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Eptifibatide and Abciximab Equally Effective in Primary PCI

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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

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

Sources: Zeymer U, et al. Randomized comparison of eptifibatide versus abciximab in primary percutaneous coronary intervention in patients with acute ST-segment elevation mycardial infarction. Results of the EVA-AMI Trial. *J Am Coll Cardiol* 2010;56:463-469;Akerblom A, et al. Eptifibatide is noninferior to abciximab in primary percutaneous coronary intervention. results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *J Am Coll Cardiol* 2010;56:470-475

Platelet aggregation is an important pathophysiological step in the development of myocardial infarction (MI), and intensive anti-platelet therapy has become a cornerstone of therapy in patients presenting with MI. In ST-segment elevation MI (STEMI), primary percutaneous coronary intervention (pPCI) has been shown to reduce mortality, but the optimal anti-platelet strategy during pPCI continues to evolve. Adjunctive glycoprotein IIb/IIIa inhibitors improve reperfusion rates and reduce subsequent events. The 2009 ACC/AHA guidelines for management of patients with STEMI list the use of adjunctive IIb/IIIa inhibitors at the time of pPCI as a class IIa indication: abciximab with a level of evidence A, and eptifibatide with a level of evidence B. However, there had previously been no head-to-head trials comparing these agents, particularly in the current era. Two recent studies have compared eptifibatide to abciximab in primary PCI, and both found them to be substantially equivalent.

Zeymer and colleagues randomized 427 patients with STEMI to receive either eptifibatide or abciximab in addition to pPCI and standard medical therapy, including aspirin, clopidogrel, and either heparin or enoxaparin. Baseline characteristics were similar in each group, with a mean age 61 years, ~20% female, and 43% of cases involved the left anterior descending coronary artery. Pro-

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cedural characteristics also were similar between groups; 95% of patients in each group underwent PCI with similar rates of direct stenting, use of drug-eluting stents, and use of adjunctive therapies, such as aspiration thrombectomy. The primary endpoint (complete ST-segment resolution) was achieved in 63% of the eptifibatide group and 56% of the abciximab group (p = NS), indicating similar rates of reperfusion. Rates of death (6.2% vs. 4.5%; p = 0.52) and target vessel revascularization (4.4% vs. 6.5%; p = 0.39) were not different between the eptifibatide and abciximab groups, respectively. However, eptifibatide resulted in lower rates of recurrent MI (0.4% vs. 3.5%; p = 0.03) at six months. Bleeding rates were similar between groups. The authors conclude that eptifibatide, as an adjunct to pPCI, is equally as effective as abciximab with respect to ST-segment resolution.

Akerblom and colleagues report from a large European registry on 11,479 patients undergoing pPCI for STEMI who received either eptifibatide (n = 2,355) or abciximab (n = 9,124). Median age was 65 years, and approximately 28% of the cohorts were female. There appeared to be differences in the baseline demographic and procedural characteristics, so the authors performed multivariable adjustments to account for these differences. After multivariable adjustment, the rates of death and myocardial infarction were no different between groups at one-year follow-up. Comparing eptifibatide to abciximab, the odds ratio [OR] for death was 0.99 (CI 0.79–1.09) and for MI the OR was 0.88 (CI 0.73–1.05), showing no difference in these outcomes. In addition, the combined endpoint of death or MI also was no different, with an OR of 0.94 (CI 0.82–1.09). The authors conclude that eptifibatide is non-inferior to abciximab in patients with STEMI undergoing pPCI with respect to death or MI over one year.

■ COMMENTARY

Perhaps the best clinical trial evidence we can get is the agreement between a randomized, controlled trial and a large real-world registry. Zeymer and colleagues' randomized, controlled trial showed non-inferiority of eptifibatide compared to abciximab. However, their trial enrolled relatively low-risk patients, with only 10% of patients having a Killip class > 1. In addition, they used a 22-hour infusion of eptifibatide, whereas we generally use 18 hours in the United States. Furthermore, clopidogrel was given more than 30 minutes prior to angiography in 52% of patients, less than 30 minutes prior in 7%, after PCI in 20%, and unknown time in 21%, but we are not told whether there were timing differences between treatment groups or whether timing influenced ST-segment resolution. It remains unknown if the benefit of IIb/IIIa inhibitors is seen in patients receiving early loading of thienopyridines. In the registry reported by Akerblom et al, the large number of patients allowed multivariable adjustment. In an all-comers registry, they demonstrated noninferiority in the hard endpoints of death and MI at one year. This is complimentary data to the reperfusion results seen in the randomized, controlled trial by Zeymer et al. However, the registry also provides no data on the timing and loading doses of thienopyridines. These studies suggest that eptifibatide and abciximab should result in similar rates of reperfusion, death, and recurrent MI in patients presenting with STEMI treated with primary PCI. ■

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Viability Studies Before Selecting Revascularization?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Sawada SG, et al. Effect of revascularization on long-term survival in patients with ischemic left ventricular dysfunction and a wide range of viability. *Am J Cardiol*. 2010;106:187-192.

