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INSIDE

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Can Chemotherapy Cardiotoxicity Be Prevented?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Cardinale D, et al. Prevention of High-Dose Chemotherapy-Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition. *Circulation*. 2006;114:2474-2481.Granger, CB. Predictiion and Prevention of Chemotherapy-Induced Cardiomyopathy. *Circulation*. 2006;114:2432-2433.

THE CARDIOTOXICITY OF ANTHRACYCLINES AND OTHER AGENTS may negatively affect clinical outcomes in cancer survivors. Data in other clinical situations and animal data on anthracycline-induced cardiomyopathy suggests that angiotensin-converting enzyme inhibitors (ACEI) may ameliorate this cardiotoxicity. Thus, Cardinale and co-workers performed a prospective randomized trial of 473 patients undergoing high-dose chemotherapy (HDC), of whom 114 showed a troponin I (TnI) release of > 0.07 ng/ml within 72 hours of the end of the first cycle of HDC. They were randomized to receive enalapril titrated to a maximum dose of 20 mg/day or nothing, which was started one month after the last cycle of HDC and continued for one year. The primary endpoint was an absolute decrease in left ventricular (LV) ejection fraction (EF) of 10% and a value below 50%. There were no significant differences in baseline characteristics between the 2 groups and the cumulative anthracycline doses were 332 ± 191 (SD) in the ACEI group and 338 ± 167 in the controls (P = NS). Average early TnI levels were 0.18 ± 0.38 and 0.22 ± 0.44, respectively (P = NS). All patients tolerated enalapril at a mean dose of 16 ± 6 mg/day. Baseline EF was 62 ± 3 and 63 ± 3, respectively. Results: 25 controls (43%) vs no ACEI patients showed a decrease in EF meeting the primary endpoint (P < .001). ACEI patients had smaller LV volumes and a higher EF at 12 months (62% vs 48%, P < .001). Cardiac events occurred in one ACEI patient (arrhythmia) and 30 controls (14 heart failures) P < 0.001. Also, in the control group a persistently elevated TnI was associated with a lower EF. The authors concluded that in high-risk HDS patients, early and continued treatment with ACEI prevents late cardiotoxicity and associated adverse clinical events.

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COMMENTARY

This is a good example of a concept that worked in animal models, translating nicely to humans. ACEI have been shown to have anti-remodeling effects in post-myocardial infarction patients and to preserve LV function in early class I LV dysfunction patients, so it is not a big stretch to the cardiotoxicity drug arena. However, the mechanism of this protective effect is unknown. This raises the issue of whether the toxic effects of HDC were abrogated by ACEI or masked by the known beneficial effects of ACEI in cardiomyopathy patients. Thus, duration of therapy becomes a concern. If damage to the myocardium is prevented, then supposedly therapy could be stopped at some point. If cardiac dysfunction is merely being masked, then therapy should be continued indefinitely. The authors argue that since ACEI worked best in those with persistent TnI release at one month, and that almost all patients have normal TnI at 12 months, that ACEI must prevent damage early and could be stopped after one year. Of note some patients in the persistent TnI release group had EFs < 50% at one year despite ACEI, so they would still have an indication for ACEI therapy. At this point it may be reasonable to stop ACEI at 12 months if TnI and LVEF are normal, but not otherwise.

This study also demonstrates how previous studies by this group lead to this successful treatment trial. In their earlier observational studies, they noted that TnI release predicted subsequent cardiotoxicity, especially if it was persistent. However, a normal TnI had a negative predictive value of 99%, so ACEI therapy could safely be withheld in these patients and they were not included in this treatment study. Also, the control group did demonstrate an increased incidence of adverse cardiac events, as would be expected, whereas the ACEI group was almost free of adverse events (one case of arrhythmias). Even if adverse events do not occur, a reduced EF limits choices for future chemotherapy if the patient relapses. Thus, these data are a powerful inducement to use ACEI in HDC patients who experience TnI release. Therapy was very well tolerated and there seems to be little downside.

There are some limitations and caveats of this study. It was not blinded and there was no placebo given, so some investigator bias cannot be excluded. Also, HDC therapy varied from patient to patient, but the total anthracycline dose was similar in both groups. In addition, only once-a-day enalapril was given at a modest dose. Higher doses and twice-a-day therapy, as has been done in heart failure trials of enalapril, could be more effective. Finally, this study represents only one approach to cardioprotection in HDS. Other therapies and approaches have also shown promise, such as beta-blockers (*see below*), and specially designed chemotherapeutic regimes. This is an area that is moving fast, so stay tuned. ■

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Questions & Comments

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Associate Managing Editor, at (404) 262-5431 or e-mail at jennifer.corbett@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Can Beta-Blockers Prevent Anthracycline-Induced Cardiomyopathy?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Kalay N, et al. Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy. *J Am Coll Cardiol*. 2006;48:2258-2262.

