Providing Evidence-based Clinical Information for 22 Years

CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

Thomson American Health Consultants Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Chronic Kidney Disease

ABSTRACT & COMMENTARY

DURING THE LAST FEW YEARS, CHRONIC KIDNEY DISEASE (CKD) HAS been increasingly recognized as a significant risk factor for the development of cardiovascular disease. An American Heart Association Scientific Statement reviewing this subject was published last fall.[1] This paper pointed out that NCEP-ATPIII did not include renal abnormalities as part of the risk factor spectrum impacting cholesterol management guidelines, although the National Kidney Foundation has previously published practice guidelines regarding dyslipidemia in CKD patients. Two recent reports in the *New England Journal of Medicine* further confirm a link between renal abnormalities and the subsequent development of significant cardiovascular disease (CVD), as well as increased morbidity and mortality. The degree of awareness of these issues in the cardiology community is unclear; it is imperative that physicians recognize that evidence of CKD, based on glomerular filtration rate (GFR), creatinine, or albuminuria, are now recognized to be of clinical significance.

A large registry from Kaiser Permanente of Northern California reports a significant "independent graded association" between decreased GFR and the risk of CVD morbidity as well as death.[2] This study utilized longitudinal measures of estimated GFR, using the Modification of Diet in Renal Disease (MDRD) GFR equation. All adults over 20 were entered into a Kaiser Permanente Renal Registry; those with significant renal disease were excluded. The initial measurement of GFR was established as baseline; changes during follow-up were estimated from serum creatinine determinations. GFR was normalized to body surface area (1.73 m). Serum albumin and proteinuria were measured, and socioeconomic status was assessed. The primary end point was total mortality, CV events, and hospitalizations from January 1996 to December 2000. Event rates were adjusted for age and the independent effect of GFR. Multiple variables that affect GFR outcomes were entered into the final model, including age, cardiovascular events, and hospitalization. The cohort included 1.12 million adults; the median number of serum creatinine measurements were 3. Estimated GFR was assessed in all using the MDRD equation.

Results: Individuals who had a decrease in GFR had a higher prevalence of CV disease, proteinura, diabetes, and hypertension, and were older than those with a normal GFR. The median follow-

VOLUME 23 • NUMBER 11 • NOVEMBER 2004 • PAGES 81-88

up was 2.8 years, amounting to 3.132 million person years. The main finding was that age-standardized rates of death, CV events, and hospitalizations increased substantially with progressively lower GFR. A baseline GFR of = 60 mL per minute per 1.73 m^2 was the reference. After adjustment for multiple factors, including social demographic characteristics and the presence of prior CV disease, it was found that "the risk of death increased sharply as estimated GFR declined"; risk increased 17% in the GFR 45-59 group; an increase 343% was found with an initial GFR of < 15. Repeat hospitalizations increased proportionally to the decrease in the GFR. Proteinuria was an independent predictor for death, cardiovascular events, and hospitalization. A greater risk of an adverse event increased markedly once GFR fell below 45mL per minute per 1.73 m^2.

Sarnak and colleagues cite other surveys that have linked increased CVD risk with higher creatinine levels including NHANES II, where a GFR < 70 was associated with a 68% increased risk of death from any cause, and a 50% increase risk of death from CV, compared to a GFR > 90. In the Kaiser cohort, the relationship between GFR and major end points was not linear, with risk rising substantially at a GFR < 60, and an even sharper decline when baseline GFR was < 45.

Discussing the potential causes for the relationship between CKD and mortality and cardiovascular disease, Sarnak et al point out that low GFR individuals had a greater prevalence of pre-existing CV disease, CV risk factors, and co-existing morbid conditions. The published literature suggests increased inflammatory markers, abnormal lipoprotein levels, elevated homocysteine levels, increased coagulability, anemia, endothelial dysfunction, and increased vascular calcification. Sarnak et al suggest that their results are more generalizable than most other reports due to the very large and ethnically diverse population. Furthermore, they emphasize the usefulness of serial estimates of GFR as morbid, and mortal events are markedly increased GFR < 45.