Although ischemic left ventricular (LV) dysfunction is an indication for revascularization, little is known about the long-term benefits of revascularization and the value of viability studies. Thus, these investigators from Indiana University performed a retrospective, observational study of their database of 14 years of dobutamine stress echocardiography (DSE) for viability. In 274 patients

with reduced left ventricular ejection fraction (LVEF), those who had revascularization therapy were compared to those who had medical therapy. Viable myocardium by DSE was present in 32% of the 274 patients. Other baseline characteristics of the two groups were similar, except that revascularized patients had more non-viable myocardium. Revascularization was performed in 47% (93% had bypass surgery). Over the mean 4.5-year follow-up, 35% of the revascularized patients died vs. 48% of the medically treated patients. After adjustment for propensity score showed that revascularized patients had a better survival (5.9 years) vs. medically treated patients (3.3 years, HR 0.42, 95% CI 0.27-0.65, p <.0001). This difference was apparent early in the first year and increased with time. Cardiac mortality showed the same results. The authors concluded that revascularization increases long-term survival in patients with ischemic cardiomyopathy and variable viability.

■ **COMMENTARY**

This study supports my practice of revascularizing patients with reduced LV function and good target vessels for revascularization. This study is not randomized, but rather they used propensity matching to compensate for this weakness. Whether this approach is reliable is debatable, but only three of 27 important clinical features of the patients were not equivalent at baseline: percent with hyperlipidemia, multivessel CAD, and viable myocardium. All three were higher in the revascularized patients. However, some key features that you expect to be different between the groups were not. The presence of nonviable myocardium was seen in 27% of the medical therapy patients and 22% of the revascularization patients (p = NS). Viability in > 25% of the LV myocardium in 29% vs. 35% (p = NS) and myocardial ischemia in 75% vs. 80% (p = NS). Both groups had a mean ejection fraction of 32%. Also, the follow-up results were adjusted for the use of beta blockers, which could affect mortality.

The results showed improved total mortality over five years of follow-up in the revascularization group and a 55% reduction in cardiac mortality after adjustment for beta-blocker use (higher usage in the revascularization group). These results are similar to previous studies that used the results of viability studies to segregate the treatment of the patients. One caveat to this study is that it is almost exclusively a coronary bypass surgery study (93%). Whether similar results would be obtained with percutaneous (PCI) interventions needs further study, but it is hard to imagine that mortality would not be lower with PCI, despite an expected need for repeat PCI in some. Thus, I believe the practice of referring patients with good target vessels and a moderately low EF to revascularization is reasonable. However, the role of viability studies is unclear. In this study not everyone had a viability study and in those that did the results between the two groups was either not different or was adjusted by the propensity score. Consequently any effect of viability testing was removed or diminished in value. Prior viability based studies using improved myocardial segmental contractility as the gold standard, have shown about an 80% sensitivity, which means that 20% of patients who have viable myocardium would be falsely labeled as non-viable. Unfortunately a similar analysis was not done in this study. A large randomized trial of viability directed medical vs. surgical therapy in heart failure patients (HEART) is underway. Hopefully, we will have results soon. Until further data is available, I use viability studies to aid the decision to revascularize, but do not rely on them exclusively because of their limited accuracy. ■

Stent Thrombosis Post Non-cardiac Surgery

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Chia KKM, et al. Frequency of late drug-eluting stent thrombosis with non-cardiac surgery. *Am J Cardiol*. 2010;106: 1-3.

There is considerable concern regarding in-stent thrombosis of drug-eluting stents (DES) when aspirin and clopidogrel are stopped for non-cardiac surgery (NCS), but a paucity of data. Thus, this group from Australia surveyed more than five million patients in two large private insurance company databases and sent questionnaires to all who had DES followed by surgery. Questionnaires were returned by 1,086 of the 4,126 patients who received them. Cardiac surgery excluded 376, leaving 710 who were suitable for analysis. None of the non-responders died within 30 days of NCS. Mean time from DES to NCS was 348 days. NCS occurred within 30 days in 3%, six months in 27%, and 12 months in 56%. Before surgery, 66% were on dual antiplatelet therapy, 21% aspirin alone, 9% on clopidogrel alone, and 4% were on no antiplatelet therapy. Surgery was performed on dual therapy in 18%, on single therapy in 23%, and no antiplatelet therapy in 59%. The average time of medication cessation prior to surgery was about one week.

Results: Perioperative myocardial infarction (MI) (confirmed by medical records) occurred in 11 (1.5%), and angiography showed that only two patients had stent thromboses while seven had new culprit lesions. Two patients did not have angiography, but one probably had in-stent thrombosis clinically, for a total of

three. None of these three patients were on antiplatelet therapy, and only one of the other eight patients was on therapy with aspirin alone. Among the 11 MIs, one occurred < 30 days post-DES, none from one to six months, six from six to 12 months, and four >12 months. The authors concluded that NCS after DES has a low morbidity despite a majority being off antiplatelet therapy and more post-operative MIs occurred because of new culprit lesions in non-stented vessels, rather than stent thrombosis.

