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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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Off-Pump vs On-Pump CABG

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Hannan EL, et al. Off-pump versus on-pump coronary artery bypass graft surgery: Differences in short-term outcomes and in long-term mortality and need for subsequent revascularization. *Circulation*. 2007;116:1145-1152.

THE EFFECTIVENESS OF OFF-PUMP CORONARY ARTERY BYPASS graft surgery (OPCAB) is controversial. Thus, Hannan and colleagues from New York evaluated the short-term and long-term results of OPCAB with sternotomy vs on-pump CABG in New York State between 2001-2004. The data were derived from the New York State's Cardiac Surgery Reporting System (CSRS) which encompassed all non-federal hospitals certified to do cardiac surgery. New York's vital statistics were used to ascertain deaths, and the CSRS was used to identify repeat CABG. The companion registry for percutaneous coronary procedures was used to assess whether any CABG patient had subsequent percutaneous revascularization. The study population included 49,830 patients; 13,889 had OPCABG. Selection bias was reduced by an analysis of 25,530 patients who were in matched pairs receiving OPCAB and CABG.

Results: OPCAB patients were older, more likely to be women, more likely to have reduced left ventricular performance, as well as significant co-morbidities. OPCAB had a lower 30-day mortality (OR 0.81, CI .68-.97) and less perioperative complications. However, in the matched pairs, 3-year mortality was not different (10%), and OPCAB patients were more likely to have subsequent revascularization (10% vs 6%, $P < .001$). Less than 2% of patients were converted from OPCAB to CABG. No subgroup showed a mortality difference, but patients with circumflex disease, a calcified aorta, and renal failure were more likely to have subsequent revascularization after OPCAB. Hannan et al concluded that OPCAB has a lower 30-day morbidity and mortality, but is associated with more subsequent revascularization vs standard CABG.

COMMENTARY

OPCAB, with sternal incision, was heralded as a way to avoid some of the complication of CABG such as "pump head", stroke from aortic cross clamp debris, depressed left ventricular function from fibrillation arrest and atrial fibrillation induced by damage from atrial cannulation. Indeed previous studies have shown lower early morbidity and mortality with OPCAB. However, concerns have arisen about the completeness of revascularization, long-term patency and need for subsequent revascularization. This large observational study has confirmed all the above. Short-term complications and mortality rates are less with OPCAB, but long-term mortality is no different, and freedom from subsequent revascularization procedures, is higher with standard CABG.

Since this is a large database study, there is a paucity of more mechanistic data. For example, we cannot ascertain whether the increased frequency of subsequent revascularization with OPCAB is due to incomplete revascularization or reduced graft patency over time. There may be selection biases in non-randomized trails. One issue here is the application of OPCAB. Overall, 28% of CABG in New York was OPCAB during the 3 years of this study, but the rates per surgeon varied considerably (rarely to >50%). The investigators tested selection bias by examining a matched subgroup, and found similar results to the entire database. Strengths of this observational study include its very large size, and it includes everyone, so higher risk patients, often excluded from randomized trials, are included.

One thing the study does not address directly is who should be considered for OPCAB. Since most of the morbidity reduction was in stroke and respiratory failure, elderly females with a higher stroke risk, and those with preexisting pulmonary disease, may be good candidates for OPCAB. Also, those with calcified ascending aortas may do better with OPCAB. Those with complex coronary lesions, severe multivessel disease, calcified coronary arteries, and diabetes may be better candidates for standard CABG. Finally, the study does not address the issue of minimally-invasive CABG, since all the patients had sternotomy. Clearly, mini CABG should reap the benefits of being off-pump, but does the limited visibility and maneuverability effect the long term results? ■

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ECG Diagnosis of Acute Myocardial Infarction

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Martin TN, et al. ST-segment deviation analysis of the admission 12-lead electrocardiogram as an aid to early diagnosis of acute myocardial infarction with a cardiac magnetic resonance imaging gold standard. *J Am Coll Cardiol.* 2007;50:1021-1028.

