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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Risk of Hemorrhage on Warfarin

By John P. DiMarco, MD, PhD
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Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

SOURCE: Fang MC, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study. *J Am Coll Cardiol* 2011;58:395-401.

In this study, the authors attempt to develop a risk stratification score to predict bleeding in patients treated with warfarin oral anticoagulation. The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study follows 13,559 adults with nonvalvular permanent atrial fibrillation enrolled in the Kaiser Permanente Health System of Northern California. Clinical characteristics for these patients are maintained in a large system-wide database. This database was searched for discharge diagnoses for extracranial hemorrhages and for primary and secondary diagnoses of intracranial bleeding events including intracerebral, subarachnoid, or subdural hemorrhages. The records of patients with an identified hemorrhagic event were reviewed by a clinical outcomes committee and classified using a formal protocol. Only events that occurred within 5 days of warfarin exposure were included. Hemorrhages that were not present on admission but occurred during a hospitalization or were procedurally related were excluded. Major hemorrhages were defined as those that were either fatal, required a transfusion of greater than or equal to two units of packed cells, or involved a critical anatomic site.

The data in this report were obtained in 9186 subjects in the ATRIA study cohort who contributed 32,888 person-years of warfarin exposure. The group was split into "derivation" and "validation" cohorts for developing and testing the risk scheme. Among these patients, there were 461 warfarin-associated major hemorrhages for an annualized

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rate of 1.4% per year. Five variables were identified as having the highest predictive value: baseline anemia, severe renal disease, age greater than 75 years, any prior hemorrhage diagnosis, and a diagnosis of hypertension. Stratification of these variables resulted in anemia and severe renal disease being assigned 3 points, age greater than 75 being assigned 2 points, and prior hemorrhage diagnosis and hypertension being assigned 1 point each. Therefore, the final risk scheme had a possible range of 0 to 10 points. The score was essentially equally effective in both the derivation and validation cohorts. In the combined derivation and validation group, events per 100 patient years ranged from 0.4 for those with a risk score of 0, 2.6 for those with a risk score of 4, and up to 12.4 and 17.25 for patients with risk scores of 9 or 10. When grouped into low (0 to 3 points), intermediate (4 points), and high-risk (5-10 points) category groups, the event rates were 0.76, 2.62, and 5.76 events per 100 patient years. The calculated c-index statistics for the three category score system was 9 and for continuous scores 0.74. These values were superior to the c-index scores for six other published risk schemes.

The authors conclude that a relatively simple scoring system based on these five parameters will help clinicians estimate the magnitude of hemorrhagic risk when prescribing or continuing anticoagulant therapy.

■ COMMENTARY

Anticoagulation therapy in patients with non-valvular atrial fibrillation requires physicians and patients to carefully weigh the potential risks and benefits of long-term therapy. The two most prevalent stroke risk scoring systems are the CHADS2 and the CHA2DS2VASc, and practice guidelines guideline rely heavily on them. Bleeding risk has received less attention in the atrial fibrillation population. Therefore, the new system proposed here should be quite valuable to clinicians planning to start therapy.

Several other factors also must be considered. Favoring a decision for anticoagulation is the observation that only intracranial bleeding is frequently fatal and/or disabling, while many strokes are not. Against anticoagulation is the frequent "minor" bleeding that adversely affects the lifestyle of many patients. We should also note that the recent release of dabigatran, an oral direct thrombin inhibitor, and the expected approval of one or more Factor Xa inhibitors for stroke prevention in atrial fibrillation have changed the playing field in oral anticoagulation. Although it is likely that the bleeding risk score here will also work for patients treated with these new agents, that will have to be documented clinically. It is also somewhat unfortunate that the authors chose not to compare their risk scheme to the recently published HAS-BLED scheme used in the recent European Society of Cardiology atrial fibrillation guidelines. The HAS-BLED score includes points for a history of a labile INR, hepatic disease, use of drugs or alcohol, and age 65-75. Both of these two new bleeding risk scoring systems are relatively simple and should prove helpful to clinicians as they deal with atrial fibrillation patients. ■

ABSTRACT & COMMENTARY

BUN and High-Dose Loop Diuretics

By Michael H. Crawford, MD, Editor

SOURCE: Testani JM, et al. Interaction between loop diuretic-associated mortality and blood urea nitrogen concentration in chronic heart failure. *J Am Coll Cardiol* 2011;58:375-382.