ANTHRACYCLINES MAY PRODUCE CARDIOTOXICITY by apoptosis and free radical formation. Carvedilol, in addition to being a nonselective beta-blocker and alpha 1 blocker, is antioxidant and anti-apoptotic. It has been shown to be effective in the treatment of anthracycline-induced cardiomyopathy, but not as a prophylactic agent. Thus, Kalay and co-workers in Turkey conducted a placebo-controlled

trial of carvedilol 12.5 mg once daily vs placebo in patients undergoing anthracycline-based chemotherapy. Therapy was continued for 6 months. The primary endpoint was echocardiographic left ventricular (LV) systolic function. Each group had 25 patients who were well matched. Baseline LV ejection fraction (EF) was 70% in both groups. Total mortality was one carvedilol patient and 4 controls (P = NS). Echocardiograms at 5 months showed no change in EF in the carvedilol group and a decrease from 69% to 53% in the controls (P = .001). Also, LV volumes were significantly increased in the controls. Heart failure requiring further therapy or hospitalization occurred in one carvedilol patient and 4 controls. Only this one carvedilol patient exhibited a drop in EF below normal. The authors concluded that the prophylactic use of carvedilol in patients undergoing anthracycline-based chemotherapy may prevent the development of cardiotoxicity.

COMMENTARY

The approach in this study is different than that taken in the ACEI study. Here carvedilol was started before chemotherapy was begun. Also, no biomarkers were used to select patients. In addition, the study terminated at 6 months. This is a potential issue because late cardiomyopathy development, even years later, has been seen with anthracyclines. Again, the issue of duration of therapy arises and dosage. Carvedilol was given only once a day at a modest dose, not at maximum doses twice a day as has been done in heart-failure trials.

The mechanisms of this protective effect of carvedilol are unknown, but if antioxidant, antiapoptotic and alpha 1 blocking are involved, then other beta-blockers without these properties may be ineffective. Not discussed is the potential for adverse effects, especially if carvedilol is given during chemotherapy when hemodynamic stability may be an issue. The biggest deficiency of this study is its small size. Nevertheless, the data are quite compelling.

So what are we to do? Give carvedilol early and check troponins, then start ACEI if TnI rises, but wait for one month? That is what these 2 trials would suggest. Will dual therapy cause unacceptable decreases in blood pressure? Should we just start both drugs in everyone prior to anthracyclines or high-dose chemotherapy? Further studies will be needed to answer these questions, but adopting this therapy also seems to have little downside and will probably be employed before definitive trials can be done. ■

The Best Stent for Saphenous Vein Grafts Is?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Vermeersch P, et al. Randomized Double-Blind Comparison of Sirolimus-Eluting Stent vs Bare-Metal Stent Implantation in Diseased Saphenous Vein Grafts. *J Am Coll Cardiol* 2006;48:2421-2431

After 8-10 years, atherosclerosis of saphenous vein grafts and symptoms of ischemia are common. Since repeat bypass surgery is associated with a higher mortality than first surgeries, percutaneous interventions (PCI) are preferred for vein graft disease. Bare metal stents (BMS) have a higher rate of restenosis, exceeding 30%, in vein grafts as compared to the native circulation. Thus, Vermeersch and colleagues hypothesized that sirolimus-eluting stents (SES) may be superior for vein graft disease and organized the Reduction of Restenosis in Saphenous vein grafts with Cypher sirolimus-eluting stent (RRISC) trial, which randomized patients with symptomatic vein graft disease to BMS or SES. Exclusion criteria included recent myocardial infarction, left ventricular ejection fraction < 25%, creatinine > 3.0 mg/dl, totally occluded grafts and previous brachytherapy. Distal protection and glycoprotein IIb/IIIa were strongly recommended during the procedure. All patients had repeat angiography with intra vascular ultrasound (IVUS) at 6 months. The angiograms and IVUS were analyzed quantitatively. The primary endpoint was 6-month in-stent late lumen loss. Several secondary angiographic, IVUS and clinical endpoints were also assessed. The study was done at a single center without industry support.

Results: The study enrolled 75 patients with 96 lesions in 80 vein grafts. In-stent late lumen loss was less with SES vs BMS (0.38 mm vs 0.79 mm, respectively, P = 0.001). Binary in-stent restenosis (% with > 50% lesion) was reduced by SES (11% vs 31%, P = 0.02) as was binary in-segment restenosis (14% vs 44%, P = 0.03). IVUS neointimal volume was less with SES (1 vs 24 mm^3, P > 0.001). Target lesion revascularization was less with SES (5% vs 27% P = 0.01). Death and myocardial infarction were not different. The authors concluded that SES significantly reduced 6-month lumen loss as compared to BMS with a corresponding reduction in repeat revascularization procedures.

