AHC Media

Vol. 32, Issue 5, May 2013
www.ahcmedia.com

Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

In-Hospital Cardiac Arrest Outcomes

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

SOURCE: Chan PS, et al, for the American Heart Association Get with the Guidelines-Resuscitation investigators. Long-term outcomes in elderly survivors of in-hospital cardiac arrest. *N Engl J Med* 2013;368:1019-1026.

The Get with the Guidelines-Resuscitation registry is a large, prospective registry of in-hospital cardiac arrests that analyzes data to promote quality improvement. In this paper, Chan and colleagues report the long-term outcomes in Medicare-age patients who suffered an in-hospital cardiac arrest and survived to discharge. The study cohort was drawn from 523 acute care hospitals that submitted data to the Get with the Guidelines-Resuscitation registry between 2000 and 2008. Data were collected on 10,316 Medicare age eligible patients. Of these, approximately 70% could be linked to Medicare claims data for the survival analysis. For patients with cardiac arrests during multiple hospitalizations, only the first event was included. The outcomes of interest were survival and freedom from readmission during the first year after discharge. Multivariable logistic-regression models were used to examine predictors of 1-year survival. The models included patient clinical characteristics, diagnoses, post-arrest neurological status, characteristics of the arrest, and clinical and administrative aspects of the arrest.

There were 6972 survivors of in-hospital cardiac arrests in the cohort. Ventricular fibrillation and pulseless electrical activity were the most common cardiac arrest rhythms. Heart failure, myocardial infarction, and renal infarction were present in 25% of patients. At hospital discharge, 48% of the patients had mild or no neurologic disability with 34% having moderate and 17% either had severe neurologic disability or were in a vegetative state. At discharge, 55% of the

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.

[INSIDE]

Liver function in heart failure
page 34

Antiplatelet therapy after PCI — different durations for different stents?
page 35

Value of biomarkers in preoperative risk stratification
page 36

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.

SUBSCRIBER INFORMATION
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Subscription Prices
United States
1 year with free AMA Category 1 credits: $349
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Canada Add GST and $30 shipping.
Elsewhere Add $30 shipping.

Back Issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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

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patients were transferred to an inpatient skilled nursing or rehabilitation facility, 40% were discharged home, and 5% went to a hospice. Life table analysis showed that the overall rate of survival was 82% at 30 days, 72% at 3 months, 59% at 1 year, and 50% at 2 years. Survival probability decreased with increasing age. Other factors associated with survival were white race, female gender, ventricular fibrillation as the presenting rhythm, and milder post-arrest neurologic disability. Hospital readmission was also common. Sixty-five percent of the patients were readmitted within 1 year after discharge and 76% had been readmitted by 2 years.

The authors conclude that the Get with the Guidelines-Resuscitation Registry provides important data about the outcomes of in-hospital cardiac arrest. If patients survive to discharge, a significant proportion will survive long-term, but repeat hospitalizations will be common.

■ COMMENTARY

It has been estimated that in-hospital cardiac arrest occurs with a frequency of about 6.6 per 1000 hospitalized adult patients, with about 50% in intensive care units and 50% in other settings. Since patients with in-hospital cardiac arrest are often already seriously ill, survival to hospital discharge is low, with most studies showing rates of less than 20-25%. However, as shown here, if patients do make it to discharge without severe neurologic damage, long-term survival is possible. This makes improvements in hospital programs to prevent and treat in-hospital cardiac arrest critically important.

The American Heart Association has recently published a position paper on strategies to improve survival after in-hospital cardiac arrest.[1] This comprehensive document should be required reading for all cardiologists who provide in-hospital care. ■

REFERENCE

1. Morrison LJ, et al. Strategies for improving survival after in-hospital cardiac arrest in the United States: 2013 consensus recommendations: A consensus statement from the American Heart Association. *Circulation* 2013; 127:1538-1563.

ABSTRACT & COMMENTARY

Liver Function in Heart Failure

By Michael H. Crawford, MD, Editor

SOURCE: Nikolaou M, et al. Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure. *Eur Heart J* 2013;34:742-749.

The incidence and predictive value of abnormal liver function tests (LFTs) in patients with acute decompensated heart failure is poorly understood. Thus, these investigators from the SURVIVE study report their experience in patients with acute decompensated heart failure due to systolic dysfunction treated with positive inotropic infusions. The SURVIVE trial compared levosimendan to dobutamine in hospitalized acute heart failure patients with left ventricular ejection fractions of < 30%. Cardiogenic shock, severe liver failure, chronic liver disease, and treatment with hepatotoxic drugs were exclusion criteria. SURVIVE showed no difference in all-cause mortality between the two groups, even though the levosimendan group exhibited greater decreases in BNP. In the 1134 with LFT measurements, > 25% had one or more abnormalities at baseline and most were modest elevations (1-2 times ULN). During therapy, the LFTs trended downward over 30 days. Multivariate predictors of abnormal alkaline phosphatase (AP) were ascites (hazard ratio [HR] = 1.8) and edema (1.7), whereas predictors of abnormal transaminase levels were acute myocardial infarction (HR = 3.1) and less worsening of heart failure after admission (0.4). Thirty-day mortality was significantly higher in those with elevated transaminases vs those with normal transaminases (18 vs 8%, $P <$ 0.001). Mortality at 180 days was higher

if AP or transaminases were elevated (34 and 32%) vs those with normal values (24 and 22%). The authors concluded that elevated transaminases are associated with signs of hypoperfusion and elevated AP are associated with signs of systemic congestion and elevated filling pressures. Also, elevated transaminases are associated with short-term mortality.