■ **COMMENTARY**

A remarkable fact of this study is the high rate of NCS after DES (44%). This may be because their database started shortly after DES was introduced in Australia in 2002, before stent thrombosis with DES was appreciated. If NCS is likely, a bare-metal stent is placed, or only balloon angioplasty is performed. Also, 41% of patients had NCS on one or more antiplatelet agents despite the known higher risk of bleeding. Perhaps the most interesting results of this study are the low rate of post-NCS MI (1.5%)and only 3 of 11 patients had stent thrombosis (0.4%). Thus, the risk of DES thrombosis is quite low with NCS. Since some patients in this study were still on antiplatelet therapy, the rate may have been approximately twice as high if all had been off therapy, but still probably < 1%. Only about one-quarter of the patients surveyed returned the questionnaire, but since those with problems may have been more likely to return it, this result may be an overestimation of post-NCS MI.

One strength of this study is that angiographic confirmation was obtained in all but one of the MI patients. This patient had terminal cancer and a small troponin leak, so it was decided to treat the patient conservatively. The angiographic results point to the value of doing angiography, since a high proportion of the MI patients had new culprit lesions. The key question is whether we should change our practice based upon this study and allow antiplatelet therapy to be withheld for NCS in post-DES patients within 12 months? If stent thrombosis with NCS on no therapy is really < 1%, it is going to be hard to argue that antiplatelet therapy is necessary in all cases. In a well-deployed proximal vessel stent, it may be safe to be off therapy for a short time but, a left-main stent, hanging into the aorta, may be too risky. Perhaps a case-by-case approach is reasonable. ■

Chest Compression-only CPR

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: Rea TD, et al. CPR with chest compression alone or with rescue breathing. *N Engl J Med*. 2010;363:423-433.

The dispatcher-assisted resuscitation trial (DART) tested the hypothesis that 911 dispatcher instructions to provide chest compressions only would be superior to similar instructions that included both chest compressions and rescue breathing. Calls to a 911 system for patients in cardiac arrest were eligible for inclusion in the trial if the dispatcher felt the patient was in cardiac arrest and bystander CPR had not yet been attempted. Emergency Medical Systems (EMS) in three localities, King County, Washington, Thurston County, Washington, and London, the United Kingdom, participated in the trial. Dispatchers attempted to exclude patients with arrest due to trauma, drowning, asphyxiation, or pediatric patients. Eligible patients were assigned to one of two CPR strategies in random sequence. Rescuers were instructed to either continuous chest compressions only or chest compressions plus rescue breathing in a sequence of two rescue breaths followed by 15 chest compressions. After an initial first cycle, the bystander was instructed to check for signs of life and, if none were present, he or she was to continue CPR using the same method. The primary outcome was survival to hospital discharge. Secondary outcomes were return of spontaneous circulation and neurologic status at the time of hospital discharge.

Over a four-year period, 5,525 cardiac-arrest victims were screened for eligibility. A total of 1,941 patients were randomized and found to be eligible. The mean age was 64 years, and 65% of the subjects were male. More than 70% of the cardiac arrests were thought to be cardiac in origin, and 44% were witnessed. Almost 90% of the arrests occurred in a residential location, with 9% occurring in a public location and 4% occurring in a nursing home. The mean time to initial EMS arrival was 6.6 minutes, and a shockable rhythm was identified in only 32% of the patients; the two groups were evenly matched for these characteristics. The dispatcher's instructions were followed by the rescuers in 80.5% of the subjects randomized to chest compression alone, compared to 72.7% of the patients randomized to chest compression plus rescue breathing.

There was no significant difference in the proportion of patients surviving to hospital discharge, according to randomization. Chest-compression instruction alone resulted in a 12.5% survival to hospital discharge, compared to a survival to hospital discharge of 11% for patients in the chest-compression plus rescue-breathing instruction group. A non-significant trend towards better neurologic

status upon discharge was seen in the chest compression-alone group (14.4% vs. 11.5%) than in the chest compression plus rescue breathing group. Among patients with a cardiac cause for their arrest, there were slightly higher proportions with survival to hospital discharge and favorable neurologic status at discharge with chest compression alone. A reverse trend was seen in patients with non-cardiac causes for cardiac arrest.

The authors conclude that dispatcher CPR instruction consisting of chest compression alone did not increase survival when compared with instructions for chest compression plus rescue breathing. However, trends for improved outcomes with chest compression alone were seen in patients with cardiac causes for arrest and patients with shockable rhythms. In view of prior findings that compression-only CPR is easier to instruct and more acceptable to many rescuers, compression-only CPR should become the standard instruction given by dispatchers.

■ **COMMENTARY**

The need for rescue breathing during the critical early phases of CPR has recently been questioned. It has been shown that if the arrest is due to a sudden arrhythmia, blood-oxygen content is maintained for some time during compression-only CPR, and overall circulation is better if compressions are not interrupted. A CPR protocol that includes rescue breathing also is inherently more complex to teach and difficult to perform. Many rescuers are reluctant to administer mouth-to-mouth rescue breathing because of fear of infection. The data in this paper, and in an accompanying study from Sweden with similar results, support a change in policy to encourage compression-only CPR in most situations where the cardiac arrest is thought to be due to cardiac causes. Rescue breathing may remain important in cases of asphyxiation, drowning, or overdose, but these only account for small number of all cardiac arrests. ■

Initial Experience with Wearable Cardioverter-Defibrillator

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Chung MK, et al. Aggregate national experience with the wearable cardioverter-defibrillator event rates, compliance, and survival. *J Am Coll Cardiol*. 2010;56:194-203.

