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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Cardiac Device-Related Infective Endocarditis

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Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

SOURCE: Athan E, et al, for the ICE-PCS Investigators. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA* 2012;307:1727-1735.

This study reports data from the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) on the clinical characteristics of infective endocarditis related to pacemakers and ICDs. ICE-PCS collected data on 3284 patients with endocarditis from 64 centers in 28 countries in a central database. Patients were enrolled if they met criteria for possible or definite infective endocarditis based on modified Duke criteria. This study includes only patients with definite infective endocarditis. The major outcomes of interest analyzed were in-hospital and 1-year mortality. Definite cardiac device infected endocarditis (CDIE) was present when valvular or lead vegetations were detected by echocardiography or the Duke criteria for infective endocarditis were met. Nosocomial infections were defined as infective endocarditis cases that developed in a patient hospitalized for more than 48 hours prior to the onset of signs or symptoms. Non-nosocomial health care associated infections were defined if endocarditis developed as a result of a health care intervention, e.g., an indwelling intravascular line. Community-acquired infective endocarditis was defined as those cases that developed before hospitalization or extensive out-of-hospital contact with health care interventions.

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Clinical Cardiology [ALERT]

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CDIE was diagnosed in 177 (6.4%) of the 2760 patients with definite infective endocarditis. This group included 152 patients with permanent pacemakers, 21 with ICDs, and four patients with an unknown type device. The median age was 71.2 years; 27.1% had diabetes mellitus; 74% were male. The most common agents involved were staphylococcal species (*Staphylococcus aureus* — 35.0%; coagulase-negative staphylococci — 31.6%). Vegetations were seen on echocardiography in 159 patients (89.8%), and in 135 patients vegetations were attached to the intracadiac leads. Coexisting valve infection was found in 66 patients. As might be expected, the tricuspid valve was the valve most commonly involved. Concomitant valve infection increased the risk for in-hospital mortality with an odds ratio of 3.31. Device and lead removal was performed in 141 of 177 patients. Thirty patients also underwent valve surgery during the index hospitalization. Twenty-six of the 177 patients (14.7%) died during the index hospitalization. The death rate was 12.8% among those who underwent device removal and 23.5% among those who did not. After hospital discharge, an additional 15 patients died and 10 were lost to follow-up. For the entire group, 126 of 177 patients were alive at 1 year, 41 (22%) had died, and 10 (5.6%) were lost to follow-up. Device removal during the index hospitalization was associated with improved 1-year survival. A presence of concomitant valve infection was found to confer worse survival. The device-related infection was thought to be health care associated in 81 (45.8%) patients with 61 nosocomial and 20 non-nosocomial infections. Health-care-associated infections were more often associated by *S. aureus* and were associated with persistent bacteremia and increased in-hospital mortality.

The authors conclude that cardiac device-related infective endocarditis is frequently associated with health care interventions, has a high rate of complications — especially concomitant valve infection — and results in high in-hospital and 1-year mortality. Device removal is associated with better survival at 1 year.

■ COMMENTARY

There are almost 2 million patients in the United States with pacemakers and ICDs. These patients often live many years with their implanted devices. As a result, the incidence of cardiac device-related infections is rising. As shown in this study, the consequences of a systemic infection involving a cardiac device are very serious with a high in-hospital and 1-year mortality.

Infections that appear within the first year after a device implant are fairly easy to manage. The device and leads can usually be removed easily and safely, and the major problem is treating the infection and supporting the patient until a new device can be implanted. When the device has been in place longer, leads become more difficult to remove and the risks of lead extraction, although low in experienced centers, increase. In current practice, more device-related infections arise after device generator changes or upgrades than with new implants, so these extraction procedures are often quite complicated.

Prevention of device infection is clearly the most important strategy. Prophylactic antibiotics around the time of device procedures have been shown to be beneficial. Whether prophylactic antibiotics should be used in all device patients undergoing any intravascular procedure or therapy is a question that will have to be addressed in future studies. Extreme caution should be exercised in any cardiac device patients with other indwelling catheters in the hospital. ■

ABSTRACT & COMMENTARY

PCI in Addition to Medical Therapy for Stable CAD — The Debate Continues

By Andrew J. Boyle, MBBS, PhD

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

SOURCE: Hannan EL, et al. Comparative outcomes for patients who do and do not undergo percutaneous coronary intervention for stable coronary artery disease in New York. *Circulation* 2012;125:1870-1879.

Medical therapy is the mainstay of treatment for coronary artery disease (CAD), resulting in improved clinical outcomes. Revascularization with percutaneous coronary intervention (PCI), in addition to medical therapy, improves symptoms in patients with stable CAD. The addition of revascularization to medical therapy has not been shown to reduce the rate of myocardial infarction (MI) or death in randomized clinical trials with restrictive inclusion and exclusion criteria. However, in real-world clinical practice, physicians do not randomize patients; they employ their clinical judgment as to who would benefit from the addition of PCI to medical therapy. Whether PCI results in better clinical outcomes in this context is not known. Hannan and colleagues studied the New York State Cardiac Diagnostic Catheterization Database to identify all patients undergoing diagnostic catheterization and linked this to the state hospital discharge database, the PCI database, and the Social Security death index. They used these four linked databases to determine the percentage of patients who undergo PCI after diagnostic catheterization, and the outcomes of patients with stable CAD who undergo PCI compared to those who have routine medical therapy.

