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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

ABSTRACT & COMMENTARY

Clopidogrel Plus Aspirin After Transient Ischemic Attack

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: Wang Y, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;369:11-19.

Transient ischemic attacks (TIAs) and minor strokes are often the harbingers of a large, debilitating stroke. Approximately 10% of patients experiencing a TIA will go on to have a large stroke within the next 3 months, with most of these events occurring early. Aspirin reduces the early risk of recurrent stroke in such patients. Clopidogrel, on the other hand, has been tested in patients with large stroke and does not reduce the risk of recurrent stroke, but actually increases bleeding. However, clopidogrel in addition to aspirin has not been tested in TIA and minor stroke, a population of patients who are at high risk for major stroke over a short period of time, but are at lower risk of intracerebral hemorrhage. Accordingly, Wang and colleagues performed a multicenter, randomized, controlled trial of aspirin plus placebo vs aspirin plus clopidogrel in patients presenting with TIA or minor stroke. Their primary endpoint was the rate of stroke at 90 days.

The Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events (CHANCE) study was sponsored by the Chinese government and was performed in 114 centers in China. After screening more than 41,000 patients, 5170 patients presenting with TIA symptoms of less than 24 hours duration were enrolled. Using the NIH stroke scale and the ABCD scale, they included only those with minor deficits, but at high risk for future

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Clinical Cardiology [ALERT]

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large stroke. They excluded patients with hemorrhage or other intracranial pathology on initial CT or MRI scan, those with only sensory symptoms (to avoid enrolling patients with other potential causes such as migraine), those with a clear need for anticoagulation (such as atrial fibrillation or prosthetic valve), patients at high risk for bleeding (such as recent gastrointestinal bleed), and those undergoing surgery or angioplasty. All patients received open-label aspirin on admission 75-300 mg, with the dose left to the discretion of the treating physician. Patients were randomized to the aspirin group (n = 2586; aspirin 75 mg daily from days 2-90) or to the aspirin plus clopidogrel group (n = 2584; clopidogrel loading dose 300 mg followed by 75 mg daily from days 2-90, plus aspirin 75 mg daily on days 2-21 followed by placebo aspirin from days 22-90). The groups were well matched in their baseline characteristics.

The primary outcome, stroke, was less frequent in the clopidogrel plus aspirin group compared to the aspirin alone group (8.2% vs 11.7%; hazard ratio [HR] 0.68; $P < 0.001$). The difference between groups was driven by a reduction in ischemic strokes, and there was no difference in the rate of hemorrhagic stroke (eight patients [0.3%] in each group; P = NS). Importantly, the benefit was seen within the first few days and the curves remained separated thereafter. The number needed to treat to prevent one stroke was 29. The benefits were consistent across all major subgroups. Analysis of secondary endpoints showed no difference in the rate of death (0.4% in each group), vascular death (0.2%), or recurrent TIA (1.2% vs 1.8%, P = NS). There was no difference between groups in moderate or severe hemorrhage (0.3%), but there was a trend toward a higher rate of any bleeding event in the clopidogrel plus aspirin group (2.3% vs 1.6%, $P = 0.09$). The authors conclude that among patients with TIA or minor stroke who can be treated within 24 hours after the onset of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage.

■ COMMENTARY

This interesting study shows that clopidogrel in addition to aspirin early after the onset of TIA or minor stroke reduces the risk of subsequent stroke. This is not consistent with the lack of benefit of clopidogrel that is seen in trials enrolling patients with larger stroke. Most likely, the disparity between the current study and prior trials is because the patients in this trial had smaller areas of brain infarction and were, therefore, less likely to develop hemorrhagic transformation. In addition, patients were enrolled very early after symptom onset in this study (median 13 hours). The study is strengthened by its rigorous design, independent blinded clinical events committee, and lack of industry involvement. However, there are several limitations that should be acknowledged. First, this was conducted solely in China. Chinese patients have higher rates of polymorphisms of the cytochrome P450 system that metabolizes clopidogrel. Therefore, their response to this drug may be different than those of other ethnicities. Second, these data should not be extrapolated to those suffering major stroke, as they have been shown to fare worse with clopidogrel. Third, those with less specific symptoms, such as vertigo or sensory symptoms, and those with lower risk of recurrence based on the ABCD scale may not benefit to the same extent. Fourth, the loading dose of clopidogrel was 300 mg; perhaps a 600 mg loading dose may result in more pronounced early benefit. In the light of the CHANCE trial data, it is reasonable to treat patients of Chinese origin presenting with high-risk TIA with a combination of aspirin and clopidogrel for 90 days. There are ongoing large, randomized trials of dual antiplatelet therapy in patients with TIA that should help refine which populations stand to benefit most from the addition of clopidogrel to aspirin, and whether higher loading doses add incremental benefit, in patients with TIA and minor stroke. ■

ABSTRACT & COMMENTARY

Troponomania or an Advancement in Care?

By Michael H. Crawford, MD, Editor

SOURCES: van Waes JA, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* 2013;127:2264-2271. Beckman JA. Postoperative troponin screening: A cardiac cassandra? *Circulation* 2013;127:2253-2256.