High-dose loop diuretics are often necessary to reduce elevated filling pressures in patients with heart failure. However, they are known to activate neurohormonal mechanisms that may be harmful. Neurohormonal activation can increase blood urea nitrogen (BUN). Thus, these investigators from the University of Pennsylvania hypothesized that BUN would predict loop diuretic-associated mortality. They examined the Beta-Blocker Evaluation of

Survival Trial (BEST) database. This was a study of the effect of adding bucindolol to ACE I in class III-IV systolic heart failure patients. All patients with a baseline BUN and loop diuretic therapy were included in this analysis (2456 of 2708 patients). High-dose loop diuretic was defined as 160 mg/day or more of furosemide or its equivalent. The primary outcome was all-cause mortality, which was not different in the bucindolol vs placebo overall results. High-dose diuretics were used in 680 patients (28%). Heart failure severity measures were higher in the high-dose group and they had a higher mortality (hazard ratio [HR] 1.56). After controlling for confounders, this association was no longer significant (HR = 1.06). Baseline BUN also was associated with higher mortality (HR = 1.28) and with other markers of high mortality. However, after controlling for confounders it was still significantly related to survival (HR = 1.3). In those taking high-dose diuretics, an elevated BUN predicted a greater risk of death (HR = 3.09) than in those not on high-dose diuretics. The authors concluded that the risk of mortality associated with high-dose diuretic use is strongly related to BUN concentrations, which suggests that neurohormonal activation is the mechanism.

■ COMMENTARY

Patients with more severe heart failure are more likely to receive high-dose loop diuretics, which confounds the data showing that mortality is higher in patients receiving high-dose loop diuretics. In this study, adjustment for covariates eliminated the higher mortality in the high-dose diuretic patients. However, BUN levels in those receiving high-dose diuretics separated those who benefitted from those who had a higher mortality, and this difference persisted after adjustment for other covariates. The cut point was the median BUN level, which was 21 mg/dL.

Urea is freely filtered at the glomerulus and is then subject to considerable tubular reabsorption. Loop diuretics block the tubular absorption of sodium chloride, which results in diuresis, but also renin release, which initializes a neurohormonal cascade. However, the net effect of all the physiologic variables in heart-failure patients make it difficult to predict who will be harmed by high-dose loop diuretics. This study suggests that BUN may be a marker for those patients with high neurohormonal activation in whom high-dose loop diuretics may be harmful. Perhaps patients with high BUN should be treated with other drugs or ultrofiltration.

There are several limitations to this study. It was retrospective and only the baseline BUN was considered. All the patients were class III-IV heart failure. The study was not blinded. Renal function at baseline varied markedly and protein intake was not known. Also, there may have been unmeasured covariates that influenced the data. Finally, this study was one of the few negative studies for beta-blockers in heart failure, so perhaps there is something atypical about the patients. Interestingly, by design, BEST had a high percentage of African American patients. Thus, before these data can be used for clinical purposes, a prospective study to see if a treatment strategy in severe heart failure subjects based on BUN improves outcomes will need to be performed. ■

ABSTRACT & COMMENTARY

Nonobstructive Coronary Plaque Detected by CT Predicts Mortality

By Andrew J. Boyle, MBBS, PhD

Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

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

SOURCE: Lin FY, et al. Mortality risk in symptomatic patients with nonobstructive coronary artery disease. *J Am Coll Cardiol* 2011;58:510-519.

Computed tomography (CT) imaging has progressed substantially in recent years, and we are now able to non-invasively image coronary artery disease in many patients. While we have copious data on outcomes of patients with obstructive coronary artery disease, little is known about the outcomes in patients who have non-obstructive coronary artery plaque. In part, this is due to the fact that we were previously unable to image the coronary arteries without invasive coronary angiography, which carries some inherent risk. Therefore, only patients with significant symptoms and/or signs of obstructive coronary artery disease, such as a positive stress test, are usually subjected to invasive angiography. In addition, invasive coronary angiography does

not image the wall of the coronary artery, only the lumen, and may miss nonobstructive coronary plaque. Lin and colleagues studied the outcomes of patients with nonobstructive plaque detected by CT coronary angiography (CTCA).

In a two-center study, 2583 consecutive patients undergoing CTCA were studied for the primary endpoint of mortality. Indications for the CTCA were chest pain in 85% and others (peripheral arterial disease, cerebrovascular disease, screening) in 15%. They excluded all patients with prior known coronary artery disease (CAD), including prior revascularization, and those with any lesions (defined as ≥ 50% stenosis). Social security death index was searched to determine all-cause mortality. They censored early death (within 90 days of CTCA) to exclude deaths attributable to acute coronary syndromes.

Over a median of 3.1 ± 0.5 years follow-up, total mortality was 2.3%. The average age was 53 ± 14 years and 42% were male, 15% had diabetes, 51% dyslipidemia, and 28% were smokers. Patients with no identifiable coronary plaque had low mortality (1.2% overall; annualized mortality 0.34%). A higher burden of plaque was associated with age, male gender, hypertension, diabetes, dyslipidemia, and past smoking. After adjustment for traditional coronary risk factors, the presence of nonobstructive plaque was associated with higher mortality. The presence of any plaque was associated with an adjusted hazard ratio of 1.98 compared to no plaque ($P < 0.05$). Furthermore, a greater extent of plaque was associated with even greater mortality. Patients with nonobstructive plaque in three epicardial vessels had an adjusted hazard ratio of 4.75 compared to no plaque ($P < 0.001$), and those with ≥ 5 segments affected had an adjusted hazard ratio of 5.12 compared to no plaque ($P < 0.001$). As a validation, they showed in their cohort that mortality was associated with age, diabetes, dyslipidemia, and smoking.

