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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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INSIDE

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Warfarin vs Aspirin for Atrial Fibrillation in the Elderly

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Mant J. et al. Warfarin Versus Aspirin for Stroke Prevention in An Elderly Community Population with Atrial Fibrillation (The Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): A Randomized Controlled Trial. *Lancet* 2007; 370:493-503.

OVER HALF OF PATIENTS WITH ATRIAL FIBRILLATION ARE OVER age 75 years, yet there is concern about the risk of serious hemorrhage in these patients on warfarin. Thus, the results of the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study are of interest. BAFTA was a prospective randomized open label study with a blinded assessment of end-points. The primary end-point was the frequency of stroke, intracranial hemorrhage or systemic emboli in patients with atrial fibrillation age 75 or greater who were randomized to aspirin 75 mg/day vs warfarin adjusted to an INR of 2-3, target 2.5. Secondary end-points included death, other vascular events and hemorrhage requiring hospitalization. The 973 patients were enrolled in primary care practices over a 3 year period and were followed for an additional 2 years. Average follow up was 2.7 years. Compliance with warfarin was 67% in this intention to treat analysis. Their INR's were therapeutic 67% of the time (19% below, 14% above). There were fewer primary end points in those on warfarin vs those on aspirin (1.8% per year vs 3.8% per year, RR = 0.48, CI 0.28-0.80, number needed to treat 50). No subgroup emerged in which warfarin was not superior to aspirin. The risk of major hemorrhage was small with 50 events (2%) per year and was not different in the 2 treatment groups. Secondary end point analysis showed that all major vascular events combined and strokes alone were less on warfarin. The authors concluded that in those age 75 or older with atrial fibrillation, warfarin is superior to aspirin for preventing embolic events including intracranial hemorrhage. However, about one third of the patients will decide the potential benefits are not worth the inconvenience of therapy with warfarin.

COMMENTARY

The ACC/AHA/ESC guidelines recommend warfarin for atrial

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fibrillation patients if they have 2 or more risk factors for stroke (CHADS) where age >75 years is one (A). On the other hand they caution that the risk of major hemorrhage is higher in the elderly, and caution that this risk needs to be considered. This is a mixed message that has resulted in a conservative approach by physicians and patients. Part of the problem is a lack of clinical trial data in patients over 75. Thus, this trial is of considerable interest.

The superiority of adjusted dose warfarin over low dose aspirin in this study is predictable. The surprise was that the risk of major hemorrhage was equal in both groups. This is especially surprising since low dose aspirin was used. The authors discuss several reasons that may help understand these results. Older trials had shown a 2-fold increase in major hemorrhage with warfarin vs aspirin and that major hemorrhage was more frequent as age increased. So this could be an alpha error in this trial. Even if this is the case the frequency of major hemorrhage will not be 2-fold higher. Some older trials used higher INR targets (up to 4.5); this trial used 2-3 (average 2.4). Current warfarin use before study entry was 40%. Therefore, there may have been a selection bias towards patients who could tolerate warfarin. There were significant cross-overs in this intention to treat study design. One third assigned warfarin switched to aspirin and 17% of those assigned to aspirin converted to warfarin. The net effect of these cross-overs would be to decrease the apparent risk of warfarin, but would also decrease the observed benefit of warfarin and the latter was not seen. About 20% of identified patients were excluded because of some contraindication to warfarin, but this does not seem excessive. Finally this was more of a real world study because patients were recruited form primary care practices rather then from hospitalized patients as has been done in other studies. Thus, they may have been a healthier group with fewer co-morbidities. Whatever the reason for the surprising results, this study makes us rethink what is a contraindication to warfarin therapy. Clearly older age alone is not a contraindication. ■

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ASSOCIATE PUBLISHER Lee Landenberger.
ASSOCIATE MANAGING EDITOR: Jennifer Corbett.
MARKETING PRODUCT MANAGER: Shawn DeMario.

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Editorial E-Mail: jennifer.corbett@ahcmedia.com

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Jennifer Corbett,
Associate Managing Editor, at (404) 262-5431 or e-mail at jennifer.corbett@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Medicine Compliance and Survival in Heart Failure

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Gislason GH, et al. Persistent Use of Evidence-Based Pharmacotherapy in Heart Failure Is Associated With Improved Outcomes. *Circulation*. 2007;116:737-744.