They included all patients with stable CAD, at least one coronary stenosis > 70%, and Canadian cardiovascular class 0-III symptoms. Excluded were patients with left main disease, life-threatening arrhythmia, valve disease requiring surgery, acute coronary syndromes, a negative or high-risk stress test, prior revascularization, and those who chose to undergo coronary artery bypass graft surgery (CABG) for revascularization. Over a 6-year period, they identified 9586 patients who underwent diagnostic angiography for stable CAD, of whom 1100 received routine medical treatment alone (RMT group). The remaining 8486 (89%) underwent PCI in addition to RMT (PCI/RMT group). Patients in the PCI/RMT group were younger, and were more likely to have private health insurance, a positive stress test and a larger area of viable myocardium, proximal left anterior descending disease, class III angina, and a normal injection fraction. They were less likely to have peripheral arterial disease or have had prior CABG. Because of these significant baseline differences between groups, the authors performed propensity score matching for 20 variables and identified 933 pairs of matched patients in the two groups. After propensity score matching, there were no longer any baseline differences between groups.

At 4 years of follow-up, the PCI/RMT group had lower rates of combined MI/mortality (16.5% vs 21.2%; $P = 0.003$), lower mortality (10.2% vs 14.5%; $P = 0.02$), MI (8.0% vs 11.3%; $P = 0.007$), and subsequent revascularization (24.1% vs 29.1%). The adjusted hazard ratio for death in the RMT group (vs PCI/RMT) was 1.46. The authors conclude that most patients in New York with stable CAD undergoing diagnostic catheterization received PCI. Patients who received PCI experienced lower mortality, mortality/MI, and revascularization rates.

■ COMMENTARY

This study is at odds with the COURAGE trial, which found that there was no reduction in mortality or MI in patients who received PCI + optimal medical therapy (OMT) compared to those who received OMT alone. The present study found that there was indeed a reduction in MI and mortality in patients who received PCI + RMT compared to those who received RMT alone. Why is there such a discrepancy between the findings of these two studies? There are several important differences between the studies that may have contributed to this. First, the COURAGE trial was randomized and prospective, whereas the current study was observational and retrospective. Randomization removes selection bias and we often think of this as a more robust way to demonstrate the benefit of a specific treatment. However, randomized trials, such as the COURAGE trial, tend to have narrow inclusion criteria (more than 35,00 patients underwent diagnostic catheterization and just over 1,000 [approx 3%] were randomized

to each arm). While registries like the current study may have some degree of selection bias, they include a much more general "all-comers" population. Thus, incorporating clinical judgment into an observational study of strategies of care may produce interesting results that could complement the results of randomized clinical trials. There are pros and cons to each study type, and when they are in agreement, this strengthens the evidence from each one. However, when they are discrepant, controversy will persist until a definitive trial is conducted.

Second, this trial used the term "routine medical therapy" rather than OMT, because the exact details of the medications, the blood pressures, lipid levels, medication adherence, and lifestyle factors are not known. In the COURAGE trial, OMT included training nurse managers to counsel patients on lifestyle and risk factor reduction, medications that were provided at no cost to the patients, and follow-up that was rigorous. There was a resultant very high adherence rate: In real-world clinical practice, such high rates of adherence are rarely achieved. Which of these studies more accurately represents our own practices? Perhaps one of the take-home messages from this study is that moving from RMT to OMT may make PCI unnecessary. It is interesting to note, however, that the repeat revascularization rates were very similar in this study and the COURAGE trial. The crossover from medical therapy to PCI was 29% in this study and 33% in COURAGE. The repeat revascularization rates in the PCI arms were 24% and 21%, respectively. Revascularization was symptom-driven. This suggests that the efficacy of the medical therapy at reducing angina was probably about the same in each trial.

Third, the study design here (linking databases from one state) may miss some patients who had events out of state or had data incorrectly logged. This is an inherent problem in all registry data. It is likely that this would make little impact on the overall outcome, but there may be some bias introduced in this way. The results should be interpreted with this in mind.

Finally, the evolution of PCI practice may explain some of the differences. In COURAGE, drug-eluting stents were only used in a minority of patients (3%). Since then, PCI practice has evolved to include higher rates of drug-eluting stent use, better antiplatelet agents, smaller catheters, and more transradial procedures, all of which are associated with better outcomes. It is likely that newer, better interventional techniques have improved PCI outcomes.

How should we treat our patients with stable CAD in the light of these new findings? Does this negate the COURAGE trial? Certainly not! All patients should continue to be treated with guideline-driven medical therapy to achieve targeted risk factor and lifestyle goals, as well as to minimize angina. In addition to this, PCI is known to reduce angina and continues to be a reasonable option in selected patients. ■

ABSTRACT & COMMENTARY

Perioperative Risk in Patients with Coronary Stents

By Andrew J. Boyle, MBBS, PhD
Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

SOURCE: Tokushige A, et al. Incidence and outcome of surgical procedures after coronary bare-metal and drug-eluting stent implantation. A report from the CREDO-Kyoto PCI/CABG Registry Cohort-2. *Circ Cardiovasc Interv* 2012;5:237-246.

