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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

ABSTRACT & COMMENTARY

Shorter Door-to-Balloon Times — No Change in Mortality

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: Menees DS, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med* 2013;369:901-909.

Primary percutaneous coronary intervention (PCI) is the preferred strategy for treating ST-segment elevation myocardial infarction (STEMI). The goal is reperfusion of the infarct-related artery as quickly was possible, and the national benchmark is to achieve this within 90 minutes of the patient's arrival at the hospital (i.e., door-to-balloon time [D2B] < 90 mins). Considerable attention has been placed on the publicly reported metric of a hospital's D2B time. It has been assumed that achieving shorter D2B times will reduce mortality associated with STEMI. Menees and colleagues took advantage of the American College of Cardiology's National Cardiovascular Data Registry (NCDR) CathPCI Registry to examine recent temporal trends in D2B times and the corresponding in-hospital mortality rates. They analyzed 96,738 admissions for patients undergoing primary PCI for STEMI from July 2005 through June 2009 at 515 hospitals throughout the country participating in the CathPCI Registry. The primary outcome of the study, in-hospital mortality, is recorded for all patents in the CathPCI Registry. They excluded patients who were transferred from another facility to receive primary PCI and patients whose D2B time was > 3 hours. In a subgroup analysis using a linked Medicare dataset, they also assessed 30-day mortality.

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Clinical Cardiology [ALERT]

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The mean age of the study population was 60.8 years, 28.0% were female, 61.0% had hypertension, 59.2% had dyslipidemia, 43.3% were current smokers, and 18.8% had diabetes. The prevalence of diabetes, hypertension, and dyslipidemia increased in each year of the study. The proportion of patients with a prior MI and previous PCI increased slightly each year. The mean ejection fraction was 46.8% and was unchanged from year to year. Patients presenting with cardiogenic shock accounted for 9.9% of all patients and it remained constant throughout the study.

Median D2B times declined from 83 minutes in 2005-2006 to 67 minutes in 2008-2009 ($P < 0.001$). The proportion of patients whose D2B was < 90 minutes increased from 59.7% in 2005-2006 to 83.1% in 2008-2009 ($P < 0.001$). However, despite improvements in D2B times, there was no change in unadjusted in-hospital mortality (4.8% in 2005-2006 and 4.7% in 2008-2009, $P = 0.43$) or in risk-adjusted in-hospital mortality (5.0% in 2005-2006 and 4.7% in 2008-2009, $P = 0.34$), nor was a difference observed in 30-day mortality ($P = 0.64$). They repeated the analyses in three high-risk subgroups: patients > 75 years of age, anterior MI, and cardiogenic shock. In all subgroups, D2B decreased over the study interval but in-hospital mortality did not change. The authors conclude that although national D2B times have improved significantly for patients undergoing primary PCI for STEMI, in-hospital mortality has remained virtually unchanged.

■ COMMENTARY

This is a very interesting study that makes us question the validity of using D2B times as a quality metric. There is an entrenched knowledge that reperfusion of the occluded infarct-related artery is beneficial, and that sooner is better than later. However, one is left to ponder just how much must we shorten the duration of ischemia to realize the maximal benefit of reperfusion? Have we already made all the gains that are possible? Is shaving off a few extra minutes of in-hospital time to reperfusion going to further improve outcomes? As the in-hospital ischemic time (i.e., D2B time) becomes shorter, it makes up less of the total ischemic time (i.e., symptom onset to balloon time). Therefore, incremental gains in D2B time are subject to the law of diminishing returns. Perhaps our focus should now shift to reducing total ischemic time, not just D2B time.

This study is strengthened by its rigorous statistical design and the large number of patients included in the analyses. There are several limitations in the data that should be acknowledged when interpreting its significance. First, this is a retrospective, observational study. There is always the potential for unmeasured confounders in observational datasets. Second, public reporting of D2B times and outcomes became more widespread during the study period. Public reporting has been shown to lead to risk-averse behavior, and it is possible that some of the sicker patients, whose outcomes are worse but who gain more benefit from primary PCI, were never offered PCI for their STEMI. Third, over the time period of the study, the patients became higher risk with more having prior MI and diabetes. Although the authors adjusted for risk with known parameters, risk adjustment is an inexact science and the cohorts may not have been directly comparable. Fourth, we are not told of the long-term effects on left ventricular function, subsequent heart failure, quality of life, or readmission rates. Mortality is not the only important endpoint. If shorter D2B time results in less heart failure or better quality of life, then the considerable resources devoted to shortening D2B time may be justified. Further long-term studies are needed.

Should we change practice based on this study? No, I think patients with STEMI should still undergo primary PCI in the most rapid time feasible. However, this study gives us pause to consider whether resources that are aimed at further reducing D2B could be better spent reducing total ischemic time. ■

ABSTRACT & COMMENTARY

Low-Gradient Aortic Stenosis Outcomes

By Michael H. Crawford, MD, Editor

SOURCES: Ozkan A, et al. Impact of aortic valve replacement on outcome of symptomatic patients with severe aortic stenosis with low gradient and preserved left ventricular ejection fraction. *Circulation* 2013;128:622-631. Wiegers SE. Symptomatic low-gradient severe aortic stenosis with preserved left ventricular ejection fraction: Now less of a clinical conundrum. *Circulation* 2013;128:576-578.

