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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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INSIDE

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Does Atorvastatin Have Anti-ischemic Effects?

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, 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: Deanfield JE, et al. Potent anti-ischemic effects of statins in chronic stable angina: Incremental benefit beyond lipid lowering? *Eur Heart J.* 2010;31:2650-2659.

STATINS ARE A CORNERSTONE OF TREATMENT FOR PATIENTS WITH CORONARY artery disease (CAD). Their powerful lipid-lowering and plaque-stabilization effects are well known, as is their ability to reduce myocardial infarction and death. Statins also have been shown to improve endothelial function, but whether this results in less myocardial ischemia in patients with CAD remains unknown. Amlodipine has been shown to reduce episodes of transient myocardial ischemia detected by ambulatory electrocardiogram (AECG) monitoring. Thus, Deanfield and colleagues performed a randomized, controlled trial to compare the anti-ischemic effects of atorvastatin and amlodipine in patients with chronic stable CAD.

Patients with chronic stable angina (≥ 2 episodes per week) were recruited from 46 centers in 13 countries. Inclusion criteria included a positive exercise test, documentation of CAD by either coronary angiography or nuclear perfusion scintigraphy, and a total cholesterol ≥ 200 mg/dL. Eligible patients underwent 48-hour AECG monitoring and could be included if they demonstrated ≥ 15 minutes of ischemia and/or ≥ 3 episodes of ischemia. Exclusion criteria were congenital heart disease, uncontrolled hypertension, systolic blood pressure < 100 mmHg, bradycardia, abnormal electrocardiogram, liver or muscle enzyme elevation, or severe dyslipidemia. After a placebo roll-in phase, patients were randomized to amlodipine (5 mg daily, increasing to 10 mg daily), atorvastatin (10 mg daily, increasing to 80 mg daily), or both. The trial continued for 26 weeks, and the primary endpoint was the number of ischemic episodes on AECG monitoring at week 26. Patients

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also underwent exercise testing, angina diaries, and blood tests for cholesterol and c-reactive protein (CRP).

Results: They enrolled 312 patients: 103 were randomized to amlodipine, 104 to atorvastatin, and 104 to the combination of both. Baseline characteristics were similar between groups, with mean age 62 years and approximately 25% diabetic. Importantly, baseline LDL, HDL, blood pressure, antihypertensives, and anti-anginal therapy were well-matched. Baseline triglycerides were slightly higher in the amlodipine arm.

At 26 weeks, there was objective evidence of ischemia reduction in all groups. AECG monitoring showed an approximate 66% reduction in the number of ischemic events compared to baseline in all three groups ($p < 0.001$). There was no difference between groups. Subjective assessment of ischemia by angina diaries also was reduced equally across all three groups ($p < 0.001$ vs. baseline). The number of nitroglycerin tablets used at week 26 was reduced in all groups compared to baseline ($p < 0.001$), but patients receiving amlodipine (alone or in combination) used significantly fewer nitroglycerin tablets than those receiving atorvastatin monotherapy ($p < 0.05$). During exercise testing, fewer patients developed angina in each group at 26 weeks compared to baseline, but there was no difference in time to angina or time to onset of ST segment changes in any group.

As expected, there was a significant reduction in LDL cholesterol and CRP with atorvastatin (monotherapy or combination) but not with amlodipine. The reduction in ischemia correlated significantly with the reduction in CRP. There was a greater reduction in blood pressure with amlodipine, but this did not reach statistical significance in this patient cohort with well-controlled blood pressure at baseline. Adverse event rates were similar across groups, with approximately 4% discontinuing the study medication in each group. The amlodipine groups had an approximately 8% rate of peripheral edema. There was one case of myalgia in each group, one case of elevated creatine kinase in each group, and no liver enzyme abnormalities. The authors conclude that atorvastatin was as potent an anti-ischemic agent as amlodipine.

■ **COMMENTARY**

Statins continue to delight us with new and unexpected salubrious effects. This study does not compare atorvastatin to placebo and, therefore, we cannot absolutely conclude that atorvastatin has anti-ischemic benefits. However, amlodipine has been shown in prior studies to have anti-ischemic effects compared to placebo, and this study, by Deanfield and colleagues, shows a similar reduction in ischemia with atorvastatin and amlodipine. In addition, the strong correlation between subjective angina reduction and reduction in objective ischemia, demonstrated on AECG monitoring, strengthens their findings. Thus, it is reasonable to assume that atorvastatin has some anti-ischemic properties. This may explain, at least in part, the reduction in ischemia with medical treatment seen in the COURAGE trial.

It is interesting that there was no incremental benefit to the combination of both treatments. They appear to have different effects on inflammation, based on the CRP lowering by atorvastatin and not by amlodipine, yet similar overall effects on ischemia, suggesting different mechanisms of action. However, the lack of additional benefit would argue against this. Further studies are needed to elucidate the mechanism of the anti-ischemic effects. ■

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Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: leslie.hamlin@ahcmedia.com

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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.

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Incidence of LV Thrombus After Anterior MI in the Modern Era

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

Source: Solheim S, et al. Frequency of left ventricular thrombus in patients with anterior wall myocardial infarction treated with percutaneous coronary intervention and dual anti-platelet therapy. *Am J Cardiol* 2010;106:1197-1200.

