Providing Evidence-based Clinical Information for 25 Years

CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Financial Disclosure:

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.

Late Stent Thrombosis

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Daemen J, et al. Early and Late Coronary Stent Thrombosis of Sirolimus-Eluting and Paclitaxel-Eluting Stents in Routine Clinical Practice: Data from a Large Two-Institutional Cohort Study. *Lancet*. 2007;369:667-678.

DESPITE THEIR ADVANTAGES IN PREVENTING RESTENOSIS, drug-eluting stents (DES) have recently been found to be at risk for late stent thrombosis. Because of the popularity of DES there has been considerable interest in this problem. Thus, these investigators from Europe present their long-term experience with sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) used at 2 large academic referral hospitals between 2002-2005. During these 3 years, 8,146 patients underwent percutaneous intervention (PCI) with these 2 stents (3823 SES and 4,323 PES). Patients who received SES had more hypertension, dyslipidemia, diabetes, and smoking. Patients treated with PES were more likely to have acute coronary syndrome and receive more and longer stents. Angiographically proven stent thrombosis occurred in 152 patients for a cumulative incidence of 2.9% over 3 years. Early stent thrombosis (0-30 days) occurred in 60% and late (> 30 days) in 40%. Late stent thrombosis occurred at a constant rate of 0.6% per year. Early stent thrombosis was similar for SES (1.1%) per year and PES (1.3%), but more late stent thrombosis was observed with PES (1.8%) vs SES (1.4%, $P = 0.03$). Aspirin was recommended indefinitely, but clopidogrel 75 mg/day was advised for at least 6 months with PES and at least 3 months for SES unless the case was complex and then 6 months was recommended for SES. One of the 2 hospitals recommended 12 months of clopidogrel for all stents. At the time of stent thrombosis, dual antiplatelet therapy was being taken by 87% of patients with early thrombosis. Of those with late thrombosis, 51% were on single-drug therapy, 23% on dual therapy, and 26% were on no antiplatelet therapy. Of the patients on aspirin monotherapy who had late stent thrombosis, in 97% thrombosis occurred after clopidogrel therapy was stopped. However, in a multivariate analysis, absence

VOLUME 26 • NUMBER 4 • APRIL 2007 • PAGES 25-32

NOW AVAILABLE ONLINE
www.ahcmedia.com

of clopidogrel was not associated with the risk of late thrombosis. Most patients with stent thrombosis presented as myocardial infarction. The authors concluded that late stent thrombosis occurs steadily for up to 3 years after stent implantation in both SES and PES.

COMMENTARY

The intense press coverage of late DES thrombosis prompted the ACC/AHA and other organizations to issue new recommendations for their use. Most practitioners are now adhering more closely to the proven indications for DES, so their use has declined. Also, most are advising their patients to stay on clopidogrel for at least one year based upon anecdotal experience. In this content, this publication of the experience with these stents at 2 large European academic centers is of interest. Although a nonrandomized uncontrolled observational study, it does reflect more of a real world experience because there was unbridled use of DES, and clopidogrel was given largely per the recommendation of the manufacturer at one hospital and for one year at the other. In addition, their patients were sicker and more omplex than the controlled clinical trial patients as evidenced by their 10% overall mortality rate.

The major message of the trial is that late stent thrombosis proceeds at a constant low rate (0.6%/year) despite dual drug therapy in many cases. In fact, clopidogrel use did not emerge as a multivariate predictor of late stent thrombosis. Various theories have been advanced to explain late stent thrombosis such as delayed healing due to the antineoplastic agent or a hypersensitivity reaction to the binding polymers, but at this point the mechanism is largely unknown and likely multi-factorial. The differences observed between SES and PES in the incidence of late stent thrombosis may have more to do with clinical factors than the stents themselves. PES was used in more acute coronary syndrome patients and in more long complex lesions.

In addition to the observational nature of the study, angiographic documentation of stent thrombosis was a limitation. Most of the stent thrombosis patients had an acute myocardial infarction. There may have been patients with less severe degrees of restenosis in the population. Also, the data for actual clopidogrel use are incomplete. We know what was advised, but not always what the patient actually did. Thus, firm conclusions about antiplatelet drug use are difficult to support based upon this study.

