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INSIDE

Inflammation and Atrial Fibrillation

ABSTRACT & COMMENTARY

THIS STUDY REPORTS THE ASSOCIATION BETWEEN INFLAMMATION as measured by C-reactive protein (CRP) and the prevalence and development of atrial fibrillation. The data are from the Cardiovascular Health Study, a large population-based study of cardiovascular disease that included 5201 men and women, aged 65 or older who were enrolled from Medicare eligibility lists in 4 cities in the United States. After initiation of the study, a second cohort of 687 African-American participants were enrolled, giving a total of 5888 subjects. Of those, 5806 had available CRP levels at baseline. Participants were followed up every 6 months through alternating telephone interviews and annual clinic visits. Discharge diagnoses and hospital records were obtained for all hospital admissions from the Medicare database. The presence at baseline or subsequent development of atrial fibrillation was identified either by either self-report, electrocardiographic documentation, or hospital discharge diagnosis. CRP levels were related to prevalence at baseline and subsequent incidence using a logistic regression analysis after logarithmic transformation of the CRP values. Other risk factors for atrial fibrillation considered in the multivariate analysis included age, gender, race, body mass index, left ventricular dysfunction, systolic and diastolic blood pressures, history of hypertension, coronary heart disease, diabetes mellitus, cerebrovascular disease, and congestive heart failure. The ratios for atrial fibrillation were calculated either by modeling CRP level as a continuous variable or by categorizing CRP levels into quartiles.

Of the 5806 patients included in the cross-sectional study, 315 had atrial fibrillation at baseline. The risk for atrial fibrillation was progressively higher with increasing CRP quartile. CRP remained an independent predictor of baseline prevalence after multivariate analysis. The adjusted odds ratios for baseline atrial fibrillation were 1.00, 1.33, 1.45, and 1.75 in the 4 CRP quartiles.

After subjects with baseline atrial fibrillation were excluded, 5491 patients were followed longitudinally to assess if CRP levels could predict future atrial fibrillation. The suggested hazard ratio was 1.31 in the patients in the highest CRP quartile. In a multivariate Cox regression analysis that treated CRP as a continuous variable, there continued to be an association between CRP and risk of future

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development of atrial fibrillation even after adjustment for multiple other risk factors.

Aviles and associates concluded that inflammation as measured by CRP levels is a predictor for both the presence and the development of atrial fibrillation (Aviles RJ, et al. *Circulation*. 2003;108:3006-3010).

COMMENT BY JOHN DiMARCO, MD, PhD

For many years, it has been recognized that factors associated with atrial enlargement, stretch, and fibrosis promote the development of atrial fibrillation. The importance of risk factors that produce atrial stretch, such as hypertension, valvular heart disease, and congestive heart failure, has long been recognized, but the role of inflammation in the pathogenesis of atrial fibrillation is a new observation. In this study, CRP is shown to be a predictor of both the presence of atrial fibrillation at baseline and the development of new atrial fibrillation in elderly patients. Inflammation is not usually a target of antiarrhythmic therapy, but conventional therapy with antiarrhythmic drugs to prevent atrial fibrillation is often unsuccessful. Clinical trials to test the hypothesis that decreasing inflammatory markers with therapy, either as the sole approach or in conjunction with antiarrhythmic drugs, will lead to a decreased prevalence and incidence of atrial fibrillation will be important. ■

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Arrhythmia Risk Stratification in Idiopathic Dilated Cardiomyopathy

ABSTRACT & COMMENTARY

Synopsis: *Left ventricular ejection fraction is the most important risk factor for both arrhythmic events and transplantation-free survival in patients with idiopathic dilated cardiomyopathy.*

Source: Grimm W, et al. *Circulation*. 2003;108: 2883-2891.

In this paper, Grimm and colleagues report on the usefulness of noninvasive testing to predict risk for arrhythmias in patients with idiopathic dilated cardiomyopathy. The data are from the Marburg Cardiomyopathy Study, a prospective study of the natural history of patients with idiopathic dilated cardiomyopathy. Patients were eligible for the study if they were aged 16-70 with a left ventricular ejection fraction of ≤ 45% and a left ventricular end diastolic diameter > 56 mm by echocardiography. They could not be in New York Heart Association class IV heart failure, have a history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF) or unexplained syncope, be receiving class I or class III antiarrhythmic drugs that could not be withdrawn, or be pacemaker dependent. Thorough investigation had revealed no specific etiology for their cardiomyopathy. After enrollment in the study, patients underwent signal-averaged electrocardiography, 24-hour ambulatory ECG monitoring, heart rate variability, and baroreflex sensitivity analyses and testing for microvolt T wave alternans. QTc dispersion was determined from standard electrocardiograms. Patients were then followed perspectively for 52 ± 21 months. Only 3 patients were lost to follow-up during this period. The primary end points were major arrhythmic events, defined as spontaneous sustained VT, VF, or sudden death, and heart transplantation-free survival. Univariate and multivariate Cox regression analyses were used to evaluate the association between these 2 primary outcome measures and the baseline variables.

