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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Delays in Transfer For Primary PCI in STEMI

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

SOURCE: Miedema M, et al. Causes of delay and associated mortality in patients transferred with ST-segment-elevation myocardial infarction. *Circulation* 2011;124:1636-1644.

Most patients with ST-elevation myocardial infarction (STEMI) present to hospitals that are not capable of percutaneous coronary intervention (PCI). Rapid transfer to PCI-capable facilities for primary PCI may result in earlier reperfusion of the infarct artery and better clinical outcomes. However, delays in transfer may diminish the mortality benefit achieved with primary PCI in STEMI. The specific reasons for and the clinical impact of delays in transfer for primary PCI are unknown. Accordingly, Miedema and colleagues prospectively studied 2034 patients with STEMI transferred to their institution for primary PCI and determined the causes of delay in transfer, as well as the clinical outcomes associated with these delays.

Between 2003 and 2009, 2034 patients suffering STEMI were transferred with the intent of primary PCI. All patients with ST-elevation or new left bundle branch block and chest pain of < 24 hours duration were included. There were no exclusion criteria. The time from first hospital contact to reperfusion (overall door-to-balloon time) was recorded and was also divided into three segments: referring center door-in-to-door-out time, transport time, and PCI receiving center door-to-balloon time. The total door-to-balloon time goal was 120 minutes and the segment goals were 45, 45, and 30 minutes, respectively. Reasons for delay were prospectively collected.

Patients with delayed overall door-to-balloon times (from arriving at referring center to balloon inflation at PCI center > 120 minutes) were older (64 vs 61 years, $P < 0.001$), were more likely to be non-

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smokers (63% vs 58%, *P* = 0.02) and diabetics (18.4% vs 14.4%, *P* = 0.02), and were more likely to be in cardiogenic shock (12.9% vs 9.6%, *P* = 0.04) than those who had no delay. Patients with delay to PCI had higher in-hospital mortality than those with no delay (6.4% vs 4.1%, *P* = 0.02), but this difference was no longer statistically significant at 30 days. The authors then examined where the delay occurred and its effect on mortality.

Delay at the referral center (door-in-to-door-out time > 45 minutes) occurred in 64% of cases. The most common reason for delay was waiting for transportation. The longest delays were for diagnostic dilemma, followed by non-diagnostic electrocardiogram (ECG), then cardiac arrest/shock, emergency department delay, and other. In-hospital mortality associated with delays was highest for those with cardiogenic shock (31%) and lowest in those with non-diagnostic ECG (0%).

Delays in transport (> 45 minutes) were less common (13%). These were usually due to weather or distance (some referral hospitals were up to 210 miles away). There was no excess mortality attributable to transport delays.

Delays at the PCI center (door-to-balloon time > 30 minutes) occurred in 16%. The most common reasons for delay were catheterization lab team delay and complex procedure. The longest delays were due to diagnostic dilemma. The highest mortality was in those with cardiogenic shock/cardiac arrest (44%). The authors conclude that treatment delays occur even in efficient systems for STEMI care, and that the clinical impact of the delay varies according to the cause of the delay.

■ COMMENTARY

Current treatment guidelines emphasize the importance of rapid reperfusion in the treatment of patients with STEMI. While PCI is a more effective reperfusion strategy than fibrinolysis when both are offered with little delay in clinical trial settings, delays at any stage of the process can prolong the ischemic time, increase myocardial damage, and reduce the benefit of PCI. Developing systems of rapid patient transfer for primary PCI are challenging, but should be a priority under the latest guidelines. The higher mortality in those with overall door-to-balloon times > 120 minutes confirms the importance of rapid reperfusion. This study defines the reasons for delay within these authors' system, which is an experienced high-volume primary PCI transfer system. Delays were very frequent at the referring hospital (64% of cases), and infrequent at the PCI center (16%). These data may inform other STEMI transfer systems that are being developed. Importantly, the reason for the delay was more important than the delay itself. Delay for an initially non-diagnostic ECG, for example, was associated with very low in-hospital mortality and this may represent a lower-risk patient group.

This study is observational in nature, and therefore a direct cause and effect relationship between the reason for delay and mortality rate cannot be assumed. It is an association. Furthermore, we are not told of the pharmacological strategies employed in their patients (how many received thienopyridines, glycoprotein IIb/IIIa inhibitors?), the procedural details (culprit lesion location, stent type, use of intra-aortic balloon pumps), or the bleeding rates. All of these may contribute to the outcomes in these patients.

Despite these limitations, this study underscores the importance of rapid transfer protocols, highlights the frequency of delays despite a rapid transfer protocol, and suggests that the reason for the delay may be more important than the delay itself. ■

ABSTRACT & COMMENTARY

BNP in Chronic Aortic Regurgitation

By Michael H. Crawford, MD, Editor

SOURCE: Pizarro R, et al. Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation. *J Am Coll Cardiol* 2011;58:1705-1714.