Another publication comes from the VALIANT Trial, a randomized study assessing the usefulness of an ACE inhibitor vs anangiotensin receptor blocker post acute myocardial infarction.[3] In this study, 14500 patients with acute MI and heart failure were randomized to captopril, valsartan, or both. GFR was measured by the MDRD equation, and a large number of variables were assessed. Subjects were randomized up to 12 days post MI, and had to have LV systolic dysfunction, clinical, or X-ray evidence of heart failure. Mean follow-up was 24.7 months. Baseline creatinine had to be < 2.5 mg/dL. Results: The primary end point was death from any cause. Multiple secondary end points were assessed. The patients were grouped into GFR strata of > 75% mL/minute/1.73 m^2; 60-74, 45-59, and less than 45. Mortality rose incrementally with each decrement of GFR. Baseline estimated GFR demonstrated a normal distribution, (mean GFR of 70). Thirty-eight percent of 14500 patients had a GFR = 75 at baseline, whereas 28% had an estimated GFR of 45-60, and 11% had a GFR of < 45. CKD criteria were present in 34%, even though creatinine was 2.5 or less at entry. Unadjusted 3-year mortality was 14% in the highest GFR cohort, 20.5% in those with a GFR 60-75, and 45.5% in the individuals with GFR < 45. Event curves diverged early. The composite end point tracked with mortality; all groups with a lower GFR (< 75) had worse outcomes, with a hazard ratio of 1.5 for the lowest GFR cohort. Treatment assignment of study drug had no effect on outcomes. Pre-existing renal disease was common, and as with the Kaiser study, Sarnak et al strongly recommend the routine use of the MDMR equation to calculate GFR.

Anavekar and colleagues point out that the Framingham risk scoring system underestimates cardiovascular risk in CKD patients. Risk factor modification and interventional therapies were lower than the general population. Anavekar et al conclude that in post MI patients, "pre-existing renal impairment should be considered a potent, independent, and easily identifiable risk factor for cardiovascular complications."

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Robert Kimball.
ASSOCIATE MANAGING EDITOR: Leslie Hamlin.
MARKETING PRODUCT MANAGER: Schandale Kornegay.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Clinical Cardiology Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcpub.com
Editorial E-Mail: leslie.hamlin@thomson.com

Subscription Prices

United States
1 year *with* Free AMA Category 1 credits: $319
(Student/Resident rate: $125).

Multiple Copies
Documents are available for multiple subscriptions. For pricing information, please call Steve Vance at (404) 262-5511.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

This CME activity was planned and produced in accordance with the ACCME Essentials.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

This CME activity is intended for the cardiologist. It is in effect for 36 months from the date of the publication.

THOMSON
AMERICAN HEALTH CONSULTANTS

Questions & Comments

Please call **Leslie Hamlin**, Associate Managing Editor, at (404) 262-5416 or e-mail at leslie.hamlin@ thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis. Dr. DiMarco is a consultant for Bayer and Novartis, is on the speaker's bureau for Medtronic and Guidant, and does research for Medtronic and Guidant. Drs. Crawford and Vernon report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Thomson American Health Consultants accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that must meet all ACCME and ANCC requirements.

COMMENT BY JONATHAN ABRAMS, MD

An excellent editorial by Hostetter, in the same issue of the *New England Journal of Medicine*, discusses the issue of whether CKD is a marker or a player, or perhaps both, with respect to CV complications, including death.[4] He points out that CKD individuals "have an excess of traditional risk factors for cardiovascular disease," but that "predisposition. . . persists even after adjustment for the overabundance of standard risk factors." Multiple metabolic and prothrombotic risk are found in CKD. These individuals may be detected by measurements of urinary protein, creatinine, or by the estimated GFR technique. Renal experts have repeatedly pointed out that serum creatinine is an imprecise measure of renal function, depending in part on body mass (eg, young healthy males vs elderly frail females), thus serum creatinine does not adequately indicate whether GFR is depressed. It would appear that no matter how CKD is diagnosed (eg, the estimated GFR formula, serum creatinine, micro or macro albuminura), the diagnosis establishes high risk either because of existing CKD, or because of the multiple non-renal factors that are likely to be deranged in such individuals. The data from the VALIANT Trial suggests that traditional risk factors in this CKD population cannot explain all of the increased risk, and this is echoed by other reports. Thus, for the prevention oriented physician and cardiologist who treat patients with evidence of CKD, the new paradigm is to aggressively treat all identifiable risk factors, and perhaps to lower LDL cholesterol to 100 mg/dL or lower. There is no trial data available to support this recommendation, but it seems reasonable. CKD now joins the list of major coronary risk factors, such as hypertension, smoking, dyslipidia, and diabetes. CKD individuals are often undertreated for these same risk factors, and may be deprived of revasculatrizion strategies due to the concerns of renal embarrassment from contrast during coronary angiography and other complications. The adverse outcomes documented in these reports suggest that a hands off approach to these individuals must be abandoned. ■

References

1. Sarnak MJ, et al. Kidney Disease As a Risk Factor for Development of Cardiovascular Disease. *Circulation*. 2003;108:2154-2169.
2. Go AS, et al. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. *N Engl J Med.* 2004;351:1296-1305.
3. Anevekar NS, et al. Relation Between Renal Dysfunction and Cardiovascular Outcomes After Myocardial Infarction. *N Engl J Med.* 2004:351:1285-1295.
4. Hostetter TH, Chronic Kidney Disease Predicts Cardiovascular Disease. *N Engl J Med.* 2004;351;13: 1344-1345.

