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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

Abstract & Commentary

Predicting Left Main and Triple-vessel Disease in ACS

By Andrew J. Boyle, MBBS, PhD

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

Source: Kosuge M, et al. An early and simple predictor of severe left main and/or three-vessel disease in patients with non–ST-segment elevation acute coronary syndrome. *Am J Cardiol*. 2011;107:495-500.

Patients presenting with acute coronary syndromes (ACS) should be administered dual anti-platelet therapy with aspirin and a thienopyridine, such as clopidogrel. However, some patients are subsequently found to have left main (LM) or multivessel disease (MVD) and require coronary artery bypass graft (CABG) surgery. For patients who have been loaded with clopidogrel, early CABG can result in excess bleeding; the alternative is costly prolonged hospitalization until the clopidogrel has worn off before performing CABG. Neither of these options is optimal. Thus, it would be advantageous to have a simple rapid screening tool on admission to identify those patients who are likely to have LM/MVD, so one could avoid clopidogrel in these patients and, thereby, facilitate early CABG without excess bleeding. Kosuge and colleagues studied patients presenting with ACS who subsequently underwent cardiac catheterization to determine if such predictors exist.

The authors identified 572 patients presenting to their hospital with non-ST elevation ACS who subsequently underwent coronary angiography. They excluded patients with uninterpretable ECGs (left or right bundle branch block, ventricular pacing, and left ventricular hypertrophy). Based on the coronary angiogram, they divided their cohort into 3 groups: severe LM/MVD (n = 55), non-severe LM/MVD (n = 57), and no LM/MVD (n = 460). They defined severe

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Clinical Cardiology [ALERT]

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LM/MVD as either one or both of the following: ≥ 75% stenosis of the left main or triple-vessel disease, with ≥ 90% stenosis of the proximal left anterior descending artery plus ≥ 90% stenosis of the right and/or circumflex coronary arteries. Not surprisingly, patients with severe LM/MVD were more likely to undergo CABG than those with non-severe LM/MVD or no LM/MVD (46% vs. 2% vs. 2% respectively; $p < 0.001$). Univariate analysis showed that patients with severe LM/MVD had higher rates of diabetes, lower blood pressure, faster heart rate, were more likely to present with Kilip class 3 or 4, higher troponin levels, and worse renal function. There were several ECG findings associated with severe LM/MVD, including more leads with ST depression, greater degree of ST depression, and greater ST elevation in aVR. After multivariable analysis, there were only two predictors of the presence of severe LM/MVD: elevated troponin (odds ratio 1.27; $p = 0.044$) and the degree of ST elevation in aVR (odds ratio 29.1; $p < 0.001$). The finding of ≥ 1mm ST elevation in aVR predicted severe LM/MVD with 80% sensitivity, 93% specificity, 56% positive predictive value, and 98% negative predictive value. Greater degrees of ST elevation in aVR were associated with higher specificity for severe LM/MVD. The authors conclude that ST elevation ≥ 1mm in lead aVR on admission ECG is highly suggestive of severe LM/MVD in patients with non-ST elevation ACS, and that selected patients with this finding might benefit from prompt angiography and withholding clopidogrel to allow early CABG.

■ COMMENTARY

The optimal management of patients presenting with non-ST elevation ACS remains controversial — in particular, it remains unclear who should undergo early invasive vs. early conservative therapy, who should receive dual or even triple antiplatelet therapy, and the optimal timing of the antiplatelet therapy. This study may help clinicians identify a subset of patients that is likely to have LM/MVD and, thus, may benefit from early coronary angiography with a view to early CABG. Because these patients should all have an ECG on admission, this test is basically free of charge and widely available. It may help reduce prolonged hospital stays, either from post-CABG bleeding or for waiting for clopidogrel to wear off, and may, thus, reduce health care costs.

ST elevation in aVR has been associated with left main or multivessel disease before, and has been shown to correlate with prognosis. This study takes this a step further, and demonstrates the independent predictive power of this simple ECG finding as superior to other clinical and ECG parameters in the ACS population. It is important to note this is an observational study. Whether changing antiplatelet therapy or timing of coronary angiography based on ST elevation in aVR results in better clinical outcomes remains speculative and must be tested prospectively in randomized trials. ■

Abstract & Commentary

ASD Closure in Older Adults

By Andrew J. Boyle, MD, PhD

Source: Humenberger M, et al. Benefit of atrial septal defect closure in adults: Impact of age. *Eur Heart J*. 2011;32:553-560.