Dual anti-platelet therapy with aspirin and a thienopyridine, such as clopidogrel, is recommended after

ST elevation myocardial infarction (MI). Prior to the era of potent anti-platelet therapy and aggressive infarct artery reperfusion strategies, left ventricular (LV) mural thrombus was seen relatively frequently after anterior MI. Coumadin is the recommended treatment for established LV thrombus and is recommended by some for the prevention of LV thrombus after anterior MI. However, there are few data about the frequency of LV thrombus following anterior MI from the modern era of rapid reperfusion and potent dual anti-platelet therapy. Consequently, current guidelines remain vague about the need for coumadin to prevent LV thrombus, in addition to dual anti-platelet therapy, for patients who have suffered anterior MI. Solheim and colleagues examined the echocardiograms and magnetic resonance images (MRI) from patients enrolled in the ASTAMI trial to determine the incidence of LV thrombus following anterior MI in the current era of rapid reperfusion and dual anti-platelet therapy. The ASTAMI trial randomized 100 patients in 1:1 fashion to intracoronary infusion of autologous bone marrow mononuclear cells vs. placebo after anterior MI that had been treated with percutaneous coronary intervention. Echocardiographic analysis was performed within the first 4 days post-MI and again at 3 months; MRI was performed at 18 days post-MI. Infarct size was assessed by serum creatine kinase (CK) measurements and by nuclear perfusion study performed 4 days post-MI.

Results: LV thrombus occurred in 15 patients (15%) following anterior MI, despite rapid reperfusion and dual anti-platelet therapy. Ten of these occurred in the first week, another four between 1 and 4 weeks post-MI, and the final one occurred between week 4 and 3 months post-MI. Comparing patients who had LV thrombus with those who did not, there were no differences in baseline clinical and demographic features. LV thrombus occurred in six patients randomized to cell therapy and nine patients randomized to placebo, suggesting no effect of the treatment on development of LV thrombus. However, patients who developed LV thrombus had larger infarcts. Peak CK was 6,128 micrograms/L in the LV thrombus group vs. 2,197 micrograms/L in those without LV thrombus ($p < 0.01$), and the percentage of the left anterior descending artery territory that was infarcted on nuclear scanning was 83% in those who developed LV thrombus vs. 64% in those who did not. Patients with peak CK levels in the highest quartile (> 4,900 micrograms/L) had a greater than 12-fold increased risk of developing LV thrombus. The authors conclude that the incidence of LV thrombus post-anterior MI in the current era is similar to previous times.

■ COMMENTARY

There is little information to guide the use of coumadin after anterior MI to prevent LV thrombus formation. Solheim and colleagues show us that this clinical problem has not been solved with the advent of rapid reperfusion and dual anti-platelet therapy. Their data of 10% rate of detection of LV thrombus in hospital is in keeping with other small recent series: A 6.2% incidence (*Am Heart J*. 2009;157:1074-1080), and 10% incidence (*J Thrombo Thrombolysis*. 2000;10:133-136) also have been described. This study extends on these prior series by follow-up imaging at later time-points and also by using another complimentary modality, MRI. They show us that LV thrombus can develop after the initial hospitalization in a further 5% of patients. Furthermore, they show an association between larger infarcts and the development of LV thrombus, which is intuitive but has not been proven in the current era. However, there are some limitations to this study. Firstly, it a small (100 patient) retrospective study and, therefore, the results should be hypothesis-generating only. Secondly, the authors do not tell us the rate of peripheral embolism from the LV thrombus, nor their treatment strategy and its success rate. Future randomized, controlled trials of anticoagulation to prevent LV thrombus are needed. ■

Complications of Device Generator Replacements

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology,

University of Virginia, Charlottesville

Dr. DiMarco receives grant/research support from Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

Source: Poole JE, et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: Results from the REPLACE registry. *Circulation*. 2010;122:1553-1561.

Implantable cardiac rhythm devices are being used in an increasing number of patients and, in addition, patients who receive them are living longer. Since battery longevity in both pacemakers and defibrillators is limited, the risks of generator replacements must be appreciated by referring and implanting cardiologists. However, relatively few data are available that detail the risks and complications associated with generator replacements. For this reason, the REPLACE investigators performed a prospective, multicenter study designed to collect complication data on patients after replacement of either a pacemaker or ICD generator. They also were particularly interested in patients who were undergoing upgrades which required lead additions.

Data were collected from 72 institutions with an essentially equal mix of academic and private hospitals. Patients were separated into two cohorts. Cohort 1 consisted of patients undergoing generator placement in which no lead revision

or addition was planned. Patients in cohort 2 included those in whom the intent at the time of the procedure was to add one or more leads. Patients with an expected heart transplant within six months or a planned lead extraction for any cause were excluded. Patients with any commercially available generator or lead could be included. The decision to perform the generator replacement or upgrade was at the investigator's discretion. After the generator replacement, follow-up included a wound examination performed according to the institution's routine practice followed by 3- and 6-month clinic visits. Definitions of major and minor complications were pre-specified and comprehensive. Major complications were those that placed the patient at significant risk, or required an intervention or subsequent procedure or a hospitalization for management of issues related to the device. Other complications were classified as minor. Reported complications were adjudicated by a clinical events committee blinded to the operator and the institution. Deaths occurring within 30 days of the procedure were reported. Death was considered to be procedure-related if there was an acute mechanical complication during the procedure or, if after the procedure, the death was unexplained and unanticipated.

