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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Rivaroxaban after Acute Coronary Syndrome

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

SOURCE: Mega JL, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;366:9-19.

After acute coronary syndromes (ACS), patients remain at risk for recurrent cardiovascular events. Antiplatelet agents are the mainstay of secondary preventive strategies aimed at reducing the rate of recurrent events. The recent development of more reliable oral antithrombin agents than warfarin has sparked interest in inhibiting not only platelet aggregation but also thrombin generation in patients who have experienced ACS. Rivaroxaban is an orally active inhibitor of activated factor X. After demonstrating non-inferiority to warfarin, it received FDA approval in 2011 for deep venous thrombosis stroke prophylaxis following knee and hip surgery, and for stroke prophylaxis in patients with atrial fibrillation (AF). Lower doses showed promise in early clinical trials of patients who had suffered ACS. This large Phase 3 trial, the ATLAS ACS 2–TIMI 51 study, studied two low-dose regimens of rivaroxaban in patients with ACS.

A total of 15,526 patients who presented with ACS were enrolled at 766 sites in 44 countries at a mean of 4.3 days after presentation. Inclusion criteria included patients > 18 years of age who presented with unstable angina, non-ST elevation myocardial infarction (MI), or ST elevation MI. Those aged < 55 years also had to have either diabetes or a prior ischemic event to be enrolled. Exclusion criteria included thrombocytopenia, anemia, creatinine clearance < 30 mL/min, gastrointestinal bleeding within 12 months, prior intracranial hemorrhage, and, for those taking dual antiplatelet therapy (DAPT), a prior stroke or transient ischemic attack. Patients were randomized to receive placebo or one of two doses of rivaroxaban: 2.5 mg twice daily or

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5 mg twice daily for up to 31 months. All patients were to receive low-dose aspirin and a thienopyridine according to local guidelines. The primary efficacy endpoint was a composite of death from cardiovascular causes, MI, or stroke.

Baseline clinical and demographic data were similar in all groups and there was a large proportion of diabetics (31%). Aspirin was used in 99% and a thienopyridine in 93%. Rivaroxaban significantly reduced the combined primary efficacy endpoint of death from cardiovascular causes, MI, or stroke, as compared with placebo, with rates of 9.1% in the 2.5 mg group, 8.8% in the 5 mg group, and 10.7% in the placebo group (hazard ratio [HR] for rivaroxaban vs placebo, 0.84; $P = 0.008$). Interestingly, the 2.5 mg dose reduced total mortality (2.9% vs 4.5%; $P = 0.002$), but the 5 mg dose did not.

There was a significant dose-related increase in bleeding with rivaroxaban compared to placebo. Major non-CABG related bleeding was four-fold higher with rivaroxaban (2.1% vs 0.6%; HR 3.96; $P < 0.001$), as were minor bleeding (1.3% vs 0.5%; $P = 0.003$) and intracranial hemorrhage (0.6% vs 0.2%; $P = 0.009$), but there was no difference in fatal bleeding. The rates of bleeding were generally higher in the 5 mg group than the 2.5 mg group. There was no difference in other adverse events between the rivaroxaban and placebo groups. The authors conclude that in patients with a recent ACS, rivaroxaban reduced the risk of the composite endpoint of death from cardiovascular causes, MI, or stroke. Rivaroxaban also increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding.

■ COMMENTARY

The addition of low-dose rivaroxaban to dual antiplatelet therapy in patients suffering an ACS reduced ischemic events but also resulted in increased bleeding. It is important to note that the doses of rivaroxaban used in this study were much lower than in atrial fibrillation (AF). The lowest dose (2.5 mg twice daily) appeared to be the most effective and safe in this trial, and this is substantially lower than the 20 mg dose that is indicated for stroke prophylaxis in AF. This is a large, well-designed study and the conclusions are strengthened by the consistency of benefit seen across most subgroups and in all geographic regions.

One important subgroup, patients with prior TIA or stroke, did not benefit from rivaroxaban. Prior stoke or TIA is also a contraindication to the use of the more potent antiplatelet agent prasugrel. One must exercise caution when prescribing anticoagulants and antiplatelet agents in this patient group.

Rivaroxaban is one of several newer anti-coagulants that demonstrate benefit in patients who have had an ACS. Factor Xa inhibitors and direct thrombin inhibitors appear to reduce recurrent ischemic events after ACS, but all appear to increase bleeding side effects. It is likely that in the coming years we will see several new anticoagulants approved for secondary prevention. The delicate balance between reducing thrombotic events and bleeding side effects will continue, and treatment regimens will become more complicated. ■

ABSTRACT & COMMENTARY

Asymptomatic Severe Aortic Stenosis

By Michael H. Crawford, MD, Editor

SOURCES: Lancellotti P, et al. Clinical outcome in asymptomatic severe aortic stenosis: Insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol* 2012;59:235-243. Flachskampf FA, Kavianipour M. Varying hemodynamics and differences in prognosis in patients with asymptomatic severe aortic stenosis and preserved ejection fraction. *J Am Coll Cardiol* 2012;59:244-245.