ATRIAL SEPTAL DEFECTS (ASD) ARE THE MOST frequent congenital heart defects. Closure of the defect (either surgically or percutaneously) is a Class 1 recommen-

dation in the ACC/AHA guidelines for management of adults with congenital heart disease when there is right heart dilation. However, there are little data on the safety and effectiveness of percutaneous device closure of ASDs in older adults. Humenberger and colleagues present data on adult patients undergoing percutaneous device closure of secundum ASDs using the Amplatzer septal occluder (ASO) device. They excluded 20% of their patients from device closure because they had defects with a stretched balloon diameter > 36 mm or difficult defect morphology, and referred them for surgical closure instead. They also excluded patients with severe increases in pulmonary vascular resistance and high left atrial pressures that rose during balloon occlusion of the defect. Device closure was attempted in a large cohort of 237 patients and was successful in all but one. They divided the patients into three age ranges: < 40 years (n = 78), 40-60 years (n = 84), and > 60 years (n = 74), and followed them clinically and with serial echocardiography. All procedures were carried out under general anesthesia, with transesophageal (TEE) guidance. Aspirin was commenced pre-procedure and continued for 6 months.

Although the size of the ASD did not differ between age groups, increasing age was significantly associated with more symptoms, higher pulmonary artery (PA) systolic pressure, larger right ventricles, and higher prevalence of both tricuspid regurgitation and atrial fibrillation. Procedural success was achieved in 99.6%, and no major procedural complications occurred. At 3-month follow-up, 3% of patients had a small residual shunt and none had large residual shunts. Thrombus on the left atrial disc was detected in one patient with hematological malignancy 5 years after implantation, and this resulted in multiple peripheral emboli. There were 15 cases of new atrial fibrillation (6.3%); all were either medically or electrically converted to sinus rhythm. After ASD closure, RV size decreased from 41 ± 7, 43 ± 7, and 45 ± 6 mm to 32 ± 5, 34 ± 5, and 37 ± 5 mm for patients < 40 years, 40-60 years, and > 60 years, respectively ($p < 0.0001$). PAP decreased from 31 ± 7, 37 ± 10, and 53 ± 17 mmHg to 26 ± 5, 30 ± 6, and 43 ± 14 mmHg ($p < 0.0001$), respectively. In those older than age 60 years, the RV size and PA pressure were higher initially, and they remained higher after ASD closure. Residual pulmonary hypertension (PA systolic pressure > 40 mmHg) after ASD closure was noted in 0%, 6%, and 51% of patients < 40 years, 40-60 years, and > 60 years, respectively. Symptoms improved in all age groups, but the younger patients achieved asymptomatic status more frequently (97%, 89%, and 69% in patients < 40 years, 40-60 years, and > 60 years, respectively). The authors conclude that at any age, ASD closure is followed by symptomatic improvement and regression of PA pressure and RV size. However, the best outcome is achieved in patients with less functional impairment and less elevated PA pressure. They recommend ASD closure irrespective of symptoms early after diagnosis even in adults of advanced age.

■ COMMENTARY

This study adds to the growing body of evidence that percutaneous device closure of ASDs in older adults is safe and has salutary effects on symptoms, PA pressure, and RV size. Procedural success was high (99.6%) and no major procedural complications occurred. Importantly, thrombosis on the device was rare. Furthermore, it confirms that the incidence of new onset atrial fibrillation remains low (6% overall), but it should be noted that the incidence was higher in the older patients than the younger patients. This should help allay some of the fears of atrial arrhythmia in older patients receiving these devices.

It should be noted that this is an observational study, not a randomized trial, and does not compare percutaneous device closure with either medical or surgical management of ASDs. It confirms previous studies, and extends that safety and efficacy data in a larger cohort of older adults. All patients received the Amplatzer ASO device, which has an excellent safety record. These results may not be applicable to all ASD-closure devices (some of which have higher rates of thrombosis and/or inferior rates of defect closure). Furthermore, the authors excluded patients with irreversible elevations in pulmonary vascular resistance, and those in whom elevated left atrial pressure rose during test-occlusion of the defect. These patients would be at higher risk of peri-procedural complications. Their results should not be extrapolated to these higher-risk patients. The better results seen in the younger patients who had less elevation of PA pressure and less RV dilation suggest that closure of the defect earlier rather than later may lead to even better outcomes. One could speculate that we need not even wait for right heart dilation, and should just close ASDs as soon as they are discovered, but this treatment strategy remains to be tested in prospective randomized trials. ■

Abstract & Commentary

Left Atrial Septal Pouch and Stroke

By Michael H. Crawford, MD

Sources: Tugcu A, et al. Septal pouch in the left atrium and risk of ischemic stroke. *J Am Coll Cardiol Img*. 2010;3:1276-1283; Gurudevan SV, et al. Septal thrombus in the left atrium: Is the left atrial septal pouch the culprit? *J Am Coll Cardiol Img*. 2010;3:1284-1286; Chandrashekhar Y, Narula J. LA septal pouch as a source of thromboembolism: Innocent until proven guilty? *J Am Coll Cardiol Img*. 2010;3:1296-1298.

