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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

ABSTRACT & COMMENTARY

Preventive Angioplasty in Myocardial Infarction?

By Andrew J. Boyle, MBBS, PhD
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Dr. Boyle reports no financial relationships relevant to this field of study.

SOURCE: Wald DS, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;369:1115-1123.

Primary percutaneous coronary intervention (PCI) is the optimal treatment for patients suffering ST-elevation myocardial infarction (STEMI). Current guidelines recommend treating the infarct-related artery, also known as the culprit artery, during the initial primary PCI procedure, and strongly recommend against treating stenoses in other arteries at the same sitting (unless the patient is in cardiogenic shock). However, many patients with STEMI also have significant stenoses in other arteries, and there is a growing body of literature that demonstrates complete revascularization is associated with better long-term outcomes. Wald and colleagues extend the principle of complete revascularization to the setting of primary PCI. They performed a randomized, controlled trial of culprit-only PCI vs also treating stenoses > 50% in the non-infarct arteries (which they termed preventive PCI) at five centers in the United Kingdom.

The authors enrolled 465 patients presenting with STEMI (including three patients with left bundle-branch block) who were undergoing infarct-artery primary PCI and also had stenoses > 50% in other coronary arteries, and randomly assigned them to either preventive PCI (n = 234) or no preventive PCI (n = 231). They excluded patients whose other stenoses were chronic total occlusions or left main disease. The majority of patients received drug-eluting stents. The use of glycoprotein IIb/

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IIIa inhibitors and/or bivalilrudin was left to the operator's discretion and these agents were used in 79% of cases. Importantly, further PCI after the index primary PCI was recommended only for refractory angina with objective evidence of ischemia. At discharge from hospital, the medical therapy was excellent in both groups (100% of patients on dual antiplatelet therapy, > 95% on statins, 90% on beta-blockers). The primary outcome was a composite of death from cardiac causes, nonfatal myocardial infarction, or refractory angina.

The data safety monitoring committee recommended that the trial be stopped early. During a mean follow-up of 23 months, the primary outcome occurred in 21 patients assigned to preventive PCI and in 53 patients assigned to no preventive PCI (infarct-artery-only PCI), which translated into rates of 9 events per 100 patients and 23 per 100, respectively (hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.21-0.58; $P < 0.001$). HRs for the three components of the primary outcome were congruent: 0.34 (95% CI, 0.11-1.08) for death from cardiac causes, 0.32 (95% CI, 0.13-0.75) for nonfatal myocardial infarction, and 0.35 (95% CI, 0.18-0.69) for refractory angina. These benefits were statistically significant by 6 months after the index procedure. The authors conclude that in patients with STEMI and multivessel CAD undergoing infarct-artery PCI, preventive PCI in non-infarct coronary arteries with major stenoses significantly reduced the risk of adverse cardiovascular events as compared with PCI limited to the infarct artery.

■ COMMENTARY

This study will challenge current paradigms. The American College of Cardiology/American Heart Association guidelines give a class III recommendation for non-infarct artery PCI at the same time of primary PCI. Data from large registries indicate that staged PCI of non-infarct arteries resulting in complete revascularization leads to better outcomes than medical therapy in patients with STEMI. The current paper by Wald et al suggests that complete revascularization can be safely achieved during the initial procedure. Early reports of adverse outcomes from PCI to non-culprit arteries during primary PCI were in the era before intensive antiplatelet and statin therapy, and may therefore no longer be applicable. Perhaps optimization of medical therapy has expanded the role for PCI in these patients to now include multivessel PCI in the acute setting.

The results of this study are strengthened by the fact that all components of the primary combined endpoint were congruous and of similar magnitude, and by the statistically rigorous trial design and execution. It is important to note that the authors screened more than 2400 patients with STEMI to find 465 who fit their inclusion and exclusion criteria. Left main disease and chronic total occlusions were notable exclusion criteria. Also, they excluded patients with cardiogenic shock, who are known to benefit from multivessel PCI. Although this study makes a case for complete revascularization in selected patients with STEMI, it does not clarify when. It may well be that a staged procedure at a later date is the superior strategy. We probably should not change our practice until more data are available. ■

ABSTRACT & COMMENTARY

Is Cardioversion After Acute Atrial Fibrillation Safe Without Anticoagulation?

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

SOURCE: Airaksinen KE, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: The FinCV (Finnish CardioVersion) Study. *J Am Coll Cardiol* 2013;62:1187-1192.

In clinical practice, patients with atrial fibrillation (AF) duration < 48 hours often undergo cardioversion without systemic anticoagulation. The Finnish CardioVersion (FinCV) study reviewed the comprehensive database from three Finnish hospitals to identify all patients undergoing cardioversion with AF onset < 48 hours prior without prior systemic anticoagulation. All AF episodes were confirmed by 12-lead ECG. The primary endpoint was thromboembolic event within 30 days after cardioversion. There were 5116 cardioversions performed in 2481 patients who all had AF onset < 48 hours and no prior anticoagulation. There were 38 definite embolic events (0.7%, 95%CI, 0.5-1.0%) in the 30 days after cardioversion, 31 strokes, four transient ischemic attacks, two pulmonary embolisms, and one systemic embolism. In addition, 11 patients died within 30 days, including two from fatal strokes. Independent predictors of embolic events included age (odds ratio [OR], 1.01; 95% CI, 1.02-1.08); female sex (OR, 2.1; 95% CI, 1.1-4.0), heart failure (OR, 2.9; 95% CI 1.1-7.3), and diabetes (OR, 2.3; 95% CI, 1.1-4.9). The highest risk of thromboembolism (9.8%) was identified in patients with heart failure and diabetes, whereas those without heart failure and < 60 years of age had the lowest risk (0.2%). None of the patients with failed cardioversions had embolic events. The authors concluded that the risk of thromboembolic complications post-cardioversion of AF of < 48 hours' duration is high in certain categories of patients when anticoagulation is not used.