Even in patients who are not considered to be at high risk (Framingham estimated 10-year risk < 10%), the presence of plaque was associated with higher mortality (3.4%; $P < 0.001$ vs no plaque). In patients who had no treatable risk factors (diabetes, dyslipidemia, hypertension), the presence of plaque was still associated with a higher mortality (6.7%; $P < 0.001$ vs no plaque). Compared to Framingham risk, the presence of any plaque showed an improved net reclassification improvement (20.5%; $P = 0.04$). Interestingly, despite the strong association between plaque burden and mortality, there was no association between plaque composition and mortality in this cohort. The authors conclude that the presence and extent of nonobstructive plaques augment prediction of incident mortality beyond conventional clinical risk assessment.

■ COMMENTARY

This is a very provocative study showing a doubling of mortality with the presence of any plaque on CTCA, and a 5-fold increase in mortality for widespread nonobstructive plaque, despite correcting for traditional risk factors. Furthermore, even patients at low clinical risk and without treatable traditional risk factors had increased mortality in the presence of nonobstructive coronary plaque. This suggests that there may be a significant gap in our current assessment and management of CAD — there are patients we are not identifying with clinical risk prediction who remain at high risk and are currently not captured by treatment guidelines. However, as with any new diagnostic test, we still do not know if treatment based on these findings will alter the clinical outcomes, and if so, whether it is cost effective to test and treat in this way. As this field evolves, carefully designed prospective clinical trials are needed to test this approach.

There are several limitations of this study that should be mentioned. First, the treatment of patients was at the discretion of the physician. Because the results of the study were disclosed, they may have altered treatment decisions and this is therefore, not truly a natural history study. Furthermore, we are not told of the treatment regimens of patients, in particular how well their lipids and blood pressure were controlled, and whether any changes based on the test results altered outcomes. Second, all-cause mortality as the primary endpoint does not necessarily define a cause and effect relationship between coronary plaque and death. There are many possible unmeasured confounders in this patient cohort and, thus, the results should be interpreted with caution. Third, this cohort was predominantly a chest-pain cohort with a minority undergoing CTCA for non-chest pain indications. Therefore, the results cannot be generalized to the community at large and one cannot recommend screening for CAD in asymptomatic patients based on the results of this study. These results, while compelling in their magnitude, should be considered hypothesis-generating only. As CTCA technology continues to evolve, and radiation doses are becoming lower with more widespread use of prospective gating, it is likely that noninvasive imaging of coronary plaque will find some place in our assessment and management of CAD. However, at this time, the precise use of CTCA remains to be more fully defined. ■

Does a Moderately Dilated Ascending Aorta Continue to Dilate After AVR for Severe AS?

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

SOURCE: Gaudino M, et al. Aortic expansion rate in patients with dilated post-stenotic ascending aorta submitted only to aortic valve replacement. *J Am Coll Cardiol* 2011;58:581-584.

In patients with severe valvular aortic stenosis (AS), ascending aortic dilatation is common, and is thought to be due to the alterations in flow caused by the stenotic valve. Surgical aortic valve replacement (AVR) is the treatment of choice for severe AS. When there is severe ascending aortic dilatation, concomitant replacement of the aortic root can be performed. In cases of mild aortic dilatation, only AVR is performed. However, in cases of moderate aortic dilatation, it is controversial whether isolated AVR or combined AVR plus replacement of the ascending aorta should be performed. Gaudino and colleagues studied the natural history of moderate ascending aortic dilatation to determine the rate of expansion of the aorta once the valve had been replaced. Over a 10-year period, 93 patients with isolated severe valvular AS in a tricuspid aortic valve and a moderately dilated ascending aorta (50–59 mm diameter) underwent AVR at their institution without repair of the ascending aorta. These patients were followed for 14.7 ± 4.8 years. Exclusion criteria were aortic diameter ≥ 60 mm, the presence of a bicuspid aortic valve, connective tissue disease, or significant coronary artery disease requiring concomitant coronary artery bypass graft (CABG). Paired CT scans of the aorta before surgery and at long-term follow-up were available in 64 patients.

The mean age was 67 years and 69% were male. Importantly, hypertension was present in only 44%. Mechanical valves were used in 71%. Surgical mortality was 1% (one patient). Over the 14-year follow-up, there was no change in aortic diameter following AVR (56 ± 2 mm before vs 57 ± 11 mm after; *P* = NS). The mean expansion rate of the aorta was 0.3 ± 0.2 mm per year and no statistical association was found between any clinical variable and aortic dilatation. Long-term mortality was 17% and in no cases was the death attributable to aortic pathology. The authors conclude that in the absence of connective tissue diseases, AVR alone is sufficient to prevent further expansion of the aorta in patients with moderate post-stenotic dilation of the ascending aorta, and that aortic replacement can probably be reserved for patients with a long life expectancy.