The source of embolic thrombotic material in patients with cryptogenic stroke is controversial. There are data supporting an association with atrial septal abnormalities, such as patent foramen ovale (PFO) and atrial septal aneurysm. Recently, attention has focused on the so-called left atrial (LA) septal pouch, which is created by incomplete fusion of the cranial part of the septum primum with the septum secundum without an intra-atrial communication. Thus, these investigators from Columbia University in New York sought to assess the relationship, if any, between a LA pouch and stroke in a study cohort of 255 stroke patients and 209 control subjects who underwent transesophageal echocardiography with contrast and the Valsalva maneuver within 3 days of stoke onset. Of the 464 individuals enrolled in the study, 89 had a PFO, 9 a closed pouch (incomplete fusion but no opening to either atria), 5 a right septal pouch (incomplete fusion of the caudal part of the septum with opening to the right atrium), and 4 an atrial septal defect. These patients were excluded. Technically, inadequate contrast echoes excluded 13 additional individuals. The remaining 344 consisted of 187 stroke patients and 157 controls. A LA pouch was found in 29%. Of the stroke patients, 37% were believed to have cryptogenic stroke after diagnostic evaluation. Stroke patients were older (71 vs. 67 years, $p < 0.001$), and more likely to have hypertension and atrial fibrillation. However, there was no difference in the prevalence of LA pouch (both groups 29%). Also, a LA pouch was not a multivariate predictor of cryptogenic stroke.

■ COMMENTARY

Cerebral vascular occlusion explains 90% of strokes, but the source of the thrombotic occlusion is often difficult to determine. It is believed that about 20% are cardioembolic, and the majority of these are LA appendage thromboembolism in patients with non valvular atrial fibrillation. Between 10% and 30% are deemed cryptogenic because the cause of the vascular occlusion is unclear. Cryptogenic strokes are more common in younger individuals, so much attention has been focused on determining their cause, so that preventive treatment can be applied. Initially there was considerable interest in PFO since paradoxical emboli had been caught transversing this defect by fortuitous imaging. Also, venous thrombus is much more common than other cardiac causes of thrombus formation in younger individuals. However, despite the frequency of PFO, the plausibility of the hypothesis and the implantation of many PFO closure devices, recent large population studies have failed to support an association and a recent PFO closure trial failed to show a benefit in stroke prevention. Now attention has focused on other sources of atrial thrombus, such as atrial septal aneurysms and pouches. Although there are case reports of thrombi found in these structures, their overall relationship to cryptogenic stroke is unclear. The LA pouch is intriguing because it was present in about a third of the subjects in this and other studies — arguably more common than PFO. However, this study failed to support a role for the LA pouch in stroke.

The major limitations to this study were the small size, imperfect matching between cases and controls, and the relatively older age of the patients. LA pouches and cryptogenic stroke are more common in younger patients. Thus, another potential cause of embolic stroke seems to be eliminated. What is clear is that we do not understand the genesis of LA thrombi seen outside of the appendage and how important such clots are in the origin of cryptogenic stroke. I am guessing not very, but we need more and better data to make firm conclusions. ■

Abstract & Commentary

Estimating Stroke Risk in Atrial Fibrillation

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

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

Source: Daccarett M, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. *J Am Coll Cardiol*. 2011; 57:831-838.

In this paper, Daccarett and colleagues from the University of Utah assessed the potential contribution of cardiac magnetic resonance imaging for detection of left atrial fibrosis to risk stratify patients for stroke with atrial fibrillation. The authors assessed patients at their institutions who were scheduled for pulmonary vein isolation for the treatment of atrial fibrillation (AF). Patients underwent delayed enhancement magnetic resonance imaging (DE-MRI) using special analysis methods that allow detection and quantification of left atrial scarring. After DE-MRI patients were assigned to one of four quartiles based on the severity of structural remodeling or scarring as follows: Stage I (< 8.5% DE), Stage II (8.6% to 16% DE), Stage III (16.1% to 21% DE), and Stage IV (>21% DE). A $CHADS_2$ score was calculated based on clinical data. Patients with and without prior stroke were then compared.

The study includes data from 387 patients. Of these, 36 (9.3%) had a history of stroke. Patients with stroke were older and predominantly female. Four of the $CHADS_2$ risk factors, (congestive heart failure, hypertension, age $\geq$ 75 and diabetes), as well as the patterns of AF were similar between those with and without a history of stroke. More severe scarring by DE-MRI was strongly associated with a history of stroke (24.4 $\pm$ 12.4% vs. 16.1 $\pm$ 9.8% scarring, $p \leq 0.001$, with and without prior stroke, respectively). Patients with only Stage I remodeling had a low stroke incidence (2.8%), whereas 52.8% of patients with Stage IV remodeling had suffered a prior stroke. Higher $CHADS_2$ scores were associated with increased left atrial fibrosis, By multivariate logistic regression analysis, AF remodeling was independently associated with stroke risk. Patients with Stage IV remodeling had a four times higher prevalence of stroke than patients with only Stage I remodeling.

The authors conclude that adding a quantitative measure of left atrial scar remodeling or scarring determined by DE-MRI may enhance risk stratification in patients with atrial fibrillation.

