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INSIDE

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Complete Revascularization with PCI in Patients with LV Dysfunction

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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

Dr. Boyle reports on financial relationships relevant to this field of study.

Source: Kirschbaum SW, et al. Complete percutaneous revascularization for multivessel disease in patients with impaired left ventricular function: Pre- and post-procedural evaluation by cardiac magnetic resonance imaging. *J Am Coll Cardiol Interv.* 2010;3:392-400.

Ischemic cardiomyopathy remains a frequent cause of heart failure. Management of patients with coronary artery disease with LV dysfunction has traditionally been achieved with coronary artery bypass graft surgery (CABG). More recently, percutaneous coronary intervention (PCI) has shown similar results to CABG in patients with multi-vessel coronary artery disease. However, the role of PCI in patients with multi-vessel disease and LV dysfunction remains to be defined. Key considerations in the decision-making process of whether or not to revascularize a patient with LV dysfunction include whether or not the LV dysfunction is due to ischemia and whether this will improve with revascularization. All methods of assessing myocardial viability have limitations. Therefore, Kirschbaum and colleagues performed a prospective study using cardiac MRI to determine the effects of PCI on LV function in patients with multi-vessel disease. They focused on comparing the effects of complete vs. partial revascularization.

Patients referred for PCI who had LV wall-motion abnormalities were prospectively enrolled in this study and underwent MRI with dobutamine stress and gadolinium-delayed enhancement. Inclusion criteria included significant stenosis (> 50%) in at least two vessels, sinus rhythm, and a wall-motion abnormality. Exclusion criteria were recent myocardial infarction (MI), unstable angina, and contraindications to MRI. Seventy-seven patients completed their first MRI, and 71 underwent follow-up MRI at 7 ± 1 months after PCI.

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Patients were considered to have had complete revascularization if all lesions greater than 50% were treated (n = 34), incomplete revascularization if one but not all lesions were treated (n = 22), and unsuccessful revascularization if no lesions were treated (n = 15). Baseline characteristics were similar between these groups. Mean age was 62 years, 64%-82% were male, and baseline LVEF was 46%-49%. The only differences between the groups were that chronic total occlusions (CTOs) were more prevalent in the incomplete and unsuccessful revascularization groups than in the complete group (86%, 67%, and 59%, respectively; $p = 0.04$), and the LAD was less likely to be involved in the unsuccessful group (25%) than the other groups (each 38%; $p = 0.04$). Patients had an average of 2.4 significant lesions. All patients received drug-eluting stents.

Results: In patients receiving complete revascularization, LVEF improved by 4% ± 5% ($p < 0.0001$), end-systolic volume index (ESVI) improved by 5 ± 8 mL/m^2 ($p < 0.001$), and cardiac output improved by 0.5 ± 1.2 L/min ($p = 0.02$). Patients with incomplete or unsuccessful revascularization had no change in LVEF, ESVI, or cardiac output. The improvement in LVEF correlated with dysfunctional but viable segments assessed by two MRI parameters: < 25% transmural infarction and contractile reserve > 7%. The sensitivity and specificity for predicting improvement in global LV function for transmural infarction < 25% were 70% and 77%, respectively. For contractile reserve, they were 100% and 75%, respectively.

Peri-procedural myocardial damage was common, occurring in 10/34 patients with complete revascularization, and this translated into three patients with newly detectable scar by delayed-enhancement MRI. However, this did not prevent improvement in overall LV function and did not significantly change overall infarct scar size. The authors conclude that complete revascularization for multi-vessel coronary artery disease improves EF, whereas EF did not change in patients after incomplete or unsuccessful revascularization. Improvement in EF can be predicted by performing cardiac MRI before PCI.

■ COMMENTARY

Not surprisingly, Kirschbaum et al showed that dysfunctional but viable segments of myocardium improve with revascularization, and that MRI parameters can predict improvement. However, the predictive value of the tests is imperfect, as with other tests of viability before revascularization. The predictive power of MRI in this study is similar in magnitude to other modalities of assessing viability, such as MRI or dobutamine echo. This study is encouraging that complete revascularization by PCI can improve ischemic cardiac dysfunction, just as has been shown for CABG in the past, particularly as some advocate only revascularizing the "culprit" lesion and only for anginal symptoms. However, several issues with this study require discussion. Firstly, this was an observational study, so no conclusions should be drawn on whether using these MRI parameters to change management will result in better outcomes. Secondly, there is inherent selection bias when including only patients who are already referred for PCI. Thirdly, the authors chose to define all coronary artery lesions greater than 50% as significant. Whether this is the appropriate cut-off, or whether functional criteria would have been better ways to define significant, remains to be tested in future clinical trials. However, the authors have taken a step toward tackling the issue of complete vs. incomplete revascularization with PCI in patients with LV dysfunction. Just as CABG usually aims for complete revascularization rather than just "culprit" lesion revascularization, perhaps PCI should also have the same aim. This remains to be studied in future randomized, controlled trials. ■

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

LV Function Deteriorates in Non-STEMI Patients Awaiting Cardiac Catheterization

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

Source: Grenne B, et al. Changes of myocardial function in patients with non-ST-elevation acute coronary syndrome awaiting coronary angiography. *Am J Cardiol.* 2010;105:1212-1218.

The optimal timing of cardiac catheterization for patients suffering non-ST segment elevation myocardial infarction (nonSTEMI) remains a subject of debate. Research on early vs. delayed cardiac catheterization has focused on event rates (death, myocardial infarction [MI], and revascularization), but little is known about the effect of waiting for cardiac catheterization in left ventricular (LV) systolic function. Accordingly, Grenne and colleagues studied patients presenting to their center in Norway, with chest pain suggestive of nonSTEMI, and performed echocardiography at admission, immediately prior to cardiac catheterization and after revascularization. Global and regional myocardial function was measured as longitudinal and circumferential strain using speckle-tracking echocardiography.