THE CURRENT POLYPHARMACY MANAGEMENT approach to chronic heart failure due to systolic dysfunction is of concern because it may lead to non-compliance. However, little is known about compliance with heart failure medications and its effect on outcome. Thus, this analysis of the initiation and persistence of evidence based therapy in all 107,072 Danish patients who survived their fist hospitalization for heart failure over a 9-year period is of interest. Via national pharmacy records, initiation of renin-angiotensin-system blockers (RASB), beta blockers and spironolactone within 90 days of discharge and statins with 180 days was recorded. Patients were stratified into 4 heart-failure severity groups by their use of diuretics. Subsequent prescription refills were used to define the persistence of therapy. Nonpersistence was defined as a > 90 day break in therapy. Only 123 (0.1%) of patients were lost to follow-up. Results: Initiation of RASB therapy was noted in an average of 43%, but was 50% during the last year of the study; 27% and 43% for beta blockers; 19 and 25% for spironolactone; and 12 and 27% for statins. Drug doses were often considerably below targets, and with the exception of carvedilol, were rarely up-titrated. Short breaks in therapy were com-

mon. Setting those who initiated treatment at 100% at the end of 5 years 70, 65, 56 and 83% were still on RASB, beta blockers, spironolactone and statins. One year mortality decreased from 39% to 35% ($P < 0.001$) over 8 years. Higher disease severity (diuretic use) correlated with therapy persistence. Nonpersistence of RASB, beta blockers, spironolactone and statins was associated with increased mortality (HR 1.37, 1.25, and 1.88, respectively). The authors concluded that once medications were started, persistence of therapy was high, but often with lower then recommended doses. Nonpersistence was associated with higher mortality.

COMMENTARY

This study is particularly strong because it includes all Danes with a heart failure diagnosis, avoiding selection biases. It has near 100% follow-up over 10 years. Accurate pharmacy data are available and small co-payments were all that was needed to fill prescriptions, avoiding non-compliance due to cost. That patients who don't take their drugs, don't do well is no surprise, but the fact that multiple drug prescriptions did not equate to noncompliance was. Apparently when drug polytherapy is started early, persistence with therapy is enhanced. Preferably, heart failure drugs should be started in the hospital, even in small doses, to enhance compliance. What is also surprising is that the doses of all drugs but carvedilol were rarely up-titrated after discharge. Perhaps this improved compliance because adverse effects were avoided, but perhaps at the expense of less efficiency. Interestingly, in the CHARM study (candesartan in heart failure) compliance with study drug or placebo was associated with better outcomes. Perhaps compliance is a marker for patients that take better care of themselves in general so drug doses are less critical. The message is if you can get your patients to be compliant with therapy, even at below recommended doses, they will do better. Heroic attempts to increase drug doses to reach recommended levels may not be worth the effort.

There are limitations to this type of study and to this study in particular. This study used administrative databases, so there is a paucity of clinical data. For example the diagnosis of heart failure was not verified and the existence of contraindications to various drugs is not known. Also, drug initiation increased over the course of the study for unknown reasons. We know Denmark had special heart failure clinics, but not how many, when and who used them. Other studies have shown increased compliance with therapy and better outcomes when patients are enrolled in such clinics. The main message of this study is to start multiple drug therapy early, preferably in the hospital, and don't forget to try to up-titrate to doses known to be effective if you can. Don't reduce compliance by forcing up-titration in the face of adverse effects, because compliance with a regimen for heart failure, even if it is based upon a placebo, will improve survival. ■

Percutaneous Aortic Valve Replacement

ABSTRACT & COMMENTARY

By Andrew Boyle, MBBS, PhD
Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco, CA
Dr. Boyle reports no financial relationships relevant to this field of study.

Source: Webb, JG et al. Percutaneous Transarterial Aortic Valve Replacement in Selected High-Risk Patients with Aortic Stenosis. *Circulation*. 2007;116:755-763.

Surgical aortic valve replacement (AVR) remains the gold standard treatment for patients with severe aortic stenosis (AS). However, a number of patients are at increased risk of mortality during AVR due to advanced age or co-morbidities. These patients have traditionally been denied surgery based on unacceptably high surgical mortality rates, but untreated severe aortic stenosis also has an unacceptably high mortality rate. Webb and colleagues report their experience in the first 50 patients treated with percutaneous AVR via the femoral artery approach. All patients had severe, symptomatic aortic stenosis and had been screened by a panel of cardiac surgeons and deemed too high risk for surgical AVR. The average patient age was 82 ± 7 years. There was one procedural death and the 30-day mortality was 12%. The expected surgical mortality in this cohort calculated by the EuroSCORE surgical risk prediction model was 28%. The procedural success improved from 76% in the first 25 patients to 96% in the second 25 patients, demonstrating a significant learning curve. Valve area increased from 0.6 ± 0.2 cm^2 to 1.7 ± 0.4 cm^2, and mean echocardiographic gradient fell from 46 ± 17 to 11 ± 5 mmHg. Peri-procedural stroke occurred in 4%. Left ventricular ejection fraction (LVEF) improved from a mean of 53 ± 15% to 57 ± 13% ($P < 0.0001$) and this was sustained for the 1

