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INSIDE

Financial Disclosure:

Clinical Cardiology Alert's physician editor, Michael H. Crawford, MD, is on the speaker's bureau for Pfizer. The peer reviewer, Ethan Weiss, MD, reports no consultant, stockholder, speaker's bureau, or other financial relationship with any company related to this field of study.

Transcatheter Aortic Valve Implantation for Aortic Stenosis

ABSTRACT & COMMENTARY

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.

Sources: Leon MB, et al. Transcatheter aortic valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010; online pre-print; Gurvitch R, et al. Transcatheter aortic valve implantation. Durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. *Circulation*. 2010;122:1319-1327.

THERE IS NO MEDICAL THERAPY FOR AORTIC STENOSIS (AS), AND BALLOON AORtic valvuloplasty (BAV) has sub-optimal long-term results. The incidence of AS increases with age and, thus, many patients have significant comorbidities. These patients are often denied surgical aortic valve replacement (AVR) because of the high risk of surgery when serious comorbidities are present, and there has been no other treatment option for them. Percutaneous transcatheter aortic valve implantation (TAVI) may represent an alternative treatment option for patients at prohibitively high risk to undergo surgical AVR. Recently, the results of the PARTNER trial were presented at the Transcatheter Cardiovascular Therapeutics meeting, and the longer-term results from a Canadian registry also were released. These studies provide data to support the use of TAVI in patients with severe AS who have are too high risk to undergo surgical AVR.

The PARTNER trail was a randomized, controlled trial performed at 21 centers (17 in the United States) of TAVI vs. standard care in patients with symptomatic severe AS who were not candidates for surgical AVR. Inclusion criteria were New York Heart Association class II-IV symptoms and an aortic valve area of < 0.8 cm^2, a mean aortic valve gradient of > 40 mmHg, or a peak aortic valve velocity of > 4.0 m/sec. All were considered too high risk for surgical AVR by at least two cardiac surgeons. Exclusion criteria included a bicuspid or non-calcified aortic valve, reduced left ventricular ejection fraction (< 20%), acute myocardial infarction (MI), coronary artery disease

VOLUME 29 • NUMBER 11 • NOVEMBER 2010 • PAGES 81-88

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requiring revascularization, severe mitral or aortic regurgitation, stroke or transient ischemic attack (TIA) in the prior six months, severe peripheral vascular disease, and aortic valve diameter that was not between 18 and 25 mm (therefore unsuitable for the currently available valve sizes). The trial was sponsored by Edwards, which manufacture the valve. The valve was implanted via the femoral artery after standard BAV in either the operating room or the cardiac catheterization laboratory. The valve consists of a bovine pericardial trileaflet valve mounted on a stainless steel frame that is balloon-expanded inside the existing aortic valve.

The baseline characteristics of the two treatment groups were similar, but the standard-care group had slightly higher rates of COPD (52.5% vs. 41.3%; $p = 0.04$), atrial fibrillation (48.8% vs. 32.9%; $p = 0.04$), and a higher logistic Euroscore (30.4 ± 19.1 vs. 26.4±17.2; $p = 0.04$). The mean age was 83 years in each group and the STS score (Society of Thoracic Surgeons score), a predictor of surgical mortality, was similar between groups (12.1 ± 6.1 vs. 11.2 ± 5.8, $p = 0.14$). TAVI resulted in immediate improvement in aortic valve area from 0.6 ± 0.2 cm^2 to 1.5 ± 0.5 cm^2, as well as a reduction in aortic mean valve gradient from 44.5 ± 15.7 mmHg to 11.1 ± 6.9 mmHg, and these improvements were maintained at one-year follow-up.

The primary endpoint was all-cause mortality at one year. Patients randomized to standard care (n = 358) had a higher one-year mortality of 50.7%, patients randomized to TAVI had a lower mortality (30.7%; hazard ratio 0.55, $p < 0.001$). Patients randomized to TAVI also had lower rates of cardiovascular death (20.5% vs. 44.6%, $p < 0.001$), death or repeat hospitalization ($p < 0.001$), and death or major stroke (33.1% vs. 51.3%, $p < 0.001$). Patients randomized to TAVI had improvement in symptoms and six-minute walk test. However, the improved mortality comes at a price. Patients randomized to TAVI had a higher rate of stroke or TIA (10.6% vs. 4.5%, $p = 0.04$), driven mainly by an increase in major stroke in the first 30 days (5.0% vs. 1.1%, $p = 0.06$). There was a higher incidence of vascular complications (32.4% vs. 7.3%, $p < 0.001$) and major bleeding (22.3% vs. 11.2%, $p < 0.001$) in the TAVI group. Importantly, there were no differences between groups in the rates of acute kidney injury, new atrial fibrillation, MI, new pacemaker requirement, or endocarditis. Despite all being considered unsuitable for surgical AVR, 17 patients in the standard-care group and two patients in the TAVI group underwent surgical AVR during the study. The authors concluded that in patients with severe AS who were not suitable for surgical AVR, TAVI significantly reduced the rates of death, the composite of death or repeat hospitalization, and cardiac symptoms, despite the higher incidence of strokes and major vascular events.