The wearable cardioverter-defibrillator (WCD) is a totally external system that can monitor a patient's cardiac rhythm and automatically treat episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF) when they are detected. The WCD was market released in the United States in 2002, and patients who wore the WCD were followed in a database maintained by the manufacturer. This paper reports the experience from that database.

The WCD system includes electrodes for monitoring two surface electrocardiographic leads, nonadhesive defibrillation electrodes incorporated into a chest strap assembly, and a defibrillator unit (microprocessors, battery and capacitors) carried on a waist belt. If an arrhythmia is detected, an alarm sequence is automatically begun that includes vibrations, audible tones, and vocal commands. Patients can prevent shocks if they actively press buttons that will inhibit the shock. If the inactivation buttons are not pressed, the device is designed to charge, extrude gel from the defibrillation electrodes, and deliver up to five transcutaneous shocks at preprogrammed energy levels. Event electrograms are stored in the devices memory. No pacing can be delivered by the WCD, but bradycardic events are sensed and their electrograms stored.

The manufacturer's database contains indications, baseline patient demographics, rates of compliance (i.e., the proportion of time worn per day), and data from arrhythmic events. Electrograms for arrhythmic events were analyzed to determine if the shock was appropriate or inappropriate. Total mortality was assessed using the Social Security Death Index and compared to a group of patients from the Cleveland Clinic who received a first ICD implant between August 1996 and May 2004.

The manufacturer's database included information from 3,569 patients who wore the WCD for at least one day. The mean age was 59.3 years, and 74% of the subjects were male. The most common reasons for WCD use were patients who had an ICD explanted for infection (23%) and those with a history of ventricular tachycardia or fibrillation who were awaiting ICD implantation (16.1%). Current U.S. reimbursement guidelines restrict ICD implantation in patients with recent myocardial infarctions, recent coronary revascularization, and recently diagnosed nonischemic cardiomyopathy with depressed systolic function. These latter three groups accounted for 13%, 9%, and 20% of the entire cohort. The median duration of use was 36 days. There were only small numbers of patients who used the device for more than 120 days. Compliance was quite reasonable. Patients used the device a median of 21.7 hours per day. One in seven patients stopped wearing the WCD prematurely because of comfort issues or other adverse reactions.

During the time that the WCD was worn, the WCD recorded 80 sustained VT/VF events in 59 patients (1.7% of the total patient population). First-shock success was noted in 79 of 80 episodes. One patient had shock resis-

tant, incessant VT, but this patient survived until pharmacologic therapy resulted in conversion. Eight patients died after successful first conversion of VT/VF, for an overall survival after a treated episode of 89.5%. Four of these patients died of recurrent arrhythmia. One patient's spouse prevented a second WCD discharge for a second episode ventricular arrhythmia. In two patients, recurrent arrhythmias were not shocked due to electrogram signal interruption caused, presumably, by the fall. One patient had interference with VF detection due to a unipolar pacemaker.

The WCD monitors for bradyarrhythmias but cannot treat them. There were 23 asystolic events, with 17 deaths and 3 deaths due to pulseless electric activity or respiratory arrest noted in patients while they were wearing the WCD, respectively. Inappropriate shocks were noted in 67 of the patients (1.9%). Inappropriate shocks resulted from inappropriate detections by the WCD and failure to suppress the shock using the response buttons by the patients.

Most of the patients who received appropriate shocks had traditional ICD indications. Thirty-three patients experienced 49 episodes of treated VT/VF. Six patients awaiting a scheduled ICD implant had nine events. Among 1,422 patients with nontraditional ICD indications, there were only 20 patients who had a total of 22 shocked VT/VF events. When survival among WCD recipients was compared to survival in a group of initial ICD recipients, the mortality curves were similar.

The authors conclude that prescription of a WCD is associated with acceptable rates of compliance and tolerance. VT/VF events are well detected and effectively treated. Patients awaiting ICD implant or reimplant with currently accepted indications are the most likely to benefit.

■ COMMENTARY

This report clearly shows that the WCD can provide effective therapy to patients at high risk for sudden death who are motivated enough to wear the device faithfully. The highest rate of use was in patients in whom a previously implanted ICD had been removed or in patients where other factors caused a scheduled ICD implant to be postponed. Use of the ICD for patients who did not have current indications for implant was infrequent and more data are needed before the WCD can be recommended for a wider group of patients. Two ongoing, randomized trials, the Vest Prevention of Sudden Death (VEST) trial and the Prediction of ICD Therapies study (PREDICT) are now underway and should provide these data for patients with recent myocardial infarction and depressed ejection fractions. I think it doubtful that the WCD will receive a high priority indication in any other large subgroups. ■

Exercise Pulmonary Hypertension in MR

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Magne, J et al. Exercise pulmonary hypertension in asymptomatic degenerative mitral regurgitation. *Circulation*. 2010; 122:33-41.

