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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

Vol. 34, Issue 10, October 2015
AHCMedia.com

ABSTRACT & COMMENTARY

A Revolution in Pacing?

By Cara Pellegrini, MD

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

SOURCES: Reddy VY, et al. Percutaneous implantation of an entirely intracardiac leadless pacemaker. *N Engl J Med* 2015. [Epub ahead of print].

Ritter P, et al. Early performance of a miniaturized leadless cardiac pacemaker: The Micra Transcatheter Pacing Study. *Eur Heart J* 2015. [Epub ahead of print].

Nearly 1 million pacemakers are implanted annually for bradycardia or heart block. Adverse events are relatively common and build cumulatively with each generator replacement. The transvenous lead(s) have often been viewed as a "weak link" susceptible to dislodgement, fracture, and insulation failure, and potentially contributing to infection, cardiac perforation, hemo- and pneumothorax, venous occlusion, and tricuspid regurgitation. Extraction of chronically placed leads can be a morbid procedure with a mortality risk of 1-2%. Despite their shrinking size, pulse generators also are associated with risk of infection, pocket hematoma, and skin erosion. For these reasons, a cardiac pacing system devoid of leads and not requiring a subcutaneous pocket is quite attractive.

Two recent multicenter, nonrandomized studies have reported early outcomes with the Nanostim (St. Jude Medical) and Micra transcatheter pacing system (TPS, Medtronic). Both devices are entirely self-contained pacing systems that are delivered to the right ventricle via a percutaneous approach and affixed with a helical screw (Nanostim) or tines (TPS); the Nanostim is longer (42 mm vs 26 mm) but slightly thinner (6 mm vs 6.7 mm diameter). Each device can be repositioned at implantation before it is fully released from the delivery system.

Financial Disclosure: *Clinical Cardiology Alert*'s editor Michael H. Crawford, MD, peer reviewer Susan Zhao, MD, associate managing editor Jonathan Springston, and executive editor Leslie Coplin report no financial relationships relevant to this field of study.

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Clinical Cardiology Alert,
ISSN 0741-4218, is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850 Atlanta, GA 30326.

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

POSTMASTER: Send address changes to *Clinical Cardiology Alert*, P.O. Box 550669, Atlanta, GA 30355.

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Online only, single user: with ***free*** *AMA PRA Category 1 Credits™*: $299

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The LEADLESS II trial by St. Jude Medical involved 100 operators at 56 sites. In this planned interim analysis, efficacy was assessed in the first 300 patients to have 6-month follow-up, and safety outcomes were reported for the entire 526 patient cohort. Medtronic's study reported on efficacy in 60 patients over 3 months and safety outcomes for a larger 140-patient cohort with a shorter overall follow-up period; 37 operators implanted the Micra TPS device at 23 sites. In both studies, mean patient age was approximately 75 years, approximately 60% of patients were male, and the majority had an indication of heart block with atrial fibrillation, though a sizable portion also had sinus node dysfunction with minimal pacing expected, allowing for the placement of a ventricular-only device.

Success rates for implantation were high: 95.8% for Nanostim and 100% for Micra TPS, with 30% and 41% repositioning rates, respectively. Efficacy exceeded the prespecified performance goal for both. Ninety percent of Nanostim patients (93.4% of those with a successful implant) had a therapeutically accepted pacing threshold (≤ 2 volts, at 0.4 milliseconds pulse width) and sensing amplitude through 6 months, exceeding the performance goal of 85%. Among the 60 patients receiving the Micra TPS device, no patient had a pacing threshold > 2 volts (at 0.24 milliseconds). In LEADLESS, there was a 6.7% incidence of device-related serious adverse events with the Nanostim in the primary cohort (6.5% in the total cohort), split among cardiac perforation (1.3%), device dislodgement (1.7%), and elevated pacing threshold necessitating device retrieval and replacement (1.3%). Two deaths were classified as procedure-related, but not device-related. In the smaller Medtronic TPS study, there was one pericardial effusion that required intervention (0.7%) and a higher rate of groin complications: bleeding (2.1%), hematoma (1.4%), and pseudoaneurysm (1.4%); notably, the patient with the effusion had had 18 device repositionings and also suffered a myocardial infarction. There were no procedure-related fatalities. The authors concluded that the leadless pacemakers appeared to be effective and relatively safe in short-term follow-up and noted that more data will be forthcoming.