The most appropriate time to intervene in asymptomatic patients with chronic severe aortic regurgitation is controversial. Since brain natriuretic peptide (BNP) is released by the heart in response to increased wall stress, it has been proposed as a biomarker of the time to intervene in chronic valvular regurgitation patients. Thus, these investigators from Argentina sought to determine the independent prognostic value of BNP in asymptomatic patients with severe aortic regurgitation and normal left ventricular (LV) function. They prospectively evaluated 294 such patients (LV ejection fraction > 55%) using the first 160 patients as the derivation set and the next 134 as the validation set. Severe aortic regurgitation was defined by quantitative echocardiography and lack of symptoms was confirmed by exercise testing. Patients with significant aortic stenosis (peak gradient > 20 mmHg) or other significant valve or cardiac disease were excluded. At least yearly evaluations were done. Mean follow-up of the derivation and validation sets were 46 and 38 months, respectively. The primary endpoint was the appearance of either heart failure or LV systolic dysfunction.

In the derivation set, 28% developed LV systolic dysfunction, heart failure, or death. Three patients (2%) died; two suddenly. Heart failure developed in 18% and LV dysfunction alone in 9%. Aortic valve surgery was performed in 31%. In the validation set, 26% developed the primary endpoint. BNP values were higher in those who developed the primary endpoint vs those who did not (149 vs 48, $P = 0.001$) in the derivation set with similar values in the validation set. The areas under the ROC curves were 0.84 and 0.82 for the two sets with an optimal cutoff value of 130 pg/mL. This cutoff value had a sensitivity of 77%, specificity of 94%, and negative- and positive-predictive values of 91% and 81% in the validation set. Multivariate analysis of all clinical and echocardiographic variables showed that BNP was the strongest independent predictor of the endpoint (relative risk [RR] 6.7, 95% confidence interval, 2.9-16.9, $P < 0.0001$) in the validation set. Other significant predictors were end systolic dimension > 24 mm/m^2 (RR 3.4), effective regurgitant orifice area > 50 mm^2 (4.3), and end diastolic dimension > 35 mm/m^2 (2.1). The authors concluded that BNP should be used in the clinical evaluation of asymptomatic patients with severe aortic regurgitation and normal LV systolic function.

■ COMMENTARY

This observational study suggests that there is a role for BNP measurements along with echocardiography for evaluating asymptomatic patients with severe aortic regurgitation. This seems like a reasonable recommendation with the caveat that until a trial randomizing patients with BNP > 130 to surgery vs continued medical therapy is done, one should not use BNP as a sole criteria for surgery. Also, experience with early surgery is limited and we do not know if this is a uniformly good strategy. The authors comment that the average time in their study from a BNP > 130 to an endpoint averaged 15 months. Thus, they suggest you can tell the patient that they are probably within 2 years of a defining event. In addition, they note that a rapid increase in BNP predicted events. Those with an event had a greater increase in BNP after 1 year than those without an event (31 vs 9 pg/mL, $P = 0.001$ in the validation set). Finally, BNP was a better discriminator than the echo parameters they measured.

It is noteworthy that most of their patients were on some pharmacologic therapy, most commonly ACE/ARB. The frequency of any specific medication use was not different between those with or without a BNP > 130 and the authors state that medical therapy did not influence outcomes. However, this should not be construed as a study of medical therapy.

Although observational, this is a well-done study with exercise test confirmed symptom status and quantitative echocardiography. Some might argue that more sophisticated tissue Doppler techniques were not utilized, but there is no evidence that such measures are any better than the standard echocardiographic measures used in this study. ■

ABSTRACT & COMMENTARY

Assessment of Functional Severity of Coronary Lesions by CT Angiography — FFR_{CT}

By Andrew J. Boyle, MBBS, PhD

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

SOURCE: Koo BK, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. *J Am Coll Cardiol* 2011;58:1989-1997.

Anatomic definition of coronary artery lesions by invasive coronary angiography (ICA) or computed tomography coronary angiography (CCTA) has limitations. The addition of physiologic assessment of coronary lesion severity has been shown to improve clinical decisionmaking. Fractional flow reserve (FFR) has been shown in the FAME study to safely and cost-effectively guide the decision on which lesion(s) to revascularize.[1] This involves placing a pressure sensing wire within the coronary artery and derives a ratio of pressure distal to the lesion divided by pressure proximal to the lesion. An FFR ≤ 0.80 indicates that the lesion causes ischemia and should be revascularized. Lesions with FFR > 0.80 can safely be treated medically. However, this is invasive and expensive. A non-invasive test that can define the anatomy and functional significance of coronary artery lesions could improve our ability to diagnose and treat coronary artery disease (CAD). Koo and colleagues describe a novel technique to non-invasively determine the FFR from CCTA studies (FFR_{CT}).

The authors studied 159 vessels in 103 patients that had CCTA and subsequently underwent ICA and FFR measurement. Inclusion criteria were age ≥ 18 years and a CCTA with at least one stenosis ≥ 50% in a vessel ≥ 2 mm that were undergoing clinically indicated ICA and FFR. Demographics were fairly standard for a CAD study population: mean age was 63 years, 74% were male, 65% had hypertension and dyslipidemia, and 36% were diabetic. However, mean BMI was 26 and only 33% were Caucasian. Exclusion criteria were pregnancy, life expectancy < 2 years, renal impairment, arrhythmia, contrast allergy, inability to take nitroglycerin, beta-blocker or adenosine, prior CABG, class IV angina, and uninterpretable CCTA. CCTA was acquired using standard protocols after administration of beta-blocker for heart rate ≥ 65/min and all patients received sublingual nitroglycerin. A core lab analyzed the CCTA images. The FFR_{CT} was analyzed by scientists at the company who developed the software. Using complex mathematical modeling (computational fluid dynamics) and making assumptions about the microcirculation based on LV mass, FFR_{CT} was calculated. It took an average of 5 hours to derive the FFR_{CT}. Invasive FFR was performed according to standard protocols with either IV or intracoronary adenosine to achieve maximal hyperemia, according to the operator's preference.