■ COMMENTARY

This is a very interesting study that may inform cardiac surgeons on whether they need to perform aortic root replacement at the time of AVR. It is important to emphasize that this does not apply to patients with aortic regurgitation, connective tissue disease such as Marfan's syndrome, or biscuspid aortic valve. The current recommendations are to replace the aortic root in these patients, and this study excluded these patients, so the results should not be extrapolated to these groups. It is likely that the pathology leading to aortic dilatation cases of aortic pathology is very different than that in isolated AS, where it is believed that the altered flow patterns across the stenotic valve lead to the aortic dilatation. This study is congruent with this theory, because once the valvular pathology is removed by AVR, the dilatation ceases. Furthermore, the very slow rate of aortic expansion in this study following AVR (0.3 mm per year) compares very favorably with prior reports in aortic aneurysms or unoperated AS, where the rates of expansion have been shown to be much faster.

Hypertension is an important contributor to arterial pathology in general, but more specifically to aortic atherosclerosis and dilatation. Hypertension was only documented in 44% of patients in this study. We are not told how well the blood pressure was controlled, and this may be an important contributing factor to aortic dilatation. The importance of blood pressure control in these patients cannot be overemphasized. This study suggests that isolated AVR may be a reasonable option in patients with moderate post-stenotic aortic dilatation. Cardiac surgeons may be pleased to hear that the more complex and invasive surgical option of ascending aortic replacement may not be required for all of these patients. ■

ABSTRACT & COMMENTARY

Importance of QRS Duration in Resynchronization Therapy

By John P. DiMarco, MD, PhD
Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

SOURCE: Sipahi I, et al. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: Meta-analysis of randomized controlled trials. *Arch Intern Med* 2011 Jun 20. [Epub ahead of print.]

Cardiac resynchronization therapy (CRT) is now accepted as a disease-modifying therapy in patients with heart failure, left ventricular dysfunction, and intraventricular conduction defects. In this paper, Sipahi and colleagues review the data on the benefits of CRT in relationship to baseline QRS duration.

The authors performed a meta-analysis after reviewing all studies involving CRT. The meta-analysis could only include trials that reported clinical outcomes stratified by QRS duration, were randomized, and had a non-CRT control group. Although 412 studies were initially identified, there were only a total of five randomized controlled trials enrolling 5813 patients that met all criteria for inclusion in the meta-analysis. These trials, however, were the large, long-term studies on CRT and, therefore, they included much of the published data on the effects of CRT. The studies were COMPANION, CARE-HF, REVERSE, MADIT-CRT, and RAFT. COMPANION and CARE-HF included patients with only class III or class IV heart failure. REVERSE and MADIT-CRT included patients with only class I or II heart failure. RAFT included mostly patients with class II, but also some with class III, heart failure. Where possible, patients were then stratified as having either moderately prolonged QRS durations (120 to 149 msec) compared to those with greatly prolonged QRS durations (greater than or equal to 150 msec). Accommodations were made if the trial used different QRS cut-off points when reporting outcomes.

In these five studies, most patients were male. About 50% had nonischemic heart failure. The mean left-ventricular ejection fractions ranged from 21% to 27%. Between 69% and 90% of the patients had left bundle branch block morphology. All studies required patients in both the control and the CRT groups to receive optimal medical therapy. In COMPANION and CARE-HF, the CRT arm involved biventricular pacing (CRT-P) only without associated defibrillation capability. In REVERSE, MADIT-CRT, and RAFT, the large majority of patients had devices with defibrillation (CRT-D) in both arms.

The meta-analysis showed that patients with a severely prolonged QRS duration randomized to CRT had a 40% risk reduction in death and heart failure hospitalization. In contrast, there was no statistically significant benefit in patients with moderately prolonged (120 msec to 149 msec) QRS durations in any of the trials and only a trend toward benefit in CARE-HF. In this latter trial, the moderately prolonged QRS duration subgroup, however, included many patients with a QRS duration between 150 msec and 158 msec. When data from all the trials were plotted, there was a statistically significant relationship between QRS duration and the log of the risk-reduction slope. Patients with QRS durations below 150 msec did not receive benefit from CRT. The magnitude of benefit became more prominent as the QRS duration became more prolonged. The same results were seen when several scenarios were tested using sensitivity analysis. The importance of baseline QRS duration was not affected by the patient's heart failure classification.

The authors conclude that the effectiveness of CRT is only demonstrable in patients with a QRS of 150 msec or greater. They urge that QRS duration should be an important criteria for selecting patients for CRT.

■ COMMENTARY

There are a number of factors that affect the probability of benefit with CRT. Higher response rates to CRT have been noted in patients with left bundle branch block as opposed to right bundle branch block, among women as opposed to men, in those with a nonischemic cardiomyopathy as opposed to a ischemic cardiomyopathy, and in those with longer QRS durations. However, for the most part, government agencies and guideline writers have taken the entry criteria for the large CRT trials and used those criteria

when writing guidelines for insertion. This means that a significant number of patients for whom CRT is currently recommended will have QRS durations below 150 msec. Unfortunately, as shown here, this group seems to have relatively little short-term benefit. We also must remember that there is significant increased risk of complications as well as expense associated with adding the left ventricular lead. The average rate of left ventricular lead complications, either failure to insert or late dislodgement or phrenic nerve stimulation, may be as high as 15%. The CRT trials usually did not count these LV lead problems as primary endpoints even if another surgical procedure or added hospitalization was required. Finally, we must also remember that many of the potential benefits of CRT may be due to a favorable influence on ventricular remodeling. These benefits may take years to become apparent and were probably not detectable in the studies reviewed here.