■ COMMENTARY

While it is obviously the early days for this technology (both devices have CE mark for sale in Europe, but are not FDA approved), the mounting evidence of feasibility, efficacy, and relative safety is encouraging and exciting. However, it is disappointing that a device whose touted advantage is the potential to decrease complications associated with pacemaker implantation has thus far had adverse event rates in excess of what would be expected with implantation of a standard transvenous device. That said, many of the disadvantages of transvenous leads and subcutaneous pockets are not immediately evident but develop over a time course well beyond the 6 month horizon of these studies. Further, complication rates with new technology generally decrease with time and more operator experience; indeed, the complication rate decreased by almost half among the experienced operators who had already performed 10 Nanostim implants in LEADLESS.

Comparison between the two devices is premature, yet a few points can be made. There were more patients with a large number of repositionings in the Medtronic TPS study (4.3% with greater than or equal to five redeployments vs 4.4% with greater than two in LEADLESS). Whether this reflects greater or perceived ease of moving the TPS device or different philosophy of the operators is unclear, but it may explain the slightly better implant rate and capture thresholds with the TPS device. Battery longevity with both is estimated to be comparable to conventional pacing systems — 15.0 ± 6.7 years with the Nanostim and 12.6 (8.6-14.4) years with TPS — though confidence in precise predictive ability is low given limited follow-up thus far. Removal of the Nanostim device has successfully been performed, with little data on the feasibility of extraction beyond 1 year.

The biggest current limitation of this

technology is that it has only been applied to right ventricular pacing, which constitutes a small minority of implanted pacemakers, particularly in the United States. Clearly, these studies are just a first step. Exactly what the niche for these products will be remains an open question. Will they be used in very few selected cases, say for patients with significant venous obstruction, much as what seems to be occurring for the subcutaneous defibrillator, or will they truly become the preferred option for pacing, and in which cardiac chambers? Time will tell. ■

ABSTRACT & COMMENTARY

MATRIX Reloaded: Bivalirudin Fails to Best Heparin in ACS

By Jeffrey Zimmet, MD, PhD

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

SOURCE: Valgimigli M, et al. Bivalirudin or unfractionated heparin in acute coronary syndromes. *N Engl J Med* 2015;373:997-1009.

In patients requiring percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS), determining an optimal anticoagulation strategy has been an elusive goal. Maximizing anti-ischemic efficacy while minimizing bleeding risk is still the ultimate measure of success. Despite the prior publication of 14 clinical trials (and the requisite meta-analysis) comparing bivalirudin to unfractionated heparin in support of PCI, no clear winner has emerged, and several important questions have remained unanswered.

The MATRIX trial, recently presented at the ESC conference and published concurrently in *The New England Journal of Medicine*, was a large multicenter European study that was designed to address three essential issues. The portion of the trial comparing outcomes between transfemoral and transradial access has been previously presented and published. Foremost in the current iteration was the question of whether bivalirudin is superior to heparin with discretionary glycoprotein (GP) IIb/IIIa use in terms of ischemic outcomes and bleeding risk. Several trials have suggested that bivalirudin poses an additional hazard in terms of early stent thrombosis risk, and prolonged post-PCI infusion of bivalirudin has been posited as a potential solution to this problem. The MATRIX trial, therefore, sought to test the efficacy of this practice.