The management of asymptomatic patients with severe aortic stenosis (AS) is controversial. Patients meeting standard echocardiographic criteria for severe stenosis have a variety of pressure gradients and flow rates that

can be divided into four categories based on normal flow vs low flow (NF vs LF) and low gradient vs high gradient (LG vs HG), where LF is defined as a stroke volume index (SVI) of < 35 mL/m^2 and LG is a mean gradient < 40 mmHg. These investigators studied 150 consecutive patients (mean age, 70 years) with an echo aortic valve area (AVA) < 1.0 cm^2, a normal exercise test, and an ejection fraction (EF) > 55%. These patients were followed every 6-12 months for 2 to 48 months (mean, 27). The primary composite endpoint was the time to the occurrence of cardiovascular (CV) death or the need for aortic valve replacement (AVR) due to the development of symptoms or EF < 50%. At baseline, the patients were divided into four groups: NF/HG seen in 52%, NF/LG in 31%, LF/HG in 10%, and LF/LG in 7%. B-type natriuretic peptide (BNP) was lowest in the NF/LG group and significantly different from the LF/HG group (22 vs 114) and the LF/LG group (22 vs 78), both P < 0.001. At 2 years follow-up, the event-free survival was 83% in the NF/LG group; 44% in NF/HG; 30% in LF/HG; and 27% in LF/LG (P < 0.001). By multivariate analysis, LF/LG (hazard ratio [HR] 5.3, 95% confidence interval [CI] 2-14, P < 0.05) and LF/HG (HR 2.4, CI 1.02-5.55, P = 0.001) were independent predictors of a poor prognosis compared to NF/HG, with LF/LG having the worst prognosis. The authors concluded that this categorization of asymptomatic severe AS patients allows for an improved determination of CV risk in subgroups of these patients.

■ COMMENTARY

The management of the asymptomatic patient with echo-Doppler evidence of severe AS can be simple, wait for symptoms, or more nuanced. The traditional approach involves careful scrutiny of the echo to be sure severe AS is present, confirmation of symptom status with a cautious exercise study, and weighing other prognostic factors such as the degree of calcification of the valve. Concern for sudden death is not a consideration, as it has been very low in most studies and was 2% in this one. This study investigates the use of hemodynamic classification to aide in predicting who might benefit from an early decision for surgery. This approach assumes that if factors predictive of the need for surgery in an observational study are used to perform early surgery that the outcomes will be better in these asymptomatic patients. This concept has never been proven in a prospective randomized trial nor is it likely to be. So, does this study add any useful information to our clinical judgment in such cases?

The hemodynamic groups are based on the combination of gradient and SVI. About one-third of the patients had NF (SVI > 35 mL/m^2) and a low gradient (mean < 40 mmHg). These patients had the best event-free survival of valve replacement and probably did not have severe AS. A valve area of < 1.0 cm^2 was part of the definition of severe AS and many believe that severe AS should be defined at 0.8 cm^2 or lower. A majority of the patients had normal flow and a high gradient and they had a lower event-free survival (44%). These represent severe AS patients with normal LV function and should be considered for surgery. The other two groups represented < 20% of the study population, which weakens any conclusions about their prognosis. However, the LF/LG group had the worst prognosis with a 27% event-free survival and an HR of 5.3 (P < 0.05). The LF/HG group had similar outcomes (HR 2.4, P < 0.001). Thus, in aggregate any asymptomatic patient with a valve area < 1.0 cm^2 and an EF > 55% who has either an HG (mean > 40) or LF (SVI < 35 mL/m^2) should be considered for surgery.

The groups with a low SVI probably have LV dysfunction that is not detected by EF. To be fair, an EF of 50-55% is abnormal by echo, but most guidelines use the 50% cutoff since this value is closer to the lower limit by angiography. In this study, BNP was a predicator, but was not an independent predicator in the multivariate analysis. Other LV function indices, such as end diastolic volume, left atrial size, and tissue Doppler longitudinal strain, had some predictive value, but the HRs were ≤ 1.12. Other factors not investigated in this study were coronary artery disease status and pulmonary hypertension. Both would likely affect outcomes and the risk of surgery. ■

ABSTRACT & COMMENTARY

Value of the ECG in Asymptomatic AS

By Michael H. Crawford, MD, Editor

SOURCE: Greve AM, et al. Clinical implications of electrocardiographic left ventricular strain and hypertrophy in asymptomatic patients with aortic stenosis: The simvastatin and ezetimibe in aortic stenosis study. *Circulation* 2012;125:346-353.

Although electrocardiogram (ECG) left ventricular hypertrophy (LVH), especially with ST-T changes (strain pattern), is known to be of prognostic value in patients with aortic stenosis, its valve in patients who are being followed is unclear. Thus, these investigators from the Simvastatin and Ezetimibe in Aortic Stenosis Study (SEAS) studied the 1533 patients in this trial with baseline ECGs suitable for assessing the presence of LVH. This was a study of patients with moderate aortic stenosis — defined as an aortic peak velocity between 2.5 and 4 m/s and normal systolic function — who were randomized to cholesterol-lowering drug therapy or placebo and followed for a mean of 4 years. The primary endpoint was major cardiovascular events, including aortic valve replacement and death, which occurred in 627 patients. On the baseline ECG, LVH with strain was present in 24%, LVH alone by Sokolow-Lyons criteria in 17%, and by Cornell criteria in 15%. By multivariable analysis, ECG LVH plus strain increased the risk of myocardial infarction (hazard ratio [HR] 3.1; 95% confidence interval [CI], 1.4-6.8; $P = 0.004$). LVH by both criteria increased the risk of heart failure (HR 5.8; CI, 2.0-16.8; $P = 0.001$); aortic valve replacement (HR 2.0, CI 1.3-3.1, $P = 0.001$); and the combined endpoint of myocardial infarction, heart failure, or cardiovascular death (2.5; 1.3-4.9; $P = 0.008$). LVH and strain remained strong predictors of a poor prognosis when adjusted for clinical parameters, aortic valve area, and gradient. LVH and strain were not altered by drug therapy. The authors concluded that ECG LVH and LVH with strain were independently predictive of cardiovascular events, including aortic valve replacement in asymptomatic patients with moderate aortic stenosis.

