Special Report From the American College of Cardiology Annual Meeting, pgs 33-37

CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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INSIDE

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COURAGE

SPECIAL REPORT FROM THE 2007 AMERICAN COLLEGE OF CARDIOLOGY ANNUAL MEETING, NEW ORLEANS

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.

Source: Boden, WE, et al. Optimal Medical Therapy With or Without PCI for Stable Coronary Disease. *N Engl J Med.* 2007; Online.

THIS LONG AWAITED STUDY TESTED THE HYPOTHESIS THAT aggressive pharmacologic therapy and lifestyle intervention (Optimal Medical Therapy or OMT) without percutaneous coronary intervention (PCI) would not be as successful in reducing major cardiovascular events as OMT in addition to PCI. COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) was a randomized trial conducted at fifty centers in the United States and Canada, with randomization between 1999 and 2004, assessing a primary outcome of nonfatal myocardial infarction (NFMI) or death from any cause during follow up of 2.5 to 7.0 years (median, 4.6 years). The COURAGE trial sought to test whether or not PCI reduced major cardiac events, and particularly NFMI and death, as previous studies have not conclusively demonstrated that PCI does more than decrease angina frequency and enhance exercise performance. The study enrolled 2,782 stable CAD subjects with significant angina and a stenotic lesion > 70% in an epicardial coronary artery with evidence of ischemia on stress testing. The latter ranged from routine treadmill -test evaluation to nuclear techniques; exclusionary criteria included > 80% coronary artery narrowing with classic angina, severe angina, a strongly positive stress test, heart failure, ejection fraction of < 30%, revascularization within 6 months, or coronary anatomy not suitable for PCI.

Patients were assigned to PCI and OMT, or OMT alone. Medical therapy consisted of aspirin or clopidogrel; metoprolol; amlodipine; isosorbide mononitrate, as well as an ACE inhibitor or ARB. Targeted lipid lowering therapy strove to achieve a LDL level of less than 85 mg/dl with simvastatin with or without ezetimibe. In the PCI group, target lesion revascularization was carried out and complete revascularization was encouraged. PCI success was < 50% stenosis

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after balloon angioplasty, and < 20% narrowing after stent implant. Clinical success was defined as angio--graphic success with no major complications. There was virtually no use of drug-eluting stents, which were not yet available for most of the study period. Many secondary outcomes were assessed, including stroke and hospitalization for unstable angina. The investigators projected major event rates of 21% in the medical therapy group and 16.4% in the PCI patients over a follow up of 2.5-7 years.

RESULTS: Multiple baseline characteristics were similar in the 2 groups. Median angina frequency was 3 attacks per week; 58% of subjects had Canadian Class II-III angina. Ninety percent of patients undergoing myocardial perfusion imaging had reversible defect(s) consistent with inducible ischemia; two thirds of the patients had multi-vessel CAD; 94% of PCI patients received at least one stent (40% more than one stent). Vessel stenosis was reduced from 83 +/- 14% to 31 +/- 34% in non-stented patients. PCI success was 93%; clinical success (all lesions dilated and no complication) occurred in 89% of randomized patients. Medication compliance was excellent; at 5 years 70% of individuals had an LDL < 85 mg/dl; blood pressures were within normal range, and half of all diabetics had a hemoglobin A1C of 7.0% or less. Smoking decreased and exercise increased during the course of this study, with a median follow up of 4.6 years. The primary outcome of death or NFMI occurred in 211 PCI patients and 202 medical therapy patients, with an estimated 4.6 year cumulative primary event rate of 19% in both groups. Secondary outcomes including stroke, were slightly higher at approximately 20% in each group. Other endpoints included hospitalization for ACS, rate of MI and death, all with identical event curves. The primary endpoint was met in 16.2% and 17.9% in the PCI and medical groups, respectively, $P = 0.29$. At follow up, 21% of PCI subjects and 32% of medical therapy patients had undergone revascularization, hazard ratio 0.60, $P < 0.001$. Revascularization occurred for intractable angina or worsening ischemia on noninvasive testing. Angina prevalence declined in both groups with a statistically significant difference throughout most of the study in favor of PCI. However, at 5 years 74% of PCI patients and 72% percent of medical therapy patients were free of angina. There were no interactions between any subgroups.

