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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Biventricular vs RV Pacing for AV Block in Heart Failure

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: Curtis AB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013;368:1585-1593.

The Biventricular vs Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial tested the hypothesis that biventricular pacing (cardiac resynchronization therapy [CRT]) would be superior to right ventricular pacing in patients with mild-to-moderate heart failure, left ventricular systolic dysfunction, and an indication for full-time ventricular pacing. The investigators enrolled patients with a New York Heart Association (NYHA) class I or II A indication for ventricular pacing due to high degree or complete atrioventricular (AV) block and also had some symptoms of heart failure and a left ventricular ejection fraction of 50% or less. Although the initial patient group only included patients who would receive pacemakers, later in the trial patients who received implantable defibrillators (ICDs) and had an indication for ventricular pacing were included. After initial screening, all patients underwent implantation of a pacemaker or ICD with biventricular pacing capability. Patients with persistent atrial arrhythmias with complete or high-grade block could be included. After implantation, the devices were programmed to right ventricular pacing for 30-60 days during which an optimal pharmacologic regimen was established. Patients then returned and were randomized in a 1:1 ratio to receive either biventricular or right ventricular pacing. This post-implant randomization visit was considered to be the baseline visit. Patients were

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Editorial E-Mail:
neill.kimball@ahcmedia.com

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then followed every 3 months with full clinical assessments. Echocardiography was performed to calculate the left ventricular end systolic volume index (LVESVI) and left ventricular ejection fraction (LVEF) at randomization and at 6, 12, 18, and 24 months. The primary outcome measure was a composite endpoint including death from any cause, any urgent outpatient or inpatient visit for heart failure that required intravenous therapy, or an increase from baseline in the LVESVI of 15% or more. Secondary outcomes, including death from any cause and hospitalization for heart failure, were also analyzed. A hierarchical Bayesian proportional hazards model was used for analysis of the primary and secondary outcomes.

The study screened 918 patients and eventually randomized 691. Device implantation was attempted in 809 patients but was unsuccessful in 51 (6.3%). Sixty-seven patients who received a successful device implant did not undergo randomization for various reasons. The mean LVEF was 43% in the pacemaker group and 33% in the ICD group; 484 patients received pacemakers and 207 patients received ICDs. Overall, more than 80% of the patients in the combined group had NYHA class II or III heart failure symptoms.

A primary outcome endpoint was reached by 53.3% of the biventricular pacing group compared with 64.3% of the right ventricular pacing group. The most common primary outcome event was a decrease in LVESVI. This was observed in 56 of 243 biventricular pacing group patients compared to 79 of 241 right ventricular pacing group patients. In the ICD groups, LVESVI-related events also accounted for more than 50% of the events. The raw numbers of deaths and number of urgent care visits for heart failure showed only minor changes. However, when the Bayesian hierarchical model was used to adjust for baseline differences, the hazard ratios for death, urgent visit for heart failure, or hospitalization for heart failure were also significantly lowered.

Adverse events were noted in 113 of the 809 patients in whom implantation was attempted. Of these, 83 events (10.3%) were related to the procedure or the cardiac resynchronization therapy (CRT) system. Left ventricular lead-related complications were noted in 6.4% of patients. The authors conclude that biventricular pacing is superior to right ventricular pacing in patients with left ventricular dysfunction who require ventricular pacing.

■ COMMENTARY

It is now generally accepted that right ventricular apical pacing may have adverse hemodynamic consequences in selected patients. Prior studies on CRT have excluded patients who had ventricular pacing indications so that the effects of CRT in patients with bundle branch blocks could be analyzed. BLOCK HF extends the observation that CRT is better than right ventricular pacing to patients who require pacing, but also points out that there are still limitations to CRT. In BLOCK HF, 6.3% of the implant attempts were unsuccessful and an added 6.4% of those who received an LV lead had later complications. Although not addressed in the time frame of this study, battery longevity is also shorter with CRT devices in general. Therefore, before we start CRT routinely in all patients with AV block, we should carefully consider the risk-benefit ratio in each patient. Thankfully, recent innovations in lead design and battery technology may mitigate some of these limitations and I expect that CRT will become standard for patients with any systolic dysfunction and a need for pacing in the near future. ■

ABSTRACT & COMMENTARY

Aortic Valve Replacement in Older Adults: Mechanical or Bioprosthetic Valve?

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: Brennan JM, et al. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: Results from the Society of Thoracic Surgeons adult cardiac surgery national database. *Circulation* 2013;127:1647-1655.

The decision to choose a mechanical or a tissue valve for patients undergoing surgical aortic valve replacement (AVR) is a complex one that involves synthesizing clinical factors such as risk of bleeding, likelihood of reoperation, and patient preference. Increasingly, older patients with more comorbidities are being referred for AVR surgery. Comparative data between valve types with long-term follow-up in this high-risk cohort are needed to inform our treatment decisions. Accordingly, Brennan and colleagues searched the Society of Thoracic Surgeons (STS) database and identified a cohort of Medicare-linked patients between 65 and 80 years of age undergoing elective or urgent AVR with a mechanical or biological prosthesis from January 1, 1991 until December 28, 1999. They excluded patients undergoing concomitant non-coronary artery bypass graft (CABG) cardiac surgical procedures, those with a prior history of any valve replacement, patients at health maintenance organizations and military hospitals where no patients were linked to Medicare records, those with potential linkage to multiple Medicare files, and those with index procedures that occurred outside a period of fee-for-service Medicare enrollment. The primary endpoint was all-cause mortality. Secondary endpoints were rehospitalization for aortic valve reoperation, stroke, hemorrhagic stroke, hemorrhage, and endocarditis. These were analyzed up to 2007, resulting in at least 8 years of follow-up for all patients.