Current guidelines recommend mitral-valve surgery for severe organic mitral regurgitation in asymptomatic patients if exercise pulmonary hypertension (PASP > 60 mmHg) is demonstrated. However, little is known about the echocardiographic correlates of exercise-induced pulmonary hypertension (PH) or its relationship to symptom-free survival. Thus, these investigators from Belgium studied 78 consecutive asymptomatic patients with moderate or more organic mitral regurgitation (MR) and preserved left ventricular (LV) systolic function, who were referred for exercise echocardiographic testing. Patients with ischemic heart disease, valve stenosis, or concomitant regurgitation, atrial fibrillation, or poor images, were excluded (n = 10). Semi-supine bicycle exercise, with two-minute stages increased by 25W at each stage, was performed with echo Doppler imaging. The results of the exercise study were not shared with the referring physician. Mean follow-up was 19 months (2-56) in 100% of the patients. Resting PH was present in 15% (PASP > 50) and 46% exhibited exercise PH. Multivariate analysis showed that only E/Ea correlated with resting systolic pulmonary artery pressure (SPAP) and measures of MR severity did not. Exercise PH was correlated with age, resting SPAP, and exercise MR severity measures. During follow-up, resting and exercise PH were associated with decreased symptom-free survival over two years compared to medically treated patients (36 vs. 59%, $p = 0.04$; 35% vs. 75%, $p < .0001$, respectively). After adjustment for age and sex, resting PH was no longer predictive (HR = 2.1, 95% CI 0.9-4.9, $p = 0.08$). Exercise PH remained predictive (HR = 2.8, 1.4-5.4, $p = 0.002$). Receiver operating curve (ROC) analysis showed that the best cut point for predicting reduced symptom-free survival was an exercise SPAP > 56 mmHg (specifically 73%, sensitively 82%, positive predictive value 72%, and negative predictive value 80%). Mitral-valve surgery was performed in 25 patients during follow-up (20 repairs and five replacements) because of symptoms. The authors concluded that an exercise SPAP > 56 mmHg predicts the occurrence of symptoms and is associated with a significantly lower symptom-free survival.

■ COMMENTARY

Deciding when to recommend surgery for asymptomatic patients with moderately severe-to-severe MR and normal LV function is a challenge. If we knew that all would get a repair, rather than a replacement, it would be easier, but this study confirms that 20% end up with a prosthetic valve. The guidelines recommend surgery for patients if they have a resting SPAP > 50 or an exercise value > 60 mmHg (class IIa, evidence C). Thus, this report is a welcome addition to our knowledge base about these criteria.

In this study, symptom-free survival was reduced if patients had SPAP values roughly above the mean value for this population: rest mean 39, receiver operating curve (ROC) cut-off 36; exercise mean 62, ROC cut-off 56. The guidelines cut points are rest 50 and exercise 60. The exercise value is consistent with the data in this study, but the resting cut point in the guidelines seems high. However, all but one patient with a resting pressure above 50 had exercise PH. So, meeting the guideline's resting cut point of 50 predicts exercise PH. This is not surprising because a major determinant of exercise PH is resting PH. Clearly, a resting value above 50 is an indication for surgery and any value above 40 is a cause for concern.

Since patients with normal resting SPAP may develop exercise PH, exercise echo testing seems to be a good idea for those with moderate-to-severe MR and normal resting SPAP. Exercise PH was frequently observed in this population (46%), which is not surprising, since about 60% had severe MR. Interestingly, MR severity did not predict resting PH, but LV filling pressure estimates did. However, exercise PH was predicted by exercise MR severity. This suggests that, at rest, LV filling pressure is a good indicator of the hemodynamic consequences of MR, and that some patients develop more MR with exercise, which seems important for predicting who will become symptomatic.

The implications of this study are that asymptomatic patients with exercise-induced PH and moderately severe-to-severe MR may benefit from early surgery. Before we jump on this bandwagon, there are a few caveats to this study. First, it is not clear that other causes of PH were excluded. This would certainly be important. Second, only echo Doppler was used to assess pulmonary pressures and right atrial pressure was estimated to be 10 mmHg in all patients at rest and exercise. This is a reasonable assumption, but may not be accurate in everyone. All their patients had mitral valve prolapse, and only 10% had a flail leaflet, so this analysis may not apply to other patient populations with more diverse etiologies of MR and a higher percentage of flail leaflets. At this point, I believe exercise echo Doppler could be useful in borderline cases to sway the decision of whether to recommend surgery, but I am not sure I would use it as the sole criterion. ■

CME Questions

15. The stent thrombosis rate with non-cardiac surgery in patients with drug-eluting stents not necessarily on antiplatelet agents is about:

a. 0.5%.
b. 1.0%.
c. 1.5%.
d. 2%.

16. Revascularization of appropriate patients with moderately reduced ejection fraction increases survival vs. medical therapy in:

a. patients with viability demonstrated only.
b. patients with no viability demonstrated.
c. all patients regardless of viability.
d. no patients.

17. CPR emphasizing chest compressions rather than rescue breathing resulted in:

a. improved survival.
b. improved survival with a good neurological status.
c. improved survival in some subgroups.
d. no significant improvement in survival.

