AHC Media

Vol. 31, Issue 9, September 2012
www.ahcmedia.com

Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Angiotensin-Converting Enzyme Inhibitor Use in Coronary Artery Bypass Graft Surgery

By Michael H. Crawford, MD, Editor

SOURCE: Drenger B, et al. Patterns of use of perioperative angiotensin-converting enzyme inhibitors in coronary artery bypass graft surgery with cardiopulmonary bypass effects on in-hospital morbidity and mortality. *Circulation* 2012;126:261-269.

Angiotensin-converting enzyme inhibitor (ACEI) therapy may be beneficial during coronary artery bypass graft (CABG) surgery because of its anti-inflammatory and other vascular benefits. However, ACEI therapy can cause vasoplegia and acute renal injury, so its use has been controversial. Accordingly, the International Multicenter study on Perioperative Ischemia Epidemiology II Research Group performed a prospective, longitudinal, observational study to characterize perioperative ACEI use in patients undergoing CABG and determine its relationship to in-hospital cardiovascular events. The primary outcome of the study was a composite of cardiac, cerebral and renal events, and mortality. Of the 5436 patients enrolled from 72 centers in 17 countries, 371 were excluded for procedural reasons and an additional 841 were excluded because they did not meet inclusion criteria (e.g., some had concomitant valve surgery). Of the 4223 remaining, 1838 were treated preoperatively with ACEI and 2386 were not treated, by physician discretion. After surgery, the patients segmented into four groups: 1) those continuing on ACEI, 2) those withdrawn from ACEI, 3) those in whom ACEI was added, and 4) those never on ACEI. Non-fatal events

Financial Disclosure: *Clinical Cardiology Alert's* Editor, Michael H. Crawford, MD, reports no financial relationships relevant to this field of study, and peer reviewer, Ethan Weiss, MD, is a scientific advisory board member for Bionovo. Managing Editor, Neill Kimball, and Executive Editor, Leslie Coplin, report no financial relationships relevant to this field of study.

Clinical Cardiology [ALERT]

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to *Clinical Cardiology Alert*, P.O. Box 105109, Atlanta, GA 30348.

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GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA, 30304 and at additional mailing offices.

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were significantly reduced in those continuing on ACEI therapy vs the never on ACEI group (odds ratio [OR], 0.69; 95% confidence interval [CI], 0.52-0.91; $P = 0.009$), as were cardiovascular events (OR, 0.64; CI, 0.46-0.88; $P = 0.006$). Similar results were seen in comparing those started on ACEI therapy postoperatively vs the never on ACEI group. Continuous ACEI vs withdrawal of ACEI decreased total events, cardiovascular events, and renal events ($P = 0.005$). Mortality and cerebral events were not different in the four groups. The authors concluded that no ACEI therapy or withdrawal of ACEI is associated with non-fatal cardiovascular and renal events.

■ COMMENTARY

It is a common practice to withdraw ACEI therapy prior to CABG and not restart it in the hospital. In this observational, multicenter study, withdrawal was done in 50% of cases. When the Kaplan-Meier event-free survival curves of the four groups were inspected, it was clear that the withdrawal group did the worst. Continuing ACEI therapy reduced adverse events by 50%, whereas withdrawing ACEIs increased renal events by 113%. The other three groups' results are more similar. Interestingly, if you compare the two larger groups of those on ACEI therapy preoperatively to those who were not, these two groups have significant differences in clinical characteristics. Those on ACEI therapy had higher incidences of heart failure, myocardial infarction, stroke, diabetes, and renal disease.

In this study, the continuing ACEI group did require more vasopressor support, which is consistent with earlier reports that led to the practice of withdrawing ACEIs before CABG. However, as discussed above, these were higher risk patients with more comorbidities, which can also explain the vasopressor needs. Despite the need for vasopressors, there was no difference in postoperative blood pressure, cardiac output, or time to extubation in the four groups.

Experimental studies have shown that cardiopulmonary bypass activates the renal angiotensin aldosterone system, which can have deleterious vascular effects beyond an increase in blood pressure. Thus, the authors believe that their observational study compels us to continue or start ACEI therapy pre- and post-operatively in CABG patients. However, observational studies have biases and confounders that cannot be fully adjusted and so are only hypothesis generating. If you look only at those on ACEI therapy, clearly the events increased when ACEIs were withdrawn. Thus, my take is that this is a poor practice and should be discouraged. However, until a randomized, controlled trial is done, I am not willing to push for the addition of ACEI therapy in patients with no indications for it. ■

ABSTRACT & COMMENTARY

Estimating Stroke and Bleeding Risk in Atrial Fibrillation

By Michael H. Crawford, MD, Editor

SOURCE: Friberg L, et al. Evaluation of risk stratification schemes for ischemic stroke and bleeding in 182,678 patients with atrial fibrillation: The Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;33:1500-1510.