The authors conclude that, "As an initial management strategy, PCI added to optimal medical therapy did not reduce the primary composite endpoint of death and NFMI as compared with optimal medical therapy alone." The COURAGE cohort was high risk, as patients had to have objective evidence of ischemia and most had extensive CAD on angiography. The authors nicely discuss the pathophysiology of stable CAD vs vulnerable plaques (responsible for ACS). They conclude that "focal management…of severely stenotic lesions with PCI…did not reduce the rate of death and MI." The medical therapy group had event rates lower than anticipated, presumably related to intensive medical therapy that included exercise and smoking cessation. Both PCI and OMT patients had a significant improvement in angina, favoring PCI/ OMT individuals in the early years, with equivalent angina rates at the end of the study. The authors stress that prior studies, including their data, have consistently demonstrated that "PCI has no effect in reducing major cardiovascular events." Thus, the data are consistent with clinical practice guidelines, allowing deferral of PCI in patients with stable coronary disease, even if multi-vessel and associated with inducible ischemia, so long as "intensive multifaceted medical therapy is instituted and maintained." One-third of the OMT group subsequently required revascularization during the study and angina rates were clearly improved in the PCI patients more than the OMT subjects. Of importance, PCI added to ideal medical therapy decreased angina but not death, NFMI, or hospitalization for ACS.

COMMENTARY

This very important report will generate considerable discussion and analysis over the ensuing months

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Questions & Comments

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and years. The study was well designed and conducted. It will be tempting, but inappropriate for some to extend the results of COURAGE to other subsets, such as patients with accelerating or unstable angina or subjects with no chest pain at all, with or with out positive stress testing for ischemia. A critical analysis of COURAGE clearly documents the high-risk state of both treatment groups, with a major event rate of approximately 4% per year. It is important to note that hospitalization for ACS in the total nonfatal MI population was equivalent in both cohorts. COURAGE patients were at least moderate risk, indicated by the inclusion criteria of at least one stenotic major coronary artery, inducible ischemia and active angina attacks, although clinically stable. This study does not address acute coronary syndromes, where the benefit of PCI with anti-platelet therapy has been demonstrated repeatedly. Neither does the data address the issue of early vs late catheterization after ACS, as this was a stable angina population. However, the medical therapy utilized in COURAGE is the same as outlined in ACC/AHA guidelines for treatment of angina, and reflects the increasingly aggressive cardio-protective therapy that is being delivered in many centers today. One would hope that these results may decrease unnecessary PCI, such as in patients with no chest pain, even with a positive stress test. The investigators are to be congratulated on a landmark clinical study that should cause all individuals treating patients with CAD reflect on the actual study details and incorporate the COURAGE lessons into clinical practice. ■

FUSION II

SPECIAL REPORT FROM THE 2007 AMERICAN COLLEGE OF CARDIOLOGY ANNUAL MEETING, NEW ORLEANS

By Michael H. Crawford, MD

THE FOLLOW-UP SERIAL INFUSIONS OF NESIRITIDE for the Management of Patients with Heart Failure (FUSION II) Trial was presented by Dr. Clyde Yancy, Director of the Baylor Heart and Vascular Institute in Houston. This trial of chronic decompensated heart failure patients evaluated the role of recombinant human B-type natriuretic peptide given as a 4-6 hour infusion once per week or twice per week vs a placebo infusion. The primary end point was the time to death from cardiovascular events or renal events requiring hospitalization over the 12 weeks that the infusions were given. In the 920 patients studied, all had ejection fractions < 40% and two-thirds had ischemic cardiomyopathy. Baseline heart failure drug therapy was excellent and was continued; 25-30% had an electrophysiologic device in place. The trial was a follow-up to the FUSION I study, which showed that the nesiritide was safe and efficacious in advanced heart failure patients.

RESULTS: Event rates were 33% lower in FUSION II as compared to FUSION I, which this was probably due to improved use of optimal evidence-based management strategies. The results of FUSION II were neutral. The primary end point was achieved in 30% of both groups and mortality was 10% in both groups. The patients were followed for 24 weeks and there were no significant differences in outcomes. There were also no significant subgroup differences although there was a trend for African American patients to do better on nesiritide. The secondary end points, including quality of life, were also not different. With regard to safety, 88% had some adverse event and this was equal between the groups. Hypotension was the most common adverse event with nesiritide. Serious adverse events and renal adverse events were equal between the groups. The investigators concluded that in advanced heart failure patients, serial outpatient infusions of nesiritide did no harm, but were also not beneficial. They believed that optimal medical and electrophysiologic device therapy diminished the benefit of outpatient serial nesiritide infusions and explains the difference between the positive results in FUSION I and the neutral results in FUSION II. In the ensuing panel discussion, the conclusion was that serial outpatient nesiritide infusions should be abandoned. Dr. Yancy commented that the main message of FUSION II "is that adherence to guideline-driven therapy and meticulous follow-up defines the benchmark for care of patients with chronic decompensated stage D heart failure." ■

