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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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INSIDE

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

Highlights from the 60th ACC Meeting: Late-breaking Trials

SPECIAL COMMENTARY

By Michael H. Crawford, MD

DR. GEORGE DOURGAS PRESENTED THE RESULTS OF THE HARMOnizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) analysis of predictors of stent thrombosis in more than 3,600 patients, and showed that higher doses of clopidogrel (600 mg) pharmacologic therapy, lesion characteristics, and the length of stents were predictors of early-stent thrombosis. Patient-related factors such as smoking and diabetes were the most important predictors of late thrombosis. The type of stent was not related to stent thrombosis at any time for up to one year (3.3% drug eluting vs. 3.4% bare metal). Thus, fears of high rates of late-stent thrombosis with drug-eluting stents seem unfounded.

Dr. Eric Bonnefoy presented the AGIR-2 study comparing pre-hospital tirofiban to cath lab administration for primary percutaneous coronary intervention (PCI) and found no difference in the angiographic results of PCI or initial clinical outcomes. However, a similar German study (ON-TIME-2) found that one-year mortality trended lower with pre-hospital tirofibran, especially in those > age 65. Thus, pre-hospital platelet glycoprotein 11b/111a inhibition remains controversial.

The STICH trial tested the hypothesis that adding ventricular reconstruction surgery to coronary bypass surgery (CABG) in patients with anteroapical LV dysfunction would improve outcomes. Dr. Robert Jones presented the results, which showed that although the left ventricular end-systolic volume was smaller, four-year mortality was not different. Thus, routine left-ventricular reconstruction during CABG for post-anterior MI patients is not indicated.

Dr. Luc Eurlings presented the results of the PRIMA study, which assessed the value of pro-BNP measurements for managing patients with heart failure as compared to usual hospital care and found no difference in mortality or rehospitalization over a two-year follow-up. However, patients who achieved and maintained a target pro-BNP

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level did do better. Thus, repeated BNP levels should not be a routine part of hospitalized heart failure patient's management.

Dr. Robert Glynn presented an analysis of the JUPITER trial secondary endpoint of venous thromboembolism, which occurred in 94 of 17,802 participants in this primary prevention trial. The rosuvastatin group had 34 and the placebo group 60 (RR 0.57, $p < .01$). If this result was due to an anticoagulant effect of rosuvastatin, there was no increased bleeding in this group. Thus, statins may decrease venous thromboembolism rates in certain individuals, for unclear reasons. (*N Engl J Med*. online.)

Dr. Carlo Brigerori presented the NAPLES-11 trial of 668 patients undergoing elective PCI who were not on statin therapy. They were randomized to atorvastatin 80 mg or placebo 24 hours pre-procedure and monitored for periprocedural MI (pp MI) based upon symptoms, ECG and CK-MB. PPMI was reduced from 16% to 10% in the atorvastatin group. This is another study demonstrating the ability of statins to reduce cardiovascular events in selected patients.

Dr. Germano Di Sciascio presented the ARMYDA-RECAPTURE study and showed that when atorvastatin therapy was given in high doses before PCI in patients on statins, there was a 48% relative risk reduction in 30-day major adverse cardiac events (MACE). He concluded that our practice should change to loading all patients with high-dose statins before PCI.

Dr. Jochen Senges presented the OMEGA trial which showed that omega-3 fatty acids were of no benefit to post-MI patients, as compared to an olive oil control group. The primary endpoint was sudden cardiac death, and neither it nor any of the secondary endpoints were significantly affected by omega-3 fatty acids in this study. Other than for treating hypertriglyceridemia, the role of omega-3 fatty acids remains controversial.

Dr. Kristan Newby presented the EARLY-ACS study of 4,722 patients with non ST-elevation acute coronary syndromes (ACS) who were randomized to eptifibatide administered early after non-ST elevation ACS vs. elective administration at the time of PCI. Early therapy did not affect MACE, and bleeding complications were more common in the early group. Thus, early use of glycoprotein 11b/111a agents in non-ST elevation ACS does not seem useful and may increase bleeding. (*N Engl J Med*. online).

Dr. Bengt Fellstrom presented the AURORA study, which randomized end-stage renal disease patients on hemodialysis to rosuvastatin vs. placebo. LDL-cholesterol was reduced 43% in the rosuvastatin group, but time to the first major adverse cardiac or cerebrovascular event (MACCE) was not altered. The authors concluded that statins do not prevent cardiovascular disease (CVD) in dialysis patients. This study is now published in full. (*N Engl J Med*. 2009;360:1395-1407.) (*N Engl J Med*. online.)

The Indian polycaps study (TIPS) was presented by Salin Yusuf. The capsule contained aspirin 100 mg, simvastatin 20 mg, atenolol 50 mg, ramipril 5 mg, and HCTZ 12.5 mg. The polycap was compared to its component drugs and their combinations in 2,400 subjects aged 45-80 years with one risk factor for CVD but no overt CVD. No outcome data were presented, but blood pressure and LDL cholesterol were lower on the polycap. Unfortunately, compliance was not good, with 18% discontinuing therapy in three months. Dr. Yusuf concluded that giving the polycap to everyone over the age of 50 could reduce CVD risk by half.

Dr. Stuart Connolly presented the results of the ACTIVE-A study comparing aspirin plus clopidogrel to aspirin alone in atrial fibrillation patients at high risk of a vascular event, but unable to take warfarin. The primary endpoint of MACCE was reduced 11% (RR 0.89) on combination therapy, mainly due to a 28% (RR 0.72) reduction in stroke. This effect was mainly on ischemic stroke. There was an increase in major bleeding. Thus, in patients with atrial fibrillation at risk of stroke, but who cannot take warfarin, aspirin plus clopidogrel may be more effective than aspirin alone at preventing ischemic stroke, but at a cost of more major bleeding. ■

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Discontinuing Anti-platelet Therapy in Patients with Drug-eluting Stents

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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

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

Source: Eisenberg MJ, et al. Safety of short-term discontinuation of antiplatelet therapy in patients with drug-eluting stents. *Circulation*. 2009;119:1634-1642.

