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B Vitamins and Restenosis

ABSTRACT & COMMENTARY

Elevated plasma homocysteine is an independent risk factor for the development of coronary artery disease (CAD) and has previously been shown to correlate with outcomes in the presence of established CAD. In previous reports, Schnyder and colleagues have demonstrated an association between elevated plasma homocysteine levels and restenosis after percutaneous coronary intervention (PCI), and that treatment with a combination of folic acid, vitamin B12, and pyridoxine reduces homocysteine levels as well as angiographic restenosis and the need for target lesion revascularization (TLR) within 6 months of follow-up.[1] The present study, which includes the patients from their original report, expands on these results, demonstrating that 6 months of homocysteine-lowering therapy decreases the frequency of adverse clinical events out to 1 year after successful PCI.

This is a randomized, double-blind, placebo-controlled trial. The study population consisted of 553 patients who underwent successful PCI at the University of Bern between May 1998 and April 1999. Patients with unstable angina, recent myocardial infarction (MI), renal insufficiency (serum creatinine > 1.8 mg/dL), or who were taking vitamin supplementation were excluded from the study. Patients were randomized to receive homocysteine-lowering therapy with folic acid (1 mg/d), vitamin B12 (400 mg/d), and vitamin B6 (10 mg/d) or placebo for 6 months. Clinical follow-up was performed at 6 months and 1 year, or earlier if recurrent symptoms warranted. Follow-up included stress testing and electrocardiography (as well as 6-month coronary angiography for the 205 patients in the previously published subgroup analysis).[1] Major adverse events were defined as death, nonfatal Q-wave MI, and need for repeat revascularization for documented ischemia. The primary end point was a composite of major adverse events at 1 year of follow-up.

The folate + B12+B6 and placebo groups were well matched in terms of baseline clinical and angiographic characteristics. Baseline homocysteine levels were comparable in the 2 groups. Twenty-nine percent of patients had mild-to-moderately elevated homocysteine levels (> 1.62 mg.L) at baseline. No patient had severe hyperhomocystinemia (> 13.5 mg/L) at baseline. Not surprisingly, patients

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treated with folate + B12+B6 had significantly lower mean homocysteine levels than those treated with placebo (1.01 mg/L vs 1.36 mg/L) at 6 months.

The mean duration of follow-up was 11 months. The composite end point was significantly lower in patients receiving homocysteine lowering therapy (15.4% vs 22.8%; $P = 0.03$). This was attributable primarily to the lower rates of TLR (9.9% vs 16.0%; $P = 0.03$), though trends toward lower rates of death and MI were also noted in the patients treated with folate + B12+B6. Adjustment for multiple demographic and angiographic factors known to be associated with higher rates of TLR (such as diabetes, vessel size, use of stents, treatment of restenotic lesion) did not alter the relationship between homocysteine lowering therapy and outcome, and in fact, resulted in an adjusted P value of 0.01. The benefit of folate + B12+B6 therapy was present in all subgroups of traditional risk factors, and was greatest in the patients with the highest terciles of total cholesterol and LDL (Schnyder G, et al. *JAMA*. 2002;288:973-979).

COMMENT BY SARAH M. VERNON, MD

This study demonstrates that homocysteine lowering therapy using folate + B12+B6 improves clinical outcomes in patients undergoing PCI, primarily by reducing the need for ischemia driven target lesion revascularization. This benefit persists out to 1 year of follow-up after a 6-month course of therapy. This study adds to a growing body of data demonstrating the value of homocysteine lowering therapy for lowering the risk of atherosclerotic coronary events even in patients without overtly elevated homocysteine levels. Schnyder et al acknowledge that the use of a folate + B12+B6 "cocktail" makes it difficult to determine the precise mechanism of this effect. Despite this imprecision, there is little downside to the folate + B12+B6 therapy. It is inexpensive, readily available, and well tolerated. In addition, the use of "vitamins" is likely to be embraced by many patients in an era when dietary supplements are somewhat in "fashion." All this and a therapy that seems to actually reduce restenosis and clinical events. ■

Reference

1. Schnyder G, et al. *N Engl J Med*. 2001;345:1593-1600.

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Significance of Ventricular Tachyarrhythmias in Trained Athletes

ABSTRACT & COMMENTARY

Synopsis: Even frequent and complex ventricular arrhythmias may be seen in competitive athletes and, in the absence of structural heart disease, they have a benign prognosis.