year follow-up interval. More importantly, 21% of patients had significant LV dysfunction (with a LVEF of < 40%) at baseline and this fell to 12% of patients at discharge and 6% of patients at 1 year follow-up. Also, percutaneous AVR was associated with improvement in mitral regurgitation (MR). MR fell from a median grade of 2 (moderate) at baseline to 1 (mild) at discharge. Moderate to severe MR was present in 53% at baseline but only 24% at 1 year. The authors concluded that percutaneous aortic valve replacement is an alternative to surgical replacement in high surgical risk patients with severe symptomatic aortic stenosis.

COMMENTARY

This is a very exciting first-in-man description of a novel technology that may offer a new therapeutic option to the no-option patient that is deemed too high risk for surgical AVR. Importantly, the patients included in this study are representative of "real-world" patients who are refused surgical AVR. They include patients with advanced age, porcelain aorta, severe lung disease, previous thoracotomy, obesity and renal failure. 90% of patients were in NYHA class III or IV heart failure. The low procedural and 30-day mortality rates in this high-risk group are encouraging but require randomized controlled studies comparing percutaneous AVR to surgical AVR, in order to confirm these findings. It should be pointed out that most of the patients had intubation and general anesthesia for the percutaneous procedure, so this risk has to be considered in these high risk patients.

The stroke rate of 4% is also encouraging, as this is a major risk during surgical AVR in this population. Furthermore, the risk of stroke is enough to make some patients who are otherwise fit for surgery refuse the operation. Also, the median length of stay was 5 days in this study, and as short as 2 days, which has the potential to reduce health-care costs.

Despite the promising early results in this trial, a few shortcomings need to be addressed. The data are not compared against surgical or medical therapy for aortic stenosis, only to the EuroSCORE predicted mortality. Comparisons to expected mortality from risk-prediction models need to be confirmed in randomized controlled trials. In addition, the arterial access sheaths were very large (22 and 24 French) in this study and thus major vascular complications occurred in 4 patients (iliac artery injury, retroperioneal bleeding and aortic perforation) requiring surgical or endovascular repair and resulting in 2 deaths. Furthermore, 2 patients developed infections at the vascular access site. These complications became less frequent as the equipment and techniques evolved.

The ongoing randomized controlled trials of this new therapy are eagerly awaited by both physicians and patients. If the findings of this early report are confirmed in larger trials, this could herald the dawn of a new and less invasive management strategy for high-risk patients with AS. ■

Detection of Diastolic Dysfunction

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Kasner M, et al. Utility of Doppler Echocardiography and Tissue Doppler Imaging in the Estimation of Diastolic Functions in Heart Failure With Normal Ejection Fraction; A comparative Doppler-Conductance Catheterization Study. *Circulation* 2007; 116: 637-647.

HEART FAILURE WITH NORMAL LEFT VENTRICULAR (LV) systolic function is thought to be due to diastolic dysfunction in most cases, but confirming LV diastolic dysfunction by echo Doppler techniques is often challenging. Thus, Kasner and associates studies 43 patients with clinical heart failure who had normal LV ejection fraction (EF) and confirmed LV diastolic dysfunction by conductance LV catheter measurements of the isovolumetric relaxation time constant; LV end diastolic pressure; LV stiffness constant and LV stiffness. They were compared to 12 controls with chest pain, normal LVEF and no symptoms or signs of heart failure. Patients with atrial fibrillation, valve disease, significant coronary disease or lung disease were excluded. The objective of the study was to see which echo Doppler parameter best predicted diastolic dysfunction measured invasively.

Results: All patients studied had normal LV volumes and EF, but the heart failure patients had increased LV mass index and left atrial volume as compared to the controls. In 70% of the heart failure patients some abnormality of standard mitral inflow velocity measures of diastolic function were found. Similar results were obtained when the pulmonary vein flow was examined, but only 72% had an adequate signal for analysis. Tissue Doppler indices at the lateral mitral annulus were abnormal in 81% of the heart failure patients and E/E' was >8 in 86%. Also,

LV end-diastolic pressure was best predicted by E/E′. The authors concluded that E/E′ was the best echo Doppler parameter for the detection of diastolic dysfunction in heart failure patients with normal EF.