It is difficult to refute the interventional community's response to this crisis of sticking more closely to evidenced-based indications for DES and a minimum of 12 months of clopidogrel, but there is no solid data to support these actions. Late DES thrombosis seems to be a small, but constant problem after successful stent deployment that we don't know the mechanism of and which we don't know how to prevent. Hopefully, more information will be forthcoming. ■

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER Lee Landenberger.
ASSOCIATE MANAGING EDITOR: Jennifer Corbett.
MARKETING PRODUCT MANAGER: Gerard Gernazian.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Clinical Cardiology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: jennifer.corbett@ahcmedia.com

Subscription Prices

United States
1 year with Free AMA Category 1 credits: $289
Add $9.95 for shipping & handling.
(Student/Resident rate: $125).

Multiple Copies
Documents are available for group subscriptions. For pricing information, please call Tria Kreutzer at (404) 262-5482.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the cardiologist. It is in effect for 36 months from the date of the publication.

Questions & Comments

Jennifer Corbett,
Associate Managing Editor, at (404) 262-5431 or e-mail at jennifer.corbett@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Patent Foramen Ovale and the Risk of Stroke

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: Di Tullio MR, et al. Patent Foramen Ovale and the Risk of Ischemic Stroke in a Multiethnic Population. *J Am Coll Cardiol.* 2007;49:797-802.

A LONGSTANDING CONTROVERSY EXISTS REGARDing the importance of a patent foramen ovale

(PFO) as a cause for TIA or stroke. This report is from NOMAS (Northern Manhattan Study), an epidemiologic study evaluating risk factors for and the incidence of stroke in Northern Manhattan, New York City. The eligible study population had no history of a cerebral event. A total of 1,100 subjects were recruited between 1993 and 1999. All had echocardiographic evaluation, a review of medical records, a physical/neurological exam, and standard blood work. Echo exams included agitated saline contrast, the Valsalva maneuver, and coughing, all employed to increase sensitivity for detection of a PFO. A PFO was confirmed by microbubbles seen in the left heart within 3 cardiac cycles following maximum right atrial opacification. An atrial septal aneurysm (ASA) was sought, diagnosed by more than 10 mm of septal protrusion behind the plane of the septum to the left or right. Telephone follow-up was done with little loss of study participants. Any possible neurologic, cardiac, or vascular event triggered an in-person interview and assessment. Subjects suspected to have a possible stroke were seen by a neurologist. Stroke was defined by the TOAST Criteria. Ischemic stroke was verified by 2 independent neurologists. The primary study outcome was the occurrence of fatal or nonfatal ischemic stroke. Kaplan-Meier and COX proportional hazards survival models were utilized. Adjustments were made for other stroke risk factors, including hypertension, diabetes, elevated lipids, smoking, and atrial fibrillation. The cohort of 1,100 patients included more women than men (640 vs 460), with a median age of 69. African Americans comprised 26%, Hispanics 50% and Caucasians 25% of the population.

RESULTS: PFO was detected in 15% of the subjects, and ASA in 2.5%; both a PFO and ASA were noted in 1.7% or 19. Groups with and without an event were similar. Aspirin utilization was not different between the 2 groups. Overall follow-up was 80 +/- 28 months. Ischemic stroke occurred in 6.2% of the subjects, with a stroke incidence of 12.2 per 1,000 person years, compared to PFO-positive individuals, 8.9 per 1,000 person years (P = 0.5). After adjusting for all stroke risk factors, the hazard ratio of a PFO for stroke was nonsignificant, 1.64 (95% CI 0.87 to 3.09). Frequency of embolic as well as cryptogenic stroke was not different in patients with or without PFO. An isolated ASA was unrelated, although the numbers were small. The non-association between PFO and ischemic stroke was not influenced by gender, age, or ethnicity. The authors conclude "the study shows no significant increase in the risk of ischemic stroke from PFO in the general population during a mean follow up of 7 years."

COMMENTARY

Because of the concern that PFO increases stroke risk, there have been a number of trials evaluating PFO closure devices. The potential world-wide market for such devices is very large. Many believe that a significant number of strokes in the United States are cryptogenic and could be caused by a thromboembolic event related to a PFO. The prevalence of a PFO in patients who have had a stroke is somewhat higher than that of strokes of known cause. Heretofore, there have been an inadequate number of truly randomized trials, and outcomes are uncertain. Many non-randomized trials have been published, usually favorable for PFO closure devices. The present study as well as other data raise the issue as to whether the question of PFO and cryptogenic stroke has been resolved. A recent commentary in *JAMA* discusses in detail the scope of the problem and focuses on the regulatory background for device approval, with particular focus in the PFO closure devices of which 2 have been widely used in the United States (Laskey, Maisel; *JAMA*. 2005;294:366-368.). Maisel and Laskey emphasize the many unresolved questions in regards to efficacy, device complications, the lack of randomized trials, and other aspects of this controversy. They state, "PFO closure device approval for a more widespread indication mandates a more rigorous, evidence-based evaluation." They point out that the American Academy of Neurology practice guidelines conclude that there is insufficient evidence to recommend routine device closure of PFO in individuals with cryptogenic strokes. The Stroke Counsel of the American Heart Association ". . .has called for physicians to enroll their patients in randomized clinical trials." While the present study does not support the association between PFO and cerebral embolic event, the adjusted and unadjusted data all trend toward such a relationship, but do not come close to statistical significance. New data, and the perceptive analysis of the state of the art, as well as previous studies published, indicate that there is no final answer regarding efficacy and safety of routine PFO closure. Physicians need to carefully consider the therapeutic options available following the identification of a PFO in an individual who has not suffered a cerebral event, or in a population of patients who have had a cryptogenic stroke. Finally, the question remains related to devices: Is the horse already out of the barn? ■