Source: Biffi A, et al. *J Am Coll Cardiol.* 2002;40: 446-452.

In this report, biffi and colleagues from the Italian Institute of Sport Science describes the prognostic significance of premature ventricular depolarizations (PVDs) in trained athletes. In Italy, all athletes undergo cardiovascular screening with a history, physical exam, and an electrocardiogram (ECG). Out of 15,889 athletes in their data bank, 355 who had > 3 PVDs on their resting 12-lead ECG or who complained of palpitations underwent 24-hour ambulatory ECG monitoring, symptom limited exercise testing, and 2-dimensional echocardiography. Selected patients who had particularly frequent or complex PVDs underwent additional studies including magnetic resonance imaging (MRI), nuclear imaging, endomyocardial biopsy, and electrophysiologic study.

Among the 355 patients in this report, 273 (77%) were male and the mean age was 24 years. They were

divided into 3 groups. Group A subjects (n = 71) had > 2000 PVDs and > 1 nonsustained ventricular tachycardia episodes (NSVT) during the 24-hour ECG. Group B (n = 153) and group C (n = 131) subjects had > 100 to < 2000 PVDs and < 100 PVDs in 24 hours, respectively. All subjects had competed on a national or international level in a variety of sports.

Of the 355 athletes, 329 showed no evidence of structural cardiac disease. The remaining 26 were found to have either mitral valve prolapse with mild-to-moderate mitral regurgitation (n = 11), arrhythmogenic right ventricular cardiomyopathy (n = 7), myocarditis (n = 4), and dilated cardiomyopathy (n = 4). Except for 5 subjects with mitral valve prolapse in group B, all other athletes with identified structural abnormalities were in group A. Approximately two thirds of the athletes had PVDs with left bundle branch block morphology, often with an inferior axis consistent with a right ventricular outflow tract site of origin. PVDs disappeared with exercise in 65% of group A subjects, 72% of group B subjects, and 93% of group C subjects. Electrophysiologic studies were performed in 24 subjects but inducible sustained ventricular tachycardia was seen in only one. Athletes in group A were excluded from competition for a minimum of 3 months. One of these individuals died suddenly during a competitive field hockey game. He was playing against medical advice at the time. There were no other deaths in any group over 8.4 ± 6.3 years. Drug therapy was used in only 8 subjects, all with identified cardiovascular disease.

Biffi et al conclude that even frequent and complex ventricular arrhythmias may be seen in competitive athletes and, in the absence of structural heart disease, they have a benign prognosis.

■ COMMENT BY JOHN P. DiMARCO, MD, PhD

Italy has a nationwide screening program for competitive athletes that provides a unique database for studies such as the one reported here. It has long been known that ECG abnormalities including increased R- or S-wave voltages, ST segment and T wave abnormalities, deep Q waves, and frequent or complex PVDs are more common in competitive athletes than in the general population. The rare tragic episodes of sudden death in athletes, however, attract considerable attention and cardiologists are often asked to "clear" individuals to participate in sports.

Although the data in this paper are, in many ways reassuring, it is difficult to translate these findings into routine practice. All of these athletes were competitors on a national and international level and they had survived years of training and competition to get to that level. Extrapolation of these data to younger, less proficient athletes more likely to present to a cardiologist cannot be justified.

Recently, NASPE published the results of a consensus conference on arrhythmias in athletes (Estes N, et al. *J Cardiovasc Electrophysiol.* 2001;12:1208-1217). These documents provide careful guidelines that clinicians should follow when asked to evaluate athletes. Those with identifiable structural abnormalities including hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, coronary artery anomalies or disease, dilated cardiomyopathy, and long QT syndromes should be restricted from competitive sports. Symptomatic individuals without structural heart disease may participate after a successful radiofrequency ablation. ■

The Ambulatory BP Monitoring Effect

ABSTRACT & COMMENTARY

Synopsis: The presser effect of ABPM for the first time could influence the diagnosis of hypertension.

Source: Hermida RC, et al. *J Am Coll Cardiol.* 2002; 40:710-707.

