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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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INSIDE

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Clinical Cardiology Alert's physician editor, Michael H. Crawford, MD, is on the speaker's bureau for Pfizer.
The peer reviewer, Rakesh Mishra, MD, reports no consultant, stockholder, speaker's bureau, or other financial relationship with any company related to this field of study.

Ranolazine for ACS

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: Scirica BM, et al. Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non-ST-segment-elevation acute coronary syndrome. Results from the metabolic efficiency with ranolazine for less ischemia in non-ST-elevation acute coronary syndrome-thrombolysis in myocardial infarction 36 (MERLIN-TIMI 36) randomized controlled trial. *Circulation*. 2007;116:1647-1652.

THIS REPORT FROM THE MERLIN-TIMI 36 INVESTIGATORS DESCRIBES the effects of ranolazine on spontaneous arrhythmias in patients with acute coronary syndrome (ACS). The MERLIN-TIMI 36 trial was designed to assess the effects of ranolazine on cardiovascular deaths and recurrent ischemic events in patients who presented with ACS. The primary end point results for the trial showed trends in favor of ranolazine therapy that were not statistically significant and that had not been previously reported (*JAMA*. 2007;297:1775-1783). The MERLIN-TIMI 36 trial included continuous days of ECG monitoring during the first 7 days of therapy.

In MERLIN-TIMI 36, patients with a non-ST elevation ACS were randomized to intravenous followed by oral ranolazine vs placebo, in addition to standard medical therapy. Patients underwent continuous ECG (cECG) monitoring during the first 7 days of therapy. Satisfactory cECG data were available from 6351 patients. Several observations were reported. Ranolazine therapy resulted in a significant reduction in the frequency of nonsustained ventricular tachycardia. Analyses were performed for nonsustained episodes of ≥ 3, 4, or 8 beats duration, and the relative risks associated with ranolazine were 0.86, 0.71, and 0.63, respectively. Sustained VT was uncommon (0.44%), and there was no difference between the ranolazine and control groups. New onset atrial fibrillation was also less frequent in the ranolazine group, but the difference between groups was not statistically significant (1.7% vs 2.4%, $P = 0.08$). The incidence of sudden cardiac death during the first year of therapy was not significantly

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affected by ranolazine, with 56 sudden deaths (1.7%) in the ranolazine group vs 65 (1.8%) in the placebo group.

Scirica and colleagues concluded that ranolazine has an overall beneficial effect on cardiac arrhythmias in patients with ACS.

COMMENTARY

Ranolazine was recently introduced for treatment of angina. During the drug's clinical development, it was shown to produce mild prolongation of the QT interval. Subsequent studies showed that ranolazine inhibits both the delayed rectifier potassium current (IKr) and the late inward sodium current (INa). The IC50 for INa inhibition is lower (6 µmol/L) than the IC50 for IKr (12 µmol/L). In experimental preparations, this combination of effects has been shown to have antiarrhythmic rather than proarrhythmic effects. Due to the question of QT prolongation, a long-term safety study in a moderate- to moderate-to-high-risk population was required for final approval of the drug. The MERLIN-TIMI 36 study design included systematic prolonged ECG monitoring to assess the effect of ranolazine on spontaneous arrhythmias in such a population. The data in this report. show that ranolazine does not result in proarrhythmia. Further studies will be needed to see if ranolazine's electrophysiologic actions can lead to its use as an antiarrhythmic drug. Based on the limited data available now, the effects seen on arrhythmias may only be due to a modest improvement in myocardial ischemia. ■

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Cognitive Decline After CABG

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Djaiani G, et al. Continuous-flow cell saver reduces cognitive decline in elderly patients after coronary bypass surgery. *Circulation*. 2007;116:1888-1895.

Cognitive decline after surgery requiring cardio-pulmonary bypass (CPB) may be due to cellular debris picked up by the cardiotomy suction device. Cell savers, which clean and process shed blood prior to retransfusion, are used extensively during non-cardiac surgery, but have not been systematically studied in cardiac surgery. Thus, Djaiani and colleagues from Toronto, Canada, hypothesized that using a cell saver instead of the cardiotomy sucker would reduce cognitive decline after CABG. A cohort of 226 patients > age 60 years scheduled for CABG were randomized to cell saver or control with cardiotomy suction. Exclusion criteria included redo surgery, other cardiac surgery required, emergency surgery, symptomatic cerebrovascular disease, or atrial fibrillation. A preoperative transesophageal echo was done to exclude a cardiac source of emboli. Transcutaneous Doppler detected emboli were assessed during aortic clamping in a subgroup of patients. Neuropsychological testing was performed one week before surgery and 6 weeks after.

