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CLINICAL CARDIOLOGY ALERT

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INSIDE

Another Vitamin Bites the Dust!

ABSTRACT & COMMENTARY

THE HOMOCYSTEINE (HC) HYPOTHESIS HAS BEEN POPULARIZED for a long time since the recognition 35 years ago that elevated HC appears to be associated with vascular disease. A number of case-controlled and retrospective studies, as well as meta-analyses, have confirmed a relationship of elevated HC with stroke and coronary artery disease (CAD), although not all reports have been concordant. A relatively harmless and inexpensive therapy, folic acid, pyridoxine (vitamin B6), and cobalamin (vitamin B12), lowers HC and has been theorized to decrease the vascular risk associated with elevated HC levels. A recent positive angioplasty trial has provoked further interest within the cardiovascular community. The Vitamin Intervention and Stroke Prevention (VISP) investigators sought to determine whether 2 different doses of folic acid, as well as vitamins B6 and B12, given to individuals following a stroke would reduce subsequence recurrent stroke and CAD outcomes. This multicenter trial enrolled 3700 individuals who had had a stroke no sooner than 72 hours prior to randomization. Subjects were carefully selected by a variety of diagnostic parameters, and all had an unequivocal CVA unrelated to hemorrhagic or embolic events.

Patients were randomized to the high- or low-dose vitamin group with stratification by trial center location, sex, and age. In regard to multivitamins, the high-dose formulation contained 2.5 mg folic acid, compared to 20 µg in the low-dose group. The amounts of pyridoxine and cobalamin were also different in the high-dose and low-dose groups. Patients were followed with "the best available surgical and medical management to prevent current stroke," including daily aspirin. Participants were contacted every 3 months; the study duration was 2 years. In addition to physical and laboratory exams, all patients were given a stroke-symptoms questionnaire. Subsequent cerebral events were evaluated by blinded neurologists, as well as by the questionnaire. Head CT or MRI were obtained in all patients at 2 years and whenever a subject had a suspected cerebral event during the study. CAD data were collected using standard clinical criteria, including nonfatal CAD and death. It was assumed that there would be an 8% probability of recurrent stroke at year 1 and 4% by year 2. The primary end point was a diagnosis of recurrent stroke. Multiple statistical analyses were carried out. During the

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trial period, there was a small decrease in the HC levels required for study eligibility due to the decline in HC levels in the United States and Canada populations due to folate fortification of the US grain supply. Recruitment took place between 1997 and 2001. The study was terminated early due to an analysis that determined that no difference in event rates between the 2 doses could be found even if the study was continued. HC eligibility cut points for entry were > 8.5 µmol/L for women and > 9.5 for men; three-quarters of screened subjects were eligible. Of all eligible patients, 75-80% were randomized to 1 of 2 HC doses. Current smokers, diabetics, and individuals with a history of chest pain had a somewhat higher likelihood of developing recurrent stroke irrespective of HC levels and dose assignment. Compliance with medication was good.

Results

At the end of the trial, there were an equivalent number of strokes in each group. Mean follow-up was approximately 20 months, and complete data collection was more than 90%. Initial values of HC were identical in 2 groups at 13.4 µmo/L. Both groups experienced a decline in HC levels over the study period, greater in the high-dose vitamin cohort by 2.0 µmo/L at 1 month and 2.3 µmo/L at 2 years. Vitamin B12 levels were substantially greater in the high-dose group and barely changed in the low-dose group. Using an intention-to-treat analysis, the primary end point of recurrent stroke was 8.1% in the low-dose HC group vs 8.4% in the high-dose cohort. Fatal or disabling ischemic strokes were comparable. CAD events were low dose 6.7%, and high dose 6.3% (P = NS), with a slightly lower incidence of CAD events of 0.5% by study completion in the high-dose cohort (NS). Using a combined end point of ischemic stroke, CAD events, and death, there was a 17.2% event rate in the low-dose group vs 16.27% in the high-dose group (NS). In the highest tertile of HC levels at baseline (> 14 µmo/L), high-dose therapy was associated with a decreased risk of stroke, CAD events, and death by approximately 10% (NS). In both treatment groups, there were "persistent and greater associations between baseline total HC and outcomes, significant for stroke at the low dose (P = .02) but NS for the high-dose group"; for CAD events P = . 001 for low dose and P = .002 for high dose, with comparable findings for death. Thus, higher HC levels were consistently associated with a greater frequency of vascular events. Although the primary end point was not reached, Toole and associates conclude that the study does support a relationship between HC and vascular disease. They offer multiple explanations for the negative results, including inadequate sample size, a short follow-up period, and most importantly, the advent of folate fortification of US grains that occurred simultaneously with the trial initiation, beginning in 1996 and mandated in 1998, which "profoundly reduced the prevalence of low folate and high total HC levels." Thus, the difference in HC levels between the groups actually narrowed over the treatment period. They suggest that food folate fortification may have reduced the cardiovascular risk of high HC. They also question whether HC may represent a marker and not a cause for vascular disease. Toole et al stress that their data are comparable to other trials indicating that baseline total HC is an independent predictor of vascular outcomes. They call for further trials to explore the relationship between HC and vascular disease, as well as longer trials.