■ COMMENTARY

This study is a retrospective subgroup analysis of a trial conducted for other purposes. Thus, it is subject to biases. Also, interesting data are not available such as other measures of hepatic function (bilirubin, albumin, and prothrombin time). In addition, there was no invasive hemodynamics or hepatic imaging done. Regardless, several interesting points were made. The authors make a clear case for measuring hepatic function parameters in all acute decompensated heart failure patients. The pattern of abnormalities may suggest the predominant hemodynamic abnormality (elevated AP with backward failure and elevated transaminases with forward failure). Also, elevated transaminases identify very high-risk patients for early mortality who need vigorous measures to increase organ perfusion. In addition, elevated liver function tests in general seem to identify higher-risk patients for 6-month mortality.

The potential mechanism of signs of cholestasis with congestion is interesting. Increased liver sinusoidal pressure probably collapses the bile ducts. Transaminase release is probably due to liver cell necrosis from ischemia due to reduced hepatic blood flow. My own clinical experience and reports from others suggest that prothrombin time is an early marker of liver injury in heart failure, and is probably due to poor perfusion that reduces liver protein production. Reduced biochemical production probably proceeds from cell necrosis. Unfortunately, prothrombin time was not measured in this study. There are obvious parallels between LFT abnormalities and renal dysfunction in heart failure, which also seems to be due to venous congestion and poor perfusion, and increases mortality. It may behoove us to pay more attention to cardiohepatic dysfunction as well. ■

ABSTRACT & COMMENTARY

Antiplatelet Therapy after PCI — Different Durations for Different Stents?

By Andrew J. Boyle, MBBS, PhD

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

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

SOURCE: Valgimigli M, et al. Should duration of dual antiplatelet therapy depend on the type and/or potency of implanted stent? A pre-specified analysis from the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY). *Eur Heart J* 2013;34:909-919.

There is considerable debate concerning the optimal duration of dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) with drug-eluting stents (DES). Clearly, there is benefit to DAPT early after PCI. The delayed vascular healing associated with DES is thought to contribute to late (and very late) stent thrombosis. The ACC/AHA guidelines recommend 12 months of DAPT for patients receiving DES, based on data from first-generation DES. The newer-generation DES that elute everolimus or zotarolimus have different potency in preventing neointimal proliferation and have lower rates of stent thrombosis than first-generation DES. European guidelines now allow for shorter duration of DAPT with some of the newer DES. Should the duration of DAPT be tailored to the individual stent type that has been implanted? To address this question, Valgimigli and colleagues present a subgroup analysis of data from the PRODIGY trial.

The PRODIGY trial had a randomized, 4 × 2 factorial design in which patients undergoing PCI were randomized to bare-metal stents (BMS) with thin struts, paclitaxel-eluting stents (PES), everolimus-eluting stents (EES), or zotarolimus-eluting stents (ZES). They were also randomized to 6 months or 24 months of DAPT with aspirin and clopidogrel. Patients were recruited if they were undergoing PCI for any indication (i.e., stable coronary artery disease, acute coronary syndromes [ACS], or ST elevation myocardial infarction [MI]). Exclusion criteria were allergy to aspirin or clopidogrel, planned surgery within 24 months of PCI (unless DAPT could be maintained throughout the perioperative period), bleeding diathesis, active bleeding, stroke in the prior 6 months, surgery within the prior 15 days, need for anticoagulation,

pregnancy, or limited life-expectancy. This was a prespecified subgroup analysis that analyzed events from 30 days to 24 months post-PCI. The primary endpoint was death, MI, or stroke.

Over a 2-year period at three centers in Italy, 1970 patients were enrolled and randomized to either 6 months or 24 months of DAPT and to one of the four stent types. The baseline characteristics were similar between groups. Mean number of stents implanted was 1.8 per patient, for a mean total stent length of 39 mm, and this did not differ across groups. Comparing 24 months of DAPT to 6 months of DAPT, the primary outcome did not differ in patients receiving BMS (hazard ratio [HR], 0.89; $P = 0.64$), PES (HR, 0.74; $P = 0.26$), or EES (HR, 0.63; $P = 0.17$), whereas it was significantly higher in ZES patients who received 24 months of DAPT [HR, 2.85; $P = 0.0018$]. The authors then performed a landmark analysis, studying the outcomes from 6 months to 24 months post-PCI, which is when the treatments really differed. There were fewer events in the patients receiving ZES with 6-month DAPT ($P = 0.002$), and there were fewer definite or probable stent thromboses in PES patients treated with 24-month DAPT ($P = 0.049$). The authors conclude that optimal duration of DAPT may be stent-specific and it does not support a clear association between stent potency and vulnerability to shorter DAPT therapy.