Gurvitch and colleagues present their data on three-year follow-up of patients undergoing TAVI in Canada. Unlike the PARTNER trial, this is not a randomized, controlled trial, it is a registry of 70 patients undergoing TAVI who were considered unsuitable for surgical AVR. The patients had a STS score 9.6 ± 3.5% and a mean age 80.7 ± 7.6 years, indicating a high-risk population. The patients received either the Edwards Sapien balloon expandable valve or the earlier generation Cribier-Edwards valve; 78.6% of cases were performed by the trans-femoral route and 21.4% via the trans-apical route. Patients were routinely prescribed aspirin for life and clopidogrel for six months after the procedure. All patients were followed for at least three years. The researchers excluded from their analysis those patients who died in the first 30 days, because these were thought to be due to procedural difficulties and the initial learning curve rather than problems with the device.

In those patients who survived the first 30 days after TAVI, survival at one, two, and three years was 81%, 74%, and 61%, respectively. One patient required re-operation from endocarditis, but no patients required re-operation for valve dysfunction. The aortic valve gradient decreased from 45 mmHg to 10 mmHg after the procedure ($p < 0.01$) and increased slightly to 12.1 mmHg after three years ($p = 0.03$). Valve area increased from 0.6 ± 0.2 cm^2 to 1.7 ± 0.4 cm^2 after the procedure ($p < 0.01$) and reduced to 1.4 ± 0.3 cm^2 after three years ($p < 0.01$). At baseline, 1%, 3%, 69%, and 17% were in NYHA class I, II, III, and IV, respectively. At one-year follow-up, 93% of patients were in NYHA class I or II. This improvement was sustained with no change from 1-3 years post-procedure. After TAVI, aortic regurgitation (AR) was common: it was trivial in 40%, mild in 44%, and moderate in 6%; no patients had severe AR. One patient with mild AR worsened to moderate; of the patients with moderate AR, two improved to mild and two remained unchanged. This

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

MANAGING EDITOR: Leslie Hamlin.
EXECUTIVE EDITOR: Russ Underwood.
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Clinical Cardiology Alert,*** P.O. Box 740059, Atlanta, GA 30374.

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

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1 year with free AMA Category 1 credits: $319
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suggests that the degree of AR seen immediately post-procedure remains largely unchanged over three years. There were no cases of valve thrombosis, deterioration, or embolization. The authors conclude that TAVI demonstrates good medium- to long-term durability and preserved hemodynamic function, with no evidence of structural failure.

■ **COMMENTARY**

Surgical AVR remains the gold-standard treatment for severe symptomatic AS. However, there remain a group of patients who are at high surgical risk due to other co-morbidities, who are unable to undergo surgical AVR. As our population ages, this patient group is likely to increase in size substantially, and there is currently a very high mortality (50% at one year) and no definitive therapy for this group. The randomized, controlled PARTNER trial demonstrated a 20% absolute reduction (40% relative risk reduction) in mortality if these patients undergo TAVI instead of medical therapy. This is a staggering improvement in all-cause mortality compared to most cardiology trials. Importantly, quality of life also is improved. The additional three-year data from Gurvitch and colleagues shows us that this early benefit is likely to be sustained. Their cohort maintained their hemodynamic and symptomatic improvement for over three years.

