Providing Evidence-based Clinical Information for 27 Years

# CLINICAL CARDIOLOGY ALERT

*A monthly update of developments in cardiovascular disease*

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

## INSIDE



**Financial Disclosure:**

*Clinical Cardiology Alert's* physician editor, Michael H. Crawford, MD, is on the speaker's bureau for Pfizer.
The peer reviewer, Rakesh Mishra, MD, reports no consultant, stockholder, speaker's bureau, or other financial relationship with any company related to this field of study.

# BNP in Mitral Valve Disease: Too Good to be True?

ABSTRACT & COMMENTARY

***By Michael H. Crawford, MD***

**Sources:** Pizarro R, et al. Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation. *JACC*. 2009;54:1099-1106. McCullough PA, Hanzel GS. B-type natriuretic peptide and echocardiography in the surveillance of severe mitral regurgitation prior to valve surgery. *JACC*. 2009;54:1107-1108.

THE TIMING OF MITRAL VALVE SURGERY IN PATIENTS WITH SEVERE organic mitral regurgitation (MR), but without symptoms, is controversial. Echocardiographic measurements of left ventricular (LV) size and function and severity of MR have shown predictive value in different studies. Also, it is known that brain natriuretic peptide (BNP) blood levels indicate increased wall stress and could be of prognostic value in valve disease patients. Thus, these investigators from Buenos Aires, Argentina, sought to determine the incremental prognostic value of BNP over echo parameters in 269 prospectively evaluated, asymptomatic patients with severe, organic MR and normal LV function (ejection fraction > 60%). The first 167 patients comprised the derivation set and the second 102 patients the validation set. Most of the patients had degenerative MR, were men, and had a mean age in their 60s. Other inclusion criteria included an echo-derived, effective regurgitant orifice area (EROA) > 40 $mm^2$ and a regurgitant volume of > 60 mL/beat, and > 7 METs of exercise on a Bruce protocol treadmill test without symptoms, ventricular arrhythmias, hypotension, or ischemic ECG ST depression. Patients with other valve diseases, ischemic MR, previous cardiac surgery, or cardiomyopathies were excluded. Decisions regarding valve surgery were made by the primary physician without knowledge of the BNP values determined at entry and at one year. The primary combined endpoint was the occurrence of heart failure, LV dysfunction, or death. If a patient was sent to surgery before they developed symptoms or LV dysfunction, they were not considered to have reached the primary endpoint.

VOLUME 28 • NUMBER 11 • NOVEMBER 2009 • PAGES 81-88

NOW AVAILABLE ONLINE
www.ahcmedia.com

**Results:** Median BNP in the derivation and validation groups were 21 and 27 pg/mL, respectively. Receiver operating curves defined a BNP cutoff value of 105 pg/mL with regard to the primary endpoint. The endpoint was achieved in 21% of both cohorts. The cutoff value identified high-risk groups where the primary endpoint frequency was 76% and 66% in the two cohorts vs. 5% and 4% in the low-risk groups. Patients with a baseline BNP > 105 were more likely to have a new flail leaflet, a larger end-systolic diameter, a bigger left atrium, higher pulmonary pressures, and higher echo indices of the amount of regurgitation. By multivariate analysis, BNP was the strongest independent predictor of the endpoint. When BNP was added to the best echo model (EROA, end systolic diameter, and atrial volume), the ROC area significantly increased from 0.80 to 0.91 ($p = 0.01$). In the validation cohort, death occurred in 2%, new heart failure in 16%, and LV dysfunction in 4% over a 31-month average follow-up. Also, 4% developed NYHA class II symptoms, 5% new atrial fibrillation, and 10% pulmonary hypertension. Mitral valve surgery was performed in 29% (63% repair). The authors concluded that BNP has incremental prognostic value to echo measures in asymptomatic patients with severe MR and normal LV function.

## ■ COMMENTARY

In asymptomatic patients with severe MR, the ACC/AHA and ESC guidelines recommend considering surgery if LV dysfunction, increased LV volume, pulmonary hypertension, or atrial fibrillation develops. This study confirms the predictive value of developing LV dysfunction (ESD/BSA > 22 mm/m$^2$, OR = 3.4, CI 1.6-10.7, $p = .01$) and adds a new multivariate echo predictor reflecting the amount of mitral regurgitation (EROA > 55 mm$^2$, OR 4.2, CI 2.1-11.4, $p = .001$). However, BNP was the strongest predictor of the primary outcome (> 105 pg/mL, OR = 4.6, CI 2.7-11.6, $p = .0001$). None of these three parameters are mentioned in the current guidelines. In addition, those with a large increase in BNP (> 25 pg/mL) over one year also had a higher incidence of the primary endpoint as compared to those with a lesser or no increase. It is hypothesized that BNP is released in these patients as a result of subclinical LV dysfunction or, perhaps, an increase in wall stress of the LV or atria.

Interestingly, other parameters in the guidelines, such as atrial fibrillation, ejection fraction, and pulmonary hypertension, were univariate predictors, but were not significant multivariate predictors. Other predictors mentioned in the literature, such as new flail leaflet, increased end-diastolic diameter, or enlarged left atrium, were univariate predictors, but also not significant in the multivariate analysis. Thus, this study would suggest that more appropriate criteria for surgery should be BNP > 105, ESD/BSA > 22, and EROS > 55. Clearly these parameters should be added to our decision-making process.

In the ACC/AHA guidelines, a IIa indication for surgery in those with severe MR and no symptoms is a likelihood of repair > 90%. The new significant parameters in this study may help to settle this controversial area, but should we operate solely on the basis of an elevated BNP? This is difficult to answer because there are many causes of an elevated BNP that would have to be excluded in a less selected patient population. Remember, a BNP measurement has been shown to be more useful in other patient populations if it is normal. I suspect the same will be true in valvular disease; a normal BNP will stay the surgeon's hand. ■

*Clinical Cardiology Alert*, ISSN 0741-4218, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305. The statement of ownership will be printed in the November issue.