Results: Baseline data were not different in the 2 groups. Cognitive dysfunction occurred in 6% of the cell saver group and 15% of the control patients (P = .038). Cognitive improvement occurred in 19 vs 17% of patients (P = NS). There was no difference in aortic atheroma. Doppler embolic counts, which could be done in about one third of patients, was 90 in the cell saver group and 133 in the control (P = NS). Retransfusion blood volume was a median of 800 mL in the control group and 401 mL in the cell saver group. Djaiani et al concluded that processing shed blood with a cell saver before retransfusion resulted in a clinically significant reduction in cognitive dysfunction post CABG.

COMMENTARY

A cardiotomy suction device that returns blood from the pericardium and thorax to the patient's circulation is an integral part of CPB that reduces blood loss and blood transfusion requirements. However, this blood has been shown to contain high levels of lipid microparticles and cellular debris, which can cause microem-

bolization of the brain. These microemboli are likely an important cause of cognitive decline after cardiopulmonary bypass. Previous studies have documented significant cognitive declines in 7-14% of patients undergoing cardiopulmonary bypass, about half of which are frank strokes, probably due to large emboli from cellular debris. The other half are more subtle declines detectable by neuropsychological testing and are probably due to microemboli from lipids. Cell savers, which are used extensively in other types of vascular surgery, separate red blood cells from plasma and debris by washing and differential centrifugation. In this study, their use decreased cognitive decline by 60% and eliminated stroke. Interestingly, Transcranial Doppler emboli counts were not different, suggesting that these come mainly from aortic manipulation, which would not be affected by the cell saver. Thus, the cell saver's effect on reducing cognitive decline is probably due to removing lipid microparticles and smaller cellular debris. Also, the cell saver removes inflammatory mediators in the plasma, which may decrease the inflammation reaction to microemboli.

The cell saver increases hemoglobin during the first 24 hours after surgery, but also increases INR by removing clotting factors and reducing platelets. Blood loss and transfusion requirements were the same in both groups in this study, but 2 times more fresh frozen plasma was administered to the cell saver group.

This study suggests that efforts to reduce aortic manipulation (large emboli prevented) and decrease lipid microembolization from the cardiotomy suction devices will have a major benefit on cognitive function after cardiopulmonary bypass. Whether the cell saver system will become the preferred technique for the latter will require more study, since it may have adverse effects on hemeostasis. ■

Minimal Extracorporeal Circulation vs Off-Pump CABG

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Mazzei V, et al. Prospective randomized comparison of coronary bypass grafting with minimal extracorporeal circulation system (MECC) versus off-pump coronary surgery. *Circulation*. 2007;116:1761-1767.

OFF-PUMP CABG AVOIDS THE COMPLICATIONS OF CARdiopulmonary bypass (CPB), but is technically demanding. Thus, a minimal extracorporeal circulation (MEC) system was developed and has been shown to be superior to standard CPB. In this study, MEC is compared to off-pump CABG in 300 patients selected from 395 patients who were scheduled for elective CABG alone and were deemed candidates for either operative technique. Excluded were patients with single vessel disease and those with an inflammatory disease diagnosis. The operative technique was randomly assigned. The primary end point was release of biomarkers reflecting myocardial injury or an inflammatory state (CK, IL-6, S-100). All patients had a median sternotomy. The left internal thoracic artery was used for the left anterior descending artery and its branches, and saphenous veins were used for other vessels. Operative results and outcome at one year were also noted.

Results: In-hospital mortality was similar (MEC 1.4% vs 2% off-pump), and there were no significant differences in morbidity. Biomarkers were not significantly different, but there was a trend toward lower S-100 values off-pump (0.13 vs 0.19 pg/mL, $P = 0.058$). Length of stay and use of blood products were similar. Long-term outcomes were not significantly different. Mazzei and colleagues concluded that post-operative morbidity and mortality with MEC is comparable to off-pump. Consequently, MEC may achieve the benefits of off-pump, but permit more complete revascularization in patients not technically suitable for off-pump surgery.

COMMENTARY

Off-pump CABG is attractive, but complete revascularization is not always possible, and long-term studies have shown higher graft conclusion rates as compared to on-pump CABG. This study suggests that MEC may be an attractive option for patients not technically suitable for off-pump CABG. Tissue injury and inflammatory markers were not significantly different, although there was a trend toward lower S-100 levels, a presumed marker of brain injury with off-pump surgery. Clinical outcomes were also not different, but the study was underpowered for these end points.