COMMENTARY

This is the first prospective randomized trial of drug-eluting stent vs BMS in occlusive saphenous vein graft disease. The major weakness of the study was the small number of patients in this single-center study, which left it underpowered for clinical outcomes. However, it was designed as a 6-month angiographic study and has several strengths. It was not industry sponsored even though only one brand of stents was used. Almost all the patients actually had their 6-month study. IVUS was used. The methodology was strong, especially their blinding technique.

The results clearly show superior 6-month outcomes with the dug-eluting stent. Prior studies of BMS vs balloon angioplasty alone have not consistently shown any advantage to stenting, so these results are clearly welcome news. However, the major remaining issue is long-term results, especially late in-stent thrombosis or restenosis. This will have to await further studies. Another issue is that the patients only received clopidogrel for 2 months. This exceeds FDA recommendations, but may not be long enough in light of new data on late thrombosis. In addition, certain exclusion criteria leave the use of drug-eluting stents in saphenous vein grafts up in the air for certain patients; large vein grafts (> 4 mm), distal vein graft disease, and acute myocardial infarction due to saphenous vein disease. These issues also await further study. At this time many laboratories are deploying drug-eluting stents in saphenous veins when sizing isn't an issue, even though this is an off-label use, based upon this study and other encouraging data. This seems justified given the impressive short-term results in these challenging patients. ■

Ablation vs Drug Therapy for Intermittent Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

Source: Pappone C, et al. A Randomized Trial of Circumferential Pulmonary Vein Ablation vs Antiarrhythmic Drug Therapy in Paroxysmal Atrial Fibrillation: The APAF Study. *J Am Coll Cardiol.* 2006; 48:2340-2347.

In this paper Pappone and his colleagues report a randomized study comparing circumferential pulmonary vein ablation (CPVA) to antiarrhythmic drug therapy in patients with paroxysmal atrial fibrillation who had previously failed at least one trial with antiarrhythmic drugs. Patients were eligible for entry into the study if they were between ages 18 and 70, and had experienced episodes of atrial fibrillation for more than 6 months with at least 2 episodes per month during that time period. Patients also were required to have developed recurrent arrhythmias during therapy with propafenone, disopyramide or quinidine, either as single agents or in combination with digoxin or verapamil. Patients were enrolled between January and May 2005 and were randomized to either CPVA or long-term antiarrhythmic therapy with either amiodarone, flecainide, or sotalol at maximally tolerated doses. CPVA was performed using the standard technique with either CARTO or NavX mapping systems. Either an 8 mm standard radiofrequency catheter or an irrigated tipped catheter was used for ablation. The pulmonary veins were isolated with mitral isthmus and cavotricuspid isthmus lines performed in all patients. Patients were treated with an antiarrhythmic drug for 6 weeks after catheter ablation and the trial's 12-month follow-up began at that point. Repeat procedures were permitted if there was a recurrence of either atrial fibrillation or atrial tachycardia beyond the first 6 weeks after the ablation. In the antiarrhythmic drug group, patients were begun on oral therapy with either flecainide, sotalol or amiodarone. There was a one-month run-in phase that allowed dosage adjustment. Combination therapy with 2 agents could be used in the case of failure of the first assigned drug. All patients were anticoagulated with warfarin but anticoagulation could be discontinued if sinus rhythm was maintained for greater than 6 weeks. During follow-up, all patients were seen in an outpatient clinic at 3, 6 and 12 months after randomization. At each visit, a 12-lead electrocardiogram, 48 hours of ambulatory electrocardiographic monitoring and a transthoracic echocardiogram were obtained. Patients also received an event recorder and were asked to record and transmit a rhythm strip one to 3 times daily routinely and whenever they experienced palpitations. Rhythm transmissions were available from all patients for 94% of the days during follow-up. The primary endpoint of the study was freedom from documented recurrent atrial tachyarrhythmia during the 12-month follow-up.

One-hundred-ninety-eight patients were randomized. The mean age was 56 years and 67% were male. The patients had experienced a mean of 6 AF episodes per month over a mean period of 6 years. A history of hypertension was seen in 56.5% and the mean left-ventricular ejection fraction was 60%. There were no significant

clinical differences between the CPVA and the antiarrhythmic drug therapy group.

In the ablation group, patients received a mean of 35 minutes of radiofrequency energy delivery with a mean procedure time of 81 minutes. After the 6- week blanking period, 85 patients remained free of antiarrhythmic atrial tachyarrhythmias, and 11 patients developed atrial fibrillation, with 5 of these controlled by antiarrhythmic drugs, and 6 requiring a repeat ablation session. The repeat procedure was successful in 5 out of 6. Atrial tachycardias were observed in 3 additional patients, all of whom underwent successful repeat ablations. At 12 months, there was a decrease in left atrial size from 40 + 6 mm to 36 + 6 mm. Serious complications were uncommon. One patient developed a brief transient ischemic attack without sequelae, and one patient was noted to have a small pericardial effusion.