In severe aortic stenosis (AS) with symptoms, aortic valve replacement is recommended. Since the symptoms associated with AS are non-specific, when there is a discrepancy between echocardiographically calculated aortic valve area (AVA) and the gradient across the valve, treatment decisions become difficult. When valve area suggests severe AS, but the gradient is < 40 mmHg and left ventricular ejection fraction (LVEF) is normal, aortic valve replacement (AVR) may be delayed since some prosthetic valves have gradients in this range. Thus, these investigators from the Cleveland Clinic conducted a prospective observational study of 1588 symptomatic patients with isolated severe AS (AVA index < 0.6 cm^2/m^2) of which 260 (16%) had preserved LVEF (> 50%) and a mean gradient < 40 mmHg. All 260 patients with symptomatic low-gradient severe AS (LGSAS) underwent a complete echocardiographic examination and were followed for a mean of 28 months. Those treated medically or by balloon valvuloplasty were considered the standard therapy group. The others were treated by AVR per physician preference. The primary endpoint was all-cause mortality. AVR was performed in 123 of the 260 patients with symptomatic LGSAS. The two treatment groups were not perfectly matched in terms of baseline characteristics. As expected, the AVR patients were generally lower-risk patients. Thus, a propensity score model was used to compare the independent effect of AVR on outcome. AVR consisted of surgery (SAVR) in 94 and transcatheter (TAVR) in 29 patients. Despite a normal EF, medical patients had other measures suggesting systolic and diastolic dysfunction. Overall, 125 patients had normal stroke volume indexes (SVI) and 135 had low SVIs, which was more prevalent in medically treated patients (59% vs 44%, $P < 0.02$). The low SVI patients had somewhat lower EFs (59% vs 62%, $P < 0.0001$). During the average 28-month follow-up, 105 patients (40%) died, 32 in the AVR group and 73 in the medical group, resulting in a hazard ratio of 0.54 (95% confidence interval, 0.32-0.94; $P < 0.001$) for AVR. LV SVI did not influence the survival rate in the AVR patients or the medically treated patients. The authors concluded that AVR is associated with a higher 2-year survival than medical therapy in symptomatic patients with LGSAS and normal LVEF.

■ COMMENTARY

The development of TAVR has focused new light on the hemodynamic characterization of AS. We have known for some time that some patients with severe AS can have low transvalvular gradients. This so-called LGSAS was originally thought to be a measurement error or due to reduced LV function, which could be sorted out using dobutamine stress echo to improve LV function. More recently, a subgroup of LGSAS has been identified with normal LVEF, which is unexpected since normal LV function should produce a robust gradient in severe AS. Several papers, including this one, have now described two subgroups of LGSAS with normal LVEF patients: those with normal stroke volume and those with reduced stroke volume. The latter group has been called "paradoxical low-flow, low-gradient AS" because the low stroke volume is unexpected with a normal EF. This is confusing because a low gradient with a normal EF itself seems paradoxical. So, I hope this term does not survive.

What does all this mean? My answer is that EF is a crude measure of LV performance that is load dependent. Depending on your LV diastolic volume, a normal EF can be associated with a normal SV or a reduced SV. This study and more sophisticated studies have shown decrements in LV performance measures beyond EF in AS patients, and biopsies in humans have shown increased fibrosis that would tend to impair diastolic function. Thus, in the case of severe AS, EF is not a particularly useful measurement.

Clinically, the patients who had AVR after adjustment for known confounders did better than those treated medically. Remember, all of these patients were symptomatic. So, if you are confident that your echocardiographic estimation of valve area is correct and the patient has a normal EF

and symptoms, then it doesn't really matter what the gradient is. Such patients did much better with valve replacement in this prospective study and previous retrospective studies. However, several aspects of this study have probably magnified the differences between medical and surgical therapy. First, a propensity score model cannot account for all variables that influence prognosis. The surgical patients were clearly healthier based on baseline characteristics. Also, important patient characteristics such as frailty and dementia, which may have affected the decision not to perform surgery, were not considered. In addition, about 25% of the patients had TAVR, which will lower the surgical group's mortality since there were no deaths within 30 days of TAVR. Despite these factors that undoubtedly increased the apparent benefit of AVR, a two-fold difference in mortality between the two groups is impressive and should be considered in symptomatic patients because they are more likely to feel better after AVR as well. This study should not be applied to asymptomatic patients and patients with moderate AS or reduced EF. ■

ABSTRACT & COMMENTARY

Right Bundle Branch Block is Associated with Large Anterior Scar

By Andrew J. Boyle, MBBS, PhD
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SOURCE: Strauss DG, et al. Right, but not left, bundle branch block is associated with large anteroseptal scar. *J Am Coll Cardiol* 2013;62:959-967.