MEC is a fully heparinized, short-closed loop circuit without a cardiotomy reservoir. This minimized blood contact with air and foreign surfaces. Blood is drained from the right atrium into a centrifugal pump and membrane oxygenator and then returned to the ascending aorta. A pericardial suction line is filtered, resulting in a cell saver type system that removes debris. Also, a cardioplegic arrest line is present. The system reduces systemic heparinization by 50% and reduces inflammatory cytokines to levels seen in off-pump cases.

Inflammation is thought to be a major contributor to myocardial damage with CABG. There were no differences in strokes between the 2 techniques, but neuropsychologic testing was not performed.

After 50 years of use, CPB is being challenged by newer techniques that reduce the adverse effects of this device. At this point, the newer techniques have only been applied to selected patients because of their own limitations. As attractive as off-pump surgery seems, it is just not universally applicable if complete revascularization is the goal. Thus, MEC looks very attractive, as it reduces inflammatory and microembolic organ damage. However, it still requires manipulation of the ascending aorta, a potential source of macro cerebral emboli. Large studies will be required to fully assess clinical outcomes with MEC, but we may be at the threshold of a new safer way to operate on the heart. ■

Weight Gain: Predictor of Heart Failure Hospitalization

ABSTRACT & COMMENTARY

By Andrew Boyle, MBBS, PhD

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

Source: Chaudhry SI, et al. Patterns of weight change preceding hospitalization for heart failure. *Circulation*. 2007; 116:1549-1554.

Weight gain has long been used as a marker of fluid retention in heart failure patients. It is a cheap, simple test that can be performed daily in patients' homes. Heart failure hospital admissions are a considerable strain on health budgets and, therefore, a number of strategies aimed at preventing recurrent hospitalizations are being implemented. Increasingly, strategies for remote monitoring of patients who remain at home are being developed, and heart failure is an obvious target where these interventions may prevent hospitalization and reduce health care costs. However, studies delineating the pattern of weight gain in ambulatory heart failure patients using remote monitoring have been lacking.

Chaudhry and colleagues studied patients enrolled in a home-based remote heart failure monitoring program that consists of daily weight transmitted via telephone line to a central location that is monitored by trained cardiac nurses. From over 10,000 patients, 393 had at least one heart failure admission over the 18-month follow-up period. They were able to match 134 patients who had heart failure hospital admissions with 134 patients who did not with age, gender, weight at enrollment, NYHA class, and month of enrollment. Mean patient age was 74 years; 55% were female, and the vast majority of patients were in NYHA class III heart failure. They showed that patients started to increase weight by around 1 pound approximately 30 days before admission due to heart failure. This was maintained until 2 weeks before admission, when patients started to gain more weight, and this pattern accelerated in the week prior to admission. They showed that the amount of weight gained in this cohort predicted the likelihood of hospital admission for heart failure. Compared to those whose weight changed < 2 pounds, the odds ratio (OR) for heart failure admission for a weight gain of 2-5 lbs was 2.77, for weight gain 5-10 lbs OR was 4.46, and for > 10 lbs weight gain OR was 7.65. From the same cohort, they chose a group of patients who were admitted to hospital for non-heart failure reasons, and matched them with a control cohort. There was no weight gain prior to non-heart failure admissions. Chaudhry and colleagues concluded that increases in weight in moderate-to-severe heart failure patients are associated with subsequent admission for heart failure and occur at least one week before admission.

■ COMMENTARY

Although weight gain has long been a surrogate for fluid retention in heart failure, the current study is important for several reasons. Firstly, they have demonstrated that a simple, safe test can be performed in patients' homes and remotely recorded accurately enough to allow prediction of a clinical event. This lends validity to the ongoing search for remote monitoring parameters for heart failure patients to prevent readmission. Secondly, it shows that fluid retention precedes admission to hospital by quite a long time, with weight gain being seen in the week prior to admission, but may be seen as much as 30 days prior to admission. This delineates a window of opportunity wherein interventions may be initiated to prevent hospitalization (eg, increase diuretic dose), but this remains to be studied in prospective clinical trials.

The study is limited by the small number of patients included from the overall cohort. This was due to problems matching them with controls, or by withdrawal due to early hospitalization in the initial 30 days, which was a pre-specified exclusion criterion. Also, the majority of patients were in NYHA class III and, therefore, the

results may not be generally applicable to patients throughout the spectrum of heart failure. Additionally, Chaudhry et al did not assess any other clinical variables, such as shortness of breath or peripheral edema, which may also predict heart failure hospitalization. No conclusion can, therefore, be drawn about the relative contribution of weight gain over other clinically-reported symptoms in predicting heart failure hospitalization. However, the study is strengthened by how well the patients were matched with controls.