ALTHOUGH ECG IS THE STANDARD INITIAL SCREENing test for acute coronary syndromes, its value for the diagnosis of acute myocardial infarction (MI) is difficult to determine because of the vagaries of serum biomarkers. Contrast-enhanced magnetic resonance imaging (MRI) is a unique gold standard for the early detection of acute MI, and may be useful for determining the diagnostic accuracy of the ECG. Thus, this study from Glasgow, United Kingdom, is of interest. They enrolled 116 patients seen at one hospital with new-onset chest pain and interpretable ECGs. MI was confirmed in 58 by the presence of delayed hyperenhancement on MRI done a mean of 50 hours after onset of symptoms. The ECG diagnosis of acute ST segment elevation MI (STEMI) followed the usual criteria, but they also included a STEMI-equivalent category with ‡ 1 mm ST depression in ‡ 2 contiguous leads, or one lead that is anatomically contiguous to one lead with ST elevation. Current ECG STEMI cri-

teria detected 50% of acute MIs, with a specificity of 97%. Adding the STEMI-equivalent criteria increased sensitivity to 84% and minimally reduced specificity (93%). Including troponin resulted in 10 false positive MI diagnoses: 6 by troponin elevation alone; 2 by ECG criteria alone; and 2 by both. Two of the 4 falsely positive by ECG met new STEMI-equivalent criteria. Hannan et al concluded that considering ECG ST segment depression, as well as elevation, significantly increases the sensitivity for acute MI diagnosis without a major impact on specificity.

COMMENTARY

ECG remains the mainstay of the early triage of chest pain patients because of its wide spread availability, low cost, and ability to identify myocardial ischemia or infarction. Imaging may be more accurate, but is not widely available. Serum biomarkers are very sensitive, but may be normal early in the course of acute MI. However, this study showed that the detection of STEMI, where triage to reperfusion strategies is most critical, using standard ECG criteria, was only 50%. This increased to 84% without significant changes in specificity when ST segment depression in 2 anatomically-contiguous leads, or in one lead anatomically contiguous to a lead with ST elevation, was considered. For example, ST segment elevation in lead aVL and ST depression in lead III (negative ST in lead III reflects ST elevation in a non-existent lead near aVL). Two contiguous leads with ST depression (eg, V1 and V2) would reflect ST elevation in 2 non-existent leads opposite them on the posterior lateral wall. This makes sense from an ECG point of view, and proved reliable in this study. Acceptance of this modification of the ECG criteria for STEMI would increase the number of patients with chest pain triaged to reperfusion, with a specificity rate in the 90% range.

Of course there are some caveats. This study showed that about one quarter of patients presented challenges in ECG interpretation, and were excluded. The challenging conditions included evidence of prior MI, left ventricular hypertrophy, rapid atrial fibrillation, WPW, bundle branch block, right ventricular hypertrophy, and extensive artifacts. The prevalence of infarction was high in this study (50%), which resulted in positive predictive values in the 90% range. If a lower MI prevalence was considered — say 20%, the positive predictive value would fall into the 75-85% range, but this requires further investigation. Contrast-enhanced MRI cannot distinguish the age of an MI, but in this study, all the MRI-diagnosed MIs had elevations and declines in serum biomarkers consistent with acute MI. Also, MRI currently has a spacial resolution of about one cubic centimeter, so smaller MIs would not be detected. Perhaps some MRI-negative, biomarker-positive patients have such small MIs. Hannan et al referred to these as "necrosettes." Presumably, such small MIs would be low-risk events, and reperfusion may not greatly influence prognosis. They may even represent "supply/demand imbalance" events rather than thrombotic occlusions. In this study, all MRI positive patients had a troponin I > 4.4 ng/mL. The average troponin I in those with a negative MRI was 1.4 ng/mL.

ECG mavens have long recognized that ST depression in I, aVL, or V1-4 may represent left main coronary artery thrombosis, so the concept that significant ST depression may represent an acute thrombotic condition, best treated with reperfusion, is not new. This study shows that it could help detect more STEMI than current ECG criteria without unacceptable increases in false positives. It seems worth keeping in mind when triaging chest pain patients.

Reduction of Atrial Fibrillation by Pacing Mode

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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

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

Source: Sweeney MO, et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. *N Engl J Med*. 2007;357:1000-1008.