Does LDL Particle Size Matter?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: El Harchaoui K, et al. Value of Low-Density Lipoprotein Particle Number and Size as Predictors of Coronary Artery Disease in Apparently Health Men and Women. *J Am Coll Cardiol*. 2007;49:547-553.

SMALL DENSE LOW-DENSITY LIPOPROTEIN cholesterol (LDL-C) particles are believed to be more atherogenic than large ones. Nuclear magnetic resonance spectroscopy (NMRS) is a new method that can measure low-density lipoprotein particle number (LDL-P) and size. Thus, these investigators used the prospective Norfolk, England, population study to perform a nested case-control analysis of the association between LDL-P and size with LDL-C and the risk of future coronary events. The Norfolk study consisted of 25,663 people between ages 45 and 79 years who attended a clinic visit. The main objective of the study was to investigate the relationship between diet and cancer, but additional data were collected to look at other diseases. Death and hospitalization data were available through the National Heath Service database. Patients with known coronary artery disease (CAD) on the first visit were excluded, and no one was on a statin at baseline. For each case that developed fatal or nonfatal CAD, one or 2 controls were matched for age and sex. Follow-up was for 6 years. Results: CAD developed in 1,003 who were matched with 1,885 controls. Cases were more likely to be smokers, diabetic, and hypertensive or obese as compared to controls. Also, LDL-C triglycerides and non-high-density lipoproteins (HDL) levels were higher in cases and HDL-C was lower as compared to the controls. LDL-P was higher in cases and the cases had more intermediate and small-sized particles. Since the level of large-sized particles was not different between the 2 groups, the increase in LDL-C in the cases was due more to smaller particles. All 5 lipid/lipoprotein measures (LDL-C, LDL-P, HDL-C, triglycerides and non--HDL-C) were correlated with future CAD events in an univariate analysis. LDL-P and HDL-C were the most potent predictors. A multivariate analysis that corrected for the other lipid parameters showed that the additional value of LDL-P was lost after adjustment for HDL-C and triglycerides and the value of particle size was abolished after adjustment for LDL particle number. In a model that adjusts for the Framingham risk score, LDL-P and HDL-C retain their ability to predict CAD, but LDL-C does not. The authors concluded that NMR determined LDL-P predicts CAD after adjustment for Framingham risk score and LDL cholesterol levels, but its value was abolished after adjusting for HDL-C and triglycerides.

COMMENTARY

Clinicians have been frustrated because LDL cholesterol does not explain all of the lipoprotein associated risk for CAD and there has been considerable debate over what is the best secondary treatment target after LDL is optimized. In fact, in patients with-elevated triglycerides, diabetes or the metabolic syndrome, increased particle number is not reflected in LDL levels. These are patients where secondary goals may be most useful. In this study LDL-P and HDL-C improved the risk prediction for CAD over LDL-C. LDL particle size did as well, but when corrected for LDL-P the predictive value of particle size was abolished. When HDL-C and triglyceride levels are considered, the predictive value of LDL-P size is lost. Thus, HDL-C may be the best secondary target of therapy.