They prospectively recruited 102 patients, and gave retrospective diagnoses after cardiac catheterization and cardiac enzyme results were known. Patients were divided into nonSTEMI (n = 56), unstable angina pectoris (UAP) (n = 23), and non-coronary chest pain (NCCP) (n = 23). Patients were excluded if they had severe valvular disease, previous heart surgery or bundle branch block, significant arrhythmia, reduced life expectancy, or very early, planned cardiac catheterization (< 10 hours). Echo was performed in parasternal views for circumferential strain and apical views for longitudinal strain. Using the 16-segment model, global strain was calculated by averaging all segmental peak-systolic strain values. Regional strain was calculated for the territory of each coronary artery, and the culprit vessel was then identified on coronary angiography.

Results: Mean time from admission to coronary angiography was 32 hours in all groups. Patients experiencing non-STEMI were older (67 ± 14 years) than those suffering UAP or NCCP (58 ± 11 and 56 ± 10 years, respectively), and were less likely to have had previous percutaneous coronary intervention (PCI) (4% vs. 30% vs. 26%; $p < 0.05$). Medication usage was similar, with the exception that the NCCP group had lower statin use at the time of cardiac catheterization (100% vs. 100% vs. 74%; $p < 0.05$).

At admission, non-STEMI patients had worse longitudinal and circumferential strain, and patients with UAP had worse longitudinal strain than patients with NCCP ($p < 0.05$). In the non-STEMI patients, global LV function deteriorated in the 32 hours between admission and cardiac catheterization ($p < 0.001$), whereas there was no change in the UAP or NCCP groups. This was demonstrated by an increase in the global longitudinal strain in the non-STEMI patients, but there was no change in the circumferential strain. The change in global strain was driven purely by a worsening in the culprit artery territory, as there was no change in the strain in the remote region. Of note, the LV ejection fraction (EF) in the non-STEMI group was 53% ± 6% at admission and 51% ± 7% at cardiac catheterization, but this change did not reach statistical significance. There was no change in LVEF in the other groups.

The authors then separated the non-STEMI group further according to whether the culprit artery was completely occluded (n = 16) or nonoccluded (n = 40). Those with occluded culprit arteries had deterioration in both longitudinal and circumferential strain from admission to cardiac catheterization ($p \leq 0.01$), and those with non-occluded arteries had deterioration in only the longitudinal strain during that time ($p < 0.001$). The authors offer an explanation for this. The predominance of longitudinal fibers in the subendocardial layer may be the reason that both occluded and non-occluded arteries result in ischemic deterioration in function here, because ischemia first affects subendocardial tissue. Thus, both complete and incomplete occlusion may render the subendocardium ischemic. With the majority of circumferential fibers being in the midwall of the LV, only the occluded artery patients experienced deterioration in circumferential strain, because only the patients with occluded arteries had transmural ischemia. This would seem to be a plausible explanation.

Follow-up of non-STEMI patients revealed that regional and global strain improved in those patients without occlusion who were revascularized, either by PCI or coronary artery bypass grafting. However, there was no benefit in those with an occluded artery. The authors conclude that myocardial function deteriorates in patients with nonSTEMIs awaiting coronary angiography, that patients with acute coronary occlusion have the most pronounced deterioration, and that this subgroup shows no recovery of function after revascularization.

■ COMMENTARY

Using a sensitive method to serially assess regional cardiac function, Grenne et al show us that there is regional deterioration in function in patients with nonSTEMI and a non-occluded artery over the first 32 hours in hospital. This corresponded to an overall decrease in global LV strain but not a significant decrement in LVEF. Importantly, this deterioration in cardiac function was reversible after revascularization. Patients with nonSTEMI and complete occlusion of the infarct artery also suffered deterioration in LV function in the first 32 hours in hospital, but this did not resolve after revascularization. It should be noted that this subgroup of patients was small (n = 16). Importantly, there was no deterioration in function in the absence of biomarkers of myocardial necrosis. It is noteworthy that the authors have not tested whether earlier intervention may prevent this deterioration in LV function. This must be tested in future prospective studies. ■

ACE Inhibitors in Acute Myocardial Infarction

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Milonas C, et al. Effect of angiotensin-converting enzyme inhibition on one-year mortality and frequency of repeat acute myocardial infarction in patients with acute myocardial infarction. *Am J Cardiol*. 2010;105:1229-1234.

The use of angiotensin converting enzyme (ACE) inhibitors in all acute myocardial infarction (MI) patients is controversial. Thus, these investigators from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) examined the association between ACE inhibitor therapy and mortality in unselected patients with acute MI. This registry started in 1995 and includes almost all patients admitted to Swedish hospitals with acute coronary syndromes until 2005. The patient population for this study is 105,224 patients with acute MI who were not treated with ACE inhibitors on admission. They were followed for one year for mortality and repeat admission for acute MI. Two groups were compared: those put on ACE inhibitors at discharge and those not. Since there were differences in baseline characteristics between the two groups, a propensity score was calculated for each patient and used to adjust for baseline characteristics and treatment.

Results: Thirty-seven percent of the patients received ACE inhibitors at discharge; 30% in 1995, increasing to 43% in 2005. The unadjusted one-year mortality rate was less in those treated with ACE inhibitors as compared to those not (10.6% vs. 12.1%, $p < 0.001$). After adjustment, the risk ratio for mortality in those on treatment was 24% less (RR = 0.76, 95% CI 0.73-0.80). The benefit was largely confined to those with a history of current heart failure. Also, in those where it was measured, the ACE inhibitor benefit was greater as the glomerular filtration rate and ejection fraction decreased. Readmission for acute MI was decreased 7% when adjusted (RR = 0.93, 95% CI 0.9-0.96), with the major effect seen in those with ST elevation MI and systolic left ventricular dysfunction (LV). The authors concluded that ACE-inhibitor treatment prior to discharge of unselected acute MI patients was associated with reduced one-year mortality, but mainly in those with heart failure and renal dysfunction. Also, there was a small reduction in recurrent MI mainly in patients with STEMI and LV dysfunction.