However, this is no free lunch. It is important to note the significant procedural risks involved with TAVI. The procedure requires large arterial sheaths that can cause significant vascular complications and bleeding. Furthermore, there is a significant peri-procedural risk of stroke. Notably, over 80% of the standard-therapy patients received BAV, which is not usually the standard of care. BAV may have increased the rate of early stroke and vascular complications in the standard-therapy group, thus underestimating the difference between the groups. We should, thus, look at the absolute rates of stroke and vascular access site complications. Interestingly, many of the late complications in the Canadian registry occurred due to combination anti-platelet therapy and warfarin, or over-anti-coagulation. In future, it will be important to define the optimal anti-thrombotic therapy in this group. TAVI is not FDA-approved for use in the United States, but is already on the market in other countries, as wel as Europe. This is a promising new treatment strategy, reducing the high mortality in this very high-risk population, but its benefits must be weighed against its early risks. ■

Control BP and Pain in Type B Aortic Dissection

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

Source: Trimarchi S, et al. Importance of refractory pain and hypertension in acute type B aortic dissection. Insights from the International Registry of Acute Aortic Dissection (IRAD). *Circulation*. 2010;122:1283-1289.

Indications for surgical or interventional management in acute type B aortic dissection (ABAD) include malperfusion syndromes, progression of dissection, and aneurysm expansion. The prognostic significance of refractory pain and high blood pressure (BP) are not completely understood. Accordingly, Trimarchi and colleagues examined the IRAD database to determine the effects of ongoing pain and incomplete blood pressure control on in-hospital outcomes.

The IRAD registry is an international multi-center registry of patients presenting with acute aortic dissection. This study presents data on patients presenting between 1996 and 2004 with ABAD. They included patients with ABAD and patients with intramural hematoma. ABAD was defined as an aortic dissection involving the descending aorta with no tear in the ascending aorta or arch, and intramural hematoma was defined as a regionally thickened aortic wall with no double lumen or entry flap. The patients were separated into group 1 (intermediate risk) with recurrent or refractory pain and/or refractory hypertension but no other clinical complications; group 2 (low risk) with no refractory pain or hypertension and no other clinical complications; and group 3 (high risk) with one or more of the following complications: shock, peri-aortic hematoma, spinal cord ischemia, pre-operative mesenteric ischemia/infarction, acute renal failure, or limb ischemia. Group 3 were excluded from this analysis, as they were considered to have indications for surgery and analysis was confined to the 365 patients in groups 1 and 2.

The mean age of patients was 63.5 years, 5% had diabetes and 33% were female. Intramural hematoma was present in 11.4%. Baseline characteristics were well matched between groups, except for a higher prevalence of Marfan's syndrome in group 1 (7.3% vs. 2.1%, $p = 0.03$), as well as higher rates of abrupt pain onset (92.2% vs. 81.3%, $p = 0.03$), migrating pain (35.5% vs. 16.6%, $p = 0.0008$), and radiating pain (51.6% vs. 33.6%, $p = 0.007$). Patients in group 1 (n = 69) were more likely to undergo surgical (36.2% vs. 8.4%, $p < 0.001$) or endovascular therapy (39.1% vs. 3.7%, $p < 0.001$) than patients in group 2 (n = 296). There was longer time to invasive treatment in group 1 than in group 2 (240 hrs vs. 99 hrs, $p < 0.01$). Overall in-hospital mortality in patients with recurrent/refractory pain or refractory hypertension (group 1) was higher than in those without (group 2) [17.4% vs. 4.0%, $p < 0.001$]. In those managed medically, group 1 also had a higher mortality (35.6% vs. 1.5%, $p < 0.001$). Multivariable analysis showed that refractory/recurrent pain or refractory hypertension are associated with higher risk of in-hospital mortality (odds ratio 3.3, $p = 0.04$), as are age > 70 years (OR 5.1, $p < 0.01$) and absence of chest pain (OR 3.5, $p = 0.05$).

The authors conclude that in uncomplicated ABAD patients, medical therapy was associated with excellent in-hospital outcomes. By contrast, the presence of recurrent pain and/or refractory hypertension was associated with increased in-hospital mortality, particularly in those patients managed medically. These observations suggest that aortic interventions, such as by an endovascular approach, may be indicated in this intermediate-risk group.

■ **COMMENTARY**

Type B aortic dissections traditionally have been managed medically, as advised in the ACC/AHA guidelines, with surgery or endovascular therapy being reserved for cases of impending aortic rupture or side-branch compromise. The current study reinforces the importance of strict BP and pain control in patients managed medically. Although this is a retrospective, observational study, rather than a prospective, randomized trial, it appears that inadequate pain or BP control is associated with higher in-hospital mortality, especially in the patients managed medically. Whether these patients should undergo more invasive therapy remains unknown, and the authors' conclusion that an endovascular approach may be warranted is probably somewhat overzealous. With the rapid evolution of endovascular therapies and the variation in regional practice patterns and experience with these technologies, it is difficult to make any conclusions from this data set. Furthermore, the equipment used in 1996 is already obsolete, and endovascular therapy was only used in the minority (38 patients; 10.4% of the cohort). Thus, the most appropriate conclusion from this study is to underscore the importance of strict BP and pain control in patients with acute type B aortic dissection. ■

Unilateral Pulmonary Edema

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Attias D, et al. Prevalence, characteristics, and outcomes of patients presenting with cardiogenic unilateral pulmonary edema. *Circulation*. 2010;122:1109-1115.