The REPLACE Registry enrolled 1,715 patients. Six patients were later censored because they met exclusion criteria. As a result, there were 1,031 cohort-1 patients and 713 cohort-2 patients. Patients in cohort 2 were less likely to be female, had a lower ejection fraction, and a higher New York Heart Association class and more prior cardiac surgeries. Both cohorts had essentially equal numbers of ICD and pacemaker patients. About 90% of the device locations were prepectoral, with most of the remainder being subpectoral implants. The reasons for lead addition in cohort 2 were an upgrade to a CRT device in 407 patients, upgrade from a single chamber to a dual chamber pacemaker, or ICD in 114 patients and an upgrade from a CRT pacemaker to a CRT-D in 13 patients. Replacement or evaluation of a suspected malfunctioning lead was the reason for lead replacement in 179 patients. Among the patients who underwent generator replacement only (cohort 1) there were no deaths during the procedure, but two patients had periprocedural complications consisting of hemodynamic instability requiring intervention. The most common post-procedure complications were lead malfunction requiring re-operation in 10 (1%) patients and re-exploration for hematomas in seven (0.7%) patients. In addition, eight patients (0.8%) experienced a major infection, and five of these patients required extraction of their generator or leads. A minor infection occurred in six (0.6%) patients who were treated with outpatient oral antibiotics. The overall major complication rate was 4.0%. The minor complication rate was 7.4%.

Complications were considerably higher in cohort 2. Intraprocedural complications occurred in 13 patients. These included cardiac perforation in five (0.7%) patients, pneumothorax or hemothorax in six (0.8%) patients, and cardiac arrest in two patients. In addition, 56 patients (7.9%) required re-operation because of lead dislodgement or malfunction. Prolonged hospitalizations due to procedural related exacerbation of heart failure or renal failure occurred in 18 patients (2.5%), and hematomas requiring evacuation developed in 11 patients (1.5%). There were 8 procedural-related patient deaths (1.1%) within 30 days of the procedure in cohort 2. Four of these occurred in patients in whom an unsuccessful attempt to place a transvenous left ventricular lead prompted a surgical thoracotomy for lead placement. In addition, there were four unexplained deaths that occurred after hospital discharge but within 30 days. The overall major complication rate in cohort 2 was 15.3%. The minor complication rate was 7.6%. Six patients (0.8%) in cohort 2 experienced a major infection, with five requiring extraction of the generators and leads. Minor cellulitis treated with antibiotics was noted in two additional patients. When complication rates were examined by the type of lead procedure, patients who underwent an upgrade or revision to a CRT had a major complication rate of 18.7%, whereas patients who had an upgrade of a single chamber pacemaker ICD to a dual chamber ICD had a complication rate of 11.1%. In contrast, the cohort-1 patients who did not receive a new lead had a complication rate of 4.4%.

The authors concluded that cardiac-rhythm device generator changes are not benign, and the risk increases dramatically when additional leads are inserted at the time of generator change. They caution that physicians considering device upgrades should be aware of these risks, appreciate them, and make sure that the anticipated benefit from lead additions outweighs the possibility of complications.

■ COMMENTARY

For many years, little attention was paid to ICD- and pacemaker-generator changes. It was only several years ago, after some ICD generator recalls led to a large number of elective generator replacements, that the risks associated with generator changes really were appreciated. In most reports, the complication rate at least equaled that seen with new implants. The data from the REPLACE registry confirm these observations and add data about the risks of adding new leads. These data are particularly important since more liberal indications for ICD and CRT therapy now permit device upgrades in many patients with previously implanted devices. The risks reported in REPLACE are quite sobering. Clearly, we need better ways to predict risks and benefits for individual patients. We should neither hesitate to upgrade patients to a CRT device if they have significant heart failure symptoms nor should we without thinking recommend upgrades for all class-I patients with a low ejection fraction. ■

Cardiac Resynchronization for Class IV Heart Failure

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: van Bommel RJ, et al. Effect of cardiac resynchronization therapy in patients with New York heart association functional class IV heart failure. *Am J Cardiol*. ;106:1146-1151.

Although cardiac resynchronization therapy (CRT) is a class-I indication for the treatment of NYHA class III-IV patients with heart failure, few class-IV patients have been treated in the reported trials. Therefore, these investigators from the Netherlands studied 61 such patients to assess the effects of CRT on left ventricular (LV) volumes, symptoms, and long-term outcome. CRT indications included LV ejection fraction (EF) of 35% and an ECG QRS width of > 120 ms. Echocardiography was performed before and 6 months following CRT.

Results: At 6 months, 15% of the patients had died and 3% were readmitted for heart failure, but 64% improved and 18% were unchanged. On echo, a significant decrease in end-systolic volume was observed (167 to 147 mL, $p = 0.009$), as well as an increase in LVEF (22 to 28% $p < 0.001$). During a mean long-term follow-up of 30 months on average, 23% of the patients were admitted for heart failure. Eventually, a total of 59% died, most from worsening heart failure (75%). Survivors generally had better composite clinical scores. Baseline estimated glomerular filtration rate was the only baseline characteristic that was independently associated with all-cause mortality. One- and two-year mortality rates after CRT were 25% and 38%, respectively. The authors concluded that CRT improves LV function in patients with class-IV heart failure, but mortality remains high.

■ COMMENTARY

The mortality rate in this study is similar to those observed in other studies of class-IV patients treated medically. Thus, one cannot conclude that CRT prolongs life in class-IV patients. However, at 6 months, 64% of the survivors had improved clinically. Also, mean LVEF increased, which may have been part of the reason symptoms declined. So, CRT in class-IV patients does seem to make them feel better.