Ambulatory blood pressure monitoring (ABPM) is a useful adjunct for evaluating white coat hypertension, but little is known about its effect on BP. Thus, Hermida and associates from Spain studied 538 patients with mild-to-moderate office hypertension using ABPM for 48 hours. Approximately one third were on no therapy and one third had more than 1 study. In both treated and untreated patients, significant reductions in BP were noted on the second day ($P < .001$), but not in heart rate. This presser effect was statistically significant for the first 6-9 hours of monitoring. Mean nocturnal BP was the same on both days. In those with repeated tests 3 months apart, this presser effect was absent. Hermida et al concluded that this presser effect of ABPM for the first time could influence the diagnosis of hypertension.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

This study makes a strong case for extending initial ABPM beyond 24 hours in order to accurately diagnose white coat hypertension. Apparently the

novelty of the first several hours of experience with the device elevates BP significantly compared to the second day whether it is contiguous (48 hours of monitoring) or 3 months later. The magnitude of the pressure drop on day 2 averaged 6-7 mm Hg systolic and 4-5 mm Hg diastolic. Also, about three quarters of the subjects experienced a significant decline in BP. Interestingly, the results were not related to heart rate or levels of physical activity. In addition, the findings were independent of sex and BP treatment. This study is robust because of a large number of subjects with a range of blood pressure and other characteristics. The application of a 2-day monitoring rule will help more accurately define hypertensive subjects and lead to better clinical and research outcomes, albeit at a higher cost. ■

Early Post-MI Pericardial Effusion

ABSTRACT & COMMENTARY

Synopsis: A mild pericardial effusion within 48 hours of a first acute ST segment elevation MI is associated with a higher risk of later moderate/severe effusion due to hemopericardium and two thirds of the later patients will develop free wall rupture or tamponade.

Source: Figueras J, et al. *Am Heart J*. 2002;144: 251-258.

Left ventricular free wall rupture is an early and usually catastrophic complication of acute myocardial infarction (MI). Figueras and colleagues from Spain explored the hypothesis that pericardial effusion on echocardiography within the first 48 hours would identify those at higher risk of free wall rupture. They studied 1149 patients with and 324 patients without ST elevation and first acute MI. A second echo was done in 300 patients 2-4 days post-MI; 100 with and 200 without an initial mild-pericardial effusion and in patients with moderate-to-severe effusion or hypotension. The first echo showed a mild effusion in 177 (12%) and a moderate-to-severe one in 51 (3%). Moderate effusion was seen almost exclusively in those with ST elevation MI and was more commonly associated with atrial fibrillation, low ejection fraction, electromechanical disassociation, and death. On the routine second echo, those with mild effusion on the first echo were more likely to have moderate/severe effusion than those without effusion on the first echo (15% vs 6%) and those with effusion on the first echo more often developed echo evidence of tamponade (7% vs 1%). Of the total 92 patients with moderate-to-severe effusion on echo 1 or 2, 60 (65%) developed tamponade and 44 died of free wall rupture (82%), cardiogenic shock (14%), or noncardiac causes (49%). Among the 64 patients with moderate/severe effusion who underwent pericardiocentesis, the fluid was sanguinous in 98%. Figueras et al concluded that a mild pericardial effusion within 48 hours of a first acute ST segment elevation MI is associated with a higher risk of later moderate/severe effusion due to hemopericardium and two thirds of the later patients will develop free wall rupture or tamponade.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

Many centers routinely perform echocardiography within 48 hours of acute MI to evaluate left ventricular function and assess for unsuspected complications. Although small pericardial effusions are occasionally seen on these studies, their significance has not been well understood. In this study half of those with an early small pericardial effusion eventually developed a large one. Also, a larger effusion in ST elevation MI patients was almost always due to hemopericardium, most likely caused by free wall rupture. Finally, half the patients with large effusions on either echo died, usually of free wall rupture.

There are limitations to this study. It is nonrandomized and most of the patients were treated with thrombolytics rather than primary angioplasty. Also, most patients did not have surgery or autopsy, so the true incidence of free wall rupture is difficult to determine. In addition, the incidence of pericardial effusion, especially larger ones, is higher in this series than others. This may be partly due to the routine performance of 1-2 echoes post-MI and the routine use of thrombolytics and heparin.