18. A comparison of abciximab vs. eptifibatide for PCI-treated STEMI showed:

a. equal resolution of ST-segment elevation.
b. equal rates of death over one year.
c. equal rates of MI over one year.
d. All of the above

19. Exercise-induced pulmonary hypertension in asymptomatic patients with moderate-to-severe mitral regurgitation predicts:

a. the occurrence of symptoms.
b. total mortality.
c. event-free survival.
d. A and C

20. Initial experience with the wearable cardioverter defibrillator suggests a:

a. 99% first shock success rate.
b. 90% initial cardiac arrest survival.
c. 2% inappropriate shock rate.
d. All of the above

Answers: 15. (a); 16. (c); 17. (d); 18. (d); 19. (d); 20. (d)

CME / Objectives

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

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

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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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Fibrates: Generally safe, but do they improve outcomes?

Source: Jun M, et al. Effects of fibrates on cardiovascular outcomes: A systematic review and meta-analysis. *Lancet* 2010;375:1875-1884.

According to this meta-analysis, the answer to the question above very much depends upon which outcome you believe is important. Conclusions are derived from 18 trials (45,058 participants) between 1950 and 2010. Although the results of individual fibrate (i.e., gemfibrozil, fenofibrate) trials have been somewhat disappointing, the combined data look more encouraging.

For instance, in the pooled data there was a 10% relative risk reduction for major cardiovascular (CV) events, and an almost 20% relative risk reduction for nonfatal coronary events in trials of fibrate vs placebo. Surprisingly, despite these favorable effects upon CV endpoints, there was no statistically significant reduction in all-cause mortality, CV death, or cardiac death.

When compared with other interventions to reduce CV risk (e.g., BP reduction, statins, antiplatelet therapies), the degree of absolute risk reduction achieved through fibrate therapy is substantially less. As might be anticipated, in trials where subjects had a higher baseline triglyceride level, risk reduction was greater.

Most at-risk patients in the United States are already receiving statins. The ACCORD trial was the only large trial in which patients that were already being treated with a statin then received a fibrate; no additional benefit from the fibrate was discerned. Nonetheless, fibrates will continue to have a role in high-risk patients, and in patients with marked triglyceride elevation at risk for pancreatitis. ■

Safety of testosterone replacement

Source: Basaria S, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363:109-122.

Of late, there has been a renaissance of interest in identification and management of hypogonadism in older men. This new enthusiasm is based upon a recognition that subnormal testosterone is both common and consequential. For instance, prevalence studies suggest that as many as 40% of healthy men older than age 50 have a subnormal morning total testosterone level. Subnormal testosterone is associated with changes in sexual function, mood, muscle mass, and central obesity. Observational data indicate that low testosterone is also associated with increased mortality. The advent of better-tolerated, easy-to-use testosterone replacement modalities (e.g., patches, gels, buccal tablets), has simplified the treatment approach, but the question about long-term testosterone safety is unanswered.

In the Testosterone in Older Men with Mobility Limitations study of senior men (n = 209; mean age, 74 years), subjects were treated with testosterone 1% gel to achieve mid-normal testosterone levels. The trial was discontinued early upon the recommendation by the Data and Safety Monitoring Board because of an increase in adverse events in the treatment group, including some serious events. For instance, there were 23 CV adverse events in the treatment group, compared with 5 in the placebo group.

The small size of the trial and the highly selected group (men with physical limitations) makes it difficult to generalize about the results. Nonetheless, clinicians should recognize that testosterone replacement may be associated with important adverse events. Larger, long-term studies will be necessary to establish the safety profile of testosterone replacement. ■

Glucosamine and low back pain

Source: Wilkens P, et al. Effect of glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis: A randomized controlled trial. *N Engl J Med* 2010; 304:45-52.

The burden of suffering attributed to low back pain (LBP) is readily identified by all who practice primary care. Indeed, it is recognized as the largest single component of dollars expended on long-term disability in the United States. Unfortunately, there is little evidence that supports any currently available interventions to alter the natural history of LBP and restore functionality. Because glucosamine has shown promise in other forms of osteoarthritis, and because lumber osteoarthritis is commonplace in persons with LBP, a trial of glucosamine for patients with both disorders was intuitively appealing.

In this randomized, double-blind trial, subjects were randomized to either 1500

mg/day glucosamine sulfate or placebo for 6 months. Outcomes were assessed at 6 months (end of active therapy) and again 6 months later (after a 6-month hiatus in treatment).

The Roland Morris Disability Questionnaire is specifically designed to address functional status in persons suffering LBP. In addition to this metric, degree of pain reduction and quality of life were assessed.

Although glucosamine was well tolerated, it did not produce a statistically significant improvement at either the 6-month or 12-month follow-up. Unless there exists another indication for the use of glucosamine, clinicians remain without supportive data to employ it for LBP associated with lumbar osteoarthritis. ■

Effects of allopurinol upon exercise in patients with angina

Source: Noman A, et al. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: A randomised, placebo controlled crossover trial. *Lancet* 2010;375:2161-2167.

Allopurinol has been shown, in heart failure, to reduce myocardial oxygen demand. The mechanism by which this occurs is not uncertain, nor is it known whether such favorable effects occur in persons without heart failure. If, during exercise, an intervention could similarly reduce myocardial oxygen demand, it could prove useful in persons with angina.

