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ABSTRACT & COMMENTARY

CABG vs. PCI for Left Main Disease at 5 Years

By Jeffrey Zimmet, MD, PhD

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

SYNOPSIS: Five-year results from the EXCEL trial, which randomized 1,905 patients with left main disease to coronary artery bypass grafting or percutaneous coronary intervention, revealed no significant difference in the primary composite outcome of death, stroke, or myocardial infarction.

SOURCE: Stone GW, Kappetein AP, Sabik JF, et al. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med* 2019;381:1820-1830.

In late 2016, the EXCEL trial investigators, who randomized patients with left main coronary artery disease to coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), published the primary analysis of this important study. The authors reported three-year outcomes, which showed noninferiority of PCI to CABG with respect to a composite of death, myocardial infarction (MI), and stroke at three years.[1] Why do the five-year data merit publication?

EXCEL was an international, multicenter, open-label trial that included patients with significant left main disease and a consensus among the heart team that either PCI or CABG was a valid consideration for revascularization. The design of the trial was such that subjects were intended to present with coronary disease that was of low or intermediate complexity, as defined by a SYNTAX score of ≤ 32. Ultimately, 1,905 patients were randomly assigned at 126 sites to PCI (948 patients) or to CABG (957 patients). Just over half presented with stable angina, with the remainder presenting with acute coronary syndromes. SYNTAX scores in both groups averaged just over 20, with most patients categorized as low complexity. Eighty percent of left main lesions involved the distal bifurcation. Most patients underwent the assigned treatments (942

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of 948 PCI patients; 940 of 957 CABG patients). The primary outcome of death, stroke, or MI at five years occurred in 22% of patients in the PCI group and in 19.2% of patients in the CABG group (difference, 2.8 percentage points; P = 0.13). In contrast, a secondary composite outcome that included ischemia-driven revascularization was more common in the PCI group (31.3% of the PCI group vs. 24.9% of the CABG group; odds ratio, 1.39; P = 0.002).

Among the individual secondary outcomes, ischemia-driven revascularization was more common in the PCI group at five years, whereas cerebrovascular events (although driven primarily by transient ischemic attack rather than by stroke) were seen more commonly among CABG patients. All-cause death at five years accounted for 13% of patients in the PCI group and 9.9% of patients in the CABG group. However, this difference was driven by noncardiovascular deaths (primarily infection and cancer), and its significance is unclear.

The authors concluded that among patients with left main disease of low or intermediate complexity randomized to PCI or CABG, there was no significant difference between the groups at five years in terms of the composite of death, stroke, or MI.

■ COMMENTARY

The interesting part of this paper is not to be found in the abstract. Indeed, the simple tally of the primary composite outcome was not significantly different between the PCI and CABG groups at five years, similar to the result of the initial publication at three years. However, when the results are analyzed during distinct periods following revascularization, a different picture emerges.

Between zero and 30 days after revascularization, PCI showed a distinct advantage over CABG regarding the composite of death, stroke, and MI, with a hazard ratio (HR) of 0.61 (95% confidence interval [CI], 0.42-0.88). This difference was driven primarily by MI, with no significant difference in the other components of the primary endpoint (including stroke, surprisingly). Between 30 days and one year, the two groups are comparable (HR, 1.07; 95% CI, 0.68-1.70). From one year to five years, the data suggest an advantage to CABG (HR comparing PCI to CABG, 1.61; 95% CI, 1.23-2.12). At this later point, the main driver appears to be spontaneous MI, which itself carries a HR of 2.16 (95% CI, 1.27-3.67).

This description of distinct periods of relative risk, wherein the early benefits of PCI from reduced procedural risk are offset by more events during later follow-up, matches a common narrative describing bypass surgery as a preventive measure against future MI.

[The authors suggested 10-year follow-up or longer may be required to fully characterize the long-term benefits and vulnerabilities of these two procedures.]

However, the degree to which this relates to the procedure itself is in question. For example, it is notable that in this randomized trial, medical therapy differed significantly between the CABG and PCI groups. Even at five years, P2Y12 inhibitor use was three-fold higher in the PCI group, while beta-blockers, anti-arrhythmic agents, and oral anticoagulants were significantly more common among CABG patients.

In the end, longer-term data will be required to answer this question more fully. The authors suggested 10-year follow-up or longer may be required to fully characterize the long-term benefits and vulnerabilities of these two procedures. ■

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ABSTRACT & COMMENTARY

Is the Physical Exam an Anachronism in Heart Failure?