**MANAGING EDITOR:** Leslie Hamlin.
**ASSOCIATE PUBLISHER** Russ Underwood.
**DIRECTOR of MARKETING :** Schandale Kornegay.

**GST Registration Number:** R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

**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.



AHC Media LLC

**Subscriber Information**

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

**Subscription Prices**

**United States**
1 year with Free AMA Category 1 credits: $319
Add $17.95 for shipping & handling.
(Student/Resident rate: $125).

**Multiple Copies**
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

**Canada**
Add GST and $30 shipping.

**Elsewhere**
Add $30 shipping.

**Accreditation**
AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

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

# Immediate Angiography or Wait until the Next Working Day for Non-ST Elevation ACS?

ABSTRACT & COMMENTARY

***By Andrew J. Boyle, MD, PhD***
*Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco*

*Dr. Boyle reports no financial relationships relevant to this field of study.*

**Source:** Montalescot, G et al. Immediate vs delayed intervention for acute coronary syndromes. A randomized clinical trial. *JAMA*. 2009;302:947-954.

MANY CLINICAL TRIALS HAVE CONFIRMED THE BENEFIT of early invasive therapy for high-risk patients presenting with acute coronary syndromes (ACS). However, the optimal timing of cardiac catheterization in this group remains unknown. Whether they should go immediately to the cardiac catheterization laboratory, even in the middle of the night, as with ST elevation myocardial infarction, or wait until the next working day to go to the cath lab was the subject of this study. Thus, Montalescot et al performed a randomized, multicenter trial, the Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention (ABOARD) study.

Thirteen centers in France enrolled patients presenting with ACS who were at moderate to high risk, as indicated by a TIMI risk score of 3 or more, and randomized them to immediate coronary angiography, with revascularization at the operator's discretion, vs. delaying the procedure until the next working day. Physicians were encouraged to perform percutaneous coronary intervention (PCI) at the same sitting, if possible, or coronary artery bypass graft surgery (CABG) as soon as possible for an inpatient. Exclusion criteria included refractory ischemia, arrhythmia, or hemodynamic instability requiring urgent cardiac catheterization, ongoing warfarin, fibrinolytic, or glycoprotein IIb/IIIa inhibitor use. All patients were loaded with high-dose aspirin (500 mg) and clopidogrel (≥ 300 mg); antithrombin use was at the physician's discretion. The primary endpoint was the peak troponin-I level during hospitalization. The key secondary endpoint was a composite of death, myocardial infarction (MI), or urgent revascularization at one month.

Baseline characteristics were well matched between patients undergoing immediate (n = 175) and delayed (n = 177) treatment. Mean age was 65 years, 72% were male, 27% had diabetes, and 74% had elevated troponin levels. Median time from randomization to sheath insertion was 70 minutes (interquartile range [IQR] 0.51-123) in the immediate group and 21 hours (IQR 18-25) in the delayed group. Radial arterial approach was used for coronary angiography in 84%, 74% went on to have PCI, and 11% had CABG. Two-thirds of patients received low molecular weight heparin, 2.9% of the immediate group and 0.6% of the delayed group received no anti-thrombin therapy, and abciximab was administered to 65.1% of the immediate group and 57.4% of the delayed group, but no statistical analysis of the rates between groups is given. Almost all patients received clopidogrel, but we are not told at what time during the hospitalization this was administered.

The primary endpoint of peak troponin level during hospitalization was similar in the two groups (2.1 [0.3-7.1] ng/mL vs. 1.7 [0.3-7.2] ng/mL in the immediate and delayed groups, respectively; $p = 0.70$). These results were similar when stratified by age, gender, diabetes, and TIMI risk score 5. The combined secondary endpoint was also similar between groups (13.7% [8.6-18.8%] vs. 10.2% [5.7-14.6%]; $p = 0.31$) in the immediate and delayed groups, respectively. Furthermore, the individual components of the combined secondary endpoint were also not significantly different between groups. Recurrent ischemia tended to be lower in the immediate group (12.0% [7.2-16.8%] vs. 18.6% [12.9-24.4%]; $p = 0.08$), and the rates of MI at 30 days tended to be higher in the immediate group (9.1% vs. 4.5%; $p = 0.09$), but these failed to reach statistical significance. Hospital stay was 22 hours shorter in the immediate group (55 hours [30-98] vs. 77 hours [49-145]; $p < 0.001$). There was no difference in bleeding outcomes between the two groups. Montalescot et al conclude that in patients with moderate- to high-risk non-ST elevation ACS, a strategy of immediate intervention compared with a strategy of intervention deferred to the next working day (mean 21 hours) did not result in a difference in MI, as defined by peak troponin levels.

## ■ COMMENTARY

Montalescot et al have demonstrated that for patients presenting with high-risk non-ST elevation ACS, it is safe to wait until the next working day to perform coronary angiography. This study is congruent with prior studies investigating the optimal timing of intervention in patients undergoing early invasive strategy, such as the TIMACS study (Mehta et al. *N Engl J Med*. 2009;360:2165-2175). Although practice patterns differ between centers and countries, this study adds more evidence that, despite slight differences in peri-procedural management, waiting until the next working day for an invasive strategy does not lead to worse patient outcomes. This study had relatively high rates of radial arterial access, high doses of clopidogrel, and relatively low rates of using direct thrombin inhibitors and glycoprotein IIb/IIIa inhibitors compared to practice in the United States. However, the medical management was exemplary, with high rates of statin, aspirin, and beta-blockers. Importantly, even the highest-risk patients, identified by a TIMI risk score greater than 5, did not benefit from earlier intervention. This study confirms that standard current practice patterns are indeed providing the best patient care. ■

# CRT Plus ICD vs. ICD Alone in Heart Failure and Wide QRS Patients

ABSTRACT & COMMENTARY

***By John P. DiMarco, MD, PhD***

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

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

**Source:** Moss AJ, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med.* 2009:361:1329-1338.

Current indications for cardiac-resynchronization therapy (CRT) require that patients have New York Heart Association (NYHA) Class III or Class IV heart-failure symptoms. However, long-standing ventricular dyssynchrony can lead to left-ventricular remodeling and decreased left-ventricular ejection fraction. In this study, the Multicenter Automatic Defibrillation Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial, Moss et al tested the hypothesis that prophylactic CRT, in combination with an ICD, would reduce the risk of death or nonfatal heart-failure events in patients with an ICD indication and a QRS duration of 130 milliseconds or more, but only Class I or Class II heart-failure symptoms.