To address this question, the authors randomized subjects (n = 65) with chronic stable exercise-induced angina to high-dose allopurinol (600 mg/day) or placebo. Inclusion criteria required consistency of time to ischemia on baseline Bruce protocol exercise treadmill testing. Subjects received 600 mg/day allopurinol for 6 weeks (or placebo) and were then crossed over.

Allopurinol did produce a statistically significant increase in time to ST depression, as well as time to onset of chest pain, with no adverse effects. As a result, the authors suggest that there may be a role for allopurinol based upon cost, efficacy, and safety. Before embarking upon utilization of allopurinol for angina, clinicians must recognize that allopurinol is known to cause (rarely) a hypersensitivity vasculitis, which has a case fatality rate of approximately 25%. ■

Is obesity a factor in asthma?

Source: Pakhale SM, et al. A comparison of obese and nonobese people with asthma: Exploring an asthma-obesity interaction. *Chest* 2010;137:1316-1323.

Population studies have shown that obesity is related to the incidence of asthma. Compared to non-obese subjects, the odds ratio per year for developing asthma among obese individuals is approximately 1.5, and increases as the degree of obesity increases. Although mechanisms through which obesity might contribute to incident asthma are poorly understood, several prospective studies have demonstrated the same relationship.

Of course, some persons who carry a diagnosis of asthma have been misdiagnosed. In this study by Pakhale et al, subjects diagnosed as asthmatic underwent formal pulmonary function testing to confirm their diagnosis. Overall, of 496 subjects, asthma was ultimately ruled out in 150 of them. Likelihood of misdiagnosis was increased especially in older males.

There was one subgroup of obese individuals among whom the likelihood of asthma misdiagnosis stood out: If an obese individual had had an urgent visit for respiratory symptoms in the past 12 months, the misdiagnosis of asthma was more than 4-fold greater than in non-obese persons.

Based upon this information, it is suggested that clinicians should consider performing objective confirmation of the diagnosis of asthma (as with pre-and post-bronchodilator spirometry), particularly among obese older males. ■

A new tool for treatment of plantar warts

Source: Gamil H, et al. Intralesional immunotherapy of plantar warts: Report of a new antigen combination. *J Am Acad Dermatol* 2010;63:40-43.

Plantar warts, most commonly found on the plantar surface of the feet but also seen on the hands and other sites, are often challenging to treat. Although available tools include destructive therapies (e.g., cryotherapy, bichloroacetic acid), topical immune modulators (e.g., imiquimod), oral agents (e.g., cimetidine, levamisole), and simple surgical excision, each of these modalities has limitations. Hence, new methods of intervention are sought.

Gamil et al investigated the use of intralesional measles/mumps/rubella vaccine (MMR, as used in standard childhood immunizations) in a pilot trial. Vaccine was injected once every 3 weeks for a maximum of three injections, in 23 subjects.

Although the duration of treatment was only 6 weeks (injections at time 0, 3 weeks, and 6 weeks), patients were followed for 9 months to evaluate for recurrence.

Complete clearance of warts occurred in 20 of 23 patients, 1 patient had partial clearance, and 2 had no response. Only 1 patient experienced recurrence over 9 months. Other than local pain during the actual process of injection, the only other reported adverse effect was a transient flu-like syndrome in 1 patient.

MMR is inexpensive and well tolerated, and intriguing as a novel immunomodulatory path for attacking plantar warts. ■

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Weight-loss Drug Effective Without Cardiac Side Effects?

In this issue: Lorcaserin submitted for FDA review, FDA advisory panel votes against phentermine/topiramate, mixed vote on rosiglitazone, advisory panel votes to remove breast cancer indication from bevacizumab labeling, no increase in seizures found with DTaP vaccine, new REMS for quinine.

Weight loss without cardiac side effects

A new weight-loss medication may soon be available in the United States. Arena pharmaceuticals has filed a new drug application with the FDA for lorcaserin, a selective serotonin 2C-receptor agonist, and will likely get a formal review this fall. Unlike previous nonselective serotonergic agonists such as fenfluramine and dexfenfluramine, which were effective at causing weight loss, but also inhibited serotonin 2B receptors in the heart and were associated with valvulopathy, lorcaserin is specific for the serotonin 2C receptor in the brain.

Results from a company-sponsored study were published in the in *New England Journal of Medicine* and validate the effectiveness of the drug. The phase III trial was conducted at 98 academic and private trial sites, where 3180 patients were randomly assigned to receive lorcaserin 10 mg or placebo twice daily. After 1 year, patients receiving the active drug were randomly reassigned in a 2:1 ratio to continue to receive lorcaserin or change to placebo. All patients were age 18-65 years with a BMI of 30-45 or 27-45 kg/m^2 with one coexisting condition, including hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea. Patients were also counseled on lifestyle modification. Echocardiography was done at baseline and every 6 months thereafter.