The study included 39,199 patients who received biological (n = 24,410) or mechanical (n = 14,789) aortic valve prostheses in 605 hospitals. The median age was 73 years and mean follow-up was 12.6 years (range, 8-17 years). Bioprostheses were used with increasing frequency over time among progressively older patients, with a 20% absolute increase from 1991 to 1999. Compared with patients who received mechanical valves, those who received bioprosthetic valves were older (74 vs 71 years; $P < 0.001$), with a higher prevalence of heart failure (43.7% vs 39.9%; $P < 0.0001$) and significant coronary artery disease (70.1% vs 65.6%; $P < 0.001$), and were more likely to have combined AVR + CABG (60% vs 55%; $P < 0.0001$). The authors performed propensity weighting, after which the baseline and operative characteristics were similar between groups. They quantified hazard ratios (HR) on these risk-adjusted groups.

The 12-year rate of all-cause mortality after AVR was very high for both groups: 70.5% for patients who received bioprosthetic valves and 60.3% for those who received mechanical valves (HR 1.29; 95% confidence interval [CI], 1.26-1.32). After risk adjustment, patients who received bioprosthetic valves experienced a similar long-term mortality rate as those who received mechanical valves (HR 1.04; 95% CI, 1.01-1.07); however, mortality rates were higher beyond 9 years of follow-up in patients treated with bioprosthetic valves. The absolute risk of long-term mortality varied widely across patient subgroups and was particularly high among patients with either preoperative renal failure (12-year mortality, 65.2%) or reduced left ventricular ejection fraction (12-year mortality, 74.1%).

By 12 years, reoperation was observed in 5.2% of patients with bioprosthetic valves and 2.3% of those with mechanical valves. After risk adjustment, bioprosthetic valves were associated with a more than two-fold increase in the long-term rate of reoperation compared with mechanical valves (HR 2.55; 95% CI, 2.1-3.0). This effect was larger among younger patients. Patients who received bioprosthetic valves also experienced a higher risk of endocarditis (HR 1.60; 95% CI, 1.31-1.94), except among the oldest patients (75-80 years; HR 1.17; 95% CI, 0.85-1.60) and those with renal failure (HR 0.69; 95% CI, 0.29-1.66).

However, the adjusted rate of stroke was significantly lower among patients with bioprosthetic valves (HR 0.87; 95% CI, 0.82-0.93).

Bioprosthetic valves were associated with a lower adjusted rate of both all-cause bleeding (HR 0.66; 95% CI, 0.62-0.70) and hemorrhagic stroke (HR 0.57; 95% CI, 0.49-0.65). The authors conclude that among patients undergoing AVR, long-term mortality rates were similar for those who received bioprosthetic vs mechanical valves. Bioprostheses were associated with a higher long-term risk of reoperation and endocarditis but a lower risk of stroke and hemorrhage. These risks varied as a function of a patient's age and comorbidities.

■ COMMENTARY

Degenerative calcific aortic stenosis is a disease that increases in prevalence with increasing age. This paper from Brennan et al presents data specific to the aging population (65-80 years old), and is thus a welcome adjunct to randomized trial data that tend to enroll younger patients. However, because this cohort has substantial burden of comorbidities, the accuracy of the results relies heavily on statistical matching between groups. This was performed in a rigorous fashion, but statistics cannot account for all comorbidities, and thus the results must be interpreted with caution. Most clinicians err on the side of caution and recommend bioprostheses to patients who are frail or have poor compliance with medications, and neither of these clinical judgments can be captured in observational database studies like this one. This is likely to bias the results in favor of mechanical valves, but to what degree remains unknown.

The unadjusted outcome data are striking in this group: mortality 66%, stroke 14%, and bleeding 17%. This underscores the high-risk profile of aging patients in general. In addition, the uniquely high-risk nature of this group also means that the data in this paper may not be generalizable to younger age groups. How should we choose between mechanical and bioprosthetic valves in patients over 65? The choice should continue to be made on a case-by-case basis, taking into account a patient's overall risk of bleeding and stroke, other clinical comorbidities, and ability to take warfarin long-term. Both appear to be reasonable alternatives in the appropriate patients. ■

ABSTRACT & COMMENTARY

Outcome of Mitral Valve Repair for Severe Mitral Regurgitation

By Michael H. Crawford, MD, Editor

SOURCE: David TE, et al. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. *Circulation* 2013;127:1485-1492.