VALIDD

SPECIAL REPORT FROM THE 2007 AMERICAN COLLEGE OF CARDIOLOGY ANNUAL MEETING, NEW ORLEANS

By Michael H. Crawford, MD

THE INFLUENCE OF ANGIOTENSIN RECEPTOR BLOCKers and blood pressure lowering on diastolic function in patients with hypertension and diastolic dysfunction: The Valsartan in Diastolic Dysfunction (VALIDD) trial was presented by Dr. Scott Solomon from the Brigham and Women's Hospital in Boston. The patho-

physiologic theory behind this trial is that hypertension leads to left ventricular hypertrophy, which leads to increased left ventricular fibrosis and eventually leads to heart failure secondary to diastolic dysfunction. Consequently, the hypothesis is that if you treat the hypertension, then you can regress the left ventricular hypertrophy and possibly improve diastolic dysfunction. Since blockade of the renin angiotensin aldosterone system has been shown to decrease left ventricular hypertrophy and fibrosis, can these drugs improve diastolic dysfunction? Thus this randomized double-blind placebo-controlled trial was conducted on 384 patients over the age of 45 with stage 1 or 2 hypertension and echo Doppler evidence of diastolic dysfunction, who were treated with valsartan titrated up to 320 mg a day vs standard therapy. The target was a blood pressure less than 135/80 using a combination of diuretics, beta-blockers, calcium-blockers, and alpha-blockers in the control group. Diastolic function was estimated by tissue-Doppler imaging on echocardiography of the lateral annulus in the 4-chamber view. The primary end point of the study was changes in E' velocity. Other diastolic parameters were secondary end points. Of the 384 patients enrolled in the trial, all had normal BNP levels and no symptoms of heart failure. At baseline, echo variables were not different between the 2 groups; 12% were African American and more than one-half had abnormal cholesterol levels. Blood pressure was significantly reduced by therapy in both groups and the degree of reduction was not different at the end of 38 weeks of therapy. The primary end point of E' increased in both groups to 8.1 in the valsartan group versus 8.0 in the placebo group, which was not significantly different. The change in E' correlated with blood pressure reductions, but the effect was nonlinear. Isovolumic relaxation time and S' were better on valsartan, but E/E' E/A were/was not. LV mass also decreased in both groups, but there was no significant difference between groups. The investigators concluded that in patients with mild to moderate hypertension and diastolic dysfunction that lowering blood pressure either with valsartan or other drugs improves diastolic dysfunction and reduces LV mass. In the discussion that ensued, it was pointed out that renin angiotensin aldosterone-blocking drugs have never been shown in clinical trials to do more than lower blood pressure, which is known to be beneficial. Whether there are other benefits beyond blood pressure lowering are still unknown. Dr. Solomon commented that the results "suggest that one of the benefits of treating hypertension may be to improve diastolic function, even in patients with mild hypertension," which may reduce the risk of developing heart failure. ■

ILLUSTRATE

SPECIAL REPORT FROM THE 2007 AMERICAN COLLEGE OF CARDIOLOGY ANNUAL MEETING, NEW ORLEANS

By Michael H. Crawford, MD

THE CHOLESTEROL ESTER TRANSFER PROTEIN (CETP) inhibitor torcetrapib has been shown to raise HDL levels significantly. In the ILLUSTRATE trial 1,188 patients with any HDL-cholesterol (C) level and a clinical indication for cardiac catheterization were randomly assigned to receive atorvastatin plus torcetrapib or atorvastatin alone. The effects of the drugs on an intra vascular ultrasound analysis of coronary atheromas were assessed initially and after months of treatment on torcetrapib. There was an amazing 61% increase in HDL-C and a 20% decrease in LDL-C, which achieved an average LDL:HDL ratio of < 1. Also, torcetrapib increased systolic blood pressure by 5 mmHg. Despite the dramatic beneficial effect on lipids, torcetrapib did not reduce progression or induce regression of coronary atherosclerosis. The principal investigator who presented the trial Dr. Steven Nissen said that these disappointing results should not completely negate the CETP-inhibitor class of drugs, since newer agents may prove to be better. ■