Over a 52-month period, MADIT-CRT enrolled 1,820 patients in the United States, Canada, and Europe. All patients met current guidelines for ICD therapy. Patients with ischemic cardiomyopathy could have Class I or Class II heart-failure symptoms, but those with nonischemic cardiomyopathy had Class II symptoms only. All patients had sinus rhythm, a left-ventricular ejection fraction of 30% or less, and a QRS duration of 130 milliseconds or more. At baseline, a 12-lead electrocardiogram for QRS duration, an echocardiogram for ejection fraction and ventricular volumes, and a six-minute walk test were performed. Patients were randomly assigned in a 3:2 ratio to receive either a biventricular ICD system (CRT-ICD) or a single- or dual-chamber ICD. The primary endpoint was death from any cause or a nonfatal heart-failure event, whichever came first. Heart-failure events required either an outpatient course of intravenous decongestive therapy or a hospital admission with augmented therapy for heart failure. Adjudication of endpoints was carried out by an independent committee unaware of study-group assignment. Analysis used an intention-to-treat approach based on initial randomization.

The study enrolled 1,820 patients with a mean age of 64; 75% were men. There were 821 patients with nonischemic heart disease and 999 patients with ischemic heart disease. The mean left ejection fraction was 0.24, and 65% of the patients had a QRS duration ≥ 150 milliseconds. Follow-up of patients in the trial averaged 2.4 years.

There were 29 patients who did not receive any device for various reasons, 11 in the CRT group (1%) and 19 (2.6%) in the ICD-only group. A total of 173 crossovers occurred. In the ICD-only group, 91 patients (12.4) were upgraded to CRT-ICD therapy during the course of the trial. In the CRT-ICD group, 82 patients (7.5%) achieved an ICD-only device because technical difficulties prevented satisfactory transvenous placement of the left-ventricular pacing lead.

There were 36 deaths (3.3%) and 151 initial heart-failure events (13%) in the CRT-ICD group, compared to 18 deaths (2.5%) and 167 heart-failure events (22.8%) in the ICD-only group. For all patients, the hazard ratio for death or heart failure in the CRT-ICD group compared to the ICD only group was 0.66 (95% confidence interval, 0.52-0.84; $p = 0.001$). For heart failure only, the hazard ratio was 0.59 (95% CI, 0.47-0.74; $p < 0.001$). There was no difference in mortality between the groups, with a hazard ratio of 1.0. The hazard ratios for these endpoints were similar for patients with ischemic cardiomyopathy and nonischemic cardiomyopathy. Subgroup analysis revealed a greater benefit of CRT-ICD therapy among women compared to men and among patients with a QRS duration of 150 milliseconds or more compared to those with a shorter QRS duration. At one-year follow-up, the left-ventricular ejection fraction increased by 11% in the CRT-ICD group compared to 3% in the ICD-only group. Favorable changes in the left-ventricular end diastolic and end-systolic volumes were also noted in the CRT-ICD group.

Adverse effects were higher in the CRT-ICD group, with higher rates of pneumothorax, infection, and pocket hematoma requiring evacuation noted. Coronary venous dissection with pericardial effusion occurred in five patients in the CRT-ICD group (0.5%). Left-ventricular lead repositioning was required during the first 30 days in 44 patients (4.0%). After 30 days, serious device-related adverse events, not further defined by Moss et al, occurred with a frequency of 4.5 per 100 device months in the CRT-ICD group, compared to 5.2 per 100 device months in the ICD-only group.

Moss et al conclude that prophylactic use of ICD-CRT therapy in asymptomatic or mildly symptomatic patients with either ischemic or nonischemic heart disease, a reduced ejection fraction, and a wide QRS complex decreases the risk of heart-failure events and improves echocardiographic measures of left-ventricular function.

■ **COMMENTARY**

The data from MADIT-CRT are very interesting but should be studied carefully before we change our current practices and guidelines with regard to resynchronization therapy. In MADIT-CRT, the primary endpoint was death and heart-failure events. The data clearly show that CRT decreases heart-failure events in those with the QRS durations over 150 m/sec. However, there were frequent complications associated with implementing CRT therapy that may well cancel out the benefits reported. Moss et al report higher rates of pneumothorax, lead dislodgement, pericardial effusion, and hematoma with CRT therapy and, presumably, many of these complications resulted in prolonged or repeat hospital stays around the time of implant. If data on total cardiac hospital days were reported, there would presumably be a diminution of the benefits seen in the CRT-ICD group. If this is true, then prophylactic CRT therapy is unlikely to be cost-effective since the biventricular ICDs are considerably more costly then single- or dual-chamber systems.