Atrial Tachyarrhythmias Following Atrial Fibrillation Ablation

ABSTRACT & COMMENTARY

Synopsis: *Focal left atrial tachycardias are an important complication after pulmonary vein isolation.*

Source: Gerstenfeld EP, et al. *Circulation*. 2004;110: 1351-1357.

PULMONARY VEIN ISOLATION HAS BECOME INCREASINGly popular as a treatment for patients with both paroxysmal and persistent atrial fibrillation. In this paper, Gerstenfield and colleagues address 1 of the more common complications associated with atrial fibrillation ablations.

Gerstenfield et al reviewed data from 341 patients who underwent pulmonary vein isolation for paroxysmal (86%) or persistent (14%) atrial fibrillation. The techniques used by Gerstenfield et al at the initial procedure involved placement of a circular mapping catheter in the pulmonary veins, and a search for atrial fibrillation within the veins. If arrhythmogenic atrial activity was located in 1 of the pulmonary veins, circumferential lesions were placed around the veins to isolate them from the rest of the atrium. No attempt was made to isolate all veins if they didn't manifest arrhythmogenic potentials, nor were left atrial linear lesions used. A total of 955 arrhythmogenic pulmonary veins were isolated in the 341 patients. In the entire group, 68 patients had recurrent atrial fibrillation after ablation, and 10 of the 68 also developed a persistent left atrial tachycardia. These 10 patients returned for electrophysiologic study with mapping and attempt at ablation 5.7 ± 2.8 months after the initial procedure.

Characteristic ECG patterns were seen in the 10 patients with left atrial tachycardias. The ECG revealed regular activation that was positive in the inferior leads in 8 out of 10 patients. Atrial depolarization was predominantly positive in V_1 and remained positive across the precordium in 8 of 10 patients. The surface ECG features of atrial activity could be used to diagnose the pulmonary vein that was the site of origin. For arrhythmias from the left superior pulmonary vein, atrial activity was flat in lead I, of lower amplitude in lead II than in lead III, negative in aVL, and M-shaped in V^1. For right superior pulmonary vein origin tachycardias, the P wave was positive in lead I, was larger in lead II than in lead III, flat to biphasic in lead aVL, and had a late peaking positive wave in V_1.

The site of origin was identified using electroanatomic mapping. A focal origin with a concentric spread of activation was noted in 8 patients. Of these, 6 of the tachycardias originated from partially reconnected pulmonary vein ostia. One patient exhibited a tachycardia that rapidly degenerated to atrial fibrillation rapidly, and therefore, could not be characterized. One patient had a macroreentrant tachycardia that traveled around the left upper and left lower pulmonary vein ostia. In the 8 cases of focal tachycardias, the tachycardia was localized and terminated with radiofrequency energy applied at the site of earliest activation. In the patient with a focal tachycardia that rapidly degenerated to atrial fibrillation, and in the patient with the macroreentrant tachycardia, linear lesions were placed guided by electroanatomic mapping, as well as repeat isolation of the pulmonary veins. After 6.7 ± 2.3 months of follow-up, 9 of the 10 patients remained arrhythmia free. Four of these patients, however, remained on antiarrhythmic therapy.

Gerstenfield et al conclude that focal left atrial tachycardias are an important complication after pulmonary vein isolation. In this series, focal ablation of the tachycardia at the earliest site of activation, reisolation of reconnected pulmonary veins, and antiarrhythmic drugs provided adequate therapy.

COMMENTS BY JOHN P. DiMARCO, MD, PhD

A number of different techniques are currently used for catheter ablation of atrial fibrillation. The technique used in this paper is similar to the approach originally developed by Haissaguerre and colleagues (*Circulation*. 2000,101:1409-1417) which involves mapping of arrhythmogenic activity exiting from specific sites in the left atrium, and isolation of those sites. With that technique, focal breakthrough is the most common failure mechanism that permits late organized tachycardias to develop, as is shown in this paper. The approach of isolation of only arrhythmogenic pulmonary veins however, can be problematic. These arrhythmogenic foci are frequently not reproducible. Permanent electrical isolation may be difficult. Ablation at or beyond the pulmonary veins may be associated with late pulmonary vein stenosis. Because of these limitations, other techniques have been developed. One technique is antral isolation in which the isolating ablation lesions are placed further from the pulmonary veins. An alternate technique proposed by Pappone and colleagues (*Circulation*. 2000;102:2619-2628) uses circular linear lesions that encompass, but are far from, the pulmonary ostia. These latter techniques also can be associated with recurrent left atrial tachycardias or left atrial flutter, however, in these situations, the placement of the lesions favors macroreentrant circuits rather than focal recurrences. These are often difficult to map and ablate, and usually require linear lesions in the left atrium rather than focal lesions within the veins.