Elevated troponin levels after non-cardiac surgery have been shown to predict postoperative myocardial infarction (MI) and death. Thus, these investigators from the Netherlands instituted a postoperative troponin monitoring program at one hospital to test the hypothesis that troponin elevations in the first 3 days after surgery would predict 30-day mortality after non-cardiac surgery. Eligible patients had to be ≥ 60 years old undergoing intermediate- to high-risk non-cardiac surgery under anesthesia and who were expected to be in the hospital for at least 24 hours. Data collection was from electronic medical records. Troponin I was measured on the first 3 days after surgery and any abnormal values were reported to the attending physician who took whatever action deemed appropriate. The primary endpoint was 30-day all-cause mortality. The secondary endpoints included postoperative MI (universal definition) and length of stay.

Among the 2216 patients with complete follow-up, 1627 had troponin measured and 907 had all three measures. At least one elevated level was seen in 315 (19%). In about half of these patients (162), the troponin was elevated on the first day. The incidence of an elevated troponin increased with age and was associated with increased mortality as compared to those with normal troponins (8.6% vs 2.2%, $P < 0.01$). The median time to death with an elevated troponin was 12 days. Also, mortality increased with higher troponin levels (hazard ratio 2.4 with minor elevations and 4.2 with large increases). Multivariate analysis showed that troponin and emergency surgery were the only independent predictors of mortality. Hospital stay doubled with an elevated troponin (10 vs 5 days). Of those with a positive troponin, 40 met universal criteria for MI, 10 (3%) had typical chest pain, and 30 (10%) had ischemic ECG changes, but only one patient (0.3%) showed ST elevation. Cardiology consultation was sought in 35% of the elevated troponin cases, but in the majority no change in management was recommended. Only 6% had coronary angiography and 4% had revascularization. The authors concluded that elevated troponin values early after non-cardiac surgery predicted 30-day all-cause mortality and routine postoperative troponin measurement could improve the care of patients undergoing intermediate- to high-risk non-cardiac surgery.

■ COMMENTARY

Although the information is not new, this is the largest study of early postoperative troponin measurements to date and it confirms that elevated levels in the first 3 days independently predict 30-day all-cause mortality. Since the median time to death was 12 days, the authors reasoned that there was plenty of time to potentially reduce mortality postoperatively. The problem is what to do since troponin is predicting all-cause mortality, not cardiac mortality or even MI. In fact, only 2% of those with troponin measured met the universal definition of MI and only one patient had an STEMI by ECG. However, almost 20% had elevated troponin measures and among these patients, only 13% had an MI. Thus, most of the troponin elevations observed were what is now referred to as demand ischemia. Other than optimizing care to improve the myocardial supply-demand equation, there is nothing else to do acutely. We usually evaluate those who do well by stress testing later to be sure they don't have fixed coronary lesions, but this may be overkill if they are active and asymptomatic postoperatively.

Interestingly, the study gave the attending physicians the troponin results and they could do what they wished with the patient. About one-third of the elevated troponin cases had cardiology consultations and, in 60% of these patients, no change in management was made; only 6% had coronary angiography and 4% had revascularization. In the remaining 30%, changes in medications were made — usually the addition of aspirin or statins.

Thus, it appears that elevated troponin levels are a nonspecific marker of illness. The editorial accompanying this paper comments that this is an underappreciated fact. The Dallas Heart Study of presumable healthy subjects showed elevated troponin T levels in 25% of the subjects at baseline. Abnormal troponins predicted all-cause and cardiac mortality in this study. However, it has been well described that troponin is elevated in pulmonary embolus, respiratory failure, sepsis,

subarachnoid hemorrhage, and sick hospitalized patients in general. For these reasons, Beckman argues against routine troponins postoperatively. He believes that the potential harm — believing that the elevation is due to MI and starting on heparin, aspirin, clopidogrel, and possibly doing a coronary intervention, all of which would increase the risk of major bleeding early postoperatively — outweighs the benefit. Also, he believes focusing on the heart may divert attention from discovering the real reason for the troponin elevation. I don't interpret this as meaning never do a troponin. In patients who are doing poorly postoperatively and in whom cardiac disease is suspected, it is reasonable to measure troponin and act accordingly. ■

ABSTRACT & COMMENTARY

Adults with Atrial Septal Defects — Surgical or Transcatheter Closure?

By Andrew J. Boyle, MBBS, PhD
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SOURCE: Kotowycz MA, et al. Long-term outcomes after surgical versus transcatheter closure of atrial septal defects in adults. *JACC Cardiovasc Interv* 2013;6:497-503.