■ COMMENTARY

Many clinicians believe that LVH voltage, especially with a strain pattern, is associated with a poor prognosis in aortic stenosis patients. This substudy of the SEAS trial solidifies this belief. ECG LVH by voltage criteria clearly increased the risk of heart failure, myocardial infarction, cardiovascular death, and aortic valve replacement, even when adjusted for other clinical prognostic factors and echo severity of aortic stenosis. The presence of LVH with the strain pattern was independently predictive of myocardial infarction. This finding is of interest because it has long been believed that the strain pattern indicates subendocardial ischemia, either due to myocardial oxygen supply-demand imbalance or silent coronary artery disease. Unfortunately, there was not enough cardiac catheterization data collected to fully analyze this issue, but the ischemia mechanism seems to be supported by these data. Thus, in the asymptomatic patient with moderate aortic stenosis and normal left ventricular function, ECG LVH and the strain pattern should be considered in determining the patient's management. ■

ABSTRACT & COMMENTARY

Stroke Risk in Atrial Fibrillation

By John P. DiMarco, MD, PhD

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

SOURCE: Healey JS, et al, for the ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;366:120-129.

The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) tested two hypotheses. The first was to see if subclinical episodes of high atrial rates detected by implanted devices are associated with an increased risk for stroke in patients without clinically manifest atrial fibrillation (AF). The second was to evaluate the efficacy of atrial overdrive pacing algorithms for preventing the development of clinical AF. Patients were eligible for inclusion in the study if they were 65 years of age or older with a history of hypertension and had undergone implantation of a St. Jude Medical dual-chamber pacemaker or implantable cardioverter-defibrillators (ICDs) in the preceding 8 weeks. Patients with a history of documented AF or atrial flutter and those who required treatment with a vitamin K antagonist for any reason were excluded. At the initial study visit, the pacemaker's device was programmed so an atrial high rate episode was detected when the atrial rate reached 190 beats per minute. Three months later, devices were interrogated to classify patients according to whether a subclinical atrial tachycardia had occurred since the time

of enrollment. A subclinical atrial tachycardia was defined as an episode of a rapid atrial rate lasting more than 6 minutes as detected by the pacemaker or the defibrillator. At that 3-month visit, patients with pacemakers (but not patients with ICDs) were randomly assigned to have either a continuous atrial overdrive pacing function programmed to either "on" or "off." This algorithm would pace the rate at a slightly higher rate than the patient's intrinsic sinus rate in hopes of preventing AF. After this visit, patients were followed every 6 months until the end of the study. For the portion of the study evaluating the prognostic value of subclinical AF, the primary outcomes were ischemic stroke and systemic embolism. The primary outcome of the trial of overdrive pacing was the occurrence of symptomatic or asymptomatic atrial tachyarrhythmia lasting more than 6 minutes.

Over a 5-year period, the study enrolled 2451 pacemaker patients and 129 ICD patients. During the first 3 months after implant, at least one atrial tachyarrhythmia was detected in 261 patients (10.1%). During the same period, a clinically evident atrial tachyarrhythmia occurred in seven patients. Among patients with a subclinical atrial tachyarrhythmia, the median number of episodes was two. Over a mean of 2.5 years of subsequent follow-up, subclinical atrial tachyarrhythmias occurred in an additional 633 patients (24.5%). Clinical atrial tachyarrhythmias documented by surface electrocardiograms occurred in 41 of the 261 patients (15.7%) who had a subclinical atrial tachyarrhythmia during the initial 3-month observation period and in 71 of the 2319 (3.1%) patients who had not had an atrial tachyarrhythmia during that time. During follow-up, 11 of the 261 patients (4.2%) in whom a subclinical atrial tachyarrhythmia had been detected experienced an ischemic stroke or systemic embolism for an annual rate of 1.69%. In comparison, 40 of 2319 patients (1.7%, 0.69% per year) without a subclinical atrial tachyarrhythmia at the 3-month time point experienced a stroke or systemic embolism. A time-dependent analysis, including all episodes of atrial tachyarrhythmias during follow-up, showed that detection of episodes lasting longer than 6 minutes as compared to detection of no episodes was associated with an increased risk of ischemic stroke or embolism with a hazard ratio of 1.76. When the patients with episodes of device-detected atrial tachyarrhythmia were stratified into quartiles based on the duration of the longest episode, there was an increase in risk in the group with the longest episodes (> 17.72 hours). The number of episodes of subclinical atrial tachyarrhythmias did not show a significant relationship to event rates. No estimate of overall AF burden was presented. The relative risk of ischemic stroke or systemic embolism was also related to baseline risk of stroke as assessed by the $CHADS_2$ score. In patients with a $CHADS_2$ score of > 2 and a subclinical atrial tachyarrhythmia, the event rate was 3.78% per year for those with 6-minute high atrial rate episodes compared to 0.97% per year for those without. The portion of the study that assessed atrial overdrive pacing showed that there was no decrease in AF (annual rate 1.96 on vs 1.44 off) or in thromboembolic events (0.78 on vs 0.86 off).