One fact that must be considered in papers such as this is that recurrent atrial arrhythmias are relatively common in the first 6 to 8 weeks after any ablation procedure for atrial fibrillation. Most authors recommend drug therapy if needed for symptom control during this period to allow for atrial scarring from the ablation to become complete before attempting a repeat ablation procedure. Since these rhythms may sometimes be quite difficult to manage, postponing a repeat ablation may represent a clinical dilemma that may not be easy to deal with. However, some of these recurrent atrial arrhythmias will disappear over time, and it is worth trying to wait for at least 6 months before attempting a repeat ablation.

The techniques for catheter ablation of atrial fibrillation continue to evolve. There are still significant limitations for these procedures, but progress is being made. ■

Systemic Vascular Resistance By Echo Doppler

ABSTRACT & COMMENTARY

Synopsis: *Doppler echocardiography can estimate SVR, and is particularly accurate at identifying a low SVR.*

Source: Abbas AE, et al. *J Am Soc Echocardiogr*. 2004; 17:834-838.

SYSTEMIC VASCULAR RESISTANCE (SVR) IS A USEFUL measure for managing critically ill patients, but often invasive procedures to measure this parameter are not done. Thus, Abbas and colleagues suggested that Doppler echocardiography may be able to estimate SVR by measuring left ventricular (LV) pressure and flow. Since peak mitral valve regurgitation velocity (MRV) is directly proportional to LV pressure, and LV outflow tract time velocity integral (TVI) is directly proportional to flow, Abbas et al hypothesized that MRV/TVI would correlate with SVR. They screened 41 patients with pulmonary

artery catheters, and 8 were excluded either because they had no detectable mitral regurgitation (MR) or they had other significant valvular disease. In the 33 remaining patients, invasive and non-invasive measures were made within 45 minutes of each other. MRV/TVI correlated well with SVR (r = 0.84). Receiver operating characteristics showed that a MRV/TVI > 0.27 had a 70% sensitivity and a 77% specificity for SVR > 14 Woods Units (normal 10-14 WU). MRV/TVI < 0.2 had a 92% sensitivity and a 88% specificity for SVR < 10 Woods Units. Abbas et al concluded that Doppler echocardiography can estimate SVR, and is particularly accurate at identifying a low SVR.

COMMENT BY MICHAEL H. CRAWFORD, MD

The choice of appropriate therapy—volume, cardiac inotropes, vasoactive agents—in critically ill patients, often hinges on an accurate hemodynamic assessment, but few intensive care unit (ICU) patients today have right heart catheterization performed for fear of complications and data showing little mortality gain. Thus, echocardiography has become the most frequently used technique to resolve these issues. Echo Doppler techniques can estimate LV size and function, right atrial pressure, pulmonary artery pressure, and LV filling pressure. This new technique adds SVR to the list. The estimation of SVR was most accurate for low SVRs. This is extremely helpful because a low SVR suggests distributive shock, eg, septic shock. A high SVR is less useful since it can be caused by hypovolemia, which is easily corrected, or cardiac failure, which is not. If the SVR is not low, then other clinical or echo parameters need to be used to determine the mechanism of shock.

There are limitations to this technique. In the ICU setting, 7% (3/41) had no measurable MR. Patients with other conditions that would affect the measurement variables, resulted in 5 exclusions (12%). Thus, in almost 20% of patients, the technique could not be used. Also, right atrial and left atrial pressures occasionally are markedly different; this technique assumes that they are nearly equal. Since low atrial pressures are more likely to be similar than high ones, perhaps this is why their method worked best in low SVR patients. Although this technique will not be useful in everyone, it is a simple, easy addition to current echo Doppler parameters, which should increase our certainty about ICU patients' hemodynamics, and improve their care. ■

Constriction vs Restriction Revisited

ABSTRACT & COMMENTARY

Synopsis: *Tissue Doppler echocardiography can distinguish between constrictive pericarditis and restrictive cardiomyopathy.*

Source: Ha JW, et al. *Am J Cardiol*. 2004;94:316-319.

THEORETICAL CONSIDERATIONS AND ANECDOTAL EXPERience suggest that tissue Doppler echocardiography (TDE) early septal mitral annular velocity (E^1) is a relatively load independent measure of left ventricular (LV) relaxation, and accordingly, may be able to differentiate between restrictive cardiomyopathy, where relaxation is abnormal, and constrictive pericarditis, where it is expected to be normal. Thus, Ha and colleagues from the Mayo Clinic studied 75 patients, 38 of whom had biopsy proven cardiac amyloidosis, 23 had surgically confirmed constrictive pericarditis, and 14 had primary restrictive cardiomyopathy by clinical and echo parameters. E^1 was significantly higher in those with constrictive pericarditis vs those with restrictive cardiomyopathy or amyloidosis (12.3 vs 5.1 cm/s, $P < .001$). An $E^1 \geq 8$ cm/s had a 95% sensitivity and a 96% specificity for constrictive pericarditis. There was no overlap in E^1 between constrictive pericarditis and cardiac amyloidosis patients. The E^1 in patients with cardiac amyloidosis was significantly lower than those with primary restrictive cardiomyopathy (4.6 vs 6.3 cm/s, $P < .001$). Also, left ventricular wall thickness was higher in patients with amyloidosis. Left atrial size and cardiac index were higher in patients with restrictive cardiomyopathy. Ha et al concluded that E^1 by TDE can distinguish between constrictive pericarditis and restrictive cardiomyopathy.