Atrial septal defects (ASD) can lead to exercise intolerance, pulmonary hypertension, right heart failure, and reduced life expectancy if they are not repaired. Surgical closure for ASD transformed the care of these patients and resulted in similar life expectancy to subjects without ASD. In recent years, transcatheter ASD closure has largely replaced surgery, but long-term data comparing the two techniques are limited. Kotowycz and colleagues performed a retrospective study of all patients ages 18-75 years who had surgical or transcatheter ASD closure in Quebec, Canada. They searched the Quebec congenital heart disease database for physician claims and hospital discharge summaries and cross-referenced with the province death database. All patients with ASD receiving surgical or transcatheter closure were enrolled in the study. To ensure they only enrolled patients with secundum ASD, they excluded cases with codes for other congenital heart diseases and those with a stroke in the preceding year (as these could have been patent foramen ovale [PFO] closure cases). The Amplatzer Septal Occluder was used in all cases of transcatheter closure. Primary outcomes were 5-year repeat intervention and all-cause mortality. Secondary outcomes were short-term (1-year) onset of congestive heart failure, stroke, or transient ischemic attack, and markers of health service use.

Between 1988 and 2005, 718 ASD closures were performed; 383 were surgical and 335 were transcatheter. At baseline, patients undergoing transcatheter closure were older (49 vs 43 years, $P < 0.001$) and more likely to have systemic hypertension (32% vs 25%, $P = 0.037$), but were less likely to have pulmonary hypertension (7.6% vs 16.4%, $P < 0.001$). Five-year mortality with transcatheter closure was similar to surgical ASD closure (5.3% vs 6.3%, P = NS). At 5 years, reintervention was more likely in patients with transcatheter vs surgical ASD closure (7.9% vs 0.3%, $P < 0.01$), but the majority of these reinterventions occurred in the first year. Secondary outcomes were similar in the two groups: The rates of heart failure, stroke, and TIA were similar between groups — the surgical group had more outpatient visits and the transcatheter group had more echocardiograms. The authors describe a steady increase in the use of transcatheter closure, and a steady decline in surgical closure, after 1998 when transcatheter closure was introduced. Interestingly, when comparing only the cases from 1998 onward, there was a trend toward lower mortality in the transcatheter group. The authors conclude that transcatheter ASD closure is associated with a higher long-term reintervention rate, but a long-term mortality that is not inferior to surgery. Overall, these data support the current practice of using transcatheter ASD closure in the majority of eligible patients and the decision to intervene on ASD with significant shunts before symptoms become evident.

■ COMMENTARY

This study adds to the growing body of literature that both surgical and transcatheter closure of secundum ASD in adults are safe and effective in the long term. This study is a retrospective cohort study, not a prospective, randomized trial,

so there is likely to be significant bias inherent in the allocation of patients to either group. Thus, conclusions should be made cautiously, taking into account the other literature that concerns ASD closure in adults. This study is consistent with the majority of such observational studies, which show similar success rates and benefits from transcatheter and surgical approaches to closing ASDs in adults. It is unlikely that large-scale, randomized, controlled trials will ever be completed comparing these techniques, so these types of studies are important in this field. It should be recognized that this study is based on administrative data and claims, so there may be inaccuracies in the coding information. Further, we are not told of antiplatelet and anticoagulation regimens used postoperatively, which may impact outcomes. Overall, however, this is one of the larger series examining surgical vs transcatheter ASD closure, and is thus important. How should we approach adults with secundum ASD in the light of these data? It is clear that secundum ASDs with large left-to-right shunts need to be closed, but there does not appear to be a single best option. The choice between transcatheter and surgical options should continue to be individualized to each patient, and both appear to be reasonable options in the long term. ■

ABSTRACT & COMMENTARY

Neurologic Complications of Infective Endocarditis

By Michael H. Crawford, MD, Editor

SOURCE: García-Cabrera E, et al. Neurological complications of infective endocarditis: Risk factors, outcomes, and impact of cardiac surgery: A multicenter observational study. *Circulation* 2013;127:2272-2284.

The relationship between neurologic complications of infective endocarditis (IE), urgent valve surgery, and outcomes is poorly understood. Thus, these investigators performed a retrospective analysis of a prospectively collected database of IE cases from 1984-2009 in seven Spanish hospitals. After excluding patients with isolated right heart and pacemaker lead infections, a total of 1345 patients with left-sided IE who had complete data and follow-up were available. Using the Duke criteria, 93% had definite IE and 7% had possible IE. A neurological event was experienced by 25%. Ischemic and presumably embolic events occurred in 56% of these patients. The majority of these events were small (72%). Cerebral hemorrhage occurred in 18%, encephalitis or meningitis in 24%, and brain abscess in 4%. Multivariate analysis showed that neurologic complications were related to vegetation size > 3 cm (hazard ratio [HR], 1.9; 95% confidence interval [CI], 1.07-3.43; $P = 0.029$), *Staphylococcus aureus* infection (HR, 2.47; 95% CI, 1.95-3.15; $P < 0.001$), anticoagulant therapy (HR, 1.3; 95% CI, 1.00-1.72; $P = 0.048$), and mitral valve involvement (HR, 1.29; 95% CI, 1.02-1.61; $P = 0.03$). Anticoagulant therapy was most associated with cerebral hemorrhage (HR, 2.71; 95% CI, 1.54-4.76; $P = 0.001$). In 86% of the patients with neurologic events, it occurred during the first week after diagnosis of IE — about one-third before antibiotic treatment and two-thirds after the onset of therapy. Hemorrhagic events were more common after therapy had begun. Early mortality (up to 30 days) was 30% and was not influenced by surgical therapy. Neurologic events increased mortality, 45% vs 24% in those without neurologic complications, but only moderate-to-severe ischemic events and hemorrhagic events were significant predictors. Also, mortality was higher if surgery was performed within 30 days of a hemorrhagic event. The authors concluded that moderate-to-severe ischemic stroke and cerebral hemorrhage complicating IE increased mortality. Early antibiotic therapy reduces cerebral events and stopping or not starting anticoagulant therapy may prevent cerebral hemorrhages.