The introduction of drug-eluting stents (DES) was met with enthusiasm from the interventional cardiology community because of the dramatic reduction in rates of in-stent restenosis (ISR). However, it came to be recognized that this clinical benefit, due to reduced proliferation of smooth muscle cells, came at a price. There is incomplete coverage of the stent struts by endothelial cells, leaving stent struts exposed to circulating platelets and, thus, the risk of stent thrombosis persists longer with DES than with bare-metal stents (BMS). Exactly how long this increased risk of stent thrombosis continues after DES implantation remains unknown, but it appears to be for at least a year. Cessation of dual anti-platelet therapy has been associated with increased risk for late-stent thrombosis, though the effects of brief interruption of anti-platelet therapy are not known. Patients with coronary artery disease who receive DES are also at risk for other common conditions, such as gastrointestinal bleeding. This, and other clinical scenarios, would normally lead to cessation of anti-platelet therapy, but this decision is not easy in patients with DES who may be at risk for stent thrombosis. Clinicians are now often faced with the question, "What is the risk of stent thrombosis if anti-platelet therapy has to be briefly discontinued in patients with DES?" Despite the widespread use of DES, there is a paucity of data in the literature about the best way to manage anti-platelet therapy in such patients.

Subacute stent thrombosis (SAT), occurring within 30 days after percutaneous coronary intervention (PCI), occurs with BMS and DES with equal frequency. However, late-stent thrombosis (LST) and very late-stent thrombosis (VLST) occur predominantly with DES. Current guidelines recommend at least one year of dual anti-platelet therapy after PCI with DES. In order to assess the association of anti-platelet therapy cessation with the timing of LST and VLST, Eisenberg et al performed a Medline search to identify cases of LST and VLST reported in the literature from 2001 to 2008. They included only cases that satisfied the Academic Research Consortium definition of definite stent thrombosis, with either angiographically proven or autopsy-proven stent thrombosis. They categorized cases on the basis of their anti-platelet (aspirin [ASA] and/or thienopyridine) therapy at the time of LST. They divided the patients into four exposure categories: 1) patients who simultaneously discontinued both ASA and thienopyridine therapy, 2) patients who discontinued ASA therapy after previously discontinuing thienopyridine therapy, 3) patients who discontinued thienopyridine therapy but continued ASA, and 4) patients who did not discontinue dual anti-platelet therapy. Their search yielded 84 studies and 161 cases of LST or VLST. They included both paclitaxel-eluting stents and sirolimus-eluting stents, and there were a similar number of cases reported with each stent type. The patients were predominantly male (88%), with a mean age of 58.4 ± 13.4 years. The left anterior descending coronary artery was involved in 64%, the right coronary artery in 24%, the left circumflex in 8%, and the left main coronary artery in 4%. The clinical presentation was acute myocardial infarction in 87%, unstable angina in 12%, and sudden death in 1%. In-hospital mortality occurred in 18 cases (13%) but vital status was not recorded in 25 cases.

In patients who stopped both ASA and thienopyridine at the same time, the median time-to-stent thrombosis was seven days after cessation of dual anti-platelet therapy. In patients who had previously stopped thienopyridine and then stopped ASA later, the median time-to-event after ASA cessation was also seven days. However, if thienopyridine was stopped but ASA was continued, the median time-to-event was 122 days ($p < 0.0001$ vs. the other two groups). In 10 cases, the thienopyridine used was ticlopidine instead of clopidogrel. No cases of stent thrombosis were reported in patients who stopped ASA but continued on thienopyridine.

Eisenberg et al then examined the proportion of patients experiencing stent thrombosis early after cessation of anti-platelet therapy. In patients who discontinued thienopyridine but continued ASA (n = 94), only six (6%) occurred within the first 10 days and only two (2%) occurred in the first five days. In contrast, in patients who discontinued both agents at the same time (n = 33), stent thrombosis occurred in 26 (79%) within 10 days ($p < 0.0001$). Furthermore, in patients who previously discontinued thienopyridine and then stopped ASA later (n = 15), stent thrombosis occurred in 10 patients (67%) within 10 days ($p < 0.0001$). They concluded that short-term cessation of thienopyridine may be relatively safe against stent thrombosis in patients with DES if ASA is continued.

■ COMMENTARY

Management of anti-platelet therapy in patients who

have DES is a common clinical problem and one in which there has been a lack of data to guide clinical decision-making. Eisenberg et al aimed to delineate the relationship of anti-platelet therapy cessation to late-stent thrombosis. Their data are evocative and may help guide clinical decision for brief interruption of anti-platelet therapy. Patients ceasing both ASA and thienopyridine had stent thrombosis at a median of seven days after drug cessation, and 67%-79% of stent thromboses occurred within 10 days. Conversely, maintaining ASA alone resulted in a much longer median time-to-stent thrombosis of 122 days, with only 6% occurring within 10 days after drug cessation. This suggests that brief interruption of thienopyridine, while continuing ASA, results in low rates of stent thrombosis within the first week or two after drug cessation. This is very helpful information in an area where no randomized, controlled trials exist.

This study has several important limitations. Literature searches are inherently hampered by reporting bias and their retrospective, observational nature. The actual risk of stent thrombosis may differ from that reported in the literature. Furthermore, the indication for drug cessation was not mentioned. Some patients discontinue because of bleeding, others to undergo surgery, and still others due to non-compliance. These patients may have very different risk profiles and, therefore, the data may not be able to be extrapolated to all clinical scenarios. It should be emphasized that peri-operative cessation of anti-platelet therapy may result in a rebound pro-thrombotic state, and the safety of interruption of dual anti-platelet therapy in this scenario was not specifically examined. These results should be interpreted with caution in patients undergoing surgery after DES implantation. ■

Cilostazol or Double-dose Clopidogrel in "Clopidogrel Resistance"?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Jeong YH, et al. Randomized comparison of adjunctive cilostazol versus high maintenance dose clopidogrel in patients with high post-treatment platelet reactivity: Results of the ACCEL-RESISTANCE (Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With Clopidogrel Resistance) randomized study. *J Am Coll Cardiol*. 2009;53: 1101-1109.