■ COMMENTARY

It has often been taught that patients with AF < 48 hours' duration can undergo cardioversion without transesophageal (TEE) echocardiogram or prior anticoagulation, while in patients with prior AF lasting > 48 hours, either 3 weeks of therapeutic anticoagulation or a TEE is needed. One of the challenges of this approach is uncertainty regarding the prior duration of AF. Unless a patient is hospitalized or has an implanted pacemaker, symptoms from AF can be unreliable. Nevertheless, there are some patients who can tell the minute their AF initiates, and then call to undergo cardioversion. It is well described that immediately after cardioversion, there is "stunning" of the left atrium, and that left atrial appendage velocities actually decrease as spontaneous thrombus can form immediately. This occurs whether cardioversion is electrical, chemical, or spontaneous. However, the duration of stunning is related to the prior duration of AF, so those with brief prior AF duration may recover left atrial function quickly. It is for this reason that some have performed cardioversion of low-risk patients on aspirin if they present within 48 hours. This study points out that although the overall stroke risk in this patient group with AF < 48 hours is low (1%), it is higher in those with stroke risk factors (~10%). Fortunately, the same risk factors that predict stroke in AF patients, namely age, diabetes, and congestive heart failure, were predictive of recurrent stroke in this study. Therefore, it seems prudent that in patients with any CHADS2 stroke risk factors, anticoagulation should be initiated and continued for 30 days after cardioversion, even if the AF duration is < 48 hours. This is much easier to do with the newer oral anticoagulants. The need for continued anticoagulation can be reassessed after 30 days, depending on the patients' rhythm. If the duration of AF prior to presentation is at all unclear, then either 3 weeks of oral anticoagulation or a TEE should be performed prior to cardioversion. Importantly, if a TEE is being performed, one should achieve therapeutic anticoagulation before cardioversion in these patients. This can be achieved by giving the first oral dose of a novel anticoagulant 2 hours prior to cardioversion. For those with truly lone AF and clear recent onset AF, the risk of stroke with cardioversion is low (< 0.2%). I still tend to start a novel anticoagulant prior to and for at least 48 hours after cardioversion in these patients, given the possible deleterious effect of left atrial stunning and low risk of bleeding with short-term anticoagulant use. ■

ABSTRACT & COMMENTARY

Dabigatran Not Safe For Prosthetic Heart Valves

By Andrew J. Boyle, MBBS, PhD
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SOURCE: Eikelboom JW, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;369:1206-1214.

Dabigatran is a novel anticoagulant that has been shown to be at least as good as warfarin at preventing thromboembolism in atrial fibrillation (AF). It is an oral direct thrombin inhibitor that requires no blood tests to monitor its effectiveness. Thus, it has distinct advantages over warfarin. Patients with mechanical heart valves require lifelong anticoagulation with warfarin. If dabigatran proved to be equivalent to warfarin, it would be an attractive alternative for patients with mechanical valves. Eikelboom and colleagues performed a randomized, controlled clinical trial of dabigatran vs warfarin in patients with mechanical heart valves. They separated their study sample into two cohorts: cohort A, who were randomized within the first week after mitral or aortic valve replacement surgery, and cohort B who were randomized at least 3 months after surgery. These cohorts were randomized 2:1 to receive dabigatran or warfarin. Interestingly, the dose of dabigatran was higher than used in the AF trials. Initial dosing began at 150 mg, 220 mg, or 300 mg twice daily, depending on renal function, and then the dose was escalated to maintain a serum trough level of over 50 ng/ml. Warfarin was dosed to an INR of 2.0-3.0, or 2.5-3.5 depending on thromboembolic risk.

The data safety monitoring board terminated the trial early because the dabigatran group had an excess of both thromboembolic and bleeding events. Two hundred and fifty-two patients were enrolled. The mechanical valve locations were aortic in 68%, mitral in 28%, and both in 4%. Ischemic stroke occurred in 5% of the dabigatran group and none in the warfarin group. Thrombosis of the mechanical valve without symptoms was detectable in 5% of the dabigatran group and none of the warfarin group. The composite endpoint of stroke, transient ischemic attack, systemic embolism, myocardial infarction (MI), or death occurred in 9% of the dabigatran group and 5% of the warfarin group (hazard ratio [HR], 1.94; 95% confidence interval [CI], 0.64-5.86; $P = 0.24$). Major bleeding occurred in 4% of the dabigatran group and 2% of the warfarin group. It is noteworthy that all major bleeding was pericardial and all occurred in cohort A (early after surgery). Bleeding of any type occurred in 27% vs 12% of the dabigatran and warfarin groups, respectively (HR, 2.45; 95% CI, 1.23-4.86; $P = 0.01$). The authors conclude that the use of dabigatran in patients with mechanical heart valves was associated with increased rates of both thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk.