This study makes a good case for a routine echocardiogram early post-MI. Those with a small effusion should have a repeat study in 2-4 days to exclude growth of the effusion, and careful attention to blood pressure control and avoidance of strenuous exercise seems prudent to prevent rupture. Those with a moderate-to-large effusion should be considered for pericardiocentesis with surgical standby. Whether such an approach would reduce mortality from acute MI will be difficult to prove and those paying hospital costs may protest the increased use of echocardiography. ■

Oral vs. Sub Q Vitamin K

ABSTRACT & COMMENTARY

Synopsis: Oral vitamin K lowers high INR more rapidly than subcutaneous administration.

Source: Crowther MA, et al. *Ann Int Med*. 2002;137: 251-254.

The anticoagulant effects of warfarin frequently need to be reversed for bleeding complications, excessively high INR values, or preprocedures. Although withholding warfarin is eventually effective, occasionally faster reduction in INR is necessary. Crowther and associates tested the hypothesis that oral vitamin K would reduce high INRs faster than subcutaneous vitamin K. Patients with an INR between 4.5 and 10.0 were randomized to receive 1 mg of vitamin K either orally or subcutaneously and warfarin was withheld. The primary outcome was INR on the day after vitamin K. In the 51 patients studied, the mean INR was 6. The INR had decreased to the 1.8-3.2 range the next day in 58% of the oral vitamin K group and 24% of the subcutaneous groups (odds ratio, 4.3; 95% CI, 1.1-17.4; P = .015, number needed to treat = 3). Two patients who received subcutaneous vitamin K had an increased INR the next day; this did not occur in the oral therapy group. Conversely, 3 patients who received oral vitamin K had INR < 1.8, whereas none of the subcutaneous group did. Crowther et al concluded that oral vitamin K lowers high INR more rapidly than subcutaneous administration.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

The use of vitamin K to reverse a high INR is to prevent bleeding complications. The risk of major bleeding in patients with INR > 6.0 is reported to be 4%.[1] In this study no episodes of bleeding were observed, so the incidence may actually be lower. Some have been reluctant to use vitamin K to reverse high INRs for fear of overshooting and precipitating thrombosis, such as in patients with prosthetic valves. Again in this study no episodes of thrombosis were observed, but 3 patients did have INR < 1.8 after oral vitamin K. The results of this study suggest that in patients with a high risk of bleeding complications and no excessive risk of thrombosis, ie, prosthetic valve, and an INR > 4.5, that low-dose oral vitamin K administration should be considered. Patients with high INR and a low risk of bleeding, such as many preprocedure patients, should merely have warfarin withheld. ■

Reference

1. Hylek EM, et al. *Arch Intern Med*. 2000;160:1612-1617.

Troponin and Exercise Testing

ABSTRACT & COMMENTARY

Synopsis: Serum troponin I levels do not increase due to stress test induced ischemia.

Source: Choragudi NL, et al. *Heart Disease*. 2002;4: 216-219.

Troponin i is a very sensitive and specific marker for myocardial damage and can be elevated in patients with clinical presentations previously categorized as ischemic episodes without infarction. The hypothesis tested in this study was that exercise-induced myocardial ischemia will not raise serum troponin I levels. The study population was 134 patients admitted for chest pain in whom an acute coronary syndrome necessitating early intervention was excluded and stress testing was being performed. Troponin I (Abbott) was measured before and 4-48 hours later; 93% measured 12-18 hours post stress. Stress testing was exercise in 43%, dipyridamole in 43%, and dobutamine in 14%. A positive test was defined as a sestamibi identified stress perfusion defect not present at rest. Positive perfusion studies for ischemia were noted in 29 of the 134 patients. Only one patient exhibited a rise in troponin I after exercise. This patient had a dobutamine stress test, which was negative for ischemia, despite having had a recent myocardial infarction (2 weeks ago). Choragudi and colleagues concluded that serum troponin I levels do not increase due to stress test induced ischemia.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

As new diagnostic tests arrive, we are confronted with the possibilities for false-positive and false-negative studies. Since troponin has now been deemed the pivotal diagnostic modality for acute MI, the issue of whether ischemia can release it is important. By contrast to experience with acute coronary syndrome patients, stress test induced ischemia does not seem to release troponin. However, there are several weaknesses of this study. The population was small and only 29 patients had ischemia on perfusion study. Almost half the patients had dipyridamole stress which is known to only produce frank ischemia, in addition to a perfusion defect, in about one

third of patients with known coronary artery disease. In addition, the sampling times for troponin were not standardized and varied widely. Thus, this is not the ideal study, but based upon the findings it would be prudent to consider troponin rises within 2 days of stress testing as MI events and not ignore them as the false-positive results of inducing brief transient ischemia. ■

Mapping and Ablation of Idiopathic Ventricular Fibrillation

ABSTRACT & COMMENTARY

Synopsis: Ventricular ectopy originating in the distal Purkinje system may be a dominant trigger for initiation of idiopathic ventricular fibrillation.