The left bundle branch supplies a coordinated electrical impulse to the left ventricle. In patients with acute chest pain, left bundle branch block (LBBB) that is new or presumably new is treated as an equivalent of ST elevation. However, the left bundle usually has dual blood supply from both the left anterior descending (LAD) and right coronary artery (RCA). Therefore, an acute myocardial infarction (MI) due to LAD occlusion should be less likely to cause LBBB and more likely to cause right bundle branch block (RBBB). To test this hypothesis, Strauss and colleagues studied the electrocardiograms (ECG) and magnetic resonance imaging (MRI) with late gadolinium enhancement (LGE) to assess the relationship between anterior wall scar and LBBB. They studied 233 patients with left ventricular ejection fraction (LVEF) < 35% receiving implantable cardioverter defibrillators (ICDs) for primary prevention. In addition, they studied 20 patients undergoing alcohol septal ablation for hypertrophic obstructive cardiomyopathy (HOCM) as a model for acute MI involving the proximal septum. All underwent MRI and ECG after the procedure.

Their cohort of 233 had a mean age of 57 years, was 77% male, a mean LVEF of 27%, and 56% were ischemic in etiology. Forty-five patients had LBBB and 19 had RBBB. There were no differences between the LBBB and RBBB groups in terms of age, gender, ethnicity, heart failure class, or LVEF. On MRI with LGE, patients with RBBB had larger scars than those with LBBB (24.0% vs 6.5% of the LV; $P < 0.0001$) and patients with non-specific left ventricular conduction delay or QRS < 120 ms had intermediate scar size (12.9% and 14.4%, respectively). In addition, those with RBBB (compared with LBBB) were more likely to have ischemic heart disease (79% vs 29%; $P < 0.0001$). When considering only the ischemic cardiomyopathy patients, a larger scar size persisted among those with RBBB vs those with LBBB (28.5% vs 14.7%; $P = 0.006$). Among non-ischemic patients, none of the RBBB patients had absence of detectable scar, whereas 20 of 32 (63%) LBBB patients had no detectable scar ($P = 0.017$). In the alcohol septal ablation cohort, 15 of 20 patients (75%) developed RBBB, but none developed LBBB. The authors conclude that in patients with LVEF < 35%, RBBB is associated with significantly larger scar size than LBBB, and occlusion of a proximal LAD septal perforator causes RBBB. In contrast, LBBB is most commonly caused by non-ischemic pathologies.

■ COMMENTARY

This study examines the relationship between extensive scar in the LV and bundle branch block. The major finding is that LBBB is more often related to non-ischemic cardiomyopathies and RBBB is associated with ischemic

cardiomyopathy with large anteroseptal scar. It is LBBB, not RBBB, that is included as a guideline to activate the cath lab during acute chest pain. This study is consistent with prior pathological studies that show RBBB is much more commonly associated with anterior MI. It is important to emphasize that the authors studied patients with chronic LV dysfunction and their results may not directly relate to patients with acute MI. There may have been significant bias in their study, with patients suffering larger infarcts dying before they could receive their ICD. In addition, their acute study of alcohol septal ablation involved occlusion of a septal perforator only and does not accurately represent the clinical presentation of anterior MI. It should be considered proof of principle that proximal septal ischemia more often results in RBBB and does not rule out the possibility of acute anterior MI existing with LBBB. How should the clinician incorporate these data into their daily management of patients? This should increase our index of suspicion for acute anterior MI when a patient with chest pain presents with a new (or presumably new) RBBB on their ECG. We should not abandon treating LBBB as potentially ischemic, because patients with chronic LBBB can subsequently develop acute MI. ■

ABSTRACT & COMMENTARY

Is 'Silent' Atrial Fibrillation in Diabetics Associated with Cerebral Neurologic Events?

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

SOURCE: Marfella R, et al. Brief episodes of silent atrial fibrillation predict clinical vascular brain disease in type 2 diabetic patients. *J Am Coll Cardiol* 2013; 62:525-530.

Patients with diabetes have twice the stroke risk of those without diabetes. Yet, only 15% of diabetic patients have symptomatic atrial fibrillation (AF). This study sought to address the question of whether there was a relationship between asymptomatic AF and cerebral events in type 2 diabetics with no evidence of AF or stroke.