Other studies have suggested that apolipoprotein B (apoB) or non-HDL-C may be a better secondary predictor of CAD. ApoB was not assessed in this study, but non-HDL-C did improve upon the risk prediction of the Framingham score and was highly predictive of events in the multivariate model. Thus, at this point measuring LDL particle size does not seem to add much to standard clinical and lipid/lipoprotein measures and cannot be recommended as a routine test. There are some limitations to this study. The patients were older and had higher LDL-C levels than expected for a general population. So the results may not apply to young subjects with lower LDL-C. Control subjects could have had sub-clinical CAD since no exclusionary testing was done. Also, CAD events could have been underestimated using death reports and hospital records. Regardless, this study provides no compelling evidence that LDL particle size or number should be routinely assessed. If available, this testing may be of value as a secondary target in high-risk patients who have had their LDL-C lowered. However, other measures may be equally valuable in this regard, such as HDL-C , non-HDL-C, and triglycerides. ■

Statins Plus Niacin: Safe?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Alsheikh-Ali AA, Karas RH. Safety of Lovastatin/Extended Release Niacin Compared with Lovastatin Alone, Atorvastatin Alone, Pravastatin Alone, and Simvastatin Alone (from the United States Food and Drug Administration Adverse Event Reporting System). *Am J Cardiol.* 2007;99:379-381.

THE FOOD AND DRUG ADMINISTRATION (FDA) cautions about increased risks of adverse events with the combination of statins and niacin, yet achieving current lipid treatment targets often requires multiple drug therapy. Thus, these investigators reviewed adverse events reported to the FDA over 5 years involving atorvastatin, simvastatin, pravastatin, lovastatin, niacin-extended release (ER) (Niaspan), and the combination of lovastatin and niacin-ER (Advicor). The primary analysis was adverse events associated with Advicor vs lovastatin or niacin-ER alone. Second, these results were compared to adverse events reported with the other statins with or without niacin-ER. Results: serious adverse events (SAEs) defined as fatal, life-threatening, or requiring hospitalization; occurred in 11.2 on Advicor, 7.5 lovastatin and 11.6 on niacin-ER per million prescriptions (P = NS). Also, the rate of SAEs on Advicor was less than that observed on simvastatin (22.6) and atorvastatin (19.6, $P < 0.01$ for both). Liver enzyme elevations were not significantly different with the agents analyzed, but rhabdomyolysis, although rare (≤ 1%) was significantly more common with simvastatin ($P < 0.01$). The authors concluded that these results do not support the idea that statins plus niacin-ER results in more adverse events and supports the use of such combination therapy in high-risk patients.

COMMENTARY

The precaution about statins and niacin was based upon a small number of case reports. This analysis represents the first large systematic study of the combination of statins with niacin and does not support the impression gained from those prior case reports. This is good news for patients with low high-density lipoprotein (HDL) and high low-density lipoprotein (LDL) cholesterol, since niacin is one of the few approaches to raising HDL, and LDL-lowering is often best achieved with statins. The use of the FDA database allowed looking at a large group of patients from all over the United States, but there are disadvantages to this approach. The FDA database does not control for possible confounders and does not contain how many people were on these drugs or their combination. Also, more adverse effects could have occurred that were not reported to the FDA. In addition, since the analysis was from data collected between 1999 and March 2005, there was insufficient data on rosuvastatin, the most potent statin. Finally, other niacin preparations were not studied such as niacin slow-release (SLO-niacin, Nicobid) and short-acting niacin. Niacin-ER was chosen because it is associated with less flushing than immediate-release niacin and less hepatotoxicity than niacin-SR. Regardless, clinicians should be encouraged to use niacin/statin combinations in high-risk patients with HDL and LDL cholesterol levels that are not at recommended targets. ■

Statins for Heart Failure?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Khush KK, et al. Effect of High-Dose Atorvastatin on Hospitalizations for Heart Failure. *Circulation*. 2007;115:576-583.

THE ROLE OF STATINS IN HEART FAILURE PATIENTS IS poorly studied and controversial. Thus, Khush and colleagues analyzed the secondary endpoint in the Treating to New Targets (TNT) study of hospitalization for heart failure. TNT was a study of over 10,000 patients with stable coronary heart disease (CHD) treated with either 10 or 80 mg/day of atorvastatin and followed for about 5 years. The primary endpoint of cardiac death, myocardial infarction (MI) and stroke was reduced 22% by high-dose atorvastatin. A history of heart failure was obtained in 8% of the patients, however, advanced heart failure or an ejection fraction (EF) of < 30% were exclusion criteria. Patients with heart failure had more hypertension, diabetes, peripheral arterial disease, prior MI and stroke, and were on higher doses of renin-angiotensin-blocking drugs and diuretics. Baseline lipid panels were similar between those with and without a history of heart failure. Lipid/lipoprotein levels were lower in the atorvastatin 80-mg group except for high-density lipoprotein cholesterol which was not. Hospitalization for heart failure occurred in about 3% of the study population; 14% of those with a history of heart failure and 2% of those without. Heart failure por-