This study sets the stage for a new era in heart failure trials utilizing remote monitoring for prevention of hospitalization. Chaudhry et al conclude that increases in body weight in a heart failure population are associated with hospitalization for heart failure, and that these changes are seen at least a week before admission. Remote monitoring of weight may identify a high-risk period during which interventions to avert decompensated heart failure may be beneficial. ■

Sildenafil and Exercise Capacity in Heart Failure

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

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

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

Source: Lewis GD, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. *Circulation*. 2007; 116:1555-1562.

An interesting therapeutic concept that has been put into clinical practice in the past several years is the use of nitric oxide donors for pulmonary hypertension. This report assesses subjects with significant pulmonary hypertension and with severe left ventricular failure and right ventricular dysfunction. Sildenafil (SIL), better known as Viagra, is a selective inhibitor of the PDE, which is "the predominate PDE isoform responsible for hydrolysis of intracellular cGMP in the pulmonary vasculature." This group previously reported a 6-month study of SIL in heart failure patients with pulmonary hypertension and normal LV function, with favorable results on exercise capacity in subjects given SIL in a double blind protocol. The present trial evaluates the effectiveness of SIL in patients with pulmonary hypertension related to impaired left ventricular systolic function (EF < 0.4) and class II-IV chronic heart failure on standard CHF therapy. Pulmonary hypertension was defined by a mean PA pressure of > 25. Thirty-four subjects were entered into the protocol and randomized to 50 mg of placebo or SIL 3 times daily for 12 weeks.

A wide variety of measurements were made, including right heart catheterization, blood gas, respiratory gas exchange during exercise, oxygen uptake, carbon dioxide output, respiratory gas exchange ratio, right-sided intra-cardiac pressures and cardiac output. Systemic and pulmonary vascular resistance was calculated. Exercise testing was measured by cardiopulmonary exercise testing with upright cycle ergometry and respiratory gas exchange. Rest and exercise first pass radionuclide ventriculography of the right and left ventricle was carried out both before and during exercise. The ejection fraction of each ventricle was calculated by standard nuclear techniques, as were LV end RV and diastolic volumes. A robust statistical analysis was utilized.

Results: Baseline cardiopulmonary testing was similar in the active SIL and placebo. Several patients required up titration of diuretics. All patients surpassed their anaerobic threshold and achieved reparatory exchange ratios over 1.0, consistent with maximum exercise effort. The primary outcome, Vo_2 at peak exercise increased in SIL patients (12.2 ± 0.7 to 13.9 ± 1.0); placebo patients had no change in Vo_2. Cardiac output increased, only in the SIL group, whose peak Vo_2 correlated directly with the baseline resting PVR and RVEF. An improvement in RVEF in the SIL group was observed at rest and during exercise; placebo patients had no change. Neither group received any effect on LVEF or LV diastolic volume.

Hemodynamic Measurements: The SIL patient had a decrease in resting PVR and PVR/SVR that was statistically significant, but there was no change in systemic and pulmonary artery pressures, wedge pressure, or cardiac index. PVR at peak in exercise with SIL fell by 23 ± 6%, $P = 0.008$ vs baseline, with an increased peak exercise cardiac output vs baseline.

Quality of life (Minnesota Living with Heart Failure Score) improved with SIL patients but not placebo (53% vs 7%) and worsened in 13% of SIL group vs 27% of placebo patients. Three patients were not able to complete the 12-week trial. Adverse events were infrequent. There were fewer hospitalizations for heart failure in the SIL treatment patients (2 vs 7, $P = 0.046$).

Long-term follow-up of the 29 patients in this study is reported, with 15 subjects continuing to take SIL for up to 6 months while three completed the 12-week trial

only. Long term benefit in a 6 minute walk was noted in those who took SIL for greater than 6 months. There were no deaths or adverse experiences, with sustained improvement in exercise capacity in the SIL group over 6 months. The drug was well tolerated and resulted in fewer hospital admissions than the placebo group. The improvement in peak Vo_2 and 6-minute walk in this trial was a finding which suggested a prior trial using a single dose administration of SIL, which resulted in improvement in a variety of parameters. Right heart systolic function was improved, "likely attributable to afterload reduction because SIL reduced PVR." Of interest, the patients with the higher PVR had the greatest improvement in exercise capacity.