The study enrolled 343 of 463 screened patients with idiopathic dilated cardiomyopathy. Of these, 263 patients were in sinus rhythm at study entry, and 80 patients were in atrial fibrillation. During follow-up, major arrhythmic events were observed in 46 patients, including sudden death in 23 patients and sustained VT or VF in another 23 patients. There were 49 deaths (14%) during follow-up, and 10 patients underwent heart transplantation. Among the

patients in sinus rhythm at study entry, left ventricular end diastolic diameter, left ventricular ejection fraction, nonsustained ventricular tachycardia, and an indeterminate microvolt T wave alternans test showed a significant association with major arrhythmic events during follow-up. However, after multivariate analysis, only left ventricular ejection fraction remained a significant independent predictor of major arrhythmic events. There was an increase in relative risk of 2.28 per 10% decrease in ejection fraction. There was also a trend toward increased risk in patients who were not treated with beta-blockers at study enrollment and for patients with nonsustained VT on the baseline 24-hour ambulatory ECG. On univariate analysis, New York Heart Association class III heart failure, digitalis use, left ventricular end diastolic diameter and left ventricular ejection fraction, an abnormal signal averaged ECG, frequent ventricular premature beats, and decreased baroreflex sensitivity all showed a significant association with death or the need for transplantation. However, multivariate analysis showed that only left ventricular ejection fraction remained a significant predictor of transplantation-free survival with a relative risk of 2.51 per 10% decrease in ejection fraction. As with arrhythmic events, there was a trend toward higher transplantation-free survival in patients with beta-blocker therapy. These predictors were also examined in the 80 patients with atrial fibrillation at study entry. On multivariate analysis, only left ventricular ejection fraction and lack of beta-blocker use were significant predictors of major arrhythmic events and transplantation-free survival.

Grimm et al concluded that left ventricular ejection fraction is the most important risk factor for both arrhythmic events and transplantation-free survival in patients with idiopathic dilated cardiomyopathy. The value of the remaining noninvasive tests was limited.

COMMENT BY JOHN DiMARCO, MD, PhD

This important paper by Grimm et al points out once again that ejection fraction is the most powerful predictor of outcome in patients with heart failure. Although all of the noninvasive studies used in this trial have been reported to be effective risk predictors in smaller series, this large prospective study shows that they provide only a small amount of additional information beyond ejection fraction for predicting either arrhythmic events or survival. This both helps and hurts clinicians. Ejection fraction is a simple value that is available in almost all patients. However, all of the patients in this study had depressed ejection fractions. Although it appears that risk increases in inverse proportion to the ejection fraction, there is no cut-off point that identifies high- and low-risk groups. Unfortunately, none of the tests examined seemed to be very helpful in further sorting out individual risks. ■

More Hazards of Air Travel

ABSTRACT & COMMENTARY

Synopsis: *There is an association between long-distance air flights and venous thromboembolism, but the role of traditional risk factors and prophylactic measures requires more study.*

Source: Hughes RJ, et al. *Lancet*. 2003;362:2039-2044.

VIRCHOW HYPOTHESIZED THAT BLOOD STASIS IS AN important factor in venous thrombosis, and it undoubtedly is a major factor in the observed association between air travel and venous thromboembolism. However, the importance of other risk factors and the precise frequency of air travel-related thromboembolism are uncertain. Thus, Hughes and colleagues in New Zealand took advantage of their geographic isolation to study this problem by enrolling volunteers traveling at least 4 hours by air who were going to return within 6 weeks. Excluded were those with previous venous thromboembolism, on anticoagulants, post-major surgery within 6 weeks, with cancer within 6 months, with renal insufficiency, or pregnant. Enrollment stopped at 1000 subjects. All had baseline D-dimer studies, and 83 were excluded because of elevated values. Another 39 failed to return for their follow-up visit, leaving a total study population of 878. All subjects were evaluated clinically and told to keep a diary about their pre-, post-, and in-flight activities. Upon return they were contacted within 72 hours for blood work including D-dimer, thrombophilic risk factors, and anticardiolipin antibodies. D-dimers were repeated at 2 weeks and 3 months after travel, and any positive values or symptoms suggestive of venous thrombosis were evaluated further by lower extremity ultrasonography, pulmonary CT angiography, or ventilation perfusion scintigraphy.