Guideline-driven earlier mitral valve repair for patients with mitral regurgitation (MR) due to degenerative disease has increased in the last 25 years. These investigators from Canada examined the outcomes in 840 such patients followed prospectively from 1985 to 2004 approximately every other year for a median follow-up of 10 years. Clinical, hemodynamic, and pathological data were analyzed for predictors of outcomes. The Society of Thoracic Surgeons risk score ranged from 0.3 to 5.5% (mean 1.5%). The surgery was elective in 90% of cases. New York Heart Association (NYHA) classification was: I 15%, II 37%, III 37%, and IV 11%. In 95%, MR was graded severe. Mitral valve prolapse was present in 99%. Death within 30 days occurred in four patients and late death due to cardiac causes in 81. Multivariate predictors of mortality included age, lower ejection fraction (EF), and higher NYHA class. Reoperation was required in 38 patients and the valve was replaced in 30 patients. The probability of reoperation at 20 years was 6%. Only three patients were discharged from the hospital with moderate MR; all the rest had less severe or none. During follow-up, 37 patients developed severe MR and 61 developed moderate MR. At 20 years, freedom from recurrent severe MR was 91% and from moderate MR was 69%. Isolated anterior leaflet prolapse was the strongest predictor of recurrent moderate-to-severe MR. At the last follow-up, 69% of the 627 survivors were NYHA class I; 22% class II, and 9% class III. The authors concluded that in the absence of class IV symptoms and reduced EF, mitral valve repair for severe MR restored lifespan to normal, and recurrent moderate-to-severe MR or repeat surgery was unusual.

■ COMMENTARY

This single-center, single-surgeon, quarter century experience with mitral valve repair for MR due to mitral valve prolapse is of interest because randomized, controlled trials are unlikely to be

done on the issues explored. In the population studied, almost all had severe MR and about half were NYHA class I-II. The excellent results presented support the guidelines recommendation that asymptomatic patients with severe MR should be repaired if feasible and appropriate based on mitral valve anatomy and comorbidities. Waiting for more marked symptoms was not supported by their experience as higher NYHA class was associated with higher mortality. The only caveat is the patient with isolated anterior leaflet prolapse, since this was the strongest predictor of recurrent MR after repair. Guidelines also recommend repair if LVEF falls below 60%, but waiting for this to happen in asymptomatic patients seems unwise based on their experience since EF was a strong predictor of mortality.

Recurrent significant MR occurred in about one-third of the survivors over 20 years. Surgery does not cure the degenerative process, and late recurrence of MR seemed to be related to further degeneration, whereas early recurrence seemed to be related to technical factors such as the inability to place a mitral annular ring. Also of interest was their experience with thromboembolism. There was a small but constant threat of thromboembolism throughout the observation period that was only associated independently with older age. Thromboembolism seemed to be unrelated to atrial fibrillation since all these patients were treated with anticoagulation. Freedom from thromboembolism was 86% at 20 years. They anticoagulated their patients for 3 months after surgery if there were no other indications for anticoagulation. After considering the data they posed the question of whether indefinite anticoagulation for all is justified. However, the risk of hemorrhage needs to be considered as there was an overall 22% serious hemorrhage rate among those on warfarin, resulting in eight deaths. ■

ABSTRACT & COMMENTARY

PCI in Patients on Warfarin: Do We Need Dual Antiplatelet Therapy?

By Andrew J. Boyle, MBBS, PhD

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

SOURCE: Dewilde WJ, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: An open-label, randomised, controlled trial. *Lancet* 2013;381:1107-1115.

Many patients need to take long-term oral anticoagulants (OAC) for indications such as atrial fibrillation (AF) or mechanical prosthetic valves. When these patients also require percutaneous coronary intervention (PCI), the concurrent requirement for dual anti-platelet therapy (DAPT) plus OAC increases the risk of serious bleeding. It is not known whether aspirin remains necessary in combination with clopidogrel plus warfarin in these patients. To address this question, Dewilde and colleagues performed a multicenter, randomized, controlled trial in 15 centers in Belgium and the Netherlands. From November 2008 to November 2011, adults receiving OAC and undergoing PCI were assigned clopidogrel alone (double therapy) or clopidogrel plus aspirin (triple therapy). The primary outcome was any bleeding episode within 1 year of PCI, assessed by intention to treat. The secondary endpoint was a composite of death, myocardial infarction (MI), stroke, target-vessel revascularization, and stent thrombosis (according to the Academic Research Consortium criteria).

A total of 573 patients were enrolled and 1-year data were available for 279 (98.2%) patients assigned double therapy and 284 (98.3%) assigned triple therapy. Mean ages were 70.3 ± 7.0 years and 69.5 ± 8.0 years, respectively. Compliance at 1 year was approximately 80% with clopidogrel in both groups and 67% with aspirin in the triple therapy group. Bleeding episodes were seen in 54 (19.4%) patients receiving double therapy and in 126 (44.4%) receiving triple therapy (hazard ratio [HR] 0.36; 95% CI, 0.26-0.50; $P < 0.0001$). In the double therapy group, six (2.2%) patients had multiple bleeding events, compared with 34 (12.0%) in the triple therapy group. Eleven (3.9%) patients receiving double therapy required at least one blood transfusion, compared with 27 (9.5%) patients in the triple therapy group (odds ratio from Kaplan-Meier curve 0.39; 95% CI, 0.17-0.84; $P = 0.011$). The lower bleeding rate with double therapy was consistent across the subgroups of age, sex, presentation of an acute coronary syndrome, indication for OAC, and stent type. Interestingly, there was no excess of ischemic outcomes in the double therapy group. The rates of the combined secondary endpoint were 11.1% in the double

therapy group and 17.6% in the triple therapy group. After correction for baseline characteristics, the HR remained similar (0.56, 95% CI, 0.35-0.91). The authors conclude that use of clopidogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in the rate of thrombotic events.