RADIANCE I & II

SPECIAL REPORT FROM THE 2007 AMERICAN COLLEGE OF CARDIOLOGY ANNUAL MEETING, NEW ORLEANS

By Michael H. Crawford, MD

THE RESULTS OF THE EFFECT OF TORCETRAPIB AND atorvastatin compared with atorvastatin alone on carotid intimal-media thickness in subjects with hyperlipidemia (RADIANCE) trials were presented by Dr. John Kastelein. The RADIANCE I trial involved patients who were heterozygote for familial hypercholesterolemia. They were randomized to either atorvastatin at an average dose of 56 mg a day vs atorvastatin plus torcetrapib. They were followed for one year by measuring carotid intimal-media thickness in 12 sites in the common carotid and the bifurcation. Over the course of a year, 14 patients dropped out of the trial. Dr. Kastelein, who is professor and chairman of the

department of vascular medicine at the academic medical center in Amsterdam, said that the curves for the primary end point of change in carotid atheroma volume "were flat as a Dutch pancake." In other words, not only were the results in the 2 groups not significantly different, there was no trend and there was no improvement by either therapy in carotid intimal media thickness. Interestingly, overall systolic blood pressure was increased by 3 mmHg with torcetrapib. These results occurred despite marked increases in HDL, decreases in LDL, increased apolipoprotein A and decreases in B in the torcetrapib group. RADIANCE II involved patients with mixed dyslipidemia also followed for one year with a 24% discontinuation rate. The mean atorvastatin dose was 13 mg/day. In these patients HDL levels almost doubled and LDL levels were decreased by 18%. The primary end point of carotid intimal-medial thickness atheroma volume was not significantly different. Severe cardiovascular adverse events were somewhat more on torcetrapib at 10% vs 6% in the atorvastatin alone group. Also in the torcetrapib group a 5 mmHg average increase in blood pressure was noted. The investigators concluded that there was no regression of atherosclerosis despite very favorable lipid effects using torcetrapib. ■

ERASE

SPECIAL REPORT FROM THE 2007 AMERICAN COLLEGE OF CARDIOLOGY ANNUAL MEETING, NEW ORLEANS

By Michael H. Crawford, MD

THE EFFECT OF RECONSTITUTED HIGH-DENSITY Lipoprotein on Aatherosclerosis: Safety and Efficacy (ERASE) trial was presented by Jean-Claude Tardif, Director of Research at the Montreal Heart Institute. Infusions of r-HDL or placebo were randomly administered to 145 patients within 2 weeks of an acute coronary event. Either 40 mg or 80 mg per kg were administered over a 4-week period. Coronary angiography with intravascular ultrasound imaging was done before and after the infusions, and the primary end point was percent change in atheroma volume. Secondary end points included changes in plaque volume characteristics and the QCA score. The data safety and monitoring board recommended discontinuation of the 80 mg arm because of liver function test abnormalities. Ninety percent of the patients were also on statins. The primary end point decreased 3.4% on r-HDL vs 1.6% on placebo, which was not statistically different. The secondary endpoints of plaque characteristics improved significantly on r-HDL, but not on placebo. Also, QCA decreased on placebo, but not on r-HDL. Both of these were significant. Although mild hypotension was frequently observed with the r-HDL infusion, there was no significant difference in any safety end points in the 40-mg-per-kg group vs placebo. The authors concluded that atheroma volume was not significantly changed by r-HDL therapy even though there were favorable effects in CQA and plaque characteristics. Thus, since there were positive outcomes only for the secondary end points, this result was viewed by the discussants as a proof of concept study. ■

Direct Renin Inhibition

SPECIAL REPORT FROM THE 2007 AMERICAN COLLEGE OF CARDIOLOGY ANNUAL MEETING, NEW ORLEANS

By Michael H. Crawford, MD

DR. SUZANNE OPARIL PRESENTED THE RESULTS OF A study of the direct renin inhibitor aliskiren in combination with the angiotensin receptor-blocker valsartan compared with either agent alone in 1,797 patients with class 1-2 hypertension. This randomized placebo-controlled double-blind study titrated valsartan from 160 mg to 320 mg a day and aliskiren from 150 mg to 300 mg a day. The primary end point was change in diastolic blood pressure. Secondary end points were changes in systolic blood pressure, achieving the target blood pressure of < 140/90 and the 24-hour blood pressure profile. There was a significant decrease in blood pressure on valsartan and aliskiren monotherapy that was augmented by combination therapy. Changes in systolic blood pressure were similar and were seen over the entire 24-hour monitoring period. The overall average effect was an additional lowering by aliskiren of 4.5 mmHg systolic and 3.2 mmHg diastolic over valsartan alone at 4 weeks of therapy. Approximately two-thirds of the patients responded to combination therapy and showed results that were better than monotherapy. Plasma renin levels were increased on valsartan and decreased on aliskiren. The addition of aliskiren did not increase the number of adverse effects, but increased potassium was more common with the combination therapy. The investigators concluded that this was the first large-scale trial showing the blood-pressure lowering effects of dual renin system blockade with angiotensin receptor blocker and a direct renin