This meta-analysis is quite useful in helping us structure our thinking, particularly in patients with class I or II heart failure who receive relatively little early benefit. For patients with an ICD indication but only moderate QRS prolongation, my preference has been to implant an ICD and then upgrade those patients who go on to either require right ventricular pacing or develop progressive widening of their QRS complex. Among patients with a borderline QRS prolongation with class III or IV heart failure who need early benefit, I discuss with the patient and the referring physician the likelihood that they will improve with CRT. For patients with shorter QRS durations (120-130 ms) or right bundle branch block, I often discourage use of the more complicated CRT device. ■

ABSTRACT & COMMENTARY

Echo Assessment of Diastolic Function

By Michael H. Crawford, MD, Editor

SOURCE: Unzek S, et al. Effect of recommendations on interobserver consistency of diastolic function evaluation. *JACC Cardiovasc Imaging* 2011;4: 460-467.

The echocardiographic assessment of diastolic function of the left ventricle (LV) involves five measurements derived from two-dimensional imaging, pulsed Doppler, Color M-mode, and tissue Doppler. Not only is it complicated, but sometimes the measurements are discordant. Thus, the American and European echo societies have put out a joint algorithm to follow, but its impact on observer concordance is unknown. Thus, these investigators from the Cleveland Clinic selected 20 patients undergoing echocardiographic LV function evaluation with interpretable studies (no atrial fibrillation, etc.) and a brain natriuretic peptide (BNP) level on the same day for analysis. The studies were interpreted by 18 experts from seven countries without clinical data except for age and sex. They scored diastolic function stage 0, I-III, and estimated filling pressure as high or normal. Their readings were compared to a reference standard of two experienced readers using the new algorithm for diastolic function stage and BNP for the filling pressure estimation (> 100 pg/mL was elevated filling pressure).

Agreement among readers for diastolic class was modest (kappa = 0.62; 1.0 would be perfect) as was estimation of filling pressure (k = 0.61). The sensitivity and specificity of raised filling pressure vs the reference read were 66 and 88%, respectively, and vs BNP > 100 pg/mL were 69 and 93%, respectively. Among the diastolic dysfunction classes, stage I (delayed relaxation) had the best concordance at 92%, stage III (restrictive) was next at 65%, and stage II (pseudo normal) was least at 58%. Normal function was 77%. The authors concluded that estimations of diastolic dysfunction and elevated filling pressure are concordant among readers in the majority of patients, but considerable variability exists.

■ COMMENTARY

Reading a paper like this one should make all of us who struggle with measuring and classifying diastolic function feel better. Even international experts have difficulty with this and do not agree at a frequency that inspires confidence. Also, the new American/European society's algorithm did not seem to help.

What is going on here? Assessing diastolic function involves synthesizing the results of several measures, each with their own limitations. Many are affected by age, loading conditions, conduction and rhythm abnormalities, mitral valve disease, and systolic LV function. Also, many of these measurements are technically challenging. In addition, diastole is complex, involving three stages, each with a different physiology.

Why didn't the new algorithm help? Basically it did not go beyond what these expert readers already knew. So it might help less advanced readers, but that remains to be shown. What would help expert readers is an algorithm that factored in known variables such as age and gave a hierarchy of measures to resolve conflicting results. For example, if E/E' is normal, but the left atrium is clearly enlarged, filling pressures are probably increased.

I suspect this is not the last word on the topic as this study had its own limitations. The reference read and BNP standards are imperfect. The number of subjects was small and there were not many with E/E' in the 8-15 range. Expect more to come. ■

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CME Questions

13. A new risk score for bleeding risk on warfarin for nonvalvular atrial fibrillation patients is heavily influenced by:
a. age.
b. anemia and renal disease.
c. hypertension and prior hemorrhage.
d. hepatic disease.

14. Cardiac resynchronization therapy works best when QRS duration is:
a. 120-140 msec.
b. 140-150 msec.
c. 150-160 msec.
d. > 160 msec.

15. Moderate ascending aorta dilatation in senile aortic stenosis is likely to follow which course following valve replacement?
a. Decrease in size
b. No change
c. Mild increase
d. Marked increase

16. High-dose loop diuretic therapy may confer increased risk when:
a. creatinine is > 2.0 mg/dL.
b. BUN is > 20 mg/dL.
c. sodium is < 134 mg/dL.
d. potassium is > 5.0 mg/dL.

17. Plaque detected by CT coronary angiography in patients mainly with chest pain is associated strongly with?
a. Diabetes
b. Age
c. Mortality
d. Smoking

18. The concordance between readers of echo diastolic function measures is best for:
a. normal function.
b. delayed relaxation.
c. pseudo normal.
d. restrictive.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.

PHARMACOLOGY WATCH

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

ACEIs and ARBs Help Patients with Aortic Stenosis

In this issue: ACEI/ARB therapy for AS; safety alert issued for dronedarone; statins and cancer risk; nesiritide and heart failure; and FDA actions.