MATRIX analyzed 7213 patients with ACS at 78 centers in Europe. Of these, 55.6% presented with ST segment elevation myocardial infarction (STEMI), while 44.4% were non-ST segment elevation myocardial infarction (NSTEMI), and more than 94% of the total underwent percutaneous coronary intervention (PCI). Patients were randomly assigned to receive either bivalirudin or unfractionated heparin. Interestingly, GP IIb/IIIa inhibitors could be administered at the start of the procedure to any patient in the unfractionated heparin group at the discretion of the operator, but was only to be given in the bivalirudin group as part of a bailout strategy for ischemic complications after PCI. This direction resulted in a large difference in GP inhibitor use between groups — 25.9% of patients in the heparin group, compared with 4.6% in the bivalirudin group. Among patients receiving bivalirudin, patients were assigned 1:1 to either stop the infusion at the end of the procedure or to continue the infusion for several hours afterward in accordance with the manufacturer's directions.

Patients were evaluated at 30 days for the co-primary outcomes — major adverse cardiovascular events (MACE), which was a composite of all-cause death, myocardial infarction, or stroke, and net adverse clinical events, which encompassed MACE plus major bleeding. At 30 days, MACE occurred in 10.3% of patients in the bivalirudin group, and 10.9% of the heparin group ($P = 0.44$). Net adverse clinical events were also not significantly different, at 11.2% and 12.4% ($P = 0.12$). However, analysis of the pre-specified secondary outcomes did show some differences. Rates of major bleeding were significantly lower among bivalirudin patients (1.4% vs 2.5%, $P < 0.001$), and this translated into lower rates of all-cause death and cardiovascular death (1.7% vs 2.3%, and 1.5% vs 2.2%, respectively). On the other hand, prior observations of higher definite stent thrombosis with bivalirudin were confirmed

(1% in the bivalirudin group vs 0.6% in the heparin group, $P = 0.048$). Analysis of the data comparing duration of bivalirudin infusion showed no difference in the primary outcomes with prolonged infusion. Disappointingly, definite stent thrombosis was not lower in the prolonged infusion group. The authors concluded that among patients with ACS referred for percutaneous intervention, bivalirudin did not lower rates of MACE or net adverse clinical outcomes as compared with unfractionated heparin. In addition, the use of prolonged infusions of bivalirudin did not significantly alter the outcomes, including rates of bleeding and stent thrombosis.

■ COMMENTARY

The bivalirudin story in acute coronary syndromes in many ways started with two pivotal trials — ACUITY in NSTEACS patients and HORIZONS-AMI in a STEMI population. Both trials are at least partially built on the premise that unfractionated heparin alone is inferior to heparin plus a GP IIb/IIIa inhibitor for supporting PCI in ACS patients. This position by nature prioritizes ischemic over bleeding complications, and preceded much of the more-recent recognition of the morbidity and mortality associated with pathologic bleeding. Therefore, the major comparisons in these trials were between bivalirudin and heparin + GP IIb/IIIa. Put simply, bivalirudin monotherapy was non-inferior to the combination of heparin plus GP inhibitors for ischemic outcomes, and superior with respect to bleeding. HORIZONS in particular reported a benefit in terms of mortality, while also showing a small-but-significant increase in early stent thrombosis with bivalirudin. The message of these studies was upended last year with the presentation of the HEAT-PPCI trial, which compared heparin with bivalirudin in a large single-center study of STEMI patients. HEAT, which used GP IIb/IIIa inhibitors in a similar-but-low percentage of both heparin and bivalirudin cases, ascribed an advantage to heparin in terms of MACE and stent thrombosis, and showed no significant difference in major bleeding.

Does the MATRIX study act as a "tiebreaker" to parse the conflicting results of prior studies? MATRIX does present the clearest direction regarding prolonged post-PCI infusion of bivalirudin, where no advantage was seen. Even here, however, the failure of the trial to mandate a consistent post-PCI infusion regimen (participants were able to choose one of two quite different dosing schedules that are described on the product label) creates uncertainty that even this question has been answered with finality.