By Michael H. Crawford, MD, Editor

SYNOPSIS: In the PARADIGM-HF trial, signs of congestion during physical exam were related to outcomes and the improved outcomes observed with valsartan/sacubitril vs. enalapril.

SOURCES: Selvaraj S, Claggett B, Pozzi A, et al. Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced ejection fraction: PARADIGM-HF. *Circulation* 2019;140:1369-1379.

Drazner MH, Stevenson LW. Relief and prevention of congestion in heart failure enhance quality and length of life. *Circulation* 2019;140:1380-1382.

In the modern bedside ultrasound and cardiac biomarker era, the value of the physical exam is unclear. Investigators from the PARADIGM-HF study of an angiotensin receptor-neprilysin inhibitor vs. an angiotensin-converting enzyme inhibitor for systolic heart failure assessed whether drug therapy influenced the physical exam and if changes in the physical exam were associated with quality of life and prognosis.

This was a study of patients with symptomatic heart failure (HF), a left ventricular ejection fraction (LVEF) < 40%, and a brain natriuretic peptide (BNP) level > 150 pg/mL (or > 100 pg/mL if they had been hospitalized for heart failure in the last 12 months). Exclusion criteria included hypotension, significant renal dysfunction, and elevated serum potassium. The physical exam parameters assessed at each visit were jugular venous distention (JVD), third heart sound (S3), rales, and edema. The primary outcome was a composite of cardiovascular death or first hospitalization for HF.

At baseline among the 8,380 patients randomized, 10% exhibited JVD, 14% edema, 10% S3, 8% rales, and 70% showed no signs of congestion. During follow-up, there was a significant graded relation between the number of signs of congestion and incidence rates for all outcomes. After multivariate adjustments, the hazard ratios for the primary endpoint for one, two, three, or four signs of congestion vs. no signs were 1.48, 1.74, 2.35, and 5.96, respectively ($P < 0.001$ for all).

Valsartan/sacubitril reduced the risk for the primary outcome regardless of the baseline physical exam, but signs of congestion decreased compared to enalapril during treatment ($P = 0.011$). Also, decreases in the number of signs of congestion was associated with improvement in the patients' quality of life (QOL) score and changes in congestion-predicted outcomes after adjusting for baseline congestion ($P < 0.001$).

The authors concluded that in HF with reduced EF patients, the physical exam for congestion is an independent predictor of outcome, even when adjusted for symptoms and BNP levels. Also, improvements in congestion signs are independently associated with fewer cardiovascular events and improved QOL.

■ COMMENTARY

For many of us who frequently manage patients with HF, these results are not surprising, but I suspect they may be for trainees who seem enamored by biomarkers, bedside ultrasound, and implantable pulmonary artery pressure (PAP) monitors. However, studies of natriuretic peptides for management decisions in HF have not shown better outcomes, but increase the cost of care.

Also, in this study, the value of the physical exam was independent of BNP levels. PAP monitors have been shown to be useful, but higher costs, the need for a staffed central monitoring site, and the small but potentially serious risks of these devices has created limited enthusiasm for their use. Bedside ultrasound to examine the JV, the inferior vena cava, and lung water is gaining in popularity, but requires special training, equipment, and more time than the usual outpatient setting allows. On the other hand, trainees' skills at performing a physical exam are waning.

Edema was the most common exam finding in this study, and I have found that trainees are fairly good at assessing edema. Pulmonary rales were least common, but I have found that trainees also are good at detecting rales. One could argue that the routine chest X-ray also is a good pulmonary venous congestion detection tool. However, it is not viable to use X-rays for every outpatient visit. JVD and S3 were equally prevalent findings and are the most challenging for trainees. Hearing an S3 often requires positioning the patient in the left lateral decubitus position and a stethoscope with a true bell. Most of

the internal medicine trainees and medical students I encounter do not own stethoscopes with bells. Detecting JVD can be challenging in obese subjects, and bedside ultrasound may be especially useful in such patients.