■ COMMENTARY

The PRODIGY study showed that 6 months and 24 months of DAPT resulted in similar event rates. Now, in this study, the authors further stratify these data by stent type. Interestingly, the primary outcome was similar between BMS and DES, regardless of DAPT duration, with the exception that patients receiving ZES and shorter DAPT appeared to have fewer clinical events. This study challenges the paradigm that there is a necessary dichotomy between BMS and DES in terms of DAPT duration. It appears that PES may derive benefit in reducing stent thrombosis with longer duration of DAPT, but the newer DES appear to have a similar rate of ischemic outcomes to BMS.

There is a belief in the interventional cardiology community that there is a trade-off between neointima formation (i.e., in-stent restenosis) and stent thrombosis, and that higher rates of restenosis are protective against stent thrombosis. The corollary is that more potent antiproliferative DES should have higher rates of stent thrombosis. Everolimus is the most powerful antiproliferative drug among the stents studied, followed by paclitaxel. Yet, EES had similar event rates to BMS, regardless of DAPT duration. PES, on the other hand, seemed to derive benefit from longer-term DAPT. ZES, which has the least potent antiproliferative drug, appeared to have the lowest event rates with short-term DAPT. The data challenge the paradigm that ischemic events in patients with DES are inversely related to the potency of antiproliferative drugs.

There are several important limitations to this dataset. First, the patients enrolled in this study were heterogeneous with respect to their presenting symptoms. We are not told whether the acuity of presentation had an effect on outcomes. There may be some interaction between ACS presentations and ischemic events, as has been shown in numerous previous trials. Second, it was not powered to detect differences in stent thrombosis. Third, this is a subgroup analysis with the attendant limitations thereof. For these reasons, these data are unlikely to alter guidelines for DAPT duration. However, this study forms part of a growing body of literature that suggest the newer generation of DES do not carry the same risks of late events that dogged the first generation of DES. Clinicians can be reassured that if patients must interrupt their DAPT late in the first year after PCI, the event rates remain reasonably low. ■

ABSTRACT & COMMENTARY

Value of Biomarkers in Preoperative Risk Stratification

By Michael H. Crawford, MD, Editor

SOURCES: Weber M, et al. Incremental value of high-sensitive troponin T in addition to the revised cardiac index for perioperative risk stratification in non-cardiac surgery. *Eur Heart J* 2013;34:853-862. Karakas M, Koenig W. Improved perioperative risk stratification in non-cardiac surgery: Going beyond established clinical scores. *Eur Heart J* 2013;34:796-798.

Newer biomarkers such as B-type natriuretic peptide (BNP) and high-sensitive troponins have been shown to be of prognostic value in patients with cardiovascular disease. These investigators from central Europe sought to determine if they were of value in risk stratification for non-cardiac surgery. Thus, they studied 979 patients from eight hospitals who were undergoing major noncardiac surgery, were > 55 years of age, and had at least one risk factor for cardiovascular disease. The primary endpoints were all-cause mortality and the combination of mortality with acute myocardial infarction, cardiac arrest, or acute decompensated heart failure. The revised cardiac index was compared to high-sensitivity troponin T (hsTnT) and NT proBNP measured 1 week before surgery. The majority of patients had two or more risk factors or known coronary artery disease (CAD). During hospitalization for surgery, 2.6% of the patients died and 3.7% experienced the combined endpoint. The cardiac biomarkers were elevated in those who died vs the survivors (hsTnT 21 ng/L vs 7 ng/L, $P < 0.001$; NT proBNP 576 pg/mL vs 166 pg/mL, $P < 0.001$). Those with a hsTnT > 14 (99th percentile for normals) had a mortality of 6.9 vs 1.2% for those below this value ($P < 0.001$) and those with a NT proBNP > 300 had a mortality of 4.8 vs 1.4% for those below this value ($P = 0.002$). hsTnT had the highest ROC curve AUC at 0.81 and in a multivariate analysis, hsTnT was the strongest independent predictor of the combined endpoint (HR, 2.6; 95% confidence interval, 1.3-5.3; $P = 0.01$). The predictive ability of NT proBNP was similar to the revised cardiac index for the combined endpoint. The authors concluded that hsTnT is additive to the revised cardiac index for risk stratification prior to major noncardiac surgery in higher-risk patients.

■ COMMENTARY

Advances in surgical procedures and anesthesia have markedly reduced the risk of major non-cardiac surgery, even in higher-risk patients. This is evident in this study of older patients undergoing major surgery (> 50% vascular and abdominal) who are clinically at higher risk (72% RCRI of 1 or more). Their hospital mortality was 2.6% and major cardiac events occurred in 3.7%. This is similar to prior contemporary studies that have shown a 2-4% risk of major cardiac events in higher-risk patients. Thus, identifying the truly high-risk patient preoperatively has been likened to finding a needle in a haystack. This paper suggests that hsTnT may aide in this quest because it predicted cardiac events better than the RCRI. In this higher-risk group, 25% had hsTnT values greater than the 99th percentile in normal (usual definition of the upper limit of normal) and 67% of those who died had abnormal values. The authors suggest using it with your favorite clinical index, not as a standalone test.