The authors conclude that subclinical atrial tachyarrhythmias are frequent in patients with pacemakers and a history of hypertension, but no prior diagnosis of clinical AF. The detection of subclinical atrial tachyarrhythmias of at least 6 minutes duration is associated with an increased future risk of stroke.

■ COMMENTARY

Based on the results of large trials on anticoagulation in patients with AF, current guidelines recommend long-term oral anticoagulation for high-risk patients with both persistent and paroxysmal clinically manifest AF. However, asymptomatic, self-terminating episodes of atrial tachyarrhythmias are frequently seen when patients undergo prolonged ECG monitoring or during interrogation of pacemakers or ICDs. Do all these patients need chronic anticoagulation? The ASSERT data would suggest that at least those patients in the quartile with longer episodes (> 17.72 hours) and a $CHADS_2$ score ≥ 2 should be anticoagulated.

The ASSERT authors chose to base their analysis on atrial high-rate episodes of at least 6 minutes duration. However, in comparison to shorter episodes, 6-minute episodes are relatively uncommon. Many patients with pacemakers or ICDs will have more shorter atrial high-rate episodes detected when their devices are interrogated. In some, even though each episode is short, the overall AF burden may be substantial. We still need further definition of the lower boundary that should trigger a decision to anticoagulate. ■

ABSTRACT & COMMENTARY

Medical Therapy or Stenting for Aortoiliac PAD?

By Andrew J. Boyle, MBBS, PhD
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SOURCE: Murphy TP, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral srtery disease. Six-month outcomes from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study. *Circulation* 2012;125:130-139.

Peripheral arterial disease (PAD) can cause symptomatic claudication and it can reduce quality of life. Medical therapy for atherosclerotic vascular disease is indicated for patients with PAD, and guidelines also advocate regular exercise, as this can improve claudication symptoms. Endovascular treatment, predominantly stenting, has emerged as a common adjunctive treatment modality for patients with PAD. However, the optimal initial treatment strategy for patients with aortoiliac PAD is not known: Should patients be treated with medical therapy alone, a supervised exercise regimen, or should they undergo endovascular stenting as the initial management strategy? Murphy and colleagues designed a randomized, controlled clinical trial to address this question.

At 22 sites, they enrolled 111 patients with moderate-to-severe symptomatic claudication and objective evidence of significant obstructive PAD at the aortoiliac level. All patients were scheduled to receive optimal medical therapy (OMT) according to the ACC/AHA guidelines. They were then randomized into three groups: OMT alone, OMT plus supervised exercise program (SE), or OMT plus stenting (ST). Patients underwent initial exercise testing with standard protocol and were then followed for 6 months for symptoms, exercise capacity, and quality of life (QOL). Patients with critical limb ischemia were excluded and all patients received cilostazol as tolerated. The primary endpoint was change in walking time.

Baseline clinical and demographic characteristics were not different between groups, although there was a trend toward more women in the SE group. Patients were well managed with mean LDL 105 mg/dL and HDL 48 mg/dL. There was no statistically significant difference in the use of aspirin, thienopyridines, and statins.

Over the 6-month study period, walking time remained unchanged in the OMT group (+1.2 ± 2.6 minutes), and increased in both the SE group (5.8 ± 4.6 minutes, $P < 0.001$ vs OMT) and the ST group (3.7 ± 4.9 minutes, $P = 0.02$ vs OMT). The improvement in walking time was significantly greater in the SE group than the ST group (2.1 minutes, $P = 0.04$). There was no change in the ankle brachial index (ABI) in the OMT and SE groups, but ABI significantly improved in the ST group (+0.29, $P < 0.001$). In the measures of QOL, both SE and ST groups showed greater improvement than the OMT group, with the ST showing a significantly greater improvement in QOL. There were four serious adverse events in the ST group, related to the procedure, and none in the other groups. The authors conclude that SE results in superior treadmill walking performance than ST for patients with aortoiliac PAD. The contrast between better walking performance for SE and better patient-reported QOL for ST warrants further study.

■ COMMENTARY

Exercise training increases collateral artery formation in lower extremity PAD and improves symptoms. Endovascular treatment in the thigh and below the knee is complicated by high rates of restenosis. While controversy exists about the optimal revascularization strategy for lower extremity PAD, aortoiliac disease is widely believed to be optimal for stenting because restenosis rates are lower here. Thus, this trial enrolled the population that one would expect the best possible outcome for ST (significant symptoms and aortoiliac disease). The significant improvement in objective walking parameters in the SE groups may be due to improved collateral vessel formation, or may be due to improved general cardiovascular health, not just due to limb-specific circulatory improvements. There also may be an element of treadmill learning associated with SE programs. This was the primary endpoint of the study and showed that SE was superior to OMT and OMT + stenting as an initial strategy. However, that is not the whole story. ST was the only treatment that improved the functional blood flow to the leg measured by ABI, and this was associated with

improved QOL, suggesting that ST may also be a reasonable strategy in some patients. OMT alone appears to be associated with the worst outcomes. It should be noted, however, that this study was conducted over 6 months, a relatively short follow-up period. Longer-term outcomes and cost-effectiveness analyses are awaited from this cohort. Also, the number of patients included in this study was small and recruitment was stopped at half the prespecified number of patients. Importantly, we do not know if the effects of SE and ST are additive or if use of one of these therapies realizes the maximal improvement possible. There was initially a combined treatment group who underwent both SE and ST, but enrollment into this group was abandoned early due to slow enrollment.