CARDIOGENIC UNILATERAL PULMONARY EDEMA IS UNUSUAL AND, if it is the presenting manifestation of heart failure, diagnosis and appropriate treatment may be delayed. Thus, these investigators from France reviewed 869 cases of cardiogenic pulmonary edema admitted over eight years to assess the prevalence and clinical features of unilateral pulmonary edema. Echocardiograms were obtained within 48 hours in 96% of the patients.

Results: Bilateral edema was present in 851 (98%) and unilateral in 18 (2%). Severe mitral regurgitation (MR) was found in 71 (8%). Unilateral edema was right-sided in most (89%). All patients with unilateral edema had severe MR, and the radiological location of the edema in the lungs was related to the direction of the MR jet. Only 6% of the patients with bilateral edema had severe MR. A murmur was heard in about two-thirds of patients with severe MR, but it was more likely in those with organic MR (83%) vs. functional MR (43%). Delay in treatment (> 6 hours from presentation) was more common in unilateral edema as compared to bilateral edema patients (33 vs. 4%, $p < 0.003$). Total in-hospital mortality was 9%, and was higher in those with unilateral edema as compared to bilateral edema (39% vs. 8%, OR 6.9, 95% CI 2.6-18, $p < 0.001$). Multivariate analysis for clinical factors associated with death showed that unilateral edema was the most predictive variable. The authors concluded that unilateral pulmonary edema is infrequent (2% of pulmonary edema cases), usually involves the right lung, and is almost always associated with acute severe MR. The presence of unilateral edema delays treatment and is associated with greater mortality.

■ **COMMENTARY**

Unilateral pulmonary edema in this series was unusual (2% of cardiac pulmonary edema), but was always associated with severe mitral regurgitation (MR). Among their patients presenting with pulmonary edema due to severe MR, unilateral edema was seen in 25%. Their series demonstrates that the diagnosis of cardiac edema was often delayed when unilateral edema was present. In fact, pneumonia was often suspected, and 61% were treated with antibiotics even though only 11% had fever. Unfortunately, you cannot rely on the presence of a murmur to help you arrive at the correct diagnosis. Although over 80% of those with organic MR had murmurs, less than half of those with functional murmurs did. Also, an elevated leukocyte count was frequent (72%) in those with unilateral edema. Thus, if you suspect a cardiac cause, an echocardiogram should be done.

Echocardiography suggested that unilateral edema is due to the regurgitant jet preferentially impacting the pulmonary veins from one lung. Prior invasive studies of patients with severe MR and eccentric jets have confirmed that pulmonary capillary wedge pressures can be higher in one lung vs. the other. Interestingly, involvement of the right lung is more common perhaps because the more common posterior leaflet prolapse usually directs the MR jet toward the right pulmonary veins. Anterior leaflet prolapse often is directed toward the left pulmonary veins. Whether the observed increase in mortality in patients with unilateral edema is due to the delay in diagnosis is unclear. In this series, these patients had lower blood pressures and were more likely to be on

mechanical ventilation and pressors. Also, all patients with unilateral edema had severe MR, whereas only 6% of those with bilateral edema did. Thus, it appears that delaying the diagnosis of severe MR is detrimental to survival. ■

Right and Left Ventricular Biopsies

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Yilmaz A. et al. Comparative evaluation of left and right ventricular endomyocardial biopsy. *Circulation*. 2010;122:900-909.

The safety and diagnostic performance of right and left ventricular endomyocardial biopsy in patients with suspected myocarditis or non-ischemic cardiomyopathy is poorly understood, especially with contemporary techniques, such as MRI guidance. Thus, these investigators from two centers in Germany studied 755 patients with suspected myocarditis (n = 481) or non-ischemic cardiomyopathy (n = 274) who underwent LV biopsy (35%), RV biopsy (18%), or both (47%) after exclusion of coronary artery disease by angiography. MRI was performed in 72%.