Various risk schemes have been promulgated for assessing the risk of stroke and bleeding in patients with atrial fibrillation (AF). These investigators used the Swedish Atrial Fibrillation cohort study to investigate the comparative utility of four schemes that have been validated in AF cohorts: CHADS2, CHA2DS2-VASc, HAS-BLED, and HEMORR2HAGES. All 182,678 hospitalized patients with a diagnosis of AF in Sweden between 2005 and 2008 were included in this prospective registry. The median follow-up was 1.4 years. Excluded were 7167 patients who either died during the initial hospitalization or had valvular AF, leaving 170,291 who met study criteria. The National Swedish Drug Registry was used to ascertain who used oral anticoagulants (OA). The 90,490 patients (53%) who never received OA were used for most of the analyses in this report. The stroke risk clearly increased with age: > 75 years (HR 5.49) and 65-74 years (HR 3.07), and was more common in women (HR 1.21). Other significant risk factors on multivariate analysis included prior cerebral events, coronary revascularization, vascular disease, hypertension, and diabetes. The discriminant ability of the stroke risk schemes (c-statistic) was 0.66 for CHADS2 and 0.67 for CHA2DS2-VASc. However, the CHA2DS2-VASc is superior for identifying very low-risk patients: A CHADS2 score of 1 has a stroke/100 years at risk of 3.0 vs 0.6 for a CHA2DS2-VASc score of 1. Significant multivariate risk factors for major bleeding in patients not on OA included age, male sex, prior stroke, prior bleeding event, heart failure, hypertension, renal failure, liver disease, anemia, coagulopathy, alcohol abuse, and cancer < 3 years ago. The discriminant ability of HAS-BLED and HEMORR2HAGES for major bleeding in patients not on OA or aspirin were 0.61 vs 0.69, with similar risks at scores between 0 and 5. When scores are greater than 5 the risk data varies, but all would be considered at high risk. The authors concluded that CHA2DS2-VASc performs better than CHADS2, especially in low-risk patients. While the two bleeding risk schema perform similarly, HAS-BLED has the advantage of simplicity.

■ COMMENTARY

Europe is leading the world in large registry studies, which is one advantage of single-payer systems. This one sheds light on some important practical issues with anticoagulation for AF. First, CHA2DS2-VASc does a better job at defining the low-risk population. A CHADS2 score of 0 is associated with a stroke risk of < 1% in AF patients not on anticoagulants or aspirin, but a score of 1 equals a 3% risk. With CHA2DS2-VASc, the stroke risk associated with each score is: 0 = < 1%, 1 = < 1%, 2 = 2%, and 3 = 3%. Second, the HAS-BLED score performs almost as well as HEMORR2HAGES, but is much simpler. With both schemas, the risk of major bleeding rises progressively with the score. At a score of 5, the two schemas give a bleeding risk on OA of 5.7 and 6.0 bleeds per year. Third, controversial risk predictors were clarified. Heart failure is in both stroke risk scores and was not a multivariate predictor of stroke, but did predict major bleeding (HR 1.15) even though it is not in HAS-BLED. Thyroid disease was not predictive of stroke or bleeding and is not in these schemas. Renal disease patients, who are not usually included in clinical trials, were predictive of bleeding and included in HAS-BLED.

One thing to consider is that this study is based on an administrative database — although a fairly robust one — and has all the limitations and biases expected. In addition, this hospital-based population included patients who probably are older and have more comorbidities than patients cared for solely as outpatients. Since no INR data were available, this variable in the bleeding schemas (labile INR) was omitted. Also, the stroke risk in those not on OA or aspirin must suffer from selection bias since these patients are likely to be lower-risk patients. So, the risk may be higher in a less selected group. Despite these significant limitations, it is unlikely that a randomized, controlled trial of these risk prediction schema will ever be done. Consequently, this large, well-done registry may be the best data we have for a long time. ■

ABSTRACT & COMMENTARY

Anticoagulant Strategy for Device Implantation

By John P. DiMarco, MD, PhD
Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

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

SOURCE: Bernard ML, et al. Meta-analysis of bleeding complications associated with cardiac rhythm device implantation. *Circ Arrhythm Electrophysiol* 2012;5:468-474.

In this paper, the authors perform a systematic review and meta-analysis of published reports comparing anticoagulation management strategies around the time of cardiac rhythm device implantation. Using standard techniques, the authors searched the medical literature and identified studies that assessed two or more anticoagulation strategies around the time of cardiac rhythm device implantation. Most of the reports identified were observational studies, not randomized, clinical trials. The potential strategies were as follows: group 1 — no therapy; group 2 — oral anticoagulation held (INR < 1.5); group 3 — oral anticoagulation continued (INR > 1.5); group 4 — single antiplatelet therapy; group 5 — dual antiplatelet therapy; and group 6 — heparin bridging strategy using either unfractionated or low molecular-weight heparin. Studies included in the meta-analysis had to have a report of bleeding complications using standard criteria and a description of follow-up. Major bleeding, in general, was defined as bleeding to transfusion, surgical intervention for pocket evacuation or revision, pericardial effusion, hemothorax, or other life-threatening bleed. All other bleeding was considered minor. Thromboembolic events were classified as transient ischemic attacks, cerebrovascular accidents, or any other systemic embolic events. Several statistical techniques were used to assess bias and heterogeneity.