Results

The frequency of confirmed venous thromboembolism (VTE) was 1% (9/878)—4 with pulmonary emboli, 3 with proximal, and 2 with distal lower limb deep venous thrombosis. The mean total duration of air travel was 39 hours, most of which was in economy class (about 80%). With total air travel of ≤ 24 hours, 10% of subjects used compression stockings and when total air travel exceeded 24 hours, 18% did. Of the 112 subjects who were evaluated for venous thromboembolism, 76 were studied on initial return contact, 30 at 2 weeks, and 8 at 30 days. All of the subjects with confirmed VTE had a positive D-dimer at the initial review; 6 had risk factors for VTE pre-travel; 2 had

thrombophilic abnormalities discovered in the post-travel testing; 2 traveled exclusively in business class; 5 used aspirin; and 4 wore compressive stockings. When those with VTE were compared to those without, there was no difference in length of travel (42 vs 39 hours), but no one with a total travel duration < 24 hours had VTE. Hughes et al concluded that there is an association between long-distance air flights and VTE, but the role of traditional risk factors and prophylactic measures requires more study.

COMMENT BY MICHAEL H. CRAWFORD, MD

The major finding of this study is that long-duration air travel is associated with VTE even in patients with low to moderate risk, since high-risk patients were excluded. VTE was associated with total flight durations > 24 hours. Since the longest flight known from New Zealand is 14 hours, risk was associated with multiple flights within the 6-week window of the study. Since patients were studied when they returned, Hughes et al do not know which flight was the culprit. Two subjects were evaluated after outward flights because of symptoms suggesting VTE, but neither had VTE confirmed. Thus, their data suggest that most VTE events occur after multiple flights within 6 weeks, usually after return from the trip.

The value of prophylactic measures was difficult to determine. One in 6 subjects used compressive stockings and almost one-third were on aspirin, which suggests that the study group may have been better informed than the more general flying public about the risks of VTE. Thus, the incidence of 1% in this study may have been an underestimate of the risk of VTE with total air travel > 24 hours. Also, the value of in-flight exercise, hydration, avoidance of alcohol, and other popular prophylactic measures could not be determined. However, some patients with documented VTE did use compressive stockings and aspirin and flew business class, so it is unlikely that these 3 measures are completely preventative. The only sure-fire preventative strategy was to not take air trips lasting > 24 hours total. ■

Preventing Syncope

ABSTRACT & COMMENTARY

Synopsis: *Water ingestion increases the tolerance to upright posture by increasing peripheral vascular resistance and may serve as a simple prophylactic measure against syncope.*

Source: Lu C, et al. *Circulation*. 2003;108:2660-2665.

Syncope is a common problem that complicates simple procedures such as blood donation. Since most forms of syncope involve an abnormal vasovagal response, Lu and colleagues tested the hypothesis that simple water ingestion would be preventative. They studied 22 healthy subjects without a history of syncope by head-up tilt table testing at 60° for 45 minutes or until syncope occurred. Each subject was tilted twice on separate days and randomized to 16 oz of water ingestion 5 minutes before tilting or nothing on the 2 days. All tilting was done in the morning after an overnight fast. Tilt table syncope was defined as systolic blood pressure < 70 mm Hg and heart rate < 50 beats/min. Tilt table presyncope was defined as a fall in the systolic blood pressure > 30 mm Hg with a decrease in heart rate of > 10 beats/min or a > 30 beats/min fall in heart rate with a > 10 mm Hg fall in systolic pressure. The primary end point was time until syncope. During the first 30 minutes of tilt, 8 of 22 without water experienced presyncope, whereas only 1 of 22 who had water did (P = .016). Water ingestion blunted the tachycardia associated with tilting (P < .001) and accentuated the increase in total peripheral resistance (P = .012). The subjects who ingested water tolerated head-up tilt 26% longer than those who did not (41 vs 33 minutes; P = .011). Water also attenuated the increase in hematocrit seen with tilting (P = .065). Plasma catecholamines increased with tilting but were largely unaffected by water ingestion. Lu et al concluded that water ingestion increases the tolerance to upright posture by increasing peripheral vascular resistance and may serve as a simple prophylactic measure against syncope.

COMMENT BY MICHAEL H. CRAWFORD, MD

Current therapy for vagally mediated syncope is expensive, rife with adverse effects, and of questionable efficacy. Consider what we offer patients—drugs such as aldosterone agonists and beta-blockers and even pacemakers for some. All this for a symptom that may never occur again or be of minor significance. On the other hand, as Lu et al point out, syncope has important medical and societal significance under certain circumstances, such as blood donation and space travel. Thus, a simple, efficacious prophylactic therapy would be of value.

Is water ingestion the answer? Perhaps, since it did have a marked hemodynamic effect during tilt testing. Interestingly, previous studies by the same group have shown that similar volumes of intravenous dextrose solutions did not protect against orthostatic symptoms. Also, they have shown that water ingestion can increase systolic blood pressure up to 11 mm Hg and may represent a significant unrecognized cause of blood pressure fluctuation between visits. In addition, this suggests that studies of pharmacologic agents for hypertension may be influenced

by taking the drugs on an empty stomach with water.