FFR_{CT} correlated well with invasive FFR ($r = 0.717$, $P < 0.001$) with a slight underestimation of FFR_{CT} compared to FFR (0.02 ± 0.12, $P = 0.02$). Using FFR as the gold standard, FFR_{CT} had the following sensitivity, specificity, positive-predictive value, and negative-predictive value: 87.9%, 82.2%, 73.9%, and 92.2%. Compared to using just the degree of stenosis on CCTA, FFR_{CT} was more accurate in detecting ischemia-producing lesions. The area under the receiver operating characteristics curve, a measure of accuracy of the test, was 0.90, indicating a high level of diagnostic accuracy. The authors conclude that noninvasive FFR derived from CCTA is a novel method with high diagnostic performance for the detection and exclusion of coronary lesions that cause ischemia.

■ COMMENTARY

This is an interesting and important study that has potential to significantly impact the way we assess patients with chest pain. Currently, Appropriate Use Criteria advocate the use of CCTA in patients with low-to-intermediate likelihood of having CAD, whereas its use in patients with established CAD is considered uncertain or inappropriate. While the absence of CAD or the presence of mild plaque in patients with acute chest pain has been associated with low likelihood of acute coronary syndromes, the use of CCTA in lesions of moderate severity has not been determined. In this study, the minority of moderate lesions were actually functionally significant by FFR or by FFR_{CT}. One could imagine foregoing ICA in patients with an intermediate stenosis on CCTA that has a non-significant FFR_{CT}, although this strategy remains to be tested. Now for the first time, CCTA appears to be able to incorporate both the anatomical definition of the lesion with the physiological significance of that lesion — this is an important step forward.

Several features about this study should be noted. First, invasive FFR actually induces maximal hyperemia in the individual patient, whereas the computational fluid dynamic analysis that derives the FFR_{CT} makes assumptions about the microvascular bed, rather than inducing hyperemia. I worry that inter-individual differences in microvascular function may lead to inaccurate diagnoses sometimes. Second, only patients undergoing ICA for ≥ 50% stenosis were included. This is important ethically in the early stage investigation of new technologies, but the exclusion of lesser degrees of stenosis may underestimate the false-positive rate. Third, the exclusion of patients with prior CABG means the performance of this modality in these patients is unknown. Finally, the huge computing power needed to derive the

FFR_{CT} means the studies took 5 hours to analyze. Future iterations of the technology are required to make it more widely applicable. Despite these limitations, this technique has significant potential. The combination of anatomy and function in a non-invasive study could improve our diagnosis and management of patients in a safer and more cost-effective way. ■

Reference

1. Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; 360:213-224.

ABSTRACT & COMMENTARY

Predicting the Response to CRT-D Therapy

By John P. DiMarco, MD, PhD

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Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

SOURCE: Goldenberg I, et al, on behalf of the MADIT-CRT Executive Committee. Predictors of response to cardiac resynchronization therapy in the multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy (MADIT-CRT). *Circulation* 2011;124:1527-1536.

This paper gives the results of a substudy from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial. The hypothesis for this substudy was that echocardiographic signs of favorable reverse remodeling would be associated with certain clinical factors that might therefore be used to predict clinical response to cardiac resynchronization therapy (CRT). MADIT-CRT was a large, randomized trial which enrolled patients with class I and class II heart failure, an indication for an implantable cardioverter defibrillator (ICD), a left ventricular ejection fraction ≤ 0.30, and a QRS duration > 130 msec. Patients were randomized to receive either an ICD only or resynchronization therapy ICD (CRT-D). The previously published main trial results showed a reduction in the combined endpoint of heart failure admission and mortality in the CRT-D therapy group.

In MADIT-CRT, an echocardiographic response was monitored by serial assessment in the left ventricular end diastolic and systolic volumes (LVEDV and LVESV) at enrollment and at 1 year. Only patients with technically adequate paired echocardiograms are included in this report. The endpoint for a clinical response was first heart failure event or death during follow-up. The authors sought to identify factors associated with a favorable echocardiographic response, defined either as a 10% or 15% reduction in LVEDV or LVESV, respectively. Once factors associated with favorable echocardiographic response were identified, these factors were weighted and a response prediction score was then calculated. Regression analysis of response in the CRT-D arm of MADIT-CRT identified seven factors associated with a favorable echocardiographic response to CRT-D therapy. The factors were: female gender, nonischemic cardiomyopathy, QRS duration ≥ 150 msec, left bundle branch block, prior heart failure hospitalization, baseline LVEDV > 125 mL/m^2, and baseline left atrial volume < 40 mL/m^2. These factors were associated with favorable echocardiographic responses in both LVEDV and LVESV. The relative effect in the regression model for each of the influential covariates was assigned a numeric value. Prior heart failure hospitalization was assigned a value of 1 point. Female gender, nonischemic cardiomyopathy, left bundle branch block, QRS duration ≥ 150 msec, and LVEDV were assigned a value of 2 points, and left atrial volume < 40 mL/m^2 a value of 3 points. Using this system, the response score might range from 0 to 14. The entire study population was then categorized into quartiles based on the distribution of the response scores. The lowest quartile had scores from 0 to 4, the next two quartiles had scores of 5 or 6 and 7 or 8. The highest quartile had a response score of 9 to 14. Response score quartiles showed a direct correlation between reduction in cardiac volumes in the CRT-D group. In contrast, when the same scoring system was applied to the ICD only arm of the trial, similar reductions in cardiac volumes were not seen. The response score also predicted clinical events. In the lowest response score quartile, there was no significant reduction in the risk of heart failure, hospitalization, or death compared to ICD only therapy. In the second and third response score quartiles, CRT-D therapy was associated with 33% and 35% risk reductions. In the highest response score quartile, CRT-D was associated with a 69%