This study did not standardize the exam, but still found it to be an independent predictor of outcomes and QOL, the accuracy of which was not related to body mass index. In this study, no confirmatory tests for congestion were performed. Also, physical exam findings could have influenced the decision to admit a patient, but when this was corrected, the relationship to outcomes persisted. Finally, in the TOPCAT trial of patients with HF and preserved EF treated with an aldosterone antagonist, the robust value of the physical exam also was demonstrated.[1] Although the term "congestive heart failure" has fallen out of favor, the importance of congestion has not. In the current patient-centered care era, it is worth noting that a reduction in congestion improves QOL. In fact, eliminating just one sign of congestion in this study significantly improved QOL. Also, reducing congestion improves outcomes. Thus, we should all maintain our physical exam skills and teach them to our trainees. They are an inexpensive and effective way to evaluate the effect of therapy on inpatients and outpatients with HF of all types. ■

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ABSTRACT & COMMENTARY

CRT Nonresponders Experience Poor Outcomes, Warrant More Aggressive Management

By Jamie L. W. Kennedy, MD, FACC

Associate Professor, Division of Cardiology, Advanced Heart Failure & Transplant Cardiology, University of California, San Francisco

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

SYNOPSIS: The ADVANCE CRT registry revealed a significant minority of patients fail to respond to cardiac resynchronization therapy, conferring a worse prognosis.

SOURCE: Varma N, Boehmer J, Bhargava K, et al. Evaluation, management, and outcomes of patients poorly responsive to cardiac resynchronization device therapy. *J Am Coll Cardiol* 2019;74:2588-2603.

Cardiac resynchronization therapy has demonstrated significant morbidity and mortality benefit for patients with systolic heart failure in studies such as COMPANION, CARE-HF, and MADIT-CRT.[1-3] However, about 30% of patients either fail to improve or decline following CRT implantation. These patients have been termed nonresponders. Varma et al sought to characterize the characteristics, management, and outcomes of CRT nonresponders.

The creators of the ADVANCE CRT registry enrolled 1,524 patients between January 2013 and November 2015 within 30 days of implantation of an Abbott CRT or CRT-D device with a quadripolar left ventricular lead. Response to CRT was determined six months after implant using two criteria. First was a site-defined assessment of response based on data such as echocardiography, six-minute walk, quality of life assessment, and New York Heart Association (NYHA) class. It was not standardized across sites. Second was the clinical composite score (CCS), which defined nonresponders as patients who suffered cardiovascular death, experienced a heart failure event (heart failure hospitalization or outpatient IV treatment), demonstrated stable or worsened NYHA class, or exhibited stable or worsened patient global assessment (PGA). Treatment decisions were made based on the site-defined assessment of response.

The patient panel is similar to other heart failure trials: average age 67.9 years, 68.5% male, 67.9% with NYHA class III symptoms, mean left ventricular ejection fraction (LVEF) 29.2%, and 39.3% ischemic etiology. Comorbid conditions included atrial fibrillation (38.4%), diabetes mellitus (37.9%), and chronic kidney disease (16.5%). Left bundle branch block (LBBB) morphology was present in 49.2%, 14.2% demonstrated a narrow baseline QRS but AV node disease warranting pacemaker implantation. Beta-blockers were prescribed to 86% of patients,

angiotensin-converting enzyme inhibitors to 55%, and angiotensin II receptor blockers to 29%. This study predates widespread use of sacubitril/valsartan. Medication doses and the use of aldosterone antagonists were not reported. Eight percent of patients were on inotropes at baseline. The baseline quality of life was similar using the Minnesota Living with Heart Failure (MLWHF) score. Three-quarters of patients underwent implantation of a CRT-D device, the remaining one-quarter a CRT device. The overall percentage of biventricular pacing was 91.4%, with 52.4% achieving ≥ 98% biventricular pacing.

At six months, 20% of patients were nonresponders using site-specific criteria. Responders were slightly but significantly younger (67.5 years vs. 69.6 years), with lower mean LVEF (29.1% vs. 30.6%) and higher NYHA class at baseline. There was no difference in response rate by sex; interestingly, Asians were more often responders and Caucasians nonresponders. Patients with ischemic cardiomyopathy and atrial fibrillation were less likely to respond. Those with LBBB were more likely to improve. Responders had higher percentage of biventricular pacing and fewer comorbid conditions. Patients on inotropes and nitrates were less likely to respond. There was no difference in response rate when comparing CRT-D to CRT patients. Interestingly, there was a higher rate of nonresponders when assessed by Canadian Cardiovascular Society (CCS) score (31%), suggesting site-specific criteria missed one-third of nonresponders.