An accompanying editorial by Hanley,[1] in the same issue of *JAMA*, laments the fact that preventive measures for recurrence of ischemic stroke in general are not carried out consistently and do not mirror the more prevalent aggressive approaches to CAD patients. He notes that the stroke rate in the VISP trial was lower than anticipated (only 8% over 2 years). Hanley suggests that HC may have differing effects on coronary vs cerebral arteries (without any data). He also calls for further research and better ways to stratify individuals with recurrent stroke (Toole JF, et al. *JAMA*. 2004;291:565-575).

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COMMENT BY JONATHAN ABRAMS, MD

This trial, as well as other data in the literature, is clearly supportive that homocysteine is related to vascular events, with higher HC levels being linearly related to adverse outcomes. However, this study, with a reasonable dose differential between the low and high multivitamin cocktails, does not support the concept that lowering HC will decrease vascular events, be they cerebrovascular or coronary. The HC gradient and clinical outcomes between the 2 cohorts might have been significant if the high-dose cohort was compared to placebo folate, which would have resulted in a greater HC differential between the cohorts. Data from a recent HC supplement study in CAD patients do not support the routine use of folate with B vitamins for the prevention of CAD. It is clear that preventive measures for first or recurrent stroke, including cigarette cessation, hypertension control, and aggressive lipid therapy, are not commonly used. Thus, far more benefit would be gained by conventional interventions as opposed to adding folate and multivitamins. Along with the demise of the antioxidant vitamins C, E, and beta-carotene, perhaps folate replacement should be rendered to the junk heap of vitamin therapy. While the final word on homocysteine is not in, and current literature clearly supports a linear relationship between HC and vascular events, this trial offers little to suggest a breakthrough. Perhaps one of the ongoing HC trials will yet make me eat my vitamins!

Reference

1. Hanley DF. *JAMA*. 2004;291:621-622.

Effusive-Constrictive Pericarditis

ABSTRACT & COMMENTARY

Synopsis: *Effusive-constrictive pericarditis is an uncommon syndrome in patients with pericarditis that often progresses to persistent constriction, although spontaneous resolution can occur.*

Source: Sagrista-Sauleda J, et al. *N Eng J Med*. 2004; 350:469-475.

EFFUSIVE-CONSTRICTIVE PERICARDITIS IS CHARACTERIZED by persistently elevated right atrial pressure after intrapericardial pressure has been normalized by removal of pericardial fluid. The constriction is due to visceral pericardial disease, which has been confirmed in surgical cases. However, little is known about this entity in nonsurgical patients. Thus, Sagrista-Sauleda and colleagues studied 190 patients with clinical evidence of cardiac tamponade who underwent pericardiocentesis and cardiac catheterization for a 16-year period. After pericardiocentesis, constriction was diagnosed if the right atrial pressure failed to decrease by 50% or to a level < 10 mm Hg, after pericardial pressure was normalized (near zero). By these criteria, 15 patients had effusive-constrictive disease. Further treatment was based upon a complete medical evaluation and often included oral nonsteroidal anti-inflammatory drugs. Corticosteroids were not used. Surgery for constriction was considered for severe and persistent heart failure after a trial of medical therapy. The 190 patients studied were derived from 218 patients with clinical tamponade among 1184 patients evaluated for pericarditis. In seven of the patients diagnosed with effusive-constrictive disease, constriction was suspected prepericardiocentesis because of abnormal left ventricular septal motion on echo and Doppler evidence of cardiac inflow abnormalities. After pericardiocentesis, pericardial pressure decreased from a median of 12 to -5 mm Hg, whereas right atrial and ventricular pressures decreased slightly but remained elevated with a dip and plateau pattern in left ventricular diastolic pressure. Pulsus paradoxus decreased from a median of 15 to 8 mm Hg. Cardiac index increased only slightly from 2.1 to 2.4 L/min. The etiology of pericarditis was diverse. Seven patients underwent pericardiectomy for persistent symptoms between 13 weeks and 4 months after pericardiocentesis, and all had thickening of both pericardial layers. Three subsequently died of their underlying disease, but 4 were well after 3-15 years of follow-up. Among the nonsurgical patients, 3 with idiopathic pericarditis resolved spontaneously; 4 with neoplastic disease responded to radiation therapy; and the final patient responded to therapy for severe left heart failure. Sagrista-Sauleda et al concluded that effusive-constrictive pericarditis is an uncommon syndrome in patients with pericarditis that often progresses to persistent constriction, although spontaneous resolution can occur.