Lewis and colleagues conclude, "The present study is the first to suggest that prolonged administration of a selective PDE5 pulmonary vasodilator improves capacity in patients with heart failure. The improvement in quality of life in patients with SIL likely reflects enhanced exercise capacity." Lewis et al discuss the poor outcome of patients who have heart failure and RV dysfunction, and note that prior studies with pulmonary vasodilators (bosentan, epoprostenol) have had no positive effects. They cite the AAHFT study using isosorbide dinitrate and hydralazine, and emphasize that the drug is a nitric oxide donor and that it may be that the "common signaling pathway involving cGMP may provide additional benefits for currently approved pharmacotherapies for heart failure." It should be stressed that as opposed to nitrates, SIL is a selective pulmonary vasodilator and tolerance is yet to be described. Finally, Lewis et al stress that "this study should be considered a pilot trial because of the small sample size." At the same time, they suggest that there may be broad applicability to the use of PDE5 inhibitors, which deserve further investigation, and then suggest that PDE5 inhibition may be an important adjunctive therapy for patients with congestive heart failure and pulmonary hypertension if larger studies confirm these results.

COMMENTARY

This is a modest pilot study that potentially packs a wallop! While SIL was the first agent released for erectile dysfunction, it is of interest that originally Pfizer was testing this compound for angina in patients, presumably because of its vasodilator effects. The hemodynamic benefits of SIL and other nitric oxide inhibitors are well known. It would be ironic if these drugs turn out to have a much greater use, particularly in the very ill patient with depressed right and left ventricular function and pulmonary hypertension. This group of individuals are extremely frustrating, even though experienced practitioners use all of the resources available, including aldosterone blockade, ACE inhibition, beta blockade, etc. It will be of considerable interest to see the results of additional trials using larger cohorts for the assessments of efficacy and side effects following the promising outcomes in the first 2 (small) trials reported by this group. ■

Statin Therapy with Major Vascular Surgery

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Feringa HHH, et al. Intensity of statin therapy in relation to myocardial ischemia, troponin t release, and clinical cardiac outcome in patients undergoing major vascular surgery. *J Am Coll Cardiol*. 2007;50:1649-1656.

Cardiac death and perioperative myocardial infarctions occur in 2-20% (mean 6) of major non-cardiac vascular surgery. Statins have been shown to have a protective effect, but the exact mechanism of this benefit is unclear. Thus, Feringa and colleagues from the Netherlands and Wisconsin prospectively studied 359 patients undergoing major vascular surgery (aorta, carotid, peripheral arteries). Statin doses and cholesterol levels were noted preoperatively. Starting one day before surgery, 72-hour continuous ECG monitoring was performed, and troponin T was measured on days 1, 3, 7 and pre-discharge after surgery. The main cardiac events were cardiac death or Q wave infarction. Patients with ECG confounders, such as bundle branch block, atrial fibrillation, left ventricular hypertrophy, or who had had a myocardial infarction < 6 months prior, were excluded. Beta-blockers were advised for all patients to keep heart rate in the 60-65 range. Also, all patients had dobutamine stress echoes prior to surgery, and were managed accordingly. Revascularization was not mandated unless appropriate for reasons not related to the surgery. Propensity analysis was used to correct for selection biases.

Results: A total of 52% of the patients were receiving statins, most of them for > 3 months. These patients were more likely to have had a prior stroke and hypercholesterolemia, but there were no differences in the occurrence of coronary artery disease, diabetes, or a positive dobutamine stress echo. Ischemic episodes by 72-hour ECG occurred in 29% of the patients, and were significantly less in those on statins and those with lower LDL

cholesterol levels. Troponin release occurred in 23% of the patients, and was also less likely in those on statins and with lower LDL cholesterols. Deaths occurred in 3%, and Q wave infarctions in 1% of the patients in 30 days and were less frequent in those on statins and with low LDLs. Late events (mean 2.3 years) were also reduced by statins. Heart rate variability was greatest before surgery and least during surgery. Lower values before and during surgery predicted troponin leaks and ischemia. Higher statin doses were associated with fewer cardiac events and higher heart rate variability. Feringa et al concluded that higher statin doses and lower LDL cholesterol levels predict less perioperative myocardial ischemia, troponin release, and cardiac events with major vascular surgery.

COMMENTARY

This study supports previous observational studies which have suggested that statin therapy and lower LDL cholesterol values predict less cardiac events with major vascular surgery. This study adds some mechanistic data that seem to support beneficial non-lipid lowering effects of statins, or the so called pleotropic effects. The higher the statin dose, the more the heart rate variability even adjusted for cholesterol levels. This suggests that statins may affect the autonomic nervous system. Also, the observation that ECG myocardial ischemia was less on statins even adjusted for cholesterol levels suggests that effects of statins, such as reduction of inflammatory markers, increased nitric oxide, and improved endothelial function, may be important in the perioperative period. In addition, statins may stabilize plaques which would explain the lower incidence of troponin leakage, Q wave infarction, and death.