reduction in the risk of heart failure or death. If response score was expressed as a continuous measure, the benefit of CRT-D therapy for reducing heart failure or death was increased by 13% for each 1 point increment in the response score. CRT response scores also predicted total mortality.

The authors conclude that baseline factors can predict favorable echocardiographic responses and this is associated with improved clinical response to CRT therapy. The degree of clinical response to CRT-D therapy can be estimated using a scoring system based on clinically available parameters.

■ COMMENTARY

ICD therapy may prolong life by preventing arrhythmic deaths, but it should not improve symptoms in patients with heart failure. CRT can improve symptoms and quality of life, and the addition of CRT to standard pacemakers and ICDs has been a major advance in device therapy. However, CRT devices are more costly, have shorter battery lives, and are associated with an increased rate of device-related complications. Selecting patients who are most likely to benefit from CRT is therefore particularly important in patients such as those in MADIT-CRT who have less severe heart failure symptoms at the time of implant. The system described here is relatively simple and can be used to stratify patients in whom the likely benefit of CRT will outweigh the disadvantages. ■

ABSTRACT & COMMENTARY

Laser Pacemaker Lead Extraction in Octogenarians

By John P. DiMarco, MD, PhD

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

SOURCE: Rodriguez Y, et al. Laser lead extraction in the octogenarian patient. *Circ Arrhythm Electrophysiol* 2011;4:719-723.

In this paper, Rodriguez and his colleagues from the Department of Cardiothoracic Surgery at the University of Miami report their experience with laser-assisted cardiac rhythm device lead extraction in a large group of patients. They separated the patients into those older and younger than 80 years of age and compared results in the two groups. During the period of study from 2004 and 2009, this center performed laser lead extractions in 506 patients. There were 118 patients 80 years of age or older and 388 patients younger than 80. Procedures were done in the operating room using laser sheaths. Indications and complications were analyzed using standard techniques for assessing lead extraction results.

The octogenarian group had a higher proportion of females, but overall comorbidities, including hypertension, diabetes, coronary disease, and renal insufficiency, were almost evenly distributed in the two age groups. In the nonoctogenarian group, 34% of the patients were classified as having New York Heart Association class III or class IV heart failure, whereas only 27% of the octogenarians had similar findings. In both groups, infection was the most common indication for lead extraction (76% among nonoctogenarians vs 84% among octogenarians). Lead malfunction accounted for 21% and 14% of the extractions in the nonoctogenarian vs octogenarian groups, respectively. A mixture of right atrial, right ventricular, and coronary sinus leads were extracted in both groups. The average implant time was higher in the octogenarian group (59.6 ± 53 months) compared to the implant duration in the nonoctogenarian group (38.6 ± 44 months). A subclavian approach could be used in 98% of the patients in both groups. All procedures were deemed successful. There was no effect of age on either success or complications. Minor complications occurred in 16 of 388 nonoctogenarians (4%), compared to 6 of 118 (5%) octogenarians. Major complications were seen in four nonoctogenarians (1%) compared to 2% of octogenarians. There was only one death secondary to pericardial tamponade and this was in a nonoctogenarian.

The authors conclude that laser lead extraction can be used safely in patients older than age 80 with results and complications comparable to those observed in younger patients.

■ COMMENTARY

This is a large series of laser lead extraction that is impressive for its efficacy and safety. The University of Miami has been the center for development of lead extraction techniques

for many years. This report is a single operator experience from one of the pioneers in the field. Therefore, it is not certain that similar excellent results could be obtained in lower-volume centers or by less-experienced operators. Recently, a consensus statement on transvenous lead extraction was published.[1] This document stressed the need for adequate training and adequate annual volumes to maintain proficiency in a high-risk procedure such as lead extraction. As more and more patients have implanted cardiac rhythm devices, we can expect to see a higher incidence of infections and lead malfunctions for which laser lead extraction may be considered. Centers planning to begin active lead management programs should make certain that they have adequate facilities, a reasonable expected annual volume, and well-trained and highly proficient operators before beginning their programs. ■

Reference

1. Wilkoff BL, et al. Transvenous lead extraction: Heart Rhythm Society expert consensus on facilities, training, indications, and patient management. *Heart Rhythm* 2009;6:1085-1104.

ABSTRACT & COMMENTARY

Indication for ICDs in Arrhythmogenic RV Cardiomyopathy Patients

By John P. DiMarco, MD, PhD

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

SOURCE: Bhonsale A, et al. Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention. *J Am Coll Cardiol* 2011;58:1485-1496.