■ COMMENTARY

As patients age, the likelihood of developing disease that requires OAC or DAPT increases. Thus, it is quite frequent to encounter patients who have indications for both. There have been surprisingly few data on this patient cohort to date, and this study by Dewilde and colleagues addresses this key issue. The study is strengthened by its randomized, controlled, multicenter design with adjudication of all clinical events by a blinded clinical endpoint committee. However, it was an open-label trial and that may introduce some potential confounding. The study was powered to assess bleeding endpoints, not ischemic endpoints. However, the rate of ischemic events numerically favored the double therapy group. The authors caution that this requires further validation, but there is no signal that suggests a downside to withholding aspirin in this patient group. How can we explain lower bleeding and lower thrombotic endpoint rates in the double therapy group in this study? Thrombin itself is an activator of platelets, so the use of OAC not only inhibits thrombin, but also secondarily has some antiplatelet effect. The authors suggest that this may lessen the effect of inhibiting cyclo-oxygenase with aspirin.

There are several limitations that should be pointed out in interpreting this study. The open-label study may introduce bias, as mentioned before. Second, there are some incomplete data. In particular, the time spent in therapeutic range on warfarin is not reported and may have a significant influence on bleeding. Also, there were baseline differences between groups, but it is not clear which differences were statistically significant and were accounted for in the multivariable analysis. Third, the results are not stratified by the patient's bleeding risk. It would have been helpful to know if there were certain clinical predictors that could guide us in which subgroups to use this approach. Fourth, we now have ticagrelor and prasugrel, and their role in conjunction with OAC is still to be defined. Despite these limitations, this study suggests that for our patients requiring OAC and DAPT, it may be reasonable to withhold aspirin and just use OAC + clopidogrel. My approach is to assess each patient's individual bleeding risk and to consider withholding aspirin if their bleeding risk is high. ■

ABSTRACT & COMMENTARY

Value of Cardiology Follow-up of Acute Chest Pain Patients

By Michael H. Crawford, MD, Editor

SOURCE: Czarnecki A, et al. Association between physician follow-up and outcomes of care after chest pain assessment in high risk patients. *Circulation* 2013;127:1386-1394.

Patients seen in emergency departments (ED) for acute chest pain who are deemed low risk for acute coronary syndrome (ACS) and relatively safe for discharge are often referred to their primary care physician (PCP) for follow-up. However, little is known about the effectiveness of follow-up care. Thus, Czarnecki and colleagues performed a retrospective database review of patients seen in the ED for chest pain who were evaluated, discharged, and survived at least 30 days. They focused on those at higher risk because of diabetes or known cardiovascular disease. They specifically evaluated whether there was a follow-up visit within 30 days and whether it was by a PCP or cardiologist. The primary outcome was all-cause mortality and hospitalization for acute myocardial infarction (MI) at 1 year. After excluding ineligible patients, 56,767 were included in the study and the duration of follow-up averaged 4 years. Follow-up visits were with a cardiologist in 17%, a PCP in 58%, and no visit in 25%. Median time to follow-up was 7 days for a PCP and 12 days for a cardiologist. Patients seeing a cardiologist had the highest rates of previous cardiac conditions and more tests, procedures, and medications than the other groups. The primary endpoint occurred in 5.5% of those seen by a cardiologist, 7.7% seen by a PCP, and 8.6% in the no follow-up group. After adjustment for confounders, the cardiology follow-up group had the lowest hazard ratio (0.85, 95% CI, 0.78-0.92) as compared to PCP and 0.79 as compared to no visit. The authors concluded that

patients referred to a cardiologist after an ED visit for chest pain had a decreased risk of mortality or hospitalization for an MI at 1 year.

■ COMMENTARY

This large database study from a Canadian health system raises several important issues. First, what should be the follow-up of patients seen in the ED for chest pain who are deemed low risk for ACS, but at higher risk of having underlying coronary artery disease? The results suggest that a visit with a cardiologist as opposed to no visit or a visit with a PCP improves the primary endpoint of all-cause death and hospitalization for acute MI at 1 year. Even after adjustments for many confounders, these data remain robust. It doesn't suggest that all patients with chest pain seen in the ED need a cardiology follow-up, only the higher risk subset.

Second, cardiologists used more tests, medications, and procedures than the PCPs, and better followed evidence-based guidelines. Whether this is what made the difference is unclear since this is a database study and there are no details on the appropriateness of the tests and procedures used. So this study cannot be used to support routine testing in all patients. However, this is the practice of most cardiologists who see such referrals and the study does not refute this practice.