COMMENT BY MICHAEL H. CRAWFORD, MD

This study demonstrates that there are characteristic Doppler echo findings in these 3 entities that exhibit restricted left ventricular filling. Constrictive pericarditis has an E^1 that is increased ≥ 8 cm/s; in restrictive cardiomyopathy atrial size is enlarged, and in cardiac amyloidosis wall thickness is increased. Of these, E^1 had the greatest discriminatory accuracy. Thus, if restricted left ventricular filling is shown on echo, TDE E^1 will help identify those with constrictive pericarditis, which is potentially curable with surgery.

I usually recommend CT or MRI confirmation of increased pericarditis thickness before recommending surgery. Recently, Ha et al have shown that in up to 20%

of patients with constrictive pericarditis, pericardial thickness is normal. However, these are usually early cases or those with effusive constrictive disease, many of whom will improve significantly without surgery. Amyloidosis is usually obvious clinically with the thickened sparkling left ventricular walls on echo and low voltage QRS complexes on ECG. Restrictive cardiomyopathy usually shows large atria and normal sized ventricles, but hemodynamic measures may be similar to those of constrictive pericarditis. Perhaps the most useful catheterization sign of constrictive pericarditis is respirophasic discordance in right and left ventricular pressures, which is usually not seen in restrictive cardiomyopathy. Based on this study, if cardiac catheterization is not desirable, E^1 and a complete echo Doppler examination may be highly accurate for distinguishing constrictive pericarditis from restrictive cardiomyopathy. ■

Antibiotics and Sudden Cardiac Death

ABSTRACT & COMMENTARY

Synopsis: *Patients who use both erythromycin and CYP3A inhibitors, particularly calcium channel blockers, had an increased risk of sudden death from cardiac causes.*

Source: Ray WA, et al. *N Engl J Med*. 2004;351: 1089-1096.

In this paper, Ray and colleagues examined a large database of Tennessee Medicaid enrollees to see if use of the antibiotic erythromycin was associated with an increase in sudden death from a cardiac cause. Erythromycin is a commonly used macrolide antibiotic that has been marketed for many years. There have been sporadic cases of torsades de pointe in patients receiving both oral and intravenous erythromycin, but the relationship with intravenous use has been more solidly established. In vitro studies have shown that erythromycin may prolong the QT interval due to blockade of the human HERG potassium channel. Erythromycin is also extensively metabolized by cytochrome P-450 3A (CYP3A) isozymes. Other drugs with this combination of properties have been associated with QT prolongation and sudden death.

Ray et al examined sudden deaths among a cohort of Tennessee Medicaid enrollees. Subjects had been enrolled in Medicaid for 1 year and were between the ages of 15 and 84. They were not residing in a long-term facility and had no evidence of a concurrent life-threatening noncardiac illness. Data from medical encounter forms, files regarding prescriptions, outpatient visits, hospital admissions, and nursing home stays were used to identify the study cohort, to determine exposure to the drugs examined, to identify potential causes of sudden death from cardiac causes, and to classify the preexisting cardiovascular and noncardiovascular conditions among the members of the cohorts. Patients who received prescriptions for erythromycin were identified. Data from patients who received amoxicillin, an antibiotic with similar clinical indications, but no potential for QT prolongation, were compared to data from the erythromycin group. The database was also examined for drug usage of compounds that significantly inhibit metabolism of cytochrome CYP3A substrates. The drugs included all had been shown to double the area under the contraction curve for CYP3A substrates. The drugs selected were the azole antifungal drugs, diltiazem, verapamil, and troleandomycin.

The study outcome was sudden death from cardiac causes occurring in community settings. Death certificates and other records were examined to identify potential cases of sudden death. Only out-of-hospital sudden deaths were included.

The study cohort included 1.25 million person years of follow-up. The mean age among members of the cohort was 45 years, with only 25% of the subjects age 65 years or older. The subjects were 70% female, and 58% were white. In the group, there was a total of 1476 sudden deaths from cardiac causes, for a rate of 1.2 deaths per 1000 person years. There were 5305 person years of current use of erythromycin and 6846 person years of use of amoxicillin. Current and former uses of erythromycin, and current uses of amoxicillin, were very similar with regard to their demographic and clinical characteristics.