Source: Haissaguerre M, et al. *Circulation*. 2002;106: 962-967.

Haissaguerre and colleagues from 6 referral hospitals in Europe and Asia describe electrophysiologic findings in 27 patients with primary idiopathic ventricular fibrillation. All patients had no evidence for structural heart disease after undergoing physical examination, electrocardiograms, echocardiography, cardiac catheterization, and in selected patients, endomyocardial biopsy. Electrocardiographic findings and exercise testing excluded Catecholaminergic polymorphic ventricular tachycardia, long QT syndrome and Brugada syndrome. Twelve patients underwent genetic testing that excluded abnormalities in several cardiac ion channels known to be associated with sudden death. Patients had had recurrent ventricular fibrillation prior to undergoing study and had failed a mean of 3.6 ± 2 antiarrhythmic drugs. Twenty-three of the 27 patients had received an implantable cardioverter defibrillator (ICD) before undergoing study but were referred because of frequent recurrent arrhythmias. Spontaneous arrhythmias were noted during their in-hospital evaluation in 24 of the 27 patients. These patients had 7841 ± 9595 premature ventricular beats per 24 hours. Three patients had no ventricular premature beats during in-hospital recording. During electrophysiologic study, runs of repetitive beats or ventricular fibrillation were initiated with short coupling intervals of extrastimuli in most patients. Similar patterns were seen during spontaneous episodes in those patients in whom they had been recorded.

Two groups of patients were identified. In 4 patients, ventricular premature beats originated in the right ventricular outflow tract. However, in the remaining 23 patients, there was evidence that the premature beats originated from the peripheral Purkinje system. The site of origin for these 23 patients was the right ventricle in 7, the left ventricle in 9, and both ventricles in 4. Purkinje sources were located in the anterior right ventricle or in a wide region of the lower half of the left ventricle. These sites were identified by a high frequency, discrete Purkinje potential that was present both before the QRS during sinus rhythm and before the ventricular premature beats. As is characteristic of ectopy arising from the Purkinje system, the QRS complex was relatively narrow compared to the complexes seen with beats originating from ventricular myocardium.

Most patients had several PVC morphologies. These morphologies were progressively eliminated by ablation at multiple sites guided by the early Purkinje potential before the premature beat. After ablation, the local electrogram showed abolition of the local Purkinje potential and a slight delay in the occurrence of the local ventricular electrogram. In 3 patients without spontaneous arrhythmias during the procedure, paced mapping was used to identify a probable source of the premature beats. If Purkinje potentials were identified at the sites, RF energy was delivered. It was noted during ablation that RF delivery could transiently worsen arrhythmias producing runs of polymorphic ventricular tachycardia or ventricular fibrillation.

After the procedure, 3 patients had a late recurrence of premature beats and were treated with an antiarrhythmic drug. During follow-up, 2 of these patients had recurrence of VF treated by their defibrillators and one patient had presyncope associated with polymorphic ventricular tachycardia. In the remaining patients, Holter recordings showed no or few (28 ± 49) isolated premature beats per 24 hours in the absence of antiarrhythmic drug therapy. In these 24 patients during a follow-up of 24 ± 28 months, there was no sudden death, syncope, or recurrence of VF.

Haissaguerre et al conclude that ventricular ectopy originating in the distal Purkinje system may be a dominant trigger for initiation of idiopathic ventricular fibrillation. Preliminary evidence suggests that radiofrequency ablation of these Purkinje foci may provide protection against recurrence.