Third, provision of rapid outpatient follow-up for these patients is a challenge in many health systems. One-quarter of their patients had no visits within 30 days despite the fact that 95% had an identified PCP they had seen in the last 3 years. They used the 30-day time frame because most patients were seen between 14-30 days, but 15% were excluded who had a visit in 30-90 days. The ideal post-ED follow-up time is unknown, but many believe within 14 days is ideal. I doubt we are doing much better than the Canadians in this regard, but it appears that we need to for the patient's sake. ■

ABSTRACT & COMMENTARY

Digoxin and Mortality in Atrial Fibrillation

By John P. DiMarco, MD, PhD

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

SOURCE: Gheorghiade M, et al. Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: Findings from post hoc propensity-matched analysis of the AFFIRM trial. *Eur Heart J* 2013; Apr 16. [Epub ahead of print.]

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial was completed more than 10 years ago. That study enrolled more than 4000 patients who were randomized to either rate-control or rhythm-control strategies for management of atrial fibrillation (AF). In this paper, Gheorghiade and colleagues perform a post-hoc propensity-matched analysis on the effects of digoxin on mortality in the AFFIRM trial.

The authors used a public use dataset from AFFIRM obtained from the National Heart, Lung, and Blood Institute. They identified 1377 patients who received digoxin as initial therapy at baseline in the trial. Digoxin was used alone in 16% of the entire group and in combination with either a beta-blocker (14%) or with a calcium channel blocker (14%).

The primary endpoint for this analysis was all-cause mortality. Secondary endpoints included all-cause hospitalization and non-fatal arrhythmias. A propensity score was estimated based on 59 relevant variables. Using a matching protocol, pairs of patients receiving and not receiving digoxin as initial therapy at baseline were collected. Comparative outcomes in these two groups are then reported. The matched patients receiving and not receiving digoxin as initial therapy had a mean age of 70 years, 40% were women, and 40% had prior hospitalizations due to arrhythmias. All-cause mortality occurred in 14 and 13% of matched patients on and off digoxin as initial therapy, respectively. The results were similar among various subgroups including those with and without heart failure. Digoxin had no association with mortality at any time point

when used either as monotherapy or in combination with other rate-control drugs. Propensity-matched and propensity-adjusted hazard ratios for all-cause mortality associated with digoxin therapy at baseline and during the 6 months prior to baseline were all close to one. There was also no significant difference in the incidence of all-cause hospitalization in the matched patients receiving (56%) and not receiving (59%) digoxin as baseline initial therapy. Finally, incident non-fatal arrhythmias were rare with only 1% of matched patients in each group having such arrhythmias.

The authors conclude that digoxin has no association with mortality in patients with heart failure in the AFFIRM study when bias is removed with a careful propensity-matched analysis.

■ COMMENTARY

Whether digoxin should continue to be used for rate control in patients with AF has become controversial. Most guidelines, however, still recommend digoxin as a second-line agent in patients with heart failure and as an alternate first-line therapy in sedentary, elderly patients. This paper is in response to another study using the AFFIRM database that reported that digoxin increased mortality.[1] An earlier study by AFFIRM investigators had also shown that digoxin was associated with increased mortality. Both of these latter studies used a time-dependent survival analysis and it is likely that digoxin was added as patients became sicker and their heart rates became more difficult to control during the course of the trial. The paper, which used propensity matching based on baseline variables only, supports the continued place of well-monitored digoxin as a second-line agent for rate control in patients with heart failure and in select patients who respond to it as monotherapy. ■

REFERENCE

1. Whitbeck M, et al. Increased mortality among patients taking digoxin — analysis from the AFFIRM study. *Eur Heart J* 2013;34:1481-1488.

CME Questions

1. A visit with a cardiologist within 30 days after an ED visit for chest pain is associated with:
   a. more testing and procedures.
   b. lower all-cause mortality and recurrent MI.
   c. lower cardiac mortality.
   d. A and B

2. The strongest predictor of recurrent mitral regurgitation after mitral valve repair for degenerative disease is:
   a. ejection fraction.
   b. higher NYHA class.
   c. isolated anterior leaflet prolapse.
   d. middle scallop posterior leaflet prolapse.

3. Analysis of the rate control vs rhythm control study for atrial fibrillation showed that initial digoxin use was associated with:
   a. increased mortality.
   b. reduced mortality.
   c. no change in mortality.
   d. early increase, then a decrease.

4. In patients with AV block with systolic heart failure, biventricular vs RV pacing results in:
   a. reduced LV systolic volume.
   b. reduced mortality.
   c. reduced hospital visits for heart failure.
   d. All of the above

5. A study of clopidogrel alone vs aspirin and clopidogrel in patients on warfarin after PCI showed that clopidogrel alone resulted in:
   a. less bleeding.
   b. more ischemic events.
   c. less in-stent restenosis.
   d. All of the above

6. A database study of patients > 65 years of age undergoing aortic valve replacement showed that compared to mechanical valves, tissue valves showed:
   a. more strokes.
   b. more intracranial hemorrhages.
   c. more reoperation.
   d. less infective endocarditis.