The study included two phases: 1) a 4-year recruitment period to enroll patients from a cohort of 1992 type 2 diabetic patients and 2) a 3-year follow-up period. Patients included in the follow-up arm had to meet the following criteria: age < 60 years, successful completion of quarterly 48-hour Holter monitors during the screening phase, and completion of brain magnetic resonance imaging (MRI). Patients with any baseline history of AF, stroke, transient ischemic attack (TIA), or structural heart disease were excluded. Four hundred sixty-four patients were enrolled and compared to 240 healthy subjects without diabetes or any of the exclusion criteria. During the screening phase, patients underwent 48-hour Holter monitors every 3 months with silent AF classified as any episode lasting at least 10 minutes and < 48 hours in duration. Patients were then classified into either a group with silent AF (SAFE group, n = 176) or a group without silent AF (non-SAFE group, n = 288). All patients were treated with aspirin 75-325 mg daily, and if CHADS2 score was > 1, oral anticoagulation with warfarin was initiated. Patients were then followed for 36 months for the occurrence of any clinical neurologic events. The incidence of "silent" AF was much higher among diabetic patients compared to healthy controls (11% vs 1.6%; $P < 0.001$). The mean AF burden was 21 ± 15 hours in the SAFE group compared to 3 ± 1.4 hours in the healthy control group ($P < 0.001$). On MRI, a subclinical thromboembolic ischemic event (SCI) was detected more often in the SAFE group compared to the non-SAFE group (61% vs 29%; $P < 0.01$). The AF burden was correlated to the size and number of SCI events. Using multivariate analysis, silent AF, left atrial size, systolic blood pressure, and duration of diabetes were independently associated with SCI. During the 36-month follow-up, clinical AF episodes occurred in 15% of patients who were excluded from the analysis; 26 patients (15%) in the SAFE group and and 19 patients (7%) in the non-SAFE group were treated with warfarin anticoagulation.

Despite this, a clinical ischemic stroke developed in more patients in the SAFE compared to the non-SAFE groups (17.3% vs 5.9%; $P < 0.01$). No strokes occurred in the healthy control group. Of the 43 stroke events, 42 were ischemic and one was hemorrhagic. The authors concluded that subclinical AF episodes are common in diabetics and predict a higher incidence of subsequent cerebral ischemic events.

■ COMMENTARY

Patients with type 2 diabetes have a higher incidence of cerebrovascular events and AF compared to those without diabetes. However, there has not been a definitive link established between the two. Diabetes is also associated with hypercoaguability and vascular endothelial dysfunction that could play a role in SCIs. This ambitious study carried out over 7 years has several important findings. First, the prevalence of silent AF in a population of type 2 diabetics is approximately 10% higher than previously reported. Second, patients with diabetes and silent AF have a very high incidence of SCI on MRI examination (61%). Finally, patients with diabetes and silent AF, even episodes lasting < 48 hours, have a high incidence of strokes during follow-up (17.3%). This should be an eye-opener to cardiologists following patients with diabetes mellitus.

Should we screen our patients with type 2 diabetes for silent AF? It is difficult to know if the patients in the centers enrolling for this study were subject to a referral bias that increased their thromboembolic risk. However, I think the data demonstrating a 10% prevalence of asymptomatic AF and strong association with both silent and overt clinical neurologic events support screening of high-risk diabetic patients for asymptomatic AF. Obviously the cost-effectiveness of this approach has not been established, nor has the efficacy of treating diabetic patients with asymptomatic AF with systemic anticoagulation. While this study was performed before the era of the newer oral anticoagulants, the advent of the oral direct thrombin and factor X inhibitors have certainly lowered the threshold for initiating systemic anticoagulation in AF patients at risk of stroke. One could certainly envision a multicenter, randomized trial screening diabetic patients for brief episodes of asymptomatic AF, and then randomizing them to aspirin or anticoagulation with a novel anticoagulant. However, until more data become available, it certainly is reasonable to have a low threshold to initiate anticoagulation in diabetic patients who have a clinical neurologic event, and to have increased vigilance screening of diabetic patients with multiple AF risk factors for silent AF. We await more data on this important topic. ■

ABSTRACT & COMMENTARY

Does Septal Atrial Lead Location Reduce Atrial Fibrillation Burden in Patients with Dual Chamber Pacemakers?

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SOURCE: Lau CP, et al. Prospective randomized study to assess the efficacy of site and rate of atrial pacing on long-term progression of atrial fibrillation in sick sinus syndrome: Septal pacing for atrial fibrillation suppression evaluation (SAFE) study. *Circulation* 2013;128:687-693.

Implanted pacemakers with atrial leads are often used to detect asymptomatic episodes of atrial fibrillation (AF). In addition, over the last 2 decades various algorithms have been attempted to use atrial pacing to reduce AF burden in patients with paroxysmal AF. These algorithms have included overdrive atrial pacing (i.e., pacing faster than the intrinsic sinus rate in order to overdrive suppress AF "triggers"), septal atrial pacing to abbreviate atrial activation time, and multisite atrial pacing. The current study examines two strategies for reduction of AF in a 2 × 2 randomized design: pacing from the left atrial septum vs standard lead positioning in the right atrial appendage and overdrive suppression pacing vs standard demand pacing. Patients with documented paroxysmal AF in the 6 months prior to randomization undergoing implantation