It is well known that the risk of perioperative major adverse cardiac events (MACE) is high in patients with coronary stents, especially early after stent implantation. The exact incidence varies from study to study but always seems to decrease with time. The effect of continuing antiplatelet therapy throughout the perioperative period on ischemic and bleeding endpoints is not known. Furthermore, the current generation of drug-eluting stents has lower stent thrombosis rates than earlier versions, so there is a need for more up-to-date data to guide us in managing patients with coronary stents who need to undergo surgery. Tokushige and colleagues present their data from a PCI registry involving 25 centers in Japan from 2005 to 2007. They describe a cohort of 12,207 patients with coronary stents, of whom 2398 (19.6%) subsequently underwent some type of surgery. Their primary ischemic endpoint was the combination of death, myocardial infarction (MI), and stent thrombosis (ST — definite

or probable). The primary bleeding endpoint was moderate or severe bleeding by the GUSTO criteria. The types of surgery were varied and ranged from major to minor procedures. If we consider "high-risk surgery" to include intraperitoneal, intrathoracic, or suprainguinal vascular surgery, then 38.1% of the cohort underwent high-risk surgery.

Not unexpectedly, patients who underwent surgery were older and had more comorbidities than those who did not. The primary endpoint of death/MI/ST after 3 years occurred in 9.6% when surgery was performed early (within 6 weeks) after PCI, but this rate declined to approximately 2% thereafter and never declined further. Interestingly, there was no difference in the rate of perioperative death/MI/ST according to whether the patient had received bare metal stents (BMS) or drug-eluting stents (DES). Single antiplatelet therapy seemed to be adequate in this study, with no extra protection (and possible harm) conferred by continuing dual antiplatelet therapy (DAPT). The authors conclude that surgical procedures were commonly performed after coronary stent implantation, and the risk of ischemic and bleeding complications in surgical procedures was low. In patients selected to receive DES or BMS, there were no differences in outcomes. Perioperative administration of DAPT was not associated with lower risk for ischemic events.

■ COMMENTARY

This registry is one of the larger registries of patients with coronary stents who subsequently undergo surgical procedures, and is also one of the most contemporary. The data are consistent with several other large registries that have been published recently, which have also shown high rates of MACE when surgery is performed early after stenting and that subsequently drop to lower levels. Some registries demonstrate higher absolute rates of perioperative MACE than this one. This may be due to several factors, including the inclusion of low-risk procedures performed under local anesthesia in this study, such as "dermatologic surgery," or endoscopic-guided GI procedures. Some series do not include such low-risk procedures. There is a need for a more uniform approach to data collection in these registries. Furthermore, there may also be differences between study populations, and data from Japan may not be generalizable to different racial groups or to more heterogeneous populations.

It is important to emphasize that of those patients who experienced the primary ischemic endpoint of death/MI/ST, 87% of them died. Other series also highlight this very high mortality from peri-operative events. Perioperative MACE events are not just low-level troponin elevations, they are significant and life-threatening cardiac events. This underscores the need to avoid elective PCI before surgery, and to postpone surgery if possible after PCI. I do not agree with the authors' conclusions that these are "acceptably low" levels. With an early MACE rate of 9.6%, and an 87% mortality within the MACE cohort, one could expect around 9% mortality from a surgical procedure performed within 6 weeks of PCI. It is hard to imagine that the surgeon performing a laparoscopic cholecystectomy would consider a 9% mortality acceptable.

The conundrum of whether to continue single or DAPT perioperatively has not been settled by this study. There are many variables to consider, including the bleeding risk from the type of surgery (e.g., neurosurgery vs dermatologic surgery) and the likelihood of surviving stent thrombosis (e.g., left main stent vs small side branch stent), that are not addressed in this study. What we can take from this paper, placed in the context of other registries, is that patients with stents should take single antiplatelet perioperatively if possible. But stopping all antiplatelet agents or continuing DAPT may also be reasonable alternatives if the clinical situation warrants it. Individual patients should be managed based on their overall ischemic and bleeding risk.

The most recent ACC/AHA guidelines suggest that all surgery be postponed for 12 months after DES, but can safely be performed after 6 weeks in patients who receive a BMS. However, the current study is consistent with other recent registries that suggest there is no difference in perioperative risk with BMS or DES. Thus, the difference between them no longer appears to be as great as once thought. ■

ABSTRACT & COMMENTARY

Oral Anticoagulants During Pregnancy

By Michael H. Crawford, MD, Editor

SOURCE: De Santo LS, et al. Mechanical aortic valve replacement in young women planning on pregnancy. *J Am Coll Cardiol* 2012;59:1110-1115.