DUAL ANTI-PLATELET THERAPY WITH ASPIRIN AND CLOPIDOGREL reduces cardiac events in patients who have acute coronary syndromes (ACS) and in patients who have percutaneous coronary intervention (PCI). Recently, the phenomenon of "clopidogrel resistance" has received much attention because of the clinical problems of stent thrombosis and recurrent ACS. However, a precise definition of this clinical entity is lacking. There are numerous platelet function tests available, yet all have limitations. Emerging data now suggest that platelet function testing may predict patients at higher risk for recurrent coronary events. At present, identifying patients at higher risk may be possible, but we have no clinical studies to guide us in managing this increased risk. Accordingly, Jeong et al compared the effect of increased maintenance dose of clopidogrel vs. addition of cilostazol on platelet function.

Three hundred patients undergoing elective PCI were screened. All received a loading dose of 300 mg of clopidogrel at least 12 hours before the procedure, ongoing clopidogrel 75 mg daily, and aspirin 200 mg daily for the duration of the study. During the PCI procedure, blood was drawn for platelet function testing by two complementary methods: light transmission aggregometry (LTA) and the P2Y12 VerifyNow assay. Patients with high post-treatment platelet reactivity (HPPR) were then randomized to receive either increased maintenance dose of clopidogrel (150 mg daily, n = 30) or addition of cilostazol 10 mg twice daily in addition to standard anti-platelet therapy (n = 30). Platelet function testing was repeated at 30 days. The baseline characteristics were well matched between groups, with average age being 63 years, 67% were male, 12% had chronic kidney disease, ejection fraction was approximately 60%, and 25% had diabetes. The lesion and procedural characteristics were also similar between the treatment groups.

There were no bleeding events and the drugs were not discontinued in any patient. After 30 days, both treatment groups had reduced rates of HPPR compared to baseline, but the group receiving adjunctive cilostazol had reduced HPPR compared to the high-dose clopidogrel group. At baseline, the maximal platelet aggregation measured by LTA in response to 5 micromol of ADP was no different between the groups (61.1 ± 7.8 vs. 61.3 ± 7.4 in high-dose clopidogrel and cilostazol groups, respectively; $p = 0.943$). After 30 days, however, the maximal aggregation was lower in both groups compared to baseline, but also lower in the cilostazol group compared to the high-dose group (43.9 ± 11.9 vs. 29.5 ± 12.7; $p < 0.001$). Similar reductions were seen in late aggregation, as well as in both maximal and late aggregation in response to 20 micromol ADP. Jeong et al confirmed these results using a different method, the VerifyNow P2Y12 assay. The percent platelet

inhibition assessed by this method was also no different between the groups at baseline (11.8 ± 12.4% vs. 11.7 ± 19.2%, $p = 0.979$). After 30 days, the percent platelet inhibition had improved in both groups, but had improved more in the cilostazol group (35.7 ± 20.3 vs. 48.4 ± 19.2; $p = 0.015$ between groups). The percentage of platelet disaggregation in response to ADP also did not differ at baseline. This percentage increased in both groups, but to a greater degree in the cilostazol group. Jeong et al concluded that among patients with HPPR undergoing coronary stenting, adjunctive cilostazol reduces the rate of HPPR and achieves intensified platelet inhibition as compared with high maintenance dose clopidogrel of 150 mg/day.

■ COMMENTARY

Differing response to anti-platelet therapy between patients is an increasingly recognized risk factor for recurrent coronary events. Unfortunately, there is no clinical trial evidence to guide us on how to manage patients who do not achieve maximal platelet inhibition. The present study by Jeong et al gives us two alternatives to further improve the platelet inhibition in patients who show HPPR. It remains unknown whether this will translate into a reduction in clinical events, and prospective, randomized clinical trials are necessary to assess this. Although all platelet function tests have limitations, Jeong et al conducted a rigorous study using differing concentrations of ADP, examining both maximal and late aggregation, and using the P2Y12 point of care assay as well. The congruent results across all these endpoints using different methodologies increase the strength of the conclusions drawn.

Cilostazol is an interesting agent, possessing both anti-platelet and anti-restenosis properties, and is widely used in Asia. In the United States, it is FDA-approved only for symptomatic peripheral arterial disease. The present study is appealing because cilostazol may represent a new weapon in the fight against both restenosis and stent thrombosis in patients with coronary stents. Although not approved for this indication, Jeong et al show that it has additional anti-platelet effects in patients who have HPPR after clopidogrel loading. It bears mentioning that cilostazol can precipitate heart failure exacerbations and is contraindicated in patients with congestive heart failure. Therefore, these results are not necessarily applicable to all coronary artery disease patients. Despite the small size of this study and the lack of clinical endpoints, this provides clinicians with an alternative (off-label) option for patients who do not achieve maximal platelet inhibition with standard dual anti-platelet therapy. It needs to be evaluated whether reduction of HPPR with triple anti-platelet therapy could be translated into improved clinical outcomes. ■

Sudden Death in Athletes

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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Dr. DiMarco is a consultant for Novartis and does research for Medtronic and Guidant.

Source: Maron BJ, et al. Sudden deaths in young competitive athletes: Analysis of 1866 deaths in the United States, 1980-2006. *Circulation*. 2009;119:1085-1092.