This study extends previous studies of PAD in the lower limbs that show SE is beneficial to now include aortoiliac disease. It strengthens the evidence base upon which we recommend to patients that they increase their exercise levels. It may be slightly premature to recommend starting "vascular rehab" programs for our patients with PAD, because the long-term outcomes and cost-effectiveness analyses are yet to be presented. However, we should continue to emphasize the importance of exercise to our patients. ■

ABSTRACT & COMMENTARY

Physician Experience and the Risk of Procedural Complications

By John P. DiMarco, MD, PhD
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SOURCE: Freeman JV, et al. Physician procedure volume and complications of cardioverter-defibrillator implantation. *Circulation* 2012;125:57-64.

In this study, Freeman and colleagues analyzed data from the National Cardiovascular Data Registry-ICD Registry (NCDR-ICD Registry) to examine the effects of physician procedure volume on in-hospital complications and death. The authors collected data on all patients who had data about their ICD implant recorded in the NCDR-ICD Registry participating hospitals between April 2006 and March 2010. Patients who received an epicardial lead and who had an ICD replacement procedure were not included. In-hospital events including cardiac arrest, cardiac perforation, valve injury, coronary venous dissection, hemothorax, pneumothorax, deep vein thrombosis, TIA or stroke, myocardial infarction, pericardial tamponade, AV fistula, lead dislodgement, peripheral embolus, peripheral nerve injury, and device-related infection were analyzed as early complications. Data on the physician implanter were collected using their National Provider Identifier number. Physician certification was correlated with the databases of the American Board of Internal Medicine, the Society of Thoracic Surgery, and the American College of Surgery. Physicians were characterized as either electrophysiologists, nonelectrophysiologist cardiologists, thoracic surgeons, physicians who met Heart Rhythm Society training standards, or none of the above.

The final dataset included 4011 physicians who performed 356,515 initial ICD implantations at 1463 hospitals. Annualized physician procedure volume varied widely. The median number was only 16 implantations per year. The lowest quartile physicians implanted ≤ 4 ICDs per year! The highest quartile physicians implanted more than 37 ICDs per year. Higher volume implanters treated patients who were slightly older, more likely to have a diagnosis of congestive heart failure, and more likely to have advanced heart failure symptoms. High-volume implanters also were more likely to be board-certified cardiac electrophysiologists. Physician volume was higher in hospitals than in teaching institutions located in urban areas with more patient beds.

The overall in-hospital complication rate after ICD implantation was 3.1%. The rate of adverse events was lower among patients who received a single chamber ICD (1.9%) compared to those patients who received a dual chamber ICD (2.9%) or a biventricular ICD (4.1%). The most common in-hospital adverse events were: lead dislodgement (1%), hematoma (0.9%), pneumothorax (0.4%), and cardiac arrest (0.3%). There was an inverse relationship between physician procedure volume and a rate of adverse events. There was a progressive decline in the frequency of both all complications and major complications with each quartile of physician annual procedure volume. This was particularly striking as the complexity of the devices increased. Physician annual ICD

volume was associated with lower event rates even after adjustment for patient characteristics, hospital characteristics, and hospital volume. Since physicians may implant ICDs at more than one hospital, a separate analysis was performed to separate the effects of physician volume from hospital volume. Individual physician ICD procedure volume was still related to better outcomes whether the procedure was performed at higher volume or lower volume hospitals. Board-certified electrophysiologists tended to be the highest volume implanters and also had a lower rate of complications. However, even within each classification of training, procedure volume was still strongly associated with improved results.

The authors conclude that their data are in agreement with previous studies on other cardiac procedures showing that individual physician volume correlates with better outcomes. This effect is most striking for higher risk procedures such as biventricular ICDs. The effect appears to be physician and not hospital-volume specific.

■ COMMENTARY

This is the largest and most comprehensive analysis of procedure volume and ICD complications yet published. As with other cardiac procedures, operator experience is related to a decreased rate of complications. What is striking is that the number of ICD implants in the lowest quartile of physicians was ≤ 4 per year. Surely these physicians shouldn't be implanting ICDs. Even the next quartile of physicians implanted only 4-16 devices per year and it's questionable if this is an adequate volume. It should also be remembered that the ICD Registry only deals with in-hospital complications. Some ICD complications, like LV lead dislodgements and infections, typically occur later after many ICD recipients have been discharged. It's likely that including these later complications would make the argument for more experienced implanters even stronger. ■

CME Questions

1. Rivaroxaban plus dual antiplatelet therapy after ACS resulted in:
a. lower mortality.
b. less major bleeding.
c. less heart failure.
d. more fatal bleeds.

2. The best treatment for aortoiliac arterial disease is:
a. intensive medical therapy.
b. an exercise training program.
c. balloon angioplasty.
d. stenting.