■ COMMENTARY

The results of this study are a blow to those on lifelong warfarin for mechanical heart valves. The ease of use of dabigatran compared to warfarin is a major step forward for many patients. But this is exactly the reason we do clinical trials. One cannot extrapolate that effectiveness in one disease state or indication for a drug will necessarily mean that it will be effective in another.

The reason for the failure of dabigatran in both thromboembolic and bleeding endpoints deserves some discussion. The achievement of adequate serum trough levels was less in the early group (cohort A) and this group had higher thromboembolic complications. However, they also had higher major bleeding rates, suggesting that it is it not purely a dosing problem. Dabigatran is successful in AF, where thrombosis occurs in the left atrial appendage under conditions of low flow due to stasis and endothelial dysfunction. But in patients undergoing valve surgery, there are large amounts of tissue factor released due to the trauma of surgery, and exposure to the sewing ring and prosthetic valve leaflets can activate the contact pathway of thrombosis. Warfarin acts at multiple sites in the coagulation cascade, including the tissue factor and contact pathways (factors VII and IX), as well as inhibiting the final common pathway, including thrombin. In contrast, dabigatran only inhibits thrombin. The authors suggest that the activation of multiple pathways may lead to an overwhelming amount of thrombin that dabigatran at these doses cannot inhibit. Warfarin's less specific mechanism of action may

be the reason it is more effective in patients with mechanical heart valves.

It should be noted that this was a phase 2 study designed to assess the serum trough levels of dabigatran. It was not designed to test efficacy of the drug. However, the data safety monitoring board terminated the study due to the excess number of endpoints in the dabigatran group. It is technically underpowered to accurately determine the magnitude of event rates, but the direction of both thromboembolic and bleeding event rates were clearly against dabigatran. For now, this means that the novel anticoagulants must not be used in lieu of warfarin for mechanical heart valves. ■

ABSTRACT & COMMENTARY

Stroke Risk from Pacemaker Leads in Patients with PFO

By Michael H. Crawford, MD, Editor

SOURCE: DeSimone CV, et al. Stroke or transient ischemic attack in patients with transvenous pacemaker or defibrillator and echocardiographically detected patent foramen ovale. *Circulation* 2013;128:1433-1441.

Pacemaker or defibrillator leads have been shown to have attached thrombi in up to one-third of cases and asymptomatic pulmonary emboli have been documented in up to 20% of patients. Thus, concern has arisen that right heart endocardial leads in patients with a patent foramen ovale (PFO) may lead to cerebral embolic events. These investigators from the Mayo Clinic in Rochester, MN, performed a retrospective analysis of 6075 patients seen in the last decade who had an endocardial lead placed in the right heart. The primary outcome assessed was a diagnosis of stroke or transient ischemic attack (TIA) consistent with a cardioembolic source. Patients were excluded who had obvious carotid, intracranial, or aortic sources and intracranial hemorrhage; who lacked adequate data to define the timing of any cerebral events; or who had an inadequate echo evaluation for PFO. Their policy during the sampling time was to perform a comprehensive echo evaluation in everyone getting an endocardial lead. The average follow-up after device implantation was 4.7 years. A definite PFO was found in 364 of these patients (6%). The two groups were similar in baseline characteristics. In the PFO group, 8.2% had a cerebral event vs 2% in the no PFO group ($P < 0.0001$). About two-thirds of the events were strokes for a rate of 5.2% vs 1.4%, repectively. The difference in the rate of events widened over time. The hazard ratio of having a PFO was 3.49 (95% CI, 2.33-5.25, $P < 0.0001$) and was similar after adjustment for known stroke risk factors and anticoagulant or aspirin use (3.3). The all-cause mortality rate was similar in the two groups. The authors concluded that the presence of a PFO on routine echo in patients undergoing endocardial lead placement increased the risk of cerebral embolic events and perhaps should encourage the use of anticoagulants, PFO closure, and epicardial lead placement in these patients.

■ COMMENTARY

Just when we thought PFO closure to prevent cryptogenic stroke was dead, this paper comes along and reopens the issue. Despite the attractiveness of the PFO theory of cryptogenic stroke and migraine causation, these relationships have been hard to prove. General population studies of PFO subjects have found no consistent association with stroke or migraines. The CLOSURE I trial randomized PFO patients after cryptogenic stroke to closure vs anticoagulant or antiplatelet therapy and found no difference in recurrent stroke.[1] However, they excluded patients with endocardial leads and most of the strokes observed were non-embolic, so the study was underpowered for embolic stroke. Endocardial lead patients are different in that these devices are nidi for thrombi and they often lie in proximity to the atrial septum. In this study, the stroke event curves didn't separate for 6 months suggesting that it takes time for lead thrombi to form or that it takes time for small emboli to raise the pulmonary pressures and increase the likelihood of right to left shunting. Lead-induced tricuspid regurgitation may take time to develop and cause increased elevated right atrial pressure. The lack of an observed mortality difference may be because the cerebral events are usually small. Thus, in these specific patients, the association between PFO and stroke/TIA may hold.