ACEI/ARB therapy for aortic stenosis

Drugs that block the renin-angiotensin system are not only safe, they are beneficial in patients with aortic stenosis (AS) according to a new study. This runs counter to current recommendations that suggest that angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are relatively contraindicated in patients with AS. The study looked at more than 2000 patients with AS in Scotland, of which the majority had mild-to-moderate stenosis, while about one-quarter had severe AS. Of the total number, nearly 700 were on ACEI or ARB therapy. Over a mean follow-up of 4.2 years, just over half the patients died, of which 48% died from cardiovascular (CV) deaths. Those treated with ACEIs or ARBs had a significantly lower mortality rate (adjusted hazard ratio [HR] 0.76; confidence interval [CI] 0.67-0.92; $P < 0.0001$) and fewer CV events (adjusted HR 0.77; 95% CI: 0.65-0.92; $P < 0.0001$) compared to those not on ACEIs/ARBs. The authors conclude that ACEI/ARB therapy is associated with improved survival and lower risk of CV events in patients with AS. These findings were consistent in patients with nonsevere and severe AS. The rate of valve replacement also was lower in patients treated with ACEIs/ARBs (*J Am Coll Cardiol* 2011;58:570-576). This study was a retrospective observational study and prospective, randomized, controlled trials are warranted to confirm these findings. ■

Drug safety alert issued for dronedarone

The antiarrhythmic dronedarone (Multaq) is again coming under scrutiny from the FDA after review of the company-sponsored PALLAS study of more than 3000 patients, which showed that the drug is associated with an increased mortality rate in patients with atrial fibrillation (AF). Dronedarone currently is approved for treatment of paroxysmal AF and atrial flutter. The new study investigated its use in patients with permanent AF. The study was halted early when the mortality rate in the treatment group was found to be double the rate in the placebo group (32 deaths [2%] in the dronedarone arm vs 14 [0.9%] in the placebo arm). The rate of unplanned hospitalization and stroke also was double in the dronedarone group vs the placebo group. All findings were statistically significant. These findings led the FDA to issue a drug safety alert on July 21, 2011. This follows a January 2011 drug safety alert regarding rare but severe liver injury associated with use of dronedarone. Currently, the FDA is recommending that physicians should not prescribe dronedarone to patients with permanent AF while they further evaluate the data (FDA Drug Safety Communication at www.FDA.gov/drugs/drug safety). ■

Statins do not increase risk of cancer

A new retrospective cohort analysis suggests that statins are not associated with an increased risk of cancer. Researchers used the General

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Electric Centricity electronic medical record database of more than 11 million adult Americans to match nearly 46,000 patient pairs by propensity scores receiving and not receiving statin therapy. With an average time in the database of 8 years, the incidence of cancer in patients taking a statin was 11.37% compared with 11.11% in matched patients not taking a statin (HR 1.04; 95% CI: 0.99-1.09). The authors conclude that this analysis demonstrates no statistically significant increase in cancer risk associated with statins, although they do suggest that more research is needed (*J Am Coll Cardiol* 2011;58:530-537). Lingering fears about cancer risk associated with statins was strengthened by the SEAS trial published in 2008, which showed the combination drug simvastatin/ezetimibe (Vytorin) was associated with a two-fold increase in the rate of cancer in a small group of patients. The FDA has continued to study these data along with data from other studies, but this new analysis adds significant evidence of a lack of association between statins and cancer. ■

Nesiritide and heart failure

Nesiritide can no longer be recommended for use in congestive heart failure based on the findings of a new study. The drug is a recombinant B-type naturetic peptide (BNP) that was approved in 2001 for use in patients with acute heart failure. The approval was based on small studies showing a reduction in pulmonary capillary wedge pressure and improvement in dyspnea 3 hours after administration. However, subsequent data raised questions about the drug's safety, especially with regard to worsening renal function and even increased mortality. Based on the recommendations of an independent panel, the manufacturer performed a placebo-controlled randomized trial of more than 7000 patients hospitalized with acute heart failure to assess the drug's safety and efficacy. Patients with heart failure were randomized to receive nesiritide or placebo for 24-168 hours in addition to standard care. The drug was modestly effective at reducing symptoms of dyspnea at 6 and 24 hours. More significantly, however, the rate of rehospitalization for heart failure or death from any cause within 30 days was no different. Nesiritide was not associated with a worsening of renal function but was associated with worsening hypotension. The authors conclude that on the basis of these results, "nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure" (*N Engl J Med* 2011;365:32-43). ■

FDA actions

The highly anticipated oral factor Xa inhibitor rivaroxaban has been approved by the FDA to reduce the risk of deep venous thrombosis, blood clots, and pulmonary embolism in patients undergoing knee or hip replacement. The once-a-day medication should be taken for 12 days by patients undergoing knee replacement and 35 days for patients undergoing hip replacement. The approval was based on three studies (RECORD 1, 2, and 3) which showed that rivaroxaban is superior to subcutaneous enoxaparin in this role. Bleeding, the primary side effect of the drug, was no more common with rivaroxaban than enoxaparin. Rivaroxaban also has been looked at in phase III trials for stroke prevention in patients with nonvalvular atrial fibrillation, and treatment and secondary prevention of venous thromboembolism, although the FDA has yet to act on approval for these indications. Rivaroxaban was developed by Bayer and is marketed by Janssen Pharmaceuticals as Xarelto.