This paper reports the results of the search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACe) Trial. This study evaluated the use of pacing algorithms that were designed to minimize the percentage of ventricular pacing in patients with symptomatic sinus-node dysfunction. Eligible patients had symptomatic bradycardia due to sinus-node disease and a normal QRS interval. At the time of implant, they could AV conduct 1:1 during atrial pacing at a rate of at least 100 bpm. Patients with a history of 2 or more cardioversions for atrial fibrillation, or second or third degree AV block, were excluded. Patients randomized to the minimal ventricular pacing group had pacemaker programming that permitted automatic lengthening of, or elimination

of, the pacemaker's AV interval in order to withhold ventricular pacing. Patients in the conventional pacing group had an AV interval programmed between 120 and 180 m/sec. Several different pacemaker models were used, so the minimal ventricular pacing algorithm was not constant. The primary end point was time-to-persistent atrial fibrillation defined as one of the following: 2 consecutive visits in which atrial fibrillation was present, at least 22 hours of atrial fibrillation for at least 7 consecutive days recorded by the pacemaker diagnostic data log, or atrial fibrillation of shorter duration, which had been terminated by an electrical or pharmacologic intervention. Secondary end points included hospitalizations for heart failure and the percentage of atrial and ventricular paced beats over time.

A total of 1,065 patients were enrolled and underwent randomization after successful implantation of a dual chamber pacemaker. The mean age was 72 years, with approximately equal numbers of males and females. The mean ejection fraction was 58%, with 37% of the patients having a prior history of atrial fibrillation. The mean lower rate limit was 61 beats in both groups. The duration of follow-up was 1.7 ± 1 year.

During follow-up, the median percentage of ventricular paced beats was 9.1% in the minimal ventricular pacing group vs 99% in the conventional pacing group. The median percentage of atrial beats was similar in the 2 groups (71.4% vs 70.4%). Persistent atrial fibrillation developed in 68 of 535 patients in the conventional dual chamber pacing group (12.7%) compared to 42 of 530 in the minimal ventricular pacing group [(7.9%); $P = 0.004$]. Kaplan-Meier estimates of time-to-persistent atrial fibrillation showed absolute reductions in the rates of development of persistent atrial fibrillation of 3.8% at one year, 6.9% at 2 years and 7.0% at 3 years. By multivariate analysis, minimal ventricular pacing was shown to be an independent predictor of protection from persistent atrial fibrillation, with a hazard ratio of 0.6 ($P = 0.009$). Subgroup analysis showed a consistent pattern of benefit with minimal ventricular pacing. There was no significant difference in mortality between the 2 groups (4.9% minimal ventricular pacing vs 5.4% conventional pacing). Hospitalization for heart failure also did not differ between the groups, but more patients in the conventional pacing group underwent late catheter ablation of the AV node, or pulmonary vein isolation, for the management of atrial fibrillation.

Sweeney and colleagues conclude that pacing algorithms that minimize ventricular pacing in patients with sinus-node dysfunction are associated with a reduction in the risk of developing persistent atrial fibrillation.

COMMENTARY

Prior studies on the optimal mode of pacing in patients with sinus-node dysfunction have indicated that atrial-based pacing modes reduce the occurrence of atrial fibrillation during follow-up. Other studies have shown that unnecessary ventricular pacing can be associated with clinical worsening of heart failure, and that a higher proportion of paced ventricular beats is associated with both heart failure and atrial fibrillation. This study is the first large study to test prospectively the hypothesis that a pacing algorithm in patients with sinus-node dysfunction, which was specifically designed to reduce the proportion of ventricular pacing, will reduce the incidence of atrial fibrillation. The incidence of atrial fibrillation was indeed reduced, and favorable trends were noted in mortality, stroke rate, hospitalization, and the need for ablation procedures for atrial fibrillation management. Sweeney et al hypothesized that this is due to a decrease in ventricular dyssynchronization induced by right ventricular pacing, but it must be recognized that dyssynchronization and ventricular function were not specifically measured in this trial. However, the observations here strongly support the clinical practice of programming pacemakers in patients with sinus-node disease in such a way that unnecessary ventricular pacing is avoided, if that can be achieved without producing hemodynamic consequences due to changes in AV conduction.

New Drug for Atrial Arrhythmias

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, Phd

Source: Singh BN, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med.* 2007;357:987-999.

THIS PAPER GIVES THE RESULTS OF 2 TRIALS THAT evaluated the effects of dronedarone, a new antiarrhythmic agent, on the recurrence of atrial fibrillation or atrial flutter. The 2 studies reported were identical placebo-controlled, double-blind, parallel-group trials, with one conducted in Europe and the other in non-European countries. The data from the 2 studies were quite similar, and in this report, only the combined data will be discussed.