Newer bileaflet mechanical heart valves require lower doses of oral anticoagulants to avoid valve thrombosis and embolism genesis. However, little is known about the safety of low-dose regimens in pregnant women who have a hypercoagulable state, yet warfarin embryopathy is known to be dose related. Thus, these investigators from Italy tested women who chose mechanical valve replacement with warfarin anticoagulation before conception was attempted, and then when they became pregnant allowed them three options: 1) the standard heparin in the first trimester, warfarin until the 36th week, and then warfarin until delivery; 2) oral anticoagulation throughout pregnancy until the 36th week, then heparin; or 3) warfarin throughout pregnancy, which was stopped 2 days ahead of planned cesarean delivery and resumed 1 day after delivery. Warfarin was dose adjusted to an INR of 1.5-2.5. Among 20 women with a mechanical aortic valve prostheses, 17 achieved the target INR with < 5 mg/day of warfarin prior to valve replacement. All 17 of these women had normal babies. One patient elected to have low-molecular weight heparin and she had a valve thrombosis in the 11th week. The mother and fetus survived emergency reoperation and she then went on warfarin. The remaining 16 chose option 3 and had no thrombolic or hemorrhage complications. The authors concluded that low-dose oral anticoagulation during pregnancy in women with modern bileaflet aortic valve prostheses is feasible and safe for both the mother and the fetus.

■ COMMENTARY

This is an observational study that resulted from a multidisciplinary program in Italy that provided preoperative counseling to women referred for valve surgery who were contemplating pregnancy. Thus, they were able to test preoperatively which women could achieve an INR of 1.5-2.5 on < 5 mg/day of warfarin. This could be achieved in 85% of the women and all but one of them selected a mechanical valve with the continued warfarin/cesarean section option. These 16 women were the study group. One problem with this approach is that the hypercoagulable state of pregnancy may negate the results of the pre-pregnancy warfarin challenge. In fact, the mean dose of warfarin during pregnancy to achieve the target INR was 4 mg/day which was identical to the pre-pregnancy challenge dose. So at least in this pilot study this approached worked.

Of course this was a highly selected population that was monitored weekly and achieved the target INR 80% of the time. Whether this could be applied to less resource intense situations successfully could be challenging. Also, one cannot condemn low-molecular weight heparin during pregnancy based on their one case, but it is consistent with other reports. Another approach could be a bioprosthetic valve and then if it deteriorates later, replace it with a transcutaneous valve. Although provocative, this study does not establish the best way to resolve the dilemma of managing prosthetic valves during pregnancy. However, it may stimulate a longer, more definitive study. ■

ABSTRACT & COMMENTARY

Riata ICD Lead Failures

By John P. DiMarco, MD, PhD

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SOURCE: Hauser RG, et al. Deaths caused by the failure of riata and riata ST implantable cardioverter-defibrillator leads. *Heart Rhythm* 2012; Mar 23. [Epub ahead of print.]

The Riata and Riata ST ICD leads manufactured by St. Jude Medical have recently come under increased scrutiny because of the observation that the conductor cables could extrude from the outer insulation. To investigate the clinical significance of this finding, Hauser and colleagues queried the FDA Manufacturers And User facility Device Experience (MAUDE) database to examine reports of deaths that may have been caused by Riata and Riata ST lead failure. The MAUDE database is a voluntary reporting system maintained by the FDA. The majority of reports are filed by manufacturers who are required by law to report device-related adverse events. They compared the incidence of lead-related reported deaths to those for another ICD lead, the Medtronic Quattro Secure Model 6947. A lead-related death was defined as a sudden or unexpected death accompanied by evidence of a lead failure. An indeterminant death was one that was either nonsudden, the circumstances were unclear, or evidence of a lead defect was not provided. Deaths were thought to be not lead related if the death was nonsudden, expected for

reasons related to the patient's health, and/or there was no evidence of lead failure. Lead malfunctions, high-voltage conductor short circuits, externalized conductor wires, inside-out abrasion, and can abrasions were also quantitated.

The authors' search of the MAUDE database using the terms "Riata death," and "Quattro Secure death" returned 133 deaths. There were 54 Riata and 17 Riata ST deaths in the MAUDE database. Of these, 18 (33%) Riata deaths and four (24%) Riata ST deaths were considered to be lead-related. There were 20 Riata (37%) and five (24%) Riata ST indeterminant deaths. In comparison, there were 62 deaths reported for the Quattro Secure lead. Of these, only five (8%) were lead-related and 25 (40%) were indeterminant. Four of the 18 (22%) and three of the four Riata ST (75%) lead-related deaths were associated with can abrasions. In an additional seven patients, insulation defects involving the high-voltage conductors resulted in short circuits and failure to deliver therapy. Can abrasions or deaths caused by short circuiting were not seen with Quattro leads. The major sign of catastrophic Riata and Riata ST lead failures was abnormal high-voltage impedance, which could lead to failure to defibrillate. Three Quattro lead-related deaths were associated with oversensing, indicating a pace sensed conductor failure, and two patients were not rescued due to high-voltage conduction defects.

The authors conclude that Riata and Riata ST ICD leads appear to have a higher risk of high-voltage failure than a comparable lead from another manufacturer. The life-threatening failures were not related to the previously identified problem of externalized conductors. Better methods to detect impending Riata or Riata ST lead failures are needed.

■ COMMENTARY

When problems with the Riata and Riata ST ICD leads were first reported, most attention focused on the unusual pattern of "inside out abrasion," which led to externalized conductors visible on fluoroscopy in 10-25% of patients. However, these wires have a double insulation and so far, electrical failures have been much less common. The data in this paper, however, suggest that the Riata lead is also prone to other types of failure in the high-voltage circuit. Since these problems may become apparent only when the high-voltage circuit is activated, they are potentially much more dangerous.