In the antiarrhythmic drug therapy group, 24 (25%) patients had their atrial fibrillation suppressed with a single antiarrhythmic drug. Combination therapy with either flecainide plus sotalol or flecainide plus amiodarone was successful in 33 of 75 patients, and the remaining 42 patients crossed over to CPVA. Adverse drug effects were noted in 23 patients. Three patients on flecainide developed proarrhythmia, 7 patients on amiodarone developed thyroid dysfunction, and sexual dysfunction was noted in 11 patients on sotalol.

Kaplan-Meier analysis of arrhythmia recurrence was performed using the end of the 6-week blanking period as time 0. Eighty-six percent of patients randomized to CPV were free of atrial arrhythmias at the end of follow-up as compared to only 22% of the antiarrhythmic drug therapy patients.

The authors conclude that among patients with a long history of paroxysmal atrial fibrillation and a previous failure of an antiarrhythmic drug, a single CPVA is mor effective than antiarrhythmic drug therapy with alternate agents.

COMMENTARY

Indications for catheter ablation to treat atrial fibrillation remain controversial. In this study, Pappone and his colleagues from Italy confirm their previous excellent results with CPVA and show that an ablation based approach results in less atrial fibrillation than antiarrhythmic drug therapy. Before catheter ablation can be routinely recommended, several points should be considered. First, these patients were really ideal candidates for catheter ablation. They were relatively young, had few comorbidities, had normal or nearly normal left atrial size and a long history of frequent episodes of atrial fibrillation. Second, they had already failed an antiarrhythmic drug. Since patients tend to segregate into drug responders and nonresponders, one would have expected a relatively high rate of recurrence on therapy with an alternate agent. Third, the techniques for catheter ablation of atrial fibrillation are still evolving. The results reported by these investigators from Italy have consistently been among the best, and many other laboratories have not been able to duplicate such high efficacy and low complication rates. When recommending catheter ablation, cardiologists must consider the results in the laboratory that will perform the procedure. Finally, the most important measure of the effectiveness of antiarrhythmic therapy for atrial fibrillation is the effect on symptoms. Although one might infer from the results reported here that symptoms were improved in the ablation group, inclusion of a formal quality-of-life measure or some other objective measure of symptom burden would help us to define better the benefit of catheter ablation relative to drug therapy. ■

Do All Brugada Patients Need an ICD?

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD
Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville
Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

Source: Sacher F, et al. Outcome After Implantation of a Cardioverter-Defibrillator in Patients With Brugada Syndrome: A Multicenter Study. *Circulation*. 2006;114: 2317-2324.

Sacher and colleagues collected data on all patients diagnosed with Brugada syndrome who received an implantable cardioverter defibrillator (ICD) in 14 centers between 1993 and 2005. Patients were included only if they had a Brugada type 1 ECG at baseline, either during a routine recording or after provocation with a class I antiarrhythmic drug. A type 1 ECG was defined as a tracing with prominent coved ST-segment elevation with either J-wave amplitude or ST segment elevation > 2 mm followed by a negative T wave. Clinical data were collected on all patients. Patients were characterized by 3 types of presentation: resuscitated cardiac arrest, undocumented syncope, or asymptomatic. Electrophysiologic testing results were classified as positive if any ventricular arrhythmia lasting greater than 30 seconds could be initiated with

a protocol of < 3 ventricular stimuli. All patients received transvenous ICD's using standard approaches. Patients were followed after implant with routine visits every 3 to 9 months or after shocks.

The study group included 220 patients; 83% male, mean age 46 + 12 years. A type 1 ECG was found spontaneously at baseline in 137 patients. In the remaining 83 patients, class I antiarrhythmic drug administration was necessary to reveal a diagnostic type 1 ECG. Genetic testing for a SCN5a mutation was performed in 97 patients and a mutation was identified in 29. At the time of entry into the study, 114 patients were asymptomatic, 88 had previously experienced syncope with no identified extracardiac cause and 18 patients had been resuscitated from an episode of ventricular fibrillation (VF). Among the asymptomatic patients, a type 1 Brugada ECG pattern and inducible ventricular arrhythmia at EP study was the indication for ICD therapy in 99 (87%) patients. ICD recipients who had negative EP studies had either a positive family history or spontaneous nonsustained ventricular arrhythmias. Supraventricular arrhythmias were present in 32 of 220 patients (15%).

Patients were followed for a median of 31 months (range 1 to 150 months) after ICD implantation. There were no deaths. In the total population, 8% experienced appropriate shocks. Appropriate shocks occurred in 22% of those with resuscitated cardiac death, 10% of those with syncope and only 4% of those who were initially asymptomatic. Inappropriate shocks occurred in 20% of the patients with an even frequency in the 3 groups. Most appropriate shocks were for polymorphic ventricular tachycardia (VT) or ventricular fibrillation (16 patients); only 2 patients had shocks for monomorphic VT. Among patients who received shocks, the median number of shocks was 4 (range of 1 to 65) with shocks occurring a median of 16 (range 1 to 140) months after ICD implantation. A Cox proportional hazards model identified the presence of documented resuscitated cardiac arrest before implantation as the only factor predictive of appropriate device discharge.