of a pacemaker with an atrial lead were enrolled. Patients were prospectively randomized in a 2 × 2 factorial design to placement of the atrial lead either in the low atrial septum or standard right atrial appendage and to an atrial overdrive pacing algorithm either ON or OFF. Patients were followed every 6 months up to a minimum of 3 years after enrollment. At each visit, all episodes of device-detected AF were recorded in addition to any clinical AF events. Atrial high rate episodes lasting > 6 minutes duration were considered to indicate an AF event. From May 2005 to November 2011, 385 patients were enrolled from 21 centers. Patients were randomized to pacing from the RA appendage with (n = 98) or without (n = 99) continuous atrial overdrive pacing and to pacing from the low atrial septum with (n = 92) or without (n = 96) continuous atrial overdrive pacing. Successful implantation was achieved in 99% of patients. As designed, RA septal pacing significantly reduced *P* wave duration and continuous atrial pacing significantly increased the percentage of atrial pacing. After a mean of 3.1 years of follow-up, there was no difference in AF burden with septal vs right atrial appendage pacing (hazard ratio [HR], 1.18; 95% confidence interval [CI], 0.79-1.75; $P = 0.65$) or with continuous atrial pacing ON vs OFF (HR 1.17; 95% CI, 0.79-1.74; $P = 0.61$). Persistent AF developed in 20% of patients in the study, with no difference in the development of persistent AF among the four randomized groups. Adverse events did not differ among the four groups ($P > 0.05$). The authors concluded that neither continuous overdrive atrial pacing nor atrial septal pacing reduced the development of persistent AF in patients with pacemakers for sick sinus syndrome.

■ COMMENTARY

Reduction in AF burden through the use of atrial pacing algorithms in patients with implanted pacemakers with atrial leads has been investigated for the past 2 decades. The incidence of AF is certainly higher in patients with sinus node dysfunction or other conduction disease, and monitoring of AF burden can easily be accomplished with modern pacemakers. Simple overdrive suppression of the premature atrial complexes that trigger AF makes good sense and has been tried in the postoperative and permanent pacemaker populations. Although new pharmaceutical agents require extensive randomized prospective trials to ensure efficacy and safety, these overdrive atrial pacing algorithms have become included in pacemaker software with little oversight or documentation of efficacy. The Septal Pacing for Atrial Fibrillation Suppression Evaluation (SAFE) trial confirms that overdrive atrial pacing has no role in the prevention of AF. Such algorithms also increase battery usage and may worsen symptoms in patients because of the increased pacing rate during sinus tachycardia. Therefore, such algorithms should be abandoned in future pacemaker software. Early studies also showed that conduction delay in the triangle of Koch may contribute to the initiation of AF with premature beats, and that pacing in the triangle of Koch prevented initiation of AF from remote atrial premature beats.[1] Abbreviating *P* wave duration also may reduce heterogeneity of refractoriness and preexcite regions of slow conduction also reducing the propensity to AF. However, the SAFE trial also confirms that septal pacing has no advantage over standard right atrial appendage pacing for the prevention of AF.

What lessons have we learned from the SAFE trial? First, when indicated, atrial lead placement should be located at a safe stable location that allows stable thresholds and good sensing, ideally the right atrial appendage. There is also no role for atrial overdrive pacing to prevent AF in patients with paroxysmal AF. This should help eliminate some unneeded software in the next generation of pacemakers. Other algorithms, such as burst pacing to terminate atrial flutters or multisite atrial pacing, still require further investigation. But in this case, simpler is better. ■

REFERENCE

1. Papageorgiou P, et al. Site-dependent intra-atrial conduction delay. Relationship to initiation of atrial fibrillation. *Circulation* 1996;94: 384-389.

CME Instructions

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CME Questions

1. Aortic valve replacement is superior to medical therapy in severe aortic stenosis patients with:
   a. symptoms.
   b. low EF.
   c. low gradients.
   d. valve area > 1.0 cm^2

2. Subclinical atrial fibrillation events detected on ambulatory ECG monitoring are:
   a. associated with strokes.
   b. common in normal subjects.
   c. frequent in diabetes.
   d. a and c

3. Which of the following reduces the incidence of persistent AF in sick sinus syndrome patients requiring a pacemaker?
   a. Atrial overdrive pacing
   b. Atrial septal lead placement
   c. Multisite atrial pacing
   d. None of the above

4. Improvements in acute STEMI door-to-balloon times in the United States have reduced:
   a. hospital mortality.
   b. 30-day mortality.
   c. risk-adjusted hospital mortality.
   d. None of the above

5. Which of the following is correct?
   a. LBBB in low EF patients indicates a larger scar than RBBB does.
   b. LBBB is caused by occlusion of the first septal perforator artery.
   c. LBBB is more common in non-ischemic cardiomyopathy.
   d. LBBB is associated with lower EFs vs RBBB.

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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Our Newest Pharmacologic Class for Treatment of Diabetes: SGLT2 Inhibitors

Source: Polidori D, et al. *Diabetes Care* 2013;36:2154-2161.

The role of the kidney in glucose regulation has been underappreciated. Although perhaps counterintuitive, after persistent exposure to elevated glucose levels in the glomerular filtrate presented to the proximal renal tubule, the kidney adapts by reabsorbing *increased* amounts of glucose, thereby *increasing* blood sugar. The sodium glucose cotransporter (SGLT2) receptor is the primary pathway for renal tubular glucose reabsorption; blockade of this receptor results in enhanced urinary glucose excretion. Currently, the only FDA-approved agent for blockade of the SGLT2 receptor is canaglifozin.