Site-defined nonresponders received more clinical interventions of all types, including education, medication adjustments, arrhythmia interventions, and device programming changes. However, a significant minority of nonresponders (44.1%) received no additional interventions despite failure to improve. Heart failure specialists evaluated 15.5% of nonresponders; the number of clinic visits with heart failure specialists did not differ between responders and nonresponders (0.1 visits per patient between six and 12 months post-implant).

Outcomes for nonresponders were significantly worse over the six to 12 months following device implant. Heart failure hospitalizations occurred in 12.6% of nonresponders vs. 2.3% of responders. Mortality was 9.2% for nonresponders vs. 2.6% for responders. When expressed by patient-year, deaths were 0.16 for nonresponders vs. 0.03 for responders. Quality of life by the MLWHF score improved from baseline for both groups but remained significantly worse in nonresponders (38.2 to 20.5 for responders vs. 39.7 to 27.9 for nonresponders). The authors concluded that there is a significant number of nonresponders to CRT, who often are managed passively and experience poor outcomes.

■ COMMENTARY

This study reinforces the poor prognosis of heart failure patients who fail to respond to CRT. Despite the poor prognosis, there were no changes in management for nearly half of the nonresponders, suggesting the significance of this prognostic indicator is underappreciated. I would like to see the response rate, subsequent interventions, and outcomes broken down by baseline NYHA class. A patient with NYHA class I symptoms at baseline has little room to improve with CRT, but should still experience a better outcome than the NYHA class IV patient who improves to class III with CRT. The authors did not report the number of patients evaluated for advanced heart failure therapies such as left ventricular assist device or heart transplantation. Presumably, it was no more than the 15.5% who saw heart failure specialists. Of note, only patients who underwent successful CRT implant were included in this registry. Implant techniques have improved over time, but approximately 5% of patients' anatomy is not suitable for coronary sinus lead placement. These patients were not captured in this registry. Furthermore, there is a low (but not zero) rate of implant complications such as pneumothorax, cardiac tamponade, and infection. These complications were not mentioned in this registry.

There are a few important lessons from this study. First, think carefully about CRT in patients unlikely to respond (older patients with multiple comorbidities, non-LBBB pattern, ischemic cardiomyopathy, and atrial fibrillation), as the risks may not justify the benefit. Second, patients should be assessed systematically for improvement six months following CRT implant. For this purpose, the CCS tool seems to be more sensitive than the site-specific assessment algorithms. Third, nonresponders should undergo a comprehensive assessment of their heart failure status and learn about options for intervention, including advanced heart failure therapies. Finally, nonresponders with significant symptom burden and no additional options for intervention would benefit from goals of care discussions. ■

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ABSTRACT & COMMENTARY

Perioperative Management of Direct Oral Anticoagulants

By Michael H. Crawford, MD, Editor

SYNOPSIS: A simple protocol for managing atrial fibrillation patients on direct oral anticoagulants perioperatively was shown to produce low levels of major bleeding and thromboembolism for 30 days postoperatively.

SOURCE: Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. *JAMA Intern Med* 2019; Aug 5. doi: 10.1001/jamainternmed.2019.2431. [Epub ahead of print].

Best practices for interruption of direct oral anticoagulants (DOACs) for elective surgeries or procedures are inconsistent and suffer from a lack of data. Investigators designed the Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) multicentered study, with 23 participating centers in Canada, Europe, and the United States. It was a prospective management study with three cohorts: those on apixaban, dabigatran, or rivaroxaban, all used for atrial fibrillation (AF). The interruption/resumption protocol for each agent was based on pharmacokinetic properties of the DOAC, procedure-associated bleeding risk, and the patient's creatinine clearance (CrCl). Blood samples were taken just before the procedure to measure residual anticoagulation levels later. Heparin bridging was not used. The primary outcomes were major bleeding and arterial thromboembolism for up to 30 days after the procedure. There were 1,257 patients on apixaban, 668 on dabigatran, and 1,082 on rivaroxaban.