MATRIX was designed to be a pragmatic real-world study, and therefore left the decision about GP inhibitor use up to the operator, at least in heparin-treated patients. This resulted in a large disparity in use of these adjunctive agents between the heparin and bivalirudin groups. In the current environment of aggressive $P2Y_{12}$ inhibitor use and declining GP inhibitor penetration (GP IIb/IIIa inhibitor use was approximately 15% in each group in the more real-world HEAT study, for example), the disproportionate use of GP inhibitors in the heparin group is one of several confounders of this study, clouding both the bleeding and ischemia outcomes. The mortality advantage ascribed to bivalirudin is an interesting point. The authors analyzed dozens of endpoints, and the lack of correction for multiple comparisons means that this finding is hypothesis-generating, but not conclusive. For now, bivalirudin without a prolonged post-procedure infusion remains a viable alternative to unfractionated heparin for the support of PCI in ACS patients, but cannot claim an advantage with respect to a composite of adverse clinical events. ■

ABSTRACT & COMMENTARY

Echocardiographic Parameters Predict Outcome in Peripartum Cardiomyopathy

By Van Selby, MD

Assistant Professor of Medicine, UCSF Cardiology Division, Advanced Heart Failure Section, San Francisco

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

SOURCE: McNamara DM, et al. Clinical outcomes for peripartum cardiomyopathy in North America: Results of the IPAC study (Investigations of Pregnancy-Associated Cardiomyopathy). *J Am Coll Cardiol* 2015;66:905-914.

Peripartum cardiomyopathy (PPCM) affects approximately one in every 2000 births. While the majority of patients with PPCM will recover left ventricular (LV) function, mortality remains high at

6-10%. Because PPCM is such a rare disease, the current evidence base is primarily limited to small, retrospective, single-center studies.

The Investigations of Pregnancy-Associated Cardiomyopathy (IPAC) study prospectively evaluated 100 women with newly diagnosed PPCM within the first 13 weeks postpartum. All subjects had an echocardiogram at baseline and again at 6 and 12 months postpartum. The mean age was 30 years, and the mean LV ejection fraction (EF) was 35 ± 0.1% at baseline. Beta-blockers were used in 88% of subjects, and angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) were used in 81%. Only one patient was treated with bromocriptine.

At 1 year of follow-up, mean LVEF improved to 53 ± 1%, with 72% of all patients achieving an LVEF > 50%. Baseline LV function and LV dimensions were strong predictors of recovery. Ninety-one percent of subjects with both LVEF > 30% and left ventricular end-diastolic diameter (LVEDD) < 6 cm at baseline had full recovery of LV function at 1-year postpartum, compared to 0% of women with both LVEF < 30% and LVEDD > 6 cm. Overall, 1-year event-free survival was 93%. LVEF at baseline was also a powerful predictor of cardiovascular (CV) events. One-year event-free survival was 82% in those with LVEF < 30%, compared to 99% in those with LVEF ≥ 30% ($P = 0.004$).

Black women were a particularly high-risk subgroup, with significantly more LV dysfunction at baseline and at 1-year postpartum ($P < 0.001$). Black women were also more likely to have CV events. At 1 year, 26% of black women had some type of CV event or a final LVEF < 0.35%, compared to 8% of other subjects ($P = 0.03$). Multiparity, maternal age, and New York Heart Association functional class were not predictive of adverse outcomes. The authors concluded that poor baseline LVEF, greater degree of LV dilation, and black race predict poorer subsequent recovery with conventional therapy.

■ COMMENTARY

This is the largest prospective study of PPCM ever conducted, with 30 centers involved. Improvement in cardiac function is more common than previously reported, with most women achieving LVEF > 50% at 1 year. However, despite evidence-based medical therapy for heart failure, more than 20% of patients still have some degree of cardiomyopathy at 1 year and 7% have a serious adverse CV event (death, heart transplant, or LV assist device implantation). Identifying these patients early in the course of the disease has the potential to improve outcomes.