At the end of 1 year, 47.5% of patients receiving lorcaserin lost 5% or more of their baseline body weight as compared with 20.3% of patients receiving placebo ($P < 0.001$). The average patient in the lorcaserin group lost 5.8% of their body weight compared with 2.2% in the placebo group ($P < 0.001$), and more patients in the active treatment group lost 10% or more of their baseline body weight than in the placebo group (22.6% vs 7.7%; $P < 0.001$). In those who lost weight with the active drug, the loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year 2 compared to those who were reassigned to placebo (67.9% vs 50.3%; $P < 0.001$). Markers of cardiovascular risk were improved in the active treatment group including C-reactive protein, fibrinogen levels, lipid levels, and insulin resistance. Systolic and diastolic blood pressures also decreased slightly in the lorcaserin group. Significantly, there was no evidence of cardiac valvulopathy found with use of lorcaserin and the rate of serious side effects was similar in the two groups.

The authors conclude that lorcaserin was associated with significant weight loss and improved maintenance of weight loss as compared to placebo (*N Engl J Med* 2010;363:245-256). Already being tagged the new, safe "diet drug," it is a sure bet that approval of lorcaserin will be associated with tremendous interest from our patients. ■

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.

Advisory panel votes against Qnexa

An FDA advisory panel recommended against approving (10-7 vote) the combination weight-loss drug Qnexa® (phentermine/topiramate) because of concerns about safety. The drug appears to be effective at inducing weight loss, but is associated with significant side effects including depression, anxiety, sleep disorders, attention, memory, and language and other cognitive disorders, as well as metabolic acidosis, increased heart rate, and teratogenicity. Qnexa is a combination of two available drugs and both remain on the market individually. Phentermine was approved in 1959 and is currently indicated as short-term treatment for weight reduction. It was part of the infamous Fen/Phen combination along with fenfluramine (later dexfenfluramine; both fenfluramine and dexfenfluramine were eventually removed from the market when they were found to cause pulmonary hypertension and cardiac valvulopathy). Topiramate is approved for the treatment of seizures and migraine prophylaxis. The FDA generally follows the recommendations of its expert panels. ■

Mixed vote on rosiglitazone

The same FDA committee also recently ruled on the embattled diabetes drug rosiglitazone (Avandia®), and the vote was decidedly mixed. GlaxoSmithKline's rosiglitazone has been under intense scrutiny since 2007 when a study from the Cleveland Clinic linked the drug to an increased rate of heart attacks (*N Engl J Med* 2007;356:2457-2471). Recently, the FDA has evaluated reports from the *New York Times* and others that the company suppressed crucial safety information about the drug for years. At the July meeting of the Endocrinologic and Metabolic Advisory Committee, 12 members voted to withdraw rosiglitazone from the market, 10 voted to keep the drug on the market with additional warnings and restrictions, 7 wanted additional warnings only, and 3 members voted for no label changes. The FDA is not required to follow the advice of its advisory panels, and it is unclear what course they will take when they finally make a decision later this year. ■

Breast cancer indication for bevacizumab

The Oncologic Drugs Advisory committee of the FDA has recommended removing the indication for breast cancer treatment for bevacizumab (Avastin®). The 12-1 vote was made after data were presented that the drug provided no survival benefit when used in combination with docetaxel, while contributing significant adverse effects. Bevacizumab, a humanized monoclonal antibody, which blocks new blood vessel formation (angiogenesis inhibitor), also carries indications for treatment of colon, lung, kidney, and brain cancers. ■

No increase in seizures with DTaP vaccine

The diphtheria-tetanus-acellular pertussis vaccine (DTaP) does not increase the risk of seizures in children, according to a recent article published on-line in *Pediatrics*. The previously used diphtheria-tetanus-whole-cell pertussis vaccine (DTP) is associated with seizures, but there were limited data on DTaP. Using data from the CDC's Vaccine Safety Data linked project, a retrospective study from 1997 through 2006 at 7 managed-care organizations was performed. Eligible children were age 6 weeks to 23 months and had not previously received DTP. Of the more than 433,000 children who were vaccinated, there were 7191 seizure events. The adjusted incident rate for seizures across all doses was 0.87 in the cohort analysis and 0.91 in the comparison group with the same patients during unexposed periods. The authors conclude that they did not observe an increased risk for seizures after DTaP among children age 6 weeks to 23 months. ■

New REMS for quinine

The FDA banned the OTC use of quinine sulfate for the treatment of nocturnal leg cramps in 1994 after receiving more than 150 reports of adverse reactions, including 23 deaths. Quinine sulfate (brand name Qualaquin®) remains the only quinine product on the market, but is approved only for the treatment of uncomplicated malaria caused by *Plasmodium falciparum*. Qualaquin, however, is much more commonly used off-label for nighttime leg cramps. The FDA continues to get reports of life-threatening hematologic reactions associated with quinine sulfate including thrombocytopenia, hemolytic-uremic syndrome/TTP, hearing loss, and cardiovascular problems. Between 2005 and 2008 there were 38 cases of serious side effects including 2 deaths. The FDA has announced a new Risk Evaluation and Medication Strategy (REMS) for Qualaquin that will include a Medication Guide explaining what the medication is and is not approved for, as well as the potential side effects of the drug. The medication guide specifically states that "Qualaquin should not be used for nighttime leg cramps," and those using it for this indication are at risk of serious side effects (FDA Drug Safety Communication, July 8, 2010). ■