■ COMMENTARY

Current guidelines recommend ACE inhibitors for acute MI with preserved LV function, but there is little data to support this practice. Previous trials have shown benefits largely in high-risk patients such as those with heart failure or reduced LV function. The guidelines are based upon data from patients with stable CAD treated over many years. So even though this is not a randomized trial, the results are of interest because unselected patients with acute MI, not treated on admission with ACE inhibitors, were analyzed based upon whether or not they received ACE inhibitors at discharge. This study represents the largest observational study of this issue, so propensity scoring adjustments for differing baseline characteristics could be made with adequate power. The results showed that ACE inhibitors reduce mortality mainly in patients with heart failure and renal dysfunction, and they reduce recurrent MI largely in patients with STEMI and reduced LV function. If I were revising the guidelines for post-MI care, I would recommend ACE inhibitors for acute MI patients if they had STEMI, LV dysfunction, heart failure, or renal dysfunction (IIa). ACE inhibitor treatment for all acute MIs would be IIb. Of course, ACE inhibitors could be used for other indications such as hypertension.

There are some caveats to this study. Propensity score adjustments may not account for all differences between groups. We do not have data on the actual ACE inhibitor the patients were on or the dose. Not all ACE inhibitors may be the same, and prior studies have shown variable effects depending on dose. This study was completed before the widespread use of angiotensin receptor blocking drugs (ARB). They accounted for < 3% of prescriptions for drugs targeting the renin-angiotensin system in this study. Also, we do not know the effect of the drugs on blood pressure in this study, which could be an important consideration.

The benefits observed in those with renal dysfunction are interesting because we often do not start ACE inhibitors if there is renal dysfunction. Also, ACE inhibitors are indicated in diabetics to prevent renal damage. Of those discharged on ACE inhibitors, 22% had diabetes. But, in subgroup analyses, diabetes did not influence the results of the study. Less than 2% of patients in the study had renal failure, but the number with renal dysfunction is not given.

Partially because the study started in 1995, only about one-third had coronary angiography and one-quarter revascularization. About half the patients were on statins. Thus, more aggressive therapy for acute MI could alter the results of this study. The major message I take from this study is that ACE inhibitors or ARBs should be reserved for those following acute MI who have definite indications such as heart failure, LV dysfunction, hypertension, or diabetes, and should be more strongly considered in those with renal dysfunction. ■

Prognosis of No-reflow Phenomenon

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Ndrepepa G, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J Am Coll Cardiol.* 2010;55:2383-2389.

LITTLE IS KNOWN ABOUT THE LONG-TERM PROGNOSIS OF THE no-reflow phenomenon after percutaneous intervention (PCI) for acute ST elevation myocardial infarction (STEMI). Thus, these investigators from Munich, Germany, studied 1,406 patients with STEMI presenting within 24 hours of symptom onset and undergoing PCI by scintigraphic infarct size measurement 7-14 days after PCI. No-reflow was defined as TIMI flow grade ≤ 2 or a TIMI flow grade of 3 but a TIMI perfusion grade of ≤ 1 at 10 minutes after PCI. The primary endpoint was five years mortality.

Results: No-reflow occurred in 410 of the 1,406 patients (29%). No-reflow patients were, in general, older, more often had prior bypass surgery, and had higher-peak troponin, CK-MB, and high-sensitivity CRP levels. Also, no-reflow patients had a longer time from symptom onset to hospital admission and were more likely to have multivessel disease. Scintigraphic MI size was larger in the no-reflow group (15% vs. 8%, $p < 0.001$). Mortality at five years was higher in the no-reflow group (18.2% vs. 9.5%, $p < 0.001$). MI size and the incidence of no-reflow were significantly associated. Multivariate predictors of five-year mortality included no-reflow, age, diabetes, killip class, CRP, multivessel disease, and infarct size. After adjusting for these predictors, the hazard ratio for no-reflow confirmed that it is an independent predictor of five-year mortality (HR = 1.7, 95% CI 1.2-2.4, $p = 0.004$). The authors concluded that no-reflow is a strong predictor of five-year mortality in STEMI patients treated with PCI, and that no-reflow provides independent prognostic information beyond infarct size.

■ COMMENTARY

Depending on your definition, no-reflow occurs in 10%-30% of STEMI cases treated by PCI. Evidence suggests that downstream thrombus embolization in resistance arteries is the cause. This study clearly demonstrates that it is associated with higher mortality, larger infarcts, lower ejection fraction, and increased remodeling. The strengths of this study are its large size and long follow-up. The weaknesses are that we do not know the time course of no-reflow. Smaller studies suggest that it can resolve, but it may take three months. Other studies show that it is persistent in 50% of patients. Also, we do not have details about pharmacologic or other therapies for no-reflow in this study and, thus, cannot assess their effectiveness. Clearly we should try to avoid no-reflow and treat it vigorously if it does occur, but how do we do this?

Prevention of no-reflow involves pre-procedure anticoagulation and antiplatelet pharmacologic therapy. During the procedure, there are mechanical adjuncts to PCI, such as thrombectomy or aspiration catheters, and distal protection wires, filters, or balloons. Studies with these devices have shown higher TIMI flow grades and less distal embolization but no change in 30-day mortality. Thus, routine use of these devices is not recommended, but selective application to those with high thrombus burdens is reasonable.