Patients qualified for the studies if they were at least 21-years-old and had had at least one episode of atrial

fibrillation within the preceding 3 months. Patients could be cardioverted after screening, but had to be in sinus rhythm for at least one hour before randomization. Use of class I or class III antiarrhythmic agents was not permitted. Other criteria for exclusion included class III or class IV heart failure, significant sinus bradycardia, or a PR interval of greater than 0.28 seconds. Patients with a serum creatinine level of ‡to 1.7 mg/dL were also excluded. Most patients had previously received treatment with one or more antiarrhythmic drugs, including amiodarone in 30%. Patients were randomly assigned in a 2:1 ratio to receive either 400 mg of oral dronedarone twice daily or matching placebo. Patients were followed with periodic transtelephonic electrocardiograms both on a regular schedule and whenever they had symptoms. They were also seen frequently for electrocardiograms and blood tests. The primary end point of the trial was time from randomization to the first documented recurrence of atrial fibrillation. For the purpose of the study, a recurrence was defined as an episode lasting for at least 10 minutes, confirmed by electrocardiography or transtelephonic monitoring.

The combined trials enrolled 820 patients who received dronedarone and 409 in the placebo group. The mean age was 63 years, and 69% were male. A history of hypertension was present in 50% of the placebo patients and in 60% of the dronedarone patients. Other structural heart disease was present in approximately 40% of the patients in both groups. The mean left ventricular ejection fraction was 58% in groups. Only a small percentage of patients had a history of congestive heart failure. Most patients had failed one or more antiarrhythmic drugs.

For the 2 trials combined, the median times to a documented recurrence of atrial fibrillation were 116 days in the dronedarone group and 53 days in the placebo group. The cumulative recurrence rate at 12 months was 64.1% in the dronedarone group and 75.2% in the placebo group (hazard ratio 0.75; *P* less than 0.001). If recurrences in the first 5 days of treatment were excluded, the hazard ratio decreased slightly to 0.72 (*P* less than 0.001). As anticipated from its pharmacologic profile, dronedarone decreased heart rate by 6.8%, prolonged the QT interval by 23.4 m/sec, and prolonged the QTc interval by 9.0 m/sec. There was no change in QRS duration. Among patients with documented recurrences, dronedarone slowed the ventricular rate from 117 ± 30 bpm in the placebo group to 103 ± 26 bpm. Hospitalization or death was seen in 30.9% of the placebo group vs 22.8% of the dronedarone group, with a hazard ratio 0.73 (*P* = 0.01). Dronedarone was well tolerated. There were no significant increase in the incidence of any of the following adverse reactions: cough, dyspnea, bradycardia, heart failure or shock, neurologic or gastrointestinal disorders, or hepatic enzyme elevations. More patients in the placebo group than the dronedarone group developed hyperthyroidism. There was no significant difference in the incidence of hypothyroidism. Serum creatinine became elevated in 2.4% of dronedarone group vs 0.2% in the placebo group (*P* = 0.004).

Singh and colleagues conclude that dronedarone is an effective antiarrhythmic drug that reduces the recurrence of atrial fibrillation with a favorable side-effect profile.

COMMENTARY

Dronedarone is an antiarrhythmic drug that is structurally similar to amiodarone and has a similar electrophysiologic profile due to effects on multiple cardiac ion channels. However, the dronedarone molecule does not contain iodine, a factor which has been linked to the thyroid and pulmonary adverse reactions observed during amiodarone therapy. In this trial, dronedarone had a modest favorable effect on the recurrence of atrial fibrillation. However, most patients in the trial had previously failed one or more antiarrhythmic drugs, and the 25% to 30% reduction in atrial fibrillation recurrence is, therefore, likely to be clinically important. It is also significant that dronedarone was quite well-tolerated. The adverse events profiles between the placebo and dronedarone groups did not differ. The trial, however, did not include patients with advanced (class III or class IV) heart failure. Patients with advanced heart failure had been previously evaluated in an earlier trial (ANDROMEDA) during which there had been a suggestion of increased mortality. Subsequent reexamination of that trial's results suggested that heart failure management had been influenced by the effect of dronedarone to raise serum creatinine, and this perhaps explained the increase in mortality in the dronedarone group. However, the effects of dronedarone on serum creatinine are not due to changes in glomerular infiltration rate, but rather to tubular secretion of creatinine, and alterations in the dosage of angiotensin converting enzyme inhibitors was probably not appropriate. Additional studies with dronedarone in older and higher-risk patient groups are now underway. If they support the safety of the drug in these later groups, dronedarone should prove an important addition to our antiarrhythmic armamentarium. ■

Revascularization for Stable Coronary Artery Disease

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis.