COMMENTARY

The non-invasive diagnosis of LV diastolic dysfunction by standard mitral inflow velocity parameters is complicated. There are numerous influences on these values that need to be considered. The biggest problem is their lack of specificity for diagnosing mild diastolic dysfunction in older individuals. Abnormal relaxation (A>E) becomes more prevalent with age and is not necessarily indicative of diastolic dysfunction.

Assessment of pulmonary venous flow parameters did not help the diagnostic accuracy for at least 2 reasons: Young people have "abnormal" patterns (D>S); and adequate pulmonary venous signals can only be obtained in 70% of individuals.

Tissue Doppler lateral mitral annulus velocity parameters alone increase sensitivity for detecting diastolic function abnormalities about 10% over standard mitral Doppler velocity and pulmonary vein flow measures, but specificity is an issue. Combining the standard Doppler E wave peak velocity with the tissue Doppler equivalent E′ results in the dimensionless ratio E/E′, which has the highest sensitivity for detecting diastolic dysfunction of any parameter (86%) and a specificity of 100% in this study at a cut-off of 8. Also, an E/E′ >8 was highly correlated with an increased LV end-diastolic pressure. Combining other parameters with E/E′ did not increase accuracy in this study.

Given these results should we rely on E/E′ alone to make the diagnosis of diastolic dysfunction in patients with heart failure and normal systolic function? Unfortunately, no one echo Doppler measure is perfect. E/E' should be the keystone of the diagnosis with the caveat that the negative predictive value is less than the positive predictive value. So in those with a high E/E′, LV end-diastolic pressure is highly likely to be elevated, but perhaps not always due to diastolic dysfunction. Extreme fluid overload, constrictive pericarditis and other unusual conditions could raise LV diastolic pressures independent of the diastolic properties of the LV. When E/E′ is normal some cases of mild diastolic dysfunction could be missed. In these cases evaluation of the other echo Doppler parameters may be useful; especially pulmonary vein flow in an older individual, if it can be obtained. It is always satisfying when all the echo Doppler and tissue Doppler parameters point to the diagnosis, but not infrequently this doesn't happen. In such cases more reliance should be placed on E/E′ with the recognition that some mild cases may be missed. Of course, this means that tissue Doppler imaging needs to be obtained in anyone suspected of having heart failure. ■

Aortic Root Size in Athletes

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Babaee Bigi, M, et al. Aortic Root Size and Prevalence of Aortic Regurgitation in Elite Strength Trained Athletes. *Am J Cardiol* 2007;100:528-530.

LITTLE IS KNOWN ABOUT AORTIC ROOT SIZE IN strength trained athletes, yet the transient increase in central aortic pressure during weight lifting could increase aortic size over time and lead to aortic regurgitation. Thus, these investigators from Iran evaluated 100 strength trained male athletes who were competitive at the national level and 128 healthy age and height-matched men by echocardiography. Resting blood pressure was higher in the athletes (138 vs 113 mmHg, $P < 0.05$). Aortic diameters at the annulus, sinuses of Valsalva, sinotubular junction and the proximal ascending aorta were all greater in the athletes. Multivariate analysis showed that the duration of high intensity strength training, height and systolic blood pressure had the strongest association with aortic root diameters. Aortic regurgitation of any severity was absent in the controls (mean age 22 years) but found in 9 athletes (5 mild and 4 moderate). The authors concluded that elite strength trained athletes had larger aortic roots than age and height matched controls.

COMMENTARY

Debate has raged back and forth for over a century as to whether the athlete's heart is a pathological condition or an adaptation to exercise training, and the pendulum has swung back and forth on this issue. Currently we are in an era where most believe that cardiac enlargement is a harmless physiologic adaptation as evidenced by the fact that despite left ventricular hypertrophy, diastolic function is normal. This is one of the few cautionary tales published recently. It makes biologic sense that repeated bouts of high blood pressure during training, which can be as high as 480/350 mmHg during weight lifting, could eventually dilate the aorta. This could be viewed as physiologic, but the persistently

higher blood pressures and the 9% vs 0% aortic regurgitation can't be good. So perhaps isotonic exercise is adaptive and good for you, but isometric is not.