ICD complications were noted in 62 of 220 patients (28%). Early complications included: pneumothoraces (3), pericardial effusions (2), lead displacements (5), vein thrombosis (2), and hematoma (2). At the time of implant, high defibrillation thresholds were noted in 24 of 160 patients and 53 had a high pacing threshold either at implantation or during follow-up. Late complications included lead malfunction requiring extraction or reimplantation (19), infection (3), pericardia effusion (1), pocket revisions (2), device failure (1), and psychological disturbance (2). Inappropriate shocks for either lead malfunction (19), T wave oversensing (10), sinus tachycardia (10), and supraventricular arrhythmias (9) were seen in 45 patients (20%, 4 + 3 shocks per patient). Factors predictive of inappropriate shocks were history of supraventricular tachycardia, T wave oversensing and low R wave amplitude at implant.

The authors conclude that there is a relatively low incidence of arrhythmic events in patients with Brugada syndrome, particularly those who do not have a documented sustained arrhythmia at the time of diagnosis. During follow-up there is a significant risk of device related complications and inappropriate shocks are 2.5 times more frequent than appropriate ones.

COMMENTARY

This large multi-center survey illustrates some of the dilemmas physicians face when they encounter patients with an ECG suggestive of the Brugada syndrome. Among patients with documented sustained arrhythmias, a consensus has been reached that ICD therapy is appropriate. Indeed, most antiarrhythmic drugs are completely ineffective. In this series, however, only 4 of 18 patients with a prior resuscitated arrest, the highest risk group, experienced appropriate shocks. Among patients with syncope, appropriate shocks were noted in 10% and noncardiac causes for syncope were identified in another 7%. Among asymptomatic individuals, only 4% received appropriate shocks during a follow-up of over 2.5 years. Clearly, predicting arrhythmic events in Brugada patients is difficult. In all 3 groups, both device complications and inappropriate shock therapy were relatively common. This makes strategies to better risk stratify patients, particularly those without documented arrhythmias, all the more important. Unfortunately, data presented here do not really help us better select patients with a Brugada type ECG for ICD therapy. Although 75% of the patients with syncope and 86% of the asymptomatic patients had inducible arrhythmias at electrophysiologic study, the event rates in both groups were low. Among the patients with resuscitated sudden death, only 4 of 11 had an inducible arrhythmia. The presence of a spontaneous type 1 ECG and the finding of a SCN5a mutation were also not significant predictors for appropriate shocks.

The most feared clinical manifestation of Brugada syndrome is sudden death. Patients are usually young and healthy when they are identified. Still, in this study, even in patients selected by strict criteria, the annual event rate appears to be low and is considerably less than the rate of complication of ICD therapy. Physicians dealing with asymptomatic patients with Brugada type ECG's must therefore make a difficult analysis of the risks and benefits in each individual before concluding that ICD therapy is appropriate. ■

Biomarkers, Better Than Conventional Risk Factors?

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD
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Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis.

Source: Wang TJ, et al. Multiple Biomarkers for the Prediction of First Major Cardiovascular Events and Death. *N Eng J Med*. 2006;355:25:2631-2639.

In recent years there has been considerable interest in the utilization of biomarkers to assist in the prediction of risk for cardiovascular events, including mortality. The most widely known marker is high-sensitivity C-reactive protein (hsCRP). Two peptides have been utilized extensively for evaluation of left ventricular function, as well as the characterization of congestive heart failure; these include B-type natriuretic peptide (BNP) and N-terminal pro-atrial natriuretic peptide (NT-ANP). A major area of interest in the biomarker field is to find markers that would help predict outcomes in addition to the classic risk factors, such as of nicotine, hypertension, diabetes, and hyperlipidemia.