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an uncommon condition with a wide spectrum of possible clinical presentations. Implantable defibrillators (ICDs) are standard therapy for treating ARVD/C patients who present with sustained ventricular tachycardia (VT) or cardiac arrest. In this paper, Bhonsale and his colleagues at Johns Hopkins report data on ICD utilization among the ARVD/C registry patients who received their devices for primary prevention of sudden death.

The Johns Hopkins ARVD/C registry is a prospective longitudinal study that enrolls patients who meet the clinical criteria for ARVD/C established and revised by an ARVD/C Task Force in 2010. The criteria include major and minor criteria describing functional and structural alterations, changes is right ventricular tissue characteristics, repolarization abnormalities on scalar ECG, arrhythmias, and family history. A "definite" diagnosis of ARVD/C is made if the subject has 2 major or 1 major and 2 minor criterion. A "borderline" diagnosis is made if the subject has 1 major and 1 minor or 3 minor criterion. A "possible" diagnosis is made if the subject has only 1 major or 2 minor criterion.

This study includes 84 patients who received an ICD for primary prevention between 1995 and 2010. Data from ICD shocks were collected, analyzed, and classified as appropriate or inappropriate. There were 70 patients with a definite diagnosis and 14 patients with a probable diagnosis of ARVD/C. The mean patient age at presentation was 32 years and the group had approximately equal numbers of men and women. There were 54 patients who were independently identified and 34 identified by screening of family members of known ARVD/C patients. Desmosomal mutations related to ARVD/C were identified in 36 of 63 (57%) of patients who underwent testing. Electrophysiologic studies (EPS) were performed in 72 patients and inducible sustained ventricular tachyarrhythmia were observed in 40 (56%).

During a mean follow-up of 4.7 years, 40 of 84 (48%) patients received one or more (median 5.5) appropriate ICD therapies. ICD shocks were commonly associated with exercise (63% of first shocks). VT storm was observed in 16 (19%) patients. Prior to receiving initial therapy, only three patients were being treated with an antiarrhythmic drug, but 36% were receiving a beta-adrenergic blocker. Predictors of appropriate ICD therapy included symptoms prior to presentation, proband status (higher risk if the patient was independently identified), and higher PVC and nonsustained VT presence on Holter monitoring. Induction of VT at EPS had a positive-predictive value of 65% and a negative-predictive value of 75% for appropriate ICD therapy. ICD-related complications including infection, pocket hematoma, lead dislodgment, subclavian vein occlusion, lead fracture, and malfunction need for revision were noted in 20

(24%) patients. Inappropriate ICD shocks for sinus tachycardia, supraventricular arrhythmias, or lead malfunction were experienced by 20 (24%) patients.

The authors propose that patients with ARVD/C can be risk stratified using four factors: proband status, PVC frequency (≥ 1000 in 24 hours), nonsustained VT, and VT induction at EPS. Risk increases in a stepwise fashion in patients with two to four of these risk factors. Patients with only one or zero risk factors can be spared ICD therapy with its costs and potential for complications.

■ COMMENTARY

Prescription of an ICD for primary prevention in a patient with ARVD/C is often difficult. In ARVD/C, a serious or fatal arrhythmia may be the first presenting major symptom. On the other hand, intervening with an ICD implant too early or in low-risk patients subjects these patients to risks for repeat procedures, infection, device malfunction, and inappropriate shocks. Effective risk stratification of ARVD/C patients therefore is quite important. In this paper, we see that findings at EPS and on Holter monitoring and proband status can be used to identify patients with a higher likelihood to benefit from a primary prevention ICD implant. Unfortunately, the data presented here constitute only the first step. We don't know anything about the reproducibility of the Holter and EPS findings on either a day-to-day or long-term basis as the disease progresses. Will it be necessary to rescreen patients periodically if their initial evaluation suggests a relatively low risk?

ARVD/C is an uncommon disorder and it is unlikely that definitive, randomized trials of therapy in these patients will ever be conducted. In the absence of data from randomized trials, registry data such as in this important paper, will likely provide the best guide to treating individual patients. ■

CME Questions

1. Which of the following is an indication for an ICD in patients with ARVD/C?
a. > 500 PVCs in 24 hours
b. Sustained VT
c. Atrial fibrillation
d. Desmosomal mutations

2. An intervention should be considered in asymptomatic patients with severe aortic regurgitation and normal LV function if their BNP is:
a. > 60.
b. > 100.
c. > 130.
d. > 160.

3. The greatest delay from initial hospital-to-balloon inflation at the accepting hospital in STEMI patients occurs:
a. during transport to the initial hospital.
b. at the initial hospital.
c. during transport to the accepting hospital.
d. accepting hospital door to balloon time.

4. Coronary CT angiography can be used to determine:
a. cardiac output.
b. coronary vascular resistance.
c. small vessel spasm.
d. fractional flow reserve.

5. Effective CRT-D response results in:
a. an increase in ejection fraction.
b. a reduction in LV volume.
c. a reduction in LA volume.
d. a reduction in RV volume.

6. Laser pacemaker lead extraction can be accomplished in octogenarians with a major complication rate of?
a. 1%
b. 2%
c. 3%
d. 4%

CME Objectives

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

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

PHARMACOLOGY WATCH

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

HPV Vaccine Now Recommended for Males

In this issue: New recommendations for HPV vaccine; guidelines for treatment of essential tremor; updates on smoking cessation drugs; and FDA actions.