Sources: Lin GA, et al. Cardiologist's use of percutaneous coronary interventions for stable coronary artery disease. *Arch Intern Med*. 2007;167:1604-1609; Moscucci M. Behavioral factors, bias, and practice guidelines in the decision to use percutaneous coronary interventions for stable coronary artery disease. *Arch Intern Med*. 2007;167:1573-1575; Boden WE, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-1516.

Exceptional attention has been paid to the recent publication of the COURAGE Trial (April 2007) regarding the efficacy of percutaneous coronary intervention (PCI) in stable coronary disease patients, whereas in acute coronary syndromes, including STEMI and unstable angina, there is reasonable consensus as to an interventional approach in patients with either PCI or CABG as opposed to medical therapy. A highly visible dialogue is now taking place regarding the appropriate approach in stable CAD. This unusual study from University of California-San Francisco reports on a series of focus groups comprised of interventional and non-interventional cardiologists in California in an effort to assess their views of PCI in stable CAD patients vs high-quality medical therapy without revascularization.

The results of COURAGE confirm that PCI for stable coronary disease does not offer a mortality or MI benefit vs aggressive medical therapy. Previous studies and metaanalyses have also shown that PCI does not improve survival or non-fatal MI reduction with a PCI strategy in stable angina patients when compared with medical therapy. The data do support earlier and greater relief of angina for PCI compared to medical therapy, but after one or more years, chest pain symptoms tend to be comparable between the strategies of PCI or medical therapy. In the United States, there is considerable geographic variation in the use of angioplasty, which suggests multiple factors other than coronary anatomy influence whether an invasive approach is utilized. In order to explore reasons for the variation in decision making, physicians from UCSF designed a qualitative study using 3 focus groups comprised of 4 to 9 cardiologists and asked the participants to discuss the issues regarding their decisions whether or not to utilize PCI in stable angina patients.

Overall, the physicians acknowledged that PCI has not been shown to reduce the hard end points of death or acute MI in chronic stable CAD patients. The "oculostenotic" reflex was cited by the physicians, who more often than not voted for PCI, even in asymptomatic patients. The 3 focus groups were similarly structured, with a moderator and 3 hypothetical case scenarios. The fictional patients all had stable CAD with either no symptoms or atypical complaints, and were felt by the study authors to represent individuals who clearly have not been shown to derive benefit from PCI. The focus groups lasted for 90 minutes and were comprised of invasive and noninvasive cardiologists, cardiology fellows, and individuals from both rural and urban environments. A systematic and detailed approach to discussion was used. New methods of triangulation were utilized to reduce bias. A summary of the major systematic discussions of each focus group was provided; the participants agreed with the summary record. Themes discussed were related to physician's medical-legal concerns, technical advances that relate to PCI. The majority believed that PCI "would benefit the patients described in our case scenarios by preventing cardiac events, even in asymptomatic patients." The participants did acknowledge that PCI was less likely than medical therapy to provide benefit in terms of preventing MI or death; however, they stressed the benefit of patients leaving the hospital with an open artery. It was also believed to be important to perform PCI for equivocal stress testing results or lesion-ischemic mismatch on stress test. Concern about not intervening on an obstructive lesion was common; the likelihood of a subsequent event was felt to be unacceptable. In general cardiologists believed that even in low-risk patients, complications due to catheterization would be more meaningful than the "potential consequences of not performing PCI". Decreased anxiety following a procedure in asymptomatic patients was commonly cited, especially in individuals who were self referred. Patients who reached the cath lab generally underwent PCI, regardless of why the patient was sent for the angiogram. Thus ". . .by the time one is this far along, the die is cast. The cath lab staff probably wouldn't leave the lab unless we did something with the lesion. . ." Medical-legal concerns were also an important motivation; not performing an intervention was believed by some to be a setup for a potential law suit after an event occurred.