In addition to potent SGLT2 receptor blockade, it has been suspected that canaglifozin might affect intestinal absorption of glucose by its modest inhibition of intestinal SGLT1. Polidori et al tested the impact of canagliflozin SGLT1 inhibition by examining the rate of gastrointestinal glucose absorption in healthy volunteers following a 600-kcal mixed-meal tolerance test.

Canagliflozin produced a very modest reduction in glucose absorption over a 6-hour interval (about 6%). The effects were accentuated in the early postprandial intervals, indicating a slowed absorption of glucose that was not attributable to delayed gastric emptying. Blunting of early postprandial glucose absorption should have a favorable effect on postprandial glucose excursions in diabetics.

Although enhanced urinary glucose excretion is the primary mechanism of plasma glucose lowering by SGLT2 inhibitors, modest gastrointestinal SGLT1 inhibition also appears to impact postprandial glucose excursion. ■

Bariatric Surgery vs Intensive Medical Therapy for Diabetes

Source: Kashyap SR, et al. *Diabetes Care* 2013;36:2175-2182.

The benefits of bariatric surgery (BAS) are increasingly recognized for obese patients with type 2 diabetes mellitus (T2DM). Indeed, the mechanisms by which diversionary surgery (e.g., gastric bypass) produces such prompt and dramatic remission in diabetic patients are still being elucidated. Long-term observational data on BAS for persons with severe obesity (body mass index [BMI] > 40) confirm durable weight reduction, improved control of diabetes, and even suggest reduced mortality.

Few trials have directly compared the efficacy of BAS with intensive medical treatment (IMT). Kashyap et al randomized T2DM subjects (n = 60) with moderate obesity (mean BMI = 36) to one of two BAS interventions (gastric sleeve or gastric bypass) or IMT in the Surgical Therapy And Medications Potentially Eradicate Diabetes (STAMPEDE) trial. Currently reported data include outcomes at 24 months.

In essentially every category assessed, BAS patients had superior outcomes to IMT. No BAS-related deaths occurred. At 2 years, degree of A1c control, LDL, HDL, total cholesterol, triglycerides, and CRP were all more improved in the BAS patients than in the IMT patients.

When comparing outcomes in the two BAS groups, even though weight loss was similar between gastric sleeve and bypass surgery, the latter achieved greater improvements in truncal fat reduction, leptin, insulin sensitivity, beta cell function, and incretin responses. BAS is more effective for multiple metabolic markers than IMT over the long term in T2DM patients. ■

Psoriasis and Risk for New Onset Diabetes

Source: Khalid U, et al. *Diabetes Care* 2013;36:2402-2407.

Inflammatory disorders like rheumatoid arthritis (RA) and psoriasis (PSOR) have recently been confirmed to be risk factors for adverse cardiovascular (CV) events, although the precise pathways through which such risk occurs remain controversial. Some have even gone so far as to say that RA should be considered an independent CV risk factor of equal potency to the already registered risk factors like hypertension, history of premature cardiovascular death, etc. Since PSOR and RA share common inflammatory pathways, it's perhaps not surprising that both are associated with CV adversity.

To date, the relationship between PSOR and diabetes mellitus (DM) has been controversial. Since DM is a major contributor to CV events, if PSOR and

DM are related, that would account for some of the increased CV risk.

Khalid et al report on an analysis of the PSOR-DM relationship discerned through a 12-year follow-up of Danish persons ≥ 10 years (n = 4,614,807). They studied the incidence of new-onset DM in PSOR subjects vs controls. A graded linear association between PSOR and new onset DM was found. Compared to the reference population, the incidence of DM in persons with mild PSOR was almost doubled, and in severe PSOR, nearly tripled. ■

Osteoporosis: Are Two Drugs Better Than One?

Source: Tsai JN, et al. *Lancet* 2013;382: 50-56.

Most women today who are receiving pharmacotherapy for treatment of osteoporosis receive oral bisphosphonates (e.g., alendronate, risedronate). Other effective treatments, like teriparatide (TERI) and denosumab (DENO) are usually reserved for more severe cases, in some part because they require parenteral administration.

Even though osteoporosis treatments have shown risk reduction for fracture and improved bone mineral density (BMD), restoration of full bone integrity remains a challenge. As one of the few anabolic tools (as opposed to anticatabolic tools like bisphosphonates), some investigators have tried to augment the favorable activity of TERI by combination with bisphosphonates, but the results have been disappointing. Whether the addition of DENO to TERI might be beneficial was the subject of investigation by Tsai et al. Postmenopausal women with osteoporosis (n = 100) were randomized to DENO, TERI, or both for 6 months. The primary outcome of the study was improvement in BMD.

Combination TERI+DENO appeared to be synergistic, with improvements in BMD greater than either agent alone and arithmetically greater than the anticipated benefit of combined monotherapies. For example, BMD increases at the hip were 4.2% for TERI+DENO, 0.8% for TERI, and 2.1% for DENO. These data support the consideration of TERI+DENO in highest-risk patients, those unable to take other treatments, or patients who fail to respond to other regimens. ■

Long-Term Impact of Weight Management on Blood Pressure

Source: Tyson CC, et al. *J Clin Hypertens* 2013;15:458-464.