CME Objectives

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

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

PHARMACOLOGY WATCH

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

Do Perioperative Beta-Blockers Reduce Mortality?

In this issue: Beta-blockers and noncardiac surgery; prenatal medication exposure and risk of autism; reasons for statin discontinuations; and FDA actions.

Perioperative beta-blockers

The use of perioperative beta-blockers has been debated for decades. Now, a large study from the U.S. Department of Veterans Affairs (VA) suggests that the drugs may be of benefit in selected patients. In a retrospective cohort analysis, exposure to beta-blockers on the day of or the day following noncardiac surgery was evaluated among a population-based sample of nearly 137,000 patients from 104 VA medical centers. The main outcome was all-cause 30-day mortality and cardiac morbidity. Overall, 55,138 patients (40%) were exposed to beta-blockers, although the rate was nearly 68% in those undergoing vascular surgery. Exposure increased with increased cardiac risk factors. Death occurred in just over 1% of patients and cardiac morbidity occurred in just under 1%. Overall, exposure to beta-blockers was associated with a lower mortality (relative risk [RR] 0.73%; 95% confidence interval [CI], 0.65-0.83; $P < 0.001$; number needed to treat [NNT], 241). The effect was greater in patients with higher cardiac risk factors, which include high-risk surgery, cerebrovascular disease, ischemic heart disease, heart failure, diabetes, and renal insufficiency. When stratified by the revised Cardiac Risk Index variables, patients with two or more cardiac risk factors had a RR of 0.63 (95% CI, 0.50-0.80; $P < 0.001$; NNT, 105), with three risk factors the RR was 0.54 (95% CI, 0.39-0.73; $P < 0.001$; NNT, 41), and with four or more risk factors the RR was 0.40 (95%CI, 0.25-0.73; $P < 0.001$; NNT, 18). This effect was limited to patients undergoing nonvascular surgery. Beta-blocker exposure also significantly reduced the rate of nonfatal Q-wave infarction or cardiac arrest by 37%. The authors conclude that in patients undergoing noncardiac, nonvascular surgery, perioperative beta-blockers significantly reduced 30-day all-cause mortality in patients with two or more cardiac risk factors and support the use of the drugs in these patients. They also suggest a multicenter randomized trial to assess the benefit in patients with low-to-intermediate risk. The authors were unable to find a benefit in stroke risk or in patients undergoing vascular surgery. They were also unable to determine if various beta-blockers (such as metoprolol vs atenolol) were of benefit or if the benefit was from various dosing regimens. (*JAMA* 2013; 309:1704-1713). ■

Medication use and pregnancy

Two studies suggest that certain medications used during pregnancy may increase the risk of autism in offspring. In the first, which looked at antidepressants in pregnancy, researchers from Sweden reviewed the records of 4429 children with autism spectrum disorder (ASD) as well as 43,000 age- and sex-matched controls. A history of maternal, but not paternal, depression was associated with an increased risk of ASD and the association was confined to women reporting anti-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

depressant use during pregnancy (adjusted odds ratio 3.34; 95% CI, 1.50-7.47; $P = 0.003$). This association was irrespective of whether serotonin reuptake inhibitors or non-selective monoamine reuptake inhibitors (tricyclic antidepressants) were used. The association was confined to autism without intellectual disability. Still, the use of antidepressants accounted for only 0.6% of cases of ASD during the study, so the drugs were "unlikely to have contributed significantly towards the dramatic increased prevalence of autism spectrum disorders" (*BMJ* 2013;346:f2059). In the other study, researchers from Denmark reviewed the records of children exposed in utero to valproate (used to treat seizures and other neuropsychological disorders in mothers). Of more than 655,000 children born between 1996 and 2006, 5437 identified with ASD, including 2067 with childhood autism. The overall risk of autism in all children was 1.53%, but of the 508 children exposed to valproate, the absolute risk was 4.42% (95% CI, 2.59-7.46%) for ASD and 2.50% (95%CI, 1.30-4.81%) for childhood autism (adjusted hazard ratio, 5.2). The risk was similar regardless of the indication for use of valproate in the mother. These findings suggest that maternal use of valproate significantly increases the risk for ASD and childhood autism in offspring. The authors suggest that a risk-benefit analysis should be considered for women on valproate in their childbearing years (*JAMA* 2013;309:1696-1703). ■

Discontinuation of statins

Most patients who stop statins due to side effects will tolerate the drugs if rechallenged, according to the findings of a new study. In a retrospective cohort study using data from two Boston hospitals, researchers reviewed the records of nearly 108,000 patients on statins and found statin-related events such as muscle pain documented in 18,778 (17.4%). Of those patients, 11,124 stopped the drugs at least temporarily and 6579 were restarted within the subsequent 12 months. The vast majority of patients restarted on a statin tolerated the drug (92.2%), although about half were eventually switched to a different statin. The authors conclude that statin-related side effects are common and often lead to discontinuation; however, most patients who are rechallenged can tolerate statins long-term. They suggest that "statin-related events may have other causes, are tolerable, or may be specific to individual statins rather than the entire drug class" (*Ann Intern Med* 2013;158:526-534). ■

FDA actions

The FDA has updated labeling of the new tamper-proof oxycodone (OxyContin), while at the same time denying approval of generic forms of the original formulation of oxycodone. The new labeling indicates that the product "has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)." The agency's refusal to approve generic forms of the original formulation was based on the increased risk of abuse inherent in the non-tamper proof form leading to the risk of serious adverse events including overdose and death. Because of this, the agency has determined that the benefits of the original OxyContin and its generics no longer outweigh its risks and it has been withdrawn from sales. The new tamper-proof formulation is more difficult to crush, break, or dissolve. If tampered with, it forms a viscous hydrogel that cannot be easily injected or snorted. Oral abuse is still possible.