Cardiologists agreed that available technological advances, such as electron beam CT and CT angiography, are and will be increasing the number of asymptomatic patients who are referred for studies. They believe that these patients should be treated aggressively, although no evidence is available that such an approach would prevent death or myocardial infarction. The availability of drug-eluting stents seems to have been important in supporting catheterization decisions. The authors comment, ". . .the current practice of cardiologists in our sample is to recommend PCI for almost all significant lesions seen at cardiac catheterization." The cardiologists believed that they were benefiting even asymptomatic patients by performing PCI." Emotional and psychological factors were important determinants of physician judgment, suggesting an overly positive belief in PCI efficacy. The authors discuss a variety of reasons why cardiologists favor an invasive approach more than being guideline driven. Physician and patient anxiety about abnormal test results, as well as the ease in doing PCI following a diagnostic catheterization "has made PCI almost inevitable in anything with a significant lesion."

The experience of the cardiologists was comparable whether they came from rural, suburban, or urban areas. The conclusion of the authors is that "cardiologists may believe they are benefiting their stable patients. . .but this belief (for PCI) appears to be based on emotional or psychological factors rather than on evidenced clinical benefits." Physicians need to find a "greater balance between emotion and beliefs and clinical evidence to provide the best treatment for patients."

In an accompanying editorial, Dr. Moscucci from the division of cardiology at the University of Michigan, discusses deviation from treatment guidelines and the potential impact of increased CT coronary angiogram availability, which will provide even more asymptomatic patients for a decision of PCI or not. Moscucci calls for the development of appropriate criteria and improved physician and patient communication.

COMMENTARY

It is likely that this subject will engender considerable comment, and hopefully, alterations in the way physicians deal with decision making. The increasing dialogue among health professionals, industry, and patients regarding invasive vs noninvasive procedures for patients with CAD hopefully will be helpful and informative for the thousands of individuals with whom decisions for or against PCI hold great importance.

The results of the University of California focus groups in dealing with PCI are of considerable interest. While the database is quite small, the authors found that there was substantial agreement among the physicians regarding various factors pro and con for the role of PCI in stable CAD. A much larger and more specific study is needed; it is likely that providers and those working in health policy will be looking carefully into this matter with great interest. One needs to expand the hypothetical case scenarios made available to the participants; the cases appear to be somewhat simplistic, and perhaps, overly amenable to a quick decision of go vs no go. The more dialogue about this matter, the better it is for our patients, physicians, and healthcare providers. It is widely acknowledged that PCI rates are extremely disparate around the United States, with 2- to 3-fold differences in utilization of angioplasty among cities. Canadian use of angioplasty and PCI is lower than in the United States on a per capita basis, yet overall survival rates do not appear to be different.

One important area that is not discussed in these 2 articles is the current emphasis on noninvasive or conservative therapy. Thus, the COURAGE trial has recently caused somewhat of a furor because of the finding that individuals who had active ischemia on stress testing, and angina with stable symptoms, had comparable morbidity and mortality at 5 years to those randomized to PCI. The impact of this study indicates that aggressive medical therapy and lifestyle changes without PCI resulted in equal outcomes of MI or cardiac death in individuals randomized to no angiogram vs those randomized to PCI. Of note, in COURAGE, the large diabetic cohort showed no difference in cardiac death or myocardial infarction when compared to the non-diabetics, thus emphasizing the outstanding outcomes achievable with aggressive medical therapy. Other trials are also persuasive in that optimal medical therapy in stable patients may be appropriate, at least until symptoms arise or worsen, without jeopardizing the patient. Street talk suggests a current 10-20% decrease in recent cardiac catheterization since COURAGE was reported. The drug-eluting stent controversy regarding late thrombosis may have also had a dampening effect on performing PCI. It appears that an algorithm is taking shape that provides a better fit for the patient and cardiologist with respect to how to deal with significant CAD in stable individuals. ■

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PS Form **3526**, September 1999 *(Reverse)*

CME Questions

65. Which is most correct concerning off-pump CABG vs standard CABG?
a. Thirty-day morbidity and mortality are reduced.
b. Long-term morbidity and mortality are reduced.
c. Thirty-day re-revascularization is reduced.
d. Long-term re-revascularization is reduced.