inhibitor in patients with stage 1 to 2 hypertension. In the discussion that ensued, one commenter mentioned that the incremental benefit was small and was similar to what is seen with hydrochlorothiazide. Also, it was noted that there have been reports of angioedema, but it is rare, occurring in 4 out of 6,000 patients treated to date. Based on this study and others, it is clear that aliskiren is effective as monotherapy and adds to combination therapy regimens. Where its niche will be in treating patients with hypertension is not clear, but the low side effect profile may make it an attractive addition to combination therapy. ■

Resuscitation Success With Chest Compressions Only

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: SOS-KANTO Study Group. Cardiopulmonary Resuscitation by Bystanders With Chest Compression Only (SOS-KANTO): An Observational Study. *Lancet.* 2007;369:920-926.

The SOS-KANTO study is a survey of survivors of out-of-hospital cardiac arrest in the Kanto region of Japan. In this paper, the SOS-Kanto investigators analyzed outcomes in patients with an out-of-hospital cardiac arrest that was witnessed by bystanders between September 1, 2002, and December 31, 2003. Emergency Medical Service (EMS) paramedics observed the technique of bystander resuscitation and asked additional standardized questions of witnesses. The technique was classified as: cardiac-only resuscitation (chest compressions only), conventional CPR (chest compressions plus breathing), pulmonary-only resuscitation (breathing only) and unidentified or not documented. In addition, the person attempting bystander resuscitation was classified as either a layperson with basic CPR training, a layperson assisted by a dispatcher, a lay- person without training or assistance, or an off-duty health worker. The primary endpoint was a favorable neurological outcome defined as a Glasgow-Pittsburgh cerebral performance category of either 1 or 2 when measured 30 days after cardiac arrest. The secondary endpoint was survival 30 days after cardiac arrest.

During the study period, 9,592 patients received advanced life-support by EMS paramedics in the Kanto region. Of these, 4,068 adult patients had a bystander witnessed cardiac arrest outside the hospital and are included in this report. In this group, 1,151 (28%) received some form of bystander resuscitation, including 439 (11%) who received cardiac-only resuscitation, and 712 (18%) who received conventional CPR. There were 2,917 (72%) witnessed cardiac-arrest victims who did not receive any bystander resuscitation. The patients who received bystander resuscitation were more likely to have their cardiac arrest occur in a public place and to have either gasping breathing or ventricular fibrillation or pulseless VT at the time of EMS arrival. When the cardiac-resuscitation only vs conventional CPR groups were compared, the baseline characteristics were similar except that conventional CPR was more likely to be performed by off-duty medical staff while cardiac-only resuscitation was more likely to be performed by laypersons without formal CPR training.

Compared to the no-bystander resuscitation group, patients who had any resuscitation attempt were significantly more likely to have a favorable neurological outcome (5% vs 2%; P = less than 0.001). Subgroup analysis showed consistent improvement in patients with a cardiac cause for their arrest, apnea at the time of EMS arrival, ventricular fibrillation or pulseless VT as the initial cardiac rhythm. Any bystander resuscitation also showed benefit for patients with both short and long EMS response times. When the cardiac-resuscitation only vs conventional CPR groups were compared, cardiac-only resuscitation resulted in a higher proportion of patients with a favorable neurological outcome. This was due to improved neurological ou comes in patients with apnea, ventricular fibrillation or tachycardia as the initial rhythm or with resuscitation starting within 4 minutes of collapse. Multiple logistic regression analysis showed that cardiac-only resuscitation resulted in higher proportions of favorable neurological outcome than with conventional CPR with an adjusted odds ratio of 2.22 (1.17-4.21). Of note, the 2 bystander resuscitation groups did not show differences in total survival at 30 days or in survival until hospital admission despite the improvement in neurological outcomes.

The authors conclude that cardiac-only resuscitation should be the preferred approach to bystander resuscitation for adult patients with witnessed out-of-hospital cardiac arrest. Improvements in neurological outcome are more marked in those with apnea, a shockable cardiac rhythm or short periods of untreated arrests.