It is not surprising that most of the CRT patients died of worsening heart failure since many also received defibrillators, which would be expected to markedly reduce or eliminate arrhythmic sudden deaths. It also is not surprising that reduced renal function was the only multivariate predictor of death. Renal function is a marker for mortality in many clinical situations. In heart failure, it suggests worse heart failure associated with reduced organ flow and elevated venous pressure in the kidney. So, it may just be a marker for heart failure so severe or progressive that CRT is only a temporizing measure.

At this time, it appears that for appropriate class-IV heart-failure patients, CRT may reduce symptoms, increase activity, and prevent sudden death (with an ICD), but not affect the high rate of heart failure death. ■

Genetic Analysis of Sudden Death Victims and Their Relatives

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: van der Werf C, et al. Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: The experience of a tertiary referral center in The Netherlands. *Heart Rhythm*. 2010;7:1383-1389.

In this paper, van der Werf and colleagues from the University of Groningen report the diagnostic yield of comprehensive cardiologic and genetic examinations in surviving relatives of sudden, unexplained death victims and in victims of cardiac arrest where the event occurred between the age of 1 and 50 years. This was a single-center study from a tertiary referral hospital that included either patients referred to the institution or with genetic analysis after unexplained sudden death of a first- or second-degree relative or patients with aborted cardiac arrest at the author's institution or within their catchment area. Standard criteria for unexplained cardiac death and cardiac arrest were used and a diagnosis of the cause of death could be made at autopsy. Subjects with identifiable noncardiac etiologies of aborted cardiac arrest were not included. Data concerning the cardiac arrest were obtained for all sudden-death index cases. For every sudden-death victim's relative, a 12-lead ECG was recorded at their first visit. If an autopsy had been performed at another center, tissue samples were reviewed by a specialized cardiovascular pathologist. Frozen tissue, if available, was collected for DNA isolation from the victim. Testing in relatives was selective based on the victim's clinical information and the resting ECG data.

All aborted cardiac-arrest victims received a very detailed evaluation including resting ECG, continuous heart rhythm monitoring, and echocardiography. Pharmacologic

challenge with ajmaline and or flecainide was performed when the Brugada syndrome was suspected. Coronary angiography was performed when indicated. Exercise testing was performed if a long QT syndrome or catecholaminergic polymorphic ventricular tachycardia was suspected and/or the event occurred during exercise. When arrhythmogenic right ventricular cardiomyopathy was suspected, cardiac magnetic resonance imaging was performed. Genetic assessment was performed in a targeted manner after review of the clinical data. The genes for known ion channelopathies or Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and hypertrophic cardiomyopathy were scanned for associated mutations.

The study eventually included the surviving relatives of 140 sudden, unexpected death victims and 59 aborted cardiac-arrest victims. A total of 650 living first- and second-degree relatives of the sudden, unexplained death victims were examined. In 47 of 140 families, a probable diagnosis was made. When examined by the age of the sudden, unexplained death victim, the diagnostic yield was 71% when the event occurred between 0 and 10 years, 38% in the age group 11 to 20 years, 39% in the age group 21 to 30 years, 29% in the age group of 31 to 40 years, and 21% in the age of 41 to 49 years. In 45 of 47 families, the diagnosis was an inherited cardiac disease. Long QT syndrome (n = 10) [21%] was the most frequent diagnosis, followed by catecholaminergic polymorphic ventricular tachycardia (n = 8, [17%]), Brugada syndrome (n = 7, [15%]), and arrhythmogenic right ventricular cardiomyopathy, (n = 6, [13%]). There also were two cases of myocarditis. In addition, an abnormality on chromosome 7q36 at the locus, which has been associated with familial idiopathic ventricular fibrillation, was identified in four patients. Diagnosis was age-dependent. A primary arrhythmia syndrome was the most common diagnosis when the victim was under age 14. Cardiomyopathies became more common between age 14 and 30. Premature coronary disease was more common in the age group of 30 to 49 years. In the remaining 94 families, sudden death remained unexplained. Among the aborted cardiac-arrest victims, certain or probable diagnosis was made in 42 (61%). In this group, the most frequent cause of aborted cardiac arrest was hypertrophic cardiomyopathy (n = 7, [70%]), followed by myocardial infarction, (n = 6, [14%]), long QT syndrome (n=5, [12%]), Brugada syndrome (n = 5, [12%]), and arrhythmogenic right ventricular dysplasia (n = 5, [12%]). Two patients with aborted cardiac arrest due to myocardial infarction had an inherited familial hypercholesterolemia. The idiopathic ventricular fibrillation risk locus on chromosome 7q36 was identified in four patients. Among the sudden, unexplained death victims, the presence of a previous early cardiac arrest in another first-degree relative was a predictor of positive findings. In the aborted cardiac-arrest victims, clinical factors identified those in whom a positive finding was likely to be made.

The authors conclude that thorough cardiologic and genetic evaluation of relatives of sudden, unexplained death victims will yield positive findings in one-third of the cases. A similar protocol will give a 60% positive yield in survivors of cardiac arrest. Inherited cardiac diagnoses associated with sudden death are the most common positive findings.

■ **COMMENTARY**

Unexpected sudden death among the young has long both fascinated and terrified cardiologists. Over the last several years, tremendous progress has been made in elucidating the various syndromes that are associated with this phenomenon.

Management of family members of young sudden-death victims has often been difficult. In this paper, the authors show that a systematic genetic and cardiac evaluation can yield a positive diagnosis in many cases. Once the etiology for sudden death in the index case is known, family members can be tested. For those identified to share the condition, appropriate genetic counseling and therapy can be prescribed. ■

Mitral Valve Prolapse in Marfan Syndrome

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Rybczynski M, et al. Frequency and age-related course of mitral valve dysfunction in the Marfan syndrome. *Am J Cardiol.* 2010;106:1048-1053.