The rate of sudden death from cardiac causes was twice as high among current users of erythromycin, (incidence-rate ratio 2.1, $P = 0.03$), as among those who did not use the compound. Former users of erythromycin or current users of amoxicillin did not show an increase risk of sudden death. There were 10 deaths among those currently taking erythromycin. Three of these deaths were in patients who were also using a CYP3A inhibitor, either diltiazem or verapamil. The incidence-rate ratio for these 3 patients was 5.35 ($P = 0.04$) indicating a risk of sudden death more than 5 times as high as that among those who use neither CYP3A inhibitors nor any of the study antibiotics. There were 7 deaths among current users of erythromycin who were not on a CYP3A

inhibitor. The incidence-rate ratio in this group was still increased at 1.79, but the confidence interval was now 0.85 to 3.76. No other drugs listed in the database were shown to be associated with sudden death.

Ray et al conclude that patients who use both erythromycin and CYP3A inhibitors, particularly calcium channel blockers, had an increased risk of sudden death from cardiac causes. Ray et al recommend that combinations of erythromycin and CYP3A inhibitors be avoided in clinical practice.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Drug-induced prolongation of the QT interval, with progression to polymorphic ventricular tachycardia, torsades de pointes was first described in patients receiving quinidine for treatment of atrial fibrillation. It is now recognized that the most common mechanism for drug induced torsades de pointes is blockade of the HERG potassium channel. This results in prolongation of repolarization, the development of repetitive early afterdepolarizations and polymorphic VT. Torsades de pointes is more common in women, and may be related to other factors which cause QT prolongation, eg, bradycardia, hypokalemia, severe hypomagnesemia, congestive heart failure, or ventricular hypertrophy. Often multiple factors are involved.

Many drugs produce minor changes in repolarizing currents, and can prolong the QT interval. The QT interval is also difficult to measure with precision, and the QT varies in the same individual over time and with changes in heart rate. Although correction factors for heart rate changes have been described, they are inexact. In most patients, minor effects on the HERG channel are easily compensated for and have no clinical sequelae. However, in patients who have either previously undetected forms of a long QT syndrome, and are exposed to higher than expected concentrations of a single drug, or are subject to effects from multiple drugs, torsades de pointe can be precipitated.

In this paper, Ray et al performed a careful examination of a large database to see if erythromycin, a drug with a known potential to block HERG channels, is actually associated with increased risk of sudden death. The database was a from a Medicaid population, so relatively few elderly individuals were involved. A Medicare population may have been more revealing. By examining this large Tennessee Medicaid database, Ray et al were able to demonstrate an increased risk ratio among all patients who used erythromycin, and in particular, among those in whom it would have been expected that erythromycin plasma concentrations would have been increased at least 2-fold. The absolute number of deaths is quite small. Without careful statistical analysis of this large database, the increase in risk would never have been detected clinically.

The clinical implications of these observations however, remain uncertain. Certainly, physicians should be aware if a drug has been reported to prolong the QT interval. If so, physicians should know the pharmacokinetic properties of the drug, and take care that the drug is not used either with other drugs which might raise its plasma concentration or in situations, for example, renal failure, where an excess concentration of the drug might be expected. In those cases, alternate therapy should certainly be prescribed. Keeping up-to-date on the potential for drug interactions, and a knowledge of the risk factors for developing torsades, should provide an adequate level of safety.

Painless Aortic Dissection

ABSTRACT & COMMENTARY

Synopsis: *Patients with painless acute aortic dissection are more likely to present with syncope, congestive heart failure or stoke, and have a higher mortality, especially with type B dissection.*

Source: Park SW, et al. *Mayo Clin Proc*. 2004;79: 1252-1257.

Although painless acute aortic dissection (AAD) has been described, there has been no systematic study of this condition. Thus, Park and colleagues, from the International Registry of Acute Aortic Dissection, assessed the clinical characteristics and outcomes of this condition to see if clinical recognition could be improved. Between 1997 and 2001, 977 patients with primary AAD were recorded in the database from 18 centers worldwide. The patients were divided into those presenting without pain (63, 6.4%) and those with pain. The painless patients were older (67 vs 62 years), and more often had an aneurysm prior to cardiac surgery. Type A dissection (ascending aorta) was more common in the painless group (75 vs 61%), and more of them were normotensive. The most common presentations of painless AAD were syncope, heart failure, and stroke. Mediastinal widening on chest X-ray was less common in painless AAD (40 vs 62%), and the time from symptom onset to diagnosis was 19 hours longer on average. Hospital mortality was higher in the painless group (33 vs 23%), and was due to a higher mortality in the painless patients who had type B dissection because of aortic rupture. Park et al concluded that patients with painless AAD are more likely to present with syncope, congestive heart failure, or stoke, and have a

higher mortality, especially with type B dissection.