Investigators from the Framingham Heart Study and other databases, including institutions in the NHLBI, sought to evaluate the efficacy of multiple biomarkers in predicting subsequent major vascular events and in particular, a first major cardiovascular event or death. The patient population was derived from participants of the 6th examination cycle-of the Framingham Heart Offspring Study (1995-1998). Ten biomarkers were chosen, all of which have been associated with major CV events and have biologic plausibility. In addition to hs-CRP, BNP, and NT-ANP, other putative markers included plasma aldosterone, plasma renin, fibrinogen, plasminogen-activator inhibitor type 1 (PAI-1), D-dimer, homocysteine (HC), and urinary albumin-to-creatinine ratio. Each of these markers represents various aspects of vascular phenomena, such as thrombosis, inflammation,neuro-hor-monal activity, endothelial function, fibrinolytic function, and glomerular endothelial function. Sophisticated and detailed use of multiple statistical approaches were employed; these will not be outlined in this review, but include multivariable proportional-hazards modeling "to examine the association of biomarker levels with the risks of death and major cardiovascular events." Participants were categorized by quintiles of a multi-marker score; the lowest 2 quintiles represented low risk; the highest, high risk, and the 3rd and 4th represented intermediate risk. Kaplan-Meier probability curves were constructed. In addition, hazard ratios were determined, adjusted for age and conventional risk factors. Any prior major CV event resulted in exclusion from the study. The C statistic was utilized "to classify risk," and is defined as "the probability of concordance among persons who can be compared." Receiver-operating characteristics were plotted for models with or without biomarkers. Secondary analyses included association of biomarkers with outcomes adjusted for age, gender, and lipid status. Of note, angina, claudication, or prior TIA were considered to be non-major CV events. After screening participants in the 6th examination of the Framingham Heart Offspring Study, 3209 individuals were selected to constitute the study sample. Mean age at the time of enrollment was 59 + 10 years. Follow-up was up to 10 years, median of 7.4 years, during which time 207 of the 3,209 participants died (6%). Multiple analyses of biomarker panel associations were made. In backward-elimination modeling, 5 biomarkers were selected as predictors of death, including CRP, NT-ANP, HC, plasma renin, and D-dimer. The final model utilized BNP, CRP, urinary albumin-to-creatinine ratio, HC, and renin.

Results: BNP and PAI-1 were predictive of future CV events; in the final model, BNP and urinary albumin-to-creatinine ratio were included with hazard ratios of approximately 1.2-1.25. Kaplan Meier curves utilizing cumulative probability of death and major CV events demonstrated a marked elevation of risk in patients with high multi-marker scores, when compared to those with low or intermediate scores. Persons with high multi-marker scores had a 4 times greater risk for death and a 2 times greater risk of CV events than those in the low marker scores, $P < 0.001$ and $P = 0.002$. C statistic ranged from 0.68 to 0.79. ROC curves were constructed utilizing conventional risk factors with and without biomarkers. Adjustment for use of statins, aspirin, and other medications did not alter the findings. PAI-1 was statistically associated with outcomes.

The authors conclude that "the most informative biomarkers for predicting death were…BNP, CRP, HC, renin, and the urinary albumin-to-creatinine ratio." The most useful biomarkers for predicting major CV events included BNP and urinary albumin-to-creatinine ratio. Importantly, they state, "nonetheless, the use of multiple biomarkers added only moderately to the overall prediction of risk based conventional CV risk factors." Prediction of subsequent risk was affected in part by the overlap in the distribution of biomarker levels in individuals with and without CV disease. Furthermore, the authors stress that conventional risk factors are quite effective in predicting risk. The authors point out that the major biomarkers listed in the analysis have been individually shown to be predictors of

death or CV events in single biomarker investigations, although PAI-1 data has been limited. CRP was predictive of death but not a major CV event, when other biomarkers were accounted for, while the risk of HS-CRP for CV events was 1.3-1.5 in other studies. The authors suggest that their data supports BNP and the urinary albumin-to-creatinine ratio as being better predictors of global CV risk than CRP. They conclude that their data supports only a moderate ability for biomarkers to predict subsequent death or major CV events when conventional risk factors are also considered. The authors suggest that biomarker assessment might be most useful in patients at intermediate risk, whereby accurate risk status might affect how aggressive one should be for treating cholesterol, hypertension, or diabetes. They also comment that the Framingham Heart Offspring population sample reflects unselected individuals with varying CV risk. They conclude that biomarkers are associated with the risk of death and major CV events, but only moderately, so when used in conjunction with conventional risk factor assessment. They posit whether new biomarkers may improve the situation in the future.

COMMENTARY

This is a rather sobering report, suggesting that targeted use of known selected biomarkers, all which have a pathophysiologic link to CV disease, may not be a particularly useful strategy. In particular, CRP turned out to only have modest predictive accuracy, consonant with other studies. While individuals with multiple biomarkers have a considerably increased risk of death in this report, they do not represent the majority of patients, and many subjects overlap with respect to biomarker prevalence without increasing predictability. Other approaches for examining prospective assessment of normal individuals with respect to future CV risk, such as carotid IMT, coronary calcium scores, or routine stress testing of healthy populations, have not fared as well as anticipated. The Framingham risk assessment instrument, while probably not widely used, has yet to be improved upon by other risk-screening approaches. Furthermore, it is well established that the large majority of individuals who develop CV disease can be predicted by standard risk factors, such as diabetes, hypertension, dyslipidemia, obesity, smoking, and inactivity. An editorial by James Ware, PhD, a biostatistician at the Harvard School of Public Health, discusses the role of biostatistics in risk prognostication, and in particular some of the results from the Wang study. He states that "the proposed biomarker score adds little to the sensitivity and specificity of a prognostic test for death within 5 years." He posits that the approach utilized in the study is of limited value in individual subjects, whereas it does contribute to the proportional-hazards model for predicting death from any cause. He concludes, "how difficult it is to achieve effective risk stratification with respect to multifactorial disease processes. Much work remains to be done before biomarkers of the type the authors consider here can provide a basis for the prognostic evaluation of the individual patient."