3. In patients with moderate aortic stenosis, ECG evidence of LVH with the strain pattern was predictive of:
a. sudden death.
b. development of angina.
c. myocardial infarction.
d. All of the above

4. Which hemodynamic subgroup of patients with asymptomatic severe aortic stenosis has the worst prognosis?
a. Normal flow, high gradient
b. Normal flow, low gradient
c. Low flow, low gradient
d. High flow, high gradient

5. Brief asymptomatic episodes of atrial fibrillation seen in pacemaker patients on device interrogation predict:
a. an increased risk of stroke.
b. an increased risk of sustained atrial fibrillation.
c. an increased risk of atrial flutter.
d. None of the above

6. Complications following ICD implants are most closely related to:
a. physician volume.
b. hospital volume.
c. patient characteristics.
d. physician specialty.

CME Objectives

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

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

PHARMACOLOGY WATCH

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

Dutasteride and Low-Risk Prostate Cancer

In this issue: New treatment for prostate cancer; avastin and breast cancer; new CMS disclosure rule; and FDA actions.

Adjunct to active surveillance?

Low-risk prostate cancers are nonpalpable, low-grade tumors associated with prostate-specific antigen (PSA) levels less than 10 ng/mL. For these patients, active surveillance is an option, allowing a period of observation to help decide who should be treated or not treated. Generally, this involves repeated biopsy sampling with the option to treat more aggressively if higher grade tumors are found. Active surveillance is more frequently utilized in Europe and Canada than in the United States, where more aggressive treatment is the norm. A new study from the U.S. and Canada investigates the safety and efficacy of the 5α-reductase inhibitor dutasteride on prostate cancer progression in men with low-risk disease. A total of 302 men ages 48-82 with low-volume Gleason score 5-6 prostate cancer were randomized to dutasteride 0.5 mg per day or placebo. Patients were followed for 3 years with prostate biopsies done at 18 months and 3 years with the primary endpoint being time to prostate cancer progression. After 3 years, 38% of men in the dutasteride group and 48% of men in the control group had prostate cancer progression (hazard ratio 0.62; 95% confidence interval [CI], 0.43-0.9; $P = 0.009$). Dutasteride was not associated with an increase in adverse events. There were no prostate cancer-related deaths and no incidence of metastatic disease in either group. The authors conclude that "dutasteride could provide a beneficial adjunct to active surveillance for men with low-risk prostate cancer" (*Lancet* published online January 23, 2012). An accompanying editorial points out the appeal of a safe oral drug that can prevent prostate cancer progression, but the author cannot recommend the drug based on this study due to several limitations — short duration, no evidence of mortality difference, and, most importantly, the risk that 5α-reductase inhibitors may decrease the volume of low-grade, but not high-grade, cancers. (*Lancet* published online January 23, 2012). This study comes at a time when physicians are actively debating the pros and cons of screening for prostate cancer. The recently published PLCO trial showed that PSA screening does not lower the risk for death from prostate cancer while there is evidence of harm (*J Natl Cancer Inst* 2012;104:125-132). Some would argue that rather than treating low-grade prostate cancers, it may be better not to diagnose it at all. This issue is sure to be a topic of discussion at the FDA if GlaxoSmithKline requests approval for dutasteride (Avodart) for the management of low-risk prostate cancer. ■

More to the avastin/breast cancer story?

In November 2011, the FDA revoked the approval of Genentech's bevacizumab (Avastin) for the treatment of breast cancer. The somewhat controversial decision was based on lack of evidence of improved survival with the drug, even though several studies have shown improvement in progression-free survival. This has sparked a debate regarding surrogate clinical endpoints, such

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as progression-free survival or pathological complete response, which is the endpoint used in two new studies recently published in the *New England Journal of Medicine*. The first study from Germany randomly assigned 1948 women with medium-sized tumors to receive neoadjuvant epirubicin and cyclophosphamide, followed by doxetaxel with or without bevacizumab, in patients with HER2-negative breast cancers. Rates of pathological complete response were 14.9% without bevacizumab and 18.4% with the drug (odds ratio 1.29; 95% CI, 1.02 to 1.65; $P = 0.04$). Patients with hormone receptor-negative ("triple negative") tumors did better while patients with hormone receptor-positive tumors saw no improvement (*N Engl J Med* 2012;366:299-309). The other study, supported by the National Cancer Institute, looked at about 1200 patients with operable HER2-negative breast cancer. Patients were given neoadjuvant therapy with docetaxel plus capecitabine or paclitaxel plus gemcitabine followed by doxorubicin-cyclophosphamide. They were further randomized to receive bevacizumab for the first six cycles. Adding capecitabine or gemcitabine to docetaxel had no effect and increased toxicity; however, adding bevacizumab increased the rate of pathological complete reponse (28.2% without bevacizumab vs the 34.5% with bevacizumab, $P = 0.02$). Bevacizumab increased the rates of hypertension, left ventricular systolic dysfunction, hand-foot syndrome, and mucositis. The authors conclude that bevacizumab significantly increased the rate of pathological complete response (*N Engl J Med* 2012;366:310-320). An accompanying editorial points out that the ongoing controversy regarding bevacizumab for the treatment of breast cancer revolves around the issue of using surrogate endpoints in clinical trials as well as broader economic issues in the treatment of cancer. Although the study showed improvement in the surrogate endpoint of pathological complete response (defined as absence of residual tumor in the breast and nodes in the European study and a less stringent criteria of absence of residual tumor in the breast only in the American study), neither study was powered to show differences in survival — the criteria the FDA used to withdraw the approval for bevacizumab (*N Engl J Med* 2012;366:374-375). It is unlikely that either of these studies will influence the FDA to change its decision until more definitive survival data are available. ■