Before we jump to this conclusion, here are a few caveats. We are not given the weight of the subjects. Although matched for height, I doubt they were matched for weight or the authors would have said so. It is reasonable to presume that weight per se would not affect aortic size, since gaining fat weight is not associated with longer aortas. However, the larger muscle mass of a weight lifter may require a larger cardiac output and hence a larger aorta. Also, the extent to which obesity is present may lead to persistent hypertension which could enlarge the aorta. In addition, individuals with large aortas may be able to withstand the pressure increases of weight lifting more and self-select for this type of sporting activity. Finally, we don't know if anabolic steroids or growth hormone were used by these athletes and what effect they would have on the aorta. So there may be other explanations or confounders that were not considered in this study.

This is a provocative study that will certainly stimulate more work in this area. It may be an early push that will start the pendulum back toward a less benign view of extreme athleticism. ■

Bradycardia Pacing Induced VT/VF

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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

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

Source: Sweeney MO. Bradycardia pacing-induced short-long-short sequences at the onset of ventricular tachyarrhythmias. A possible mechanism of proarrhythmia. *J Am Coll Cardiol* 2007;50:614-622.

SWEENEY ET AL ANALYZED THE INITIATION OF ventricular arrhythmias on stored event electrograms from 1055 patients enrolled in 2 large ICD trials. (PainFREE Rx II and EnTrust). In these trials, the programming for ventricular tachycardia (VT) and ventricular fibrillation (VF) detection was standardized by protocol. In the VF zone, detection required 18 of 24 R-R intervals that were < 320 ms. In the VT zone, the cycle length range for detection was either 320 to 360 ms or < 400 ms. for 16 consecutive intervals. Pre-onset electrogram storage was turned on in all patients. Dual chamber ICDs were used in 75% of the PainFREE Rx II study patients and in 100% of the EnTrust trial patients. In the latter group, 92% were programmed to the Managed Ventricular Pacing (MVP) mode. MVP functions basically as an AAI/R mode that monitors ventricular conduction during atrial based pacing and switches to DDD/R pacing if AV block occurs.

All stored episodes of VT/VF were analyzed. Episodes were then classified into 4 groups: 1) non-pacing associated, 2) pacing associated, 3) pacing permitted, and 4) pacing facilitated. VT/VF episodes associated with "short-long-short (S-L-S) sequences were called "pacing permitted" if the pacing mode passively allowed pauses longer than the specified lower rate interval. Episodes were called "pacing facilitated" if the pacing mode initiated or terminated a S-L-S sequence at the onset of VT or VF with a ventricular paced beat.

In the database used for this report, a total of 1,356 spontaneous episodes of VT/VF with pre-onset electrograms were available for analysis. Non-pacing associated and pacing associated onset patterns were seen in 44.0% and 29.8% of all episodes. Pacing permitted or pacing facilitated S-L-S sequences were associated 26.2% of the events with the frequency related to the basic programmed pacing mode. Pacing permitted initiation was more common with the VVI/R and MVP modes since these modes try to avoid unnecessary ventricular pacing. Pacing facilitated initiation was more common with the DDD/R mode. The VVI/R mode was associated with longer pauses at VT/VF initiation since the lower rate limit in this mode was typically set at 40 beats per minute. Pacing facilitated S-L-S initiation was observed in 2.6% of patients with the MVP mode, 5.2% of the DDD/R pacing, and 3.3% of the VVI/R patients. Most pacing facilitated S-L-S episodes were monomorphic VT as opposed to VF. A small number of patients had only pacing permitted or pacing facilitated episodes of VT/VF.

The authors conclude that ventricular pacing can result in S-L-S sequences that may initiate episodes of VT/VF in ICD patients. Further refinement in bradycardia pacing algorithms are needed to reduce the frequency of this complication.

■ COMMENTARY

Sudden changes in ventricular cycle length and short-long-short sequences leading to abnormal patterns of ventricular repolarization can cause ventricular tachycardia and ventricular fibrillation.

Bradycardia pacing arrhythmias can produce such cycle length changes and new pacing modes designed to reduce the frequency of right ventricular pacing may unintentionally make sudden cycle length change more common. In this paper, Sweeney et al demonstrate that all forms of ventricular pacing can result in VT/VF initiation. Different patterns were observed with the MVP, VVI/R, and DDD/R modes but all modes could be associated with episodes. In some patients, only pacing facilitated VT/VF episodes were seen. This problem has been under recognized in the past. Unfortunately many ICD's do not have pre-onset electrogram storage programmed on, so data about the initiation of individual VT/VF episodes is often not available to the electrophysiologist caring for the patient. This paper should make us aware that the programmed bradycardia pacing mode may actually be contributing to the frequency of VT/VF episodes and supports approaches designed to minimizing unnecessary ventricular pacing. ■

Significance of Short QT Intervals

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Anttonen O, et al. Prevalence and prognostic significance of short QT intervals in a middle-aged Finnish population. *Circulation* 2007;116;714-720.