The meta-analysis eventually included 13 studies involving 5978 patients. The lowest rate of bleeding was seen in patients receiving no anticoagulation or antiplatelet therapy. The highest rate of bleeding was noted with heparin bridging strategies. The estimated rate of bleeding complications for patients on no therapy was 1%. The estimated odds ratios for the strategies were 8.3 in the heparin bridging strategy group, 5.0 for dual antiplatelet therapy, 1.7 for oral anticoagulation held, 1.6 for oral anticoagulation continued, and 1.5 for single antiplatelet therapy. The risk for bleeding was significantly increased for both the dual antiplatelet therapy and the heparin bridging strategy groups. The heparin bridging strategy was associated with a 5.3-fold increase in increased bleeding compared to a strategy in which oral anticoagulation was continued. Minor bleeding events were more common than major bleeding events, but the relative distributions among the anticoagulation strategy groups were similar. Only seven studies reported thromboembolic events with a low cumulative event rate of nine of 2375 patients (0.4%). Rates of thromboembolic events were 0.5%, 0.2%, and 0.5% in the oral anticoagulation held, oral anticoagulation continued, and heparin bridging strategy groups, respectively.

The authors conclude that a strategy of continued conservative oral anticoagulation is superior to any heparin bridging strategy with regard to bleeding complications. This applies to all patients undergoing these procedures. Dual antiplatelet therapy also carries a higher risk of bleeding.

■ COMMENTARY

Cardiologists and surgeons who implant pacemakers and ICDs must often deal with anticoagulation issues around the time of device insertion. In the past, a strategy that involved discontinuation of warfarin for several days and bridging with unfractionated or low molecular-weight heparin was recommended for high-risk patients, e.g., mechanical heart valves, recent thromboembolic events, and atrial fibrillation with CHADS2 scores of > 3. Physicians are also reluctant to hold dual antiplatelet therapy in patients with recent coronary stents. This meta-analysis shows that both a heparin bridging strategy and, to a lesser degree, dual antiplatelet therapy markedly increase bleeding risks and heparin bridging does little to increase safety.

Device-related bleeding is a nightmare for implanters. Early after implantation, the generator in the pocket prevents any effective use of pressure to stop bleeding, unless the bleeding is coming from the superficial suture line. Closed drainage of a pocket hematoma runs the risk of infection. Spontaneous resolution of a large hematoma may take weeks during which anticoagulation cannot be maintained at optimal levels. If a heparin bridging strategy is used, the problem occurs after the procedure when heparin is restarted. I have seen major bleeds as late as 7 days after implant in patients who were given heparin as warfarin was restarted.

The most important observation here is that device implants can be performed with low therapeutic INR values. This is the strategy adopted in my laboratory and we have found it be both safe and effective. We typically hold warfarin for only 0-48 hours so that the INR is near the low end of the therapeutic range and we have not had a problem with bleeding.

This meta-analysis doesn't address how to manage patients on both dual antiplatelet therapy and an oral anticoagulant and patients receiving dabigatran or rivaroxaban. Further careful reports on experience with such patients would certainly be helpful. ■

ABSTRACT & COMMENTARY

Radial vs Femoral Access in STEMI

By Andrew J. Boyle, MBBS, PhD

Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

SOURCE: Romagnoli E, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome. The RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol* 2012; Jul 27. [Epub ahead of print.]

Primary percutaneous coronary intervention (PCI) saves lives in patients suffering from ST-elevation myocardial infarction (STEMI). However, these patients are at high-risk for bleeding complications due to the invasive nature of the procedure in combination with the use of antithrombins and antiplatelet agents. Radial artery access is associated with lower bleeding rates compared to femoral artery access for PCI. However, adoption of radial access has been slow in the United States, with a small minority of cases performed via this route. The recent RIVAL trial showed that radial access results in lower vascular access complications and bleeding rates than femoral access in patients with acute coronary syndromes. Subgroup analysis suggested that there was a mortality benefit in the group of patients presenting with STEMI. In this study, Romagnoli and colleagues perform a multicenter, randomized study comparing radial vs femoral access as the initial strategy in patients presenting with STEMI.

Over a period of 2 and a half years, 1001 patients with STEMI undergoing primary PCI were randomized to radial (n = 500) or femoral (n = 501) access. The study was performed in four high-volume centers and all operators performed at least 150 PCIs per year, with at least 50% performed via the radial artery. Exclusion criteria included contraindication to either radial or femoral access, stroke within the preceding 4 weeks, anticoagulant therapy with a presumed international normalized ratio > 2, or other severe bleeding diathesis. Importantly, cardiogenic shock and/or hemodynamic instability were not exclusion criteria. The primary endpoint of the study was the 30-day incidence of net adverse clinical events (NACE), defined as the composite of cardiac death, myocardial infarction (MI), stroke, target lesion revascularization, and non-coronary artery bypass graft (CABG)-related major bleeding. Secondary endpoints were 30-day individual components of NACE and length of stay.