Once no-reflow is recognized in the catheterization laboratory, pharmacologic therapy can be deployed. Several different types of pharmacologic agents have been used: metabolic agents, vasodilators, anticoagulant, and antiplatelet agents. In hopes of maximum effects, these agents are often given intracoronary (IC). Vasodilators that have been used include adenosine, nitroprusside, diltiazem, verapamil, and nicardipine. Anticoagulation or antiplatelet agents given include abciximab and glycoprotein 11b/111a inhibitors. Despite IC delivery, systemic effects can occur; the most worrisome is hypotension. Thus, vasodilators, even IC, are relatively contraindicated in the face of hypotension and shock. Usually, hypotension is transient, and most patients respond to a brief pressor infusion.

Long-term care of no-reflow patients is focused on left-ventricular performance. These patients should receive ACEI/SRBs for at least three months regardless of the discharge ejection fraction. They should be reassessed at three months to plan further therapy. ■

Dronedarone vs. Amiodarone in Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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

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

Source: Le Heuzey J-Y, et al. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: The DIONYSOS study. *J Cardiovasc Electrophysiol*. 2010;21:597-605.

Dronedarone is an antiarrhythmic drug with structural and electrophysiologic similarities to amiodarone that was released in 2009. Dronedarone's structure includes a benzofuranyl ring but, unlike amiodarone, the ring is not iodinated. This, and a side chain modification, give dronedarone a shorter half-life and reduced tissue accumulation. The study reported here was designed to compare the short-term efficacy and safety of dronedarone and amiodarone in patients with atrial fibrillation.

Patients in atrial fibrillation of at least three days duration were eligible for inclusion. The main exclusion criteria were: prior treatment with amiodarone, thyroid disease, severe congestive heart failure, severe bradycardia or AV block, or use of other antiarrhythmic drugs. Patients underwent a screening period of 30 days and then were randomly assigned to either dronedarone 400 mg twice daily or amiodarone 600 mg daily for 28 days. Electrical cardioversion was scheduled between days 10 and 28 if the patient had not converted spontaneously to sinus rhythm. The study duration was six months. Heart rhythm assessment was performed by 12-lead ECGs during scheduled clinic visits. The main endpoints included recurrence of atrial fibrillation, premature study discontinuation for lack of efficacy, and premature drug discontinuation for intolerance. Other endpoints included unsuccessful electrical cardioversion and no spontaneous cardioversion with no electrical cardioversion.

The study enrolled and randomized 504 patients. The mean age was 64 $\pm$ 11 years, with 20% of the population older than 75 years. The most common cardiovascular diagnosis was hypertension (66.9%); 18% had coronary artery disease. At baseline, the majority of patients were treated with oral anticoagulants (96%) and beta adrenergic blocking agents (63%).

Amiodarone appeared to be more effective than dronedarone. Overall, atrial fibrillation recurrence or persistence was documented in 64% of dronedarone patients compared to 42% of the amiodarone patients. Documented atrial fibrillation was seen after conversion in 37% of the dronedarone patients vs. 24% of the amiodarone patients. Unsuccessful electrical cardioversion was noted in 12% of the dronedarone patients vs. only 6% of the amiodarone patients. There was no spontaneous cardioversion and no electrical cardioversion in 15% of the dronedarone patients vs. 11% of the amiodarone patients. Study drug was prematurely discontinued in 10% of the dronedarone patients and 13% of the amiodarone patients.

Side effects were more common during amiodarone treatment. Thyroid disorders, neurologic events, and skin reactions were all more common with amiodarone. Diarrhea, nausea, and vomiting were more frequently seen in the dronedarone group. Hepatic enzyme elevations were seen with a similar frequency in both groups. Both groups experienced a moderate increase in creatinine plasma levels. There were more supratherapeutic INR levels in the amiodarone group. A higher incidence of hemorrhagic events was also seen in amiodarone. No pulmonary toxicity was noted in either group in this short-term study. Study drug was discontinued early due to an adverse event in 11% of the amiodarone patients compared to 5% of the dronedarone patients.

The authors conclude that dronedarone was less effective than amiodarone for preventing AF recurrence but had a better safety profile due to a reduced frequency of thyroid and neurologic adverse reactions and a lessened potential for interaction with oral anticoagulants.

■ COMMENTARY

Dronedarone was released in the United States for treatment of atrial fibrillation in 2009. Approval was largely based on the results of the ATHENA trial. ATHENA enrolled more than 4,600 patients, who were randomized to either dronedarone or placebo. The primary outcome was mortality and cardiovascular hospitalization, which were decreased by dronedarone treatment. Atrial fibrillation recurrence, however, was not carefully tracked in ATHENA, and DIONYSOS was performed to give a comparative look at the relative efficacies of dronedarone and amiodarone. In this study, dronedarone appears to be less effective an antiarrhythmic agent compared to amiodarone. The side-effect profile is somewhat better. Physicians starting patients on rhythm-control therapy for atrial arrhythmias will have to consider this risk-benefit profile when choosing between dronedarone and amiodarone. ■

Epicardial Ablation Experience

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Sacher F, et al. Epicardial ventricular tachycardia ablation. *J Am Coll Cardiol*. 2010;55:2366-2372.

In this study, Sacher and colleagues, from three well-know ablation centers, report their experience with epicardial ventricular tachycardia (VT) ablation. During the period from 2001 to 2007, 913 VT ablations were performed in the three centers. Of these, 156 (17%) involved epicardial mapping or ablation. Cardiac diagnoses included: ischemic cardiomyopathy in 51 patients, nonischemic cardiomyopathy in 39 patients, arrhythmogenic right ventricular cardiomyopathy in 14 patients, miscellaneous cardiomyopathies in 13 patients, and 17 patients with no structural heart disease. Pericardial access was obtained using either a percutaneous subxiphoid puncture or, in patients where this was not possible, a surgical subxiphoid or lateral incision. In a few patients

who were to undergo associated cardiac surgery, a median sternotomy was used. Ablation was performed using radiofrequency catheters. In the latter portions of the study, the Biosense Webster ThermaCool 3.5 mm tip irrigated catheter was the standard ablation tool. Coronary arteriography was used to avoid damage to the coronary arteries. High output pacing was performed before ablation on the lateral wall to exclude phrenic nerve injury.