The major limitation of this study is that they studied a select group of relatively high-risk patients undergoing higher-risk surgery. It may not apply more broadly and the authors don't recommend indiscriminant use. Also, the median follow-up period was 11 days, which represented the hospital stay in most. Typically, surgical complications are defined as those that occur in 30 days. Finally, the number of endpoints is small. Clearly, a larger study is in order before widely applying this approach to risk stratification.

The study implies that once the high-risk patient has been identified, he/she should be treated more aggressively to prevent cardiac events. This could mean drugs such as beta-blockers or coronary angiography and revascularization. We are told that about half the patients were on beta-blockers and one-quarter had known CAD, so they may have had coronary revascularization. The impact of these and other therapies on the results of this study are unknown. At this point, I may use troponin levels when I am unsure about the patient's risk, but I don't plan wide use at this time. ■

ABSTRACT & COMMENTARY

Natural History of Mixed Aortic Valve Disease

By Andrew J. Boyle, MBBS, PhD

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SOURCE: Zilberszac R, et al. Outcome of combined stenotic and regurgitant aortic valve disease. *J Am Coll Cardiol* 2013;61:1489-1495.

The prevalence and natural history of aortic stenosis (AS) are well known. However, there is a paucity of data about the natural history of combined AS and aortic regurgitation (AR). AS and AR confer differing types of stress on the left ventricle, and it stands to reason that the combination may result in worse outcomes than either AS or AR alone. To test this hypothesis, Zilberszac and colleagues prospectively followed asymptomatic patients with at least moderate AS and at least moderate AR, and preserved left ventricular (LV) function (LV ejection fraction ≥ 55%). They describe the clinical outcomes and predictors of progression to requirement for surgical aortic valve replacement (AVR).

The study involved 71 consecutive patients; 21 were women and the mean age was 52 ± 17 years. They excluded patients with concomitant moderate or severe lesions involving other valves and those with symptoms. Thirty-five patients had a bicuspid aortic valve, the rest had degenerative calcific AS; there were no cases of rheumatic valve disease. Eight patients had concomitant coronary artery disease, 31 had hypertension, 10 had diabetes, and 22 had dyslipidemia. All measurements were made by echocardiography. Multiple transducer positions were used to record aortic valve peak jet velocity (AV-Vel) and aortic valve area was calculated using the continuity equation. Severe AS was defined by an aortic valve area ≤ 1.0 cm^2 and moderate AS by a valve area of 1.0-1.5 cm^2. Severe AR was defined by a vena contracta of more than 6 mm and a prominent diastolic flow reversal in the descending aorta. Moderate AR was defined by a vena contracta of 3-6 mm. Importantly, when grading lesion severity, the authors took into account the effects of AS and LV hypertrophy on the measurement of AR, and the increased flow in the presence of AR on increasing AV-Vel when grading AS. The patients were followed every 6 months in a dedicated valve clinic. They were referred for valve replacement if they met criteria for valve replacement for either AS or AR, and exercise testing was used in a selected minority of patients.

The patients were followed for a median of 8.9 years. During that time, 50 patients developed an indication for AVR, and the development of symptoms was the most common indication. Forty-three actually underwent valve replacement surgery, six refused surgery, and one was denied surgery because of limited life expectancy from metastatic cancer. Overall event rates were high with an event-free survival [defined as freedom from cardiovascular death and need for valve replacement] for the entire patient population of 82 ± 5%, 62 ± 6%, 49 ± 6%, 33 ± 6%, and 19 ± 5% at 1, 2, 3, 4, and 6 years, respectively. Three patients died after they developed indications for surgery but refused. There was one noncardiac death, one operative death, and no postoperative deaths. Interestingly, aortic valve area and severity of AR did not predict progression. AV-Vel independently predicted event-free survival. Patients with AV-Vel 3.0 to 3.9 m/s who did not progress had an excellent prognosis, but rapid progression of AV-Vel and subsequent clinical events were common. Progression of AV-Vel resulted in a hazard ratio [HR] of 3.3 for clinical events ($P < 0.001$). The presence of concomitant coronary artery disease was the other independent predictor of events (HR 4.01; $P = 0.01$). The authors conclude that asymptomatic patients with combined aortic valve disease can be safely followed until surgical criteria defined for AS, AR, or the aorta are reached. However, high event rates can be expected, even in younger patients and those with only moderate disease. AV-Vel, which reflects both stenosis and regurgitant severity, provides an objective and easily assessable predictive parameter.

■ COMMENTARY

This study, although small, is an important contemporary view of mixed aortic valve disease. There were no cases of rheumatic valve disease in this cohort, which reflects the shifting etiology of aortic valve disease from mainly rheumatic in previous decades to predominantly degenerative. Despite the young age of this cohort and the fact that this was predominantly moderate disease, there was a high rate of progression to require surgery. Compared to historical controls with isolated AS and AV-Vel 3.0-3.9, patients with mixed AS and AR and AV-Vel 3.0-3.9 have lower event-free survival rates, suggesting more rapid progression of mixed disease.