COMMENTARY

The standard method for cardiopulmonary resuscitation for many years has been a combination of chest compression and ventilation. Recently, the importance of ventilation during CPR has been questioned. There are a number of reasons for this. Most importantly, many bystanders are reluctant to perform mouth-to-mouth ventilation. This decreases the number of cardiac arrest victims who receive any bystander resuscitation at all. Conventional CPR is a complex technique, is difficult to teach and its complexity intimidates many. There are many reasons why ventilation may not be necessary. Mouth-to-mouth ventilation causes interruptions in chest compression and this can decrease cardiac outputs. Mouth-to-mouth or positive ventilation may also change intrathoracic pressures in a deleterious fashion. At the onset of a primary cardiac arrest, the blood in the lungs should be fully oxygenated and enough oxygenation to maintain organ function will be maintained for several minutes of chest compression. These concepts have been supported by data from experimental laboratory preparations showing that ventilation is not beneficial in the early stages of resuscitation. The SOS-KANTOS Study now has demonstrated this to be also true in an observational study in a clinical population. Adoption of this finding into ACLS guidelines should simplify our ability to train people in CPR and also benefit outcomes. Victims of drowning, drug overdose or asphyxia will still require ventilation, but chest-compression-only CRP should become the standard for most cardiac arrest victims. ■

Long QT Syndrome and Pregnancy

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Seth R, et al. Long QT Syndrome and Pregnancy. *J Am Coll Cardiol.* 2007;49:1092-1098.

SETH AND HIS COLLEAGUES REPORT ON THE EFFECTS of pregnancy in women with the long QT syndrome (LQTS). The International Long QT Syndrome Registry enrolls patients and family members with LQTS in a longitudinal observational study. In this report, women of child bearing age who had either a known LQTS related gene mutation or carried a clinical diagnosis of LQTS on the basis of a QTc greater than 470 msec were categorized as either having one or more live births (n = 564) or as being nulliparous (n = 520). The child bearing age range was considered to be ages 15 through 40 years of age. The women in the live-birth category were subdivided into those who gave birth before 1980 (n= 173) and after 1980 (n = 391) to reflect the availability of beta blocker therapy for treatment of LQTS. The cardiac risks associated with pregnancy were analyzed by peripartum time intervals immediately before, during, and after a live birth in 9-month segments. A post-postpartum time interval was defined as the time after the immediate postpartum 9-month interval until the date of last follow-up or age 41. If a woman had more than one child, the time intervals for each pregnancy were analyzed. The outcomes analyzed were LQTS-related death, aborted cardiac arrest and syncope. Results of standard genetic tests for LQTS mutations were available in 153 patients. Of these, 82 had LQT1, 59 LQT2, and 12 LQT3 mutations.

When nulliparous women were compared with women who had a live birth, the nulliparous women had a shorter average follow-up time, a higher event rate before age 15 and a higher use of beta blockers at age 15 than the other 2 groups. The authors cite multiple potential explanations for these findings. The remainder of the article dealt only with those women who had a live birth after 1980. Cardiac event rates were relatively stable in the intervals more than 9 months before first pregnancy, the pre-pregnancy 9-month interval, and during pregnancy. There was a significant rise in the annualized cardiac event rate in the 9 months immediately postpartum and then a decrease in the post-post partum interval. The annualized cardiac event rate in the 9-month postpartum period was 0.23 events per year. For the entire group, the hazard ratio during pregnancy was 0.28, during the postpartum period 2.7, and in the post-postpartum period 0.91. Among women in whom genotype data were available, the high rate of postpartum events was primarily due to events in the women with the LQT2 genotype. Of the 391 women who had live births after 1980, 104 were using beta blockers at conception, 116 at the time of childbirth, and 128 at 9 months after giving birth. Beta blockers were associated with a reduction in annualized cardiac event rate with an annualized rate of 3.7 events per year in the absence of beta blockers vs 0.8 events per year with beta blockers. A Cox proportional hazard survival analysis indicated a hazard ratio of 0.34 (0.14 to 0.84) associated with beta blocker therapy.

The authors conclude that the 9-month postpartum period is associated with a significant increased risk of experiencing a cardiac event in women with LQTS and this increase in risk is most noticeable in subjects with the LQT2 genotype. Thus, beta adrenergic blocker

should be continued in LQTS patients before, during, and after pregnancy.