HPV vaccine and anal cancer risk

The human papillomavirus (HPV) vaccine is routinely administered to adolescent girls; now the CDC's Advisory Committee on Immunization Practices is recommending the vaccine for 11- and 12-year-old boys as well. The vaccine has been approved for use in both adolescent girls and boys to protect them against HPV but has been somewhat underutilized in girls and rarely used in boys. HPV causes genital warts and cervical cancer in women and the vaccine effectively reduces the rate of both. The vaccine is generally recommended for 11 and 12 year olds when they get other routine vaccines, and before they become sexually active. Although the vaccine is approved for boys, the CDC had not made a recommendation on routine use until now. After evaluating data on efficacy in males, the committee felt that the vaccine could protect boys against genital warts, as well as throat and anal cancer caused by HPV, and could help prevent spread of the virus to girls.

In related news, a new study shows the HPV vaccine is effective in preventing anal intraepithelial neoplasia in men who have sex with men. In a double-blind study of 602 men (ages 16-26) who have sex with men, half were randomized to the quadravalent HPV vaccine and half to placebo. The vaccine reduced the risk of anal intraepithelial neoplasia caused by the four subgroups of HPV covered by the vaccine (HPV-6, 11, 16, and 18) by half in the intention-to-treat population and by 77% in the per-protocol population. Anal intraepithelial neoplasia caused by HPV of any type was reduced by 25.7% and 54.9%, respectively. Rates of anal intraepithelial neoplasia per 100 person years were 17.5 in the placebo group and 13 in the vaccine group in the intention-to-treat, and 8.9% placebo vs 4.0% vaccine in the per-protocol population. The rate of grade 2 or 3 anal intraepithelial neoplasia related to HPV subtypes covered by the vaccine was reduced by 54.2% (intention-to-treat) and 74.9% (per-protocol). The vaccine was well tolerated. The authors conclude that the HPV vaccine reduced the rate of anal intraepithelial neoplasia in men who have sex with men and may help reduce the risk of anal cancer (*N Engl J Med* 2011;365:1576-1585). ■

Treatment of essential tremor

The American Academy of Neurology has published its updated guideline for the treatment of essential tremor. Propranolol and primidone remain first options with a Level A recommendation (established as effective). Alprazolam, atenolol, gabapentin as monotherapy, sotalol, and topiramate are graded as Level B (probably effective), while nadolol, nimodipine, clonazepam, botulinum toxin a, deep brain stimulation, and thalamotomy remain as level C (possibly effective). There is not enough evidence to make a recommendation for gamma knife therapy. The new guideline also states that there is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozipine. Levetiracetam and 3,4 diaminopyridine are ineffective and flunari-

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zine is probably ineffective. The guideline was published online in *Neurology* October 19, 2011 (doi: 10.1212/WNL.0b013e318236f0fd). ■

Chantix and neuropsychiatric side effects

There is good news for the smoking cessation drug varenicline (Chantix). Following concern about neuropsychiatric side effects, the FDA sponsored two epidemiologic studies that evaluated the risk of neuropsychiatric hospitalizations associated with the drug. Neither study found a difference in risk of neuropsychiatric hospitalization between varenicline and nicotine replacement therapy, although hospitalization was the only endpoint evaluated and they did not rule out an increased risk of other neuropsychiatric events. While reassuring, the FDA is recommending that health care professionals and patients continue to follow the recommendations previously established and monitor for neuropsychiatric symptoms when prescribing or using varenicline. The manufacturer is conducting a large safety study of the drug to assess neuropsychiatric adverse effects but the results will not be available until 2017 (www.fda.gov/Drugs/DrugSafety/). In related news, the inexpensive partial nicotine agonist cytisine is an effective adjunct to smoking cessation, according to a new study in the *New England Journal of Medicine*. Cytisine is extracted from the seeds of *Cysisus laborinum L.* (Golden Rain acacia) and has been available worldwide for years, particularly in Eastern Europe, where it can be purchased for $6-$15 per course. Researchers randomized 740 smokers to cytisine or matching placebo for 25 days along with counseling. The rate of sustained 12 months abstinence was 8.4% in the cytisine group compared with 2.4% in the placebo group ($P = 0.01$). GI side effects were slightly more prevalent in the treatment group. The authors conclude that cytisine was more effective than placebo for smoking cessation and may be "an affordable treatment to advance smoking cessation globally" (*N Engl J Med* 2011;365:1193-1200). ■

FDA Actions

The FDA is continuing to review the association of oral contraceptives and thrombotic risk, particularly oral contraceptives containing drospirenone. On October 27, the FDA issued a preliminary Drug Safety Communication, with the full report due out in early December. Reviewing the records of Kaiser Permanente members in California and state Medicaid programs in Tennessee and Washington, which included 835,826 women receiving contraceptive prescriptions from 2001-2007, an increased risk of venous thromboembolism (VTE), deep venous thrombosis, and pulmonary embolism was noted with several contraceptives, with low estrogen hormonal contraceptives as a reference. Products containing drospirenone had relative risk of VTE of 1.74 (95% confidence interval [CI] 1.42-2.14). The norelgestromin/ethinyl estradiol transdermal patch was associated with relative risk of 1.55 (95% CI 1.17-2.07) and etonogestrel/estradiol vaginal ring was associated with a relative risk of 1.56 (95% CI 1.02-2.37). The risk was higher in younger users then older women (www.FDA.gov./DRUGS/DrugSafety/ucm277346.htm).