The FDA has approved ticagrelor, a new antiplatelet drug for patients with acute coronary syndrome, including unstable angina and myocardial infarction (MI). The approval was based on studies that coupled ticagrelor with low-dose aspirin. The approval recommends use with aspirin although it carries a warning that aspirin doses above 100 mg per day may decrease the effectiveness of the drug. Ticagrelor requires twice a day dosing in contrast to the other drugs in this class, clopidogrel and prasugrel, which can be dosed once daily. The approval was based on the PLATO trial, a head-to-head study with clopidogrel which showed that in combination with aspirin, ticagrelor resulted in the lower composite endpoint of cardiovascular death, stroke, or MI (9.8% vs 11.7% with clopidogrel, $P < 0.001$).

The FDA has approved six manufacturers for the 2011-2012 flu vaccine. The strains included this year are A/California7/09 (H1N10), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 — the exact same components as last year's vaccine. One of the manufacturers, Sanofi Pasteur, has received permission to market Fluzone Intradermal, the first flu vaccine administered via a novel intradermal microinjection that is touted as being more comfortable than intramuscular injections. The new intradermal system in approved for adults ages 18-64 years. ■

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By Louis Kuritzky, MD

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Can Appendicitis be Cured with Antibiotics Alone?

Source: Vons C, et al. *Lancet* 2011;377:1573-1579.

SOMETIMES, ACUTE APPENDICITIS (AAP) just goes away. We know this because of abdominal explorations that disclose evidence of chronic appendicitis, indicative of one or more prior episodes. Four randomized trials support the relevance of antibiotic treatment for AAP, but definitive conclusions about the appropriate role of antibiotics in AAP treatment have been limited by aspects of previous study design.

Vons et al performed a controlled trial of adult patients with CT-confirmed uncomplicated AAP who were randomized to antibiotics (amoxicillin/clavulanic acid 3-4 g/d) or surgery. Although one group was assigned to surgery alone, the surgical group also actually received a single parenteral 2 g dose of amoxicillin/clavulanic acid at induction of anesthesia; additionally, if complicated appendicitis was discovered at surgery (i.e., the appendicitis had progressed or was misdiagnosed by CT), antibiotics were subsequently administered even in the surgery group.

Peritonitis within 30 days of intervention — the primary endpoint of the trial — occurred more often in the antibiotic group (8% vs 2%), hence the noninferiority of antibiotic treatment was NOT confirmed. If future tools can do a better job of identifying those who truly have uncomplicated appendicitis, antibiotics may prove to be a more valuable first-line treatment. ■

Antihypertensive Medication Nonadherence and Blood Pressure

Source: Rose AJ, et al. *J Clin Hypertens* 2011;6:416-421.

IT COMES AS NO SURPRISE THAT WHEN PATIENTS do not take their blood pressure (BP) medication, a lapse in BP control is anticipated. On the other hand, when a patient presents with an elevated BP and acknowledges omitted doses, it is difficult to be sure whether the observed elevation in BP is solely due to recent omissions, an underlying worsening of BP (requiring an augmentation rather than just simple restoration of treatment), rebound BP elevation, or some combination of these elements. To gain a more concrete insight into the anticipated impact of omitted BP medication in a typical patient population, Rose et al reviewed data from a population (n = 869) enrolled in a trial investigating the effects of physician communication on BP control. A component of the study design was utilization of medication bottles with memory caps that recorded timing and frequency of opening, providing a detailed view of medication administration.

When comparing BP after a 7-day period of poor adherence (< 60% of prescribed medication administered) to a prior period of excellent adherence, BP was 12/7 mmHg higher immediately following the week of poor adherence.

Clinical inertia — failure to intensify treatment despite suboptimal goal attainment — is sometimes innocently propagated by clinician uncertainty about whether uncontrolled BP should simply be attributed to missed doses or needs treatment augmentation. The authors suggest that clinicians consider a maximum BP excursion of 15/8 mmHg as potentially likely due to poor medication adherence, and that when BP elevation is greater than this amount, consider augmentation of antihypertensive treatment rather than simply encouraging better adherence to the existing regimen. ■

PDE5 Inhibition and Cognitive Function

Source: Shim YS, et al. *Int J Impot Res* 2011;23:109-114.

THE THERAPEUTIC REALM OF PDE5 INhibitors has expanded to include not only erectile dysfunction (ED) but also pulmonary hypertension. Animal studies have identified PDE5 activity in the brain, which can be impacted by currently available PDE5 inhibitors since they readily cross the blood-brain barrier. In the animal CNS, increased cyclic GMP (a pharmacodynamic effect of PDE5 inhibition) is seen in pathways associated with memory; studies have confirmed enhanced cognition in animals with impaired cognition related to diabetes, anticholinergic medications, and hyperammonemia who are treated with PDE5 inhibitors.