COMMENT BY MICHAEL CRAWFORD, MD

The major message of this study is that painless AAD presents as other types of cardiovascular disease, which delays the diagnosis and increases the mortality. The mechanism of painlessness was not discernable in this database study, but it is interesting that the mediastinum was often not widened in the painless group. Perhaps dissection was slower, as opposed to more rapid expansion which may cause pain more often. However, this slow dissection delayed the diagnosis, increasing the incidence of rupture in type B dissections. The last such patient I saw presented as a stroke and a type A dissection, was detected on a routine echocardiogram. Most patients with heart failure, stroke, or syncope get a transthoracic echo (TTE), but the sensitivity of TTE for AAD, in general, is not high. In this study, both transesophageal echo and CT were used equally to make the diagnosis, but why these tests were ordered, is not described in the report. Clearly, a high index of suspicion is going to be needed not to miss this diagnosis. ■

CME Questions

18. New risk factors for coronary artery disease include:
- a. low vitamin C levels
- b. chronic liver disease
- c. chronic renal insufficiency
- d. All of the above

19. Erythromycin should not be combined with:
- a. diltiazem
- b. verapamil
- c. CYP3A inhibitors
- d. All of the above

20. Atrial tachyarrhythmias following atrial fibrillation ablation may respond to?
- a. Repeat isolation of the pulmonary veins
- b. Antiarrhythmic drugs
- c. Focal ablation
- d. All of the above

21. Which is more correct concerning the differentiation of cardiac constriction vs. restriction using echo Doppler?
- a. E > 20 cm/s usually cardiac amyloidosis
- b. E > 8 cm/s usually constriction
- c. Amyloidosis is associated with myocardial thinning
- d. Constrictive pericarditis is associated with myocardial thickening

22. Which is most correct concerning echo Doppler estimation of SVR?
- a. Highly accurate for SVR < 10 Wood units
- b. Highly accurate for SVR > 14
- c. Can be obtained in 100% of patients
- d. Can be obtained in < 33%

Answers: 18. (c); 19. (d); 20. (d); 21. (b); 22. (a)

Annual Statement of Ownership, Management, and Circulation

United States Postal Service
Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Clinical Cardiology Alert	0 7 4 1 - 4 2 1 8	10/1/04
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305
Contact Person: Robin Salet
Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*
Publisher *(Name and Complete Mailing Address)*
Brenda Mooney, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305
Editor *(Name and Complete Mailing Address)*
Leslie Hamlin, same as above
Managing Editor *(Name and Complete Mailing Address)*
Glen Harris, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
Thomson American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Thomson Healthcare, Inc.	Five Paragon Drive Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: Clinical Cardiology Alert
14. Issue Date for Circulation Data Below: September 2004

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1530	1267
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	995	940
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	7	6
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	43	40
	(4)	Other Classes Mailed Through the USPS	33	42
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			1078	1028
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	47	13
	(2)	In-County as Stated on Form 3541	2	2
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			26	25
f. Total Free Distribution *(Sum of 15d and 15e)*			75	40
g. Total Distribution *(Sum of 15c and 15f)*			1153	1068
h. Copies Not Distributed			378	199
i. Total *(Sum of 15g, and h.*			1530	1267
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			94	96

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2004 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 9/27/04

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PHARMACOLOGY WATCH

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

The FDA and Merck Fielding Concerns About Vioxx

Merck announced on September 30th that it is voluntarily withdrawing rofecoxib (Vioxx) from the worldwide market. The decision was based on data from the APPROVe (Addenomatous Polyp Prevention on Vioxx) trial, a company sponsored perspective randomized, placebo-controlled trial designed to assess whether the drug reduces the risk of colorectal polyps in patients with a history of colorectal adenomas. However, after 18 months of the study, patients on 25 mg of rofecoxib were noted to have an increased risk of cardiovascular events such as myocardial infarction and stroke, compared to those patients taking placebo. The FDA supported Merck's action and acknowledged that, while the risk to any individual on rofecoxib is small, the risk increases with continued use. The APPROVe trial showed that the risk of cardiovascular events with rofecoxib was twice that of placebo, according to information published on the FDA News website (fda.gov/bbs/topics/news/2004/NEW01122.html). Previous studies, including a recently reported Kaiser Permanente/FDA retrospective trial, showed the risk to be 3 times that of placebo. The FDA is investigating whether cardiovascular risk may be a class effect of COX-2 inhibitors (coxibs), and is reviewing data from similar trials with celecoxib (Celebrex) and valdecoxib (Bextra). Meanwhile, Merck is initiating a buy-back program for unused Vioxx prescriptions, reimbursing patients for their unused prescriptions. The withdrawal has enormous implications for the company and its shareholders, not only from the loss of nearly $2 billion in revenues from drug, but lost share value for the company stock and the risk of future legal action. It is estimated that 2 million patients in the United States were taking Vioxx at the time of the withdrawal, and over 84 million people worldwide have taken drug at some point since its approval in May 1999. The October issue of the *New England Journal of Medicine* has 2 scathing reviews of Merck and the FDA with regard to the approval and marketing of rofecoxib. Dr. Eric Topol of The Cleveland Clinic, who was one of the first to raise concerned about rofecoxib, calls for a full Congressional review of this case. The senior executives at Merck, and the leadership of the FDA, share responsibility for not having taken appropriate action and not recognizing that they are accountable for the public health (*N Engl J Med.* 2004;351:1707-1709). Dr. Garrett FitzGerald of the University of Pennsylvania suggests evidence has been there all along that coxibs, including celecoxib and valdecoxib, may promote cardiovascular disease by blocking prostaglandin I2, which inhibits platelet aggregation, promotes vasodilation, and prevents the proliferation of vascular smooth muscle cells in vitro. At the same time, coxibs have little effect on thromboxane A2, which is responsible for platelet aggregation.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@ thomson.com.