COMMENT BY MICHAEL H. CRAWFORD, MD

Several important points can be made from this report. Effusive-constrictive pericarditis is unusual, but not rare, probably occurring in 5-10% of patients with clinical evidence of pericardial tamponade. In this series, about half of the cardiac catheterization proven cases were suspected clinically. Thus, had catheterization not been done, half would have been initially missed, leading to delays or misdiagnosis with potentially serious

consequences. This experience argues for performing pericardiocentesis in the catheterization laboratory whenever possible with careful hemodynamic measurements done before and after pericardicentesis to detect constriction. Bedside pericardiocentesis should be reserved for true life-threatening emergencies.

Once underlying constriction has been identified in patients with cardiac tamponade, conservative management should be attempted. In this series, the only nonspecific therapy used was nonsteroidal anti-inflammatory agents. Corticosteroids were avoided, probably because of their known propensity to increase the frequency of relapse upon withdrawal and the possibility that an undiagnosed infectious etiology such as tuberculosis would be worsened. Most of the patients in this series died of their underlying disease rather than recurrent tamponade or constriction, and several improved spontaneously. About half eventually required surgical pericardiectomy. There were no recurrences noted after surgery.

Of note, echocardiography was not particularly useful in identifying effusive-constrictive patients, but some believe that transesophageal echocardiography may be superior in this regard, because characteristics of the pericardial space are more clearly seen. It was not reported in this study and probably not widely used. I have been impressed that cardiac MRI is useful for detecting underlying visceral pericardial disease, but constriction is a hemodynamic diagnosis in the final analysis. So no matter what sophisticated imaging technique is used, cardiac catheterization should always be done. ■

Transient-Constrictive Pericarditis

ABSTRACT & COMMENTARY

Synopsis: *A small subset of patients with evidence of pericardial constriction, perhaps 1 in 6, experience spontaneous resolution without surgical intervention.*

Source: Haley JH, et al. *J Am Coll Cardiol*. 2004;43: 271-275.

Traditionally, constrictive pericarditis has been characterized as a rare progressive fibrosis, with or without calcification, of the pericardium, which leads to refractory heart failure unless surgical resection of the pericardium is performed. Recently, there have been reports of spontaneous remissions, such as the one by Sagrista-Sauleda et al (*see page 19*). Thus, Haley and colleagues at the Mayo Clinic in Rochester, Minn, report their experience with 36 such patients seen over a decade. The cases were obtained by identifying 212 patients in their echocardiography database who had signs of pericardial constriction. Of these, 36 showed spontaneous resolution of the echocardiographic findings and represent the subjects of this report. Almost all of these patients had symptoms (92%), with chest pain (53%) and dyspnea (44%) being the most common. Among the 22 patients who were seen for their entire illness at Mayo, resolution occurred in a mean of 8 weeks. Most (86%) received medical treatment; nonsteroidal anti-inflammatory agents (56%) and corticosteroids (44%) were the most common. After a mean follow-up of 2.3 years, there have been no recurrences. A pericardial effusion was documented in 24 patients (67%), 8 of whom underwent pericardiocentesis. Among the 17 who had CT or MRI, 10 (59%) showed increased pericardial thickening. A variety of presumed causes were determined, which were generally consistent with the usual causes of pericarditis. Haley et al concluded that a small subset of patients with evidence of pericardial constriction, perhaps 1 in 6, experience spontaneous resolution without surgical intervention.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

Although it is a retrospective, observational study from a referral center, several important points emerge from this report. The data suggest that in the course of acute pericarditis some patients develop constrictive physiology presumably due to a transiently thickened and inelastic pericardium, which resolves as the disease process abates. A smaller, earlier report from Sagrista-Sauleda et al[1] suggested that transient constriction may occur in up to 10% of acute pericarditis cases. The evidence cannot be estimated from the Mayo report because it is a retrospective analysis of patients with constriction on echo. Why some patients go on to chronic constriction is not clear, but it is interesting that one diagnostic cause of pericarditis is missing in this report, namely radiation. Perhaps radiation-induced constrictive pericarditis is less likely to resolve spontaneously.