AV-Vel predicted event-free survival, yet aortic valve area did not. In mixed aortic valve disease, the assessment of severity of either lesion can be confounded by the coexisting lesion. AV-Vel measures not only the increased velocity through the stenotic valve, but also reflects the increased volume from AR. Thus, it has contributions from both lesions, and appears

to be an excellent tool in stratifying the overall hemodynamic load of combined AS and AR. My take-home messages from this study are that patients with asymptomatic, moderate, or greater mixed aortic valve disease should have close follow-up because there is a high rate of progression, and that AV-Vel is an integral part of the assessment of these patients. ■

ABSTRACT & COMMENTARY

Value of Yoga Training in Paroxysmal Atrial Fibrillation

By John P. DiMarco, MD, PhD
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SOURCE: Lakkireddy D, et al. Effect of yoga on arrhythmia burden, anxiety, depression, and quality of life in paroxysmal atrial fibrillation: The YOGA My Heart study. *J Am Coll Cardiol* 2013;61:1177-1182.

In this paper, the authors report the results of a study that examined the impact of yoga training on patients with paroxysmal atrial fibrillation (AF). The authors enrolled 101 patients with paroxysmal AF who were on a stable medical regimen. Patients served as their own controls in a single-center, prospective, pre-post cohort study. Clinical characteristics and quality of life, anxiety, and depression scores were assessed at baseline, at the end of a 90-day control period, and at the end of a 90-day yoga intervention period. During the yoga intervention period, patients underwent structured Iyengar yoga training at least twice weekly. The sessions were group sessions conducted by a certified yoga instructor and lasted for at least 60 minutes. Patients were also encouraged to practice yoga at home on their own on a daily basis. The primary outcomes included the burden of symptomatic true AF, asymptomatic non-AF, and asymptomatic AF episodes. Secondary outcomes included changes in the Short Form 36 (SF-36) quality of life score, the Zung self-assessment anxiety score (SAS), and the Zung self-assessment depression score (SDS). AF burden was estimated using symptom triggered event monitors. Routine daily ECG transmissions were also made for all patients.

The study cohort included approximately equal numbers of men and women with a mean age of 61 ± 11 years. The mean duration of AF since diagnosis was 5 years. Most patients had only no or mild left atrial enlargement and a normal left ventricular ejection fraction. Hypertension and hyperlipidemia were the most common comorbid conditions. Patients with significant heart failure were not included. During the yoga intervention period, the number of symptomatic AF episodes decreased from 3.8 ± 3 to 2.1 ± 2.6. Symptomatic episodes not due to AF also decreased from 2.9 ± 3.4 to 1.4 ± 2.0. Asymptomatic AF episodes also decreased from 0.12 ± 0.44 to 0.04 ± 0.2. There were 11 patients (22% of the entire group) who had no documented AF during the yoga intervention phase. There was no change in the SF-36, the SAS, or the SDS scores during the control period. However, after the yoga intervention phase, the self-reported depression scores and self-reported anxiety scores improved significantly and the SF-36 scores improved in several domains: physical functioning, general health, vitality, social functioning, and mental health. Also noted was a decrease in resting sinus heart rate and diastolic blood pressure.

The authors conclude that this small proof-of-concept study suggests that yoga may be helpful in patients with highly symptomatic, long-standing paroxysmal AF.

■ COMMENTARY

Unfortunately, both antiarrhythmic drug therapy and catheter ablation approaches are frequently unsuccessful at completely eliminating AF. Yoga has been shown to be an effective adjunct in other chronic conditions, and the preliminary data in this paper suggest that it may be an additional tool that can make recurrent AF more tolerable for patients. Yoga can produce changes in autonomic nervous system activity, and it is likely that these effects both directly decrease the frequency of AF episodes and also make episodes that do occur better tolerated.

Not all patients are likely to be candidates for yoga therapy for their AF. We also need better controlled data to demonstrate that it is effective in a typical group of AF patients. However, for patients willing to try yoga, it may be possible to decrease symptoms and make the disease more tolerable. ■

CME Questions

1. The best predictor of outcome in moderate mixed aortic valve disease is:
   a. aortic valve area.
   b. aortic valve flow velocity.
   c. left ventricular volume.
   d. left ventricular systolic function.

2. Which of the following tests is the strongest predictor of major cardiac events after non-cardiac surgery?
   a. hsCRP
   b. hsTnT
   c. NT proBNP
   d. ANP

3. Which of the following liver function tests identifies acute heart failure patients with a poor 30-day survival?
   a. Transaminase levels
   b. Bilirubin
   c. Alkaline phosphatase
   d. Prothrombin time

4. Post-coronary stenting major adverse cardiac events may be related to:
   a. stent type.
   b. duration of dual antiplatelet therapy.
   c. patient factors.
   d. antineoplastic agent potency.

5. Yoga training in patients with paroxysmal atrial fibrillation can reduce:
   a. symptomatic episodes.
   b. asymptomatic episodes.
   c. symptoms not due to atrial fibrillation.
   d. All of the above

6. The readmission rate for survivors of in-hospital cardiac arrest is:
   a. 25%.
   b. 33%.
   c. 50%.
   d. 65%.

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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Volume 18, Number 5 | Pages 9-10 | May 2013

Extended Treatment of VTE with Dabigatran vs Warfarin

Source: Schulman S, et al. *N Engl J Med* 2013;368:709-718.