■ COMMENT BY JOHN P. DiMARCO, MD, PhD

During the last 30 years, considerable attention has been directed toward the syndrome of patients with structurally normal heart and ventricular fibrillation. Several genetic patterns have been identified including

the long QT syndromes, catecholaminergic polymorphic ventricular tachycardia, and the Brugada syndrome. Other causes of ventricular fibrillation in patients with normal hearts may include commotio cordis, coronary spasm, electrolyte abnormalities and drug effects. All of these etiologies were excluded in the patients in this report.

Finding that ectopy in these patients had a site of origin in the distal Purkinje system and that ablation of these sites was associated with intermediate protection against recurrent VF is quite exciting. However, it must be remembered that introduction of extra stimuli during electrophysiologic studies in truly normal individuals should not initiate polymorphic ventricular tachycardia or ventricular fibrillation. Therefore, one must be cautious and not conclude now prematurely that these patients do not have additional abnormalities that will become manifest over time.

In prior studies, the long-term prognosis of patients without structural heart disease who were resuscitated from a cardiac arrest has been favorable compared to the prognosis of patients with advanced structural heart disease. However, since these patients have normal cardiac function, recurrent arrhythmias are truly tragic. The observations in this paper suggest that at least some of these patients may be effectively treated with catheter ablation. However, at the present time, a conservative course using ablation in conjunction with defibrillator implantation seems most reasonable until the long-term natural history of this disorder is better understood. ■

Treatment of Hypertension: Does Choice of Drug Therapy Make a Difference?

ABSTRACT & COMMENTARY

Synopsis: Doxazosin was less effective in preventing major CV events, particularly CHF, than the individuals who received the diuretic chlorthalidone.

Source: Davis BR, et al. *Ann Int Med*. 2002;137: 313-320.

Randomized clinical trials in hypertension over the past decade have suggested that specific drug classes used for the treatment of hypertension may make a difference in clinical outcomes, irrespective of the efficacy of blood pressure lowering. All available active hypertension agents will lower blood pressure significantly in two thirds of individuals who receive monotherapy. However, the majority of hypertensive patients require 2 or more drugs, particularly diabetics. Thus, it has been difficult to know if choice of a specific agent makes a difference. Meta-analyses have suggested that differences in outcomes are related to drug class, with ACE inhibitors and beta-blockers associated with decreases in coronary events, while calcium channel blockers appear to lower stroke risk. Recently, the NHLBI ALLHAT study (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) issued an alert, discontinuing the alpha blocker doxazosin (dox) from the active drug regimens because of an increase in "major cardiovascular events." The present report is an analysis of the data relating to that decision, and confirms the original policy of the steering committee to halt the dox arm of ALLHAT (January 2000). The initial data demonstrated an increase in major cardiovascular disease, particularly congestive heart failure (CHF), with a 25-100% increased risk compared to the diuretic chlorthalidone (chlor) alone. Furthermore, it was concluded that it was unlikely that dox could ever show a benefit over chlor for the primary study end point of nonfatal CAD or nonfatal MI. The ALLHAT Trial enrolled 42,418 patients who were randomized to chlor vs. amlodipine, lisinopril, or doxazosin. Secondary end points included other major CAD events and stroke. (Another component of ALLHAT as yet to be reported, is assessing the use of a pravastatin vs usual care). Eligible individuals were older than 55 years of age, with a blood pressure of ≥ 140/90 mm Hg, and one additional major CAD risk factor (prior MI, ECG LVH, diabetes, smoking, or low HDL cholesterol). Enrollment took place between 1994-1998. Hypertensive patients were added in a step approach with a target of blood pressure (BP) end point of < 140/90 mm Hg. Chlor was given at 12.5 and 25 mg; dox was dosed at 2, 4, and 8 mg depending on the BP response. If optimal BP control was not achievable with one agent, other drugs could be added, including reserpine, clonidine, atenolol, or hydralazine, at the discretion of Davis and colleagues.