■ COMMENTARY

This relatively large database study helps refine the use of anticoagulants and surgery in IE and details the impact of various neurologic complications on management. They show that overall, one-fourth of patients have neurologic complications, most of which are vascular embolic events. About one-third occur before the diagnosis of IE is made and most of the rest occur during the first week of therapy. The most important risk factors for cerebral complications overall are *S. aureus* infection (HR 2.47) and vegetation size (HR 1.9), but only with vegetations > 3 cm in

diameter. Older, smaller studies have shown that vegetation size > 1 cm predicted poor outcomes, suggesting that such vegetations constituted an indication for surgery. However, this was never widely accepted as a criterion for surgery, perhaps because our experience didn't support the gravity of a 1 cm vegetation vs the risk of surgery in IE. A vegetation of > 3 cm is a different matter and probably will drive surgery. Thus, strong indications for surgery will be a > 3 cm vegetation, failure to control infection, or hemodynamic deterioration that cannot be effectively managed medically. The critical period for infection control is the first week because few cerebral complications occur thereafter.

One-fifth of those with cerebral complications had cerebral hemorrhage. The major risk factor for this subgroup was anticoagulant therapy (HR 2.71). The major reasons for anticoagulant treatment were pre-existing conditions, such as prosthetic valves and atrial fibrillation, and treatment of the neurological complication, especially if it was present at initial presentation. Their results suggest that early anticoagulation for neurologic presentations is unwise if IE is suspected. Also, they recommend that oral anticoagulation be suspended when the diagnosis of IE is made, especially in those at highest risk of cerebral complications. Although this is not a controlled trial, this advice seems prudent.

Surgeons are often reluctant to operate when neurologic complications have occurred, even when clear indications for surgery are present. The results of this study suggest that mild neurological events do not affect the outcomes of surgery and should not preclude or delay surgery if indicated. On the other hand, moderate-to-severe cerebral events clearly increased the risk of surgery and the authors suggest that surgery be delayed for at least 2 weeks in such cases. For cerebral hemorrhage, they suggest delaying 4 weeks.

Overall mortality in this series remained high at 30% in 1 month. If cerebral complications were present, it was 45% and if absent 24%. So clearly, prevention of cerebral events is important. Strategies suggested by this study include early effective antibiotic therapy, judicious use of anticoagulants, and consideration of early surgery with very large vegetation sizes. ■

ABSTRACT & COMMENTARY

Can Athletes with ICDs Participate in Competitive Sports?

Edward P. Gerstenfeld, MD

Professor of Medicine, Chief, Cardiac Electrophysiology, University of California, San Francisco

Dr. Gerstenfeld does research for Biosense Webster, Medtronic, and Rhythmia Medical.

SOURCE: Lampert R, et al. Safety of sports for athletes with implantable cardioverter-defibrillators: Results of a prospective, multinational registry. *Circulation* 2013;127:2021-2030.

Young athletes with an inherited arrhythmia syndrome, such as long QT syndrome (LQTS) or hypertrophic cardiomyopathy (HCM), may undergo implantation of an implantable cardioverter defibrillator (ICD) if they are believed to be at high risk of sudden death. American College of Cardiology (ACC) guidelines have typically recommended that such individuals should be prohibited from vigorous sports. Yet for many young athletes, prohibition of participation in any competitive sport may be a life-altering event, followed by poor grades or depression. There is a paucity of data in athletes with ICDs and despite the ACC guidelines and physician recommendations, many athletes with ICDs continue to participate in competitive sports. Thus, the results of a prospective, multinational registry of patients with ICDs, the ICD Sports Safety Registry, is of interest. This registry enrolled and followed patients with implanted ICDs aged 10-60 years who participated in organized competitive sports having intensity more vigorous than golf or bowling. Most of the enrolled patients were already participating in competitive sports, regardless of medical advice, at the time of enrollment. Patients were asked to notify the center if they received any ICD shocks, and were questioned about the circumstances of the event. All enrollees were also called by phone every 6 months throughout the study. Stored