The weight loss maintenance (WLM) trial randomized adults (n = 741) with hypertension (HTN) and/or dyslipidemia — but without evidence of cardiovascular disease — to one of several weight loss management programs. Although the initial outcome reports from WLM addressed the relative efficacies of different weight loss strategies over time, this report stratified study participants into those who lost, maintained, or gained weight over the 5-year study period. Tyson et al compared blood pressure effects between the three categories of weight impact, irrespective of which particular method of weight loss had been applied.

At study end, the weight-stable group had gained 0.6 kg, as compared with a 9.1 kg increase in the weight-gain group, and a 7.1 kg decrease in the weight-loss group. The weight-stable and the weight-gain groups were noted to have similar increases in systolic blood pressure (SBP) over 5 years (SBP increase mean 4.2 mmHg), whereas the weight-loss group SBP was not statistically significantly changed.

In contrast to some other trials that report a "legacy effect" (prolonged beneficial impact of early intervention, even after the intervention has ceased), initial weight loss in WLM was not associated with favorable SBP effects if weight was regained. On the other hand, sustained modest weight reduction (< 10% of baseline BMI) had a sustained effect to maintain SBP. Although simply maintaining weight over the long term might appear to be a laudable goal, it is apparently insufficient to favorably affect SBP. ■

The WEAVE Study: Does Special Training in Domestic Violence Improve Outcomes?

Source: Hegarty K, et al. *Lancet* 2013; 382:249-258.

Intimate partner violence (IPV) is a public health problem that knows no boundaries of age, country of residence or origin, economic status, or education. Primary care clinicians, particularly family physicians, are often the first point of clinical contact for victims of IPV, but may lack confidence in their ability to identify and/or address IPV. Hegarty et al report on a trial from Australia in which women who screened positive for concerns about fear of their partner (n = 272) received care from family physicians who were randomized to receive special training in IPV or no intervention. The intervention group physicians participated in the Healthy Relationships Training program, which is intended to provide the ability to respond effectively to women who have experienced IPV and give brief counseling. The primary outcomes of the trial were changes in quality of life (as per the WHO QOL-BREF), safety planning and behavior, and mental health (as per the SF-12) at 1 year.

At 1 year, there was no difference in the primary endpoint between the intervention group and controls. A favorable impact on depression (a secondary endpoint) was seen. However, since the primary endpoint was not achieved, the potential for benefits on depression must remain considered as hypothesis generating. ■

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PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

More Side Effects of Fluoroquinolones Coming to Light

In this issue: New side effects of fluoroquinolones; probiotics and antibiotic-related diarrhea; prostate cancer risk and 5-ARIs; and FDA actions.

New study finds dysglycemia risk

Fluoroquinolones, such as levofloxacin, ciprofloxacin, and moxifloxacin, are useful broad-spectrum antibiotics, but they have been associated with tendinopathy, including tendon rupture and QT interval prolongation. Now, two new potential side effects are coming to light. In a new study from Taiwan, more than 78,000 diabetic patients who received fluoroquinolones were monitored for dysglycemia, including hyperglycemia and hypoglycemia. The study looked at users of levofloxacin, ciprofloxacin and moxifloxacin, cephalosporins, and macrolides. The absolute risk of hyperglycemia was 6.9 per 1000 for moxifloxacin and 1.6 for macrolides. The risk for hypoglycemia was 10.0 for moxifloxacin and 3.7 for macrolides. The adjusted odds ratios for hyperglycemia compared to macrolides were: moxifloxacin 2.48 (95% confidence interval [CI], 1.50-4.12), levofloxacin 1.75 (95% CI, 1.12-2.73), and ciprofloxacin 1.87 (95% CI, 1.20-2.93). For hypoglycemia, the adjusted odds ratios were moxifloxacin 2.13 (95% CI, 1.44-3.14), levofloxacin 1.79 (95% CI, 1.33-2.42), and ciprofloxacin 1.46 (95% CI, 1.07-2.00). The risk of hypoglycemia associated with moxifloxacin was even higher if patients were taking insulin. The authors suggest that fluoroquinolones, especially moxifloxacin, are associated with severe dysglycemia in diabetic patients and that clinicians should "prescribe quinolones cautiously" in diabetic patients (*Clin Infect Dis* published online August 14, 2013. DOI: 10.1093cid/cit439). In related news, the FDA is requiring labeling changes for fluoroquinolones regarding the risk of neuropathy. The FDA Drug Safety Communication states that "serious nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken and may be permanent." The warning is for both oral and parenteral forms of the drugs, but not topicals. The FDA recommends that if a patient develops symptoms of peripheral neuropathy associated with a fluoroquinolone, the drug should be stopped immediately and the patient should be switched to a non-fluoroquinolone antibiotic. Further information can be found at the FDA's website at www.fda.gov/Safety/MedWatch. ■