Current data from the national ICD registry indicate that almost 50% of the primary prevention ICD implants in the United States are CRT devices. This suggests that implanting physicians are already using fairly loose criteria for diagnosing Class III functional status in patients with a wide QRS complex in order to stay within current guidelines. MADIT-CRT supports this approach for patients with a QRS duration more than 150 m/sec. For patients with a QRS duration less than 150 m/sec and class I or II functional status, I would argue that a single- or dual-chamber ICD should remain the preferred choice, with later upgrade if symptoms progress. ■

# Direct Thrombin Inhibitor for Atrial Fibrillation

ABSTACT & COMMENTARY

***By John P. DiMarco, MD, PhD***

**Source:** Connolly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009:361: 1139-1151.

DABIGATRAN ETEXILATE IS AN ORAL COMPOUND THAT IS converted after absorption by a serum esterase to dabigatran, a direct competitive inhibitor of thrombin. Dabigatran has previously been evaluated and found to be effective in patients with venous thrombolism. In this study, Connolly et al report a large, randomized trial comparing dabigatran, 110 mg or 150 mg twice daily, with adjusted-dose warfarin for prevention of thromboembolic events in patients with atrial fibrillation. The Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial enrolled patients from 951 clinical centers in 44 countries. Eligible patients had atrial fibrillation documented on an ECG within the previous six months and at least one of the following risk factors for thromboembolism: previous stroke or transient ischemic attack, left-ventricular ejection fraction less than 40%, New York Heart Association Class II or higher heart failure symptoms, age greater than 75, or age 65 to 75 plus diabetes, hypertension, or coronary artery disease. Patients with valvular heart disease, recent stroke, increased baseline risks for bleeding, renal and hepatic dysfunction, and pregnancy were excluded. The patients were randomly assigned to receive either open-label, adjusted-dose warfarin or blinded-dose dabigatran, 110 or 150 mg twice daily. For patients on warfarin, the international normalized ratio (INR) target was 2.0-3.0, with the INR measured at least monthly. Follow-up visits occurred at two weeks, one and three months, and then every three months thereafter. Liver function tests were performed monthly during the first year of the follow-up for the first 6,000 patients in the study and subsequently at regular study visits.

The primary study outcome was stroke or systemic embolism. The primary safety outcome was major hemorrhage, defined as a reduction in the hemoglobin level of at least 20 g/liter, a need for transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. The study was designed as a noninferiority comparison between the two doses of dabigatran and warfarin.

A total of 18,113 patients were enrolled over a two-year period. The mean age for the entire group was 71 years; 63.3% were men. Approximately equal proportions of patients with persistent, paroxysmal, and permanent atrial fibrillation were enrolled. The mean CHADS2 score was 2.1. Seventy-nine percent of the patients had a history of hypertension and 23% a history of diabetes mellitus. Approximately 50% had previously been treated with a vitamin K antagonist. For patients taking warfarin, the mean percentage of time during which the INR was between 2.0 and 3.0 was 64%.

The annual rates for stroke or systemic embolism were 1.3% for patients receiving 110 mg of dabigatran, 1.11% for patients receiving 150 mg of dabigatran, and 1.69% for patients on warfarin. Both doses satisfied criteria for noninferiority compared to warfarin, and the 150 mg dose was also superior to warfarin (relative risk, 0.66; 95% confidence interval, 0.53-0.82: $p < 0.001$). Hemorrhagic stroke occurred at an annual rate of 0.3% in the warfarin group, compared to 0.12% in the 110 mg dabigatran group ($p < 0.001$) and 0.1% in the 150 mg dabigatran group ($p < 0.001$). Total mortality was 4.13% per year with warfarin, compared to 0.375% per year with 110 mg dabigatran and 3.64% per

year with 150 mg dabigatran. These mortality reductions with both doses of dabigatran were not statistically significant. Slightly higher myocardial infarction rates were seen in patients on dabigatran as compared to warfarin.

Major bleeding occurred at an annual rate of 3.36% per year with warfarin, compared to 2.71% per year in the 110 mg dabigatran group ($p = 0.003$) and 3.11% per year in the 150 mg dabigatran group ($p = 0.31$).

Dyspepsia was more common with dabigatran than with warfarin, occurring at rates of 11.8% and 11.3% in the 100 mg and 150 mg dose groups, respectively, compared to a rate of 5.8% in the warfarin group. Increase in liver function test values and interactions with creatinine clearance were not noted. After two years of therapy, 21% of the patients receiving both doses of dabigatran had discontinued therapy, compared to 17% of those receiving warfarin.

Connolly et al conclude that in comparison with warfarin, dabigatran 110 mg twice daily was associated with similar rates of stroke and systemic embolism and lower rates of major hemorrhage, and that the 150 mg dose of dabigatran had lower rates of stroke and embolism with a similar rate of major hemorrhage.

## ■ COMMENTARY

Stroke and systemic embolism are major complications of atrial fibrillation. Numerous trials have established the role of warfarin therapy in atrial fibrillation. However, many factors can make warfarin therapy difficult for patients. Warfarin response is often influenced by dietary factors, and many drugs have interactions with warfarin metabolism. Warfarin metabolism is highly variable in the population. Even in a well-run clinical-trial setting, only about two-thirds of INR values are within the desired range. The need for frequent INR monitoring is costly and inconvenient for patients. Bleeding, both major and minor, is frequently seen with warfarin, particularly during early-dose titration. The RE-LY trial results show that an orally effective, direct thrombin inhibitor, dabigatran etexilate, may provide a potential alternative to warfarin therapy.

In RE-LY, both the efficacy data and safety data were in favor of dabigatran, particularly with the 110 mg, twice-daily dose. If dabigatran is approved for general use, these data, plus the convenience of predictable dosing without the need for frequent blood tests, will make it the preferred choice for many patients and physicians.

There are now several other alternatives to warfarin in various stages of clinical development. These include other thrombin inhibitors, oral and injectable Factor Xa inhibitors, and warfarin congeners with more predictable metabolism. Hopefully, within the next few years, we will be able to offer patients a safer and more reliable approach to chronic anticoagulation. ■

# Coffee Consumption and Incident Heart Failure in Men

ABSTRACT & COMMENTARY

***By Andrew J. Boyle, MD, PhD***

**Source:** Ahmed et al. Coffee consumption and risk of heart failure in men: An analysis from the cohort of Swedish men. *Am Heart J.* 2009;158:667-672

The effects of coffee on the heart remain incompletely described. There are conflicting reports of coffee's effects on the incidence of coronary artery disease, heart failure (HF), atrial fibrillation, and glucose homeostasis. There are plausible biological reasons that coffee may increase the incidence of HF (such as predisposing to hypertension) or decrease it (such as improving calcium sensitivity of cardiomyocytes). To address the issue of coffee intake and incident HF, Ahmed et al utilized this cohort of Swedish men to determine outcomes in men who self-reported varying levels of coffee consumption.