There are some potential limitations to the study. The crossover design resulted in a noticeable increase in orthostatic tolerance on the no-water day when it was second vs first. Also, there is no placebo for water ingestion, which may have influenced the results. Finally, no subject ever reached the primary end point of syncope as defined a priori. Finally, the mechanism of increased peripheral vascular resistance observed is not clear from this study. Plasma catecholamine levels were not influenced by water ingestion, but dopa levels were. Since the gastrointestinal tract is a major source of dopa, this may explain why water ingestion, but not intravenous infusion, increases peripheral vascular resistance. ■

Rosuvastatin vs Atorvastatin

ABSTRACT & COMMENTARY

Synopsis: *In heterozygous familial hypercholesterolemia patients, rosuvastatin produced significantly greater reductions in LDL cholesterol, increases in HDL cholesterol, beneficial changes in other lipid values, and achievement of NCEP cholesterol goals than observed with equivalent doses of atorvastatin with a similar adverse event profile.*

Source: Stein EA, et al. *Am J Cardiol*. 2003;92: 1287-1293.

ROSUVASTATIN IS A NEW STATIN WHOSE EFFICACY was compared to that of atorvastatin in 623 patients with heterozygous familial hypercholesterolemia. The study design was 3:1 weight randomized to the new drug, double-blind, parallel group, and forced titration to 80 mg per day. There was a 6-week run-in period of no cholesterol-lowering drugs and the National Cholesterol Education Program (NCEP) step I diet. Then randomization was begun with 20 mg/d of each drug for 6 weeks, then 40 mg/d for 6 weeks, and finally 80 mg/d for 6 weeks. Subsequently, patients were offered an open-label, long-term extension on rosuvastatin 80 mg/d. The primary end point was change in LDL cholesterol at 18 weeks. Mean LDL cholesterol after the 6-week run-in phase was 292 mg/dL in the rosuva group and 288 in the atorva group (P = NS); HDL cholesterol was 48 and 47 and triglycerides were 160 and 159, respectively. Rosuva reduced LDL more than atorva (-58 vs -50%; $P < .001$) and increased HDL more (12 vs 3%, $P < .001$). Also, apolipoprotein B was reduced more and apolipoprotein A-1 was increased more by rosuva. Changes in triglycerides were similar with the 2 agents. The percentage of patients achieving NCEP LDL cholesterol goals was higher on rosuva (58 vs 44%; $P < .001$). Both agents reduced high sensitivity CRP similarly. Both drugs were well tolerated: adverse events resulting in drug discontinuation were 3% and 2%, with myalgia, asthenia, and nausea being most common. Clinically significant increases in alanine aminotransferase (> 3× upper limit of normal on 2 consecutive occasions) were observed in < 1% of patients. No clinically relevant increases in creatine kinase (> 10× upper limit of normal) occurred. Stein and associates concluded that in heterozygous familial hypercholesterolemia patients, rosuvastatin produced significantly greater reductions in LDL cholesterol, increases in HDL cholesterol, beneficial changes in other lipid values, and achievement of NCEP cholesterol goals than observed with equivalent doses of atorvastatin with a similar adverse event profile.

■ **COMMENT BY MICHAEL H. CRAWFORD, MD**

For those patients who could not achieve cholesterol-lowering goals with 80 mg/d of atorvastatin, we used to have cervistatin until it was removed from the market due to excessive adverse events. Fortunately, we now have another potent statin alternative that seems to have a low incidence of adverse events. Even in the open-label extension, the incidence of clinically evident myopathy was < 1%. This is good news given the bad experience with cervistatin. What is also remarkable is the robust increase in HDL cholesterol with this drug (12%). Triglyceride values were also reduced but by a similar amount on both drugs. Whether these impressive changes in the lipid profile will translate to a reduction in clinical events that is greater with rosuvastatin remains to be proven. Interestingly, high-sensitivity CRP was reduced similarly by both agents. ■

BNP and Diastolic Dysfunction

ABSTRACT & COMMENTARY

Synopsis: *In ambulatory hypertensive patients with heart failure symptoms but normal cystolic LV function, BNP is higher in those with diastolic dysfunction. However, it is usually in the normal range and thus, it is of little diagnostic value.*

Source: Mottram PM, et al. *Am J Cardiol*. 2003;92: 1424-1438.