The practical implication of this report is that findings of constrictive pericarditis on echocardiography in patients with acute pericarditis should be treated expectantly with specific and nonspecific therapy, with an expected resolution in about 3 months if there is going to be resolution. Patients with persistent symptomatic constriction after 3-6 months should be considered for surgery. This advice probably does not apply to patents with chronic constrictive pericarditis who present long after their initial illness for evaluation or in whom the

initial bout of pericarditis was never recognized. Spontaneous resolution would be much less likely in such individuals. ■

Reference

1. Sagrista-Sauleda J, et al. *Am J Cardiol*. 1987;59: 961-966.

Rate or Rhythm Control in Persistent Atrial Fibrillation?

ABSTRACT & COMMENTARY

Synopsis: *Quality of life is impaired in patients with atrial fibrillation compared to healthy controls, but treatment strategy for atrial fibrillation results in the same net effect on quality of life.*

Source: Hagens VE, et al, for the RACE Study Group. *J Am Coll Cardiol*. 2004;43:241-247.

The rate control vs electrical cardioversion for Persistent Atrial Fibrillation (RACE) study compared a rate control strategy vs a rhythm control strategy in patients with persistent atrial fibrillation. Hagens and colleagues had previously reported that there was no significant difference in mortality and that there was an excess of adverse cardiac events associated with the rhythm control strategy. In this paper, they deal with quality-of-life issues.

Patients were eligible for RACE if they had recurrent, persistent atrial fibrillation. Follow-up quality-of-life questionnaires were administered at baseline after 1 year and at the end of follow-up. Patients who died during follow-up (18 patients in each group) were not included. Quality-of-life data were not complete in another 134 patients, and 1 or more of the quality-of-life questionnaires was not available. The patients excluded did not differ significantly from included patients in terms of their baseline characteristics.

Quality of life was assessed using the Medical Outcomes Study Short-Form 36 (SF-36) questionnaire. This instrument has been translated and validated in the Netherlands, the country in which RACE was conducted.

At baseline, all patients were compared with a healthy, age-matched control group consisting of 172 Dutch individuals who originally served to validate the Dutch version of the SF-36. At baseline, at 1 year, and at the end of the study, the scores on all the subscales of the SF-36 were compared between the rate control and rhythm control groups.

At baseline, there were no significant differences in quality of life between the rate and rhythm control groups; however, quality of life was lower for patients in RACE compared with a healthy, age-matched control group. Differences in physical and emotional role limitations were highest. Differences in vitality, social functioning, and general health were also significant. Bodily pain was higher in the atrial fibrillation patients. Low quality-of-life scores for physical health at baseline were more frequent among females, patients younger than 69, patients with an atrial fibrillation duration above the median of 32 days, and patients with reduced exercise tolerances. Low quality-of-life scores for mental health were more frequent among patients older than 69. The correlation between complaints associated with atrial fibrillation (fatigue or palpitations) had a reduced score for both physical and mental health parameters. There was an improvement in many of the quality-of-life parameters over time during the study in both groups. In the rate control group, 4 subscales of the SF-36 had improved. At study end, 3 subscales had significantly improved. These were role limitations due to physical problems, social functioning, and mental health. In the rhythm control group, quality of life improved at 1 year on 3 subscales, but at the end of the study, no significant changes were present compared with baseline scores. From the scores on the SF-36, subscales at the 12-month follow-up and study end were compared between the rate and rhythm control groups; no significant differences were found in any of the 8 subscales. Complaints of palpitations, fatigue, and dyspnea, which were thought to be related to atrial fibrillation, were common in both groups. An analysis of baseline variables that might be associated with quality-of-life changes was performed. Stepwise regression analysis showed that age younger than 69, symptoms of atrial fibrillation (fatigue, palpitations, or dyspnea), a short duration of atrial fibrillation, and sinus rhythm at the end of follow-up were determinants of relevant quality-of-life improvement during follow-up. Interestingly, although sinus rhythm at the end of follow-up was a predictor of improved quality of life, the type of randomized strategy (rate or rhythm control), was not associated with improved quality of life.

Hagens et al conclude that quality of life is impaired in patients with atrial fibrillation compared to healthy controls, but treatment strategy for atrial fibrillation results in the same net effect on quality of life.