The rate of major bleeding was 1.35% for apixaban, 0.90% for dabigatran, and 1.85% for rivaroxaban. In patients undergoing a high bleeding risk procedure, major bleeding occurred in 2.96%, 0.88%, and 2.95%, respectively. The proportion of patients with preoperative DOAC levels of < 50 mg/mL was 90.5%, 95.1%, and 96.8%, respectively. In the subgroups at high bleeding risk, 98.8% registered DOAC levels < 50 mg/mL. The authors concluded that in AF patients on a DOAC undergoing an elective surgery or procedure, a standard perioperative management strategy without heparin bridging or coagulation function testing was associated with low levels of major bleeding (< 2%) and thromboembolism (< 0.5%) over 30 days after procedure. Almost all patients recorded little or no residual anticoagulant levels at the time of the procedure.

■ COMMENTARY

The Douketis et al standard perioperative management protocol was simple, resulting in an adherence rate of 95%. For patients undergoing low bleeding risk procedures, stop DOACs one day prior (except for dabigatran with CrCl < 50 mL/min, then stop two days prior). For high bleeding risk patients, stop DOACs two days prior (except for dabigatran with CrCl < 50 mL/min, then stop four days prior). For low bleeding risk procedures, resume DOACs one day after procedure. For high bleeding risk procedures, resume DOACs two to three days after procedure (assuming hemostasis has been achieved). This was a revelation to me, as I have been managing all DOAC AF patients as if they were undergoing a high bleeding risk procedure by this protocol. Considering the excellent data in this study, it would be hard to prove my approach is safer and more effective for preventing thromboemboli. Even minor to mild bleeding was < 10% with Douketis et al protocol.

The big questions are who were these patients, and were they like the ones you and I see? They were relatively similar to AF patients in population studies. Most patients were Caucasian, mean age was about 72 years, two-thirds were male, body mass index averaged around 30 kg/m^2, and there were considerable comorbidities. The mean CrCl level was ≥ 78 mL/min, < 15% were on aspirin, < 1% were on a P2Y12 inhibitor, and two-thirds were undergoing a low bleeding risk procedure. These were relatively high-risk patients, with a mean CHA_2DS_2-VASc score of 3.5 and a mean HASBLED score of 2. Also, this study should be generalizable, as 85% of those screened participated.

However, few received neuraxial anesthesia, and the size of the dabigatran cohort was considerably smaller than the other two DOAC groups. In addition, if, as some believe, the ideal level of a DOAC prior to surgery should be < 30 mg/mL, this was achieved in 93.1% apixaban patients, 98.9% dabigatran patients, and 85.4% rivaroxaban patients. The authors stated that the lower percentage in the rivaroxaban cohort needs further analysis. Finally, patients with venous thromboembolism and those taking edoxaban were not studied. I believe these data are robust enough to change what I recommend for AF patients on a DOAC undergoing elective procedures or surgery. I plan to use the Douketis et al protocol going forward. ■

ABSTRACT & COMMENTARY

Predicting the Progression of Chronic Aortic Regurgitation

By Michael H. Crawford, MD, Editor

SYNOPSIS: A large database observational study of patients with chronic aortic mild or moderate regurgitation (AR) largely due to bicuspid aortic valve or aortic root dilatation showed that it was largely an indolent disease, with only 20% progressing to moderately severe AR in five years.

SOURCES: Yang LT, Enrizquez-Sarano M, Michelena HI, et al. Predictors of progression in patients with stage B aortic regurgitation. *J Am Coll Cardiol* 2019;74:2480-2492.

Vanoverschelde JL, Vancraeynest D. Progression of aortic regurgitation: The missing link between disease severity and clinical complications. *J Am Coll Cardiol* 2019;74:2493-2495.

Little is known about the progression of mild, asymptomatic aortic valve regurgitation (AR) to severe AR. Investigators from the Mayo Clinic examined their echocardiographic database for patients with any degree of AR short of severe from 2004 to 2017 who met the following criteria: baseline echo with the severity of AR quantitated and at least one other such echo ≥ 3 months hence.

Yang et al excluded those with moderate or more aortic stenosis or mitral valve disease and other cardiac conditions such as complex congenital heart disease. Patients who progressed to moderately severe AR as defined by the American Society of Echocardiography criteria were considered progressors. The primary outcome considered was all-cause mortality. The authors identified 1,077 patients (mean age, 66 years), of whom 18% had trivial or mild AR, 43% had mild to moderate AR, and 39% had moderate AR. Median time to the second echo was 19.5 months. Progression to moderately severe AR in these three severity groups at four years was 4.2, 4.4, and three years, respectively. In total, 21% of study patients progressed over a median of four years; at 10 years, it was 36%.