The FDA has approved the first generic olanzapine (Zyprexa) to treat schizophrenia and bipolar disorder. The generic carries the same warnings as the brand regarding increased risk of death in elderly people with psychosis or dementia. Generic olanzapine will be available from several manufacturers as tablets and orally disintegrating tabs.

The FDA has announced that drotrecogin alfa (Xigris) is being withdrawn from the market by Eli Lilly & Co. The withdrawal is based on the results of the recently completed PROWESS-SHOCK trial in which drotrecogin alfa failed to show a survival benefit in patients with severe sepsis and septic shock. The FDA is recommending that the drug should be stopped in any patients currently being treated and should not be initiated in new patients. All remaining product should be returned to the supplier.

The FDA has approved tadalafil (Cialis) for the treatment of benign prostatic hyperplasia (BPH) either alone or when it occurs along with erectile dysfunction (ED). The drug was approved in 2003 for treatment of ED. The approval was based on two trials in which men taking tadalafil 5 mg daily experienced significant improvements in BPH symptoms compared with those taking placebo. A third study in which men had both BPH and ED, tadalafil 5 mg daily improved both symptoms of BPH and ED compared to placebo. Tadalafil should not be used in patients taking nitrates or in combination with alpha blockers for the treatment of BPH.

The FDA has approved a combination of sitagliptin and simvastatin for the treatment of adults with type 2 diabetes and hypercholesterolemia. This represents the first combination drug for treating these two conditions. The fixed dose combination is available in three strengths: 100 mg sitagliptin/10 mg simvastatin, 100 mg/20 mg, and 100 mg/40 mg. The approval was based on "substantial experience with both sitagliptin and simvastatin" and is a "convenience combination," according to the FDA. Sitagliptin/simvastatin will be marketed as Juvisync by MSD International GmbH Clonmel in Tipperary, Ireland. ■

Clinical Briefs in Primary Care™

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By Louis Kuritzky, MD

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Lifetime Risk of Developing COPD: A Longitudinal Population Study

Source: Gershon AS, et al. Lifetime risk of developing chronic obstructive pulmonary disease: A longitudinal population study. *Lancet* 2011;378:991-996.

WORLDWIDE, CHRONIC OBSTRUCTIVE pulmonary disease (COPD) is the fourth most common cause of death, and is predicted to become the third most common cause in the near future, especially if smoking habits in populous nations like China — where more than half of adult men are currently smokers — continue on their same trajectory. According to Gershon et al, no prior publications have provided adequate insight into the lifetime risk of developing COPD. Hence, using health administrative data from the entire population of Ontario, Canada (n = approximately 13 million), they reported on a 14-year follow-up of persons who did *not* have COPD at baseline.

Based on the window of observation from 1996-2010, the population was divided categorically into: a) physician-diagnosed COPD, b) reached age 80 without a COPD diagnosis, or c) death. By age 80, more than one-fourth (28%) of persons free of COPD at baseline had been diagnosed with COPD by a physician. To put this into perspective, a new diagnosis of COPD was more likely than congestive heart failure, acute myocardial infarction, or even diabetes.

The authors mention that they have observed less public awareness of COPD than might be merited based on its epidemiological presence, and they encourage greater energies be invested in smoking cessation and public education about COPD. ■

The Burden of Painful Diabetic Peripheral Neuropathy

Source: Abbott CA, et al. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care* 2011;34:2220-2224.

RECENTLY PUBLISHED TELEPHONE SURVEYS of large populations of diabetics indicate a low level of recognition of the diagnostic terminology "Diabetic Neuropathy," despite commonplace problematic symptoms consistent with this disorder. Diabetic peripheral neuropathy (DPN) and diabetic peripheral neuropathic pain (DPNP) are associated with major morbidities. For instance, the leading cause of amputation in diabetics is foot ulcer subsequent to impaired sensation in the feet from diabetic neuropathy. Similarly, DPNP is often worsened by activity, which tends to compromise exercise capacity and may also interrupt sleep.

The North-West Diabetes Foot Care Study screened 15,692 adult diabetics in northwest England. The presence of neuropathy was established using scoring systems as well as specific nerve function testing (vibration, pin-prick, temperature, and reflex testing). Screenings took place during routine annual evaluations by primary care clinicians.

Overall, one-third of study subjects experienced painful neuropathy. DPNP was twice as common in persons with type 2 diabetes than type 1. Women and persons of South Asian ethnicity were disproportionately affected. Based on these findings, clinicians might anticipate an important positive yield from routinely screening for symptoms of DPNP and signs of DPN. ■

Predictive Value of Postprandial Glucose for CV Events in Type 2 Diabetes

Source: Cavalot F, et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: Lessons from the San Luigi Gonzaga Diabetes Study. *Diabetes Care* 2011;34:2237-2243.