■ COMMENTARY

Stroke is the most feared complication of atrial fibrillation. Unfortunately, anticoagulation to prevent stroke is associated with its own set of problems with serious or major bleeding noted with a rate of approximately 2% per year. Effective risk stratification is, therefore, a key to successful management. Current risk stratification schemes including the $CHADS_2$ score cited here and the updated CHA_2DS_2VASc score cited in the recent European Society of Cardiology guidelines are frequently used but have only modest predictive power. They are, however, easily calculated based only on easily obtained clinical findings. In this paper, Daccarett and his colleagues show that adding information about left atrial scarring may enhance our ability to predict stroke risk. The correlations made here were in a population of patients referred for ablation and the strokes occurred before the DE-MRI studies were performed. Prospective use of the proposed scoring scheme needs to be tested in future trials. Even with new agents for anticoagulation becoming available, the risks, costs, and inconvenience of such therapy are substantial. Techniques such as these that may enhance our ability to predict stroke may prove to be very valuable. ■

Abstract & Commentary

LV-assist Device: Bridge to Myocardial Recovery?

By Michael H. Crawford, MD

Sources: Birks EJ, et al. Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacological therapy: A prospective study. *Circulation.* 2011;123:381-390; Maybaum S. Cardiac recovery during continuous-flow left ventricular assist device support: Some good news from across the Atlantic. *Circulation.* 2011;123:355-357.

The HeartMate II left ventricular assist device (LVAD) is a continuous flow device compared to the pulsatile flow Heartmate I. It is smaller, less traumatic, quieter, and more durable than the prior LVAD. These investigators from the Harefield Hospital in the United Kingdom implanted 33 of these new devices over a 3-year period in patients hospitalized for severe heart failure requiring LVAD support. Twenty-three of these patients had non-ischemic dilated cardiomyopathy and were considered candidates for a two-staged recovery protocol. The first stage consisted of maximal medical therapy with ACE inhibitors, angiotensin II blockers, aldosterone antagonists, beta-blockers, and digoxin. When maximum reversed LV remodeling was achieved by echocardiography, the beta blocker was switched to a beta 1 blocker and clenbuterol was administered to stimulate physiologic hypertrophy. When prespecified hemodynamic and echocardiographic criteria of myocardial recovery were met, LVAD explantation was performed and the stage one medications were resumed.

Twenty patients survived LVAD placement and are the subjects of this report. The mean age of the 20 patients was 35 years and 16 were men. Preoperatively, mean cardiac index was 1.44 mm/m^2, pulmonary wedge pressure was 32 mmHg, and ejection fraction was 15%. Explanation criteria were met in 12 patients after a mean of 286 days, and their 3-year survival was 83%. Both deaths (2 of 12) were within the first 30 days after explantation. In the 10 survivors, no heart failure occurred on maximal drug therapy in the 3 years of follow-up. The authors concluded that up to one half of patients with severe heart failure due to dilated non-ischemic cardiomyopathy can be bridged to recovery with a Heartmate II and maximal medical therapy.

■ COMMENTARY

The shortage of donor hearts has increased efforts to mechanically support selected heart failure subjects and try to stimulate myocardial recovery. Use of the older generation pulsatile LVADs has shown variable recovery in up to 25% of patients with non-ischemic cardiomyopathy. This report suggests that up to one half of such patients may be recoverable with the newer continuous flow LVADs and maximal medical therapy. This is encouraging news and opens up a whole new dynamic in severe heart failure management.

The caveat is that this is a small group of relatively young (16 to 58 years) patients who have non-ischemic dilated cardiomyopathy. Also, two-thirds of them had heart failure symptoms for < 6 months. On the other hand, they had severe LV dysfunction (EF 7%-34%) and were on at least one positive inotropic agent intravenously. The majority of patients in the United States with advanced heart failure have ischemic cardiomyopathy and often have less advanced systolic dysfunction, but advanced diastolic dysfunction. Thus, this approach may only apply to a minority of advanced U.S. heart-failure patients.

This study did not establish that the new continuous flow LVADs are superior to the older pulsatile ones with regard to outcomes, since LVAD therapy was coupled with aggressive medical therapy and there was no comparison group. Maximum tolerated doses of ACE inhibitors, angiotensin II blockers, aldosterone blockers, beta-blockers and digoxin were used in Phase 1. Phase 2 continued these agents, but switched carvedilol, a non selected beta blocker, to the beta I selective blocker bisoprolol and added the beta agonist clenbuterol at 25 times the usual asthma therapy dose, to stimulate physiologic hypertrophy of the LV. The importance of Phase 2 is difficult to

ascertain from the study and Clenbuterol is not available in the United States. Another way to potentially increase physiologic hypertrophy is to decrease the LVAD continuous flow to allow the LV to open the aortic valve and experience afterload.

Perhaps the most remarkable thing about this study was the demonstrated durability of the recovery in those who survived explantation. In more than 3 years of follow-up, there were no deaths, transplantation, or heart failure recurrences in these patients. Thus, it would appear that these patients completely recovered. Of course they were still on medical therapy, and it is not known if they would have normal LV function off medications. Also, we do not know if these results could be obtained in a similar group of patients treated with a different protocol. The promise of this approach stimulated a U.S. Harefield Recovery Protocol Study (HARPS) which will be reported shortly. ■

Abstract & Commentary

Sex Differences in CRT-D for Class I-II Heart Failure

By John P. DiMarco, MD, PhD

Source: Arshad A, on behalf of the MADIT-CRT Executive Committee. The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) trial. Cardiac resynchronization therapy is more effective in women than in men. *J Am Coll Cardiol*. 2011;57:813-820.