Traditional NSAIDs and aspirin block thromboxane production, accounting for their cardioprotective effects. Dr. FitzGerald states, "It is essential to determine whether cardiovascular risk is or is not a class effect." The burden of proof now rests with those who claim that this is a problem for rofecoxib alone, and does not extend to other coxibs." (*N Engl J Med*. 2004;351:1709-1711).

Erythromycin and the Risk of Sudden Death

Erythromycin may be associated with an increased risk of sudden death, according to new study in the *New England Journal of Medicine*. Oral erythromycin, which is extensively metabolized by cytochrome P-450 3A (CYP3A), prolongs cardiac repolarization, and has been associated with reports of torsades de pointes. Commonly used medications that inhibit CYP3A may increase plasma erythromycin levels, increasing the risk of ventricular arrhythmias and sudden death. Researchers from Vanderbilt reviewed data from a Tennessee Medicaid cohort that included more than 1.2 million person-years of follow-up and 1476 confirmed cases of sudden death from cardiac causes. The patients in the study were relatively young, with a mean age of 45. Seventy percent were female, and 58% were white. The multivariate adjusted rate of sudden death from cardiac causes among patients using erythromycin was twice as high as that among those who had not used any of the study antibiotic medications (incident-rate ratio 2.01; 95% CI, 1.08-3.75; $P = 0.03$). There was no increase in sudden death among patients using amoxicillin, or former users of erythromycin. For patients who were taking erythromycin with concurrent use of a CYP3A inhibitor (nitroimadazole antifungal agent, diltiazem, verapamil, or troleandomycin), the adjusted rate of sudden death was 5 times as high (incident rate ratio 5.35; 95% CI, 1.72-16.64; $P = 0.004$). The authors conclude that erythromycin should be avoided in patients who are taking CYP3A inhibitors (*N Engl J Med.* 2004;351:1089-1096).

Vaccine Shortage Putting Americans At Risk

Just as healthcare providers are about to start their annual flu vaccination program, British regulators have shut down Chiron Corporation's Liverpool flu vaccine manufacturing plant due to sterility problems. Chiron was expected to supply nearly 50 million doses of vaccine this year, half of the hundred million doses health officials expected to be administered to Americans this fall. Aventis, the other major supplier of vaccine, has told health officials that he could produce an additional million doses this year, but no more. Compounding the shortage, is the addition of 2 groups of patients recommended to receive the vaccine this year—children between the ages of 6 and 23 months (who require 2 doses 1 month apart) and pregnant women (or women who anticipate being pregnant during the flu season). Other high-risk patients include people over age 65, people in nursing homes, people with chronic illnesses, and those caring for people in these groups. Healthcare workers are also considered the highest priority for vaccination. The nasal flu vaccine, FluMist, does little to alleviate the shortage since it is only indicated for healthy children and adults between the ages of 5 and 49 years.

FDA Actions

The FDA will move ahead with warnings for many antidepressants stating that the drugs sometimes raise the risk of suicidal behavior in youth. The recommendation comes after an agency advisory panel, on a split vote, recommended a Black box warning. The agency may not go that far, however, since some advisors were concerned that warnings may discourage treatment of depressed children and teens who can benefit from antidepressants medications. The drugs subject to the warning are those with the brand names Prozac, Paxil, Wellbutrin, Zoloft, Celexa, Effexor, Luvox, and Remeron.

The recently approved antidepressant duloxetine (Cymbalta) has received FDA approval for treatment of pain associated with diabetic neuropathy. This is the first drug approved for this indication in this country. In 2 studies submitted to the FDA, the drug reduced 24-hour average pain levels, compared with placebo, in patients who had diabetes for an average of 11 years, and had neuropathic pain for average of 4 years.

The FDA has approved a new extended release formulation of hydromorphone for the management of persistent moderate-to-severe pain in patients requiring continuous, round-the-clock opioid pain relief for extended periods of time. The product is an extended release formulation that can be dosed once a day, and will be available in 12, 16, 24, and 32 mg capsules. The drug is only recommended for patients already receiving opioid therapy who have demonstrated opioid tolerance, and who require a minimum total daily opioid dose equivalent to 12 mg of oral hydromorphone. It will be marketed by Purdue pharmaceuticals with the trade name Palladone.