ICD electrograms were reviewed by two cardiac electrophysiologists to confirm whether the shocks were appropriate or inappropriate. The primary endpoint was a serious adverse event occurring during or up to 2 hours after sports participation. Serious adverse events were defined as tachyarrhythmic death or externally resuscitated tachycarrhythmia, postshock pulseless electrical activity, or severe injury resulting from a shock or syncope. The lowest ICD treatment zone was set to 200 bpm. There were 328 athletes enrolled; 44 participated in sports considered "high-risk," such as basketball, soccer, or downhill skiing. The most common arrhythmia diagnoses included LQTS, HCM, and arrhythmogenic right ventricular cardiomyopathy (ARVC). Most, but not all, patients (62%) were taking beta-blockers. The most common sports that patients participated in during the registry were running, soccer, and basketball; 60 participants were on high school or college sports junior varsity/varsity teams. The median follow-up was 31 months. Two patients died during the study: a 52-year-old cyclist who died at his desk at work after receiving multiple ICD shocks and a 34-year-old volleyball and softball player with DCM who died while hospitalized for congestive heart failure. There were no occurrences of the primary endpoint during sports participation among those patients completing the study. The 95% confidence interval for events at 1 year was 0-1.2%, and at 2 years was 1-1.5%. Overall, 77 individuals (21%) received appropriate ICD shocks and 40 (11%) received inappropriate shocks. Those with ARVC or idiopathic ventricular fibrillation were more likely to receive appropriate shocks compared to those with HCM or LQTS. There were no injuries reported. There were 13 lead malfunctions during the study period. The authors concluded that participation in competitive sports by athletes with an ICD is possible without failure to terminate arrhythmias or suffering injuries.

■ COMMENTARY

The population of young athletes with inherited arrhythmia syndromes remains a difficult population to manage. In patients at low risk for life-threatening events, a consensus document has outlined the relative safety of various competitive sports.[1] Patients are often directed from high-risk to lower-risk sports such as golf or bowling. For higher-risk patients who undergo ICD implantation, conventional wisdom has been to counsel against participation in competitive sports. Yet patients will often ask, "Now that I have this safety device which can save me in the event of a cardiac arrest, can I resume participating in competitive sports?" Most electrophysiologists have answered "no" to this question, out of fear of damage to the device or leads during sporting events, triggering of a life-threatening arrhythmic event, injury to the patient, and potential medico-legal implications. Yet, we all know some patients who continue to participate despite our recommendations. Is the accompanying article strong enough to change these recommendations and allow athletes with ICDs to participate in competitive sports? First, one must consider the type of inherited arrhythmia and the type of sporting activity. In patients with ARVC, the disease may progress more rapidly in those who exercise vigorously, and arrhythmic events are commonly triggered during extreme exercise. In the Sports Safety Registry, patients with ARVC had significantly more arrhythmic events than other inherited arrhythmias. Patients with LQTS type I have a risk of sudden death during swimming, so competitive swimming should certainly be avoided. Contact sports such as football or rugby should also clearly be avoided, as damage to the device may occur with repeated trauma. Sports with a very high aerobic exercise level, such as full court basketball or soccer, may also be more likely to trigger arrhythmic events. The authors of this article should be congratulated on contributing the first data on patients with ICDs who participate in sports. In general, I would continue to dissuade patients with inherited arrhythmias (particularly ARVC) and ICDs from participating in competitive sports. However, it does appear that some ICD patients may participate in certain competitive sports without an undue risk of injury or mortality. This should only be considered after a thorough discussion between the patient, the cardiologist, and a physician with an expertise in managing inherited arrhythmias. ■

REFERENCE

1. Maron BJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation* 2004;109:2807-2816.

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CME Questions

1. An elevated troponin I level on the first day following non-cardiac surgery indicates:
   a. an MI has occurred.
   b. all-cause mortality is increased.
   c. nothing of importance.
   d. a and b

2. Competitive athletes who receive ICDs should:
   a. discontinue all vigorous exercise.
   b. continue with their sporting activities.
   c. carefully weigh the pros and cons of continuing sports.
   d. have it put in a location compatible with their activity.

3. Long-term comparison of ASD closure by a percutaneous device vs surgery has shown:
   a. similar 5-year mortality.
   b. more reintervention with device closure.
   c. more stroke with device closure.
   d. a and b

4. Stroke reduction following a TIA is best achieved with:
   a. aspirin plus clopidogrel.
   b. aspirin alone.
   c. clopidogrel alone.
   d. oral anticoagulants.

5. Cerebral hemorrhage in infective endocarditis is most closely associated with:
   a. brain abscess.
   b. early surgery.
   c. anticoagulation therapy.
   d. *S. aureus* infection.

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.

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Continuing Warfarin for Pacemaker/ICD Implantation is Safer Than Bridging

Source: Birnie DH, et al. *N Engl J Med* 2013;368:2084-2093.

The decision process to determine the optimal scheduling of antithrombotic therapy in the perioperative period is complex. The most recent AT9 CHEST guidelines suggest discontinuation of warfarin 5 days prior to pacemaker/implantable cardioverter-defibrillator (PCM-ICD) implantation, complemented with heparin bridging. This method is somewhat unwieldy, expensive, and has not been confirmed by a large, randomized trial as optimizing risk reduction. During transition from warfarin to heparin, an interval of increased risk for thromboembolism occurs in some, and the use of heparin has also been shown to frequently be associated with device-pocket hematoma.