There are several limitations to this study. Retrospective studies are subject to various biases and causality cannot be definitively proven. Also, the specific role of anticoagulant and antiplatelet therapy in this study could not be determined and may have influenced the results. Transesophageal echocardiography (TEE) was done in about one-third of patients and may have biased the study toward stroke patients who are more likely to get TEE. Also, TEE increases the sensitivity of PFO detection. In those who got TEE, the PFO rate was 14% vs 6% in the study overall. Given that pathologic and other studies have found PFOs in up to 25% of normal individuals, this study seems insensitive, which may have biased it toward larger PFO patients who are more likely to have paradoxical emboli. This study used routine clinical echoes and we don't know how many used contrast or Valsalva. Finally, no right ventricular pressure data were reported.

For all these reasons, this study is hypothesis-generating. However, the results make us pause again. Should we view endocardial lead patients differently? Should they all have TEEs to detect PFOs? If PFOs are detected should they all take antiplatelet or anticoagulant agents? Should those with especially large PFOs or higher right atrial pressures have their PFO closed or epicardial leads used? Do we need to survey endocardial lead patients periodically to assess for the development of large thrombi? None of these questions can be answered by this study, but the issues are real because the consequences of stroke can be devastating. ■

REFERENCE

1. Furlan AJ, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012;366:991-999.

ABSTRACT & COMMENTARY

Is a Totally Subcutaneous ICD Safe and Effective?

Edward P. Gerstenfeld, MD

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SOURCE: Weiss R, et al. Safety and efficacy of a totally subcutaneous implantable cardioverter-defibrillator. *Circulation* 2013;128:944-953.

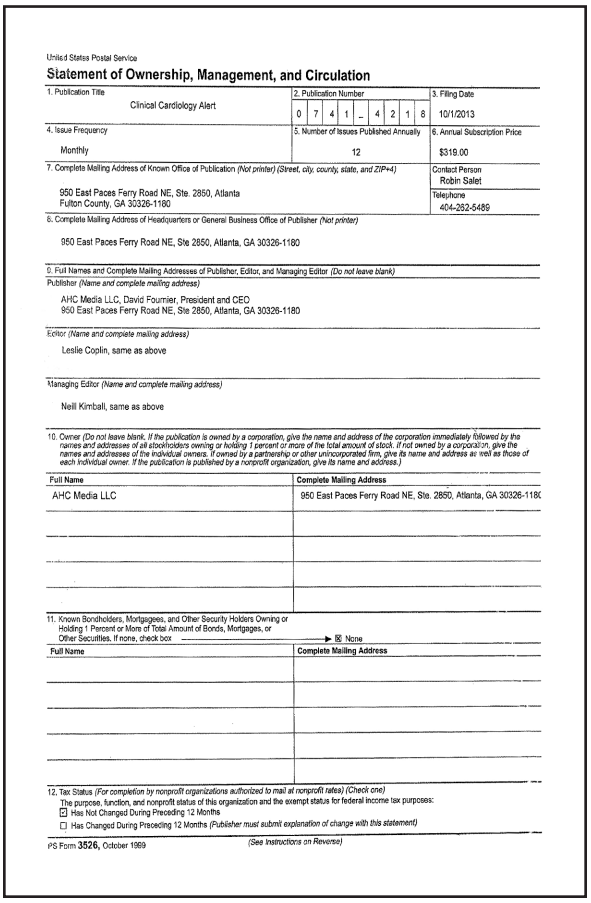
Multiple prospective, randomized trials have shown a mortality reduction in patients with reduced left ventricular ejection fraction who undergo prophylactic implantable cardioverter-defibrillator (ICD) therapy. However, enthusiasm for ICDs has been tempered by chronic lead complications, including infections, fracture, and insulation breach. Several ICD leads have been recalled by the manufacturer due to faulty manufacturing design, and require regular surveillance. The totally subcutaneous ICD is implanted extrathoracically, completely avoiding the intravascular space. The advantages to avoiding the intravascular system are clear. Limitations include the inability to perform pace-termination of ventricular tachycardia, the unclear effectiveness of defibrillation therapy clinically, and the larger size defibrillator generator. The current study is a prospective, nonrandomized, multicenter, observational study of patients undergoing implantations of the subcutaneous-ICD (S-ICD). Patients who had a standard ICD indication were enrolled. The primary safety endpoint was the 180-day S-ICD complication-free rate. The primary effectiveness endpoint was the acute induced ventricular fibrillation (VF) conversion rate during the time of implantation. Patients were followed up at 30, 90, and 180 days, and then semiannually. A total of 321 patients underwent S-ICD implantation; 276 patients had a follow-up duration > 180 days. Most patients (79%) underwent implantation for primary prevention of sudden death. The mean left ventricular ejection fraction was 36 ± 16%; 15% had atrial fibrillation and 41% had a prior myocardial infarction. The 180-day complication-free rate was 99%. The conversion rate of induced VF during implantation was 100%. This did not include 16 patients who were deemed not evaluable because of clinical circumstances, including hemodynamic instability, left ventricular thrombus, or inability to induce VF. There were eight deaths during the study period; five were deemed noncardiac, two were sudden, and one was unclear. A total of 119 spontaneous ventricular tachycardia (VT)/VF episodes occurred in 21 patients — 38 discrete VT/VF episodes and 81 episodes associated with VT storm in four patients. Of the 38 discrete VT episodes, 43 appropriate shocks were delivered. The S-ICD converted 35/38 episodes (92.1%) on the first shock and