B-TYPE NATRIURETIC PEPTIDE (BNP) LEVELS ARE GAINing in popularity as a screening test for heart failure

in patients with suggestive symptoms. Although there are reports that BNP is elevated in systolic as well as diastolic dysfunction, its diagnostic use for the latter is unclear. Thus, Mottram and associates prospectively studied 72 ambulatory patients with hypertension under treatment and exertional dyspnea. Patients were excluded if their symptoms warranted hospitalization; if ischemic heart disease was present by history or resting echo; if respiratory disease was present; if significant valvular disease was detected; or if their left ventricular ejection fraction was < 50%. BNP values were classified as normal or abnormal based upon the upper limit of normal adjusted for age and sex. Left ventricular (LV) diastolic function was classified as either normal, impaired relaxation, pseudonormal, or restrictive using standard Echo-Doppler criteria. In addition, tissue Doppler was used to measure LV strain and strain rate. Also, Echo and blood pressure measurements were used to calculate LV mass and wall stress. By the standard Doppler criteria, about half of the patients had isolated diastolic dysfunction, most had impaired relaxation, and a few had pseudonormal filling. Those with normal diastolic function were younger, but there was no difference in LV mass or blood pressure between the 2 groups. BNP levels were higher in those with diastolic dysfunction (46 vs. 20 pg/mL; P = .004) and were independently positively associated with systolic blood pressure, strain rate, left atrial area, systolic wall stress and age, and negatively with diastolic blood pressure and mitral annular late diastolic velocity. BNP levels were in the normal range in 97% of the patients with normal diastolic function but also in 79% of the patients with abnormal diastolic function. Mottram et al concluded that in ambulatory hypertensive patients under treatment with symptoms of heart failure and normal systolic LV function, BNP is elevated with diastolic dysfunction but is usually within the normal range and, therefore, is of little diagnostic value.

COMMENT BY MICHAEL H. CRAWFORD, MD

BNP is the new troponin. Everyone in the emergency department and most hospitalized patients now get them done in the hopes of a positive value, which ensures a transfer to the cardiology service. Thus, it is welcome news that most ambulatory patients with hypertension, dyspnea, and a mild LV relaxation abnormality have a normal value. However, more than 60% of the few patients with more advanced diastolic dysfunction did have elevated values. These results are consistent with other studies done in hospitalized patients, which showed a high incidence of elevated BNP in diastolic heart failure patients. Somewhat disturbing was the observation confirmed in this study that BNP is related to the blood pressure level and perhaps the pulse pressure. Thus, uncontrolled hypertension may cause elevations and provoke inappropriate hospital admissions.

The major weakness of this study is that it included few patients with advanced diastolic dysfunction. It is not surprising that in a group of ambulatory patients, not considered sick enough for admission, with symptoms only on exertion, that Echo-Doppler estimated filling pressures were normal, as was BNP. A major strength of this study was the sophisticated Echo-Doppler parameters measured; this was a state of the art study. Unfortunately, there were few associations between any of these sophisticated measures and BNP. By multivariate analysis, the only sophisticated parameter of diastolic function related to BNP was mitral annular late diastolic velocity, which is a measure of the vigor of atrial function and LV stiffness. BNP was independently related to more mundane measures such as blood pressure, age, left atrial size, and systolic wall stress. In summary, it would appear that the measure of BNP levels should be restricted to patients with marked symptoms, requiring hospitalization, where an elevated value will point to a cardiovascular cause. Thus, there may be little reason for an emergency department physician to order a BNP level. It can be done by the admitting physician in those requiring hospitalization. ■

Systemic Lupus Erythematosus and Accelerated Atherosclerosis

ABSTRACTS & COMMENTARY

Synopsis: *SLE now joins the list of conditions that are associated with an increased risk of the development of vascular disease, particularly CAD.*

Sources: Roman MJ, et al. *N Engl J Med*. 2003;349: 2399-2406; Asanuma Y, et al. *N Engl J Med*. 2003; 349:2407-2415; Hahn BH, et al. *N Engl J Med*. 2003; 349:2379-2380.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) SHOULD now be established as an additional major risk factor for the development of coronary atherosclerosis. Thus, along with chronic kidney disease and metabolic syndrome, physicians must be alert and aggressive with respect to identification of all coronary artery disease (CAD) risk factors, as well as preventive measures for SLE individuals. Two reports published simultaneously,

one from Medical College of Cornell University (Roman and associates), and the other from Vanderbilt University School of Medicine (Asanuma and associates), unequivocally confirm that SLE is associated with premature vascular disease, often asymptomatic, and this is a particularly important problem in younger individuals with SLE. The studies included SLE patients and matched controls. The Cornell group used carotid ultrasonography for assessment of vascular disease; 197 SLE patients and matched controls were included. The Vanderbilt group studied 65 patients with SLE and matched controls and used electron beam computed tomography (EBCT) for coronary calcification as the primary screening method to identify CAD. Both studies included a variety of serum markers and evaluated the risk of SLE for vascular disease using conventional risk factors, including gender, age, and lipids. In addition, the Cornell group assessed SLE-specific therapy as a potential factor in increasing or decreasing CAD risk. They used sophisticated laboratory analyses, including tests for double-stranded DNA antibodies, Smith antibodies, ribonuclear protein, and antiphospholipid antibodies. Interleukin-6, TNF55, and 75 receptors were assayed; in addition, VCAM-1, ICAM-1, and homocysteine levels following a methionine load were part of the evaluation process. The Vanderbilt group relied on imaging with EBCT and measured only standard lab tests, including LP(α) lipoprotein and homocysteine.