tended a poor prognosis. In the atorvastatin 80-mg group, 2.4% were hospitalized for heart failure vs 3.3% in the atorvastatin 10-mg group ($P < 0.02$). This protective effect was strongest in those with a history of heart failure, but was not different in a variety of other subgroups. One-third of the patients who developed heart failure had angina or MI prior to the event as compared to 15% overall of patients who did not have heart failure. Hospitalization for heart failure decreased as low-density cholesterol decreased. There was no relation between heart failure and blood pressure. The authors concluded that intensive treatment with atorvastatin in stable CHD patients reduces the incidence of heart failure hospitalization as compared to less intensive treatment, but only in those with a history of heart failure. A reduction in coronary events did not seem to explain the results.

COMMENTARY

Most large statin trials have excluded patients with heart failure, but interestingly they have shown a reduction in heart failure endpoints. Small studies of heart failure patients have also shown reduced heart failure endpoints. This study suggests a benefit in patients with a history of heart failure with high-dose atorvastatin, but not low dose. The mechanism of this effect is unclear. The heart failure benefit was associated with-lowering LDL cholesterol levels, but those whose LDL decreased were mainly in the atorvastatin 80-mg group, so it could be an effect of high-dose atorvastatin alone. Since most of the heart-failure hospitalization patients did not have a preceding ischemic event, it is unlikely that an anti-ischemic effect is the mechanism. Other possible mechanisms that have been suggested include increased endothelial function, reduced inflammation, reduced sympathetic tone and reduced remodeling. There are no data in this study to support any particular mechanism.

One major limitation of the study was that left ventricular function measurements were not part of the protocol. Some patients had a known EF < 30% but they were excluded. Also, patients with advanced heart failure were excluded, so the results may not apply to them. In addition, evidence of silent ischemia was not sought. Finally, there may have been unrecognized confounders that skewed the results.

Since this was a study of stable CAD patients, it is likely that the plaque stabilization that markedly lowering LDL produces would lead to stabilization or actual improvement in left ventricular function. This is another reason why CAD patients, whatever their lipid profile, should be on statins. As one of my colleagues said of CAD patients, "Whatever their cholesterol is, it is too high for them." ■

Sleep Apnea and Atrial Fibrillation

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: Gami AS, et al. Obstructive Sleep Apnea, Obesity, and the Risk of Incident Atrial Fibrillation. *J Am Coll Cardiol.* 2007;49:565-571.

GAMI AND HIS COLLEAGUES FROM THE MAYO CLINIC describe in this paper relationships between obesity, obstructive sleep apnea, and atrial fibrillation (AF). The authors identified adult residents living in Olmsted County, Minnesota, who underwent diagnostic polysomnography between 1987 and 2003. Patients with a previous history of atrial fibrillation were excluded. Subjects were defined as having obstructive sleep apnea (OSA) if they had an apnea-hypopnea index during their sleep study greater than or equal to 5. The occurrence of incident AF was timed from the date of the sleep study by querying the Mayo Clinic electronic medical index. Any diagnosis of AF or atrial flutter made during any medical contact if the occurrence of AF was confirmed by an electrocardiogram was considered an event. Time-to-event analyses were performed using Kaplan-Meier methods to identify univariate predictors of incident AF. The parameters included subject, age, gender, body mass index, relevant comorbidities, OSA status and severity, and physiological sleep variables. Multivariate analyses were performed using Cox proportional hazards regressions methods. Furthermore, in an analysis that included only subjects with OSA, the effect of continuous positive airway pressure after the sleep study was introduced into the multivariate model.

During the period of the study, 3,542 subjects underwent polysomnography and OSA was present in 2,626 (74%). After an average follow-up of 4.7 years (up to 15 years), incident AF occurred in 133 subjects for a cumulative frequency of 14%. By univariate analysis, age, male gender, hypertension, the presence of coronary disease, heart failure, a history of smoking, the presence of diabetes, body mass index, obstructive sleep apnea, and measures of the severity

of sleep apnea, all were related to the risk of incident atrial fibrillation. There was a significant interaction between OSA and age. Therefore, the authors performed a stratified analysis for subjects younger than 65 years and 65 years or older. Among the subjects less than 65 years old, age, male gender, body mass index, and a history of coronary artery disease independently predicted incident AF. The decrease in nocturnal oxygen saturation was also an independent predictor of incident AF. In contrast, for subjects greater than or equal to 65 years old, only heart failure independently predicted incident AF. In a multivariate regression model that included only subjects with OSA, the use of continuous positive airway pressure did not positively or negatively affect the incidence of AF. In the multivariate regression model both OSA and obesity independently predicted incident AF.