ANTTONEN AND HIS COLLEAGUES ANALYZED THE prevalence and long-term prognostic significance of a short QT interval in a sample of the Finnish population. The study group included 10,957 men and women between 30 and 59 years of age. The initial screening exam for entry into this longitudinal study was between 1966 and 1972 and included 12 lead ECG was obtained. A recording on which the QT interval could be reliably measured was available in 10,822 subjects. QT intervals were measured by trained technicians and all QT intervals measuring less than 360 ms were confirmed by one of the authors. Raw QT intervals were corrected for heart rate by the Bazett's (QTc) and Fridericia's (QTfc) formulae and by a population based nomogram (QTnc). Subjects were followed long-term as an epidemiologic cohort with the primary end points for this analysis being all cause mortality, cardiovascular mortality, and death due specifically to coronary artery disease. The significance of a short QT interval was adjusted for other variables known to effect cardiovascular mortality.

There were 11 of 10,822 (0.1%) subjects who had a QTc < 320 ms using the Bazett's correction. This number was reduced to 9 and 7 if the Fridericia or nomogram based corrections were used. If a cut-off of <340 ms was used, 43 (0.4%), 33 and 34 subjects met criteria using the 3 correction methods. The increased prevalence of a short QT interval using the Bazett's formula was due to overcorrection of the QT interval at low heart rates — a phenomenon well described previously.

As had also been noted in other studies, QT intervals were longer in woman with 4.4% of males and only 1.3% of woman having a QTc < 360 ms. Short QT intervals also were associated with younger age, lower heart rates, and lower systolic blood pressure.

During long-term follow-up, a short QT interval was not associated with any significant change in total, cardiovascular, or sudden death mortality. This was true when cut-off values of <320, <340, and <360 ms were used. For example, in the patients with a QTfc <340 ms there were 15 deaths and only 3 cardiovascular deaths during the over 30 year follow-up period. Additional data indicated that none of the individuals with a short QTc interval had been hospitalized for syncope or ventricular arrhythmias or had been prescribed anti-arrhythmic medications.

The authors concluded that the incidental finding of a short QT interval in an asymptomatic individual without a familiar history of ventricular arrhythmias does not require intervention.

■ COMMENTARY

Recently several groups have described families with the "short QT syndrome." Effected individuals had short QT intervals defined by using rare cut-offs ranging from 310 to 340 ms. Four genetic patterns have been described with the syndrome due to "gain-of-function" mutations in K+ channel genes(HERG, KvLQT1, KCNJ2) or a "loss of function" mutation in a Ca++ channel gene (CACN2).

In the reported cases, the short QT interval was associated with a high risk for atrial and ventricular arrhythmias and cardiac arrest. In this paper, Anttonen and his colleagues used a population based approach rather than a symptomatic proband-based approach to assess the significance of a short QT interval. Their data suggest that although rare, short QT intervals are not associated with an adverse prognosis in the general population. Unless arrhythmias are present or a positive family history is noted, no action needs to be taken when a short QT is detected. ■

Weekly Statins

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Backes JM, et al. Effects of Once Weekly Rosuvastatin Among Patients With a Prior Statin Intolerance. *Am J Cardiol*. 2007;100:554-555.

STATINS ARE USUALLY WELL TOLERATED, BUT SOME patients have adverse effects even on every other day therapy. These investigators describe the results of once a week rosuvastatin in 10 patients intolerant to once-a-day statins due to myalgias, high liver function tests and gastrointestinal side effects. Once-weekly rosuvastatin was dosed between 5-20mg (most were on 10mg) and the patients were followed for an average of 4 months. Two patients could not tolerate once-a-week therapy because of the same side effects. The other 8 experienced an average LDL cholesterol drop of 29% (range -6 to -62%). HDL rose in 5 of the 8 (14 to 45%) and dropped in 3 (-4 to -27%). Triglycerides were unchanged overall. The authors concluded that once-a-week rosuvastatin may be an effective option for those intolerant to once-daily statin.