The incidence and significance of mitral valve prolapse (MVP) in patients with Marfan syndrome is poorly understood. Thus, these investigators from Germany prospectively studied patients with classic Marfan syndrome (Ghent criteria). Echocardiograms were performed at 6- to 12-month intervals in 174 patients for a mean of 4.4 years. MVP was present in 82 (40%); severe mitral regurgitation (MR) in 25 (12%); and mitral valve endocarditis in five (2.5%). Any degree of MR was present in 57%. The risk of severe MR and endocarditis increased with age. The presence of MVP was most strongly associated with skeletal involvement, as compared to other classic features of Marfan ($p < 0.001$). Severe MR was more common in sporadic Marfan vs. familial forms ($p < 0.006$). The authors concluded that MVP is common in Marfan syndrome and is associated with an increased risk of severe MR and endocarditis.

■ **COMMENTARY**

The incidence of MVP in this large series of patients is much higher than the 1%-2% estimated in the general population. The number of patients going on to develop severe MR or endocarditis seems higher than MVP series in non-Marfan patients. So, it appears that MVP in this patient population is associated with a higher frequency of complications. One reason may be that half of the Marfan patients exhibited bi-leaflet MVP, which is much less common in non-Marfan MVP.

More patients with Marfan had some degree of MR, as compared to those who had MVP (57% vs. 40%), as would be expected, since MR can have many causes including senescence. However, severe MR was only observed in those with MVP. The study population included subjects aged 0-77 years of age, but severe MR was rare in children. Thus, Marfan syndrome patients should have more frequent echocardiographic screening so that the window for surgical intervention is not missed. ■

BNP in Pregnancy

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Tanous D, et al. B-Type natriuretic peptide in pregnant women with heart disease. *J Am Coll Cardiol*. 2010;56:1247-1253.

Increases in cardiac volume in the non-pregnant state increase BNP, but little is known about pregnancy and BNP levels. Thus, these investigators from London and Toronto, Ontario, Canada, sought to elucidate changes in BNP during pregnancy in normal women and those with heart disease, and determine the relationship between BNP levels and cardiac events during pregnancy. A total of 66 pregnant women with heart disease were prospectively enrolled and compared to 12 controls without heart disease. Of the 66 women with heart disease, 49 had congenital heart disease, but none were cyanotic. BNP levels were measured in the first trimester, the third, and after delivery. BNP levels were low and did not increase during pregnancy in the normal women. In women with heart disease, BNP levels were higher than the controls (peak median 79 pg/mL vs. 35 pg/mL, $p < 0.001$). In those with heart disease, peak median BNP ranged from 15 to 1,425 pg/mL, and was highest in those with left ventricular dysfunction (137 pg/mL). During pregnancy, BNP levels > 100 pg/mL were observed in 38% of the women with heart disease; 5% had values > 500 pg/mL. No normal control had values > 100 at any time during pregnancy. All women who experienced cardiac events during pregnancy had a BNP > 100, and none of those with BNP < 100 had an event (negative predictive value = 100%). The authors concluded that in women with heart disease, BNP levels are often elevated and may help determine if adverse events are cardiac in origin.

■ **COMMENTARY**

Cardiologists are frequently consulted when women with heart disease become pregnant and there is considerable anxiety about their risk for adverse cardiac events. This study suggests that a normal BNP level is strong reassurance that the woman is handling the hemodynamic load of pregnancy and adverse cardiac events are unlikely. An elevated BNP would increase the risk of an event, but the positive predictive value is difficult to determine from this study since some BNP values were drawn after an event occurred. Also, many patients with elevated BNP had no evidence of heart failure and never had events. BNP values were highest in those with known left ventricular dysfunction, and previous studies have shown that NYHA class and an abnormal left ventricular ejection fraction predict adverse cardiac events in pregnant women with heart disease. Although BNP is elevated in preeclampsia, it does not predict fetal events or pregnancy associated hypertension. Thus, like other clinical applications of BNP measurements, they are most useful when normal.

The major limitation of this study is the small number of subjects. This made the evaluation of the value of BNP in subgroups by cardiac diagnosis impossible. Also, BNP was measured in the first and third trimesters, and most had an increase between these two measurements. Often, high values were noted only after an event. The value of second-trimester measurements is unknown, but may increase the value of BNP measurements. In addition, women with structurally normal hearts and arrhythmias were not studied, yet this is a common problem in pregnancy. Finally, these women were cared for in specialized centers that may achieve better outcomes than obstetric units in general hospitals.

How should we apply this new information? It does not seem warranted to measure BNP levels in all pregnant women to screen for heart disease. In women with known heart disease, an initial BNP when pregnancy is diagnosed seems reasonable, but if it is normal, should you do a second one, and when? Certainly, if an event occurs that may be cardiac, a BNP level would be of value. If everything is going well, it may make sense to do another level in the late second or early third trimester to be sure there is no subclinical deterioration in hemodynamic status after the full effect of blood volume and cardiac output increases have been experienced for awhile. ■

CME Questions

27. Which of the following is not anti-ischemic?

a. Amlodipine
b. ACE inhibitors
c. Atorvastatin
d. Coronary artery stenting

28. In the last decade, the incidence of LV-thrombus post-anterior MI has:

a. increased.
b. decreased.
c. stayed the same.
d. dropped to zero.