A total of 156 epicardial ablation mapping or ablation procedures were performed in 134 patients. Access to the pericardial space was successful in 136 of 151 attempts. The most common reason for failure was a history of prior cardiac surgery. Major complications were observed acutely or before discharge after 14 of the 156 procedures (9%). However, only eight of these were strictly related to the epicardial approach. There were seven patients who had epicardial bleeding and one patient who had an asymptomatic coronary artery stenosis. Six of the 14 complications were related to concomitant endocardial ablation. These included: pulmonary emboli (2), cardiogenic shock, pericardial effusion, AV block, and bilateral groin hematomas (2). Right ventricular puncture without significant bleeding was observed during an additional 23 procedures. Most patients developed chest pain as a result of pericardial inflammation and required nonsteroidal antiarrhythmic drugs. Delayed reactions included a major pericardial inflammatory reaction, one delayed tamponade, and an acute inferior myocardial infarction two weeks after the procedure. The total acute and delayed major complication rate was 7%.

The authors concluded that epicardial ablation was a valuable adjunct in 13% of patients referred for VT ablation. Although the risk for acute and delayed major complications is significant, they seem justifiable by the absence of therapeutic alternatives for this population.

■ **COMMENTARY**

Over the last several years, it has been recognized that epicardial catheter ablation has been able to control monomorphic VT in some patients with failed endocardial ablation attempts. This is particularly true when the VT occurs in the setting of a nonischemic cardiomyopathy. This paper demonstrates that epicardial VT ablation is possible, but that the procedure carries substantial risks. It would be helpful if the authors had described their success rate so that the reader might weigh risks vs. benefits. In another report from the Boston group that contributed many of the patients included in this paper (*J Cardiovasc Electrophysiol*. 2010;21:406-411), combined endocardial and epicardial ablation eliminated all inducible VT in 50% and the target VT in another 30%. These results appear to justify the added risks associated with epicardial procedures even in experienced hands. ■

Ambulatory Cardiac Telemetry

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Kadish AH. Frequency of serious arrhythmias detected with ambulatory cardiac telemetry. *Am J Cardiol*. 2010;105:1313-1316.

Ambulatory cardiac telemetry uses a cellular phone monitor to continuously receive transmissions from a sensor on the patient, interpret them, and send ECG strips, considered to be possibly dangerous arrhythmias, to a central station for review and possible intervention. This system has the potential to detect life-threatening arrhythmias and precipitate rapid interventions. This report analyses a nine-month experience with a large system (Life Watch) involving more than 26,000 consecutive patients. The monitor activates when it senses atrial fibrillation, tachycardia, bradycardia, or pauses using preset criteria i.e. ≥ 150 beats/min. for > 10 seconds. After central analysis, physicians are called for certain arrhythmias believed to be dangerous using a tiered action system (emergent, urgent, regular notification). About 80% of the patients presenting had atrial fibrillation, syncope, conduction abnormalities, and palpitation. Physician notification criteria were met in 21% of the patients. Emergent action arrhythmias were present in 1% of patients and urgent arrhythmias in an additional 3%. The authors concluded that only 1% of patients referred for ambulatory cardiac telemetry had life-threatening arrhythmias over a three-week period but, for these patients, this device could be life-saving.

■ **COMMENTARY**

For patients at high risk for, or are suspected of having, serious cardiac arrhythmias, various non-invasive devices exist for recording arrhythmias: holter monitors, patient-activated event recorders, automatically activated event recorders, and ambulatory cardiac telemetry. Previous comparison studies have shown that ambulatory cardiac telemetry has the highest yield. An implantable loop recorder would be expected to have a comparable yield, but is invasive and requires interrogation periodically. The major advantage of ambulatory telemetry is that using pre-set criteria, certain arrhythmias can be transmitted to a monitoring station and immediate action can be taken if appropriate. The purpose of this retrospective study was to evaluate the frequency of various rhythm disturbances and assess the potential for life-saving interventions. In this study, only 1% of the patients had such events, which, in this large study, were 260 patients. Of these, 120 had wide complex tachycardias > 15 beats; 100 had pauses ≥ 6 sec; and 40 had sustained rates < 40 beats/min. Not included

in the emergent rhythms, 704 patients had sustained tachycardias > 180 beats/min.

The major limitation of this study is that it was a retrospective analysis of the central-station database. No detailed clinical information or outcomes were known. Of interest, more women than men were monitored (59%), but men had more rhythm disturbances that met physician notification criteria than women (26 vs. 17%, $p < 0.001$). The fact that almost 80% of patients had nothing worth notifying a physician about is consistent with other ambulatory ECG studies, and suggests that this may be an overused technology. In my experience, most ambulatory ECG studies are ordered by non-cardiologists, probably to protect themselves from lawsuits. Thus, more appropriate use of this technology may be difficult to achieve. ■

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. ■

CME Questions

1. **Regional LV function deteriorates in which patients with ACS awaiting cardiac catheterization?**
   a. Non-cardiac chest pain
   b. Unstable angina
   c. Non-ST elevation MI
   d. All of the above
2. **LV function is most likely to improve in PCI patients with:**
   a. complete revascularization.
   b. culprit lesion revascularization.
   c. partial revascularization.
   d. All of the above
3. **Which of the following is most correct concerning dronedarone for atrial fibrillation?**
   a. It is more effective than amiodarone.
   b. It is less effective that amiodarone.
   c. It has more side effects than amiodarone.
   d. It has less pulmonary toxicity.
4. **Which of the following is most correct concerning epicardial ablation of VT?**
   a. Half of VT patients could benefit.
   b. Cardiac puncture is rare.
   c. Major complications occur in < 10%.
   d. All of the above
5. **No-reflow after PCI for STEMI is associated with:**
   a. higher five-year mortality.
   b. larger infarct size.
   c. lower ejection fraction.
   d. All of the above
6. **ACE-inhibitor treatment of unselected acute MI patients results in:**
   a. lower mortality.
   b. higher readmission rates.
   c. worsening renal function.
   d. All of the above
7. **The major advantage of ambulatory cardiac monitoring vs. other techniques is:**
   a. the ability to record every beat.
   b. no patient intervention is required.
   c. the ability to trigger a rapid intervention if necessary.
   d. a technician prescreens the recordings.