Procedural anticoagulation was achieved with unfractionated heparin and the choice of additional antithrombotic agents (e.g., glycoprotein IIb/IIIa inhibitors or bivalirudin). Unless clinically indicated for another reason, all anticoagulants were discontinued at the end of the procedure, whereas glycoprotein IIb/IIIa inhibitor boluses were followed by a ≥ 12-hour

infusion. All patients were pretreated with aspirin plus a loading dose of clopidogrel (300 to 600 mg) and were discharged on dual antiplatelet therapy for 12 months. More than 75% of all STEMIs presenting to the participating centers during the enrollment period were enrolled in the study, around 10% were in Killip class III/IV, and 8% required intra-aortic balloon counterpulsation during the procedure.

The baseline characteristics were similar between groups. There was no difference in symptom-to-balloon or door-to-balloon times between groups. The primary endpoint of 30-day NACE was lower in the radial arm compared with the femoral arm (13.6% vs 21.0%; *P* = 0.003). Analysis of individual NACE components showed fewer cardiac deaths in the radial group compared with the femoral group (5.2% vs 9.2%; *P* = 0.020), but similar rates of MI (1.2% vs 1.4%; *P* = 1.000), target lesion revascularization (1.2% vs 1.8%; *P* = 0.604), and stroke (0.8% vs 0.6%; *P* = 0.725). Bleeding was less frequent in the radial group (7.8% vs 12.2%; *P* = 0.026), mainly due to a 60% decrease in access site-related bleeding (2.6% vs 6.8%; *P* = 0.002). Indeed, non-access site-related bleeding (53% of total bleeding events) was similar (5.2% vs 5.4%; *P* = 1.0). Hospital stay was shorter in the radial group than in the femoral group (5 [range, 4 to 7] days vs 6 [range, 5 to 8] days, *P* = 0.008).

Multivariate analysis confirmed the radial approach as an independent negative predictor of 30-day NACE (hazard ratio [HR] 0.7; *P* = 0.028). The overall rate of access site crossover was 9.6% (n = 47) in the radial arm and 2.8% (n = 14) in the femoral arm. Cardiogenic shock at presentation (HR 3.4; *P* = 0.01), unknown peripheral vascular disease (HR 2.6; *P* = 0.02), and previous thrombolytic administration (HR 2.2; *P* = 0.041) were the main determinants of vascular access crossover.

The authors conclude that radial access in patients with STEMI is associated with lower morbidity and cardiac mortality. Thus, it should become the recommended approach in these patients, provided adequate operator and center expertise is present.

■ COMMENTARY

In clinical trials involving PCI, bleeding is universally associated with worse long-term outcomes, not just in-hospital outcomes, often including higher mortality rates. The precise mechanism of this remains obscure. The converse is also true — bleeding avoidance strategies are usually associated with improved outcomes, and the choice of radial over femoral access is just that, a bleeding avoidance strategy. This approach has been shown to result in fewer access site complications and lower bleeding rates in prior clinical trials. The current study takes the highest risk PCI population — those with STEMI — and demonstrates that radial access is associated with lower bleeding rates and lower cardiac mortality.

This is a large study performed in four high-volume centers, and the clinical trial design was robust. These factors strengthen the conclusions drawn from the paper. There are some important limitations to the manuscript. We are never told what methods of closure were used for the femoral arteries, and this may have an impact on bleeding. In addition, there was a low rate of bivalirudin use (~ 8%). This may have contributed to the high rate of bleeding in the femoral arm.

There appeared to be equipoise between radial and femoral access in patients presenting with ACS in the RIVAL trial, yet there is a mortality benefit with radial access for patients with STEMI in this trial. This raises a conundrum: Should operators use radial access in the STEMI patients, the sickest patients in whom they are rushing to reach door-to-balloon times? Should they continue to use femoral access in other cases? The answer is not immediately clear. This study was performed by high-volume, experienced radial operators and the results may not be applicable to occasional radial operators. Less experienced operators may take longer to perform the PCI radially and this may offset the clinical benefit of reduced bleeding. In the era of widespread closure devices and more specific antithrombins, such as bivalirudin, is radial access still superior? This is not known. However, radial access is associated with lower costs and increased patient satisfaction. There may also be a clinical benefit to using radial access as the preferred strategy in STEMI. ■

ABSTRACT & COMMENTARY

A Better Technique for Ablation of Persistent Atrial Fibrillation?

By John P. DiMarco, MD, PhD

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

SOURCE: Narayan SM, et al. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol* 2012;60:628-636.