■ COMMENT BY JOHN DiMARCO, MD, PhD

These data about quality of life from the RACE trial are quite important. The data here show that there is no

clear-cut advantage to a rhythm control strategy even in terms of symptoms. However, the observation that there was a trend toward an improvement in symptoms if sinus rhythm could be maintained has 2 implications. First, patients who are highly symptomatic in atrial fibrillation are more likely to get benefit from an initial rhythm control strategy. Unfortunately, these patients are also those who are often the most likely to go back into atrial fibrillation so the net long-term effect in a large group is small, but the individual effect in the proportion who respond may be great. Therefore, the data from this trial and data that will be published from the AFFIRM study suggest that asymptomatic patients will probably not benefit much from attempts to maintain normal sinus rhythm. However, if there are significant symptoms and if the patient falls into that minor fraction in which sinus rhythm can be restored and maintained in a relatively simple fashion, then a rhythm control strategy may be indicated. In all cases, an appropriate anticoagulation program should also be followed. ■

Azimilide in Patients With Implantable Cardioverter Defibrillators

ABSTRACT & COMMENTARY

Synopsis: *Data indicate that azimilide is a well-tolerated antiarrhythmic drug that decreases the frequency of ICD discharges or pacing in patients with ventricular tachycardia.*

Source: Singer I, et al. *J Am Coll Cardiol*. 2004;43: 39-43.

Azimilide is a new antiarrhythmic drug that is being developed for treatment of primarily supraventricular, but also ventricular, arrhythmias. In this study, Singer and colleagues report the results of a multicenter, double-blind, placebo-controlled trial of azimilide for reduction of antiarrhythmic therapy in patients with implantable cardioverter defibrillators (ICDs). A total of 172 patients were recruited from 37 centers in the United States and randomly assigned to receive placebo, 35 mg, 75 mg, or 100 mg oral azimilide daily. Patients could be included in the study if they met one of the following criteria: an ICD implantation had occurred 30 days or more before randomization and the patient had had at least one ICD shock within the preceding year; or an ICD had been implanted for symptomatic VT within 30 days of randomization and the patient had an inducible sustained monomorphic VT. Patients with a history of class IV New York Heart Association failure, those taking other antiarrhythmic drugs, with unstable or recent ischemia, with a QTc longer than 440 msec or a history of polymorphic VT, hypertrophic cardiomyopathy or restrictive heart disease, or significant liver and renal dysfunction were excluded. After beginning therapy, all patients were evaluated at 0.5, 1, 3, 6, 9, and 12 months after beginning azimilide or placebo. Noninvasive electrophysiologic testing was performed to determine the defibrillation threshold at baseline and at the 1-month visit. The ICD was interrogated at every visit, and stored electrograms were retrieved. Patients were also seen after a documented ICD shock. An Andersen-Gill proportional hazard model was used to analyze recurrent ICD therapies. Only tachycardia detections that were treated appropriately with either shocks or antitachycardia pacing (ATP) were used in the analysis. The ICD therapy rates per patient-year exposure across treatment groups were compared using the log-rank test.

Of the 172 patients randomized in the study, 37 patients received placebo, 45 patients received 35 mg of azimilide, 45 patients received 75 mg of azimilide, and 46 patients received 125 mg of azimilide. A total of 2011 appropriate ICD therapies were detected in this study with a mean number per patient of 18 ± 50 and a median of 4. A total of 358 appropriate ICD shocks were detected with a mean number of shocks per patient of 4 ± 5 with a median of 2.

There was no difference between the groups in terms of age, left ejection fraction, or gender. Ten percent of patients had class III New York Heart Association congestive heart failure. No differences were observed in blood pressure, heart rate, or ECG variables. The use of concomitant medication was similar among the groups. The overall proportion of patients who reported adverse events was similar across all groups. Seven (19%) were withdrawn from placebo and 33 (24%) from the 3 azimilide groups. There were 3 reported episodes of torsades de pointes in 2 patients. Both patients were receiving 125 mg of azimilide daily. Azimilide significantly reduced the frequency of appropriate ICD therapies in all active drug groups compared to placebo by 69%. There was no difference between the 3 doses. The hazard ratio for all 3 groups was 0.31. Azimilide therapy at these doses was not associated with any significant changes in defibrillation threshold or pacing threshold.

Singer et al conclude that their data indicate that azimilide is a well-tolerated antiarrhythmic drug that decreases the frequency of ICD discharges or pacing in

patients with ventricular tachycardia.

COMMENTS BY JOHN DiMARCO, MD, PhD

Azimilide is an investigational class III antiarrhythmic drug currently undergoing clinical trials as a treatment of supraventricular and ventricular arrhythmias. It is unique in that it blocks both the rapid (IKr) and the slow (IKs) components of the delayed rectifier cardiac potassium channel. The data presented here, however, are quite surprising. There was no dose response over a greater than 3-fold dose range of 35-125 mg daily. In trials for therapy of atrial fibrillation, azimilide has only consistently shown effects at doses of 100 mg or 125 mg per day. If the data presented here are to be accepted at face value, that azimilide would seem to be effective in ventricular arrhythmias at lower doses with no greater effect at higher doses remains to be explained.