37/38 (97%) episodes with one or more shocks. The remaining episode terminated spontaneously during charging. There were 18 device infections; four required device removal. The overall incidence of inappropriate shocks was 13.1%, for supraventricular tachycardia or oversensing of T waves, QRS complexes, or external noise. The mean time to therapy was 14.6 ± 2.9 seconds. The authors concluded that this study supports the efficacy and safety of the S-ICD system.

■ COMMENTARY

The ICD has revolutionized the treatment of sudden death, with the SCD-HeFT trial demonstrating a 7% absolute mortality reduction in all patients with EF < 35%, regardless of etiology.[1] However, device morbidity has tempered enthusiasm for prophylactic ICD implantation by many physicians. The primary limitation of these devices has been the intravascular leads. Lead fracture and insulation break can lead to inappropriate painful shocks in some patients. Systemic infection typically requires device removal and lead extraction, which in itself poses life-threatening risks. The S-ICD can potentially alleviate these chronic lead concerns, particularly in young patients who are more active and face many years of potential lead problems, and in patients with prophylactic indications where the likelihood for receiving a shock and the need for antitachycardia pacing therapy is lower. The "leads" of the S-ICD are tunneled subcutaneously along the inferolateral border of the ribcage and sternum and attached to a generator placed in a pocket in the left mid-axillary line. The results thus far of the S-ICD have been promising. There were no patients in the study who did not have successful termination of a clinical episode of VT/VF. The safety of the S-ICD implant was also impressive. Finally, the inappropriate shock rate of 13% is lower than most intravascular ICD studies, and is likely to improve with better programming and detection algorithms. In my experience, the main current limitation is the large size of the subcutaneous can (145 gm), which lies along the lateral thoracic ribcage and can be quite prominent in thin patients. The battery longevity is also shorter than typical intravascular systems, estimated at 5-8 years.

Is the S-ICD ready for prime-time? In my opinion, the technology is promising, but the number of treated patients and VF episodes is still far too small to recommend implantation of the S-ICD over a traditional intravascular device. Patients with congenital heart disease without intravascular access or those with prior lead infections should



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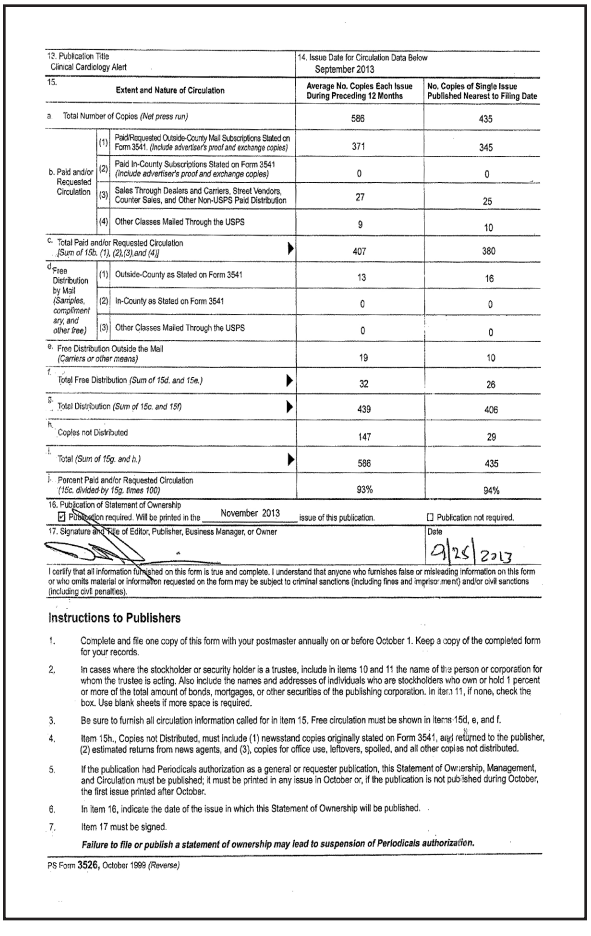

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be considered reasonable candidates. In the future, young patients with inherited cardiomypathies, such as Long QT syndrome and hypertrophic cardiomyopathy, would also be the most likely to benefit. Comparative trials between the S-ICD and standard intravascular ICD are being planned. Next-generation devices will undoubtedly be smaller and have longer battery longevity. Until more data arise, the implantation of the S-ICD should be limited. But over time, we will likely see a growing use of this promising technology. ■

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2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the evaluation is received, a credit letter will be sent to you. ■

CME Questions

1. The main disadvantage of a subcutaneous, extra-thoracic ICD is:
   a. reduced efficacy.
   b. increased pain with shocks.
   c. large device size.
   d. more inappropriate shocks.