In a multivariate analysis, aortic root size (annulus and sinotubular junction) and effective regurgitation orifice area (EROA) were strongly associated with progression, but not sinus of Valsalva or ascending aorta size, blood pressure, or medications. Overall survival at five and 10 years was 83% and 67%, respectively. Strong multivariate predictors of survival were age, comorbidities, functional class, resting heart rate, and left ventricular ejection fraction (LVEF). LV end-systolic diameter index was only predictive of survival in those with progression to moderately severe AR. The authors concluded that based on the progression of AR severity observed in their population, echoes performed at five-, three-, and one-year intervals for trivial/mild, mild to moderate, or moderate AR, respectively, should be adequate to detect clinically significant changes in AR parameters such as EROA, regurgitant volume, and annulus and sinotubular junction aortic diameter.

■ COMMENTARY

The most important finding of this study is that chronic mild or moderate AR is an indolent condition over five to 10 years. In contrast, aortic stenosis is uniformly progressive over this time. About 20% of patients progressed to moderately severe AR in five years and 36% at 10 years.

Since severe AR is considered significant regarding surgical decision-making, Yang et al wanted to set this degree of AR as their endpoint, but had to select moderately severe to observe enough patients who progressed to create a robust analysis of factors leading to progression. The major organization guidelines do not recognize the moderately severe category, but the American Society of Echocardiography guidelines do. Also, the authors confirmed older data that show most patients maintain a normal LVEF, and a low EF is an uncommon indication for surgery.

Yang et al did not directly address indications for surgery, but rather sought to determine factors that predict progression. In their multivariate analysis, the authors found the severity of AR by echo, aortic root size, and New York Heart Association class predicted progression. These results are hardly surprising, but do confirm the importance of echocardiography for following chronic AR patients. The authors proposed a follow-up sequence based on AR severity that is different from major guidelines.

However, they confined their study population to those whose echo permitted an advanced quantitative assessment of AR severity. This and other exclusion

criteria eliminated 70% of patients with AR in their database. Quantitation of AR by Doppler echo often is challenging, especially with eccentric jets such as those frequently found in bicuspid aortic valves. Also, all the quantitation measures feature significant shortcomings so that an overall gestalt based on several measures is used to arrive at the severity classification, which is not ideal.

Also of interest is the finding that neither a history of hypertension or elevated systolic blood pressure were related to progression. However, about two-thirds of these patients were on an angiotensin modulator or a calcium blocker. In addition, the importance of diastolic LV size was predictive only in relation to severity of AR, but not as an independent factor. LV end-systolic volume index was predictive only of outcomes in patients with moderately severe or worse AR. In the end, the most reliable predictor of progression may be symptoms; however, symptoms can be difficult to assess since other comorbidities are common in these patients, and the patients age over time.

There were several weaknesses to this study, besides its retrospective design. Yang et al required adequate echoes for quantitation, which limited the sample size. At least two echoes were performed, which would bias the study toward those with more comorbidities. Also, the timing of repeat echoes was variable and inconsistent.

In addition, the authors did not consider the etiology of AR, but two-thirds of their patients featured a dilated aortic root or a bicuspid valve. Thus, applicability to other etiologies of AR may be limited. ■

CME/CE QUESTIONS

1. **Using common clinical measures of response to cardiac resynchronization therapy, what percentage of patients are nonresponders?**
   a. < 5%
   b. 5-10%
   c. 20-30%
   d. 40-50%

2. **Which is the most common clinical sign of congestion in heart failure patients?**
   a. Edema
   b. Jugular venous distention
   c. Third heart sound
   d. Lung rales

3. **In atrial fibrillation patients undergoing elective surgery, except for those on dabigatran with CrCl < 50 mL/min, how many days before the procedure is it safe to stop their direct oral anticoagulant?**
   a. Four
   b. Three
   c. Two
   d. One

4. **A large observational study of chronic mild to moderate aortic valve regurgitation (AR) has shown that which parameter is a strong predictor of progression to moderately severe AR?**
   a. Left ventricular ejection fraction
   b. Systolic blood pressure
   c. Aortic root size
   d. Resting heart rate

5. **An analysis of the outcomes of a large randomized trial of percutaneous coronary intervention vs. coronary artery bypass grafting (CABG) for left main disease showed the superiority of CABG during which period after procedure?**
   a. Zero to 30 days
   b. 30 days to six months
   c. Six months to one year
   d. One year to five years