Disclosure rule open for comments

The Centers for Medicare and Medicaid Services is requesting comments on a proposed rule that would require drug and device companies to report all financial relationships with physicians. The new rule is part of the Affordable Care Act. It would require disclosure of payments for food, entertainment, gifts, consulting fees, honoraria, research funding for grants, education or conference funding, royalties or licenses, and insurable contributions. Physicians would also need to disclose stock ownership in pharmaceutical and device companies, with all this information provided on a public website. Failure to disclose this information would mean substantial fines for physicians. Comments will be accepted until mid-February with the final rule expected later in 2012. ■

FDA actions

Responding to concerns about increasing antibiotic resistance, the FDA has issued an order that prohibits the use of cephalosporins in cattle, swine, chickens, and turkeys effective April 15, 2012. This rule is intended to limit the indiscriminate use of cephalosporins and preserve the effectiveness of the drugs in humans.

The FDA has approved a once-weekly, extended-release formulation of exenatide for treatment of type 2 diabetes. The drug is a glucagon-like peptide-1 receptor agonist and is indicated as an adjunct to diet and exercise for improved glycemic control. It is the first once-weekly diabetes drug to be approved. The approval was based on the DURATION-5 trial, which compared once-weekly exenatide with twice-daily exenatide injection. Exenatide extended-release is approved with a Risk Evaluation and Medication Strategy (REMS) because of concerns regarding acute pancreatitis and the potential risk for medullary thyroid cancer, as well as concerns about QT prolongation and cardiovascular risk. Exenatide extended-release will be marketed by Amylin Pharmaceuticals and Alkermes plc as Bydureon.

The FDA has approved vismodegib to treat adult patients with advanced basal cell carcinoma who are not candidates for surgery or radiation, and for patients with metastatic disease. The drug was approved under the agency's priority review program and is the first approved drug for metastatic basal cell carcinoma. The once-a-day oral pill inhibits the Hedgehog pathway, a molecular pathway found in basal cell carcinomas but few other normal tissues. The approval was based on a single, multicenter trial of 96 patients in which 30% of patients with metastatic disease experienced a partial response and 43% patients with locally advanced disease experienced a complete or partial response. Vismodegib is marketed by Genentech as Erivedge. ■

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Long-Term Effects of Bariatric Surgery: Improved CV Outcomes

Source: Sjostrom L, et al. *JAMA* 2012; 307:56-65.

INCREASES IN BODY MASS INDEX (BMI) above normal are linearly associated with cardiovascular (CV) morbidity and mortality. The increased incidence of hypertension and diabetes in overweight and obese individuals explains some of this association. Since the weight reduction subsequent to bariatric surgery (BARS) is usually accompanied by improvements in blood pressure and metabolic profile, one would hope that this would translate into a reduction of CV events.

The Swedish Obese Subjects study provides data from this prospective controlled study of BARS (n = 2010) vs "usual care" (n = 2037) for adult obese subjects. The minimum BMI for inclusion was 34 kg/m^2 in men and 38 kg/m^2 in women. Subjects were followed for a median of 14.7 years.

The BARS subjects enjoyed a 53% relative-risk reduction in CV deaths (28/2100 vs 49/2037) and a 33% risk reduction in overall fatal and nonfatal CV events (199/2100 vs 234/2037) over the almost 15 years of follow-up.

Although the degree of excess BMI did not correlate with outcomes — i.e., persons who had higher baseline BMI did not enjoy a greater (or lesser) risk reduction than comparators — there was a correlation with insulin resistance. As manifest by baseline plasma insulin concentration, subjects with the highest degree of insulin resistance had the greatest degree of CV risk reduction. This long-term follow-up of a large surgical population is encouraging that BARS reduces CV risk. Demonstration of risk reduction requires both a large population and enduring follow-up, since most of the participants were much younger than are typically enrolled in CV risk reduction trials. ■

Long-Term Survival in SHEP Trial Participants

Source: Kostis JB, et al. *JAMA* 2011;306: 2588-2593.

THE SYSTOLIC HYPERTENSION IN THE ELderly (SHEP) trial was a prospective, randomized, controlled trial of diuretic (chlorthalidone) vs placebo in 4736 subjects with isolated systolic hypertension over the age of 60. At the conclusion of the trial (4.5 years mean follow-up), chlorthalidone resulted in a statistically significant reduction in cardiovascular (CV) *events*, but only a favorable trend (NOT statistically significant) in CV *mortality*. Because of the favorable initial results, at the conclusion of the trial all SHEP participants were advised to use active treatment.

Kostis et al report on 22 years of follow-up of SHEP trial participants. According to their analysis, there was a beneficial difference noted between persons originally assigned to diuretic vs placebo: a statistically significant 11% reduction in CV death, although total mortality was not significantly different between the two groups. Benefits seen years after a clinical trial intervention has ceased are commonly termed "legacy effects," and suggest that a sustained period of blood pressure control with chlorthalidone may extend CV risk reduction over a much longer interval. Because all trial participants were encouraged to receive active treatment post-trial, the favorable between-group differences seen would likely be an underestimate of true attainable benefits. ■

Exercise and Weight Loss in Persons with Pre-existing Coronary Heart Disease

Source: Ades PA, et al. *Chest* 2011;140: 1420-1427.