Results: LV biopsy resulted in four major complications (0.64%), and consisted of two perforations and two strokes. RV biopsy resulted in four perforations (0.82%). Minor complications included transient chest pain, pericardial effusion, and non-sustained VT in both groups. Transient hypotension and temporary heart block was observed in RV-biopsy patients only. The minor complication rate varied from 2%-5% depending on which ventricle biopsy a pericardial effusion was assigned. Diagnostic results were obtained more often with bilateral biopsies (79%) vs. one ventricle (67%, $p < 0.001$). Using gadolinium enhancement on MRI to direct the biopsy did not enhance the diagnostic yield. Diagnostic histologic findings were absent in 28% of patients. Using biopsy diagnosis as the gold standard, late gadolinium enhancement presence had a sensitivity of 54% and a specificity of 64% for the diagnosis of myocarditis. The authors concluded that both LV and RV biopsy are safe, and combining both enhances the diagnostic yield, but MRI guidance does not.

■ COMMENTARY

The two interesting aspects of this retrospective review of the experience with endomyocardial biopsies at two German centers are the very low complication rates and the relatively high diagnostic yield. Previous studies of myocardial biopsy for suspected acute myocarditis showed a low yield and no improvement in outcomes. This study used modern diagnostic techniques in addition to histopathology and obtained diagnostically useful information in four out of five patients. Of course, this study was broader than the prior acute myocarditis studies, as they included patients with chronic cardiomyopathies, such as amyloidosis. Also, they used PCR to detect viral genomes. Tissue evidence of myocarditis occurred in 44% of their patients and viral genomes were found in 42%, for a combined diagnostic yield in their series of 61%. The combined yield in those with bilateral biopsies was 71% vs. 51% in those with one ventricle biopsied.

Encouraging data from MRI reports have suggested that MRI with late gadolinium enhancement may be a noninvasive technique for diagnosing myocarditis, or at least a tool for guiding biopsy to higher yield areas. This potential was not realized in this study. MRI exhibited modest sensitivity and specificity for the diagnosis of myocarditis. MRI was performed selectively in about three-quarters of the patients. Late gadolinium enhancement was seen in 53%. It was not feasible to reach every enhanced area with the bioptome, but it could be used to select which ventricle to sample. There was no relation between the location of MRI enhancement and the diagnostic yield of the biopsies. Thus, MRI appears to be of little value in the management of patients with suspected myocarditis.

The low major complication rate of biopsies in this series (< 1% for both ventricles) is encouraging. Of course these are large, experienced centers, so results may vary in different institutions. However, the data suggest that bilateral biopsies should be done, since they significantly increased the diagnostic yield without increasing the major complication rate. Of note, stroke was only observed with LV biopsy. Perforations with hemopericardium were observed with both ventricles.

In experienced hands, bilateral ventricular biopsies are safe and increase the diagnostic yield, especially if modern diagnostic techniques are applied to the samples. What is still unknown is whether this enhanced diagnostic ability alters outcomes in patients with myocarditis. ■

New Therapy for Inappropriate Sinus Tachycardia

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD
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Dr. DiMarco receives grant/research support from Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

Source: Calo L, et al. Efficacy of ivabradine administration in patients affected by inappropriate sinus tachycardia. *Heart Rhythm*. 2010;7:1318-1323

Inappropriate sinus tachycardia (IST) is a nonparoxysmal arrhythmia characterized by either a continuous sinus tachycardia or intermittent periods of inappropriately rapid sinus rates. It occurs most frequently in women, many of whom are health care workers. In this paper, Calo and associates from Rome, Italy, report the effects of the novel I_f current blocker, ivabradine, in a small group of patients with IST. The authors identified 18 patients with IST characterized by recurrent palpitations and physical stress intolerance. Secondary causes of sinus tachycardia and significant structural heart disease were excluded. All patients had failed trials with either beta adrenergic blockers and/or nondihydropyridine calcium-channel blockers. At baseline, each patient underwent physical examination, a resting ECG, a 24-hour ambulatory ECG (AECG), and a symptom-limited exercise test. The same panel of tests was repeated at three and six months follow-up during ivabradine therapy. This was an observational, uncontrolled study. The starting dose of ivabradine was 5 mg twice daily, and the dose could be titrated up to 7.5 mg twice daily at the three-month follow-up in patients with persistent symptoms, or could be lowered to 2.5 mg twice daily if side effects developed.