What is most impressive is the utility of standard echocardiographic parameters for risk-stratification in PPCM. The finding that among those with both low EF and LV dilation at baseline, none recovered function at 1 year is particularly valuable, as this identifies a subset that requires not only aggressive medical therapy for heart failure but possibly early referral to an advanced heart failure center for further evaluation. Black women also clearly have worse outcomes, a finding that is consistent with previous studies.

The IPAC analysis also found several previously identified predictors of poor prognosis were not significant in multivariate analyses. This includes multiparity, older maternal age, and blood pressure. It is also worth noting that breastfeeding was not associated with worse outcomes in this study. Because it increases prolactin in the postpartum period, some have suggested breastfeeding should be avoided in mothers with PPCM. Given the multiple proven benefits of breastfeeding, providers should reconsider this recommendation in women with PPCM.

There are several limitations worth mentioning. There was substantial heterogeneity in time to diagnosis. In particular, black women presented significantly later. Black women were also more likely to be hypertensive as well. Both of these factors could help explain the lower EF at baseline and worse outcomes in these patients.

There are currently no clinical guidelines with recommendations regarding the management of PPCM. Going forward, the risk factors identified in this study may serve as targets for investigation. Previous trials of agents such as bromocriptine, pentoxifylline, and intravenous immunoglobulin did not show clear benefit in PPCM. However, this may be due to the fact that a majority of PPCM patients will recover LV function regardless of the intervention. Designing clinical trials for PPCM patients at increased risk (i.e., reduced EF, LV remodeling, black race) may facilitate the identification of effective therapies.

Echocardiography is a relatively inexpensive and risk-free test. It should be considered in any pregnant woman presenting with dyspnea or other symptoms of heart failure, and is the most important prognostic tool in PPCM. Those with high-risk findings require aggressive medical therapy for heart failure, close monitoring, and consideration of early referral to an advanced heart failure center. ■

ABSTRACT & COMMENTARY

Role of Transthoracic Echo in Staph Bacteremia

By Michael Crawford, MD, Editor

SOURCES: Showler A, et al. Use of transthoracic echocardiography in the management of low-risk *Staphylococcus aureus* bacteremia: Results from a retrospective multicenter cohort study. *JACC Cardiovasc Imaging* 2015;8:924-931.

Kaasch AJ, Michels G. *Staphylococcus aureus* bloodstream infection: When is transthoracic echocardiography sufficient? *JACC Cardiovasc Imaging* 2015;8:932-933.

Bacteremia due to *Staphylococcus aureus* (Staph) can be associated with infective endocarditis (IE). Transthoracic echo (TTE) may be falsely negative early in IE, so transesophageal echo (TEE) is often recommended. However, the role of TTE in diagnosing IE in patients with Staph bacteremia is unclear. Thus, investigators from Toronto conducted a retrospective cohort study of 833 hospitalized patients with Staph bacteremia from seven hospitals over a 3-year period between 2007 and 2010. Echoes were performed at the discretion of their primary physician. The primary outcome was diagnosis of IE within 90 days of Staph bacteremia. The 536 patients who received a TTE within 28 days of bacteremia were randomly assigned to derivation and validation cohorts. Multivariate analysis was used to identify high-risk criteria for developing IE in the derivation group, which were then applied to the validation group. Bacteremia was community-acquired in 28%, healthcare-associated in 37%, and nosocomial in 34%. Within 28 days of the first positive blood culture, 54% of the total population had a TTE, 11% TTE and TEE, and 3% had a TEE alone. TTE was normal in 69%, met criteria for IE in 22%, and was indeterminate in 9%. Four clinical criteria predicted IE: indeterminate or positive TTE; community-acquired bacteremia; IV drug use; and the presence of a high-risk cardiac condition. The presence of any one of these criteria in the validation group had a sensitivity of 97% and a specificity of 52%. The negative predictive value was 99% and the positive 25%. The authors concluded that in patients without community-acquired Staph bacteremia, a high-risk cardiac condition, or IV drug use, a negative TTE excluded IE.