2. Cardioversion of atrial fibrillation of < 48 hours duration without prior anticoagulation or a TEE:
   a. has a high incidence of stroke.
   b. can be safely done in CHADS2 = 0 patients.
   c. is completely safe.
   d. should never be entertained.

3. PCI of non-culprit lesions during primary PCI for STEMI:
   a. is generally contraindicated.
   b. is indicated in diabetics.
   c. results in better 30-day outcomes.
   d. is indicated with complete occlusions.

4. The use of dabigatran vs warfarin for prosthetic valves is associated with:
   a. more embolic events.
   b. more bleeding.
   c. more valve thrombosis.
   d. All of the above

5. Why might paradoxical emboli occur in patients with PFO and right heart endocardial leads?
   a. The propensity for lead thrombi
   b. Lead proximity to the PFO
   c. Lead-induced tricuspid regurgitation
   d. All of the above

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.

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

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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Finasteride for Prevention of Prostate Cancer: 18 Years of Follow-up

Source: Thompson I, et al. *N Engl J Med* 2013;369:603-610.

THE PROSTATE CANCER PREVENTION TRIAL (PCPT) was a randomized, double-blind, placebo-controlled trial (n = 18,880) performed to evaluate the efficacy of the 5-alpha-reductase inhibitor finasteride (FIN) for prevention of prostate cancer. At the end of 7 years, the good news was a 25% reduction in total prostate cancer; the bad news was that there was a 27% *increase* in higher-grade prostate cancers, intimating that although the total amount of prostate cancer was reduced, overall outcomes could possibly be worsened by the increase in more aggressive cancers. Mitigating explanations for the increased risk of higher-grade tumors included alpha-reductase inhibitor-induced shrinkage of healthy prostate tissue (thereby increasing the likelihood of biopsy-positive results) and alteration of tissue architecture induced by FIN; insufficiently reassured by these explanations, most primary care clinicians have opted not to use FIN for prostate cancer prevention.

The outcomes of this population in very long-term follow-up can better answer the question of whether the risk-benefit balance was indeed unfavorably tipped by high-grade prostate cancers. Reviewing the outcomes of patients originally enrolled in PCPT, the survival rates at 18 years were essentially identical among men who had been randomized to FIN or placebo. Although FIN treatment did not appear to reduce mortality, the increased incidence of higher-grade Gleason scores among FIN-treated patients did not appear to increase mortality either. In the absence of mortality improvement, unless men are seeking alpha-reductase treatment for symptomatic benign prostatic hyperplasia, FIN treatment for prevention of prostate cancer would appear unwarranted, albeit otherwise safe. ■

Addressing Diabetic Neuropathy

Source: Tesfaye S, et al. *Diabetes Care* 2013;36:2456-2465.

TYPE 2 DIABETES (T2DM) REMAINS THE No. 1 cause of atraumatic limb loss in the United States. Neuropathy is a primary culprit in the process beginning with undetected foot injury that progresses to deep-seated infection and, ultimately, limb loss. Hence, it is hoped that early identification and management of diabetic peripheral neuropathy (DPN) might improve outcomes. Unfortunately, of the microvascular consequences of T2DM, neuropathy appears to be the most recalcitrant to glucose control: Glucose control appears to forestall progression of neuropathy, but not improve nerve function or reverse neuropathy.

In clinical practice, it is recommended that the diagnosis of DPN should be based on typical symptoms and physical examination (e.g., lower extremity deep tendon reflex changes). On the other hand, clinical trials usually employ sophisticated techniques such as nerve conduction testing. Comparison of tuning fork testing vs monofilament testing found the former to be the most sensitive test for identification of neuropathy. The postulated pathophysiology of DPN is uncertain and may be multifactorial, but there is some support for dysfunction of the neural microvasculature.

FDA-approved agents for DPN pain are duloxetine and pregabalin, although venlafaxine, gabapentin, carbamazepine, and alpha-lipoic acid have also demonstrated some efficacy. A recently published algorithm created by the Toronto International Neuropathy Consensus Group suggests that when traditional agents are not effective, opioid analgesia may be considered. ■

When Metformin and Sulfonylurea Are Not Enough: Canagliflozin or Sitagliptin?

Source: Schernthaner G, et al. *Diabetes Care* 2013;36:2508-2515.

MANY TYPE 2 DIABETES (T2DM) PATIENTS are unable to achieve or maintain their A1c goals even when appropriately treated with oral agents. Currently, the combination of metformin with a sulfonylurea (MET/SFU) is a very commonplace initial combination. Because T2DM is a progressive disorder, and because some agents lose efficacy over time, most patients must recognize that augmentation of treatment is usually required. But which next step is best when MET/SFU is insufficient?

Canaglifozin (CAN) is the first approved member of a new class of agents for T2DM, known as the SGLT2 inhibitors, which work by blocking renal reabsorption of excess glucose, leading to increased urinary glucose excretion. Sitagliptin (SIT) is one of three approved

DPP-4 inhibitors that work by increasing blocking glucagon and stimulating insulin production when glucose is elevated.