The population in this study is quite unusual. The patients had a very large total and mean number of VT or VF events. Although many of these events were probably terminations of runs of ventricular tachycardia with ATP in a few individuals, the median numbers of ATP therapies and the numbers of appropriate shocks are still quite substantial. This raises the possibility that the placebo group was just a true outlier and what we're seeing in the other 3 groups is just an absence of meaningful drug effect.

There is currently a larger study, the Shock Inhibition With Azimilide (SHIELD) study in progress to confirm the results of this pilot study. It will be interesting to see if the data presented here can be confirmed in this larger trial.

Risks Associated with Diastolic Dysfunction

ABSTRACT & COMMENTARY

Synopsis: *The risk of new AF or HF in subjects older than 65 with echocardiographic evidence of abnormal relaxation increased linearly with the degree of LA enlargement.*

Source: Tsang TS, et al. *Am J Cardiol*. 2004;93: 54-58.

Although echo doppler mitral inflow velocity evidence of "abnormal relaxation" is frequent in otherwise healthy older adults, recent observations suggest that mild diastolic function abnormalities may be associated with an increased mortality risk. Thus, Tsang and colleagues from the Mayo Clinic in Rochester, Minn, identified a cohort of local patients older than 65 with abnormal left ventricular (LV) relaxation from their echocardiographic database for follow-up chart review. Abnormal LV relaxation was defined as a mitral inflow velocity E/A wave ratio of < 0.75 or an E deceleration time of > 240 msec. Patients were excluded if they were not in sinus rhythm or had a history of heart failure, valvular heart disease, or stroke. Of the 717 subjects selected, 569 had abnormal relaxation and 148 controls had normal LV relaxation. The primary end point was a combination of first documented atrial fibrillation (AF) or heart failure (HF). Of the 569 subjects with abnormal relaxation, 105 (18%) developed the primary end point over a mean follow-up period of 4 years. Multivariate analysis showed that age, history of myocardial infarction, diabetes, ECG LV hypertrophy, and enlarged left atrial (LA) volume index were independent predictors of achieving the primary end point. A stepwise increase in age-adjusted risk was related to tertiles of LA size (< 27 mL/m^2; 27-37, and > 37). The risk of achieving the primary end point was not different between the controls and those with abnormal relaxation and an LA volume of < 27 mL/m^2. Tsang et al concluded that the risk of new AF or HF in subjects older than 65 with echocardiographic evidence of abnormal relaxation increased linearly with the degree of LA enlargement.

COMMENT BY MICHAEL H. CRAWFORD, MD

Mild abnormalities in echo Doppler measures of diastolic function are so common in individuals older than 65 years and especially in those older than 75 that some echocardiographers do not ever comment on these findings because of a perceived lack of specificity for predicting future cardiac events. This study confirms some of these concerns in that more than half of their referral population had abnormal relaxation, and it was not particularly specific for predicting AF and HF. The presence of obvious clinical risk factors for these cardiac end points augmented the predictive value, but these variables are predictive of events in their own right. The most important finding was that LA size in the upper 2 tertiles really helped separate those with abnormal relaxation at higher risk of AF and HF from those at a risk equivalent to the normal diastolic function controls. Presumably as the LV stiffens, LA emptying is impaired, prolonging E velocity deceleration and augmenting A velocity. At this stage, the risk of events is not increased, but as the LA enlarges, the risk of cardiac events increases to beyond that of those with normal LV relaxation. Thus, accurate measurements of LA volume indexed for

body size need to be part of almost every echo examination. In my experience, too many labs are still relying on M-mode measures of LA dimension, which are known to be inaccurate in estimating LA volume. ■

Cardiac Surgery Briefs

Off-Pump Cardiac Surgery

Source: Khan NE, et al. *N Engl J Med*. 2004;350: 21-28.

Despite the effectiveness of coronary artery bypass surgery for anginal symptom relief, many believe the use of cardiopulmonary bypass (CPB) is the major cause of postoperative morbidity, including neuropsychological impairment. Thus, Kahn and colleagues preformed a randomized trial of CPB vs off-pump coronary artery surgery in 104 patients with multivessel disease. Repeat coronary angiography was performed at 3 months post-op. Troponin T levels were higher post-op in the CPB vs the off-pump patients, but at 3 months 98% of the grafts were open in the CPB group vs 88% of the off-pump group (P = .002). There were no deaths. Despite evidence of more early myocardial damage, 3-month graft potency rates were significantly less in the off-pump group. These results have implications for the long-term results of off-pump surgery and dampen enthusiasm for this technique in patients with multivessel disease. ■

Sutureless Bypass Graft Connector

Source: Cavendish JJ, et al. *J Am Coll Cardiol*. 2004; 43:133-139.