66. The sensitivity of the ECG diagnosis of acute STEMI can be enhanced by:
a. increasing the number of leads with ST elevation necessary.
b. increasing the height requirement for ST elevation.
c. requiring ST depression in reciprocal leads to ST elevation.
d. adding selected ST depression criteria.

69. Setting a pacemaker to favor atrial pacing in sinus-node dysfunction patients:
a. decreases subsequent heart failure.
b. reduces mortality.
c. reduces subsequent atrial fibrillation.
d. reduces ventricular tachycardia.

68. Which is most correct concerning dronedarone?
a. It is less expensive than amiodarone.
b. It has a low incidence of side effects.
c. It is more efficacious than amiodarone.
d. All of the above

67. Reasons given for preferring PCI to medical therapy for chronic stable angina, despite no evidence of its superiority, include:
a. oculostenotic reflex.
b. medical-legal concerns.
c. benefits of an open artery.
d. All of the above

Answers: 65. (a); 66. (d); 67. (c); 68. (b); 69. (d)

CME Objectives

The objectives of *Clinical Cardiology Alert* are to:

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

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

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

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

PHARMACOLOGY WATCH

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

Are Thiazolidinediones (TZDs) Safe?

In this issue: *Are thiazolidinediones safe? New study shows Zometa reduces risk of hip fractures and improves survival; Merck HIV vaccine proven ineffective in clinical trials; no causal association found between exposure to mercury from thimerosal; and FDA approvals.*

There's no hotter topic in medicine right now than the safety of the thiazolidinediones (TZDs) rosiglitazone (Avandia) and pioglitazone (Actos). Several meta-analysis have pooled data from multiple clinical trials and come to different conclusions regarding the safety of the drugs. The September 12 issue of *JAMA* contained two papers, both meta-analysis, the of first which suggests that pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. An increase in heart failure was noted, although no increase in mortality (*JAMA* 2007; 298:1180-1188).

The second paper looked at rosiglitazone and noted that in patients with impaired glucose tolerance or type 2 diabetes, use of rosiglitazone for at least 12 months was associated with a significantly increased risk of myocardial infarction and heart failure, again without a significant increase risk of cardiovascular mortality (*JAMA* 2007; 298:1189-1195). This followed on conflicting meta-analysis regarding the risk of rosiglitazone published in the *New England Journal of Medicine* in June and July, the first of which suggested the rosiglitazone was associated with an increase risk of myocardial infarction and increased risk of death from cardiovascular causes (*NEJM* 2007; 356:2457-2471), while the second showed an increased risk of heart failure but no increased risk of myocardial infarction or death from cardiovascular causes (*NEJM* 2007;357:28-38). The studies led to congressional hearings, multiple editorials in medical journals and eventually led the FDA to recommend black box warnings regarding the risk of heart failure for both drugs in July. But despite cries from consumer groups suggesting that this was the Cox-2 debacle redux, the FDA stopped short of taking rosiglitazone off the market. The most recent entry into the fray is a new meta-analysis from the Lahey Clinic in Boston. This review analyzed over 3000 studies of which 7 were used for the analysis—all randomized double-blind clinical trials of drug-related congestive heart failure in prediabetic or diabetic patients given either rosiglitazone or pioglitazone. In over 20,000 patients, 360 had congestive heart failure, 214 on TZDs and 146 on comparators. As with other studies there was an increase risk of heart failure associated with both drugs (relative risk 1.72, 95% CI 1.21-2.24, P= 0.002), but again no increase in cardiovascular death was noted with either drug (RR 0.93). The authors suggest that TZDs cause worsening heart failure, but are not associated with progressive systolic or diastolic dysfunction of the left ventricle that leads to death. They also suggest that more studies are needed (*Lancet* 2007;370:1129-1136). The take home message from all the studies is to use caution in TZDs in patients with diabetes and heart failure (NYHA I and II), and to carefully monitor patients for worsening signs and symptoms including weight gain and edema. Initiation of these drugs in patients with established NYHA Class III or IV heart failure is contraindicated.