The FDA MAUDE database is a very crude tool since it does not collect data in a standardized format. Many problems are thought to be significantly underreported. However, as shown here, the data, if searched diligently, may be helpful in alerting electrophysiologists, companies, and regulators to previously unsuspected problems.

When this paper was first scheduled for publication, St. Jude Medical took the unusual step of criticizing the data and asked that the paper be retracted. In this observer's opinion, for a company to ask that a peer-reviewed paper be retracted is almost always a mistake. Patient safety should always be the top concern. Rather than criticizing a paper, the company should just try harder to collect better data that can be used by clinicians to protect their patients. ■

ABSTRACT & COMMENTARY

New Cardiomyopathy

By Michael H. Crawford, MD, Editor

SOURCES: Cheng Z, et al. Danon disease as a cause of concentric left ventricular hypertrophy in patients who underwent endomyocardial biopsy. *Eur Heart J* 2012;33:649-656. Maron BJ. A phenocopy of sarcomeric hypertrophic cardiomyopathy: LAMP2 cardiomyopathy (Danon disease) from China. *Eur Heart J* 2012;33:570-572.

Concentric left ventricular hypertrophy (cLVH) is occasionally unexplained. Thus, these investigators from Beijing, China, sought evidence for Danon disease, a glycogen storage disease, in patients being evaluated for cLVH who underwent endomyocardial biopsy. They identified 50 patients with cLVH defined as a wall thickness on echocardiography of > 13 mm and a ratio of the interventricular septum to posterior wall thickness of < 1.3 in whom there was no obvious cause. On biopsy, 14 of these patients showed classic amyloid disease. The remaining 36 had genetic analysis for the lysosome associated membrane protein 2 (LAMP2) gene and three had a mutation of this gene consistent with Danon disease (8%). The remaining 33 patients had cLVH for uncertain reasons. The Danon disease patients tended to be young males (mean age 15 years) with mild mental retardation and Wolff-Parkinson-White (WPW) syndrome (2/3). All had markedly increased LV voltage on ECG with deep T-wave inversion. Also, all had elevated serum CK, BNP, and hepatic enzymes, but normal troponin

levels. All three were still alive and were not hospitalized for cardiac reasons over a mean 20-month follow-up. In addition, all three were NYHA class I and had normal systolic LV function. Their biopsies all showed autophagic vacuoles containing glycogen particles. The authors concluded that Danon disease may explain a significant number of cLVH cases in young men and can be diagnosed by genetic evaluation of the LAMP2 gene.

■ COMMENTARY

Danon disease should be part of the differential diagnosis of young men with LVH. Although they characteristically have concentric LVH, some have asymmetric septal hypertrophy that resembles hypertrophic cardiomyopathy (HCM). Danon disease is an X-linked dominant disease, unlike HCM. Both can present in young men, but Danon disease patients have a higher incidence of mental retardation (70%), WPW on ECG (2/3), and marked increases in serum hepatic enzymes and CK. Also, very high voltage on the ECG and marked T-wave inversions are often present. Thus, based on the ECG, Danon disease falls into the marked precordial T-wave inversion group, which includes HCM and arrhythmogenic right ventricular cardiomyopathy (ARVC). When this abnormality is found on ECGs done in young men being screened for sports participation, further evaluation is indicated. The prevalence of Danon disease varies with the population studied: 1-4% in all comers with LVH, 6% if HCM and ARVC are excluded, and 8% if amyloid is also excluded. The diagnosis can be confirmed by genetic analysis of the LAMP2 gene. The diagnosis is important because Danon patients have a poor prognosis, dying early of heart failure or sudden arrhythmic death. Interestingly, implantable defibrillators do not always terminate lethal arrhythmias in Danon disease. Thus, early cardiac transplantation is the only effective treatment. ■

CME Questions

1. The most common cause of cardiac electrophysiologic device infective endocarditis is:
a. poor dental hygiene.
b. skin infections.
c. gastrointestinal infections.
d. health care interventions.

2. Deaths due to Riata ICD lead failures were due to:
a. failure to pace.
b. failure to defibrillate.
c. oversensing.
d. undersensing.

3. New data on managing chronic anticoagulants during pregnancy support the safety of:
a. low-dose warfarin.
b. keeping the INR between 1.5-2.5.
c. low molecular weight heparin the first trimester.
d. both a and b.
e. All of the above

4. Which of the following is a cause of deep precordial ECG T-wave inversions in young men?
a. Hypertrophic cardiomyopathy
b. Arrhythmogenic right ventricular cardiomyopathy
c. Danon disease
d. All of the above

5. A new registry study in New York state shows that stable CAD patients who receive PCI vs those who do not experience:
a. lower mortality.
b. fewer myocardial infractions.
c. less subsequent revascularization.
d. All of the above

6. The best strategy for avoiding coronary stent thrombosis perioperatively in patients undergoing elective surgery is to:
a. continue dual antiplatelet therapy.
b. switch to low molecular weight heparin.
c. use bare metal stents if surgery is anticipated.
d. delay surgery until 12 months post stent.