Results

After 3.3 years of follow-up, the dox arm was discontinued because of a significant increase of CHF events vs. chlor. Approximately two thirds of subjects in both cohorts required additional antihypertensive therapy over the study drug. Individuals in the dox arm did worse whether they received a second or third hypertensive agent. There was a 2.5 to 3-fold increased risk with dox monotherapy, somewhat less in those who took an open-label additional drug. The increase in CHF with dox did

not appear to be related to BP or blood pressure control. Patients who received chlor at either dose had less CHF. Dox patients had a slightly greater systolic BP on treatment than chlor by 2-3 mm Hg, with no differences in diastolic BP. Subjects with a lower BP on dox actually had a higher risk of CHF. The study concluded that dox was less effective in preventing major CV events, particularly CHF, than the individuals who received the diuretic chlorthalidone. No conclusion could be made as to whether the diuretic was a more potent active control than dox, or there was harm induced by dox. Dox patients were one third more likely than chlor to receive additional antihypertensive therapy. Time to development of heart failure was shorter with dox than chlor. Davis et al conclude that dox causes excessive risk for heart failure in high-risk hypertensive individuals. They state that "the degree of difference in blood pressure does not explain the increased risk for heart failure in the dox group compared to chlor." They emphasize that chlor resulted in a 50% decrease of CHF in patients with isolated diastolic hypertension in the SHEP trial (Kostis JB, et al. *JAMA*. 1997;278:212-216).

■ COMMENT BY JONATHAN ABRAMS, MD

This study, along with the HOPE, LIFE, and PROGRESS data, suggests that the type or class of antihypertensive agent is important, and that small differences in blood pressure achieved in a trial do not seem to account for differences in clinical outcomes. For instance, in the HOPE trial, where many of the patients did not have hypertension, it was concluded that the stroke reduction achieved with the ACE inhibitor ramipril vs. placebo were unrelated to the small blood pressure decrement in the active treatment arm. In the recently published PROGRESS trial, a post-CVA-TIA trial using an ACE inhibitor and a diuretic, combination therapy resulted in a greater decrease in subsequent brain events, and it appeared that the addition of the diuretic to the ACE inhibitor was critical for a beneficial clinical outcome. Greater BP reduction was associated with a greater reduction in stroke; however, stroke risk was decreased even in nonhypertensive patients, particularly with the combination, whereas single drug with perindopril therapy was not associated with a decrease in stroke. Thus, this study suggests that even in the absence of hypertension, the combination of an ACE inhibitor and a diuretic, which was associated with BP lowering in normotensives, results in maximal benefit for recurrent stroke. In the recently published LIFE trial (Abrams J. *Clinical Cardiology Alert*. 2002;21[6]:46-47), losartan was found to decrease stroke rates more than atenolol, in spite of identical blood pressure lowering with both agents. These individuals were high risk, as they had ECG and/or echo LVH. Furthermore, in the diabetic substudy of LIFE, there was broader risk reduction, including coronary artery events, which were not reduced in the overall LIFE trial.

What can be made from these recent trials, as well as other data in the literature? It would appear that in high-risk hypertensive individuals, particularly diabetics, an ACE inhibitor should be part of the drug regimen. In addition, the use of diuretics, long confirmed to be associated with decreased event reduction in hypertension alone or in combination with a beta-blocker, should be standard antihypertensive therapy. Alpha blockers have no role in the sole treatment of hypertension, but can be used in individuals with prostatic hypertrophy in combination with other antihypertensives. Calcium channel blockers have been shown to be effective in systolic hypertension of the elderly, and in hypertensive therapy meta-analyses decreased stroke rates, but showed some increase in myocardial infarction. Thus, these agents should not be used as first-line therapy in individuals without known CAD and isolated systolic hypertension. Beta-blockers are effective in all individuals, but not necessarily as first-line therapy. There remains some controversy about the use and efficacy of beta-blockers in the elderly, but recent commentaries support such a policy. Nonetheless, the LIFE trial results suggest the use of an ARB over a beta-blocker. Other trials are needed to confirm this since beta-blockers do prevent coronary artery events. In individuals with any degree of renal insufficiency, an ACE or an ARB should be used as initial therapy.

Finally, most of the data that have accumulated over the past decade indicates that in treating hypertension, lower is better. Target BP should be no higher than 145/85 mm Hg, and in individuals with multiple risk factors or diabetes, optimal blood pressure control of < 135/80 mm Hg is the name of the game. ■

CME Questions

17. Which of the following has been shown to reduce major adverse events following percutaneous coronary interventions?

a. vitamin A
b. vitamin B complex
c. vitamin C
d. vitamin E

18. Frequent and complex ventricular ectopy in an athlete indicates:

a. possible structural heart disease.
b. excellent athletic training.
c. bulemia.
d. steroid use.