■ COMMENTARY

Staph bacteremia is frequent in hospitalized patients and often raises concerns for IE. All guidelines recommend echocardiographic imaging in these cases, but differ in their recommendation for employing TEE. The Infectious Diseases Society of America recommends TEE in all, but various American and European cardiac societies recommend the selected use of TEE. This study addresses this issue and demonstrates that clinical plus TTE data can identify a low-risk group that does not need TEE because the incidence of subsequent IE is < 1%. In their series, using these criteria would decrease TEE use by half. The sensitivity of their criteria for IE was 97% with a negative predictive value of 99%. Specificity and positive predictor values were lower (52 and 25%), but this is probably because of the strict criteria they used for a negative TTE. Not only did the echo have to lack any major Duke Criteria (oscillating mass, perivalvular leak, or abscess), it also lacked nonspecific abnormalities, such as valve thickening, new regurgitation, or non-mobile masses. Also, their clinical criteria excluded patients with any cardiac-foreign material, congenital heart disease, cardiac transplant, valve disease, or a history of IE. Additionally, 15% of the patients had more than one TTE performed. Consequently, none of the patients who would not have needed TEE developed IE in the 90-day follow-up period. Finally, the study is biased toward patients more likely to have IE, since 32% of the total population did not get an echocardiogram. These patients were more likely on a surgical service and less likely community-acquired or associated with IV drug use. So despite being a retrospective observational study, the results are robust and agree with the recommendation of cardiac societies to use TEE selectively in Staph bacteremia.

In this study with an IE prevalence of 14%, TEE would have been indicated in 55% of the patients by their criteria. Interestingly, TEE was performed in only 21% of the 566 patients that had any echo performed, and only 5% had only a TEE performed. Thus, their criteria would actually increase the number of TEEs performed in these seven hospitals. It would appear that TEE is underutilized in practice and few are following the Infectious Disease Societies' recommendation that all Staph bacteremia patients should have TEE. In the absence of better data, we should employ these new, more selective criteria, which are skewed toward higher sensitivity, since Staph IE is such a serious disease with a high incidence of morbidity and mortality. ■

ABSTRACT & COMMENTARY

Two Drugs Better Than One for Pulmonary Arterial Hypertension

By Van Selby, MD

Assistant Professor of Medicine, UCSF Cardiology Division, Advanced Heart Failure Section, San Francisco

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

SOURCE: Galiè N, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015;373:834-844.

Pulmonary arterial hypertension (PAH) is often treated with a step-by-step approach, starting with a single drug and adding subsequent therapies only when a patient fails to respond. Upfront therapy with a combination of drugs targeting different pathways may be a superior strategy, but has not been evaluated in a large randomized trial.

The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial randomized 500 treatment-naïve subjects with PAH and functional class II or III symptoms to combination therapy with ambrisentan (an endothelin receptor antagonist) plus tadalafil (a phosphodiesterase type 5 inhibitor), ambrisentan-monotherapy, or tadalafil-monotherapy. The target doses of tadalafil and ambrisentan were 40 mg and 10 mg daily, respectively. The primary endpoint was time to clinical failure, defined as a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. Combination therapy was compared to a pooled-monotherapy group (patients receiving either tadalafil or ambrisentan-monotherapy).

Upfront combination therapy reduced the risk of clinical failure by 50% compared to monotherapy (hazard ratio, 0.50; 95% confidence interval, 0.35-0.72; $P < 0.001$). The difference was primarily driven by a lower risk of hospitalization in the combination therapy group. There was no difference in the risk of death between the two groups. Combination therapy was also associated with greater reduction in mean N-terminal pro b-type natriuretic peptide level and improvement in 6-minute walk distance (48.98 vs 23.80 meters; $P < 0.001$). There was no significant difference in change in functional class between the groups. Subjects randomized to combination therapy had higher rates of peripheral edema, headache, nasal congestion, and anemia. There were no significant differences in the discontinuation of the study drug or serious adverse events between the groups. The authors concluded that among subjects with PAH who are treatment naïve, initial combination therapy with tadalafil and ambrisentan is associated with significantly lower risk of clinical failure than initial monotherapy with either tadalafil or ambrisentan.