CME Objectives

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

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

PHARMACOLOGY WATCH

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

Critical Drug Shortages Are on the Rise

In this issue: Drug shortages; metformin and cancer prevention; migraine prevention guidelines; and FDA actions.

What's causing the shortages?

Drug shortages are happening at an unprecedented rate. Just in the last 2 months, we have seen shortages of diazepam, methotrexate, leucovorin, naltrexone, oxymorphone, mitomycin, fentanyl, metoclopramide, pantoprazole, ondansetron, and dexamethasone among others. What is causing the shortages and is there any end in sight? Although it seems like a new problem, we have seen an increasing number of drug shortages going back to 2005. But while there were about 50 drug shortages in the mid 2000s, last year more than 260 drugs were in short supply, including many commonly used and clinically vital drugs. The cause of these shortages is multifactorial. Some sources in the industry blame price controls, especially for generic drugs. Medicare and Medicaid impose strict controls on most generics, squeezing pharmaceutical companies' ability to make a profit. Some companies have simply decided to drop out of the generic market altogether. Others blame fewer manufacturers. The *Wall Street Journal* reports that there were 26 vaccine makers in the United States in 1967, while currently there are only six. But even these issues do not explain the severe shortages we are seeing. Most experts agree the two major issues causing the current shortages are supply chain disruptions, especially disruptions in raw materials, and problems with manufacturing, especially safety issues, which force the FDA to shut down production of a product line or an entire factory. Safety shutdowns are the most common cause of shortages of sterile injectable drugs. But in other cases, companies limit production themselves when they either have an absolute shortage of raw materials or they decide to divert limited supplies of raw materials from less expensive generics to more expensive brand-name drugs. This is a current issue with some of the attention deficit hyperactivity disorder drugs that have been in short supply for several months. Last month, the FDA initiated a series of steps to increase the supply of critically needed cancer drugs, including allowing the importation of drugs in shortage from Europe and elsewhere. The agency is also fast tracking approval of new manufacturers for short-supply drugs like methotrexate. The FDA, as well as the Obama administration, is also requiring companies to give early warning of potential drug shortages. Finally, the Justice Department will aggressively pursue possible incidences of collusion or price gouging among drug distributors who may be taking advantage of shortages. Despite these steps, there will likely be no short-term easing in drug shortages. ■

Does metformin prevent cancer?

Last month, we reported that low-dose aspirin may be protective against some cancers. Now it looks like metformin may have similar properties. A new study from the American Association for Cancer Research suggests that the diabetes drug may improve the prognosis with pancreatic cancer. In a retrospective study, researchers at the University of Texas studied 302 patients with diabetes and

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pancreatic cancer; 117 of these patients were taking metformin. The 2-year survival rate was 30.1% for the metformin group vs 15.4% for the non-metformin group ($P = 0.004$; x^2 test). The pancreatic cancer patients on metformin lived 4 months longer than non-metformin patients (15.2 months vs 11.1 months). The authors suggest that metformin should be evaluated as a supplemental therapy for patients with pancreatic cancer (*Clin Cancer Res* published online March 31, 2012; doi: 10.1158/1078-0432.CCR-11-2994). Data presented at the AACR meeting in Chicago earlier this year suggest that the drug may also be beneficial for men with prostate cancer, although further research is needed. ■

Migraine prevention in adults

The American Academy of Neurology and the American Headache Society have published their new guideline on pharmacologic treatment for episodic migraine prevention in adults. The highest level (Level A) recommendation for prevention was given to antiepileptic drugs, including divalproex sodium, sodium valproate, and topiramate. Other level A drugs included the beta-blockers metoprolol, propranolol, and timolol as well as the triptan frovatriptan, but this last agent is just for short-term use for menstrually associated migraine (MAM) prevention. Level B drugs included the antidepressants amitriptyline and venlafaxine, the beta-blockers atenolol and nadolol, and the triptans naratriptan and zolmitriptan (also only for short-term MAM prevention). Possibly effective medications included lisinopril, candesartan, some beta-blockers, and carbamazepine. There was little or no evidence to support any other drugs including selective serotonin reuptake inhibitors, calcium channel blockers, or acetazolamide. Drugs that should not be offered include lamotrigine and clomipramine. In a separate section on nonsteroidal anti-inflammatory drugs (NSAIDs) and complementary treatments, Petasites hybridus (butterbur) were given recommended status, while NSAIDs were listed as probably effective (*Neurology* published online April 24, 2012; doi: 10.1212/WNL.0b013e3182535d20, and doi: 10.1212/WNL.0b013e3182535d0). ■

Fibrate use in elderly patients

Fibrate use in elderly patients is associated with worsening renal function and increased risk of hospitalization, according to a new study. Researchers reviewed data from a large Canadian database of patients over the age of 65 who were started on a fibrate or ezetimibe (comparator). Many patients in both groups were also on statins. Fibrate users were more likely to be hospitalized for an increase in serum creatinine (odds ratio [OR] 2.4 [95% confidence interval (CI), 1.7 to 3.3]). Fibrate patients were also more likely to consult a nephrologist, but there was no difference in all-cause mortality or need for dialysis. In a subgroup of 1110 patients in which serum creatinines were available at baseline and within 90 days, 9.1% of fibrate users and 0.3% of ezetimibe users had an increase in serum creatinine of 50% or more (OR 29.6 [CI, 8.7 to 100.5]). The risk was higher if patients had chronic kidney disease. The authors conclude that new fibrate use in the elderly is associated with an increase in serum creatinine and a small increase in hospitalization and nephrology consultation (*Ann Intern Med* 2012;156:560-569). ■