These results suggest that all vascular surgery patients should be treated with statins perioperatively regardless of their cholesterol levels. In this study, only 52 % were on stains. Also, the study suggests that doses > 50% of maximum recommended doses are more effective. Unfortunately, we don't have prospective, randomized trails to identify the best candidates for statins, the right dosage/agent, or the duration of therapy, especially preoperatively. In addition, this study has limitations. Although various statistical adjustments were made, the effect of selection biases in this observational study can never be fully elucidated. The inclusion of carotid surgery patients may have confounded the heart rate variability data, since carotid manipulation can affect autonomic tone. The observations in this study can only be applied to major vascular surgery and not necessarily in other high risk surgery or in other high-risk patients. Finally, about 75% of the patients in this study were on beta-blockers, which are recommended by the most recent guidelines for the management of high-risk perioperative patients. Thus, the results were seen on top of this therapy. The current guidelines do not recommend statins due to the lack of randomized trials, but also do not discourage their use (*Circulation*. 2007; 116:1971-1996). ■

Sex Differences in ICD Use

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Lesley H et al. Sex Differences in the Use of Implantable Cardioverter-Defibrillators for Primary and Secondary Prevention of Sudden Cardiac Death. JAMA. 2007;298:1517-1524.

Lesley and colleagues analyzed a 5% national sample of Medicare inpatient, outpatient, and carrier files to examine the use of ICD therapy for both primary and secondary prevention of sudden cardiac death. Patients classified as having a primary prevention indication had a diagnosis of acute myocardial infarction and either heart failure or cardiomyopathy. Patients with a secondary indication had a prior diagnosis of cardiac arrest or ventricular tachycardia. Data on gender and comorbid conditions were collected and analyzed. The proportion of patients in each cohort who received ICD therapy was then analyzed

The analysis eventually included 136,420 individuals in the primary prevention cohort and 99,663 individuals in the secondary prevention cohort. The mean age was approximately 78 years, and approximately 9% of the total group was black. From 1999 through 2005, there was a 4-fold increase in the one year cumulative incidence of ICD use among men. A similar pattern was noted among women, but the absolute rates of ICD use were approximately 75% lower.

In the secondary prevention cohort, rates of ICD use among men more than doubled between 1999 and 2004. Absolute rates were lower among women and increased only slightly during the course of the study. When ICD use rates were controlled for comorbid conditions, geographic region, and year of cohort entry, men continued to be more likely to receive ICD therapy than women, with a hazard ratio of 3.15. It was also noted that black patients were less likely than white patients to receive ICD therapy, with a hazard ratio of 0.85.

In the secondary prevention cohort, men were still

more likely than women to receive ICD therapy, with a hazard ratio of 2.44, and black patients were again less likely than white patients to receive ICD therapy with a hazard ratio of 0.71. The presence of dementia, chronic renal disease, and metastatic solid tumor were independently and negatively associated with ICD use. When the group was analyzed according to age ≤ 75 years, men were still more likely to receive ICD therapy in both the primary and secondary prevention cohorts.

The relationship between ICD use and mortality were also examined. The hazard ratio for mortality was 17% lower in the first 180 days, but this difference was not statistically significant. Adjustment for comorbid conditions, year of cohort entry and probability of treatment, however, showed that the hazard of mortality at one year was not significantly lower. However, in the secondary prevention cohort, the hazard for mortality was 37% lower among patients who received an ICD within 30 days of cohort entry. After adjustment for age, comorbid conditions, years, and cohort entry and probability of treatment, the hazard of mortality remained significantly lower, with a hazard ratio of 0.62 for men and 0.68 for women.

Lesley et al concluded that in a representative sample of Medicare beneficiaries, men were 3.2 times more likely to receive ICD therapy for primary prevention and 2.4 times more likely than women to receive ICD therapy for secondary prevention. Thus, there may be factors unaccounted for in this study that explain the differences observed.