Off-pump coronary artery bypass surgery has resulted in a need for devices to speed attachment of the grafts to the aorta and coronary arteries. The Symmetry Bypass Connector (St. Jude Medical, St. Paul, Minn) was the first device approved for this use. This device is used to attach saphenous vein grafts to the aortic wall via a star-shaped nitinol connector, without suturing. Early implantation results are excellent, but few long-term data exist. Cavendish and associates report on 5 cases at their institution out of 121 where the device was used, who developed acute coronary syndromes 2-5 months after surgery. In all 5 cases, the saphenous vein grafts placed were either occluded (n = 6) or had severe ostial stenosis (n = 5). One patient had repeat surgery. The other 4 were stented percutaneously. Two patients presented later with ostial in-stent restenosis, one of whom was treated with brachy therapy but then had another recurrence. Cavendish et al suggest that until more long-term data are available, this device should only be used in cases where the risk of stroke during aortic cross-clamping is unacceptably high. ■

CME Questions

13. Folic acid and B vitamins given to stroke victims:
a. reduce subsequent strokes.
b. reduce subsequent cardiovascular events.
c. reduce subsequent mortality.
d. None of the above

14. Effusive-constrictive pericarditis:
a. can resolve spontaneously.
b. may go on to constriction.
c. is common in pericardial tamponade.
d. a and b

15. Constrictive pericarditis:
a. may resolve spontaneously.
b. is almost always due to radiation therapy.
c. can be prevented by corticosteroids.
d. always exhibits pericardial thickening by CT scan.

16. Rhythm control vs rate control in atrial fibrillation shows:
a. substantially improved quality of life.
b. reduced mortality.
c. reduced stroke rates.
d. None of the above

17. Azimilide therapy for patients with ICDs and ventricular arrhythmias:
a. reduces mortality.
b. reduces the frequency of appropriate ICD discharges.
c. is more effective at higher doses.
d. causes intractable side effects in many.

18. The cardiovascular event risk in patients with mild diastolic dysfunction:
a. is greater at older ages.
b. is higher in diabetics.
c. increases with increasing left atrial size.
d. All of the above

19. Off-pump multivessel coronary artery bypass surgery:
a. is associated with lower troponin levels post-op.
b. reduces perioperative mortality.
c. is associated with less patent grafts at 3 months.
d. a and c

20. The Symmetric Bypass Connector for attaching saphenous veins to the aorta without sutures:
a. reduces operative times.
b. reduces aortic manipulation.
c. may result in ostial vein graft stenosis.
d. All of the above

Answers: 13(d); 14(d); 15(a); 16(d); 17(b); 18(d); 19(d); 20(d)

PHARMACOLOGY WATCH

Sinus and Allergy Health Partnership Releases New Guidelines for Treatment of Bacterial Rhinosinusitis

New guidelines for the treatment of bacterial rhinosinusitis were published in the January supplement of *Otolaryngology- Head and Neck Surgery* by the Sinus and Allergy Health Partnership. The goal of the guidelines is to reduce the use of antibiotics for viral infections and to use the most appropriate antibiotic for bacterial infections. The guidelines recommend antibiotics if patients are getting worse after 5-7 days or if they are not better after 10-14 days. Patients with mild disease should be treated with cefpodoxime (Vantin), cefuroxime (Ceftin), amoxicillin, amoxicillin/clavulanate (Augmentin), or cefdinir (Omnicef). Patients with moderate disease or those with recent antibiotic exposure should receive amoxicillin/clavulanate, ceftriaxone, or one of the respiratory fluoroquinolones including gatifloxacin (Tequin), moxifloxacin (Avelox), or levofloxacin (Levaquin). The respiratory quinolones do not include ciprofloxacin. This is a follow-up to the group's first guidelines, which were published in 2000 (*Otolaryngol Head Neck Surg*. Supplement. 2004;130:1).