In a 1-year trial comparing the addition of CAN or SIT to MET/SUF (n = 755), A1c reduction with CAN was substantially greater (-1.03 vs -0.66) and both agents were well tolerated. SGLT2 inhibitors are potentially useful when A1c goals are not attained or maintained with MET/SUF. ■

Wedge Insoles for Knee Osteoarthritis: Probably Not

Source: Parkes MJ, et al. *JAMA* 2013;310:722-730.

In the United States, osteoarthritis is the No. 1 cause of disability. The "graying" of America, in concert with an ever-growing prevalence of obesity, portends an equally expanding population of osteoarthritis.

Osteoarthritis of the knee (OA-K) can be particularly disabling, and currently available medical treatments, such as NSAIDs, topical analgesics, and opioids, each have limitations. Hence, short of surgical intervention, alternatives — such as non-pharmacologic treatment — are sought.

Medial OA-K is one of the most common subtypes. In theory, load reduction on the medical compartment might alleviate symptoms, disease progression, or both. By placing an angulated wedge under the sole of the foot, such load reduction can be achieved. A meta-analysis was performed (n = 885) by Parkes et al to evaluate the efficacy of mechanical interventions intended to unload the medial knee compartment including wedges or structured shoes.

Overall, studies did confirm a positive effect of devices to unload the medial compartment, although the effect size was not large. Additionally, trials with an active control (such as a neutral vs an offloading wedge) failed to confirm positive effects. These mixed results call into question whether clinicians can be confident in the efficacy of wedge insoles. ■

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Post-Stroke Blood Pressure Targets: Recent Lacunar Stroke

Source: The SPS3 Study Group. *Lancet* 2013;382:507-515.

Cerebral infarction related to small vessel disease, known as lacunar stroke, is strongly associated with hypertension (HTN). Numerous clinical trials have confirmed that control of HTN provides substantial stroke reduction overall (≥ 40%), without specifically distinguishing the effects on lacunar stroke.

The Secondary Prevention of Small Subcortical Strokes trial compared two levels of systolic blood pressure (SBP) among patients with a recent MRI-confirmed lacunar stroke for impact on recurrent stroke. Because of concern that excessive SBP lowering in the face of acute cerebral ischemia might be detrimental, subjects were randomized at least 2 weeks after the identifying event. Subjects (n = 3020) were randomized to one of two groups: SBP goal 130-149 mmHg or SBP goal < 130 mmHg. Clinicians were allowed to use whatever medications they preferred to attain SBP goals.

At 3.7 years, there was no statistically significant difference in the primary outcome of the study: all stroke. On the other hand, a secondary endpoint (which must be considered "hypothesis generating" since the primary endpoint failed) of hemorrhagic stroke was reduced by almost two-thirds in the SBP < 130 group. This finding prompted the consideration by the authors that since there was no difference in overall outcomes, but the suggestion of substantial reduction in hemorrhagic stroke by more strict blood pressure control, some clinicians might consider the more stringent SBP at least potentially beneficial. ■

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Can We Identify Persons on Zolpidem at Risk for Driving Mishap?

Source: Farkas RH, et al. *N Engl J Med* 2013;369:689-691.

Benzodiazepines can impair consciousness. It has been recognized that the elderly — and anyone with renal impairment because they metabolize zolpidem (ZOL) more slowly — should receive a lower dose (ZOL 5 mg) than other adults (ZOL 10 mg). Soon after the advent of immediate-release ZOL, a controlled-release formulation became available. Prospective studies of ZOL indicated that plasma levels > 50 ng/mL were associated with impairment in driving skills. As formulations of ZOL evolved, pharmacokinetic studies found that the 10 mg approved dose of immediate-release ZOL was associated with ZOL levels > 50 ng/dL in as many as 15% of women (who metabolize ZOL more slowly).

Recognition of the potential for ZOL to produce impairment in driving has resulted in FDA recommendations for dose reductions in various ZOL formulations, especially in women.

Insomnia and other sleep disorders are, of course, associated with an increased risk of auto accidents due to excessive daytime sleepiness. Clinicians should maintain vigilance that appropriate dose limitations are observed — since patients often do not perceive the impairment induced by benzodiazepines — and that patients do not drive sooner than the recommended interval after taking their dose of medication. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Medications for Risk Reduction of Breast Cancer in Women

In this issue: USPSTF issues new guidelines for risk reduction of breast cancer; safety of Chantix in patients with depression; polypills for cardiovascular disease; and FDA actions.

Risk reduction of breast cancer

The U.S. Preventive Services Task Force (USPSTF) has published new guidance regarding medications for risk reduction of primary breast cancer in women. The group reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce breast cancer, specifically the selective estrogen receptor modulators tamoxifen and raloxifene (Evista). The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce the risk. Women who are at increased risk for breast cancer and have a low risk for adverse medication effects should be offered one of the risk-reducing medications (B recommendation). However, the group recommends against the routine use of these medications in women who are not at increased risk of breast cancer. High-risk women are defined as those with a 5-year risk of ≥ 3% based on the National Cancer Institute's Breast Cancer Risk Assessment Tool (www.cancer.gov/bcrisktool/). Tamoxifen and raloxifene are shown to reduce the risk of estrogen receptor-positive breast cancer, but not estrogen receptor-negative cancer, which is more difficult to treat. Tamoxifen is associated with a moderate benefit for breast cancer but a slightly higher risk of endometrial cancer. Raloxifene is associated with a slightly smaller benefit for breast cancer but no risk for endometrial cancer. Both drugs may reduce the risk of nonvertebral fractures with greater benefit for raloxifene. Both drugs also increase the risk of venous thromboembolism with the risk being age-dependent (*Ann Intern Med* published online September 24, 2013). ■