Current recommendations for treatment of uncomplicated venous thromboembolism (VTE) in the absence of persistent risk factors for recurrence (e.g., protein C, protein S deficiency) suggest at least 3 months of antithrombotic therapy, typically with warfarin. Risk of recurrence, however, is not insubstantial, and recent clinical trials have shown that extending the duration of antithrombotic therapy after a course of warfarin (with aspirin, for instance) reduces the risk for recurrent VTE.

When warfarin is used for extended VTE recurrence prophylaxis, serious bleeding risk is about 1% annually. In comparison trials to warfarin, major bleeding rates on dabigatran have been generally comparable to warfarin, and intracerebral bleeding was demonstrably less with dabigatran than warfarin. Since dabigatran does not require monitoring, monthly physician visits, or dietary modulation, and has infrequent potential for drug interaction, it provides an attractive alternative.

Schulman et al report the results of two randomized, controlled, double-blind trials of dabigatran 150 mg twice daily vs warfarin or placebo in patients who had completed at least 3 months of warfarin treatment. Dabigatran was found to be noninferior to warfarin for prevention of recurrent VTE, with less frequent bleeding than warfarin (0.9% vs 1.8%). Dabigatran may be a viable alternative for extending DVT prophylaxis after a "traditional" course of warfarin. ■

Selection Criteria for Lung Cancer Screening

Source: Tammemagi M, et al. *N Engl J Med* 2013;368:728-736.

The national lung screening trial (NLST) reported in 2011 that low-dose CT screening in selected smokers (n = 53,454) reduced mortality from lung cancer by 20%. Entry criteria for the NLST included age 55-74 years with at least a 30 pack-years smoking history (former smokers, if they had quit within the last 15 years, were also enrolled). Subsequently, national organizations have variously endorsed lung cancer screening for persons matching NLST eligibility criteria.

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) developed a lung-cancer risk prediction model based on 154,901 subjects. The PLCO determined other predictors of lung cancer beyond age and smoking duration used in the NLST, including body mass index, family history of lung cancer, and presence of chronic obstructive pulmonary disease. Because the PLCO duration of follow-up was longer than NLST (9.2 years vs 6.5 years), the strength of the PLCO prediction model might be anticipated to be greater than NLST.

A comparison between the NLST and PLCO prediction models found that the PLCO criteria had greater sensitivity and specificity, ultimately missing 43% fewer lung cancers than NLST. The PLCO prediction model has the potential to improve outcomes for persons at risk of lung cancer. ■

Special Subgroups in Hypertension: Obese Hypertensives

Source: Weber MA, et al. *Lancet* 2013; 381:537-545.

The inter-relatedness of obesity, hypertension, and cardiovascular (CV) events is complex. Obesity is independently associated with high blood pressure, all-cause mortality, and CV mortality. Yet, some reports have suggested that when parsing out CV events among a secondary prevention population (persons with *existing* CV disease), subjects with *normal* body weight bear a disproportionately *greater* risk than overweight and obese persons.

To further clarify this counterintuitive knowledge base, Weber et al report on an analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial (ACCOMPLISH). ACCOMPLISH was performed to determine the relative efficacy of an angiotensin-converting enzyme (ACE) inhibitor + hydrochlorothiazide (HCTZ) vs ACE + amlodipine (CCB) in patients (n = 11,506) with Stage 2 hypertension (blood pressure > 160 mmHg). The trial ultimately demonstrated that ACE + CCB provided a significant mortality advantage over ACE + HCTZ.

In this report, ACCOMPLISH study subjects were divided into normal weight (body mass index [BMI] < 25), overweight (BMI 25-29), and obese categories (≥ BMI 30). CV events were most

frequent in the normal weight group, and least frequent in the obese patients in the ACE + HCTZ arm of the trial. In the ACE + CCB arm, there were no differences between weight categories in outcomes.

The seemingly paradoxical relationship between overweight and outcomes in persons with established CV disease (myocardial infarction, cerebrovascular accident, or existing hypertension) is difficult to explain. It may be that obesity-related hypertension is mediated by a different, more benign pathophysiology, hence producing more favorable outcomes, although this concept has been insufficiently explored. Finally, because of relatively higher event rates with ACE + HCTZ in normal-weight patients, clinicians should select ACE + CCB since event reduction is equivalent across weight groups for this combination. ■

Omalizumab for Asthma in Real Life

Source: Grimaldi-Bensouda L, et al. *Chest* 2013;143:398-405.

In evidence-based medicine terminology, "efficacy" is the term used to reflect results achieved within a clinical trial, whereas "effectiveness" indicates the results seen in "typical practice settings," commonly called "real-life settings." Clinical trials are anticipated to provide results superior to those in practice settings, where patients cannot be so readily de-selected or excluded, where resources may be more limited, and where rigorous regimentation for administration of treatment is less abundant.