■ **COMMENTARY**

Cardiologists are often asked to help manage women with LQTS during pregnancy. This paper from the International Long QT Syndrome Registry demonstrates that pregnancy itself does not place the patient at unusually high risk, but that the early postpartum period is associated with increased risk. The reasons for this are uncertain. There are physiologic and hormonal changes that occur after pregnancy during this period that may contribute. In addition, however, the observation that LQT2 patients were at higher risk suggests that environmental stimuli associated with early childbearing may also be an important factor. LQTS type 2 patients are more likely to have sudden auditory stimuli events serve as triggering events. Such events and sleep deprivation might well be common in mothers caring for a young infant.

Also, the data presented here argue that beta blockers should be continued peripartum in patients with long QT syndrome, particularly if they have a known LQT2 genotype. ■

CME Objectives

The objectives of *Clinical Cardiology Alert* are:

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

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

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

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

CME Questions

24. The initial management of chronic stable angina with a positive, but low-risk stress test should be:
A. optimal medical therapy
B. cardiac cath with percutaneous intervention
C. coronary CT angiogram
D. EECP

25. Weekly nesiritide infusions in heart failure patients results in:
A. increased blood pressure
B. reduced morbidity and mortality
C. significant renal dysfunction
D. none of the above

26. What treatment improves LV diastolic dysfunction in hypertensive patients?
A. angiotensin receptor blockers
B. calcium channel blockers
C. beta blockers
D. all of the above

27. Cholesterol transfer protein receptor inhibitor treatment results in:
A. increases in HDL
B. reductions in coronary atheroma volume
C. reduction in carotid intimal media thickness
D. all of the above

28. Reconstituted HDL infusions produce:
A. reductions in coronary atheroma volume
B. favorable effects on plaque characteristics
C. reduced clinical CV events
D. hepatotoxicity at low doses

29. Direct rennin inhibition with aliskiren produces:
A. kidney toxicity
B. increased plasma rennin levels
C. additive blood pressure lowering with valsartan
D. no blood pressure lowering as monotherapy

30. The risk of sudden death with pregnancy in patients with long QT syndromes is highest during:
A. the 40 weeks of pregnancy
B. the 9 months after delivery
C. during delivery
D. before conception

31. The most successful cardiac arrest resuscitation technique is :
A. chest compressions and intermittent breathing
B. breathing only
C. chest compressions only
D. none of the above

Answers: 24.(a) 25.(d) 26.(d) 27.(a) 28.(b) 29.(c) 30.(b) 31.(c)

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.

Long-Awaited Torcetrapib Will Not Be Released, Too Risky

Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, has been in development by Pfizer for nearly 15 years. The drug has been shown to elevate HDL levels while reducing LDL levels, prompting hopes that torcetrapib would be the first in a new class of important cholesterol medications. In December, Pfizer abruptly pulled the plug on further development of torcetrapib when the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events trial showed an increase in death from all causes associated with the drug, including an increased rate of cardiovascular events and hypertension. A new study points out a possible mechanism for the lack of cardiovascular benefit. In the international study, 1,188 patients with cardiovascular disease underwent intravascular ultrasonography. They then received atorvastatin and were randomized to receive 60 mg of torcetrapib daily or placebo along with atorvastatin for 24 months. Atorva/torcetrapib resulted in a 61% relative increase in HDL and a 20% further reduction in LDL, resulting in an average HDL higher than LDL. But the drug combination was also associated with an increase in systolic hypertension of 4.6mm Hg, and more importantly an increase in atheroma volume of 0.12%, compared to an increase of 0.19% in the atorvastatin alone group (P = 0.72). The authors conclude that treatment with the CETP torcetrapib was associated with improved lipid endpoints, but was also associated with an increase in blood pressure and no significant decline in coronary atherosclerosis (*N Engl J Med.* 2007;356:1304-1316.). In an accompanying editorial, Dr Alan Tall holds out hope that other CETP inhibitors may not show the same adverse effects but suggests that further development of this class of drugs needs to proceed with caution (*N Engl J Med*. 2007;356:1364-1366). ■

IBS-Drug Treatment Pulled, CV Side Effects

Tegaserod (Zelnorm), Novartis Pharmaceutical's drug for irritable bowel syndrome has been removed from the market by the FDA based on recent findings of increased risk of serious cardiovascular events associated with use of the drug. Tegaserod was approved in 2002 for women with irritable bowel syndrome whose primary symptom was constipation. It was given the additional indication in August 2004 for chronic constipation in men and women under the age of 65. Withdrawal was based on analysis of 29 studies involving more than 18,000 patients that showed a small, but statistically significant increase in the risk of cardiovascular side effects (0.1% serious adverse effects with tegaserod vs 0.01% with placebo). The FDA may allow continued use of the drug in a limited number patients for whom no other treatment options are available and the benefits of tegaserod outweigh the chance of serious side effects. The FDA may consider limited reintroduction of the drug at a later date if the population patients can be identified in whom the benefit of the drug outweighs the risk. ■