The U.S. National Registry of Sudden Death in Athletes assembles and analyzes data on the deaths of young athletes who participate in competitive sports. The Registry systematically collects reports of death in athletes using a number of different search techniques, including informational databases, news media accounts, internet search engines, and voluntarily submitted reports. In the Registry, an athlete is defined as "someone who participates in an organized team or individual sport that required regular competition against others as a central component, placed a high premium on excellence and achievement, and required systematic and, in most instances, vigorous training." Deaths related to participation in intramural sports or informal recreational activities are not included.

During a 27-year period, the Registry collected data on 1,781 athletes who died suddenly and 85 athletes who survived an episode of cardiac arrest. The absolute number of reports has increased over time at a rate of about 6% per year, with a higher proportion of female athletes also noted over time. There were 513 deaths that could not be classified due to incomplete information.

In the entire group of 1,866 sudden deaths or cardiac arrests, a probable or definite cardiovascular cause was identified in 1,049 (56%). Hypertrophic cardiomyopathy was the most common abnormality identified, occurring in 251 of the 1,049 cases. In order of frequency, the next most common cardiovascular conditions identified were: coronary artery anomalies (119 cases), myocarditis (41 cases), arrhythmogenic right ventricular cardiomyopathy (30 cases), and long QT syndrome (23 cases). In 75 of these athletes, the cardiac disorder had been diagnosed during their lifetime but they had continued to participate in organized competitive sports. In six, this was despite restriction recommended by their physician. The mean age at the time of death was 18 ± 5 years, with 65% of the events occurring in those £ age 17, 29% between 18 and 25, and 7% between age 26 and 39.

Hypertrophic cardiomyopathy and congenital coronary anomalies were more common causes of death among non-Whites than among Whites. Ion channelopathies were more common among Whites. After cardiovascular disorders, trauma was the next most common cause of sudden death. There were 416 deaths that resulted directly from blunt trauma, most frequently with injuries to the head and neck. Blunt injury as a cause of sudden death during sports was most frequently seen during motor sports (97), football (140), skiing (15), boxing (42), track and field (25), and equestrian competition (24). There were 65 cases of commotio cordis, with sudden death or cardiac arrest occurring immediately after a blunt precordial blow. Additional nontraumatic, non-cardiac causes of death included heat stroke (46), drug use (34), asthma (15), and pulmonary embolism (13). Sudden cardiovascular death events occurred most commonly during or just after physical activity. However, 20% of the sudden deaths among trained athletes occurred under circumstances not immediately associated with sports activity. Using an estimate of 10.7 million sports participants, the incidence of sudden death was 0.61 per 100,000 person years.

Maron et al concluded that sudden death in U.S. competitive athletes is a low-frequency event. Cardiovascular disease and blunt trauma are the most commonly identified causes. The low frequency of events among participants makes design of effective screening programs to reduce sudden death during athletics difficult.

■ COMMENTARY

Sudden death during athletic competition is a fortunately infrequent, but very high-profile topic. The death of an athlete stirs the public interest and arouses emotions about a young life needlessly lost. These data from a long-running national registry highlight some of the problems involved in combating this problem. In Europe, the approach has been to mandate pre-participation screening of all athletes with history, physical exam, and ECG. In the United States, the current recommendations are more conservative in that they do not include routine ECG recordings. This is due to the costs and difficulty involved in obtaining ECGs in the millions of athletes below the college level and of doing follow-up tests if abnormalities are detected. The issue of positive ECG findings that are not clinically significant is highlighted by reports that up to 30%-40% of elite college athletes may have some abnormal ECG finding in the absence of any cardiac condition that should restrict activity. We have a similar experience here at the University of Virginia where all varsity athletes are screened as part of an ongoing research program. ■

ICD Complications

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Peterson PN, et al. Gender differences in procedure-related adverse events in patients receiving implantable cardioverter-defibrillator therapy. *Circulation*. 2009;119:1078-1084.

THIS REPORT FROM THE IMPLANTABLE CARDIOVERTER defibrillator (ICD) portion of the National Cardiovascular Data Registry focuses on the relationships of gender to in-hospital, ICD-associated adverse events. The National ICD Registry (NICDR) was established in 2006 after the Centers for Medicare & Medicaid Services required that all ICD implants in Medicare recipients for primary prevention of sudden cardiac death be included in a comprehensive registry. Most hospitals report all ICD implants to the NICDR, including implants for both primary and secondary prevention indications and implants in non-Medicare recipients. The NICDR collects baseline data about each patient at the time of implant. After hospital discharge, trained reviewers analyze the hospital chart for in-hospital complications. Major adverse events prospectively defined in the NICDR include: cardiac arrest, cardiac perforation, cardiac valve injury, coronary venous dissection, hemothorax or pneumothorax, deep phlebitis, transient ischemic attack, stroke, myocardial infarction, pericardial tamponade, and AV fistula. Other adverse events of interest include: drug reaction, new conduction block, pocket hematoma, lead dislodgement, peripheral embolus, and device-related infection. Hospital length of stay is also collected.

In this report, data from 161,407 patients undergoing a first ICD implantation between January 2006 and December 2007 were analyzed. Repeat procedures for generator changes were excluded. Of these patients, 73% were men and 27% were women. The mean age was similar between men and women (67.9 vs. 67.0 years). There were also no differences in the proportion of men and women who received their ICD for a primary prevention indication (72% vs. 72.2%) or in reported left-ventricular ejection fraction (27.1% vs. 27.6%). Women, however, were more likely to be Black (10.9% vs. 17.5%), to have New York Heart Association class III or IV congestive heart failure (50.1% vs. 57.2%), and to have a nonischemic cardiomyopathy (27.2% vs. 44.3%). More women than men received biventricular ICDs (39.1% vs. 34.1%).