This paper discusses the clinical utility of impulse and rotor mapping to guide atrial fibrillation (AF) ablation and is a follow-up to the acute observations discussed in *Clinical Cardiology Alert* several months ago.[1] The authors hypothesized that AF is sustained by localized sources that may be targeted during AF ablation procedures. They then developed a computational mapping approach that allows real-time detection of localized sources of AF during ablation procedures that could then be targeted during the procedure. Focal impulse and rotor modulation (FIRM) mapping was performed using 64-pole basket catheters placed in the left and right atria. Mapping was performed during stable, spontaneous, or induced AF using a proprietary computational methodology. This technique allows identification of both electrical rotors, defined by sequential clockwise or counterclockwise isochronal contours around a center of rotation and focal impulse sources, defined by centrifugal activation patterns from a single point of origin. Rotors and focal impulses were considered AF sources if they showed consistent patterns in recordings over at least 10 minutes. Mapping results were not used to guide ablation (FIRM-blinded group) in 71 patients and were used (FIRM-guided group) in 36 patients. In FIRM-guided patients, the catheter was maneuvered to the basket electrodes overlying each identified source and radiofrequency bursts were applied for 15 to 30 seconds within that region. The endpoint was either termination or slowing of AF. FIRM-guided ablation was permitted at up to three sources for up to 10 minutes at each source. A conventional ablation set of lesions was performed after FIRM-guided ablation in the FIRM-guided group and as the sole therapy in the FIRM-blinded group. Wide areas, circumferential pulmonary vein isolation with the possible addition of left atrial roof lines, or flutter lines were employed. After follow-up, monitoring was performed at regular intervals. Implanted AF monitors or cardiac rhythm devices with atrial electrogram storage were used in the majority of FIRM-guided patients and in a smaller proportion of the FIRM-blinded group. The prespecified primary long-term efficacy endpoint was defined as an AF burden less than 1% using a continuously implanted monitor or freedom from AF of longer than 30 seconds during intermittent monitoring. Freedom from any AF was a secondary endpoint.

Persistent AF was present in 81% of the FIRM-guided group and in 66% of the FIRM-blinded group. Electrical rotors and focal impulses were present in 98 of 101 patients with sustained AF during their procedure. The mean number of rotors or focal impulse sources was 2.1 ± 1 with 70% rotors and 30% focal sources. These sources were observed virtually any place in the left or right atrium. Right atrial sites were identified in 24% of patients. Sources were more numerous in patients with persistent AF than paroxysmal AF. FIRM-guided ablation alone achieved the acute endpoint of AF termination or AF slowing in 31 of 36 (86%) patients. In four patients, FIRM-guided ablation could not be completed since an identified source was adjacent to either the phrenic nerve, atrial pacing lead, compact AV node, or esophagus. Total FIRM-guided ablation time for targeted sources was 16.1 ± 9.8 minutes. In contrast, among the 71 FIRM-blinded patients, the acute endpoint was achieved in only 13 of 65 patients with sustained AF after 43.4 ± 28 minutes of ablation. Total ablation times were similar in the two groups. During follow-up, single procedure freedom from AF was 82.4% for FIRM-guided cases compared to 44.9% for FIRM-blinded cases over a median duration of 273 days. For the endpoint of freedom from any atrial tachyarrhythmia after a single procedure, the results were 70.6% in the FIRM-guided group compared to 39.1% in the FIRM-blinded group.

■ COMMENTARY

The results of AF ablation procedures in patients with persistent AF have been disappointing. The

procedures themselves are complicated and tedious with uncertain acute endpoints. Multiple procedures are often required and late recurrences are common. Although pulmonary vein isolation alone may be adequate in patients with paroxysmal AF and no or limited heart disease, the long-term success rate of this in patients with persistent AF is limited. Many investigators have felt that an approach that targets both potential triggers, often in the pulmonary veins, and the areas that allow AF to continue is necessary to improve outcomes.

The details of the computational mapping system are still proprietary and the system hasn't been evaluated yet in a large number of labs. However, the results presented here look very promising and this technique might represent the conceptual breakthrough needed to advance the field. ■

Reference

1. DiMarco JP. New insights into atrial fibrillation ablation. *Clin Cardiol Alert* 2012;31:53-54.

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CME Questions

1. The best schema for identifying very low-risk atrial fibrillation patients for stroke is:
   a. CHADS2.
   b. CHA2DS2-VASc.
   c. HAS-BLED.
   d. HEMORR2HAGES.

2. Continuation of preoperative ACE inhibitors with CABG is associated with a reduction in:
   a. stroke.
   b. mortality.
   c. renal dysfunction.
   d. wound healing.

3. Radial vs femoral access in STEMI results in reduced:
   a. net adverse clinical events.
   b. cardiac deaths.
   c. major bleeding.
   d. All of the above

4. Which procedure improved ablation results in persistent atrial fibrillation patients?
   a. Left atrial roof lines
   b. Circumferential pulmonary vein isolation
   c. Focal impulse and rotor modulation
   d. Flutter lines

5. The best anticoagulant strategy for device implantation in patients requiring anticoagulation is:
   a. continuation of anticoagulants, INR > 1.5.
   b. anticoagulants held, INR < 1.5.
   c. substitute dual antiplatelet therapy.
   d. heparin bridging.