Answers: 1. (c); 2. (a); 3. (b); 4. (c); 5. (d); 6. (a); 7. (c)

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

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Coronary Calcium Scores enhance risk prediction

Source: Polonsky TS, et al. *JAMA* 2010; 303:1610-1616.

PROBABLY THE MOST WIDELY RECOGNIZED scoring system for predicting CV risk is the Framingham Risk Score (FRS). The United States Preventive Services Task Force (USPSTF) has recently published the opinion that novel risk markers such as C-reactive protein do not sufficiently enhance risk prediction enough to justify their routine utilization in addition to traditional scoring systems like FRS Coronary Calcium Score (CCS) has a number of appealing attributes that suggest consideration as a powerful prediction tool.

In the Multi-Ethnic Study of Atherosclerosis (MESA) trial of persons without known CHD at baseline, a CCS > 300 was associated with a 10-fold increased risk for CHD events. A critical issue, however, is whether new or additional prediction score tools add meaningfully to existing methods. A metric known as Net Reclassification Improvement (NRI) has been recently proposed to distinguish whether the incremental impact of a scoring system or risk factor upon already existing methods is meaningful.

Using the cohort of MESA (n = 6814 adults; age > 45), Polonsky et al compared risk prediction as derived from FRS vs FRS + CCS. The addition of CCS to FRS resulted in a statistically significant NRI. An additional 23% of persons who experienced CHD events but had not been identified by FRS as high risk were correctly reclassified by the addition of CCS. Similarly, an additional 13% of subjects not classified by FRS as low risk (and who did not suffer events), were reclassified as low risk by the addition of CCS. Whether the preferential (or additional) use of CCS for risk prediction can improve outcomes over traditional risk scores alone will require further definition, although many are already sufficiently encouraged by the predictive power of CCS to currently employ it. ■

Exacerbations of COPD: Not so innocent

Source: Donaldson GC, et al. *Chest* 2010;137:1091-1097.

ACUTE EXACERBATIONS OF COPD (AE-COPD) are sometimes misconstrued as minimally consequential "bumps in the road" along the journey of progressive COPD. Unfortunately, the toxicity of ae-COPD has been underappreciated; ae-COPD are associated with hospitalizations, loss of lung function that is typically not regained, and mortality. Donaldson et al direct our attention to a newly recognized additional burden of morbidity associated with ae-COPD: MI and stroke.

The Health Improvement Network (THIN) database contains anonymized medical records of patients seen by GPs in England and Wales. Over a 2-year period, 25,857 COPD patients provided a dataset with which to compare the incidence of MI and stroke during "stable" periods of COPD with the immediate post-ae-COPD period.

The incidence of acute MI was increased more than 2-fold in the 5-day period immediately following an ae-COPD; similarly, stroke incidence was increased more than 2-fold in the 49-day period immediately post-ae-COPD. Both findings were statistically significant.

No pharmacologic treatment of COPD has been proven to be disease-modifying. Yet, since various pharmacotherapies have been shown to reduce ae-COPD, perhaps such treatments will ultimately be shown to impact disease outcome by affecting the above-mentioned consequences of ae-COPD: increased stroke and MI. ■

Vitamin E, but not pioglitazone, improves NASH

Source: Sanyal AJ, et al. *N Engl J Med* 2010;352:1675-1685.

STEATOSIS IS THE ACCUMULATION OF FAT, derived primarily from triglycerides in hepatic cells. Progressive steatosis can lead to hepatic inflammation, which, when not associated with alcohol, is known as non-alcoholic steatohepatitis (NASH). Obesity and diabetes are the two conditions most commonly associated with NASH. Because as many as 15% of NASH cases may ultimately progress to cirrhosis, effective treatments are eagerly sought.

Since the pathologic underpinnings of NASH often include insulin resistance, hypetriglyceridemia, and type 2 diabetes, pharmacology with thiazolidinediones (TZD) appears logical. Unfortunately, results from pilot trials of TZDs have been conflicting.

The NASH Clinical Research Network, established by the NIDDK, conducted a

placebo-controlled trial of pioglitazone or vitamin E in non-diabetic NASH patients (n = 247). Subjects received 800 IU/d vitamin E, 30 mg/d pioglitazone, or placebo for approximately 2 years. The primary outcome was histologic status of NASH.

At 96 weeks, vitamin E did demonstrate a statistically significant rate of NASH histologic improvement, but pioglitazone did not. Even though there were some favorable histologic effects, neither intervention showed a reduction in hepatic fibrosis, so we remain uncertain about whether vitamin E can impact the development of serious long-term liver disease. Pioglitazone did not achieve an effect on the primary outcome, but explanations for why TZDs may still be considered for NASH therapy are presented by the authors. ■

Best use of home BP monitoring

Source: Pickering TG, et al. *J Am Soc HTN* 2010;4:56-61.

The largest body of information guiding treatment of hypertension (HTN) is based upon office BP management. Nonetheless, home BP monitoring (HBPM) is documented to be a better predictor of CV risk than office BP. For instance, patients with high office BP but low HBPM are recognized to be at substantially lower risk than office BP predicts; similarly, high HBPM pressures compared to office BP portends greater risk than indicated by office BP alone. Simply the fact that HBPM offers the opportunity for many more BP readings than is readily accessible in clinical care provides both a more comprehensive and consistent BP profile.