While this study adds to the disappointment of biomarker utilization in healthy individuals to predict subsequent risk, it would appear to clear the air, and emphasizes the importance of adherence to proven risk factors that are so well known to everyone, but too often ignored in patient care. ■

CME Questions

7. In patients with Brugada Syndrome who received ICDs
A. ICD complication rates were very low
B. 8% had appropriate shocks
C. 50% had inappropriate shocks
D. Resuscitated cardiac arrest patients were less likely to get appropriate shocks

8. Intermittent atrial fibrillation is prevented most effectively by
A. Amiodarone plus a type I agent
B. Beta-blocker plus a type I agent
C. Catheter ablation
D. Overdrive pacing

9. Newer Biomarkers as compared to clinical risk factors for predicting CHD risk are
A. Superior
B. Most useful in those at intermediate risk
C. Not additive in predicting death and CV events
D. All of the above

10. Anthracycline based high-dose chemotherapy-induced cardiomyopathy can be prevented by
A. ACEI
B. Beta-blockers
C. Spironolactone
D. A & B

11. Short-term results of saphenous vein graft revascularization favors
A. Angioplasty
B. Bare metal stent
C. CABG surgery
D. Drug-eluting stent

Answers: 7.(b) 8.(c) 9.(b) 10. (d) 11.(d)

CME Objectives

The objectives of *Clinical Cardiology Alert* are:

• To present the latest information regarding diagnosis and treatment of cardiac disease;

• To discuss the pros and cons of these interventions, as well as possible complications;

• To discuss the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• To present the current data regarding outpatient care of cardiac patients. ■

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.

This Month's Issue Focuses on Women's Health

Breast Cancer Rates Have Dropped Since WHI of 2002

Several important papers have been published in the last 2 months, none more important than the realization that breast cancer rates have dropped precipitously since the publication of the Women's Health Initiative (WHI) in 2002. The issue of estrogen-alone (not in combination with a progestin) and the risk of breast cancer is addressed in a new paper, as is the use of herbal supplements to treat postmenopausal vasomotor symptoms in women who have stopped HRT. Finally the duration of treatment of bisphosphonates for osteoporosis gains some clarity with publication of new data from the Fracture Intervention Trial.

The WHI study of combined estrogen and progesterone was halted in 2002 when it was found that women on the drug combination were at increased risk of breast cancer. Prior to the publication of the study, it was estimated that 30% of American women over the age of 50 were taking HRT. Within 6 months of the publication of WHI, half of those women had discontinued HRT. Now preliminary data suggests that breast cancer rates dropped precipitously in 2003 compared to 2002. The decline was most pronounced in women over the age of 50, and the biggest decline was in estrogen-receptor-positive breast cancer. Breast cancer rates had been rising steadily in this country at an average of 1.7% per year until 1998 when the rate began declining at 1% per year. The 7% drop seen in 2003 was the largest single decrease ever seen within a single year. The data was presented at the 29th Annual San Antonio Breast Cancer Symposium by researchers from MD Anderson. In a separate study, researchers from Northern California presented their own data that showed a decrease in hormone use of 68% between 2001 and 2003, and a decrease in breast cancer rates of 10-11%, which was sustained to 2004 (*J Clin Oncology* 2006;24:e49-50). The implication is that the sudden decrease in HRT use is responsible for the decrease rate of breast cancer, a conclusion supported by the dramatic decrease in ER positive cancers in postmenopausal women.

In contrast to the findings of the estrogens/progesterone wing of the Women's Health Initiative, the estrogen-only wing showed no increased risk of breast cancer (*JAMA*. 2004;291:1701-12). This was in contrast to several European studies, including the Million Woman Study, which showed an increased rate of breast cancer with unopposed estrogen (*Lancet*. 2003;362:419-427). Now a new study also suggests that estrogen-only is associated with a slightly increased risk of breast cancer. The study from Finland looked at nearly 85,000 women using oral or transdermal estradiol, 8,000 women using oral estriol (widely used in Europe but uncommonly used in the United States), and 18,000 women using vaginal estrogens for least 6 months were followed from 1994 through 2001. There was no increase risk for breast cancer for estradiol use of less than 5 years. Women who used estradiol for more than 5 years had a relative risk of breast cancer of 1.44 (1.29-1.59). Oral and transdermal estradiol conveyed similar risk. Oral estriol and vaginal estrogens did not increase breast cancer risk. The authors con-

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clude that the use of estradiol for more than 5 years is associated with a increased risk of breast cancer (*Obstet and Gynecol*. 2006;108:1354-1360).