The MADIT-CRT trial compared the effects of implanting defibrillators with and without resynchronization therapy in patients with New York Heart Association (NYHA) functional class I and II heart failure symptoms, indications for an ICD and a QRS duration ≥ 130 m/sec. This report compares results in men versus women in MADIT-CRT.

MADIT-CRT enrolled a total of 1,820 patients randomly assigned in the 3:2 ratio to receive an ICD either with (CRT-D) or without resynchronization. Patients were followed longitudinally with death and heart failure hospitalization as the primary endpoints. Secondary endpoints included ventricular function, reverse cardiac remodeling, and adverse events.

There were 1,367 men and 453 women in MADIT-CRT. Female patients were more likely to have nonischemic cardiomyopathy and left bundle branch block conduction patterns than male patients. Men were more likely to have ischemic heart disease, prior coronary revascularization procedures, and renal dysfunction. The average follow-up duration was 2.4 years. The primary endpoint of heart failure or death occurred in 376 patients. Among women, 29 of 275 (11%) with CRT-D and 51 of 178 (29%) with an ICD reached a primary endpoint. In contrast, among men, the event rate was 159 of 814 (20%) with CRT-D compared to 137 of 553 (25%) with an ICD. The hazard ratios for death or heart failure, heart failure only, or death at any time in women were 0.31, 0.30, and 0.28. In contrast, the hazard ratios for the same endpoints in men were 0.72, 0.65, and 1.05. Other factors associated with increased likelihood of benefit were the diagnosis of nonischemic cardiomyopathy, QRS durations of greater than 150 msec in men but not women, and the presence of left bundle branch block conduction patterns. Echocardiographic findings confirm this pattern with women showing consistently greater improvements in cardiac reverse remodeling with CRT-D therapy than did men. Once again, the most significant differences were seen in patients with QRS durations greater than 150 m/sec or left bundle branch block. Device-related adverse events were seen in 10.5% of women

vs 7.9% of men. Women were more likely to have pneumothorax (3% in women vs 0.7% in men), but men more commonly had lead dislodgments (1.7% in women vs 3.2% in men).

The authors conclude that women with class I or II heart failure are more likely to respond favorably than men if they receive CRT-D therapy as opposed to a standard ICD.

■ COMMENTARY

In MADIT-CRT, there was clearly an enhanced benefit of early CRT in women compared to men. Although benefit was seen in both genders, the hazard ratios are strikingly lower in women than in men. As discussed by the authors, the reasons for this are not clear and a similar increased benefit among women has not been seen in all studies on CRT. They propose that since women have a baseline QRS duration that is about 10 msec shorter than men, for any given QRS duration women are more likely to have dyssynchrony. This hypothesis, in combination with the higher proportion of women with nonischemic cardiomyopathy and left bundle branch block, may well explain the observation. For clinicians the message is that they should not hesitate to recommend CRT therapy in women even though the complication rate may be slightly higher. ■

CME Questions

15. Percutaneous ASD closure is successful in what percentage of adults without Eisenmenger physiology?

a. 50%
b. 75%
c. 87%
d. 99%

16. Which of the following is least likely to be associated with cryptogenic stroke?

a. Left atrial septal pouch
b. ASD
c. PFO
d. Atrial septal aneurysm

17. LVAD support and maximum medical therapy can more likely result in myocardial recovery in severe heart-failure patients with:

a. ischemic cardiomyopathy.
b. non-ischemic cardiomyopathy.
c. shorter duration of heart. failure
d. B and C

18. Which of the following factors favors reduced events with CRT-D therapy in NYHA class I and II heart failure?

a. Female sex
b. Non-ischemic cardiomyopathy
c. Left-bundle branch block
d. All of the above

19. The estimate of stroke risk in atrial fibrillation can be enhanced by:

a. cardiac CT scanning.
b. cardiac MR with angiography.
c. cardiac MR with delayed enhancement.
d. doppler echo LV strain rate imaging.

20. Which of the following has not been associated with cryptogenic stroke?

a. Atrial septal aneurysm
b. Patent foramen ovale
c. Left atrial septal pouch
d. Atrial septal defect

Answers: 15. (d); 16. (a); 17. (d); 18. (d); 19. (c); 20. (c)

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.

[IN FUTURE ISSUES]

Cryo-ablation vs. Radiofrequency for AVNRT

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

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Do Topical Steroids Lead to Glaucoma or Cataract?

Source: Haeck IM, et al. Topical corticosteroids in atopic dermatitis and the risk of glaucoma and cataracts. *J Am Acad Dermatol* 2011;64:275-281.