The cohort comprised 48,850 men aged 45-79 years residing in Sweden who were followed prospectively for nine years. Dietary, lifestyle, demographic, and behavioral factors were self-reported at the beginning of the study. Clinical events of HF hospitalization and HF deaths were extracted from the Swedish inpatient dataset and the Swedish death registry, respectively. After excluding subjects with pre-existing cancer, HF, diabetes, myocardial infarction (MI), improbable self-reported energy intake, and incorrect national registration number, 37,315 men were included. The data were statistically corrected for age, activity, body-mass index, sodium intake, fat intake, smoking, dyslipidemia, education level, marital status, aspirin use, alcohol intake, tea intake, and family history of premature MI. The primary endpoint was HF hospitalization or death.

During the study period, 690 men were hospitalized with HF and 94 died of HF, which corresponds to 24.5 cases per 10,000 person-years. This is comparable to the reported overall HF hospitalization rate in Sweden of 23.7 per 10,000 patient-years. Subjects were stratified into five groups according to coffee intake: 1 cup per day, 2 cups per day, 3 cups per day, 4 cups per day, and 5 cups per day. Ahmed et al found that coffee consumption was not a significant predictor of incident heart failure. This lack of association was not changed when analyzed by number of cups per day, overweight status, current smoking, or alcohol intake. The initial analysis was not controlled for hypertension, but when Ahmed et al also controlled for this variable, there was still no relationship between coffee consumption

and HF. Analysis of those with prior MI or diabetes, who were excluded at baseline, revealed there was no association between coffee consumption and HF in that population either. Ahmed et al then performed an additional analysis by excluding the incidences of heart failure in the first two years, in case baseline symptoms had affected caffeine intake. There was still no relationship between coffee consumption and incident HF. Finally, Ahmed et al analyzed all-cause mortality, and showed no difference based on coffee consumption. They conclude their results do not support the hypothesis that high coffee consumption is associated with increased rates of HF hospitalization or mortality.

■ **COMMENTARY**

I am asked relatively frequently about the effects of coffee consumption on the heart. The data have been conflicting, with some studies showing a detrimental effect, some showing a positive effect, and others showing no effect at all. This large cohort study included over 37,000 men and, thus, has strong statistical power. The multivariable model Ahmed et al used adjusted for many baseline variables. However, some limitations to this study must be acknowledged. The clinical variables are self-reported, and often binary, whereas blood pressure is really a continuous variable, and under-reporting may occur if subjects are not aware of the problem. It would be more robust to have used the subjects' measured blood pressure. Furthermore, dietary consumption (including coffee) is self-reported, but then so is our patients' coffee consumption. This study was only in men, so the results should not be generalized to women.

The types of coffee and the strengths of coffee vary by location. It is not clear from this study whether the predominant type of coffee is drip coffee, instant, or boiled coffee. Nor is the study controlled for caffeine content. Therefore, the number of cups per day quoted in this study may not translate for all types or strengths of coffee. Furthermore, the use of decaffeinated coffee was not explored in this study, nor was the use of caffeinated non-coffee drinks, such as cola or energy drinks. Until definite evidence regarding the effects of caffeine on heart health emerge, moderation continues to be appropriate, but there does not appear to be a need to tell patients to abstain from coffee to prevent incident HF. ■

# Dietary Manipulation to Stabilize INR

ABSTRACT & COMMENTARY

***By Michael H. Crawford, MD***

**Source:** de Assis MC, et al. Improved oral anticoagulation after a dietary vitamin k-guided strategy: a randomized controlled trial. *Circulation*. 2009;120:1115-1122.

ERRATIC INTRAINDIVIDUAL INR VALUES ON CHRONIC warfarin therapy are thought to be due to variability in vitamin K intake in the diet. Thus, de Assis et al from Brazil hypothesized that a dietary, vitamin K management strategy would result in improved long-term anticoagulation as compared to traditional systems based upon drug-dose adjustments alone. In a single-center open trial, 132 patients requiring chronic anticoagulation with mechanical valves (58%) or atrial fibrillation (35%) were randomized to vitamin K-rich food intake manipulation based upon their INR, rather than warfarin dose adjustments. The other group had conventional INR-guided, drug-dosage adjustments. The primary endpoint was the percentage of patients within their target INR range 90 days after randomization. Patients eligible for the study were those on therapy for > 3 months who had an INR value out of range but > 1.5 and < 4.0 and not experiencing bleeding or thrombosis.

**Results:** One patient died, but not related to anticoagulation. The vitamin K group reached their target INR range more quickly then the conventional group and, at 90 days, 74% in the vitamin K group were at target compared to only 58% of the conventional group ($p = 0.04$). Minor bleeding was more common in the conventional group vs. the vitamin K group (seven vs. one patient, $p = 0.06$). de Assis et al concluded that a vitamin K dietary management strategy to achieve target INR in anticoagulated patients is feasible, safe, and may enhance achievement of target INR.

■ **COMMENTARY**

Maintenance of target INRs in patients over time is challenging. I have often told frustrated patients that if they ate the same thing every day we could keep them in perfect balance, but no one ever does that for obvious reasons. However, this study suggests that by paying attention to the intake of 16 foods, INR stability can be achieved. These foods are: arugula, asparagus, broccoli, brussel sprouts, cabbage, cauliflower, collard greens, cucumbers, green peas, green tea, lettuce, liver, spinach, turnip, vegetable oil, and watercress. They do not recommend not eating these otherwise healthy foods, but keeping their intake constant. In the trial, they adjusted INR, if it was high, by cutting the intake of the vitamin K-rich foods by half. If the INR was low, they increased their intake by 100%. No restrictions on serving size were given, only directions to change the number of servings per week. Very few patients required parenteral vitamin K administration for over anticoagulation; two in the conventional group and one in the vitamin K group. Crossover to conventional management occurred in 11 patients in the vitamin K group (16%) because target

INR could not be achieved with diet adjustments alone. Most of these patients never achieved target INR during the study period and, in three, their final INR was > 4.0.