Probiotics and antibiotic-related diarrhea

Probiotics may not prevent antibiotic-associated diarrhea (AAD), including *Clostridium difficile* infections. That was the finding of a randomized, double-blind, placebo-controlled trial in nearly 3000 inpatients aged ≥ 65 years who were exposed to one or more oral or parenteral antibiotics. Patients were randomized to a multistrain preparation of lactobacilli and bifidobacteria or placebo for 21 days. The rate of AAD was 10.8% in the probiotic group and 10.4% in the placebo group ($P = 0.71$). *C. difficile* was uncommon and occurred in 0.8% of the probiotic group and 1.2% of the placebo group ($P = 0.35$). The authors state that "we identified no evidence that a multistrain

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preparation of lactobacilli and bifidobacteria was effective in the prevention of AAD or CDD." (*Lancet* published online August 8, 2013. doi: 10.1016/S0140-6736(13)61218-0). An accompanying editorial wonders if this study can tip the balance of probiotic evidence, as it was a rigorously performed study vs previous small studies showing a positive effect. But, the current study used only two types of non-pathogenic bacteria (doi: 10.1016/S0140-6736(13)61571-8). Still, the cost effectiveness of routine probiotic use must be questioned based on this study. ■

Prostate cancer risk and 5-ARIs

The debate regarding 5-alpha reductase inhibitors (finasteride [Proscar] and dutasteride [Avodart]) and the risk of prostate cancer continues. Despite good evidence that the drugs reduce the overall risk of prostate cancer, there is also evidence that the drugs may increase the risk of high-grade prostate cancers (Gleason score 7-10). This was a finding of the Prostate Cancer Prevention Trial (PCPT) that was published in 2003. That finding was recently questioned in a study published in the *British Medical Journal* that found no risk of higher-grade prostate cancers (*BMJ* 2013;346:f3406, reported in the August *Pharmacology Watch*). Now, 10 years after the PCPT was originally published as an 8-year study, the 18-year follow-up has been published in the *New England Journal of Medicine*. Of the nearly 19,000 men who underwent randomization in the PCPT, prostate cancer was diagnosed in 10.5% of the finasteride group and 14.9% of the placebo group, a 30% reduction in the rate of prostate cancer (relative risk 0.70; 95% CI, 0.65-0.76; $P < 0.001$). But all of the reduction was in lower-grade prostate cancers. There was a slightly higher rate of high-grade cancer in the finasteride group (3.5% vs 3.0%, $P = 0.05$), but there was no difference in overall mortality. There was also no increase in mortality in men diagnosed with high-grade prostate cancer. The authors conclude that finasteride reduced the risk of prostate cancer by about one-third, and although high-grade cancer was more common in the finasteride group, there was no difference in overall mortality or survival after the diagnosis of prostate cancer (*N Engl J Med* 2013;369:603-610). Dutasteride was also studied in the REDUCE trial and similarly found lower rates of low-grade prostate cancers but increased rates of higher-grade cancers (*N Engl J Med* 2010;362:1192-1202). Some have argued that the higher rate of high-grade cancers is due to higher surveillance and "detection bias," but regardless of the cause, it is reassuring to know that there is no higher risk of mortality, at least in the PCPT. The FDA changed the labeling to both finasteride and dutasteride in 2011 regarding the increased risk of high-grade prostate cancers. ■

FDA actions

The FDA has issued a Drug Safety Communication regarding a case of progressive multifocal leukoencephalopathy (PML) in a patient who was taking fingolimod (Gilenya) for the treatment of multiple sclerosis. This is the first reported case of PML associated with fingolimod in patients who had not previously taken natalizumab (Tysabri). The patient, who lives in Europe, had been on the drug for about 8 months and had previously taken interferon beta-1a, azathioprine, and steroids. Novartis, the manufacturer of fingolimod, indicated it is possible that the patient had PML prior to starting the drug. PML is a rare neurologic disease caused by latent infection with the JC virus. It has been associated with immunosuppressive drugs, including natalizumab.

The FDA has approved a new topical agent to treat facial redness in adults with rosacea. Brimonidine, an alpha-2 agonist, is currently used as an ophthalmic preparation for treating glaucoma. The drug constricts dilated facial blood vessels for up to 12 hours. It is approved in a 0.33% topical gel that is applied once daily. Patients with depression, coronary artery disease, Raynaud's, or other conditions that may be exacerbated by an alpha agonist should use the drug with caution. Brimonidine gel is marketed by Galderma as Mirvaso.

The FDA has approved dolutegravir, a new once-daily HIV integrase inhibitor. It is the third integrase inhibitor on the market after raltegravir and elvitegravir. The drug is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infections in adults and children ≥ 12 years of age weighing at least 40 kg. It may be used in treatment-naïve patients or treatment-experienced patients, including those who have previously taken an integrase inhibitor. Approval was based on four trials in more than 2500 patients that showed efficacy in combination with other antiretrovirals. A fifth trial showed efficacy in HIV-infected children as young as 12 who had not taken an integrase inhibitor. Dolutegravir is marketed by ViiV Healthcare as Tivicay. ■