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Drug Combo Better for Migraine Treatment

Naprosyn plus sumatriptan is better than either drug alone for the treatment of acute migraine according to a new report. In 2 studies, nearly 3,000 patients with a history of migraine were randomized to sumatriptan 85 mg plus naproxen sodium 500 mg, both drugs alone, or placebo to be used after the onset of a migraine with moderate to severe pain. The primary outcome was headache relief at 2 hours, absence of photophobia, absence of phonophobia, absence of nausea, and sustained pain-free response. Sumatriptan plus naproxen was superior to placebo in all measures and was superior to either drug alone in sustained pain-free response. The incidence of adverse effects was the same for the combination as for the individual medications. The authors conclude that sumatriptan 85 mg plus naproxen 500 mg as a single pill for acute treatment of migraine is more effective than either drug as monotherapy (*JAMA*.2007; 297:1443-1454.). Pozen Pharmaceuticals/ GlaxoSmithKline is developing the combination pill, which is expected to be approved later this year under the trade name Trexima. ■

Pergolide Off the Market, Heart Disease Risk

Pergolide (Permax) is being withdrawn from the market after reports of serious valvular heart disease associated with the drug. Pergolide is a dopamine agonist used for the treatment of Parkinson's disease, hyperprolactinemia and pituitary tumor (?). The action was prompted by 2 reports in the January 4, 2007, *New England Journal of Medicine* that showed increased rates of valvular dysfunction in Parkinson's patients who were taking the drug. These findings coupled with the availability of other dopamine agonists prompted the FDA's action. Valeant Pharmaceuticals is removing Permax brand pergolide as are all generic manufacturers. ■

Hormone Treatment, Does Timing Matter?

Further analysis of the Women's Health Initiative suggests that the timing of the initiation of hormone therapy may have an effect on the risk of cardiovascular disease. The analysis looked at postmenopausal women who had undergone a hysterectomy and were randomized to conjugated estrogen or placebo and women who had not had a hysterectomy who were randomized to conjugated estrogen plus medroxyprogesterone or placebo. The main outcomes were coronary heart disease (CHD) and stroke. Women who initiated hormone therapy within 10 years of menopause had a lower incidence of CHD (HR 0.76 [95% CI, 0.50-1.16]), which equates to 6 fewer events per 10,000 person-years. For women who initiated therapy 10-19 years after menopause the hazard ratio was 1.10 (95% CI, 0.84-1.45), and for women who initiated therapy 20 years after menopause the hazard ration was 1.28 (95% CI, 1.03-1.58) or 12 excess events per 10,000 person years. CHD risk increased when patients were stratified by age as well. Hormone therapy increased the risk of stroke with no significant difference based on time since menopause or age. There was a non-significant trend for improved overall mortality in younger women. The authors conclude that women who initiated hormone therapy closer to menopause had a reduced risk of CHD, with an increase risk among women more distant from menopause although the trends did not meet their criteria for statistical significance (*JAMA*. 2007:297;1465-1477.). ■

FDA Actions

The FDA has approved Cangene's immune globulin to prevent reinfection with the hepatitis B virus in certain liver transplant patients. The product was previously approved for preventing hepatitis B infection after exposure in 2006. It is marketed as HepaGam B.

The FDA has banned rectal suppositories that contain trimethobenzamide due to lack of efficacy in preventing nausea and vomiting. The popular suppositories have been marketed under various trade names including Tigan, Tebamide, T-Gen and others. The drug will still be available as oral and injectable preparations. The evaluation which eventually led to the withdrawal is part of the FDA's ongoing Drug Efficacy Study Implementation (DESI) which evaluates older drugs previously approved based on safety data to make sure that they are also effective.

The FDA has approved Merck's combination diabetes drug Janumet, which combines sitagliptin with metformin. Sitagliptin, which is a dipeptidyl peptidase-4 inhibitor, has been marketed by Merck since last October under the trade name "Januvia." The combination is approved for the treatment of patients with type 2 diabetes; it should be dosed twice daily with meals with gradual dose escalation. ■