Omalizumab (OMA) is not generally regarded as a first-line asthma medication, but rather an appropriate add-on when guideline-based foundation therapies (inhaled steroids, long-acting beta agonists, and leukotriene receptor antagonists) are insufficient to provide control. Although only 30-50% of asthmatics have a prominent underlying allergic component, among difficult-to-control asthmatics, the number may be as high as 80%. Clinical trials indicate that OMA, by blocking IgE, is a useful add-on in such resistant asthma cases. But do "real-life" settings reflect similar benefit?

Grimaldi-Bensouda et al report on refractory asthma patients (n = 767) recruited by more than 100 physicians who prescribed OMA as an add-on treatment. During a follow-up period of almost 2 years, study subjects who received any doses of OMA enjoyed a 43% relative risk reduction in likelihood of hospitalization or emergency department visits for asthma. Subjects on treatment with OMA demonstrated an even greater benefit: 60% relative risk reduction.

In real-life settings, OMA provides substantial improvement in clinically important endpoints for patients with difficult-to-treat asthma. ■

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

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Tenofovir: New Hope for Hepatitis B Patients

Source: Marcellin P, et al. *Lancet* 2013; 381:468-475.

Hepatitis B (HEP-B) is responsible for approximately half of hepatic carcinoma cases worldwide. While HEP-B treatment has been shown to reduce risk for liver failure and hepatic cancer in cirrhosis, whether currently available antiviral therapies actually reverse the underlying disease process is less well studied. Indeed, previous prevailing wisdom had opined that the fibrotic changes of cirrhosis might not be amenable to attempts at regression.

Tenofovir (TFV) is a potent HEP-B polymerase/reverse transcriptase inhibitor. Marcellin et al report on the results of an open-label trial of TFV in patients who had completed a 48-week antiviral treatment with either adefovir or TFV. Subjects were subsequently assigned to once-daily TFV for up to 7 years. Approximately one-fourth of patients had cirrhosis at baseline, and all subjects agreed to follow-up liver biopsy in the fifth year of the trial (240 weeks).

TFV was well tolerated and confirmed to be associated with regression of fibrosis (in the cirrhosis group) and improvement in liver histology (in the non-cirrhosis group) at 240 weeks. This large dataset is very supportive of a role for TFV not just in arresting disease progression, but actually in regression of cirrhosis. ■

H. pylori: Frequency of Recurrence After Successful Eradication

Source: Morgan DR. *JAMA* 2013;309: 578-586.

Worldwide, *Helicobacter pylori* appears to be responsible for the majority of cases of gastric cancer. A Chinese clinical trial of *H. pylori* eradication through pharmacotherapy noted an almost 40% reduction in gastric cancer over the subsequent 15-year observation period. Initial eradication of *H. pylori* provides important risk reduction. Of course, initial treatment is sometimes not effective, and even when initial treatment is effective, there is potential for recurrence.

From a population of study subjects (n = 1091) cleared of *H. pylori* (confirmed by post-treatment negative urea breath tests), only 125 evidenced recurrence over a 1-year follow-up (11.5%). Factors associated with recurrence included non-adherence to *H. pylori* treatment regimens and methodology of the treatment regimen (i.e., 14-day triple therapy, sequential therapy, or concomitant therapy, with sequential therapy being most successful). These recurrence rates are typical of low-income countries, whereas recurrence rates are as much as 30% less in high-income countries. Overall, *H. pylori* treatment is well tolerated, provides important risk reduction for gastric cancer, and is associated with few recurrences that can be managed by appropriate retreatment. ■

PHARMACOLOGY WATCH

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

New Study on Chelation Therapy Proves Controversial

In this issue: Chelation therapy for cardiovascular disease; statins and kidney injuries; chlorthalidone for hypertension; and FDA actions.

Does chelation therapy work?

The National Center for Complementary and Alternative Medicine (NCCAM) is attempting to fulfill its mandate to prove or disprove the value of alternative treatments. A division of the National Institutes of Health, NCCAM has done research on everything from supplements to meditation. This latest study looks at chelation therapy in patients with cardiovascular disease. Chelation therapy with ethylene diamine tetra-acetic acid (EDTA) has been used for decades to treat lead toxicity, and it has also been found to reduce metastatic calcium deposits. Despite the fact that small studies have never shown a benefit for chelation in treating cardiovascular disease, many alternative clinics continue to tout its value in this role. A recently published NCCAM-funded study to evaluate the value of chelation enrolled more than 1700 patients ≥ 50 years of age with a history of myocardial infarction (MI) at least 6 weeks prior. The study was a double-blind, placebo-controlled, 2 × 2 factorial randomized trial from 2003 through 2011. There were 289 patients who withdrew consent from the study, of which 60% were in the placebo group. The study consisted of 40 EDTA/vitamin infusions vs placebo infusions (given weekly for 30 weeks then at 2-8 week intervals). About 15% of patients in both groups dropped out during therapy. The primary outcome was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. The primary endpoint occurred in 222 (26%) in the chelation group and 261 (30%) in the placebo group (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69-0.99; $P = 0.35$). There was no effect on total mortality, but there was slight improvement in other outcomes with chelation. The authors conclude that among stable patients with a history of MI, chelation therapy modestly reduced the risk of adverse cardiovascular outcomes. They conclude that this study provides evidence to guide further research but is not sufficient to support the routine use of chelation therapy in patients with cardiovascular disease (*JAMA* 2013;309:1241-1250). Editorialists in the same issue of *JAMA* immediately leveled strong criticisms, ranging from allegations of noncompliance with regulations for the protection of research participants to questioning the professional credentials of the study sites and investigators. The *JAMA* editorial board did an extensive review of the data, and despite concerns, decided to publish the study with the caveat that "these findings do not support the routine use of chelation therapy as secondary prevention for patients with previous myocardial infarction and established coronary disease." (*JAMA* 2013;309:1291-1292.) Another editorialist, however, suggests that "limitations in the design and execution" of this trial compromise the findings. For example, the high number of withdrawals of consent in the placebo group suggests that the study was not truly blinded. There is also concern about the use of "softer" endpoints such as coronary revascularization and hospitalization for angina.