■ COMMENTARY

Currently approved therapies for PAH act on one of three pathways, and there are several reasons why combination therapy would be superior to monotherapy. First, no single drug has been shown to be effective in all PAH patients. Second, PAH is associated with progressive right ventricular failure and death. It makes sense that aggressive, upfront control of the disease would minimize the right ventricular remodeling that ultimately leads to morbidity and mortality in this population. Several studies have shown benefit to multi-drug therapy in PAH, and most patients with PAH will eventually end up on multiple drugs. AMBITION is the first large trial to show a clear benefit from upfront combination therapy. The findings from AMBITION and other recent PAH trials will likely cause a general shift toward more aggressive, upfront, multi-drug therapy for PAH. Similar to the approach used in conditions such as left heart failure or hypertension, there are advantages to initiating aggressive therapy as quickly as possible to get the disease under control rather than waiting to take action until a patient is deteriorating. One small, non-randomized study even looked at the benefits of upfront, three-drug therapy, and it would not be surprising to see this strategy evaluated in a larger trial.

The superiority of combination therapy was observed in all of the subgroups analyzed, including those with milder (WHO functional class II) symptoms. These patients may be more likely to receive single-drug therapy and less frequent follow-up. AMBITION reminds us that even class II patients are at risk for adverse outcomes, including hospitalizations, and the reduction in clinical failures associated with

combination therapy was even greater in the class

II patients than those with class III symptoms.

One important question is whether AMBITION demonstrates the benefit of the particular tadalafil/ambrisentan combination or the general strategy of upfront, two-drug therapy. There is no obvious reason why this particular combination would be particularly synergistic. That said, strict believers in evidence-based medicine will argue that available data only support this combination. Based on the findings of AMBITION, new guidelines published last month from the European Society of Cardiology give a class I recommendation for the use of tadalafil and ambrisentan as initial combination therapy for PAH, while other drug combinations receive class II recommendations.

In light of AMBITION and other recent trials, the era of starting PAH patients on a single drug and seeing them again for follow-up 6 months later is over. Outside of large PAH centers, those who are comfortable prescribing multiple classes of PAH therapies may choose to continue managing some PAH patients on their own. For many providers the increasingly complex PAH landscape and need to at least consider combination therapy in all patients will prompt more referrals to specialized centers. The results of AMBITION support initiating these referrals as soon as possible to begin an appropriate regimen in a timely manner. ■

CME QUESTIONS

1. **A transthoracic echo is useful for excluding infective endocarditis in patients with Staph bacteremia, but without:**
   a. community-acquired Staph.
   b. a high-risk cardiac condition.
   c. IV drug use.
   d. All of the above

2. **At this time, early device complications for the new, self-contained right ventricular pacing systems compared to standard systems are:**
   a. higher.
   b. lower.
   c. the same.
   d. not reported yet.

3. **Recent trials suggest that symptomatic patients with pulmonary arterial hypertension should be started on:**
   a. ambrisentan.
   b. tadalafil.
   c. both A and B.
   d. epoprostenol.

4. **An adverse prognosis in peripartum cardiomyopathy can be predicted by which echo parameters?**
   a. LVEDD > 5 cm
   b. LVEF < 30%
   c. LVESD > 3.5 cm
   d. TAPSE < 2.0

5. **A recent large trial has shown that the use of bivalirudin vs heparin in acute coronary syndromes treated invasively results in:**
   a. lower major adverse cardiac events.
   b. lower major bleeding.
   c. lower stent thrombosis.
   d. All of the above

CME OBJECTIVES

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

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