In the Bridge or Continue Coumadin for Device Surgery Randomized Controlled trial, 681 PCM-ICD patients were randomized to continued warfarin or heparin bridging. Patient selection criteria also included high baseline annual thromboembolism risk (≥ 5%). The primary outcome of the trial was incidence of significant device-pocket hematoma (DPH), which can result in prolongation of hospitalization, need to stop anticoagulation, or additional surgery.

There was a dramatic difference in risk for the DPH primary endpoint between subjects continued on warfarin uninterrupted (3.5%) and subjects randomized to heparin bridging (16%). Risk reduction through continuation of warfarin was not associated with any increased incidence of major surgical adversities compared with bridging. Continuation of warfarin, uninterrupted, was associated with more than 80% reduction in risk of DPH compared to bridging, while not compromising other measures of safety. ■

Bariatric Surgery Impact on Cholesterol Metabolism

Source: Benetti A, et al. *Diabetes Care* 2013;36:1443-1447.

Bariatric surgery techniques are often described as restrictive (e.g., gastric banding) or diversionary (e.g., biliointestinal bypass). While diversionary surgery (DIV) is associated with greater weight loss and more rapid metabolic changes than restrictive surgery (RES), the greater simplicity and reversibility of the latter are pertinent in selecting which intervention is preferred.

Although the impact of bariatric surgery on diabetes has been much publicized, the impact of bariatric surgery on cholesterol is less well recognized. To date, most of the favorable impact on cholesterol has been attributed to weight loss. Over the long term, DIV is associated with greater weight loss than RES. However, since DIV and RES are associated with similar overall weight loss during the first postoperative 6 months, one could compare cholesterol metabolism of the two types of surgery independent of weight loss.

Benetti et al compared cholesterol metabolism in DIV with RES (n = 20). They found that with DIV, reduced cholesterol absorption produced a decrease in LDL and non-HDL, associated with enhanced catabolic LDL receptor activity in the liver.

Because metabolic changes in both groups in reference to glucose, insulin, insulin resistance, and weight loss were similar, the authors suggest that these favorable cholesterol metabolic changes are induced specifically with DIV, and because weight loss over the specified interval was essentially equivalent, the changes in lipids are not fully explained by weight loss. ■

The Do-it-Yourself Diabetes Diagnosis Kit

Source: Bethel MA, et al. *Diabetes Care* 2013;36:1483-1488.

In the last decade, the threshold for diagnosis of diabetes has expanded to lower levels of fasting glucose, inclusion of reference laboratory A1c, and refinement of the definitions of prediabetes. Use of the oral glucose tolerance test (OGTT) appears to be less and less necessary, considering the relative convenience of other diagnostic tests. Could a self-administered OGTT change the balance and be a positive addition to the diagnostic portfolio?

Bethel et al report on a self-administered OGTT home use kit (SmartGRA) used by 30 diabetic and non-diabetic subjects. The kit includes instructions to guide the user through the process of timed capillary glucose measurement as well as a wireless data recorder for glucose levels, the results of which are *not* visible to the user (glucose measurements are wirelessly transmitted to the clinic for evaluation).

Was self OGTT accurate? In a word,

yes. Comparison of OGTT reports generated by SmartGRA vs office-based testing found comparable reproducibility of results. Although the results of home OGTT tended to overestimate glucose levels compared to the reference laboratory, this emerged as a problem with device calibration, which should be able to be remediated. Overall, subjects found the device easy to use.

As a proof-of-concept trial, these results lend credence to the idea that OGTT — generally conceded to be sufficiently unwieldy so that other diagnostic tests are preferred — might merit reconsideration if a well-calibrated, similarly patient-friendly device comes to market. ■

Low Creatinine Excretion Associated with Mortality in Type 2 Diabetes

Source: Sinkeler SJ, et al. *Diabetes Care* 2013;36:1489-1494.

Creatinine excretion (CER), as measured by the 24-hour urinary excretion of creatinine, has recently been noted to be associated with increased mortality, both in persons with underlying renal disease and the general population. CER reflects overall lean muscle mass, so that declines in CER may simply reflect deconditioning, loss of muscle mass, cachexia, malnutrition, etc., each of which may have a negative impact on mortality.

Sinkeler et al report on data accrued from two previously completed trials of angiotensin receptor blockers in diabetic nephropathy: Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan trial and the Irbesartan Diabetic Nephropathy trial. Twenty-four hour urinary CER was measured at baseline for the majority (n = 2360) of participants. Since mortality data from both trials are available, the relationship between CER and mortality can be evaluated.

Across the population studied, each halving decrement of CER was associated with a doubling of mortality risk. Since the primary association of CER is with muscle mass, the authors pose the interesting question of whether efforts expended to improve muscle mass, such as enhanced exercise and nutrition, might favorably effect mortality in this population. ■

Diabetes and Cognitive Function

Source: Spauwen PJJ, et al. *Diabetes Care* 2013;36:1554-1561.

The relationship between vascular disease and type 2 diabetes is consistent: Risk for microvascular events (retinopathy, neuropathy, and nephropathy) and macrovascular events (stroke and MI) is increased compared to non-diabetics. Additionally, when diabetics suffer macrovascular events, the consequences are typically more severe than similar events in non-diabetics.