COMMENTARY

This paper documents that among US Medicare recipients, men, particularly white men, are more likely than women to receive ICD therapy. In the primary prevention cohort, Lesley et al weren't able to use data concerning left ventricular ejection fractions since this information is not included in the National Medicare Database. Since women are more likely to have symptoms of congestive heart failure with preserved systolic function, this may account for much of the difference in ICD utilization in the primary prevention cohort. However, in the secondary prevention cohort, the reason for the gender discrepancy is less apparent. It may be possible that women may have more arrhythmias that were thought to be due to transient causes, but this can't be determined from this database. Another factor that may influence physicians is that women tend to have more technical complications with ICD implants. In thin or frail individuals, device erosion or pocket problems are more common, and many elderly women would fall into this category. ■

CME Questions

68. Minimal extracorporeal circulation vs off-pump CABG results in:
a. lower inflammatory biomarkers.
b. higher inflammatory biomarkers.
c. no difference in inflammatory biomarkers.
d. None of the above

69. A cell saver system with cardiopulmonary bypass results in:
a. a 50% reduction in cognitive decline.
b. no difference in cognitive function.
c. higher levels of clotting factors.
d. no difference in clotting factors.

70. Statin use with non-cardiac major vascular surgery results in:
a. less myocardial ischemia.
b. less troponin leak.
c. less cardiac events.
d. All of the above

71. ICD use for primary and secondary prevention is more prevalent in:
a. white women.
b. white men.
c. black women.
d. black men.

72. The use of ranolazine for ACS results in:
a. fewer cardiac events.
b. lower mortality.
c. fewer ventricular tachyarrhythmias.
d. less sudden death.

Answers: 68. (c); 69. (a); 70. (d); 71. (b); 72. (c)

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. ■

CLINICAL CARDIOLOGY ALERT®
A monthly update of developments in cardiovascular disease

CUMULATIVE INDEX

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yes ○ no ○ 1. Are you able to describe new findings in differential diagnosis and treatment in your field?

yes ○ no ○ 2. Are you able to describe controversies, advantages, and disadvantages of those advances?

yes ○ no ○ 3. Are you able to describe cost-effective treatment regimens?

yes ○ no ○ 4. Are you able to describe the pros and cons of new screening procedures?

yes ○ no ○ 5. Were these objectives consistent with the overall goal of the newsletter?

yes ○ no ○ 6. Were the test questions clear and appropriate?

yes ○ no ○ 7. Were you satisfied with the customer service for the CME program?

yes ○ no ○ 8. Did this activity change your clinical practice? If so, how? _____

9. How many hours do you estimate it will take you to complete this entire semester (6 issues) activity? Please include time for reading, reviewing, answering the questions, and comparing your answers to the correct ones listed. _____ hours

10. Do you have any general comments about the effectiveness of this CME program?
_____

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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.

Adult Immunization Guidelines from CDC Released

In this issue: *Updated Immunization Guidelines from the CDC; Do antivirals have a role in the treatment of Bell's palsy? Topiramate is a promising treatment for alcohol dependence; and FDA Actions.*

The *Annals of Internal Medicine* has published updated Adult Immunization Guidelines from the CDC as an early release article on their website dated October 18. Full guideline will be available in the November 20 print edition. The guideline has several important changes and updates.

The new herpes zoster vaccine is added to the guideline this year. The vaccine should be given routinely to all immunocompetent adults age 60 and older. It is not recommended for immunocompromised adults as it is a live attenuated virus. The vaccine is given once in a lifetime, and does not require a booster.

The new human papilloma virus has also been added. The vaccine protects against 4 types of HPV, which causes 90% of genital warts and 70% of cervical cancers. It is recommended for women aged 11 to 26 years. It requires three doses given at zero, 2 and 6 months. It should not be given to pregnant women.

The new pertussis vaccine is coupled with diphtheria and tetanus to form Tdap (Adacel- Sanofi Pasteur). This is a 1-time, 1-dose vaccine that should be given to all adults age 64 or younger when they are scheduled for their next tetanus (Td) booster. Tetanus boosters should be given every 10 years, but the interval may be shortened to as little as two years for high-risk patients including postpartum women, close contact of infants younger than 12 months of age, and all healthcare workers with direct patient contact. It has not been tested in adults age 65 or older. This vaccine is different from the previously approved Tdap for adolescents aged 10 to 19 (Boostrix-GlaxoSmithKline).

There are now 15 indications for influenza vaccine. New indications include those who have difficultly handling respiratory secretions or have increased risk of aspiration. All women who are pregnant or will be pregnant during the flu season should be vaccinated. All healthcare workers should be vaccinated unless they have strong contraindications.

Hepatitis B vaccine recommendations have changed, and the vaccine is now recommended for all sexually active adults who are not in a long-term mutually monogamous relationship.

Because of several recent large-scale mumps outbreaks in this country, a mumps vaccine booster is now recommended for specific age groups, especially adults who work in healthcare settings. The standard is to give MMR, even if immunity exists for one or more of the components of MMR.