CME Objectives

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

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

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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.*

Volume 17, Number 9 Pages 17-18 September 2012

Risk for Zoster from the Vaccine in Immunosuppressed Persons

Source: Zhang J, et al. *JAMA* 2012;308: 43-49.

The prevailing wisdom suggests that because herpes zoster vaccine (ZOS) is a live virus, it should not be administered to persons receiving immunosuppressive treatments, such as biologic agents or methotrexate for rheumatoid arthritis, or chronic prednisone therapy of 20 mg/d or more. The concern is that instead of mounting an immune response to the vaccine, vaccinees might actually experience a case of shingles as a result of the vaccine.

To examine the real-life risk of an acute zoster infection after ZOS, a retrospective analysis was performed on a large Medicare database (n = 463,541) of persons with a diagnosis of rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease. Any one of these disorders would be commonly treated with immunosuppressive agents, corticosteroids, or both.

The analysis looked at the number of cases of shingles within 42 days of ZOS, anticipating that if the live virus vaccine had induced shingles, it should certainly have happened within that 6-week window after vaccination.

No increased incidence of shingles was seen in ZOS recipients, even in patients on biologics. Indeed, ZOS was associated with a 39% lower risk of shingles during the 42-day window of observation, and a reduced risk during the subsequent 2 years (median) of follow-up. ZOS appears to be beneficial even in immunocompromised individuals, and the authors challenge the propriety of current recommendations that advise against ZOS administration in such populations. ■

Cerebral Aneurysms: What's in Your Patient's Future?

Source: UCAS Japan Investigators. *N Engl J Med* 2012;366:2474-2482.

The UCAS (unruptured cerebral aneurysm) Japan study began enrolling patients with incidentally discovered cerebral aneurysms (CRAs) for an observational study in 2001. The primary purpose of the study was to better delineate the natural history of incidentally discovered CRAs (as opposed to discovery through neurologic signs or symptoms). Prior to this trial, it had been generally recognized that CRAs < 7 mm rarely rupture, and that posterior circulation CRAs have a greater risk than anterior.

This prospective cohort study included patients (n = 6413) with incidentally discovered CRA and minimal, if any, disability. Subjects were followed for up to 8 years. During this interval, the annual rate of CRA rupture was approximately 1%. When rupture did occur, it was fatal in 35% of cases, or led to moderate-severe disability in another 29%.

The most important predictive factors for rupture were size of the CRA, age, and gender (females are at greater risk). For example, when compared with lesions < 7 mm, a 7-9 mm lesion had a three-fold increase of rupture, and a lesion > 10 mm had a nine-fold increased risk. Risk in women was 1½ times as great as men, and persons over age 70 were 21% more likely to experience aneurysm rupture. Because the entire population of enrollees was Japanese, the generalizability of these results may have limitations, but nonetheless provide perhaps the most accurate mapping of risk factors for rupture of CRAs. ■

Elucidating the 'Best' Interval for Bone Density Screening in Osteoporosis

Source: Yu EW, Finkelstein JS. *JAMA* 2012;307:2591-2592.

Once a baseline bone mineral density (BMD) has been obtained, it is unclear when the study should be repeated. For one thing, the literature suggests that only about 30% of bone strength may be attributable to bone density. Additionally, some of the interventional trials using bisphosphonates have found fracture reduction despite continuation of bone density *loss* over the first year or two of intervention. Finally, the rate at which BMD declines has been linked to the baseline BMD.

For instance, a study that looked at menopausal women (age > 67 years) for progression of BMD loss found some fairly startling results: It would take approximately 15 years for 10% of women with normal baseline BMD (T score < -1.5) to incur sufficient loss of BMD to cross the diagnostic threshold for osteoporosis (T score < -2.5). Similarly, for women with osteopenia (T score -1.5 to -2.0) at baseline, it would require 5 years for 10% of

them to progress to frank osteoporosis. At the greatest level of osteopenia (T score -2.0 to -2.5), progression to osteoporosis in 10% of women would be expected to occur within 1 year. These projections assume no addition of new risk factors known to accelerate bone loss.

Although it is tempting to get BMD more often, it may not be helpful. Although the data are sufficiently uncertain that the USPSTF has been unable to provide confirmation of a preferred schedule, Yu et al suggest following rescreening intervals for postmenopausal women: for women with normal BMD at baseline, 10 years; for women with mild osteopenia and low FRAX score at baseline, 5-10 years; for women with moderate osteopenia or FRAX score approaching treatment threshold, 2 years. ■

An Unexpected Connection Between PTSD, ACE Inhibitors, and ARBs

Source: Khoury NM, et al. *J Clin Psychiatry* 2012;73:849-855.

Several lines of evidence suggest that modulation of the renin-angiotensin-aldosterone system with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) might potentially have positive effects on post-traumatic stress disorder (PTSD). Preclinical data indicate favorable cerebral effects of ARBs, such as stress reduction and anxiolysis. Some ARB trials have reported positive effects on cognition, quality of life, and depression or anxiety.