The major limitation to this study is the short follow-up. We do not know if dietary adjustments will permit long-term stability without drug-dose changes. I suspect dosage adjustments and dietary control will be necessary long term, but if diet-control techniques minimize dosage changes and prolong the interval between blood samples, this would be a significant advantage. I am sure the nurses who often run anticoagulation clinics can learn how to asses diet and suggest adjustments; algorithms for this already exist. Whether long-term costs will be altered by this approach is not known. As a start, I am going to give my patients on warfarin a list of the 16 foods and tell them to keep the combined total number of servings of these foods the same each week and see if this helps stabilization. ■

# CME Questions

**25. CRT+ICD vs. ICD alone in class I-II heart failure patients with QRS > 130 resulted in:**
a. fewer deaths.
b. less heart failure.
c. improved LV function.
d. B and C

**26. The ideal timing of cardiac catheterization in high-risk NSTE ACS patient is:**
a. immediately.
b. within 24 hours.
c. next working day.
d. within a week.

**27. Dabigatran vs. warfarin showed:**
a. superiority to warfarin.
b. non-inferiority to warfarin.
c. increased major hemorrhage.
d. abnormal liver function tests.

**Answers:** 25. (d); 26. (c); 27. (b)

# CME Objectives

The objectives of *Clinical Cardiology Alert* are to:

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

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

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

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

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 | 10/1/09 |
| 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)*: Robert Mate, President and CEO, AHC Media LLC, 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)*: Russ Underwood, 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 |
|---|---|
| AHC Media LLC | 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 |
|---|---|
| Thompson Publishing Group Inc. | 805 15th Street, NW, 3rd Floor |
| | Washington, D.C. 20005 |

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 2009

| 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)* | | | 784 | 742 |
| b. Paid and/or Requested Circulation | (1) | Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)* | 567 | 552 |
| | (2) | Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)* | 1 | 0 |
| | (3) | Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution | 25 | 24 |
| | (4) | Other Classes Mailed Through the USPS | 41 | 26 |
| c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)* | | | 634 | 602 |
| d. Free Distribution by Mail *(Samples, Complimentary and Other Free)* | (1) | Outside-County as Stated on Form 3541 | 15 | 15 |
| | (2) | In-County as Stated on Form 3541 | 0 | 0 |
| | (3) | Other Classes Mailed Through the USPS | 0 | 0 |
| e. Free Distribution Outside the Mail *(Carriers or Other Means)* | | | 20 | 20 |
| f. Total Free Distribution *(Sum of 15d and 15e)* | | | 35 | 35 |
| g. Total Distribution *(Sum of 15c and 15f)* | | | 669 | 637 |
| h. Copies Not Distributed | | | 115 | 105 |
| i. Total *(Sum of 15g, and h.* | | | 784 | 742 |
| Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)* | | | 95% | 95% |

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2009 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: President and CEO — Date: 9/28/09

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.
6. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
7. Item 17 must be signed.

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

PS Form **3526**, September 1999 *(Reverse)*

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

VOLUME 14, NUMBER 11 PAGES 21-22 NOVEMBER 2009

## Dabigatran vs warfarin: Less bleeding?

**Source:** Connolly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-1151.

Numerous prospective trials have confirmed that anticoagulant therapy with warfarin (WRF) provides substantial stroke risk reduction for patients with atrial fibrillation (AF). Overall, AF patients enjoy as much as a two-thirds reduction in risk of ischemic stroke when WRF has been compared with placebo in clinical trials. These benefits notwithstanding, utilization of WRF is complex and entails significant risk of bleeding. Direct thrombin inhibitors (DTIs) such as ximelagatran have previously demonstrated comparable stroke risk reduction in AF as WRF, with less risk of serious bleeding; additionally, direct thrombin inhibitors do not require ongoing monitoring to assure a therapeutic range, simplifying the level of involvement required of the patient. Unfortunately, clinical trials with earlier DTIs (e.g., ximelagatran) showed a significant risk of hepatotoxicity, precluding clinical use in the United States.

Dabigatran (DAB) is an oral DTI administered twice daily. Based upon favorable results from pilot trial data in AF and venous thromboembolism, a major clinical trial (n = 18,113) was undertaken to compare warfarin with DAB in AF.

After a median follow-up of 2 years, DAB fulfilled expectations that it provided risk reduction as great as or superior to WRF, with similar or fewer bleeding events. The orally administered DTI class shows great promise as an alternative to WRF. ■

## Does SHBG increase risk of diabetes?

**Source:** Ding EL, et al. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N Engl J Med* 2009;361:1152-1163.

Sex hormone-binding globulin (SHBG) is a protein that might seem to be most interesting to the endocrinologist, since its sole function — until very recently — has been thought to be regulation of the availability of gonadal steroids. For instance, in women with acne, the primary therapeutic effect of estrogen therapy (as in oral contraceptives) is that estrogen increases SHBG levels; the increased SHBG binds plasma testosterone, leaving less free (unbound) testosterone to drive acne.

It may be that SHBG has other pertinent functions. The Women's Health Study provided the data set from which the relationship between plasma SHBG and incidence of type 2 diabetes could be examined. Comparing the SHBG level in women with newly diagnosed diabetes to controls (total n = 718), a steep inverse linear relationship between SHBG and odds ratio for developing type 2 diabetes was demonstrated. Compared to women in the lowest quartile of SHBG, those in the highest quartile were more than 10 times less likely to have incident diabetes. Corroborating results were found in men looking at a similar population from the Physician's Health Study. The mechanism by which SHBG affects diabetes risk is speculated to be related to direct modulation of gonadal steroids on tissues, but is otherwise ill-defined.