In the entire cohort, in-hospital adverse events were noted in 3.6%. The adverse event rate was higher in women than in men (4.4% vs. 3.3%, $p < 0.001$). Adverse events that

were more commonly seen in women were typically procedure-related technical issues, including pneumothorax and hemothorax, coronary venous dissection, pericardial tamponade, perforation, and lead dislodgement. There was no difference between men and women in in-hospital mortality. Hospital length-of-stay was longer for patients who had a reported complication (7.1 days) compared to those without a complication (3.8 days, $p < 0.001$). After adjustment for various factors, women had a significantly higher odds ratio (OR) for experiencing any adverse event (OR 1.32) or a major adverse event (OR 1.71) compared to men.

Peterson et al then discussed possible reasons why women are more likely to have complications with ICD implantation than men. In the NICDR, there was no difference in age or most co-morbidities between men and women. Since the increased frequency of adverse events was primarily due to technical issues, they postulate that body size may be a factor. Unfortunately, the NICDR does not collect data on body size or BMI, so this remains only a hypothesis.

Peterson et al conclude that data from the NICDR should be used to guide efforts to reduce the frequency of adverse events associated with ICD implantation in both men and women.

■ COMMENTARY

These data from the NICDR point out how valuable the Registry will be for analyzing the risks and benefits associated with ICD therapy. In the past, information about ICD complications was usually derived either from single-center surveys or from reports from randomized, clinical trials. However, in routine clinical practice, patients who receive ICDs tend to be older and may have more comorbidities than the patients seen in clinical trials. The size of the NICDR database and the fact that it includes over 90% of all ICD implants in the United States allows it to be an important tool for analyzing various aspects of ICD therapy.

It is important to recognize, however, that this paper deals with only in-hospital complications. Many infections, or some lead dislodgments, particularly coronary sinus leads, will occur after hospital discharge for elective procedure, and would not be captured. Other major complications of ICD therapy, such as inappropriate shocks and lead and generator failures, also usually occur later during the course of therapy. Thus, the total complication rate is likely to be substantially higher than the figure quoted here. At the same time, some of the adverse events listed, e.g., myocardial infarctions and strokes, even though they occurred during the same hospitalization, the ICD implants were probably due to the patient's underlying disease and were not strictly device related

The reasons for the gender-based differences in complications are not obvious. As an implanting physician, I agree that body habitus may make a difference in the complications that are related to vascular access and lead placement; these complications accounted for a large fraction of major gender-related differences reported in this paper. The observations reinforce the need for careful attention to technique when implanting ICDs in both men and women. The NICDR is a valuable resource toward this goal, and it should be strengthened to allow more long-term follow-up data to be collected and analyzed. ■

Endothelial Function and Atherosclerosis

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

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

Source: Halcox JP, et al. Endothelial function predicts progression of carotid intima-media thickness. *Circulation*. 2009;119;1005-1012.

MANY REPORTS EVALUATING CORONARY RISK FACTORS in overtly healthy individuals have been highlighted in a variety of preventative cardiology programs, guidelines, and sources. The Framingham Study gave an amazingly powerful kick start to the recognition of coronary risk factors. This somewhat sophisticated article suggests that the vascular endothelium is an important piece of the risk-factor puzzle, and supports a relatively new methodology for coronary risk-factor identification as it relates to endothelial function status.

Halcox et al state, "the vascular endothelium has a central role in the maintenance of vascular health and the nature of endothelial cell function. . .recognizing and responding to local physical and chemical signals, endothelial cells are able to influence vasomotor, thrombotic, inflammatory, and cellular pathways that affect the short- and long-term biology of the vessel wall." Thus, disordered endothelial function and vascular dysfunction may predict cardiovascular (CV) outcome in high-risk subjects.

Halcox et al in London have assessed the implications of atheroma progression in the carotid arteries using carotid intima media thickness (CIMT) in asymptomatic subjects selected from the Whitehall II study population. The protocol features a serial assessment of CV risk factors. The study subjects consisted of healthy, older non-smokers without diabetes or CV disease. The main Whitehall II study consists of more than 10,000 subjects, of which 282 participants

were selected for this vascular protocol (phase 5, 1997-1999); initial enrollment took place from 1985 to 1987. Halcox et al sought to prospectively evaluate the influence of endothelial dysfunction on the progression of CV disease and CIMT thickness. Subjects underwent a complete CV risk-factor analysis, including CIMT (right and left common carotid artery) and brachial artery vasomotor function with arterial diameter and high-resolution ultrasound, with reassessment at a mean of 6.2 years (phase 7 - 2003-2005). A total of 213 participants completed the two studies.

Risk Factor Measurement: Blood pressure, waist circumference, fasting plasma glucose, cholesterol, and standard lipid particles were measured. Vascular studies included brachial artery function (flow mediated dilation or FMD) and CIMT, measured by experienced staff. Statistical analysis indicated that CIMT and the annual rate of CIMT progression were normally distributed. The value of using FMD to predict adverse progression of CIMT was also assessed.

Results: At baseline, age, blood pressure, and waist circumference were all inversely related to FMD. Women increased CIMT after menopause. Framingham risk score was strongly correlated with CIMT and, inversely, with FMD. Mean annual rate of progression of CIMT was similar in both men and women, and correlated with age. After adjustment for age and sex, FMD was the sole parameter that remained associated with CIMT. Other markers did not affect the relationship between FMD and CIMT. Reactive hyperemia was not associated with IMT progression.

Halcox et al claim, ". . . for the first time, we can now demonstrate that impaired endothelial function is associated with more rapid progression of structural arterial disease in a general, middle-aged population." The data indicate that the findings are robust and independent of conventional risk factors and the Framingham risk score. Endothelial function testing with FMD may, therefore, have a role in identifying those individuals at increased of CV risk. They conclude that a blunted FMD is associated with more rapid progression of development of arterial disease in this middle-aged population without clinical CV disease. Furthermore, they suggest, as noted, that endothelial function testing may be able to identify subjects at a high or increased risk of disease progression, including those with increased and/or progression of disease.