Khoury et al performed a cross-sectional observational data analysis of PTSD patients (n = 505) comparing symptoms in those who were being treated with an ARB/ACE vs controls (no ARB/ACE treatment). Overall, PTSD symptom scores were almost 25% lower among patients treated with ACE or ARB therapy ($P = 0.04$).

The better symptom scores among PTSD patients treated with ARB or ACE therapy were not simply due to the fact that hypertension (which is more common in PTSD patients) was treated; no other antihypertensive medications (e.g., calcium channel blockers, diuretics, beta-blockers) were found to have similar favorable effects.

The mechanism through which ACE/ARB treatments impact PTSD is not well established, but may be through modulation of the noradrenergic system. ■

The Right Amount of Vitamin D to Prevent Fractures

Source: Bischoff-Ferrari HA, et al. *N Engl J Med* 2012;367:40-49.

Inclusion of vitamin D (VTD) in the regimen for fracture prevention is time honored and condoned by major guidelines. Intuitively, VTD should be helpful, but the analyses of data in reference to this topic are mixed. For instance, although one meta-analysis indicated an 18% reduction in hip fracture if a minimum of 482 IU/d VTD was prescribed, equally prominent data concluded that VTD alone was of *no benefit*. So, how about further investigation of the subject?

Bischoff-Ferrari et al performed an analysis on 11 double-blind, randomized, controlled trials of oral VTD supplementation (n = 31,022) seeking to determine if supplementation (with or without calcium) reduced hip fracture. According to their analysis, there was no statistically significant reduction in fracture risk in subjects assigned to VTD. Story over? Well, maybe not quite.

First, although hip fracture was not reduced, there was a marginally statistically significant 7% reduction of total non-vertebral fractures. Additionally, when analyzed from the viewpoint of the *actual intake* of VTD instead of what subjects were assigned to, the picture looks quite different. Specifically, subjects in the highest quartile of actual VTD intake (prescribed supplementation plus dietary intake) enjoyed a statistically significant 30% reduction in hip fracture. For the time being, at least 800 IU/d VTD supplementation is recommended in persons ≥ age 65. ■

Prevention of Diabetes

Source: Perreault L, et al. *Lancet* 2012; 379:2243-2251.

It appears that one's ounce of prevention may have to be weighed more carefully to attain the fullest pound of cure. Why? The answer lies in subgroup analysis of recent trials in diabetes prevention.

There have been many diabetes prevention trials, essentially all of which have been successful to a varying degree. Overall, diet and exercise appear to be as efficacious as any other intervention. Pharmacologically, numerous classes of agents have been successfully tried (metformin, thiazolidinedione, alpha-glucosidase inhibitor, etc.). What has been learned is that successful incorporation of diet/exercise or pharmacotherapy over a 4- to 6-year period reduces the likelihood of progressing from prediabetes to diabetes (typically, 6-10%/year) by half or more. But there is more to the story.

After successful treatment (pharmacotherapy or lifestyle), the majority of those who are prevented from progressing to frank diabetes still fulfill criteria for prediabetes (A1c 5.7-6.4). Between 20-50% of treated subjects are restored to currently recognized normal glucose levels.

The analysis by Perrault et al indicates that persons with prediabetes in whom normal glucose homeostasis was restored are half as likely to progress to frank diabetes over a 3-year, post-trial observation period as individuals whose glucose control was improved, but still reflected prediabetes. Striving for the best glucose control in prediabetes may have long-term benefits. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
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Does Finasteride Cause Permanent Sexual Side Effects?

In this issue: Side effects of finasteride; new ruling on pharmaceutical companies paying generic manufacturers; and FDA actions.

Sexual side effects of finasteride

Finasteride — the popular drug used to treat male pattern baldness and symptomatic benign prostatic hypertrophy — may cause long-term sexual dysfunction, according to a new study. Several recent studies have shown that the drug, which is marketed as 1 mg (Propecia) and 5 mg (Proscar), can cause sexual side effects that persist after stopping the drug in as many as 20% of men. In April, the FDA required new labeling for both strengths regarding libido, ejaculation, orgasm disorders, and even infertility that may persist after treatment ends. The new study looked at 54 men, with an average age of 31, who reported ≥ 3 months of sexual side effects after taking the 1 mg strength for male pattern baldness. All men were previously healthy without previous history of sexual dysfunction, medical conditions, psychiatric conditions, or prescription medication use. After 9-16 months of follow-up, 96% of subjects reported persistent sexual side effects (based on the Arizona Sexual Experience Scale). The duration of finasteride use did not correlate with changes in sexual dysfunction scores. The authors urge prescribers of finasteride to warn men of potential adverse effects (*J Sex Med* published online July 12, 2012). ■