The treatment of atopic dermatitis (ATD) usually is initiated with topical steroids (TPS). Because ATD is a chronic remitting and relapsing disorder and may occupy a large cutaneous area, exposure to TPS can be extensive. Since both glaucoma and cataracts are associated with ophthalmic TPS, and ATD may require periocular application of TPS, it is important to learn whether non-ophthalmic utilization of TPS could lead to increased intraocular pressure. The use of inhaled steroids for asthma has been associated with development of cataracts, but not glaucoma.

To study the impact of TPS in ATD upon glaucoma and cataract, 88 adults with chronic ATD were evaluated. For each study subject, data on total amount of TPS prescribed over the last 2-5 years was available. Two-thirds of the study subjects had applied TPS in the periocular region, since they suffered from ATD on the eyelids and periorbital region. The authors cite the *average* amount of periocular TPS use within this group as "3.9 days/week, 6.4 months/yr, for 4.8 years."

There was no sign of increased incidence of glaucoma among TPS users. Corticosteroid-induced cataract was seen in 2 of the 88 subjects, both of whom had received courses of systemic steroids in addition to TPS. These data are reassuring that TPS application does not appear related to the development of glaucoma or cataracts, even when TPS needs to be applied in the periorbital region. ■

Can Exenatide Prevent Glucocorticoid-Induced Hyperglycemia?

Source: Van Raalte DH, et al. Glucagon-like peptide-1 receptor agonist treatment prevents glucocorticoid-induced glucose intolerance and islet-cell dysfunction in humans. *Diabetes Care* 2011;34:412-417.

Clinicians anticipate that administration of systemic glucocorticoids, such as prednisone (PRED), to persons with diabetes worsen hyperglycemia. PRED reduces insulin sensitivity and impairs beta-cell function, resulting in hyperglycemia.

Chronic PRED administration is associated with increased risk for osteoporosis and peptic ulcer; preventive strategies for each of these adverse effects has been developed. To date, no such plan for mollifying exaggerated glucose excursions due to PRED has been offered.

The glucose dysregulation secondary to PRED appears to be primarily postprandial, rather than fasting. Clinical trials of metformin failed to confirm efficacy in preventing glucocorticoid-induced hyperglycemia (GIH). Because exenatide (EXE) has prominent effects specifically on postprandial glucose, it was logical to investigate whether EXE might favorably impact GIH.

Healthy adult men (n = 8) received a PRED load of 80 mg orally for two days (prednisolone, actually, but prednisone and prednisolone are mg-for-mg equivalent). They were randomized to also receive placebo or EXE. GIH was prevented by concomitant EXE administration.

This proof-of-concept trial should stimulate further investigation to determine whether the demonstrated ability of EXE to prevent GIH is similarly favorable in diabetics. ■

COPD: Beyond Pulmocentricity

Source: Nussbaumer-Ochsner Y, Rabe KF. Systemic manifestations of COPD. *Chest* 2011;139:165-173.

Chronic obstructive pulmonary disease (COPD) generally is regarded as a pulmonary process induced by toxic insult—usually cigarettes, but sometimes other environmental exposures. Why only a small subset of chronic smokers develops COPD (20-25%) remains a mystery. Progressive loss of pulmonary function continues even after smoking cessation, suggesting that some inflammatory process, once set in gear in susceptible individuals, becomes self-perpetuating.

Experts recognize other non-pulmonary tissue compartments are involved in COPD. Musculoskeletal wasting, metabolic syndrome, and depression are disproportionately comorbid with COPD. Biopsy studies have found increased inflammatory cytokines in intercostal muscles, providing an explanation for dyspnea that goes beyond simple damage to alveolar capacity for gas exchange.

Both diabetes and chronic kidney dis-

ease have been found to be associated with COPD. In the absence of a visible etiologic link, systemic inflammation is a suspected culprit. Indeed, early data indicate that smoking cessation slows progression of renal failure. In reference to diabetes, smoking cessation is associated with short-term worsening of diabetes risk, attributed to the weight gain commonly seen after smoking cessation. COPD is increasingly viewed as part of a systemic process. ■

Aspirin and Risk of Death from Cancer

Source: Rothwell PM, et al. Effect of daily aspirin on long-term risk of death due to cancer: Analysis of individual patient data from randomized trials. *Lancet* 2011;377:31-41.

In animal models, aspirin (ASA) has favorable effects on the incidence and/or growth rate of some cancers (CA). Most clinical trials of ASA have been for primary or secondary prevention of cardiovascular disease. Rothwell et al analyzed data from three UK clinical trials that included CA mortality outcomes, although none of the trials was designed specifically to study the impact of ASA upon CA as a primary or secondary endpoint. Their data set of almost 24,000 adult men and women divided treatment groups by duration of follow-up: 0-5 years of treatment, and > 5 years of ASA treatment.

ASA was associated with an 18% relative risk reduction in deaths due to cancer; risk reduction was greatest in subjects treated for more than 5 years. Gastrointestinal (GI) cancer deaths were reduced most prominently, but other cancers (e.g., lung) also showed favorable impact from ASA treatment. Although bleeding induced by ASA typically is viewed as an adverse effect, it has been suggested that ASA treatment also makes GI tumors more likely to bleed, facilitating their discovery. There appears to be a "latent period" of at least 5 years before the effects of ASA impact esophageal, pancreatic, brain, and lung cancer.