THERE IS STILL SOME DEBATE ABOUT THE relationship between being overweight and cardiovascular (CV) health, since among overweight individuals there is great diversity in levels of CV fitness as well as CV risk factors (e.g., hypertension, diabetes, dyslipidemia). Much of the insight we have today about the benefit of cardiac rehabilitation programs was gleaned from trial data in the 1970s and 1980s, at which time many fewer study subjects were obese or morbidly obese. Hence, determining the impact of exercise and weight loss in persons more representative of current coronary heart disease (CHD) demographics is pertinent.

Obese adults (mean baseline BMI = 32.3 kg/m^2) with established CHD (n = 38) participated in a regimen of weight loss combined with one of two different intensity exercise programs (walking 45-60 minutes vs 25-40 minutes per session) for 4 months.

Endothelial function, as assessed by flow-mediated dilation, was improved in both groups, but improved more in the group with greater intensity of exercise. The authors also comment that the amount of endothelial functional improvement seen with weight loss was similar in magnitude to that attained with statin treatment. Degree of endothelial functional improvement correlated with amount of weight lost, suggesting a dose-response effect. In an era when more than 80% of persons entering cardiac rehabilitation programs are overweight or obese, it is encouraging that participation in rehabilitation programs that result in weight loss and sustained physical activity improve endothelial function. ■

Predicting Adverse Outcomes in Asthmatics: The Severity of Asthma Score

Source: Eisner MD, et al. *Chest* 2012; 141:58-65.

In the United States, approximately 5,000 persons die each year from asthma. Several metrics for predicting outcomes in asthmatics are available including the asthma control test, work productivity and impairment index-asthma, FEV_1, and severity of asthma score (SOA). The SOA score is a validated questionnaire that incorporates asthma symptom frequency, medication use history, and hospitalizations for asthma among its 13 items. The Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma study is an observational study of omalizumab or placebo in asthmatics with demonstrated inhalant allergen sensitivity. In the placebo arm (n = 2878), the SOA score was compared with the other metrics mentioned above for its ability to predict five asthma-related outcomes: exacerbations, hospitalizations, unscheduled office visits, emergency room visits, and need for systemic steroid treatment.

Of all the metrics chosen, SOA had the best predictive capacity, and was singular in that it had significant positive-predictive value for all five of the adverse asthma-related outcomes, whereas other tools were positively predictive in only a portion of the five outcomes. One of the attractive aspects of the SOA is that no special tools, lab tests, or measurements of pulmonary function are required to score it. ■

Subclinical Atrial Fibrillation

Source: Healey JS, et al. *N Engl J Med* 2012;366:120-129.

I have been a student of atrial fibrillation (AF) for some time, but had never come upon the term "subclinical" AF until this *New England Journal of Medicine* publication. The authors point out that although AF is often brought to our attention by awareness of an arrhythmia, it is often asymptomatic — what they call subclinical. Indeed, it is not uncommon to see patients presenting with ischemic stroke, heart failure, or syncope, only to discover that asymptomatic AF is the underlying etiology.

Healey et al report on a population of hypertensive seniors in whom either a pacemaker or defibrillator had been implanted but who had no prior history of AF (n = 2580). The implanted devices were programmed to report any episode of heart rate 190 beats per minute (bpm) or greater. Subclinical atrial tachyarrhythmia — defined as an asymptomatic occurrence of atrial rate > 190 bpm for more than 6 minutes — was detected in 35% of study subjects over 2.5 years of observation; asymptomatic episodes far outnumbered symptomatic tachyarrhythmia. The risk for ischemic stroke in persons experiencing any atrial tachyarrhythmia was increased by 2.5 fold.

These data may help to explain some of the ischemic stroke cases that have no immediately visible antecedent. On the other hand, the complex terminology that separates AF into persistent, paroxysmal, subclinical, permanent, etc, may not be helpful; the phrase "once a fibber, always a fibber" simplifies the fact that (except for transient AF associated with perioperative stress), any episode of AF, regardless of duration or extinguishability, elevates thrombotic risk. ■

Real-life Use of Sunscreen in Ski Areas

Source: Buller DB, et al. *J Am Acad Dermatol* 2012;66:63-70.

Current recommendations for sunscreen include three fundamental steps: 1) application up to 30 minutes before exposure, 2) use of a sun protection factor (SPF) of at least 15 (higher if ultraviolet [UV] radiation is high), and 3) reapplication every 2-3 hours. Skiing is associated with high UV exposure because of the combination of altitude and snow reflection.

Buller et al interviewed adult skiers in the western United States and Canada (n = 4837). Subjects were interviewed face-to-face while riding on chairlifts and gondolas (I don't ever remember getting offered one of those tough, technical scientific jobs!).

Almost 50% of subjects reported using sunscreen with SPF 15 or higher, and most applied it 30 minutes before sun exposure. Reapplication was only performed by 20%. Only 4% of respondents fulfilled all three components of appropriate sunscreen use. Overall, men were substantially less compliant than women.

Messages about the importance of skin protection appear to be reaching the public, including young athletic adults. Further education about the need for reapplication, coupled with insights about circumstances of increased exposure risk (like skiing), might improve compliance in the future. ■

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