The authors conclude that obesity and the magnitude of nocturnal oxygen desaturation are independent risk factors for incident AF in individuals less than 65 years of age.

COMMENTARY

A number of arrhythmias are commonly seen in patients with organic sleep apnea. This paper shows that atrial fibrillation is strongly related to the presence of OSA. A number of mechanisms may be responsible for this. OSA is associated with diastolic dysfunction which can lead to increases in atrial size and atrial stretch. Rapid swings in intracardiac pressures can activate atrial ion channels that may contribute to AF initiation. Surges in autonomic nervous system activity may also occur. During OSA-associated bradycardia, atrial repolarization prolongs and then with elevation of sympathetic activity during apnea catecholamine sensitive ion channels may lead to increased automaticity. This combination should be a potent mechanism for AF initiation. Finally, OSA has been reported to be associated with systemic inflammation, another potential cause of atrial fibrillation.

It is disappointing that the authors cannot demonstrate that the use of continuous positive airway pressure (CPAP) favorably influenced the risk for atrial fibrillation. However, in this study CPAP was used mostly in the patients with the most severe form of OSA and a prospective study will likely be required to see if CPAP has a favorable influence on the incidence of AF.

In conclusion, physicians should consider sleep apnea as an important potential cause of atrial fibrillation. Weight reduction and treatment of OSA should be part of the management of AF in patients at risk. ■

Electrophysiologic Implanted Device Failure

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: Hauser RG, et al. Clinical Experience With Pacemaker Pulse Generators and Transvenous Leads: An 8-Year Prospective Multicenter Study. *Heart Rhythm.* 2007;4:154-160.

THIS PAPER DESCRIBES RESULTS FROM A MULTI-CENter registry located at the Minneapolis Heart Institute Foundation that collects data on device failure in pacemakers and implantable defibrillators. For each device failure or removal at centers participating in the registry, data is collected concerning the model number, the manufacturer, the dates of implant, failure or removal, how the failure was detected, symptoms associated with failure, how the failure was verified, the actual presumed cause of failure, and resolution of the problem. During the period of the study, 2,652 pacemaker pulse generators from 12 manufacturers were removed from service and were included in this registry. The devices were removed an average of 7.3 + 3.1 years after implant. Battery depletion was the reason for explant in 92% of these models. In 95% of these cases, the generator exhibited normal battery function and jus reached its elective replacement indicator after more than 3 years of service. Most battery depletion was routine and managed according to standard protocols. Severe battery depletion was noted in 43 cases and was associated with either loss of telemetry (n = 18), no or inadequate stimulation output (n = 18), or other signs of failure (n = 5). For both single and dual chamber pacemakers, battery longevity was shorter if the device had rate response capability. Major adverse clinical events were experienced by 62 patients when their pulse generators failed or reached end of life. One patient died when an electronic component failure resulted in sustained rapid pacing that led to acute heart failure. Severe battery depletion was associated with syncope in 11 patients, heart failure in one patient, and tachycardia in one patient. After battery depletion, the next most common reason for removing a pulse generator was an advisory or recall. This was noted in 4% of cases. Other reasons for removal included electronic failures (2%), connector failures (1%) and unspecified causes (1%). Electronic and connector failures caused syncope or near syncope in

16 patients and heart failure in 2 patients. Normal battery depletion was not totally benign. Major symptoms at the time of normal battery depletion were reported by 21 patients, including syncope (13), heart failure (5), tachyarrhythmia (2) and angina (1). An additional 133 patients reported minor symptoms. Usually, this was caused by reversion to a VVI or non-rate responsive mode when the battery reached its end-of-service indicator.

Transvenous lead failures were noted in 615 leads during the study. Insulation defects were the most common cause of failure with a median time to failure of 7.2 + 5.2 years with a higher number of polyurethane lead failures noted. Conductor failures, fixation mechanism failures, or unknown causes also contributed. Major adverse clinical events were seen in 16% of the leads failures. The most common symptom was syncope, but there were 11 non-fatal surgical complications and one death associated with lead extraction.

The authors conclude that the vast majority of pacemaker pulse generators are reliable and perform as expected. However, unexpected device failure is frequently associated with major adverse clinical events and even normal battery depletion may cause symptoms. In addition, lead failures were commonly associated with clinical events and surgical extraction was not benign. The authors argue that major opportunities for improving the clinical performance of cardiac pacing systems exist.