The results from the 2 studies are concordant and unequivocally indicate that SLE is a potent risk factor for early CAD and vascular disease, no matter the age and gender. The risk ratios were considerable, and in younger SLE women, were estimated to be up to 50 times the risk of having CAD when compared to matched controls. Assessment of plaque by carotid ultrasound was 2-3-fold more likely in the SLE patients and 5-6 times greater in SLE individuals younger than 40. Intimal-medial thickness, however, was less and luminal diameter greater in SLE patients than controls. Serologic markers of lupus were less common in those individuals with plaque than those without. Antidouble-stranded DNA and antiphospholipid antibodies were no different between those with and without plaque; anticardiolipid antibodies were less common in SLE patients with carotid plaque. Current or prior prednisone therapy was less likely to be associated with plaque, and cyclophosphamide and hydroxychloroquine use was lower in individuals with plaque. Inflammatory markers were not different, including CRP, IL-6, TNF receptors, CD40 ligand, ICAM-1, and VCAM-1. Major predictors of atherosclerosis in SLE patients in the Cornell study included age, disease duration, and a damage-index score. Negative predictors included cyclophosphamide use, anti-SM antibody, and hydroxychloroquine use. In the Vanderbilt patients (EBCT expertise was provided by Dr. P. Raggi of Tulane University School of Medicine), coronary artery calcifications was more frequent in SLE patients (20 of 65) than in controls (6 of 69; $P = .002$). The mean Agatston calcification score in the lupus patients was 69 vs 9 in the controls; lipid profiles were not abnormal in the SLE patients, although levels of triglycerides and homocysteine were elevated. Coronary calcifications were common in older males, but measurement of disease activity in the lupus individuals were similar in those with and without coronary calcification. Coronary calcification was more common in younger patients with SLE than controls, increasingly with age. The Vanderbilt authors concluded that "asymptomatic atherosclerosis is frequently present in patients with lupus and cannot be predicted by the presence or absence of other cardiovascular risk factors." This is essentially similar to the Cornell conclusions. Overall, SLE patients had little differences in their lipid profiles from controls. The Vanderbilt, but not the Cornell, cohort tended to be hypertensive when compared to controls.

The Cornell investigators suggest that chronic inflammation may be a major player in atherogenesis in the SLE population. An increased prevalence of atherosclerosis was seen in individuals with longer duration of SLE, a higher damage-index, and in general, less aggressive immunosuppressant therapy. However, markers of inflammation were not increased in those individuals with carotid plaque vs without. The Cornell investigators believe "the presence of plaque is a more potent predictor of clinical events, particularly myocardial infarction, and is a better index than the intimal-medial thickness." They postulate that there are essentially 2 patterns of SLE: one with a protracted course and "less virulent disease that fosters atherosclerosis," and the other dominated by autoimmunity and a more aggressive clinical course, resulting in a greater likelihood of receiving immunosuppressive therapy. They emphasize the "significant negative ratio between the use of hydroxychloroquine and the presence of atherosclerosis," and conclude, "SLE is associated with an increased prevalence of atherosclerosis, which was most striking in young patients." They point out that traditional CAD risk factors cannot explain the accelerated course; the data from the EBCT cohort are congruous.

COMMENT BY JONATHAN ABRAMS, MD

These 2 publications unequivocally resolve the long-standing controversy as to whether having SLE and/or being treated with steroids over a long period of time

are related to the development of atherosclerosis. The data in these case controlled reports are very convincing. Cerebrovascular atherosclerosis was assessed by carotid ultrasound and coronary atherosclerosis by coronary calcium score. The more sophisticated Vanderbilt report provides a great deal of laboratory analysis, which turned out not to be particularly helpful in differentiating high- vs low-risk individuals. Nevertheless, there were certain differences in the prevalence of a number of markers in patients with and without carotid plaque that do support the Cornell authors' hypothesis that SLE may be associated with 2 divergent clinical courses. It is unlikely that the carotid or the coronary imaging techniques are sensitive enough to allow for much greater distinctions among SLE patients regarding the subsequent risk of CAD. The total number of patients studied with SLE in the 2 trials is approximately 250, a clinical base that makes these observations valid. However, differentiation of plaque in the carotid vessels, or EBCT calcium scores, particularly when not very high, do not have sufficient specificity and sensitivity to rule in or out the presence of vascular disease in a given patient with SLE.