THE DECODE DATA (DIABETES EPIDEMIOLOGY Collaborative Analysis of Diagnostic Criteria in Europe) indicated that all-cause mortality, as well as cardiovascular (CV) events, were better predicted by postprandial glucose (PPG) than fasting blood glucose (FPG). Indeed, the DECODE data set indicates a linear rise in relative risk for mortality as one progresses from normoglycemia, to impaired glucose tolerance, to frank diabetes.

Although much of the literature is consistent in finding that PPG outperforms both FPG and A1C in predicting adverse CV events (and mortality), one criticism aimed at these data reminds us that PPG data were, for the most part, obtained from oral glucose tolerance testing (OGTT). Since only a small minority of patients outside clinical trials actually have OGTT performed, obtaining a PPG after actual meals might better reflect the pathophysiology occurring in long-term

management of diabetics.

Cavalot et al report on a 14-year follow-up of type 2 diabetes patients (n = 505) in whom A1C, FPG, and PPG (*not* obtained by OGTT) were measured at baseline, seeking to discern the relationship of each of these metrics with CV events and overall mortality.

For mortality as well as CV events, both A1C and PPG were strong predictors (especially post-lunch PPG). FPG was not a good predictor. It remains to be determined whether interventions specifically targeting PPG will provide meaningful benefit beyond simple traditional diabetes control. ■

Vitamin E and Prostate Cancer

Source: Klein EA, et al. Vitamin E and the risk of prostate cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2011;306:1549-1556.

Observational epidemiologic data had suggested that selenium, vitamin E, or both might reduce the incidence of prostate cancer (PCa). Based on this hypothesis, the SELECT trial (Selenium and Vitamin E Cancer Prevention Trial) was performed. The basic structure was a randomized, placebo-controlled trial of vitamin E 400 IU/d (VitE), selenium 200 mcg/d (SEL), or both in 35,533 men. Seven years after enrollment, the trial was stopped because of a lack of any demonstrated benefit along with futility analysis indicating no potential of future benefit. That was in 2008.

This report extends follow-up of the same population through 2011. At this point, a statistically significant *increased* risk of prostate cancer was seen in men taking VitE (17% increase). While the numbers for SEL as well as SEL plus VitE trended toward worse outcomes, they were not statistically significant.

Why VitE might produce an increased risk for PCa is unclear: There was, for instance, no measurable effect of VitE on PSA. Although many clinicians have opted to be essentially silent in discussions of vitamin supplements with patients — since, after all, vitE was presumed to be innocuous — these data suggest consideration of intervention to discourage VitE in healthy men. Although the data were insufficient to definitively indict selenium, there is no support for endorsing it either. ■

Is There a Relationship Between Insulin Glargine and Cancer?

Source: Morden NE, et al. Further exploration of the relationship between insulin glargine and incident cancer: A retrospective cohort study of older Medicare patients. *Diabetes Care* 2011;34:1965-1971.

Recent retrospective studies in Europe have created concern because of an observed increased risk of cancer (hazard ratio = 1.55) in users of insulin glargine (GLAR) compared to nonusers. Similarly, increased risk of breast cancer in GLAR users was reported in two other analyses (hazard ratio 1.99-3.9). These reports, in addition to the limitations of their retrospective design, also had limitations such as failure to adjust for potential confounders such as BMI, GLAR dose, the impact of socioeconomic selection bias, and the relatively short periods of observation (6 years or less).

To remedy some of the limitations of early reports, the authors reviewed a Medicare database of more than 81,000 diabetics, including a subpopulation of 16,945 on GLAR and 49,455 on insulins other than GLAR. After adjustment for recognized confounders, there was no association seen between GLAR and any cancer. Indeed, combination insulin regimens were associated with increased risk of breast cancer, an association not previously consistently identified.

The results of this large data set should be generally reassuring about the safety profile of GLAR in reference to cancer of any type. The association of breast cancer with combination insulin regimens noted here should not be considered definitive because various reports have come to conflicting conclusions. ■

Saw Palmetto and BPH: *Not*

Source: Barry MJ, et al. Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: A randomized trial. *JAMA* 2011;306:1344-1351.

Although benign prostatic hyperplasia (BPH) and its consequences are rarely a mortal concern, the quality-of-life impact of LUTS (Lower Urinary Tract Symptoms) associated with BPH is often substantial. Antihypertensive alpha blockers (e.g., doxazosin, terazosin), site-selective alpha blockers (e.g., alfuzosin, tamsulosin), and alpha-reductase inhibitors (e.g., dutasteride, finasteride) have each been shown — either alone or in combination (i.e., alpha blockers + alpha reductase inhibitors) to improve LUTS. The latter have even been shown to reduce the need for surgery and the incidence of acute urinary retention in BPH study subjects.

Despite the well-demonstrated efficacy of proprietary agents, many BPH patients opt for "natural" treatments, such as saw palmetto (SWP). An early Cochrane review (2002) of SWP was generally supportive; less positivity was reflected in the 2009 Cochrane review, because more recent, rigorous trials found lesser benefit. Most trials utilized SWP 160 mg b.i.d. Is it possible that *more* SWP might gain greater therapeutic efficacy?

Barry et al performed a randomized, double-blind trial of higher-dose SWP, including doses up to 960 mg/d. Men with BPH (n = 369) were followed for 72 weeks. At the conclusion of the trial, no beneficial effects on LUTS were seen, despite the higher dose. No serious adverse effects attributable to SWP were seen. Based on these data, SWP is not beneficial for men with BPH. ■

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