COMMENTARY

Statin's are our most effective agents for lowering high levels of LDL cholesterol in patients with atherosclerosis. Although well tolerated by most, a few patients have intolerable adverse reactions. Common strategies included lowering the dose and every-other-day dosing for such patients, but these measures do not always work. This report describes 8 out of 10 patients tried on once-weekly rosuvastatin who had success with LDL lowering and tolerability. The reason for this success is not clear, but rosuvastatin is very potent and has a long half life.

In the acute coronary syndrome patients where the target is an LDL < 85 mg/dL, the average 29% drop may not achieve this target. However, evidence suggests that some lipid lowering is better then none. Also, diet, niacin, ezetimibe and other agents may help achieve targets with this low-level background statins, without increasing adverse effects. In patients in whom LDL lowering is critical, this approach would certainly be worth trying in those who cannot tolerate statins. The only contradiction would be life-threatening adverse effects. ■

CME Objectives

The objectives of Clinical Cardiology Alert are:

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

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

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

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

CME Questions

58. Rosuvastatin may be effective when dosed
A. daily
B. every other day
C. weekly
D. all of the above

59. Strength trained elite athletes may show
A. left ventricular hypertrophy
B. diastolic dysfunction
C. enlarged aortic root
D. A and C

60. The polypharmacy of chronic heart failure management
A. is better adhered to if started early
B. reduces compliance in proportion to the number of pills
C. is often at lower doses than recommended
D. A and C

61. The best measure of diastolic dysfunction in heart failure patients with normal LVEF is?
A. E/A of mitral velocity
B. pulmonary vein flow pattern
C. E/E′ by tissue Doppler
D. none of the above

62. Percutaneous aortic valve replacement is associated with?
A. a 4% risk of stroke
B. a low procedural mortality
C. A 12% 30-day mortality
D. all of the above

63. Short QTc intervals are of concern when
A. < 360 ms
B. < 340 ms
C. < 320 ms
D. associated with symptoms

64. Bradycardia ventricular pacing can
A. induce atrial fibrillation
B. induce VT/VF
C. cause heart failure
D. cause asystole

Answers: 58.(d) 59.(d) 60.(d) 61.(c) 62.(d) 63.(d) 64.(b)

PHARMACOLOGY WATCH

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

Stopping Statins in At-Risk Patients — Just Too Risky

In this issue: *Make sure your patients don't stop statins after a stroke or surgery; MRSA is becoming more resistant to mupirocin; new asthma treatment guidelines; and FDA approvals and warnings.*

Stopping statins, even briefly, after stroke or cardiovascular surgery increases vascular complications according to 3 new studies. Spanish investigators looked at 89 patients who were on chronic statin therapy and were admitted with acute stroke. Half were randomized to statin withdrawal for the first 3 days after admission, while the other half immediately received atorvastatin 20 mg/day. After 4 days, the statin withdrawal group was also started on atorvastatin. The primary outcome was death or dependence after 3 months as defined by modified Rankin scale of 2 or more. After 3 months, 60% of those in the statin withdraw group were disabled to the point of dependence compared with 39% of those that continued statin therapy (P = 0.043). Early neurologic deterioration was also far greater in the statin withdrawal group (65.2% versus 20.9%; $P < 0.0001$). Statin withdrawal patients also had greater infarct volume (P = 0.002). The authors conclude that statin withdrawal in the first few days after stroke is associated with a markedly increased risk of death or dependency at 90 days; hence, treatment should continue the acute phase of an ischemic stroke (*Neurology* 2007; 69:904-910).

In another study, researchers in Italy looked at stroke patients who discontinued statins after discharge from the hospital. The study population included 631 stroke patients (322 men, 309 women) without evidence of heart disease. All patients were discharged on a statin, but 38.9% discontinued the drug within 12 months. In the 12 months of follow-up, 116 patients died. After adjustment for all confounders and interactions, the hazard ratio for mortality in patients who quit a statin was 2.78 (95%CI, 1.96-3.72; P = 0.003) or nearly 3 times higher risk of death (*Stroke* 2007, published online ahead of print 8/30/07).