The FDA has approved a fixed combination of doxylamine succinate and pyridoxine for the treatment of nausea and vomiting due to pregnancy. This is a reintroduction of a product widely used between 1956 and 1983. Then marketed as Bendectin, the product was voluntarily withdrawn by the manufacturer due to lawsuits related to birth defects, although evidence of risk was not supported by scientific evidence. The reapproval was based on a study of 261 women experiencing nausea and vomiting due to pregnancy in which the drug was more effective than placebo in relieving symptoms. Since the 1980s, observational studies have shown that doxylamine and pyridoxine do not pose an increased risk of harm to the fetus. The recommended starting dose is two tablets taken at bedtime on an empty stomach. The combination is marketed by Duchesnay Inc. as Diclegis.

The FDA has approved prothrombin complex concentrate for the rapid reversal of anticoagulation by warfarin and other vitamin K antagonists. Plasma is the only other option for this use currently available, and prothrombin complex can be given at significantly lower volume than plasma. The product is made from pooled plasma of healthy donors that is processed to minimize the risk of viral and other diseases. The approval was based on a study of 216 patients who were anticoagulated and had major bleeding. Plasma complex concentrate was found to be similar to plasma in its ability to stop major bleeding. Plasma complex concentrate is marketed by CSL Behring as Kcentra. ■

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By Louis Kuritzky, MD

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Risks and Benefits of an Extended 10-year Tamoxifen Regimen for Breast Cancer

Source: Davies C, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of estrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805-816.

The prevailing 5-year tamoxifen regimen for breast cancer has been shown to reduce breast cancer mortality by as much as one-third over a 15-year interval; a comparison with a shorter regimen (1-2 year) found the longer duration to be superior. Would even longer tamoxifen administration (i.e., > 5 years) provide even greater risk reduction of breast cancer and its consequences, and if so, would longer regimens induce greater toxicity to other non-targeted tissues (e.g., induction of endometrial cancer)?

The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial randomized women with estrogen receptor-positive breast cancer (B-CA) to either 5 years (n = 3418) or 10 years (n = 3428) of tamoxifen. Follow-up continued for 5 years after conclusion of the 10-year tamoxifen course. The estrogen-receptor positive B-CA group actually represents only about half of all of the women enrolled in ATLAS; the estrogen-receptor negative population of ATLAS demonstrated no risk reduction through longer tamoxifen administration.

Numerous outcomes favored 10-year tamoxifen over 5 years and were statistically significant: B-CA recurrence (617 vs 711 cases), B-CA mortality (639 vs 722 deaths), and ischemic heart disease death or hospitalization (127 vs 163 cases). On the negative side of the equation, all-cause mortality was not impacted by the longer tamoxifen regimen, and there was a significant increase in pulmonary embolism (41 vs 21 cases) as well as endometrial cancers (116 cases vs 63 cases).

These results were apparently sufficiently impressive enough to make the cover story in the *Lancet*. Your reviewer, however, takes pause at the fact that — similar to the situation with results for prostate cancer screening, which has recently been diminished by convincing evidence that screening may reduce prostate cancer mortality but not total mortality — a 10-year tamoxifen regimen reduces B-CA mortality but not total mortality, and has not-insubstantial adverse effects as well as costs. ■

Is There More Pro than Con in Probiotics in Critically Ill Adults?

Source: Barraud D, et al. Impact of the administration of probiotics on mortality in critically ill adult patients. *Chest* 2013; 143:646-655.

The technical definition of probiotic offered by the World Health Organization and the Food and Agriculture Organization sounds promising enough: "viable microorganisms that, when ingested in a sufficient amount, can be beneficial for health." Unfortunately, the existing literature on the benefits of probiotics is not quite so convincing.

Barraud et al performed a meta-analysis of randomized, controlled trials published between 1950-2012 in which probiotics were used in the intensive care unit (ICU) setting, ultimately netting 13 clinical trials, all published after 2002 (n = 1439). The probiotic used in each of these trials was in the *Lactobacillus* family, and although some trials used only one *Lactobacillus* strain, several trials used mixed strains of *Lactobacilli*. Endpoints included ICU mortality, hospital mortality, ICU infections, incidence of diarrhea, and duration of mechanical ventilation.

Of the above-mentioned endpoints, a statistically significant favorable odds ratio was seen only for the incidence of ICU-acquired pneumonia, even though the overall larger category of ICU-acquired infections was not statistically significantly improved. Although the failure to achieve significance to numerous endpoints is disconcerting, the authors point out that since probiotic administration is generally safe, the favorable impact on ICU-acquired pneumonia (a reduction of approximately 40%) might prompt consideration for use in patients known to be particularly at risk for this consequence. ■

Are OSA Outcomes Better in the Hands of Sleep Specialists than Primary Care Clinicians?