The pneumococcal vaccine recommendations remain the same. The vaccine should be given at age 65 unless the patient has specific risk factors, in which case it should be given to those younger than 65. A small subgroup of patients should be given a second booster. If the vaccine was initi-

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ated under age 65 for high-risk patients, a booster should be given at age 65 or five years after the initial vaccine. If the vaccine was initiated over age 65, a booster should only be given to immunocompromised patients after five years. The vaccine should not be given every five years (a common misconception). In fact, no one should receive more than two doses under any circumstances. There is even some evidence that more than two doses may be harmful and could potentially attenuate the immune response.

Antivirals and Bell's Palsy?

Do antivirals have a role in the treatment of Bell's palsy? This question has been debated for decades, with several small studies indicating a relationship between herpes simplex infections and facial paralysis. Despite this, treatment with acyclovir or valacyclovir has not been proven to be effective in treating Bell's palsy. Regardless, antivirals are frequently prescribed along with oral steroids. A new study confirms that steroids are useful, but antivirals are not. Nearly 500 patients with new onset of Bell's palsy were randomized to 10 days of treatment with prednisolone, acyclovir, both agents, or placebo. The primary outcome was recovery of facial function. At three months, the proportion to patients who had recovered facial function were 83.0% in the prednisolone group compared with 63.6% among patients who did not receive prednisolone ($P < 0.001$) and 71.2% in the acyclovir group as compared to 75.7% among patients who did not receive acyclovir (adjusted $P = 0.50$). After nine months, recovery was 94.4% for prednisolone and 81.6% for no prednisolone ($P < 0.001$) and 85.4% for acyclovir and 90.8% for no acyclovir (adjusted P = 0.10). For patients treated with both drugs, recovery was 79.7% at 3 months ($P < 0.001$) and 92.7% at nine months ($P < 0.001$). There were no serious adverse effects in either group. The authors conclude that early treatment with prednisolone significantly improves the chance of complete recovery, while there's no evidence of benefit with acyclovir alone or in combination with the steroid (*NEJM*. 2007; 357:1598-1607).

Topiramate Promising for Alcohol Treatment

Topiramate is a promising treatment for alcohol dependence according to a new study. The drug was shown to be effective in this role in a small study published in 2003. This new, larger multisite 14 week double-blind, randomized, placebo controlled trial enrolled 371 men and women age 18 to 65 years who were diagnosed with alcohol dependence. Up to 300 mg per day of topiramate was given to 183 participants while 188 were treated with placebo. Both groups were enrolled in a weekly compliance enhancement intervention program. The primary end point was self-reported percentage of heavy drinking days, while secondary outcomes included other self-reported drinking measures along with laboratory measures of alcohol consumption. Topiramate was more efficacious than placebo at reducing percentage of heavy drinking days from baseline to 14 weeks (mean difference 8.44%; 95% CI, 3.07%-13 .80%; $P = .002$). Topiramate also reduced all of the drinking outcomes ($P <.001$ for all comparisons). Adverse events were more common with topiramate, including paresthesia (which occurred in over 50% of those on the drug), taste perversion, anorexia and difficulty with concentration. In general, however, the drug was safe and consistently efficacious for treating alcohol dependence (*JAMA*. 2007;298:1641-1651). An accompanying editorial points out that the benefits of topiramate were still increasing at the end of the study, indicating the longer treatment may be more effective (*JAMA*. 2007;298:1691-1692).

FDA Actions

The FDA has announced new warnings on phosphodiesterase type 5 inhibitors regarding hearing loss. The drugs include sildenafil (Viagra, Revatio), tadalafil (Cialis) and vardenafil (Levitra). The agency has received 29 cases of sudden hearing loss associated with use of the drugs dating back to 1996. Most cases were unilateral and temporary.

Modafinil (Provigil) has also been the subject of new warnings including serous rashes and psychiatric symptoms. The drug, which is used for narcolepsy, obstructive sleep apnea, shiftwork disorder, and multiple sclerosis, has been associated with severe rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. The FDA suggested caution should be exercised when modafinil is given to patients with a history of psychosis, depression, or mania.

An FDA advisory panel has recommended restricting childhood cold medications to children over the age of six years. They also recommend strong limits on marketing these products for younger children. This follows a voluntary withdrawal from the market of infant cough and cold medications by most manufacturers of these products. Voluntary withdrawal involves medications used in children younger than two years. The drugs that contain decongestants and antihistamines have been associated with more than one hundred deaths since 1969. ■