When evaluating the risk-benefit of ASA for cardiovascular risk reduction, the favorable impact of ASA upon cancer mortality also should be considered. ■

Reducing Incontinence After Prostatectomy

Source: Goode PS, et al. Behavioral therapy with or without biofeedback and pelvic floor electrical stimulation for persistent postprostatectomy incontinence: A randomized controlled trial. *JAMA* 2011;305:151-159.

When prostate cancer (PCA) was diagnosed primarily at the later stages of disease, post-surgical adverse effects such as incontinence or erectile dysfunction weighed less heavily on the risk-benefit scale, since without surgery outcomes were poor. In an era when most PCA is diagnosed at a stage of localized disease, much of which would be destined to never evolve to clinical relevance, balancing adverse surgical consequences, becomes more complex.

Incontinence occurs and persists in the majority of men after radical prostatectomy. Two-thirds of men have persistent incontinence 5 years postoperatively. Encouraging results have been seen in trials that incorporate behavioral and physical therapies promptly after surgery. Little insight is available about the success of intervention for persistent incontinence distant from surgery.

Goode et al enrolled 208 men who had undergone prostatectomy and continued to suffer incontinence 4-5 years later. Participants were randomized to behavioral therapy (pelvic floor exercises, bladder control methods, fluid management) plus biofeedback and/or pelvic floor electrical stimulation versus control.

The reduction in incontinence was significantly greater in treatment groups (55% reduction) than in the control group (24% reduction). Neither biofeedback nor pelvic floor electrical stimulation added effectiveness to behavioral therapy alone. Clinicians should be encouraged that even late employment of behavioral therapies can provide substantial incontinence improvement. ■

Real-life Efficacy of Herpes Zoster Vaccine

Source: Tseng HF, et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. *JAMA* 2011;305:160-166.

Herpes zoster vaccine (zostavax) was licensed in the United States in 2006 subsequent to the publication of the Shingles Prevention Study, a large (n = 38,546) prospective trial that demonstrated a 51% reduction in zoster and a 67% reduction in postherpetic neuralgia in vaccines compared to controls. Clinicians may wonder whether the favorable results seen in a major clinical trial would be replicated in their private clinical settings. According to this report by Tseng et al, that may very well be the case.

Enrollees in the Southern California Kaiser Permanente health plan older than 60 years of age who had received zoster vaccine (n = 75,761) were compared with age-matched controls (n = 227,283) in this retrospective analysis. The Kaiser Permanente study population was comprised of healthy, immunocompetent, community-dwelling adults. The primary outcome of interest was incidence of zoster.

The rate of zoster in the vaccine recipients (6.4/1000 person-years) was significantly less than the rate in unvaccinated study subjects (13.0/1000 person-years). This 55% relative risk reduction is highly concordant with the reductions seen in the Shingles Prevention Study, confirming the generalizability of their results. ■

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Apixaban and Rivaroxaban Near Approval for Nonvalvular AF

In this issue: Apixaban and rivaroxaban near approval for nonvalvular atrial fibrillation; fidaxomicin for *C. difficile* infections; guideline for intensive insulin therapy; and FDA Actions.

Dabigatran for stroke in patients with nonvalvular atrial fibrillation

Dabigatran, a direct thrombin inhibitor, recently was approved for prevention of stroke in patients with nonvalvular atrial fibrillation. The evidence for its benefit is strong enough that the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society recently upgraded their atrial fibrillation guidelines to include dabigatran (*Circulation* published online February 14, 2011). Meanwhile, the direct factor Xa inhibitor rivaroxaban is working its way through the FDA approval process for the same indication, with approval expected later this year. The latest player in the field is apixaban, also a direct factor Xa inhibitor. Apixaban was studied in a double-blind Phase 3 study of 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable. Patients were randomized to receive apixaban 5 mg twice daily or aspirin 81-324 mg per day with a mean follow-up of 1.1 years. The primary outcome was occurrence of stroke or systemic embolism. The study was terminated early because of a clear benefit in favor of apixaban. There were 51 events (1.6 % per year) in the apixaban group vs 113 events (3.7% per year) in the aspirin group (hazard ratio with apixaban 0.45, 95% confidence interval 0.32-0.62; P < 0.001). The death rate was 3.5% in the apixaban group vs 4.4% in the aspirin group (P = 0.07). The rates of major bleeding or intracranial hemorrhage were similar; however, the risk of first hospitalization for cardiovascular causes was significantly lower with apixaban. The authors suggest that apixaban is more effective than aspirin. In indirect comparisons, apixaban is more effective than aspirin plus clopidogrel and at least as effective as warfarin in preventing stroke or systemic embolism in patients with atrial fibrillation (*N Engl J Med* published online February 10, 2011). Apixaban is currently being studied head-to-head with warfarin in the ARISTOTLE trial. If the data from that trial looks favorable, it is likely that both apixaban and rivaroxaban also will be approved for this indication in the not-too-distant future. Dabigatran and apixaban are both dosed bid while rivaroxaban is a once-a-day drug. The extent to which these drugs gain general usage at the expense of warfarin in large part will be due to patient preference and cost. ■