The etiology of cognitive impairment is often multifactorial, including vascular insufficiency. Diabetics have a higher prevalence of cognitive impairment than non-diabetics, but the rate of cognitive decline in diabetics has not been studied.

The Maastricht Aging Study is comprised of 10,396 adults residing in the province of Limburg, the Netherlands. A sample from this population (n = 1290) underwent extensive neuropsychological testing at baseline, 6 years, and 12 years. At baseline, approximately 5% of the population had type 2 diabetes, with an incidence of an additional 5% over subsequent 6-year intervals.

When compared with controls, diabetics had a significant rate of cognitive decline over 6 and 12 years. Even when adjusted for variables that are more commonly comorbid in diabetics (hypertension, dyslipidemia, obesity), the acceleration in cognitive decline was greater in diabetics. As might be intuitive, diabetics with baseline cognitive impairment progressed at a more rapid rate than those without. Whether any specific intervention among diabetics (e.g., better control of glucose, lipids, blood pressure) might ameliorate the exaggerated rate of cognitive decline remains to be determined. ■

Benefits of Screening for Lung Cancer with Low-Dose CT

Source: The National Lung Screening Trial Research Team. *N Engl J Med* 2013;368:1980-1991.

Lung cancer (LCA) is responsible for more deaths than any other cancer worldwide. The burgeoning growth of smoking in developing countries suggests that this dismaying fact is unlikely to diminish in the foreseeable future. Clinical trials of screening for LCA through chest x-ray (CXR) did not show improved outcomes, likely because of its relatively poor discriminative ability in early disease.

The National Lung Screening Trial enrolled smokers and ex-smokers with at least a 30 pack-year history. Participants were randomized to an annual low-dose CT × 3 (n = 26,714) or standard chest x-ray (n = 26,035).

A positive radiographic finding on at least screening was seen in three times as many CT screenees as chest x-ray (27.3% vs 9.2%). LCA was diagnosed in 1.1% of the CT group vs 0.7% in the CXR group.

Screening for LCA was found to reduce LCA-related mortality by 20% and all-cause mortality by 7%.

Most of the abnormalities detected by low-dose CT screening were benign, so that the positive-predictive value for a positive CT was only 3.8% (i.e., about 4% of study subjects with any positive suspicious finding on CT turned out to have LCA). Reassuringly, repeatedly negative low-dose CT had a negative predictive value of 99.9% (i.e., essentially no one who had negative sequential CT screening was diagnosed with LCA during the screening and follow-up period). ■

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PHARMACOLOGY WATCH

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Prostate Medications and Cancer Risks — New Evidence

In this issue: Risk of high-grade prostate cancers; clopidogrel and stroke risk; antibiotics and statins; and FDA actions.

Prostate cancer risk and 5-ARIs

The 5-alpha reductase inhibitors (5-ARI) finasteride (Proscar) and dutasteride (Avodart) are used to treat lower urinary tract symptoms in men. They are known to reduce prostate-specific antigen (PSA) levels and there was hope that they may also reduce the incidence of prostate cancer. But in two large trials, PCPT (finasteride) and REDUCE (dustasteride), despite a nearly 25% reduction in the overall rate of prostate cancer, the risk for high-grade prostate cancers was increased (Gleason score 8-10). Debate has raged for the last several years about the significance of these findings and whether the increase was real or spurious due to detection bias. A new study from Sweden attempts to clarify this issue. Using the National Prostate Cancer Register along with prescription data, nearly 27,000 cases of prostate cancer were identified along with some 134,000 matched controls. More than 7800 men were exposed to a 5-ARI, including 1500 with prostate cancer and 6300 controls. As noted in previous studies, the risk of prostate cancer decreased with increasing duration of use of a 5-ARI. With 3 years of treatment, the risk of prostate cancer was 28% lower in the treatment group (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.59-0.89; $P < 0.001$ for trend). The reduction was seen primarily for Gleason score 2-6 and score 7 tumors ($P < 0.001$ for trend for both). However, as opposed to previous studies, the risk for higher grade tumors was not significantly increased, although the risk was not decreased either. By 3 years, the OR was 1.23 (95% CI, 0.90-1.68; $P = 0.46$ for trend), but did not reach statistical significance. The ORs for shorter exposures were 0.96 for 0-1 year exposure, 1.07 for 1-2 years, and 0.96 for 2-3 years. The authors conclude that men treated with a 5-ARI for lower urinary tract symptoms had a lower risk of prostate cancer with Gleason scores 2-7 and no evidence of increased risk of Gleason score 8-10 of cancers up to 4 years of treatment (*BMJ* 2013;346:f3406). The FDA issued a safety warning in 2011 regarding finasteride and dutasteride and the risk of high-grade prostate cancers and it is unlikely that this study alone will reverse that, but it is reassuring for the millions of men who take these drugs for lower urinary tract symptoms. ■