■ COMMENTARY

This study explored whether endothelial testing can help identify preclinical disease. Although these conclusions only apply to low- and intermediate-risk individuals, endothelial dysfunction is well known to be associated with a poorer prognosis. The results suggest that the combination of both CIMT and FMD are markers of progression. FMD testing is an attractive measure of vascular status in the assessment in both the earlier and later stages of atherosclerotic disease.

Of interest, women and men had equal rates of CIMT progression (women had a lower initial CIMT, which increased after menopause), with similar subsequent progression of increased CIMT. FMD was most closely associated with a change in CIMT over a six-year period, suggesting endothelial factors are a causal determinant of atherosclerosis.

This large, detailed study is consistent with the concept that endothelial pathobiology may identify presymptomatic coronary disease. Increased CIMT indicates an abnormal vessel wall, presumably due to atherosclerotic disease. The methodology for obtaining accurate FMD and CIMT are feasible in high-quality clinical practices or clinical research units. It is critical to have highly trained technicians and strict adherence to testing methods. Flow-mediated dilatation is more labor intensive, with fewer publications than with CIMT. In conclusion, we all need to become educated about these emerging vascular diagnostic techniques in carotid and coronary arterial studies. ■

CME Questions

24. Abnormal flow-mediated vasodilation in apparently healthy middle-aged individuals predicts:
a. abnormal carotid vessel wall.
b. sudden death.
c. strokes.
d. All of the above

25. Thrombosis of drug-eluting stents is reduced if the patient is taking:
a. aspirin.
b. clopidogrel.
c. Both
d. All of the above

26. In patients who do not have an optimal platelet response to clopidogrel, which is the most effective option?
a. Increase clopidogrel to 150mg/day
b. Increase aspirin to 325mg/day
c. Add cilostazol therapy
d. None of the above

Answers: 24. (a); 25. (d); 26. (c)

CME Objectives

The objectives of *Clinical Cardiology Alert* are to:

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

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

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

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

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*.

FDA Warning: Pharmaceuticals in "Natural" Products

In this issue: Aspirin dose and cardioprotection; uncovering modafinil's abuse potential; proton-pump inhibitors and clopidogrel; FDA actions.

Finding pharmaceuticals in natural products

Some natural products are not so "natural" after all. The FDA has warned consumers for several months that a number of weight-loss products contain undeclared pharmaceutical ingredients. The newest products to join the list are Herbal Xenicol which contains cetilistat (a drug similar to orlistat that is not approved in this country), as well as Slimbionic and Xsvelten, both of which contain sibutramine (the prescription medication also known as Meridia®). The FDA's list of over-the-counter weight-loss agents that contain undeclared active pharmaceutical ingredients now includes 72 products. Some of the other undeclared pharmaceutical ingredients found in these products include fenproporex (an amphetamine derivative no longer available in this country), fluoxetine (Prozac®, an SSRI), furosemide (Lasix®, a loop diuretic), and even phenytoin (Dilantin®, an antiseizure medication). The FDA is seeking recalls on many of these products; however, some are available only online and previous recall efforts have proved inadequate.

In a related story, the FDA has announced a voluntary recall of Zencore Plus, the heavily marketed product for "natural male enhancement," which has been found to contain benzamidenafil, a new PDE5 inhibitor not yet available in this country. Benzamidenafil is similar in action to sildenafil (Viagra®) and tadalafil (Cialis®). PDE5 inhibitors are noted to have a drug interaction with nitrates, leading to potential life-threatening risk of sudden and profound drop in blood pressure. Zencore Plus is distributed by Hi-Tech Pharmaceuticals in Norcross, GA, and is widely sold in health food stores, by mail order, and by Internet sales.

Aspirin dose and cardioprotection

What is the best dose of aspirin for patients taking dual therapy with clopidogrel to prevent cardiovascular events? Investigators looked at 15,595 patients with cardiovascular disease or multiple risk factors in an observational analysis from a double-blind, placebo-controlled randomized trial. Patients were randomized to doses of aspirin less than 100 mg (75 mg or 81 mg), 100 mg, or greater than 100 mg (150 mg or 162 mg) with or without clopidogrel. The primary efficacy outcome was the composite of myocardial infarction, stroke, or cardiovascular death and the primary safety endpoint was severe life-threatening bleeding. In patients given aspirin alone, the hazard ratio for the efficacy and safety endpoints were the same regardless of aspirin dose. In patients given aspirin with clopidogrel, there was a statistically nonsignificant associated reduction in efficacy with aspirin doses over 100 mg, and a

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

significantly higher increase in harm (hazard ratio, 1.30 with clopidogrel plus aspirin greater than 100 mg). The authors conclude that daily doses of aspirin greater than 100 mg were not associated with benefit and may be associated with harm in patients also taking clopidogrel. Therefore, daily doses of aspirin 75-81 mg optimize efficacy and safety in patients requiring long-term aspirin therapy, especially in patients receiving dual antiplatelet therapy (*Ann Intern Med* 2009;150:379-386). This is especially important given the recent U.S. Preventive Services Task Force recommendation that encourages men ages 45-79 years to take aspirin preventively when the potential benefit of a reduction of myocardial infarction outweighs the potential harm of an increase in gastrointestinal hemorrhage. Women ages 55-79 years are also encouraged to use aspirin when the potential benefit of a reduction in ischemic stroke outweighs the potential harm of increased gastrointestinal hemorrhage (*Ann Intern Med* 2009;150:396-404).

PPIs and clopidogrel

Increasing evidence suggests that proton pump inhibitors (PPIs) may attenuate the effect of clopidogrel on platelet aggregation. PPIs are often used prophylactically in patients with acute coronary syndrome (ACS), as patients on clopidogrel and aspirin may be at higher risk for GI bleeding. A new study from VA researchers was set up to determine if there are clinical implications from the interaction between PPIs and clopidogrel.