Fidaxomicin for *C. difficile* infections

A new option may soon be availiable for treating *Clostridia difficile* infections. Fidaxomicin (not yet approved in this country) is a non-systemic (poorly absorbed) narrow spectrum macrolide antibiotic that is bacteriocidal against *C. difficile* infections. It recently was compared to vancomycin in a head-to-head Phase 3 noninferiority study of 629 adults. Patients with a positive stool toxin test to *C. difficile* were randomized to

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fidaxomicin 200 mg twice a day or vancomycin 125 mg four times a day. The primary endpoint was clinical cure and the secondary endpoint was recurrence within 4 weeks and global cure (no recurrence). Fidaxomicin was noninferior to vancomycin in both the intention-to-treat (88.2% cure rate with fidaxomicin vs 85.8% with vancomycin) and per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients had recurrence with fidaxomicin in both groups (15.4% vs 25.3%, $P = 0.005$ intention-to-treat, and 13.3% vs 24.0%, $P = 0.004$ per protocol) although the lower rate of recurrence was in the less virulent strains. For the more virulent strains, the recurrence rate was about 25% for both drugs. Fidaxomicin was associated with a higher rate of hyperuricemia and elevated transaminases (*N Engl J Med* 2011;364:422-431). An accompanying editorial points out that the incidence and virulence of *C. difficile* infections is increasing at an alarming rate in this country. Fidaxomicin inhibits vegetative forms of *C. difficile* while preseving intestinal flora, a combination that holds promise, and if borne out "this new agent could become a recommended therapy for *C. difficile* infection" (*N Engl J Med* 2011;364:473-475). ■

Guideline for intensive insulin therapy

A guideline from the American College of Physicians (ACP) recommends against aggressively controlling blood glucose in hospitalized patients. Intensive insulin therapy (IIT) is no longer recommended for patients in intensive care units, regardless of whether they have diabetes. Specifically, the ACP recommends not using IIT to strictly control blood glucose or even normalized blood sugar in surgical ICU or medical ICU patients, and recommends a target blood glucose level of 140-200 mg/dL if insulin therapy is used. The recommendation is based on multiple studies that show no reduction in mortality with a blood glucose target of 80-180 mg/dL compared with higher targets using a variety of intensive insulin regimens. This includes treatment of patients with myocardial infarction, stroke, acute brain injury, or those under perioperative care. The guideline further recommends that avoiding targets less than 140 mg/dL should be a priority because harm is likely with lower blood glucose targets (*Ann Intern Med* 2011;154:260-267).

FDA actions

The FDA is warning against the use of terbutaline for prevention or prolonged treatment of preterm labor in pregnant women. The drug, which is approved for treatment of asthma, has been used off label for treatment of preterm labor and uterine hyperstimulation; however, the agency has received postmarketing reports of serious adverse reactions, including heart problems, and even maternal deaths, associated with the drug. The FDA has added a Boxed Warning and Contraindication to the labeling of the drug warning against these uses. This extends to both the IV and oral forms of terbutaline.

The FDA has approved hydroxyprogesterone caporate injection to reduce the risk of preterm delivery before 37 weeks of pregnancy in a pregnant woman with a history of at least one spontaneous preterm birth. The drug is not intended for use in women with a multiple pregnancy, such as a twin pregnancy, or other risk factors for preterm birth. The drug was approved under the FDA's accelerated approval regulations, and, as such, additional studies will be required after approval to show that the drug does indeed have clinical benefit. Hydroxyprogesterone caproate is given once a week by injection into the hip beginning at week 16 and no later than week 21. The drug is marketed by Hologic Inc. as Makena.

The FDA has issued a drug safety alert regarding the risk of serious liver injury with dronedarone (Multaq). The drug — which is approved for prevention of atrial fibrillation/flutter — has been associated with multiple cases of severe liver injury, including two cases that required liver transplantation. Dronedarone previously was found to double the risk of death in patients with severe heart failure and was approved with a REMS designed to prevent its use in that patient population. Physicians are reminded to advise patients to contact a health care professional immediately with any signs of hepatic injury or toxicity. All patients on dronedarone should get periodic hepatic serum enzymes especially during the first 6 months of therapy.

The FDA has approved a new treatment for head lice. Spinosad is an insecticide originally derived from a naturally occurring soil bacterium. The 0.9% topical suspension was shown to be effective in two Phase 3 active-control, randomized studies in which 86% of patients treated with the active drug were lice free after 14 days compared to 44% of controls. The product should not be used in children under 6 months of age because it contains benzyl alcohol. Spinosad is applied as a single 10-minute application which may be repeated in one week if lice are seen. It will be marketed by ParaPro LLC as Natroba. ■