Clopidogrel could reduce stroke risk

Adding clopidogrel to aspirin in patients with minor stroke or a transient ischemic attack (TIA) may help reduce the risk of stroke within the next 90 days, according to a new study from China. In a randomized, double-blind, placebo-controlled trial, nearly 5200 patients were seen within 24 hours after onset of minor ischemic stroke or high-risk TIA and randomized to a combination of clopidogrel with aspirin or aspirin alone. The combination group was given clopidogrel at an initial dose of 300 mg followed by 75 mg per day for 90 days along with aspirin 75 mg per day for the first 21 days, while the aspirin alone group got placebo plus aspirin 75 mg for 90 days. The primary outcome was stroke (isch-

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emic or hemorrhagic) during 90 days of follow-up in an intention-to-treat analysis. Stroke occurred in 8.2% of the clopidogrel-aspirin group as compared to 11.7% in the aspirin alone group (hazard ratio 0.68; 95% CI, 0.57-0.81; $P < 0.001$). Moderate or severe hemorrhage occurred in seven patients in the clopidogrel-aspirin group and eight in the aspirin alone group. The rate of hemorrhagic stroke was the same (0.3%) in both groups. The authors conclude that among patients with TIA or minor stroke who are seen within the first 24 hours of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the next 90 days. The combination does not increase the risk of hemorrhagic stroke or hemorrhage (*N Engl J Med* published online June 26, 2013). An accompanying editorial states that this trial "proves the concept that dual platelet therapy can be more effective than single platelet therapy in preventing early recurrent stroke in patients with acute symptomatic atherothrombosis...," and also shows that dual platelet therapy can be given without excess harm in patients with acute focal brain ischemia. There is slight concern that the results may not apply to non-Chinese patients with different forms of underlying arterial disease (*N Engl J Med* published online June 26, 2013). ■

Antibiotic coprescription and statins

Use caution if you prescribe clarithromycin or erythromycin to patients on statins. Both drugs (but not azithromycin) inhibit cytochrome P450 isoenzyme 3A4, which can increase blood concentrations of statins, especially atorvastatin, simvastatin, and lovastatin. Researchers from Canada looked at the records of continuous statin users who were prescribed clarithromycin (n = 72,591) or erythromycin (n = 3267) with azithromycin use as a comparator (n = 68,478). The risk of hospitalization for rhabdomyolysis within 30 days was the main outcome. Although the absolute risk was low, concomitant use of clarithromycin/erythromycin with atorvastatin, simvastatin, or lovastatin was associated with a higher rate of hospitalization with rhabdomyolysis, especially in those with acute kidney injury. There was also an increase in all-cause mortality when the drugs were combined (absolute risk for rhabdomyolysis 0.02%, with acute kidney disease 1.26%, all-cause mortality 0.25%, relative risks 2.17, 1.78, and 1.56, respectively). These data suggest that coprescription of clarithromycin or erythromycin with a statin that is metabolized by CYP3A4 (atorvastatin, simvastatin, and lovastatin) increases the risk of statin toxicity (*Ann Intern Med* 2013;158:869-876). ■

FDA actions

The FDA has approved paroxetine for the treatment of hot flashes (vasomotor symptoms) associated with menopause. Paroxetine is a selective serotonin reuptake inhibitor (SSRI) and has the same active ingredient in the antidepressant Paxil. It is the first non-hormone based drug approved for this indication. The safety and efficacy of the drug was established in two randomized, double-blind, placebo-controlled trials of 1175 postmenopausal women with moderate-to-severe hot flashes that showed paroxetine was more effective in relieving symptoms than placebo. This new form of paroxetine contains 7.5 mg of the drug and is dosed once daily at bedtime. Paroxetine for depression and other psychiatric indications is dosed at 10-40 mg. All forms of paroxetine carry a boxed warning about increased risk of suicide. There is also concern about reduced effectiveness of tamoxifen if both medications are taken together. Paroxetine 7.5 mg for hot flashes is marketed by Noven Therapeutics as Brisdelle.

The FDA has approved a new formulation of selegiline — a once-daily, orally dissolving tablet — for the treatment of Parkinson's disease (PD) in patients who are losing responsiveness to levodopa/carbidopa. Most PD patients start treatment with levodopa/carbidopa, but for many, the effectiveness wanes with increasing "off" periods during which time symptoms worsen. In clinical trials, the new combination of selegiline reduced "off" periods by an average of 2.2 hours per day compared to 0.6 hours for placebo. The dissolvable tablet uses a new system that delivers more drug at a lower dose. The drug company claims this results in fewer side effects. Selegiline, a monoamine oxidase (MAO) inhibitor, has been available as a generic and also as the branded drugs Eldepryl and Zelapar. Like other MAO inhibitors, it can cause severe, even fatal, reactions if given in combination with certain other drugs including meperidine, tramadol, SSRIs, TCA antidepressants, and the over-the-counter medication dextromethorphan. The new orally dissolving selegiline is marketed by Valeant Pharmaceuticals as Zelapar.

The FDA has approved the TNF blocker golimumab for the treatment of ulcerative colitis. The drug was previously approved to treat rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The approval for ulcerative colitis was based on two studies of more than 800 patients, one group had failed other treatments and the other group were responders who were evaluated for maintenance. In both groups, golimumab was superior to placebo. Golimumab is marketed by Janssen Biotech as Simponi. ■