In a retrospective cohort study of 8205 patients with ACS taking clopidogrel, 63.9% were also prescribed a PPI at discharge, during follow-up, or both. Death or rehospitalization for ACS occurred in 20.8% of patients taking clopidogrel without a PPI and 29.8% patients taking clopidogrel with a PPI. Use of clopidogrel plus a PPI was associated with an increased risk of death or rehospitalization for ACS compared with use of clopidogrel without a PPI (adjusted odds ratio, 1.25; 95% confidence interval, 1.11-1.41). Patients taking a combination of the two drugs were at higher risk for hospitalizations for ACS and revascularization procedures, but not for all-cause mortality. Patients taking a PPI without clopidogrel were not at higher risk for rehospitalization. The authors conclude that concomitant use of clopidogrel and a PPI after hospital discharge for ACS is associated with an increase risk of adverse outcomes, suggesting that PPIs may attenuate the benefits of clopidogrel, and that PPIs should only be used with clopidogrel if there is a clear indication, and not for routine prophylaxis (*JAMA* 2009;301:937-944).

Modafinil's abuse potential

Modafinil (Provigil®) is a wake-promoting medication used to treat narcolepsy and other sleep disorders. Recently, the drug has be used off-label to enhance cognition in psychiatric patients and even in healthy patients seeking a memory boost. Modafinil has been touted as having a low abuse potential; however, a new study questions that assumption. Most stimulant medications, such as methylphenidate and amphetamine, increase brain dopamine levels. Modafinil was thought to exert its effect in the brain on pathways other than dopamine, but now there is evidence that dopamine is involved. Researchers from the National Institute on Drug Abuse looked at 10 healthy male volunteers to measure the effects of modafinil at therapeutic dosing of 200 mg and 400 mg given orally. PET scans were used to measure the effect of modafinil on extracellular dopamine and dopamine transporters. Modafinil increased extracellular dopamine and showed evidence of occupancy of dopamine transporters, effects similar to drugs with the potential for abuse. The authors conclude that, considering the increasing use of modafinil, there needs to be heightened awareness for potential abuse of and dependence on modafinil in vulnerable populations (*JAMA* 2009;301:1148-1154).

FDA Actions

The FDA is requiring the manufacturers of metoclopramide (Reglan®) include a boxed warning on their labeling regarding the risk of long-term or high-dose use and tardive dyskinesia. Manufacturers will also be required to implement a risk evaluation and medication strategy (REMS) to ensure patients are provided with a medication guide that discusses the risk. Metoclopramide is approved for the treatment of gastric motility problems associated with GERD, diabetic gastroparesis, and nausea and vomiting.

A new proton pump inhibitor has been approved by the FDA, bringing the number of PPIs on the market to six. Dexlansoprazole is the purified active isomer of lansoprazole (Pepcid®). The drug has a delayed-release formulation designed to provide two separate releases of the medication. It is approved for the treatment of GERD and erosive esophagitis. Takeda Pharmaceuticals will market dexlansoprazole as Kapidex™. ■

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Best management of acute ankle sprain

Source: Lamb SE, et al. Mechanical supports for acute ankle sprain. *Lancet* 2009;375:575-581.

A SEVERE ANKLE SPRAIN (ANK-S) might seem like a minor injury, but clinicians may be underestimating the burden of consequence. In addition to the immediate period of limited mobility, full functional restoration takes between 3-9 months for as many as 70% of affected individuals. Indeed, it is not uncommon to see long-term symptoms referable to the ankle sprain, including recurrent swelling, pain, and limitation of activity. Because ANK-S is a commonplace event, confirming the best approach to initial management merits investigation.

Lamb et al randomized participants presenting to EDs in the United Kingdom with severe ANK-S (n = 584) to 1 of 4 treatments: an Aircast® brace, Bledsoe boot, below-knee cast, or double-layer tubular compression bandage.

Participants generally used treatments short-term, i.e., 10 days, and then PRN. Tubular compression bandage was the least efficacious method at 1, 3, and 9 months and was similar in efficacy to the Bledsoe boot. The below-knee cast was the most effective treatment, but Aircast outcomes were similar for ankle functionality at 3 months. Overall, the below-knee cast showed the best early symptomatic recovery, as well as functional recovery by 3 months. Although the philosophy of early mobilization has achieved some popularity, these data would suggest that tools that limit mobilization early (i.e., cast, Aircast), should be considered preferential. (Note: There is more than one Bledsoe boot; because Bledsoe provides boots with either flexion-extension mobility or full immobilization, it is possible that other versions of the Bledsoe boot might be more efficacious). ■

Metabolic syndrome and salt sensitivity

Source: Chen J, et al. Metabolic syndrome and salt sensitivity of blood pressure in non-diabetic people in China. *Lancet* 2009;373:829-835.

ALTHOUGH DEFINITIONS OF WHAT constitutes metabolic syndrome (MBS) vary, there is general agreement that insulin resistance (IR) is a fundamental component. By leading to sodium retention, IR may contribute to the development of hypertension (HTN).

Blood pressure effects of salt restriction are highly variable, but one would anticipate that MBS subjects might respond more intensely based upon the IR-to-sodium retention link. To investigate this, Chen et al studied 1881 nondiabetic subjects, of whom 283 had MBS. All participants were fed a low-sodium diet (= 3 g NaCl/d) for 7 days, followed by a high-sodium diet (= 18 g NaCl/d) for 7 days. At baseline, the mean BP in the MBS group was 128/81 mm Hg vs 115/72 mm Hg in those without MBS.

High-salt sensitivity was defined as a BP change of 5 mm Hg or more in response to dietary salt modulation. At the end of each diet period, MBS subjects had a threefold or greater odds ratio for high-salt sensitivity (both to a rise in BP with sodium load, as well as a reduction in BP with sodium restriction). The benefits of salt restriction in persons with MBS may be more substantial than the general population. ■

Oseltamivir-resistant influenza

Source: Dharan NJ, et al. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA* 2009;301:1034-1041.