29. In a pregnant patient with dyspnea, a BNP < 100 pg/mL suggests:

a. a non-cardiac cause.
b. nothing.
c. pulmonary embolus.
d. coronary vasospasm.

30. Which of the following is most correct concerning MVP in Marfan syndrome?

a. MVP is uncommon.
b. Complications are more common.
c. MVP involves only the anterior leaflet.
d. All of the above

31. The risk of major complications with generator changes is:

a. 0.4%.
b. 4%.
c. 20%.
d. 40% .

32. Evaluation of the victims and relatives of sudden-death victims yields:

a. little useful information.
b. mainly evidence of acquired heart diseases.
c. predominantly anomalous coronary arteries.
d. inherited cardiac diagnoses were common.

33. Cardiac resynchronization therapy of class-IV heart-failure patients results in:

a. increases in LVEF.
b. reduces end systolic LV volume.
c. markedly reduces mortality.
d. A and B

Answers: 27. (b); 28. (c); 29. (a); 30. (b); 31. (b); 32. (d); 33. (d)

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. ■

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How to Improve Office-based Colon Cancer Screening?

Source: Nadel MR, et al. Fecal occult blood testing beliefs and practices of U.S. primary care physicians: Serious deviations from evidence-based recommendations. *J Gen Intern Med* 2010;25:833-839.

COLON CANCER SCREENING (CCS), WHEN properly done, has been shown to improve outcomes. Unfortunately, available screening methods suffer from underutilization, misinterpretation, and inappropriate follow-up.

Nadel et al compared data obtained from the National Survey of Primary Care Physicians' Recommendations and Practices for Cancer Screening during two time intervals (1999-2000 and 2006-2007), compiling responses from PCPs (n = 1134).

Before exploring the results, it is important to note recommendations about CCS. First, in-office screening of samples obtained through digital rectal examination (DRE) is not a recommended strategy; a single, in-office fecal occult blood testing subsequent to DRE will miss 95% of advanced neoplasia. Rather, annual CCS by means of three separate stool samples collected at home is appropriate: ACS guidelines suggest annual screening by three out-of-office samples tested with high-sensitivity guaiac or FIT.

One-fourth of primary care physicians reported using a single in-office sample in 2006-2007, down from one-third in 1999-2000. Low-sensitivity guaiac utilization decreased in the same interval from 77.4% to 61.1%. ■

Extended-release Carvedilol + Lisinopril in Hypertension

Source: Bakris GL, et al. Effect of combining extended-release carvedilol and lisinopril in hypertension. *J Clin Hypertens* 2010;12:678-686.

SINCE THE PUBLICATION OF THE ALLHAT TRIal, clinicians have progressively relied upon diuretic-based regimens to manage hypertension (HTN). On the other hand, in the ALLHAT trial, overall mortality was similar with diuretic, calcium channel blocker, or ACE inhibitor, lending credence to the idea that any of the treatment choices is reasonable, at least for the endpoint of all-cause mortality. There was no beta blocker arm in the ALLHAT trial; instead, beta blockers were used as add-on treatment.

Ultimately, only a small minority (about 25%) of patients with HTN are able to be controlled with monotherapy. Hence, clinicians must feel comfortable taking best advantage of available combinations of treatment. The COSMOS Study (Coreg and Lisinopril Combination Therapy in Hypertensive Subjects) randomized 656 hypertensive patients to treatment with extended-release carvedilol, lisinopril (LIS), or both. Each agent, as monotherapy or in combination, was used in the full range of therapeutic doses (e.g., LIS 10 mg, 20 mg, and 40 mg).

Although perhaps counter-intuitive, it was only when the highest doses of combination therapy were compared with highest-dose monotherapy that an advantageous differential of diastolic BP lowering was seen. This is the first clinical trial to combine these specific agents, and the fact that simultaneous initiation of both medications was very well tolerated is reassuring. ■

Aspirin Resistance and Established Hypertension

Source: Ozben B, et al. Aspirin resistance in hypertensive adults. *J Clin Hypertens* 2010;12:714-720.

THE PROPHYLACTIC USE OF ASPIRIN (ASA) provides risk reduction when used for secondary prophylaxis. Nonetheless, the protective effects of ASA are imperfect, which is to some degree explained by the concept of ASA resistance, variously measured by failure of aspirin to reduce thromboxane production, platelet activation, or platelet aggregation. Because various methodologies have been used to measure antithrombotic activity of ASA (such as platelet aggregability or thromboxane), the prevalence of ASA resistance in the literature is widely variant. ASA resistance has not been the subject of much study, specifically in hypertensive patients.

Ozben et al used a device called the Ultegra Rapid Platelet Function Assay-ASA to measure the degree of platelet aggregation reduction attained in persons with established hypertension receiving 100-300 mg/d of ASA. The Ultegra device measures light transmission in whole blood to which a platelet activator has been added: If ASA is doing its job, platelets will not activate. If ASA is not doing its job, fibrinogen will agglutinate with platelets, obscuring light transmission. Patients who were taking any other

agents that might influence platelet aggregation were excluded from the trial (e.g., clopidogrel).

In the 200 study subjects, ASA resistance was found in 21%. ASA resistance was more common in uncontrolled hypertension, women, chronic kidney disease, and persons with lower platelet counts. Measurement of ASA resistance is not yet a readily applied clinical tool. Whether persons with ASA resistance merit higher doses of ASA, alternative pharmacotherapy (e.g., clopidogrel), or other intervention is unclear. ■

Dementia and Aggressive Behavior

Source: Kunik ME, et al. Causes of aggressive behavior in patients with dementia. *J Clin Psych* 2010;71:1145-1152.