Chantix safe in patients with depression

Varenicline (Chantix) was approved in 2006 to treat smoking addiction. Since its approval, the drug has been plagued by reports of worsening depression and increases in suicidality, prompting the FDA to issue an alert in 2008 noting "serious neuropsychiatric symptoms" associated with the drug. But a new study suggests that varenicline may be safe and effective in smokers with a history of depression. In a study sponsored by Pfizer, 525 adult smokers with stably treated current or past major depression and no recent cardiovascular events were randomized to varenicline 1 mg twice daily or placebo for 12 weeks with 40 weeks of nontreatment follow-up. The primary outcome was carbon monoxide-confirmed continuous absence rate (CAR) for weeks 9-12. Other outcomes included ratings of mood, anxiety, and suicidal ideation or behavior. About two-thirds of patients in both groups completed the study. Patients treated with varenicline had double the quit rate at weeks 9-12 (CAR 35.9% vs 15.6%; odds ratio, 3.35; 95% confidence interval [CI], 2.16-5.21; $P < 0.001$). The quit rates were also approximately double from weeks 9-24 and from weeks 9-52, with the CAR at week 52 for the varenicline group at

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20.3% vs 10.4% for placebo. There were no clinically relevant differences between groups in suicidal ideation or behavior, or overall worsening depression or anxiety. About 27% of the treatment group experienced nausea as the most frequent adverse event. The authors conclude that varenicline increased smoking cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety (*Ann Intern Med* 2013;159:390-400). ■

Polypills for cardiovascular disease

Is a "polypill" the answer to adherence in patients with cardiovascular disease (CVD)? Long-term medication adherence is notoriously poor in these patients. Even in high-income countries, adherence rates are only 50% in patients with coronary disease and 35% in those with those a history of stroke. Polypills combine several cardiovascular medications in one, including aspirin, a statin, and one or more blood pressure medications. A recent study was designed to see if these fixed-dose combination (FDC) pills would improve compliance, LDL cholesterol, and blood pressure levels compared to usual care. Two polypills were evaluated in the study. The first pill contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg. The second pill substituted hydrochlorothiazide 12.5 mg for atenolol. About 1000 patients received one of the FDCs with about 1000 controls continuing on usual care. After an average follow-up of 15 months, adherence was higher with the FDC vs usual care (86% vs 65%, $P < 0.001$), but there were only modest reductions in systolic blood pressure with FDC of about 2.6 mmHg and also modest reductions in LDL cholesterol of 4.2 mg/dL vs usual care. Subgroups of patients who showed poor adherence at baseline had higher levels of improvement in blood pressure and LDL cholesterol. There was no significant difference in cardiovascular events (5% FDC vs 3.5% usual care; relative risk, 1.45; 95% CI, 0.94-2.24; $P = 0.09$). The authors conclude that among patients at high risk of CVD, use of a FDC "polypill" improved medication adherence with small improvements in systolic blood pressure and LDL cholesterol (*JAMA* 2013;310:918-929). ■

FDA actions

Treatment of chronic pain has changed dramatically in the last 3 years, shifting from concern about undertreating patients with chronic pain to concern about the safety of overuse of extended-release and long-acting opioid analgesics. With overdoses of prescription opioids skyrocketing and far outnumbering overdoses from illegal drugs, the FDA has decided to take action. The agency is requiring labeling changes and new postmarketing study requirements for these drugs, including oxycodone (Oxycontin), controlled-release and extended-release morphine (MS Contin and Avinza), and fentanyl patches (Duragesic). The labeling changes are being required to "combat the crisis of misuse, abuse, addiction, overdose, and death from these drugs that have harmed too many patients and devastated too many families and communities." The updated indications for the extended-release and long-acting opioids state that these drugs are indicated "for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate." The goal of the postmarketing studies is to further assess the known serious risks of these drugs, including misuse, abuse, hyperalgesia, addiction, overdose, and death.

The FDA is also requiring additional labeling changes to fentanyl patches due to 32 accidental pediatric exposures, including 12 deaths in the last 16 years. The labeling requirements include printing the drug's name and strength in the clearly visible, long-lasting ink on the patch, in a color that is clearly visible to the patient and caregivers. The FDA also recommends that for disposal the patch be folded in half, sticky sides together, and flushed down the toilet immediately. These labeling changes apply to both generic fentanyl patches and brand-name Duragesic patches.

The FDA has approved the first generic version of the anticancer drug capecitabine (Xeloda), an oral chemotherapy agent used to treat metastatic colorectal cancer and metastatic breast cancer. The new generic is manufactured by Teva Pharmaceuticals while the branded product is manufactured by Roche. Two years ago, Roche settled a patent infringement case against Mylan over the same drug. It is unclear whether Mylan will now also launch its own generic. ■

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