There are identified genes associated with production of SHBG. Both SHBG levels and gene identification may become useful to predict risk of type 2 diabetes. ■

## Effect of CYP2C19 variants on clopidogrel

**Source:** Shuldiner AR, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 2009;302:849-857.

Clopidogrel (CPG) and aspirin (ASA) are widely utilized as antiplatelet agents for both primary and secondary prevention of cardiovascular disease. Because platelet activation, adhesion, and aggregation are modulated by multiple redundant pathways, it should come as no surprise that any single pharmacologic intervention might be imperfect in its ability to curtail platelet activity. Additionally, even when an antiplatelet agent is mechanistically highly effective, intra-individual variations in metabolism and genetics exert great influence on pharmacokinetics.

CPG must be converted into an active metabolite by the P450 2C19 pathway to functionally impair platelet activity. The impact of genetic variations in 2C19 activity may be examined in vitro through platelet aggregometry. If the laboratory discerns meaningful differences in platelet activity related to genetic variations in 2C19, the next question would be whether such factors impact clinical endpoints.

Chromosomal analysis indicates a strong relationship between genetic variations in 2C19 activity and platelet aggrega-

bility in response to clopidogrel, consistently predicting incomplete CPG activity upon platelets.

After confirmation of the 2C19-clopidogrel relationship, a population of individuals undergoing PCI (after which clopidogrel treatment is standard) were followed for 1 year. During this year, those with genetic variants impairing the antiplatelet activity of CPG were more than twice as likely to incur a CV ischemic event or death. In the future, therapeutic choices may be directed by knowledge of such genetic variation. ■

## Denosumab for osteoporosis

**Source:** Cummings SR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756-765.

It appears that osteoporosis (OSPS) is the end result of a war lost by the osteoblasts to the conquering osteoclasts, whether by frailty of the former, vociferousness of the latter, or some similar combination of factors. Indeed, our most popular tools for the prevention and treatment of OSPS — bisphosphonates — mediate improvements in bone mineral density through downregulation of osteoclasts.

Denosumab is an antibody against the activator of osteoclasts called RANKL. Once RANKL is antibody-blocked, osteoclast activity is reversibly inhibited. Denosumab has the desirable characteristic of only requiring a subcutaneous injection every 6 months.

The study by Cummings et al enrolled almost 8000 osteoporotic women who were randomized to denosumab or placebo twice yearly for 3 years. Over that interval, a 40%-60% decrease in hip fracture and vertebral fracture was seen (compared to placebo), with no incidence of the osteonecrosis that has been troublingly reported (albeit rarely) with bisphosphonates. The favorable tolerability of this agent (adverse effect profile similar to placebo) adds to the allure of this yet-to-be approved alternative for OSPS. ■

## CRP and HTN treatment

**Source:** Fulop T, et al. C-reactive protein among community-dwelling hypertensives on a single-agent antihypertensive treatment. *J Am Soc Hypertens* 2009;3:260-266.

C-reactive protein (CRP) is a recognized marker of inflammation, and is linearly associated with acute cardiovascular endpoints (e.g., MI, stroke). Whether this association is causal, concomitant, or consequent remains a matter of great debate. Indeed, even for advocates of the "CRP-leads-to-CVD events" hypothesis, it remains to be determined whether interventions which specifically lower CRP reduce events, and if so, whether event reduction is secondary to CRP reduction, or another cotherapeutic effect (i.e., as in statin therapy, wherein CRP is reduced, but so is LDL).

Hypertension is recognized to be the most important modifiable risk factor for cardiovascular disease. Different classes of antihypertensive therapy might have different effects upon CRP. To address this, a subgroup of the Genetic Epidemiology Network of Arteriopathy study group was analyzed. In this population, 662 subjects who were on monotherapy for hypertension (HTN) had their CRP measured. After adjustment for a variety of other factors (e.g., age, gender, BMI, smoking, diabetes), there were distinct differences in mean CRP depending upon which class of HTN monotherapy was being used. Overall, CRP levels were lowest in persons on inhibitors of the renin-angiotensin-aldosterone group (e.g., ACE inhibitor, ARB) and highest in the group on diuretics.

Current expert opinion suggests that simple blood pressure reduction is the primary effector of CV risk reduction, regardless of therapeutic class. The debate about whether therapeutic side-stream characteristics (e.g., class of agent, activity upon the renin-angiotensin-aldosterone system, metabolic effects) are important in selection of treatment will likely gain further fuel by these observations that various classes of HTN treatment differ in their effect upon the inflammatory marker CRP. ■

***Clinical Briefs in Primary Care*** is published monthly by AHC Media LLC.

**Associate Publisher:** Coles McKagen. **Editor:** Stephen Brunton, MD. **Senior Managing Editor:** Paula Cousins. This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

**Subscriber Information**
**Customer Service: 1-800-688-2421**
**E-Mail Address:** paula.cousins@ahcmedia.com
**World Wide Web:** www.ahcmedia.com
**Address Correspondence to:** AHC Media LLC
3525 Piedmont Road, Building Six, Suite 400
Atlanta, GA 30305.

AHC Media LLC

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*.

# SSRIs and Pregnancy: Increase in Septal Heart Defects

***In this issue:*** Depression and pregnancy, new vaccine recommendations from the CDC, corticosteroids and/or antivirals for Bell's palsy, rasagiline and Parkinson's disease, and FDA Actions.