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Zometa and hip fractures

A single 5 mg infusion of zoledronic acid (Zometa) within 90 days of a hip fracture reduced the risk of new fractures and improved survival according to new study. Zoledronic acid is a long acting bisphosphonate that is approved for once yearly treatment of postmenopausal osteoporosis. The drug is effective at reducing vertebral, hip, and non-vertebral fractures in women with osteoporosis. In this current study, 1065 men and women with hip fractures were assigned to receive yearly intravenous zoledronic acid 5 mg IV or placebo, the infusions were administered within 90 days of surgical repair of a hip fracture. All patients received vitamin D and calcium. Mean age was 74.5 years, with approximately 75% women. The rate of new clinical fracture was 8.6% in the zoledronic acid group and 13.9% in the placebo group (35% risk reduction, $P = 0.001$). The respective rates of new clinical vertebral fractures were 1.7% vs 3.8% ($P = 0.02$) and for non-vertebral fractures 7.6% vs 10.7% ($P = 0.03$). The death rate was 28% less in the zoledronic acid group (101 of 1054 [9.6%] vs 141 of 1057 [13.3%], $P= 0.01$). No cases of osteonecrosis of the jaw were reported and no adverse effects of healing fractures were noted. The authors conclude that an annual infusion of zoledronic acid within 90 days of a low trauma hip fracture was associated with reduced rate of new fractures and improved survival (published early at www.NEJM.org September 17, 2007).

Merck HIV Vaccine Ineffective in Clinical Trial

After years of development and clinical trials Merck has announced that their HIV vaccine is ineffective in a large clinical trial, and the company has halted further test vaccinations. Other HIV vaccines have also failed but many had hoped that the Merck vaccine, which worked by stimulating T cells, might be more effective. The trial, which was begun in 2004 vaccinated 3000 uninfected volunteers in the US and Latin America. Among 741 patients who received a least one dose of the vaccine, 24 new HIV infections were identified, compared to 21 infections in 762 patients who received placebo. Work continues on other HIV vaccines, currently 30 worldwide are in clinical trials, but the failure of the Merck vaccine is seen is a major setback for HIV researchers.

Thimerosal and Mercury Exposure

Thimerosal has been the subject of intense scrutiny for years regarding its potential link to various neuropsychological deficits in children. Thimerosal has been used as a preservative in vaccines and gamma globulin for decades, although it is rarely used now because it is metabolized to mercury and thiosalicylate, potentially leading to high mercury levels in children. In a new study from the CDC and several large HMOs, 1047 children between ages of seven and 10 years were enrolled and tested for 42 neuropsychological outcomes, then the medical records were examined for history of exposure to mercury from thimerosal. Prenatal mercury exposure from thimerosal was associated with better performance on one measure of language and poor performance on one measure of attention and executive functioning. Exposure in infancy up to seven months old was associated with better performance in one measure, fine motor coordination, and on one measure of attention and executive functioning. Increasing mercury exposure from birth to 28 days was associated with poorer performance on one measure of speech articulation and better performance on one measure of fine motor coordination. The authors conclude that they could not find a causal association between early exposure to mercury from thimerosal and deficits in neuropsychological functioning at age 7 to 10 years (*NEJM* 2007; 357: 1281-1292).

FDA Actions

Eli Lilly has received approval from the FDA to market raloxifene (Evista) for the indication of reducing the risk of breast cancer in postmenopausal women with osteoporosis and postmenopausal women who are at high risk for invasive breast cancer. Raloxifene is a selective estrogen receptor modulator (SERM) that is already approved for prevention and treatment of osteoporosis in postmenopausal women. The drug was recently required to add labeling regarding an increased risk of fatal strokes in women taking the drug. It also carries a black box warning regarding risk of thromboembolism in women who are at high risk (those with an active or past history or thromboembolism).

Just in time for the winter flu season, the FDA has approved nasal influenza vaccine (FluMist) for use in children between the ages of 2 and 5. Previously the vaccine was only approved for children 5 years old and older and adults up to age 49. The CDC is recommending all children between the ages of 6 months to 59 months receive a flu vaccine. Children ages 2-8 who have never received a flu vaccine will initially require two doses of fluMist at least one month apart.

The FDA has approved a new oral granules form of terbinafine for the treatment of tinea capitis (ringworm) in children. The preparation may be sprinkled on food, allowing easier administration to children who may not otherwise take medicine over the two weeks required to treat tinea. Terbinafine granules are indicated for the treatment of tinea capitis in children age 4 years and older. It is marketed by Novartis AG as Lamisil Oral Granules. ■