Recording HBPM twice daily (morning and evening), when averaged over 1 week, provides a sufficient BP profile to help guide management. By HBPM, HTN is > 135/85 mmHg and normotension is < 125/75 mmHg. Borderline HBPM (125-135/75-85 mmHg) merits consideration of 24-hour ambulatory BP monitoring for further clarification. The authors, writing on behalf of the American Society of Hypertension, provide a list of validated home BP monitoring devices at: www.dableeducational.org/. ■

Suicide risk with anticonvulsants

Source: Patorno E, et al. *JAMA* 2010;303:1401-1409.

Although the term "anticonvulsant" is indicative of a therapeutic class, pharmacologically the class is diverse. Despite dissimilarities, an analysis by the FDA (2008) discerned a relative doubling of suicide behavior/ideation in anticonvulsant recipients compared to placebo, resulting in a change in labeling.

The HealthCore Integrated Research Database provides data with which to assess the relative risk for suicidal acts in persons receiving a variety of anticonvulsant agents. During a 5-year interval (2001-2006), almost 300,000 new prescriptions for various anticonvulsants were documented in this population. When compared to treatment with either topiramate or carbamazepine (reference drugs), important distinctions emerged in reference to suicidal acts and violence. For instance, the hazard ratio for suicidal acts was 1.42 for gabapentin, 1.84 for lamotrigine, and 1.65 for valproate, compared to topiramate.

The mechanism by which some anticonvulsants incur an increased suicide risk is not known, despite the recognition that anticonvulsants can have impact upon mood. The first 2 weeks after initiation is recognized to be a higher risk period. Clinicians should be vigilant for behavior or mood changes in patients treated with anticonvulsants, noting lesser apparent risk for topiramate or carbamazepine. ■

For type 2 diabetes, after metformin, what next?

Source: Phung OJ, et al. *JAMA* 2010;303:1410-1418.

In the absence of contraindications, metformin is the preferred initial treatment for most patients with type 2 diabetes (DM2). Unfortunately, monotherapy is unlikely to maintain adequate glycemic control, requiring additional treatment. Although the addition of insulin to metformin is an appropriate next step, and has been labeled Tier 1 in the most recent guidelines published by the American Diabetes Association, some patients are reluctant to use insulin, and the considerable weight gain experienced by some insulin users, as well as risk of hypoglycemia, is problematic.

Among the non-insulin therapeutic choices, there is a great degree of variation in tolerability issues, such as amount of weight gain and frequency/severity of hypoglycemia that may help guide treatment decisions. Phung et al analyzed data from 27 randomized controlled trials (n = 11,198), most of which were 6 months or less in duration, to compare weight changes and hypoglycemia when non-insulin agents were added to metformin.

As might be anticipated, when TZDs, sulfonylureas, and glinides were added to metformin there was a 1.8-2.1 kg weight gain. GLP-1 mimetics, alpha-glucosidase inhibitors, and DPP-4 inhibitors were either weight neutral or associated with minimal weight loss. Sulfonylureas were associated with higher rates of hypoglycemia.

Of course, progressive treatment of DM2 must be individualized, and should include consideration of characteristic tolerability issues such as weight gain and hypoglycemia. ■

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

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PPIs, *Clostridium difficile*, and Bone Fractures

In this issue: *New reports about proton pump inhibitors and the effects of gastric suppression, pioglitazone vs vitamin E for non-alcoholic steatohepatitis, metformin and vitamin B12 deficiency, and FDA Actions.*

PPIs, C. difficile, and bone fractures

Since H2 antagonists were introduced 30 years ago followed by proton pump inhibitors (PPIs) 20 years ago, there has been speculation whether long-term gastric acid suppression might have adverse effects. Billions of doses later, there is new evidence that chronic PPI use may lead to infections, especially *Clostridium difficile* infection (CDI), and may also contribute to bone fractures.

In the first of several studies published in the May 10 issue of *Archives of Internal Medicine*, researchers looked at more than 101,796 discharges from a tertiary care medical center during a five-year period, reviewing the level of acid suppression therapy and its relationship to CDI. As the level of acid suppression increased, the risk of CDI increased from 0.3% in patients not receiving acid suppressive therapy to 0.6% in those receiving H2 antagonists to 0.9% in those receiving daily PPIs and finally 1.4% in those receiving high-dose PPI therapy. After adjustment for a number of factors including comorbid conditions, age, and antibiotic use, the odds ratio for CDI infections were: 1 with no acid suppressing treatment, 1.53 (95% confidence interval [CI], 1.12-2.10) with H2 antagonist, 1.74 (95% CI, 1.39-2.13) with PPIs, and 2.36 (95% CI, 1.12-2.10) with high-dose PPI therapy. The authors conclude that increasing levels of pharmacologic acid suppression are associated with increased risk of nosocomial *C. difficile* infections, and the risk increases with more aggressive acid suppression (*Arch Intern Med* 2010;170: 784-790).

In a second study from the same journal, researchers from the VA system in Massachusetts performed a retrospective, cohort study of 1166 inpatients and outpatients with CDI to determine if PPI use affected recurrence rates. During treatment for CDI, 45% of patients received a PPI while 55% did not. Recurrent CDI was more common in those exposed to PPIs than in those not exposed (25.2% vs 18.2%). The hazard ratio for recurrent CDI in those exposed to PPIs was 1.42 (95% CI, 1.11-1.82). The risk was higher in patients older than 80 years and in patients exposed to antibiotics not targeted to CDI infections The authors conclude that PPI use during treatment for CDI was associated with a 42% increased risk of recurrence (*Arch Intern Med* 2010;170:772-778).