## Use of SSRIs during pregnancy

Depression is common in pregnancy, affecting up to 20% of women, with about 13% taking an antidepressant during pregnancy. A new study from Denmark suggests that use of sertraline (Zoloft®) and citalopram (Celexa®) by mothers during pregnancy is associated with an increased risk of septal heart defects in their children. Researchers utilized the Danish nationwide registry to review nearly 500,000 births from 1996 to 2003. Selective serotonin reuptake inhibitors (SSRIs) in general were not associated with major malformations, but were associated with septal heart defects. Among the individual drugs, sertraline conveyed the highest risk (odds ratio [OR], 3.25; confidence interval [CI], 1.21-8.75), followed by citalopram (OR, 2.52; CI, 1.04-6.10). Use of more than one SSRI was associated with an OR of 4.70 (CI, 1.74-12.7). The absolute prevalence of septal heart defects was 0.5% among unexposed children, 0.9% among children whose mothers received any SSRI, and 2.1% among children whose mother were prescribed more than one SSRI (*BMJ* 2009:339:b3569; Epub ahead of print 23 Sept 2009). Significant in this study was the low overall rate of heart defects and the lack of association of heart defects with paroxetine (Paxil®) or fluoxetine (Prozac®), although the authors consider this a "class effect," and the greatest risk was noted if more than one drug was used during pregnancy. ■

## CDC issues new vaccine recommendations

The Centers for Disease Control and Prevention has recently revised several vaccine recommendations:

***Quadravalent meningococcal conjugate vaccine.*** The Advisory Committee on Immunization Practices (ACIP) is recommending revaccination of persons at prolonged increased risk for meningococcal disease. In a statement in the September 25th *Morbidity and Mortality Weekly* Report, ACIP is recommending that persons with increased susceptibility to meningococcal disease, such as those with persistent complement component deficiencies, functional asplenia, prolonged exposure such as those traveling to or living in nations where the disease is epidemic or hyperendemic, should receive a booster with the quadravalent meningococcal conjugate vaccine 5 years after their previous vaccination if they received it at age 7 or older. Children who received the first vaccine between ages 2 and 6 should be revaccinated after 3 years. Those who remain at high risk should continue to be revaccinated every 5 years. The recommended booster vaccine is the MCV4 vaccine (Menactra®).

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

**Haemophilus influenzae *type b vaccine.*** The FDA recently approved Hiberix® for *Haemophilus influenzae* type b (Hib) ending a prolonged shortage of the Hib vaccine. Hiberix is approved as a booster for children ages 15 months to 4 years who have received a primary series of shots. The Centers for Disease Control and Prevention has now issued recommendations that the vaccine can be given as early as age 12 months to facilitate timely booster vaccination. Children who missed a booster because of the recent shortage should receive a booster with any of the Hib vaccines, including Hiberix, at the earliest opportunity.

***Hepatitis A vaccine.*** Hepatitis A vaccine is now recommended for all close household contacts and international adoptees when the children are from intermediate-risk or high-risk areas, with an initial dose being given at least 2 weeks before the child's arrival.

***Quadravalent human papilloma virus vaccine.*** In related news, an FDA advisory panel is recommending that the quadravalent human papilloma virus vaccine (Gardasil®) be approved for males ages 9-26 to prevent genital warts. The vaccine is currently approved only for females in that age group. Meanwhile, the same FDA advisory panel has endorsed the approval of GlaxoSmithKline's Cervarix®, a bivalent HPV vaccine which targets HPV 16 and HPV 18, leading causes of cervical cancer. If approved it would also be recommended in women ages 10-25. The new vaccine protects against 2 of the HPV strains covered by Gardasil, but also contains an adjuvant, which is designed to enhance the immune system's response to these HPV strains. Whether this imparts clinical difference is yet to be seen. The FDA is yet to act on the advisory committee's recommendations. ■

## Bell's palsy: Corticosteroids and/or antivirals?

For treatment of Bell's palsy, corticosteroids with or without antivirals have been the subject of much debate. A new meta-analysis suggests that combination therapy may lead to better outcomes. The review included 18 trials with 2786 patients. The outcomes were unsatisfactory facial recovery at 4 months, unsatisfactory short-term recovery, synkinesis and autonomic dysfunction, or adverse effects. Combination therapy with corticosteroids and antivirals resulted in slightly better outcome than steroids alone ($P = 0.05$). Antiviral agents alone did not show a benefit (*JAMA* 2009;302:985-993). At least one source (UpToDate) recommends a typical treatment regimen for Bell's palsy of prednisone 60-80 mg per day along with valacyclovir 1000 mg three times a day for 1 week. ■

## Rasagiline and Parkinson's disease

Does rasagiline slow the progression of Parkinson's disease? A recent study suggests lower doses of the drug may be beneficial. In this multinational study, 1176 subjects with untreated Parkinson's disease were randomized to rasagiline 1 mg or 2 mg per day for 72 weeks or placebo for 36 weeks followed by rasagiline for 36 weeks. Disease progression was rated on a standard rating scale. Patients who were started at baseline on rasagiline 1 mg met all endpoints in the primary analysis: a slower rate of worsening between weeks 12 and 36 ($P = 0.01$), less worsening of the score between baseline and week 72 ($P = 0.02$), and non-inferiority between weeks 48 and 72 ($P \leq 0.001$). Interestingly, all 3 endpoints were not met with the higher dose of 2 mg per day. The authors conclude that early treatment with rasagiline at a dose of 1 mg per day provided a possible disease-modifying effect, but suggested the results must be interpreted with caution (*N Engl J Med* 2009;361: 1268-1278). Although the findings of this paper are somewhat confusing, it offers some hope since there is currently no effective therapy to slow or stop disease progression in Parkinson's disease. ■

## FDA Actions

The FDA has approved asenapine (Saphris®) for the treatment of schizophrenia and bipolar I disorder in adults. The drug is approved for first-line treatment of both conditions. Schering-Plough provided the agency with safety data in 4500 patients, some of whom were treated for more than 2 years. Like other antipsychotics, asenapine will carry a warning regarding increased mortality in elderly patients with dementia-related psychosis. The drug is expected to be available in the fourth quarter of 2009.

The FDA has lowered the approved age limit for levocetirizine (Xyzal®) to 6 months for children with chronic hives and perennial allergic rhinitis and 2 years for children with seasonal allergic rhinitis. Previously the drug had been approved for children 6 years and older. Levocetirizine is marketed by UCB and Sanofi Aventis. ■