Another study from the Netherlands looked at a brief interruption in statin therapy associated with major vascular surgery. Nearly 300 patients on statins underwent major vascular surgery, and statin therapy was interrupted in the perioperative period in 70 patients for mean duration of 3 days. An association was observed between statin discontinuation and an increase risk of postoperative troponin release (HR 4.6) and the combination of MI and cardiovascular death combined (HR 7.5). Because many surgical patients are NPO and unable to take oral statins, and there's no intravenous statin available, the only extended release statin was tried on a subset of patients preoperatively. Patients receiving extended-release fluvastatin had fewer perioperative cardiac events compared to other statins (*Am J Cardiol* 2007; 100:316-320). The message of these studies is that statin interruption, even for a brief period during hospitalization, may lead to serious adverse events in patients at risk.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

Mupirocin Less Effective Against MRSA

Mupirocin (Bactroban) is becoming less and less effective against MRSA, even in hospitals with low levels of mupirocin use. Researchers from Washington University in St. Louis performed nasal swab cultures for MRSA in all patients admitted to their surgical intensive care unit (SICU) on admission, weekly during hospitalization, and at discharge. Of the 302 positive MRSA isolates, 13.2% were resistant to mupirocin, with 8.6% having high-level resistance. Patients with mupirocin-resistant MRSA were more likely to be older, have a history of a previous admission in last year, and had higher in-hospital mortality. The authors conclude that patients carrying mupirocin-resistant MRSA acquired it through contact with the health-care system; the strains were probably not acquired in the SICU (*Clin Infect Dis* 2007; 45:541-547). Mupirocin is commonly used to decolonize patients who are *staph aureus* carriers or have nasal colonization with MRSA. With resistance patterns increasing nationwide, this strategy may need to change.

New Guideline for Asthma Diagnosis/Management

The National Asthma Education and Prevention Program has issued an update to their clinical practice guidelines for diagnosis and management of asthma (Expert Panel Report 3 [EPR-3]). The new guideline emphasizes the importance of asthma control and highlights 4 areas of emphasis including assessment and monitoring, patient education, control of environmental factors and other asthma triggers, and pharmacotherapy. The new guideline recommends continued use of a stepwise approach to asthma control in which medication doses or types are stepped up or down as needed based on asthma control. Recommendations now are based on 3 age groups, 0-4 years, 5-11 years (a new category), and 12 years and older.. The new age group was added because of evidence that children respond differently to medications than adults. The entire guideline can be found at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf .

FDA Actions

The FDA announced on August 14 that manufacturers of rosiglitazone (Avandia) pioglitazone (Actos), and other combination medications containing the 2 drugs will be required to add a "black box" warning to their labeling to reflect the risk of heart failure associated with the 2 drugs. Both drugs have been associated with reports of significant weight gain and edema, and some cases continuation of therapy has lead to poor outcomes including death. The black box warning advises health-care professionals to carefully observe patients taking these drugs for signs and symptoms of heart failure including rapid weight gain, shortness of breath, edema. The warning also recommends not starting either drug in patients with a history of congestive heart failure. The agency continues to review rosiglitazone for the possible increase risk of myocardial infarction associated with use of the drug.

The FDA has approved a new indication for zoledronic acid (Reclast) as a once-a-year treatment for postmenopausal osteoporosis. Reclast is administered as an annual 15-minute intravenous infusion. The drug is a bisphosphonate similar to oral bisphosphonates such as alendronate and risedronate.

Anesiva has received approval to market lidocaine topical powder intradermal injection system (Zingo) to provide local analgesic prior to venipuncture or peripheral intravenous cannulation in children ages 3-18. Zingo is a single-use helium powered system that is administered 1-3 minutes prior to needle insertion. The system is also being studied in trials of adults.

The FDA has approved a new combination of carbidopa, levodopa, entacapone (50 mg/200 mg/200 mg) for the treatment of Parkinson's disease. The new preparation helps reduce the pill burden for Parkinson's patients on multiple medications. Carbidopa/levodopa/entacapone will be marketed by Orion Corporation as Stalevo.

Omrix Biopharmaceuticals has received approval to market human thrombin (Evithrom) to promote blood clotting and control bleeding during surgery. Evithrom is the first human thrombin approved since 1954 and the only product currently available for this indication. It is applied to the surface of bleeding tissue during surgery and may be used in conjunction with absorbable gelatin sponge. Other thrombins currently on the market are derived from cattle plasma.

Nursing mothers who were taking codeine may put their babies at risk of morphine overdose if they are "ultra-rapid metabolizers of codeine," a condition that may affect up to 28% of the population. Codeine is generally recommended for nursing mothers as a cough suppressant and pain medication; however, ultra-rapid metabolizers quickly convert codeine to morphine and excrete it in breast milk. At least one infant death has been associated with this condition. The FDA has issued warning regarding codeine use by nursing mothers, recommending that mothers observe their infants closely while taking the medication for signs of morphine overdose including sleepiness, difficulty breast feeding, breathing difficulties or limpness. ■