COMMENTARY

In 2005, there was major media and public attention focused on the failure risks associated with cardiac pacemakers and defibrillators. The cause for the increased interest was the unfortunate death of a 23-year-old man with hypertrophic cardiomyopathy whose defibrillator malfunctioned and failed to prevent his sudden death. As a result of the controversy, all major manufacturers have enhanced their product performance reports and provide much clearer information on product performance for both physicians and patients. The data in this paper, however, point out that pacemaker generator and lead failures unfortunately remain common clinical problems. The data here cover only devices that were removed. An event that might have led to a death where the device was not recovered would not have been detected by this registry. The registry also only provides the numerators and we don't know what proportion of implanted devices actually fail. The manufacturers' product performance reports now give a better picture of the probability of failure. Fortunately, the reliability of the devices has greatly improved over the last several decades, and efforts to improve the safety of implantable rhythm management devices should obviously continue. ■

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

17. Cryptogenic stroke is strongly correlated with which of the following?

A. Patent foramen ovale
B. Atrial septal aneurysm
C. Both
D. None of the above

18. Which is most correct concerning the combination of statins and niacin-ER?

A. Serious adverse events are increased
B. More liver function test elevations occur
C. Rhabdomyolysis is increased
D. No increase in adverse events noticed

19. High-dose atorvastatin has been shown to?

A. Lower LDL cholesterol
B. Reduce coronary events in high-risk patients
C. Reduce hospital admissions for heart failure in CAD patients
D. All of the above

20. Which is most correct concerning late stent thrombosis?

A. It occurs at a low, but steady rate
B. It is more common right after stopping clopidogrel therapy
C. It is related to smoking
D. All of the above

21. The most useful secondary goal in CAD patients after LDL cholesterol is?

A. LDL particle number
B. LDL particle size
C. HDL cholesterol
D. High sensitivity CRP

22. Which are risk factors for atrial fibrillation?

A. Age
B. Obstructive sleep apnea
C. Obesity
D. All of the above

23. Pacemaker pulse generator replacement is usually done because of?

A. A manufacturer recall
B. Battery depletion
C. Elective component failure
D. Lead connector failures

Answers: 17.(d) 18.(d) 19.(d) 20.(a) 21.(c) 22.(d) 23.(b)

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.

Which Inhaler Combination is Best for COPD Treatment?

Two recent large studies have looked at the effects of various inhaler combinations on outcomes in patients with COPD. In the first, published in the February 22 issue of the *New England Journal of Medicine*, researchers from the United Kingdom looked at over 6,000 patients with COPD in a randomized, double-blind trial comparing salmeterol plus fluticasone inhaler twice daily (in a single inhaler) vs salmeterol alone, fluticasone alone, or placebo for 3 years. The primary outcome was death from any cause, the frequency of exacerbations, health status, and spirometry values. The all-cause mortality was 12.6% in the combination therapy group, 13.5% in the salmeterol group, 16.0% in the fluticasone group and 15.2% in the placebo group. The hazard ratio for death in the combination therapy group was 0.825 vs placebo ($P = 0.052$), a level that did not reach statistical significance, but was associated with a 17.5% relative reduction in mortality. The mortality rate for salmeterol alone or fluticasone alone did not differ from placebo. Combination therapy was associated with a statistically significant lower rate of exacerbations ($P < 0.001$). The probability of having pneumonia was higher among patients receiving fluticasone alone or medications containing fluticasone (*N Engl J Med*. 2007;356:775-789). An accompanying editorial suggests that the findings show that monotherapy with fluticasone should not be recommended, monotherapy with a bronchodilator may be an option, and that combination therapy "offers statistically significant advantages for health status, frequency of exacerbations, use of oral steroids... and protection against a decline in lung function" (*N Engl J Med*. 2007;356:851-854).

In the second study, 449 patients with moderate or severe COPD were treated with the anticholinergic inhaler tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus fluticasone/salmeterol. The primary endpoint was COPD exacerbation that required treatment with systemic steroids or antibiotics. After one year there was no difference in the rate of exacerbation between tiotropium alone (62.8%), tiotropium plus salmeterol (64.8%), or tiotropium plus fluticasone/salmeterol (60.0%). Tiotropium plus fluticasone/salmeterol improved lung function ($P = 0.049$), disease-specific quality of life ($P = 0.01$), and reduced the number of hospitalizations for COPD exacerbation and all-cause hospitalization compared with tiotropium plus placebo. The authors conclude that adding fluticasone/salmeterol to treatment with tiotropium did not influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates (early release *Annals of Internal Medicine* 2/20/2007, print date 4/17/2007). So, what is the upshot of these papers? Combination inhalation therapy in patients with COPD works best, bronchodilator plus steroid inhalation therapy should continue to be the recommended regimen perhaps along with an anticholinergic inhaler.