It has also been postulated that suppressing gastric acid may affect digestion and absorption of certain nutrients, specifically calcium. Although this has never been definitively proven, multiple studies have shown that chronic PPI use is associated with bone fractures. The most recent study, also published in the May 10 issue of *Archives of Internal Medicine*, was a prospective analysis of more than 160,000 women enrolled in the

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Women's Health Initiative study. In more than 1 million person-years of follow-up, there were 1500 hip fractures, 4881 forearm or wrist fractures, 2315 clinical spine fractures, and more than 21,000 total fractures. The multivariate-adjusted hazard ratios for current PPI use was 1 for hip fracture, 1.47 (95% CI, 1.18-1.82) for clinical spine fracture, 1.26 (95% CI, 1.05-1.51) for forearm or wrist fractures, and 1.25 (95% CI, 1.15-1.36) for total fractures. Bone mineral density did not vary between PPI users and non-users. The authors conclude that use of PPIs in women was not associated with hip fractures but was modestly associated with clinical spine, forearm or wrist, and total fractures (*Arch Intern Med* 2010;170:765-771). This study confirms the findings of several large epidemiological studies that suggest that PPI use is associated with increased osteoporotic fracture risk. On May 25, the FDA issued a warning regarding the possible fracture risk associated with high-dose long-term use of PPIs. The Agency will require labeling changes to describe the possible risk.

As noted in these studies, PPI use is associated with risk of osteoporotic fractures and *Clostridium difficile* infections. Other studies have linked the PPIs to a higher risk of hospital- and community-acquired pneumonia, as well as enteric infection such as *Salmonella* and *Campylobacter* gastroenteritis. In an editorial in the May 10 issue of *Archives of Internal Medicine*, Mitchell Katz, MD, notes that of the more than 110 million prescriptions for proton pump inhibitors filled each year, many are for inappropriate indications, making PPIs one of the most overprescribed medication classes in the world. He suggests that "for most patients the adverse effects of PPIs outweigh the benefits" and urges physicians to offer other treatments for dyspepsia, prescribe shorter courses, and consider a trial of discontinuing PPIs in patients who are asymptomatic (*Arch Intern Med* 2010;170:747-748). ■

Pioglitazone vs vitamin E for NASH

Non-alcoholic steatohepatitis (NASH) is a common liver disease that is difficult to treat and often progresses to cirrhosis. A new study compares the thiazolidinedione pioglitazone (30 mg daily) to vitamin E (800 IU daily) in a placebo-controlled trial for 96 weeks in 247 nondiabetic NASH patients. The primary outcomes were standardized scores for steatosis, lobar inflammation, hepatocellular ballooning, and fibrosis as determined by liver biopsy. Vitamin E therapy was associated with a significant improvement in non-alcoholic steatohepatitis (43% vs 19%; $P = 0.001$), but pioglitazone did not show statistical improvement (34% vs 19%; $P = 0.04$). Serum transaminases improved with both treatments, and both reduced hepatic steatosis and lobular inflammation, but neither improved fibrosis. Pioglitazone caused significant weight gain compared to vitamin E or placebo. The authors conclude that vitamin E was superior to placebo for the treatment of NASH in adults without diabetes (*N Engl J Med* 2010;362:1675-1685). ■

Metformin and vitamin B12 deficiency

Monitor your patients on metformin for vitamin B12 deficiency. This is the message of a recent study from the Netherlands. The study enrolled 390 patients with type 2 diabetes on insulin and initiated metformin 850 mg three times a day or placebo for an average of 4.3 years. Metformin treatment was associated with a mean decrease in vitamin B12 concentrations of 19% ($P < 0.001$) and an increase in homocysteine concentrations of 5% ($P = 0.091$). Longer-term treatment with metformin was associated with larger declines in vitamin B12 levels. The authors conclude that metformin likely causes malabsorption of vitamin B12 and recommends routine monitoring of vitamin B12 levels in patients who are treated with metformin (*BMJ* 2010;340:c2181). ■

FDA actions

The FDA has approved a new formulation of oxycodone (OxyContin®) that is designed to discourage chewing, crushing, or dissolving the drug. The FDA admits, however, that although the new formulation reduces the risk of snorting or injecting the drug, it can still be abused by simply ingesting larger doses than recommended. Vocal critics have called for oxycodone's withdrawal from the market due to an explosion in abuse of the drug nationwide and calls this new formulation "too little too late."

The FDA has recommended resuming use of Rotarix® rotavirus vaccine and to continue using RotaTeq® rotavirus vaccine. Rotarix was found to have elements of the porcine circovirus 1 (PCV1) in March, which resulted in an advisory to clinicians to stop using the vaccine. Subsequently, DNA from PCV1 and PCV2 was discovered in the RotaTeq vaccine. The FDA now says that there is no evidence that PCV causes illness or infection in humans while the benefits of the vaccine are substantial. ■

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This issue of your newsletter marks the start of a new continuing medical education (CME) semester and provides us with an opportunity to review the procedures.

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Upon completing this program, the participants will be able to:

1. discuss the most current information related to cardiac illness and the treatment of cardiac disease;
2. explain the advantages and disadvantages, as well as possible complications, of inter ventions to treat cardiac illness;
3. discuss the advantages, disadvantages and cost-effectiveness of new and traditional diag nostic tests in the treatment of cardiac illness; and
4. discuss current data regarding outpatient care of cardiac patients.

Each issue of your newsletter contains questions relating to the information provided in that issue. After reading the issue, answer the questions at the end of the issue to the best of your ability. You can then compare your answers with the correct answers provided in an answer key in the newsletter. If any of your answers were incorrect, please refer back to the source material to clarify any misunderstanding.

At the end of the semester, you will receive an evaluation form to complete and return in an envelope we will provide. Please make sure you sign the attestation verifying that you have completed the activity as designed. Once we have received your completed evaluation form, we will mail you a letter of credit. This activity is valid 36 months from the date of publication. This CME activity is intended for the cardiologist.

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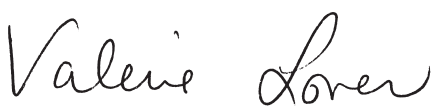

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