FDA actions

The FDA has approved the first PDE5 inhibitor in a decade for the treatment of erectile dysfunction (ED). Avanafil (Stendra) joins sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) as the fourth drug approved for this indication. Avanafil will be marketed as having a shorter onset and a shorter half-life than the other drugs in this class. Men should take avanafil as needed 30 minutes before sexual activity with onset of action as quickly as 15 minutes. The approval was based on three randomized, placebo-controlled clinical trials of 1267 patients with ED in which 57% of men achieved erections sufficient for intercourse, up from a baseline of 15% (compared to 27% with placebo). Like other PDE5 inhibitors, avanafil should not be taken with nitrates. Commonly reported side effects include headache, flushing, nasal congestion, nasopharyngitis, and back pain. Avanafil will be marketed by VIVUS of Mountain View, California, as Stendra.

The FDA is requiring new labeling on finasteride — Merck's testosterone blocker used for the treatment of benign prostatic hypertrophy (5 mg as Proscar) and male pattern baldness (1 mg as Propecia). The new labeling addresses sexual adverse events such as libido disorders, ejaculation disorders, orgasm disorders, and even male infertility and poor semen quality. Some of these issues, such as libido disorders and ejaculation disorders, may continue after stopping the drug, while infertility and poor semen quality improve or normalize after discontinuation. The labeling change is based on event reports filed with the FDA, although a clear causal relationship has not been made. Still, the agency is recommending that a discussion of the risks and benefits of finasteride include the possibility of sexual side effects. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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Statins and Dyslipidemia: Should we be Looking Beyond LDL?

Source: Boekholdt SM, et al. *JAMA* 2012;307:1302-1309.

TREATMENT OF DYSLIPIDEMIA WITH STATINS produces consistent, durable lowering of low-density lipoprotein cholesterol (LDL-C), which is associated with substantial reductions in myocardial infarction and stroke. Other lipoprotein markers — in particular apolipoprotein B (apoB) and non-high-density lipoprotein cholesterol (non-HDL-C) — are also associated with vasculopathy. Indeed, the putative pathogenetic role of apoB has garnered some enthusiasm from lipidologists who encourage more routine measurement and modulation of apoB as a primary goal.

Risk reduction with statins is imperfect. That is, substantial risk for vascular events and death exists even with excellent LDL-C reduction. Might levels of apoB or non-HDL-C in patients already on a statin help us to discern which ones remain at high risk?

Boekholdt et al performed a meta-analyis of statin trials (n = 62,154) that included data on apoB and non-HDL-C, examining the relationship between on-treatment levels of LDL-C, apoB, non-HDL-C, and cardiovascular outcomes. For each increase of one standard deviation in the level of any of these three markers, the risk for a cardiovascular event increased, and to a very similar degree (13%-16% increase per standard deviation). However, when comparing the three markers with one another, non-HDL-C showed a statistically significantly greater association with increased risk than the other two markers. The authors suggest that based on this and other data, stronger consideration should be given to promoting non-HDL-C as an important target for reduction in subjects with dyslipidemia. ■

When Thiazides are Associated with Hyponatremia

Source: Rastogi D, et al. *J Clin Hypertens* 2012;14:158-164.

CONTROL OF HYPERTENSION IS REWARDED with important reductions in myocardial infarction, stroke, and cardiovascular death. Yet, the job of hypertension control is daunting, since on a worldwide basis it is estimated that more than one-fourth of all adults have hypertension! It has been known for more than 5 decades that thiazides can produce electrolyte disarray, including hypokalemia, hyponatremia, and hypomagnesemia, any of which can result in serious adverse effects and/or hospitalization. Rastogi et al performed a retrospective case-control study to elucidate risk factors for hyponatremic hospital admission while on a thiazide diuretic. They compared 1802 cases of hospitalized thiazide-associated hyponatremia with controls (n = 9003).

Risk for hyponatremic hospitalization doubled with each 10-year increase in age. The only other statistically significant associations were coadministration of an ACE inhibitor and concomitant hypokalemia. The coadministration of an ARB had a strong trend toward increased risk, but was marginally non-significant. Patients with comorbid diabetes, dyslipidemia, and gastroesophageal reflux disease were also more likely to be admitted for hyponatremia. Hopefully, recognition of these associations will assist clinicians to prevent hyponatremia, or at least detect its presence earlier. ■

Broadening Perspectives on Maintaining Healthy Erectile Function

Source: Meldrum DR, et al. *Int J Impot Res* 2012;24:61-68.

FOR MORE THAN A DECADE, IT HAS BEEN recognized that nitric oxide (NO) is critical in the attainment and maintenance of an erection. Accordingly, pathology that induces endothelial dysfunction, and hence impaired generation of NO, is consistently associated with erectile dysfunction (ED). Traditional cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and cigarette smoking are each associated with increased prevalence and incidence of ED. Increases in oxidative stress appear to be a common denominator for many of the paths that lead to endothelial dysfunction.