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) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

First Antihypertensive Drug Approved in Last 10 Years: Aliskiren

The FDA has approved the first of new class of antihypertensive drugs, and the first new antihypertensive medication to be approved in more than 10 years. Aliskiren is an oral renin inhibitor, inhibiting the renin-angiotensin system earlier in the cascade than angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The drug is a once-a-day oral agent that is approved for use as monotherapy or in combination with other antihypertensives.

Aliskiren's effect is additive with hydrochlorothiazide, and seems to be well-tolerated with other cardiovascular agents. It will be available in 150 and 300 mg doses. The FDA approval was based on 6 placebo-controlled trials in more than 2,000 patients in which the blood- pressure-lowering effect was maintained for up to one year. The drug seems be effective across all age ranges, but is slightly less effective in African-American patients as compared to Caucasians and Asians, as is the case with ACEI's and ARBs. The primary side effect is diarrhea, which was seen in 2% of patients, usually on higher doses. Angioedema was also rarely noted. As with other drugs that affect the renin-angiotensin system, aliskiren should not be used during pregnancy. Aliskiren will be marketed by Novartis Pharmaceuticals, and will be marketed under the trade name Tekturna.

Alternate Treatment for Osteoporosis

Antiresorptive agents are standard therapy for osteoporosis. These drugs, which include the bisphosphonates (alendronate, risedronate, etc.) prevent bone breakdown, but they do not stimulate production of new bone. A new study looks at recombinant human parathyroid hormone (1-84) (PTH), a bone forming agent, as an alternative treatment for osteoporosis. In an 18 month, randomized, double-blind, placebo-controlled, parallel group study, 2,532 postmenopausal women with low bone mineral density at the hip or lumbar spine were randomized to receive 100 µg of PTH or placebo daily by subcutaneous injection. All received additional calcium 700 mg/d and vitamin D 400 U/d. The main outcome was new or worsened vertebral fractures, changes in bone mineral density as well as safety of the medication. PTH significantly reduced the risk for new or worsened vertebral fractures. The relative risk varied depending on the assumptions about women who did not complete the trial, but there was improvement in all subgroups. PTH also resulted in increased bone mineral density compared to placebo of 6.9% at the spine and 2.1% at the hip compared to placebo, but decreased bmd at the forearm. PTH also resulted in increased percentage of participants with hypercalciuria, hypercalcemia, and nausea by 24%, 23%, and 14% respectively compared to placebo. The authors conclude that parathyroid hormone (1-84) reduced the overall risk for new or worsened vertebral fractures in postmenopausal women with osteoporosis, and suggest that PTH provides an alternative therapy option for fracture prevention (*Ann Int Med.* 2006;146:326-339). This study adds a second option for anabolic (bone-forming) agents along with teriparatide.

Roche's Oseltamivir: Scrutiny, Bird Flu, and New Drug Applications

Roche's oseltamivir (Tamiflu) has come under scrutiny in Japan after 2 students who took the drug fell to their deaths in February. The drug has been associated with abnormal behavior in anecdotal reports including a Japanese boy who ran in front of a truck after taking the drug in 2004. Roche counters that influenza can cause abnormal behavior and denies a link between the medication and psychiatric problems. The drug has previously been associated with delirium, and the FDA has required labeling urging close monitoring for abnormal behavior since November 2006. Countries worldwide are stockpiling oseltamivir in case of avian influenza outbreak. Meanwhile Roche has filed a new drug application with the FDA for pediatric doses of the drug for children one year and older. The new capsules and a 30 milligram and 45 mg capsule would join the 75 mg adult strength capsule.

FDA Actions

The FDA has approved duloxetine (Cymbalta) for the treatment of generalized anxiety disorder. The drug is currently approved for the treatment of major depressive disorder in the management of diabetic peripheral neuropathic pain. The FDA approved duloxetine 60 mg once daily for the treatment of anxiety based on three randomized, double-blind placebo-controlled trials in 800 patients.

The FDA has approved lisdexamfetamine dimesylate capsules for the treatment of attention deficit/hyperactivity disorder in children age 6-12. Lisdexamfetamine is a pro-drug of dextroamphetamine that may be associated with less drug abuse than dextroamphetamine. The once-a-day drug will be available in 30, 50, and 70 mg strengths. Lisdexamfetamine is marketed by New River Pharmaceuticals under the trade name Vyvanase. ■