METRICS DESIGNED TO MEASURE AGGRESsion in dementia patients list activities such as spitting, verbal aggression, hitting, kicking, pushing, biting, and making inappropriate sexual advances either verbally or physically. Because such behaviors can be highly disruptive, it would be helpful to shed light on factors associated with aggressive behavior.

To be included in the trial, subjects had to be free of a history of aggressive behaviors for the previous 12 months. Factors that were measured included depression (Hamilton Depression Scale), pain, caregiver burden (based upon a validated scoring system that measures psychological, physical, emotional, financial, and social impact of being a caregiver), and an item titled "mutuality," which measures the positive qualities of the caregiver-to-care-receiver relationship, including frequency of contact, positive interactions, degree of attachment, and emotional support. The authors looked at data from 215 patients with dementia, of whom 41% developed aggression over a 2-year interval.

Predictors of increased risk for aggression were low baseline mutuality, high caregiver burden, pain, and depression. Although some of the predictors for aggression may be difficult or impossible to modify, others are clearly modifiable and might reduce likelihood for aggression. ■

Dabigatran vs Warfarin for AFib

Source: Wallentin L, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation. *Lancet* 2010; 376:975-983.

WARFARIN (WAR) DOES AN IMPRESSIVE job of stroke reduction in patients with atrial fibrillation (AFib): Clinical trials indicate a relative risk reduction of 65%. Unfortunately, chronic WAR therapy is not without obstacles, including need for ongoing monitoring, expense, vigilance to diet and pharmacotherapy, etc. Dabigatran is an orally administered direct thrombin inhibitor that does not require routine monitoring, and is not significantly affected by vitamin K content in food. In October 2010, the FDA approved dabigatran for reduction of risk of stroke in persons with AFib.

The RE-LY trial randomized AFib patients (n = 18,113) to anticoagulation with warfarin (target INR, 2.0-3.0) or dabigatran. Dabigatran was administered as either 110 mg bid or 150 mg bid. Patients were followed for 2 years.

Initial reporting of RE-LY results found that lower-dose dabigatran (110 mg bid) was non-inferior to warfarin, and that higher-dose dabigatran (150 mg bid) was superior to warfarin. This article further examined whether trial results were impacted by the degree of success with which study sites were able to keep patients within the therapeutic range with warfarin.

Ultimately, the efficacy of dabigatran 150 mg bid relative to WAR for stroke prevention was found not to be dependent upon the efficacy with which clinical trial centers maintained INR within the therapeutic range. On the other hand, for the endpoints of all vascular events, nonhemorrhagic events, and mortality, differences between dabigatran and WAR were greater at study sites with less efficacy at maintaining in-range INR. Dabigatran appears to be at least as effective as WAR, although some advantages of dabigatran are magnified by inconsistencies in maintaining good INR control. ■

When Should a Non-diabetic A1c Be Rechecked?

Source: Takahashi O, et al. A1c to detect diabetes in healthy adults: When should we recheck? *Diabetes Care* 2010;33: 2016-2017.

RECENTLY, THE ADA HAS ADVOCATED THE use of A1c to diagnose diabetes, indicating that we may now make a diagnosis of diabetes with an A1c ≥ 6.5. We do not have explicit guidance about the frequency with which persons whose A1c falls below the diagnostic threshold should be rechecked.

Takahashi et al followed all adults participating in preventive health checkups (n = 16,313) at the Center for Preventive Medicine at St. Luke's International Hospital, Tokyo, from 2005 to 2008. Three years after enrollment, among those without diabetes at baseline, 3.2% had reached an A1c ≥ 6.5. However, the likelihood of progressing to diabetes varied widely and was dependent upon the baseline non-diabetic A1c: Only 0.05% of persons with an A1c < 5% became diabetic vs 20% of those with an A1c 6.0%-6.4% at baseline.

Based upon their observations, the authors suggest that if baseline A1c is < 6.0%, rescreening is unlikely to be valuable in less than 3 years. On the other hand, the high frequency of A1c progression when baseline A1c is 6.0%-6.4% merits consideration of annual rescreening. ■

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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.

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Tiotropium for Uncontrolled Asthma

In this issue: Tiotropium for uncontrolled asthma, sibutramine pulled from market, incidence and mortality data from WHI, FDA Actions.

Tiotropium for uncontrolled asthma

Tiotropium, a long-acting anticholinergic inhaler, is approved for treatment of chronic obstructive pulmonary disease. A new study suggests that it may also be effective for patients with asthma.

In a study of 210 adults with asthma with inadequate control with inhaled glucocorticoids, tiotropium was compared to doubling the dose of glucocorticoids, and was also compared to the addition of salmeterol, a long-acting beta agonist (LABA). Tiotropium was superior to doubling the dose of inhaled glucocorticoid as assessed by measuring the morning peak expiratory flow (PEF) ($P < 0.001$). It also improved evening PEF, asthma control days, and FEV1, as well as daily symptom scores. The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and was superior to salmeterol in measures of prebronchodilator FEV1 ($P = 0.003$).