Pharmaceutical company ruling

Is it legal for pharmaceutical companies to pay generic manufacturers to keep their products off the market? Until now it has been. Brand-name manufacturers have written enormous checks to keep their low-cost generic competitors off the market. That may change, however, after a federal appeals court in Philadelphia ruled that the practice is anticompetitive, a decision that is counter to three previous federal circuit courts rulings. *The New York Times* cites the example of Bayer Pharmaceuticals which paid generic drug maker Barr Laboratories and other generic houses $400 million to withhold their generic version of ciprofloxacin, their $1 billion a year blockbuster antibiotic. The case could eventually end up at the Supreme Court. At stake is billions of dollars in lost profits for pharmaceutical manufacturers, but an equal amount of savings for Medicare/Medicaid, health plans, and consumers. ■

FDA actions

The FDA has approved the second new weight-loss medication within a month. The new product combines phentermine along with topiramate in an extended-release product. Phentermine has been marketed since 1959 and was part of the infamous "fen-phen" combination that was popular in the 1990s (fenfluramine was eventually banned due to cardiac valvulopathy in 1997). Topiramate is currently marketed as an anticonvulsant and for migraine prophylaxis as Topamax. The combination was rejected by the

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FDA in 2010 due to safety concerns, but Vivus Pharmaceuticals submitted additional data to the agency and recently won approval in July. In the process, the company changed the brand name from Qnexa to Qsymia. Similar to the recently approved lorcaserin (Belviq), phentermine/topiramate is approved as an addition to a reduced-calorie diet and exercise for weight management in adults with a BMI of 30 or greater, or with a BMI of 27 or greater with at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. In two placebo-controlled trials, 3700 obese and overweight patients lost an average of 6.7-8.9% of their body weight, depending on the recommended or higher dose therapy (slightly better results than those seen with lorcaserin). Patients who have not lost at least 3% of their body weight by week 12 should discontinue the drug. Because of continued safety concerns, the drug was approved with a Risk Evaluation and Mitigation Strategy (REMS), which consists of a medication guide, prescriber training, and pharmacy certification. The drug cannot be used during pregnancy or in patients with recent stroke or heart disease, and patients should have their heart rates monitored during therapy. Vivus will market Qsymia immediately, but will be required to conduct 10 postmarketing studies to assess safety.

The FDA has approved aclidinium bromide, a dry powder inhaler for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Aclidinium is a long-acting antimuscarinic agent that works primarily on the M3 receptor causing sustained bronchodilation. The approval was based on three studies of nearly 1300 patients with COPD. The drug may cause anticholinergic side effects, including worsening narrowing-angle glaucoma and urinary retention. It should not be used as a rescue inhaler and is not recommended for those 18 years of age or younger. It is dosed twice a day. Aclidinium inhaler is the second anticholinergic inhaler to be approved after tiotropium (Spiriva), which was approved in 2004. Aclidinium will be distributed by Forest Laboratories and will be marketed as Tudorza Pressair.

The FDA has approved mirabegron to treat adults with overactive bladder. The drug is a novel, once-daily beta-3 adrenergic agonist that works by enhancing storage function and relaxing the urinary bladder, a unique effect and distinct from currently marketed antimuscarinics that inhibit bladder contraction. The once-a-day medication will be available in 25 mg pills. The dose can be increased to 50 mg after 2 months if needed. The approval was based on three placebo-controlled trials that showed statistically significant improvement in incontinence episodes and number of urinations per 24 hours. The most common adverse effects were hypertension, nasopharyngitis, urinary tract infection, and headache. Mirabegron will be marketed by Astellas Pharma as Myrbetriq.

The FDA has approved a new colon cleansing agent for colonoscopy prep. The new prep is sodium picosulfate, magnesium oxide, and citric acid in powder form that is dissolved in water and taken in two doses the night before and the morning of the procedure. It may also be taken the afternoon and the evening before the procedure (Day-Before regimen). The safety and efficacy of the new agent was studied in two studies of about 1200 patients undergoing colonoscopy in which standard PEG plus electrolytes was used as a comparator, and the new prep was found to be at least as effective as the standard prep. Ferring Pharmaceuticals will market the new two-dose prep as Prepopik.

The FDA has approved icosapent ethyl, a new fish oil preparation for the treatment of hypertriglyceridemia. It is approved as an adjunct to diet to treat patients with triglyceride levels greater than 500 mg/dL. The drug contains ultra purified ethyl EPA, an omega-3 fatty acid. The new product follows GlaxoSmithKline's Lovaza, another fish oil that is currently marketed for the same indication and generates more than $1 billion in annual sales. The new product is manufactured by Amarin Corporation and will be marketed as Vascepa. Fish oils are effective at lowering triglycerides but evidence is lacking that they are effective for secondary prevention of cardiovascular disease (*Arch Intern Med* 2012;172:686-694).

An FDA advisory committee has recommended an new indication for Genentech's ranibizumab (Lucentis) for the treatment of diabetic macular edema, an indication for which there is currently no approved therapy. The drug is approved to treat neovascular age-related macular degeneration and macular edema following retinal vein occlusion. Diabetic macular edema is commonly treated with laser therapy, a procedure that has the potential side effect of some vision loss. The FDA generally follows its advisory committee's recommendations and should make a final recommendation later this year. ■