Herbal Supplements to Treat Vasomotor Symptoms

Many women who have stopped HRT have tried herbal supplements to treat vasomotor symptoms. A new study compares the effectiveness of black cohosh, multibotanicals, and soy with HRT and placebo. Researchers from the University of Washington enrolled 351 women who were in menopausal transition or were postmenopausal. They were given black cohosh 160 mg daily, multibotanical with black cohosh 200 mg plus 9 other ingredients, multibotanical plus dietary soy counseling, HRT with conjugated equine estrogen 0.625 mg daily with or without medroxyprogesterone 2.5 mg daily, or placebo. There was no difference in vasomotor symptoms between the herbal interventions and placebo at 3, 6, or 12 months or for the average over-all follow-up time points ($P > 0.05$ for all comparisons), with the exception that symptom intensity was significantly worse with the multibotanical plus soy compared with placebo ($P = 0.016$). Hormone therapy was effective at reducing vasomotor symptoms ($P < 0.001$). The authors conclude that black cohosh alone or as part of a multibotanical regimen was ineffective at treating menopausal vasomotor symptoms (*Ann Int Med*. 2006; 145: 869-879). As pointed out in an accompanying editorial, even though herbal supplements were found to be ineffective, the good news is that women in the placebo group had a 30% reduction in the severity and frequency of vasomotor symptoms during the 12-month follow up, a number that probably reflects the natural history of postmenopausal symptoms (*Ann Int Med*. 2006;145:924-925).

Bisphosphonates to Treat LBD, After 5 Years?

Since WHI, bisphosphonates have become the drugs of choice for many women with low bone density. Treatment with bisphosphonates for 5 years is safe and effective; however, treatment beyond 5 years has been debated with some experts recommending a "drug holiday" after 5 years because of a concern about diminished bone strength and microfractures. A new study suggests that there is no harm in extending treatment beyond 5 years, although there is minimal benefit. In the Fracture Intervention Trial (FIT), 1,099 postmenopausal women who had used alendronate for 5 years were randomized to 5 more years of alendronate 5 mg per day, 10 mg per day, or placebo. Outcomes were hip bone mineral density (BMD) with an exploratory outcome measure of fracture incidence. Compared to women who continued alendronate, those who were switched to placebo at 5 years had declines in BMD at the total hip (-2.4%; 95% CI, -2.9% to -1.8%; $P < 0.001$) and spine (-3.7%; 95% CI, -4.5% to -3.0%; $P < 0.001$). Still, despite discontinuing alendronate, BMD remained at levels above pretreatment levels 10 years earlier. The cumulative risk for non-vertebral fractures was not significantly different between those continuing or discontinuing alendronate (19% vs 18.9%). Those who continued alendronate had significant lower risk of clinically recognized vertebral fractures, however, (5.3% placebo vs 2.4% alendronate) but no significant reduction in morphometric vertebral fractures. Of the women continuing alendronate, 18 underwent bone biopsies and none showed any qualitative abnormalities. The authors conclude that discontinuing alendronate after 5 years results in a moderate decline in BMD, a gradual rise in biochemical markers, but no higher fracture risk other than for clinical vertebral fractures compared to women who continued alendronate. The data also suggests that stopping alendronate at 5 years is safe, although the authors suggest that high-risk women may want to continue beyond 5 years (*JAMA*. 2006;296:2947-2953). Interestingly, no cases of osteonecrosis of the jaw were reported in women who took alendronate for 10 years.

FDA Actions

The FDA has approved a new estradiol gel for the treatment of moderate to severe vasomotor symptoms assisted with menopause. The gel, which is applied daily, supplies the lowest dose of estradiol approved by the FDA for this indication. Estradiol gel will be marketed as "Elestrin" by Kenwood Therapeutics.

The FDA has approved Novartis' combination antihypertensive "Exforge." The drug combines valsartan and amlodipine in one pill that is dosed once daily. It is expected to be marketed by September 2007.

The FDA has approved the first generic ondansetron injection (Zofran) for the prophylaxis of postoperative nausea and vomiting, and nausea and vomiting associated with cancer chemotherapy. The generic is manufactured by Teva pharmaceuticals.

The FDA has also approved generic oxybutynin extended release tablets (Ditropan XL). 'The new generics will be available in 5 mg and 10 mg extended-release tablets made by Mylan, and 50 mg extended-release tablets manufactured by Impax Laboratories. Oxybutynin is indicated for once daily treatment of overactive bladder in patients with urge incontinence, urgency, and frequency.

A generic bupropion extended-release tablet has been approved by the FDA. The generic version of Wellbutrin XL for the treatment of depression will be available in 150 mg and 300 mg tablets. The new generic is manufactured by Anchen Pharmaceuticals. ■