PROGRESSIVE RESISTANCE OF INFLUENza A virus (FLU-A) to adamantanes (i.e., amantadine, rimantadine) led to the 2006 CDC recommendation against their use. Initial resistance patterns of next-generation pharmacotherapies for FLU-A, the neuraminidase inhibitors (i.e., oseltamivir, zanamivir), were very reassuring. Recently, growing resistance patterns to oseltamivir (OSTV) are shaping revised CDC recommendations.

Volunteer clinicians around the United States, known as sentinel physicians, monitor patients who present with influenza-like illness and send samples to the CDC for confirmation of influenza virus status. Among FLU-A viruses assessed in the 2007-2008 influenza season, only 12.3% were OSTV-resistant. Comparison of the demographics of subjects with OSTV-resistant FLU-A to subjects with non-resistant profiles did not provide any insight into particular at-risk groups (or protected groups), including age, geography, symptoms, etc.

OSTV resistance profiles changed dramatically in the FLU-A samples from Sept. 28, 2008, to Feb. 19, 2009: 98.5% of H1N1 FLU-A samples (264/268) were OSTV-resistant! Experts are uncertain about the mechanism by which OSTV resistance has proliferated.

Current options in an environment of high OSTV resistance include zanamivir, or OSTV plus rimantadine. ■

Low back radiology: Roadmap or mirage?

Source: Chou R, et al. Imaging strategies for low-back pain. *Lancet* 2009;373:463-472.

LOW BACK PAIN (LBP) IS RESPONSIBLE for as much as one-third of all disability dollars spent in the United States. When patients present with acute LBP, clinicians are tempted to perform radiographic studies (MRI, CT, plain films) to try to identify the source of the symptomatology. Unfortunately, the preponderance of current evidence suggests that findings commonly reported on radiographic studies such as narrowed disk space, loss of lumbar lordosis, and osteoarthritic changes, are just as common in asymptomatic volunteers as in symptomatic LBP sufferers.

Chou et al performed a meta-analysis of clinical trials which enrolled patients and included immediate imaging (CT, MRI, or plain films) and compared them with trials of similar patients who did not undergo imaging (total n = 1804). In addition to reporting radiography utilization, included trials had to provide information on outcomes of pain or function, quality of life, mental health, overall improvement, and patient satisfaction.

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Chou et al found that in the absence of signs of a serious underlying condition (e.g., fever, weight loss, history of cancer), immediate imaging was not associated with improved outcomes. Indicative of the need for more public education, the article also reminds us that in one study, patient preference to undergo radiography was as high as 80%.

Routine radiography for acute LBP does not improve outcomes, is associated with substantial cost, and may suggest pathology which is, in effect, unrelated to the symptomatology. ■

Bariatric surgery and reversal of dysglycemia

Source: Salinari S, et al. First-phase insulin secretion restoration and differential response to glucose load depending on the route of administration in type 2 diabetic subjects after bariatric surgery. *Diabetes Care* 2009;32:375-380.

MOST TYPE 2 DIABETICS (DM2) WHO undergo bariatric surgery enjoy a prompt reversal—or at least a substantial diminution—of their dysglycemia. These salutary effects occur both after malabsorptive surgery (diverting the digestive tract around to bypass components of the small intestine) or restrictive surgery (diminishing gastric capacity). The mechanisms by which surgery improves glucose regulation appear to go beyond simple weight loss; indeed, glucose regulation improves well before meaningful weight loss has occurred, suggesting that some change in intestinal glucose modulation factors must be involved.

Salinari et al studied glucose metabolism in 9 DM2 subjects who underwent biliopancreatic diversion bariatric surgery, comparing their glucose metabolism with healthy, normal-weight controls.

The healthy pancreas provides a bolus of preformed insulin immediately in response to mealtime increases in plasma glucose. One of earliest manifestations of DM2 is loss of first-phase insulin secretion, leading to a consistent mismanagement of glucose, since early elevations of plasma glucose are not met with a prompt matching insulin bolus. In this trial, the first-phase insulin response was restored by 1 month after surgery. Similarly, beta-cell responsiveness to glucose elevation was normalized; and lastly, insulin sensitivity was restored to essentially normal. Concordant with the concept that elimination of some intestinal component is central to these phenomena, sensitivity to oral glucose was improved to a greater degree than was intravenous glucose. Incretin levels (GLP, GIP), however, were unchanged.

Malabsorptive bariatric surgery provides prompt regression of DM2, apparently due (at least in part) to some as yet unidentified intestinal hormone, and independent of identified incretin hormones such as GLP and GIP. ■

Herpes zoster in TNF-treated RA patients

Source: Strangfeld A, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-α agents. *JAMA* 2009;301:737-744.

THE EVOLUTION OF PHARMACOTHERAPY for rheumatoid arthritis (RA) has led to the development of agents which, at least, offer major symptomatic improvement, and at best, promise remission. Because TNF agents involve modulation of steps critical to immune integrity, vigilance for serious bacterial infections is required. Yet, whether TNF agents impact the incidence of viral infections, which is also important, has been little-studied. Population studies on patients with RA have demonstrated a doubling of risk for herpes zoster compared to a control population.

Strangfeld et al enrolled RA patients (n = 5040) receiving either TNF agents or conventional DMARDS, such as methotrexate. Herpes zoster incidence was monitored over 36 months.

Overall, TNF agents were associated with an increased zoster incidence (hazard ratio = 1.82) compared to conventional treatment. Among the TNF agents, there was a distinct difference between etanercept, which did not show a statistically significant increase in zoster risk, vs infliximab and adalimumab, which did. The authors suggest that patients treated with the latter two agents merit particular vigilance for early signs and symptoms of herpes zoster to allow prompt intervention. ■