Additional lifestyle factors that have been associated with endothelial dysfunction include insufficient exercise, obesity, and specific dietary components (e.g., high carbohydrate diet).

Many of the risk factors associated with endothelial dysfunction are modifiable. For instance, obesity is associated with insulin resistance, which lowers vascular NO. Exercise improves NO levels systemically. A high-fat intake may in-

crease oxidative vascular wall stress.

There is some literature support for multifactorial intervention in men with ED to help restore sexual function. Meldrum et al suggest a list of factors that might favorably impact endothelial health (and hence, sexual functionality), including: 1) maintenance of healthy weight; 2) regular aerobic exercise; 3) low-fat, low glycemic-index diet; 4) smoking cessation; 5) alcohol moderation; 6) folate and omega-3 fatty acid supplementation; and 7) ARB rather than ACE treatment of hypertension. ■

Cancer Risks Associated with Diagnostic X-rays

Source: Linet MS, et al. *CA Cancer J Clin* 2012;62:75-100.

Within a few years after the initiation of diagnostic X-rays, toxic effects were noted, including increased risk for skin cancer, leukemia, dermatitis, and cataracts. In this early period, doses of X-ray, especially from fluoroscopy, were high. Protective devices for patients as well as persons occupationally exposed to diagnostic radiation demonstrably reduced such adverse consequences.

The dose of radiation that is required to induce cancer is not clearly known. However, populations who have been exposed to calculable levels of radiation through wartime exposure (i.e., Japanese atomic bomb survivors) and subjects receiving radiation therapy help us to predict a dose-response relationship. It is not yet clear to what extent the high-dose radiation exposure and subsequent development of cancer reflects cumulative lower dose exposures. Nonetheless, because radiation toxicity may be related to total exposure, peak exposure, or both, radiation from commonly used diagnostic procedures has stimulated concern.

For instance, a CT of the abdomen, commonly used investigationally for persons with acute or chronic abdominal pain, incurs the same amount of radiation exposure as 750 chest X-rays. Linet et al quote recent estimates suggesting that the 70 million CT scans performed each year in the United States could lead to 29,000 additional cancers.

The authors recommend a number of steps to reduce unnecessary radiation exposure, including 1) learning about radiation doses associated with various imaging techniques, 2) consideration of imaging without radiation (i.e., ultrasound, MRI), and 3) avoidance of elective X-rays in pregnant women. ■

The REDEEM Trial: Dutasteride for Management of Localized Prostate Cancer

Source: Fleshner NE, et al. *Lancet* 2012; 379:1103-1111.

Prostate cancer (PCA) comprises 25% of all newly diagnosed cancers in men in the United States. PCA chemoprevention trials with 5-alpha-reductase inhibitors have had mixed results. The first major PCA prevention trial with finasteride showed a 25% decrease in total PCA vs placebo, but an increase in more aggressive (high Gleason score) cancers. A similarly designed large prevention trial with dutasteride again found a 25% decrease in total PCA, but there was an increase in more aggressive cancers (albeit not statistically significant in this trial). Based on these mixed results, clinicians have been reluctant to use 5-alpha-reductase inhibition for PCA prevention.

Might 5-alpha-reductase inhibitors prove more useful for treatment of PCA rather than prevention? The REDEEM trial randomized men with localized PCA (n = 300) who had elected active surveillance for their disease to dutasteride 0.5 mg/d or placebo. At 3 years time, the risk of PCA progression was reduced by 38% in men on dutasteride.

Because dutasteride is generally well tolerated, men with non-aggressive Gleason scores (six or less) who might otherwise select active surveillance for localized disease may have reduced risk of disease progression with the addition of dutasteride. ■

Amantadine for Traumatic Brain Injury

Source: Giacino JT, et al. *N Engl J Med* 2012;366:819-826.

In young adults (age 15-30), traumatic brain injury (TBI) is the most common cause of death and disability. As many as one in seven TBI hospital admissions leaves the hospital in a vegetative state. Amantadine (AMT) has achieved some popularity for inclusion in pharmacotherapy regimens for disorders of consciousness, although the mechanism by which AMT effects positive change is uncertain. Certainly it has been shown that AMT blocks N-methyl-D-aspartate, and is an indirect agonist of dopamine, but what these pharmacologic effects do to enhance outcomes is unclear. In any case, initial trials have supported its use, and a major observational trial indicated better outcomes in TBI for persons who had received AMT.

Patients who had sustained TBI (n = 184) and who were either vegetative or minimally conscious for at least 1 month (and no longer than 16 weeks) after injury were randomized to AMT or placebo. AMT was administered initially at 100 mg b.i.d., and titrated to 200 mg b.i.d. if the Disability Rating Scale had not shown improvement. The course of treatment was 4 weeks in duration, and patients were monitored for 2 weeks after continuation of treatment.

AMT treatment was associated with statistically significantly better functional recovery outcomes than placebo. AMT is not a new medication, so its adverse effects profile, characterized by mild, transient adversities, is well known. These data support the inclusion of AMT in the pharmacologic regimen of serious TBI. ■

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