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Also, the trial design was altered midway through the study because of the length of the trial. Given these concerns, "including missing data, potential investigator or patient unmasking, use of subjective endpoints, and intentional unblinding of the sponsor, the results cannot be accepted as reliable and did not demonstrate a benefit of chelation therapy." (*JAMA* 2013;309:1293-1294.) ■

Statins and renal function

When prescribing a high-dose statin, physicians no longer need to monitor liver function tests, but might want to consider monitoring renal function, at least for the first 3 months. Last year, the FDA removed labeling requiring periodic monitoring of liver enzyme tests, but now a Canadian study suggests that high-potency statins (defined as doses of at least 40 mg simvastatin, 20 mg atorvastatin, or 10 mg rosuvastain) may be associated with acute kidney injury. Researchers reviewed records of more than 2 million patients from nine population-based cohort studies comparing current and past use of high-potency vs low-potency statin therapy. Patients hospitalized for acute kidney injury were matched with 10 controls. About 3% of patients had chronic kidney disease (CKD) at the onset of the study. Within 120 days of starting therapy, there were 4691 hospitalizations for acute kidney injury in patients without CKD and 1896 hospitalizations in patients with CKD. In patients without CKD, current users of high-potency statins were 34% more likely to be hospitalized with acute kidney injury compared to low-potency statin users (fixed effect rate ratio 1.34; 95% CI, 1.25-1.43). In patients with CKD, the increase was about 10% with high-potency statins (risk ratio, 1.10; 95% CI, 0.99-1.23). The authors conclude that use of high-potency statins is associated with an increased rate of acute kidney injury compared to low-potency statins, with the effect strongest in the first 120 days of treatment. The authors further suggest that since there is a relatively small incremental cardiovascular benefit between high-potency and low-potency statins, and given the increased risk of rhabdomyolysis, diabetes, and acute kidney injury, patient selection for risk-benefit is important (*BMJ* 2013;346:f880). ■

Chlorthalidone for hypertension

Thiazide diuretics are recommended as first-line treatment for hypertension. Hydrochlorothiazide (HCTZ) is the most commonly used diuretic in North America, but some experts have recommended chlorthalidone in this role, suggesting that it may be superior. A new study, however, suggests that chlorthalidone may cause more electrolyte abnormalities than HCTZ. Nearly 30,000 patients ≥ 66 years of age who were newly treated for hypertension were evaluated. About one-third were treated with chlorthalidone and the rest with HCTZ. None of the patients had been hospitalized for heart failure, stroke, or MI within the last year. The primary outcome was a composite of death or hospitalization for heart failure, stroke, or MI, and safety outcomes included hospitalization with hypokalemia or hyponatremia. After 5 years of follow-up, there was no difference in the primary outcome between the two drugs — 3.2 events per 100 person years for chlorthalidone vs 3.4 events per 100 person years for HCTZ. However, patients treated with chlorthalidone were three times more likely to be hospitalized with hypokalemia (adjusted HR, 3.06; CI, 0.81-1.06). Hyponatremia was also more common (HR, 1.68; CI, 1.24-2.28). The findings suggest that in typical doses, chlorthalidone is not associated with fewer adverse cardiovascular events or deaths compared to hydrochlorothiazide, but it is associated with a greater incidence of electrolyte abnormalities, especially hypokalemia (*Ann Intern Med* 2013;158:447-455). ■

FDA actions

The FDA has issued a warning regarding azithromycin and cardiac toxicity. The drug has been associated with fatal heart rhythms — especially in patients already at risk — including those with prolonged QT intervals, torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure. Other patients may be at risk as well, including those with low potassium or magnesium levels, those using drugs that prolong the QT intervals, and elderly patients with cardiac disease. The warning was based on a study published in *The New England Journal of Medicine* last year.

An FDA advisory committee is recommending against the use of calcitonin salmon (Miacalcin and Fortical nasal sprays, and Miacalcin injection) for the treatment of osteoporosis in postmenopausal women because the risk of cancer outweighs any potential benefit. The recommendation is based on an FDA review that questions the drug's effectiveness in reducing fractures. Another review found a small increased risk of cancer associated with the drug. The drug could still be used for Paget's disease, acute bone loss due to immobilization, and hypercalcemia. The FDA has yet to rule on the advisory committee's recommendations. ■