The authors conclude that tiotropium is superior to doubling the dose of glucocorticoid in patients with inadequately controlled asthma, and is equivalent to the addition of salmeterol in the same patient group (published online *N Engl J Med* Sept. 19, 2010). This study is important because it may result in options for patients with poorly controlled asthma beyond adding a LABA. Recently, asthma experts and the FDA have questioned the safety of LABA therapy (FDA Drug Safety Communication June 2, 2010), and a recent meta-analysis suggests that use of LABAs without concomitant inhaled corticosteroids increase the risk for intubation or death (*Am J Med* 2010;123:322-328). ■

Sibutramine pulled from market

Abbott Laboratories announced in October that it is withdrawing the weight-loss drug sibutramine (Meridia®) from the market. The move comes a month after the FDA finished a review of the drug and found that patients with cardiovascular disease or diabetes given sibutramine had a significantly higher rate of serious cardiovascular events compared to placebo. The drug was originally approved in 1997. In a news release, the FDA states "physicians are advised to stop prescribing Meridia to their patients and patients should stop taking this medication." *The Wall Street Journal* reports that while Meridia may be off the market, sibutramine is still available illegally in many weight-loss nutritional supplements, most of which are available via the Internet from oversee suppliers. The supplements are marketed as "all-natural" and their labels list only herbal ingredients. The FDA recently advised consumers that Slimming Beauty Bitter Orange Slimming Capsules contains sibutramine, and last year published a list of more than 50 other supplements containing the banned drug. For complete list of supplements containing sibutramine go to: www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm136187.htm. ■

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. Dr. Elliott reports no financial relationships to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Incidence and mortality data from WHI

In 2002, the Women's Health Initiative (WHI) study was stopped early after 5.6 years when data showed that combination estrogen and progesterone therapy increased the risk of breast cancer. Mortality data had never been reported from WHI, however, and other studies have suggested that hormone therapy-associated breast cancers might have a more favorable prognosis than other breast cancers. A new analysis of WHI data dispels that notion.

The current study is a follow-up study of more than 16,000 women enrolled in WHI who were randomized to conjugated equine estrogen 0.65 mg per day plus medroxyprogesterone 2.5 mg per day (Prempro®) or placebo. Participants were followed for an average of 11 years with the main outcome measure being breast cancer incidence and breast cancer mortality. Women on hormone therapy had a higher rate of breast cancer compared to women on placebo (0.42% vs 0.34% per year; hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.07-1.46; $P = 0.004$) and breast cancers in the hormone group were more likely to be node-positive (23.7% vs 16.2%; HR, 1.78; 95% CI, 1.23-2.58; $P = 0.03$). The death rate associated with breast cancer was higher in the hormone group (0.03% vs 0.01% per year; HR, 1.96; 95% CI, 1.00-4.04; $P = 0.049$), a finding that barely reached statistical significance because of the low number of cancers in either group.

The authors conclude that estrogen plus progesterone was associated with a higher breast cancer incidence, as well as cancers that were more commonly node-positive. Breast cancer mortality was also higher in the combined hormone group (*JAMA* 2010;304:1684-1692). An accompanying editorial points out that despite the borderline statistical significance of these findings it is likely that "the increase in breast cancer deaths due to hormone therapy has been underestimated in the current study." However, it is still unclear whether short courses of hormone therapy for relief of postmenopausal symptoms right after menopause may be safe and further research is needed "to determine whether lower doses or shorter durations of hormone therapy could alleviate menopausal symptoms without increasing cancer risk" (*JAMA* 2010;304:1719-1720). ■

FDA actions

The FDA has approved fingolimod, the first oral drug for the treatment of relapsing forms of multiple sclerosis. Fingolimod is a sphingosine 1-phosphate receptor modulator that is believed to reduce migration of lymphocytes into the central nervous system. Compared to interferon beta-1a, the annualized relapse rate was significantly lower with fingolimod. Patients need to be monitored for decreased heart rate and elevation of liver transaminases. Fingolimod is given as a once-daily 0.5 mg tablet. It is marketed by Novartis as Gilenya™.

As anticipated, the **FDA has approved dabigatran to prevent strokes and blood clots in patients with atrial fibrillation.** The drug is a direct thrombin inhibitor and is given orally twice a day. The approval was based on the RE-LY trial, which showed that dabigatran at 150 mg given twice a day was superior to warfarin for this indication. Unlike warfarin, dabigatran requires no monitoring. Dabigatran will be available in 75 mg and 150 mg capsules and will be marketed as Pradaxa® by Boehringer Ingelheim Pharmaceuticals.

The FDA has ordered a labeling change for bisphosphonates, warning of the risk of atypical femoral fractures. In March, the FDA announced an ongoing safety review of bisphosphonates and the occurrence of subtrochanteric and diaphyseal femoral fractures. The new warning is a result of that review and, while not acknowledging a direct link, the warning suggests that these fractures may be related to use of bisphosphonates for longer than 5 years. The agency further suggests that health care professionals consider periodic reevaluation of the need for continued bisphosphonate therapy in patients who have been on the drugs for more than 5 years. The labeling change will only affect bisphosphonates approved for osteoporosis, which include alendronate (Fosamax®), risedronate (Actonel®), ibandronate (Boniva®), and zoledronic acid (Reclast®).

The FDA has approved extended-release naltrexone to treat and prevent relapse of patients with opioid dependence who have undergone detoxification treatment. Extended-release naltrexone is administered by intramuscular injection once a month, and blocks opioid receptors in the brain. It was initially approved in 2006 to treat alcohol dependence. The drug is only approved for patients who have completed rehabilitation, otherwise it may trigger opioid withdrawal. The efficacy of naltrexone was shown in a 6-month placebo-controlled trial in which treated patients were more likely to stay in treatment and refrain from using illicit drugs. Extended-release naltrexone injection is marketed as Vivitrol® by Alkermes Inc. ■

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