Udenafil is a PDE5 inhibitor not available in the United States but already in use in other countries (e.g., Korea, Russia) for treatment of ED. Shim et al undertook a trial of udenafil in men with ED but without known cognitive dysfunction (n = 30). Subjects underwent a battery of tests of cognitive function at baseline and 8 weeks later. Testing metrics included measures of general cognitive function,

verbal learning for episodic memory, and frontal executive function.

Several tests of cognitive function showed statistically significant improvement. Cognitive function improvement was greater in men whose sexual function scores improved the most. The authors suggest further exploration of the effects of PDE5 inhibition on cerebral flow to gain greater understanding of the favorable cognitive effects they have demonstrated. ■

What Things are Making us Gain Weight?

Source: Mozaffarian D, et al. *N Engl J Med* 2011;364:2392-2404.

Since two-thirds of americans are overweight or obese, most of us should probably be trying to better understand why. Perhaps the observation that the daily number of calories per capita continues to increase, while daily energy expenditure dwindles, is enough to satisfy the casual observer. Or is the *character* of caloric intake — such as high glycemic index carbohydrate vs low — a critical factor? As yet, despite simple answers (just reduce calories), there are few simple solutions (folks cannot/will not adhere to calorie-based dietary restrictions).

Might it help to identify commonplace "culprit" foods — that is, dietary components associated most often with weight gain, rather that just total calorie counts?

Based on follow-up of healthy U.S. adults during observational periods lasting as long as 20 years (n = 120,877), Mozaffarian et al determined that several commonplace dietary and lifestyle factors were associated with weight gain. For instance, over a 4-year interval, for every additional daily serving of potato chips, there was a 1.69 lb weight gain. Sugar-sweetened beverages were next on the list of items associated with weight gain. Perhaps, not surprisingly, physical activity, fruits, grains, nuts, and vegetables were inversely associated with weight.

Despite widespread public awareness of the health consequences of being overweight and obesity, most are not able — using currently advised methods — to reverse the trend for weight gain. Whether targeting elimination of specific dietary components (e.g., sugar-sweetened beverages) and/or the augmentation of selected favorable components (e.g., nuts, grains, fruits) will prove to be effective remains to be determined. ■

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Disease-Modifying Antirheumatic Drugs and Risk for Developing Diabetes

Source: Solomon DH, et al. *JAMA* 2011; 305:2525-2531.

Prior to the advent of disease-modifying antirheumatic drugs (DMARDs), the possibilities for remission of disorders like rheumatoid arthritis (RA) and severe psoriasis (PSOR) were remote. Along with the welcome dramatic clinical improvements seen with DMARDs, concerns about adverse effects — such as adversities associated with either the consequences of their immunomodulatory activity or direct toxic effects — require a high level of vigilance. Recently, however, there has been recognition that biologic DMARDs such as TNF inhibitors or hydroxychloroquine, when used in RA or PSOR, might be associated with a lesser risk of diabetes.

Solomon et al performed a retrospective study of RA/PSOR patients who began treatment with a DMARD (n = 121,280) in the United States and Canada. Compared with nonbiologic DMARDs (examples include sulfasalazine, leflunomide, cyclosporine, and others), use of biologic DMARDs was associated with a 23%-46% lesser risk of new-onset diabetes. Because cardiovascular (CV) risk is magnified in persons with RA, treatment choices may be influenced by consideration of agents less likely to further augment CV risk through induction of diabetes. ■

The Ipswich Touch Test for Diabetic Peripheral Neuropathy

Source: Rayman G, et al. *Diabetes Care* 2011;34:1517-1518.

Type 2 diabetes (dm2) remains the #1 cause of atraumatic limb amputation in the United States. The primary cause of foot ulcers that progress to limb loss is diabetic neuropathy, which decreases sensory awareness of tissue trauma, allowing destruction to progress without warning signs that would otherwise stimulate seeking care for injuries or infections. Albeit consistently recommended by consensus guidelines, routine examination of the feet remains markedly suboptimal by both clinicians and patients alike. Although monofilament and tuning fork testing are highly effective in identifying the presence of diabetic neuropathy, they also remain underutilized.

The Ipswich Touch Test (named after the United Kingdom Hospital in which it was developed) is performed by "lightly touching/resting the tip of the index finger for 1-2 seconds on the tips of the first, third, and fifth toes and the dorsum of the hallux." The presence of neuropathy is defined by this method as having two or more of the eight sites (four sites on each foot) being insensate.

The gold-standard for identification of diabetic neuropathy in this trial was vibration perception threshold as determined by a neurothesiometer. Both monofilament and the Ipswich Touch Test were highly sensitive and had strong positive-predictive value for the presence of neuropathy. When the Ipswich Touch Test compared with monofilament testing, there was near-perfect agreement. As discussed by the authors, perhaps the lack of requirement for specialized measurement tools will prompt clinicians to be more consistently proactive in seeking to define diabetic neuropathy in the feet. ■