Source: Chai-Coetzer CL, et al. Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: A randomized trial. *JAMA* 2013;309:997-1004.

The recognition of obstructive sleep apnea (OSA) as a health burden of compelling epidemiologic presence with significant impact on both quality of life

and cardiovascular health has been recognized by health care providers of essentially all disciplines. Increasingly, sophisticated sleep laboratory monitoring devices allow ever more detailed (and usually more costly) understanding of sleep dysregulation. At the same time, awareness of the frequency and consequences of OSA among diverse disciplines of medicine has resulted in a sufficiently burgeoning population of individuals who merit screening that sleep labs are often unable to keep pace with the increasing demand.

A proliferation of simpler, home-based tools for the identification and potential management of OSA that can be used by sleep specialists and primary care clinicians alike has prompted the question of whether outcomes for OSA patients attended by sleep specialists (who are usually not primary care clinicians), typically with complex sleep analysis tools (which are most commonly employed in a specific sleep laboratory), are superior to outcomes for patients attended by primary care clinicians with less sophisticated home-based tools.

The authors report on a randomized, controlled, non-inferiority trial of patients with OSA identified and treated either in a university sleep laboratory by sleep specialists or by community primary care practices. The primary outcome was improvement in the Epworth Sleepiness Scale, a commonly used and validated scoring system for monitoring sleepiness associated with OSA.

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At the end of the 6-month trial, scores on the Epworth Sleepiness Scales were identical in both groups, and outcomes in the primary care group were determined to be non-inferior to sleep specialist care. Hopefully, primary care clinicians will become more involved in the identification and management of OSA, since equally salutary outcomes are seen in their hands as in the hands of sleep specialists. ■

Inhaled Steroids Increase Risk of TB in COPD Patients

Source: Kim J, et al. Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. *Chest* 2013; 143:1018-1024.

Reactivation of tuberculosis (TB) is an ongoing concern among patients who receive immunosuppressive agents such as TNF-alpha agents for rheumatoid arthritis. Similarly, long-term use of systemic steroids (i.e., ≥ 30 days) in amounts as small as 7.5 mg/day of prednisone increases the risk of TB. Inhaled corticosteroids (ICS) have been associated with systemic effects such as growth retardation (in asthma), reduced bone mineral density, and increased risk of pneumonia (in chronic obstructive pulmonary disease [COPD]). Whether ICS might also be associated with risk for development or reactivation of TB has not been fully clarified.

Kim et al performed a retrospective analysis of COPD patients (n = 620) in a university hospital in South Korea (where the background prevalence of TB is substantially greater than many other nations) to compare the rate of TB activation in persons who had received ICS with controls. To eliminate the confounding factor of systemic steroid use, COPD patients who had received ≥ 7.5 mg for 1 month or more were excluded from the analysis.

There was a substantially greater and statistically significant risk for development of active TB among COPD patients who had been treated with ICS (hazard ratio = 9). In patients whose baseline chest x-ray showed evidence of prior (but quiescent) TB, the hazard ratio for activation of TB was 25!

Although the prevalence of TB is much greater in Korea than in the United States, these data suggest greater vigilance for TB activation in patients chronically using ICS, especially if their x-rays indicate evidence of prior TB. ■

The ASH Position Paper on Orthostatic Hypotension

Source: Shibao C, et al. ASH position paper: Evaluation and treatment of orthostatic hypotension. *J Clin Hypertens* 2013;15:147-153.

Standing from a seated or supine position is normally associated with minimal, if any, blood pressure (BP) change, thanks to homeostatic mechanisms that alter splanchnic and peripheral blood compartments by selective intravascular redistribution and vascular tone. When BP change upon standing exceeds 20/10 mmHg, a diagnosis of orthostatic hypotension (OH) is established. Although tilt-table testing is often suggested for formal diagnosis, simple office measurement of BP 1-3 minutes after standing suffices.

Although sometimes OH produces minor distracting symptoms of dizziness that may be diminished by standing slowly, leg crossing, maintenance of good fluid balance, etc., it can also be a cause of falls, with anticipatable subsequent catastrophes such as hip fracture. Additionally, OH epidemiological data have noted an association between OH and stroke.

A variety of commonly used medications can precipitate or exacerbate OH, including alpha blockers, diuretics, vasodilators, dopamine agonists, and tricyclic antidepressants, modulation of which may OH improve symptoms. Pharmacologic treatments for OH include fludrocortisone (to increase intravascular volume), midodrine (a short-acting vasopressor agent), and other sympathomimetic agents.

OH is also seen in several primary neurologic disorders such as Parkinson's disease, multiple system atrophy, and Lewy body dementia.

Clinicians should suspect OH particularly in patients who report dizziness, unexplained falls, or syncope, although even symptoms such as blurred vision or neck/shoulder pain ("coat hanger" distribution pain) may reflect OH. Fortunately, a variety of lifestyle and pharmacologic treatments can be helpful. ■