The implication for primary care physicians and rheumatologists, as well as cardiologists, is quite simple: very aggressive CAD risk factor strategies should be employed in SLE subjects. While there are no data confirming that aggressive lipid or blood pressure control will make a difference, it is likely to be the case; given the virulence of chronic SLE, it makes sense to reduce the CAD risk factor burden as much as possible. Furthermore, SLE patients, particularly the younger ones, probably should be tested for LP(a) and homocysteine. If homocysteine is elevated in SLE patients, therapy with folate and B vitamins would appear to be appropriate.

In conclusion, SLE now joins the list of conditions that are associated with an increased risk of the development of vascular disease, particularly CAD. These include chronic kidney disease, the metabolic syndrome, rheumatoid arthritis, and even uncomplicated type II diabetes. Many physicians do not recognize that all such individuals are at substantially increased risk and demand aggressive risk factor assessment, as well as therapeutic approaches. Although SLE is a very potent inducer of atherosclerosis, lupus is relatively uncommon when compared to these other conditions. Nevertheless, the recognition that a diagnosis of SLE, whether freshly made or chronic, should trigger a search for vascular disease markers and risk factors, is news for the general medical community and deserves our attention. ■

CME Questions

6. Nontraditional risk factors for coronary artery disease include all but which of the following?
a. Rheumatoid arthritis
b. Systemic lupus erythematosis
c. Chronic renal insufficiency
d. Chronic hepatitis

7. Elevated C-reactive protein levels are predictive of all but which of the following?
a. Coronary artery atherosclerosis
b. Stroke
c. Deep venous thrombosis
d. Acute myocardial infarction

8. Which of the following is independently predictive of ventricular tachyarrhythmias in dilated cardiomyopathy patients?
a. Ejection fraction
b. PVCs on Holter monitor
c. Absence of ACE inhibitor therapy
d. b and c

9. Venous thromboembolic events are more common under which air travel circumstances?
a. Economy class seat
b. Total air travel > 24 hours
c. Lack of compression stockings
d. Lack of aspirin use

10. Vasovagal syncope can be prevented by which of the following?
a. Avoidance of emotional situations
b. Intravenous fluids
c. Ingestion of water
d. Avoidance of prolonged sitting

11. Which statin raises HDL considerably more than the others?
a. Rosuvastatin
b. Atorvastatin
c. Simvastatin
d. Pravastatin

12. Most patients with which condition have elevated BNP values?
a. Asymptomatic mild diastolic dysfunction
b. Acute renal colic
c. Congestive heart failure
d. Asthma

Answers: 6(d); 7(c); 8(a); 9(b); 10(c); 11(a); 12(c)

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Clinical Cardiology Alert*. Send your questions to: Christie Petrone, *Clinical Cardiology Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Clinical Cardiology Alert* via the internet by sending e-mail to christie.petrone@thomson.com. ■

PHARMACOLOGY WATCH

Valacyclovir Reduces Genital Herpes Transmission

A once-a-day dose of a valacyclovir reduces the rate of transmission of genital herpes (HSV-2) from an infected partner to an uninfected susceptible partner, according to a new study. The study group included 1484 immunocompetent, heterosexual, monogamous couples in which 1 partner had symptomatic genital HSV-2 and the other was susceptible to HSV-2. The infected partners were randomized to valacyclovir 500 mg once daily or placebo for 8 months. At the end of the study period, clinically symptomatic HSV-2 infections developed in 4 of 743 susceptible partners in the valacyclovir group vs 16 of 741 in the placebo group (HR, 0.25; 95% CI, 0.08-0.75; $P = 0.008$). Overall acquisition of HSV-2, including asymptomatic infections, was observed in 14 partners in the valacyclovir group compared to 27 in the placebo group (HR, 0.52; 95% CI, 0.27-0.99; $P = 0.04$). Valacyclovir significantly cut down on viral shedding in the infected partner and also significantly cut down on the rate of HSV-2 outbreaks in the infected partner. The authors caution that 37% of couples in the study did not use condoms even though counseled to do so, and that condom use and abstinence during attacks are the most effective methods of preventing transmission (*N Engl J Med*. 2004;350:11-20).

Erythropoietin Safe for Cancer Patients?

A fascinating news item published in the December 17 issue of *Journal of the National Cancer Institute* raises the question of whether erythropoietin is safe to use in cancer patients. According to the news report, several studies suggest that many cancer cells have erythropoietin receptors that may be stimulated by erythropoietin injections. Erythropoietin is commonly given to cancer patients to treat chemotherapy-related, or cancer-related anemia. Two recent trials have shown that erythropoietin use is associated with decreased survival in some cancer patients according to the news report. Erythropoietin receptors have been found on head and neck cancer cells, prostate cancer cells, and ovarian cancer cells, as well as breast, renal, and uterine cancer cells. Preliminary data suggest that some of these cancers may actually proliferate in the presence of erythropoietin. The association between erythropoietin and decreased survival for some cancer patients needs further evaluation (*J Natl Cancer Inst*. 2003;95:1820-1821).

