for COX-2 inhibitors to block production of prostacyclin—thus blocking antiaggregatory and vasodilatory effects, while having no effect on thromboxane, which is responsible for platelet aggregation. Blockage of thomboxane is a COX-1 effect and accounts for the majority of the cardioprotective effects of aspirin and other NSAIDs. Rofecoxib, the most COX-2 specific of the drugs tested, may unbalance thromboxane and prostacycline accounting for the cardiovascular risk.

Some have considered a strategy of adding aspirin to a COX-2 inhibitor, but a new study suggests that aspirin negates the GI benefits of the COX-2 inhibitor, the primary benefit of COX-2 inhibitors over nonselective NSAIDs.

Researchers from USC performed a double-blind trial of rofecoxib, rofecoxib plus low-dose

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aspirin, ibuprofen, or placebo in patients without ulcers or erosive esophagitis. Endoscopies were performed at baseline, 6 weeks, and 12 weeks. At 12 weeks, the cumulative index of ulcers was placebo 5.8%, aspirin 7.3%, rofecoxib plus aspirin 16.1%, and ibuprofen 17.1% ($P < 0.001$ for rofecoxib plus aspirin and for ibuprofen vs each of placebo and aspirin). Over the same time, rofecoxib plus aspirin and ibuprofen both significantly increased the number of erosions (both $P < 0.001$ vs aspirin and placebo). The authors conclude that low-dose aspirin does not significantly increase ulcer recurrence, but that the addition of a COX-2 inhibitor with aspirin increases the rate of ulceration to a rate that is similar to a nonselective NSAIDs (*Gastroenterology.* 2004;127:395-402).

Viagra: Maximum Capacity at High-Altitudes?

High-altitude hikers may soon be requesting sildenafil (Viagra) prescriptions based on the results of a new study. The drug, which is a phosphodiesterase-5 inhibitor, is known to cause pulmonary vasodilation. German researchers postulated that such an effect may increase exercise capacity during induced hypoxemia at low altitudes and at Mount Everest base camp. Fourteen healthy mountaineers and trekkers were assessed with measurements of systolic pulmonary artery pressure, cardiac output, and peripheral arterial oxygen saturation at rest and during assessment of maximal exercise capacity on cycle ergometry while breathing a hypoxic gas mixture at low altitude, and retested at high-altitude at the Mount Everest base camp. Sildenafil 50 mg significantly increased arterial oxygen saturation during exercise ($P = 0.005$), reduced systolic pulmonary artery pressure at rest ($P < 0.001$), and during exercise ($P = 0.031$). Sildenafil also increased maximum workload and maximum cardiac output compared with placebo. At high-altitude, the drug had no effect on arterial oxygen saturation at rest nor during exercise compared with placebo, however, the sildenafil reduced systolic pulmonary artery pressure at rest ($P = 0.003$), during exercise ($P = 0.021$), increased maximum workload ($P = 0.002$), and cardiac output ($P= 0.015$). Two patients noted worsening headache at high-altitude with the drug. The authors conclude that sildenafil is the first drug to increase exercise capacity during severe hypoxia both at sea level and at high-altitude (*Ann Intern Med.* 2004;141:169-177). An accompanying editorial suggests that sildenafil is not a substitute for acclimatization to high-altitude and suggests that the findings of the study are compelling and that further research into a phosphodiesterase inhibitors in the treatment of pulmonary vascular disease is needed (*Ann Intern Med.* 2004;141:233-235).

FDA Actions

Eli Lilly has received FDA approval to market duloxetine (Cymbalta) for the treatment of major depression. The drug is a serotonin and norepinephrine reuptake inhibitor (SNRI), similar to venlafaxine (Effexor-Wyeth). The drug is also being studied for the treatment of stress urinary incontinence and diabetic neuropathic pain. Lilly, and the drug approval process for duloxetine, came under scrutiny earlier this year when a 19-year-old female volunteer committed suicide after discontinuing the drug during clinical trials. The patient had no history of depression prior to the study.

Shire Pharmaceuticals has received expanded indication for its mixed amphetamine product Adderall XR for the treatment of adults with attention deficit hyperactivity disorder (ADHD). The drug is a one-a-day preparation that has been widely used in children since 2001.

The FDA and Genentech have issued a warning to physicians regarding the risk of serious arterial thromboembolic events associated with bevacizumab (Avastin). The drug is an angiogenesis inhibitor, a novel antineoplastic used to treat metastatic colon cancer and other solid tumors. Reports of cerebral infarctions, myocardial infarctions, transient ischemic attacks, and angina have all been associated with use of the drug.

The FDA has approved an orally disintegrating form of carbidopa/levodopa for the treatment of Parkinson's disease. The preparation dissolves rapidly in the mouth without the need for water, allowing for dosing even when patients are rigid or suffering from "off periods," when producing can be problematic. It will be marketed under the trade name Parcopa and will be available in 10/100 tabs, 25/100 tabs, and 25/250 tabs, similar to brand name Sinemet levodopa/carbadopa.