Steroids Not Linked to Risk of Fractures

Long-term use of inhaled steroids for the treatment of respiratory diseases or nasal steroids for the treatment of allergic rhinitis are not associated with an increased risk of fractures if they are used in normal doses, according to a study from Canada. Researchers conducted a case-control study of all elderly Québec residents who were dispensed respiratory medications and could be followed for at least 4 years from 1988 to 2001. The rate of hip or upper extremity fractures was not increased in those patients who used daily inhaled corticosteroids (RR, 0.97). The rate of upper extremity fractures increased by 12% with every 1000 µg increase in the daily inhaled corticosteroid, but the rate of hip fractures did not increase. The rate of hip fractures was only elevated with very high doses (more than 2000 µg per day) of inhaled corticosteroid. Nasal steroids did not increase the risk at any dose. The authors conclude that long-term use of inhaled and nasal corticosteroids at usual recommended doses is not associated with the risk of fracture (*Am J Resp Crit Care Med*. 2004;169:83-88).

ADT Puts Men at Risk for Osteoporosis

Men treated for prostate cancer with androgen deprivation therapy (ADT) are at risk for osteoporosis and fractures, according to a new study. One year of ADT resulted in 2-8% bone loss in the lumbar spine and 1.8-6.5% bone loss

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in the femoral neck. The study was a meta-analysis of 9 studies that included a total of 208 patients. The authors suggest that men starting ADT should be considered for bone mineral density measurement, and men at high risk should be offered a bisphosphonate (published online January 19, 2004. *Cancer*).

Study Shows Valsartan May Improve Sexual Function in Postmenopausal Women

A new study suggests that valsartan may improve sexual function in hypertensive postmenopausal women. Researchers randomized 120 postmenopausal women aged 51-55 with mild-to-moderate hypertension to valsartan 80 mg daily or atenolol 50 mg daily for 16 weeks. Doses were doubled if diastolic blood pressures remained above 90 mm Hg. The end point was a questionnaire that self-evaluated various aspects of sexual desire, orgasmic response, and coital activity. The drugs lowered blood pressure equally effectively. Women in the valsartan group noted significantly improved sexual desire (38% increase, $P < .01$), changes in behavior (45% increase, $P < .001$), and sexual fantasies (51% increase, $P < .001$). In the atenolol group, scores for sexual desire and sexual fantasies significantly worsened (18% decrease, $P < .01$, and 23% decrease, $P < .001$, respectively). The authors conclude that in the study group, hypertensive postmenopausal women in their 50s, valsartan improved some aspects of sexual function, whereas atenolol worsened it. They further speculate the drugs may have differential effects on serum hormone levels, specifically testosterone (*Am J Hyperten*. 2004;14:77-81).

New Direct-to-Consumer Pharma Advertising Rules Considered

Anyone who watched the Super Bowl can verify that direct-to-consumer advertising of prescription pharmaceuticals is big business. Now the FDA is considering tighter restrictions on the content of these ads, requiring pharmaceutical companies to highlight key risks associated with the drugs rather than listing the large number of potential side effects in small print. The guidelines encourage companies to use less cluttered formats for print ads, perhaps even using bullet points to set the import risks apart. Print ads currently contain an extensive list of side effects similar to the package insert, often in a similarly small font, frequently on a separate page from the main advertisement. The FDA is also considering changing the criteria for "reminder" ads that simply name the drug without giving the indication for its use. Currently, these ads do not require information on adverse effects and often run close to disease awareness campaigns also paid for by the drug company. These new FDA restrictions have not been finalized and are sure to be opposed by Pharma.

FDA Actions

Boehringer Ingelheim Pharmaceuticals has received FDA approval to market tiotropium bromide inhalation powder (Spiriva) for the treatment of COPD. Tiotropium, a once-daily anticholinergic agent, is indicated for the long-term maintenance treatment of bronchospasm associated with COPD.

Modafinil (Provigil) has been approved for improving wakefulness in patients with excessive sleepiness due to obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder. The drug is currently approved for improving wakefulness in patients with narcolepsy.

The FDA has approved a 3-day course of azithromycin (Zithromax) for the treatment of acute bacterial sinusitis. The drug, which is dosed at 500 mg once a day, is the only 3-day regimen approved for this indication. Azithromycin is currently approved for the treatment of community-acquired respiratory infections and skin infections, as well as otitis media.

Olanzapine (Zyprexa) has been approved for maintenance treatment of bipolar disorder. The drug appears to be effective in delaying relapse into either mania or depression in bipolar patients. Olanzapine was approved in 2000 for the short-term treatment of acute mixed or manic episodes associated with bipolar disorder.

The FDA has also approved a combination of olanzapine and fluoxetine (Prozac) for the treatment of bipolar depression. The combination drug will be marketed under the trade name Symbyax. Quetiapine fumarate (Seroquel) was also recently approved for monotherapy and adjunct therapy with lithium and divalproex, for the short-term treatment of acute manic episodes associate with bipolar I disorder. ■