WHI, ALLHAT Trials Still Spur Research

It appears that 2 landmark studies have significantly changed practice patterns in this country. The Women's Health Initiative (WHI) study published in July 2002, and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) published in April 2000 both showed negative results with some of the most widely prescribed pharmaceuticals in this country. WHI suggested that combined estrogen/progesterone increases the risk of breast cancer and cardiovascular disease in postmenopausal women. Researchers from Stanford looked at prescription trends in hormone therapy from 1995 to July 2003. Annual hor-

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mone therapy prescriptions increased dramatically between 1995 in 1999 and then remained stable through June 2002. Following publication of the WHI in July 2002, prescriptions for Prempro, the combination estrogen/progesterone used in the study, declined by 56%. New prescriptions for conjugated estrogen also declined significantly. Small increases were seen with topical estrogens and low-dose estrogen preparations over the same time period (*JAMA*. 2004;291:47-53). ALLHAT was terminated early and the results released in December 1999, and published in April 2000 because early results showed that doxazosin, an alpha-blocker, was significantly inferior to diuretics with respect to preventing stroke, congestive heart failure, and a composite of other cardiovascular outcomes. The same group from Stanford reviewed alpha-blocker prescription trends from 1996 to 2002. Steady increases in alpha-blocker prescriptions were seen in between 1996 and 1999, but new prescriptions for the drugs declined 26% between 1999 and 2002. Changes in pricing, generic version, drug promotion, or competition did not have a confounding effect. The authors conclude that modest declines in alpha-blocker prescribing were seen after publication of ALLHAT (*JAMA*. 2004;291:54-62).

Alpha-Blockers Useful in BPH Treatment

Alpha-blockers are useful in treatment with benign prostatic hyperplasia (BPH). Now a new study shows that the combination of the 5-alpha-reductase inhibitor finasteride (Proscar) with an alpha-blocker may be superior to either drug alone in treating BPH. Researchers randomized 3047 men to placebo, doxazosin, finasteride, or combination therapy with the end point of clinical progression of BPH. Clinical progression was defined as an increase in the American Urologic Association symptom score of these 4 points, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection. Both doxazosin and finasteride significantly reduced clinical progression (doxazosin-39% risk reduction, $P < 0.001$; finasteride 34% risk reduction $P = 0.002$) compared to placebo. The combination of doxazosin and finasteride however resulted in a 66% risk reduction compared with placebo ($P < 0.001$). Mean follow-up was 4.5 years. The authors conclude that long-term combination therapy with doxazosin and finasteride was safe and significantly reduced the risk of clinical progression of BPH and was superior to either drug alone (*N Engl J Med*. 2003;349:2387-2398).

T4 Alone is OK for Hyperthyroidism Therapy

Hypothyroidism is one of the most common clinical disorders in general practice. Controversy about replacement therapy has raged for years regarding the need for liothyronine (T3) in addition to thyroxine (T4). A new study from Bethesda suggests that thyroxine alone is optimal therapy. In this randomized, double-blind, placebo-controlled trial, 46 hypothyroid patients were randomized to their usual dose of levothyroxine, or combination therapy in which their dose of levothyroxine was decreased by 50 µg/d, and liothyronine 7.5 µg was given twice daily for 4 months. TSH levels were followed and remained stable throughout the study. The main outcomes were scores on the hypothyroid specific health-related quality of life questionnaire, body weight, serum lipid levels, and 13 neuropsychological tests before and after treatment. After 4 months, body weight and serum lipid levels were unchanged in both groups. Quality of life scores improved in both groups (23% improvement levothyroxine group [$P < .001$], 12% improvement combination group [$P = .02$]). There is no statistical difference in neuropsychological testing between the 2 groups except for better performance in the Grooved Peg Board test in the levothyroxine group. The authors conclude combination therapy with levothyroxine plus liothyronine offers no advantage over single therapy with levothyroxine for the treatment of hypothyroidism (*JAMA*. 2003;290:2952-2958).

FDA Ban on Ephedra Awaits Final Ruling

The FDA has issued a consumer alert, banning the dietary supplement ephedra. The ban will become effective 60 days after the publication of a final rule stating that dietary supplements containing ephedra represents an unreasonable risk of illness or injury. This unprecedented move, the first time the FDA has banned a supplement, comes after several high-profile deaths linked with ephedra including professional athletes. Overall, the FDA has reports of 155 deaths associated with ephedra and more than 16,000 complaints. The drug is commonly used for weight loss and is present in many over-the-counter preparations. It is also widely used in Chinese herbal medicine practices, where it is known as Ma huang, and has been a staple of therapy for thousands of years for a variety of ailments including asthma and fever. The FDA has allowed an exemption for practitioners of Chinese medicine as long as is not used in high dose for weight loss. ■