Sixteen patients successfully completed the study. One patient stopped ivabradine because of the development of phosgenes, an ocular toxicity seen with ivabradine, and one patient was noncompliant with the protocol. The final group included 14 women and two men, with a mean age of 41 $\pm$ 14 years. At baseline, the mean heart rate on resting ECG was 107 $\pm$ 7 bpm. During 24-hour AECG, the mean, maximal, and minimal heart rates were 98 $\pm$ 5 bpm, 151 $\pm$ 21 bpm, and 62 $\pm$ 4 bpm, respectively. The maximum heart rate during exercise testing was 157 $\pm$ 24 bpm. This heart rate was achieved despite relatively low workloads, with 75% of the patients only reaching workloads of $\leq$ 75 watts. During ivabradine therapy, the mean resting heart rate at three months had declined to 85 + 5 bpm, and it declined further at six months to 72 + 5 bpm. Similar magnitude heart-rate reductions were noted by ambulatory ECG. The mean 24-hour heart rate decreased to 76 $\pm$ 8 bpm after three months and to 68 $\pm$ 4 bpm after six months. Similar changes also were noted in maximum heart rate at both three and six months. The minimum heart rate also declined to 52 $\pm$ 5 bpm at three months and 50 $\pm$ 6 bpm at six months. During exercise, similar percentage reductions in maximum heart rate were observed at both follow-up time points. The maximum workload achieved during exercise increased in all patients, with 75% now reaching workloads over 100 watts. Symptoms had completely resolved in 12 of 16 patients by the three-month time point and in all 16 patients at six months.

The authors conclude that ivabradine offers a new pharmacologic option for patients with IST.

■ **COMMENTARY**

Inappropriate sinus tachycardia can have several different presentations. Some patients are persistently tachycardic and do not have normal heart rates even during sleep. Others may have marked variability in heart rate during normal activities, swinging between periods of bradycardia and tachycardia unpredictably. Some other patients, such as those with the postural orthostatic tachycardia syndrome, have other manifestations of autonomic nervous system dysfunction.

Patients with inappropriate sinus tachycardia are often quite difficult to manage. Many do not respond to beta-adrenergic blockers or calcium-channel blockers. Although catheter ablation may be attempted, successful long-term results are difficult to achieve. I have had true success with ablation only in those patients who present with continuous tachycardia. In this paper, the authors present preliminary evidence that ivabradine may be successful in patients with IST. Ivabradine is an I_f channel blocker with little or no effect on other cardiac ion channels. Although ivabradine is available for general use in Europe for the treatment of angina, unfortunately, it is not now available in the United States. Clearly, larger randomized trials of ivabradine in patients with IST are needed to prove its value, but the data here suggest that it may be uniquely helpful in this group of patients. ■

Arrhythmias in Adults with Repaired Tetralogy of Fallot

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Khairy P. Arrhythmia burden in adults with surgically repaired tetralogy of fallot. *Circulation*. 2010;122:868-875.

In this paper, Khairy and colleagues from the Alliance for Adult Research in Congenital Cardiology (AARCC) conducted a multi-center, cross-sectional study on the prevalence of arrhythmias in adult patients who had previously undergone surgical repair of either tetralogy of Fallot or pulmonary atresia with ventricular septal defect. The patients were collected by the 11 U.S. and Canadian centers that participate in the AARCC and followed in a single database. Data analyzed included demographic variables, comorbidities, anatomical features, surgical history, antiarrhythmic catheter interventions, medical therapy, and clinical arrhythmias. Arrhythmia-specific data included current rhythm, most recent QRS

duration, history of sustained arrhythmias, and history of arrhythmia interventions, including electrophysiologic studies, catheter ablation procedures, and pacemaker or implantable cardioverter-defibrillator (ICD) insertions. Data from 556 patients are included in this report. The mean age at the time of data collection was 36.8 ± 12 years. The patients had undergone a mean of 2.5 ± 1.5 cardiac surgeries with prior palliative shunts in 47%, pulmonary transannular patches in 80%, RV-to-pulmonary-artery conduits in 11%, and pulmonic valve replacement in 43%. The median age at corrective surgery was 5.0 years. The average left ventricular ejection fraction at last follow-up was 58 ± 9%. LV diastolic dysfunction was present in 25%, and 16% had moderate or greater systolic right ventricular dysfunction. Pulmonic and tricuspid regurgitation of at least moderate severity was present in 47.6% and 15.3% of the group, respectively. Sustained atrial arrhythmias had been noted in 89 patients, sustained ventricular arrhythmias in 81 patients, and no arrhythmias in 408 patients.

A history of at least one clinically sustained arrhythmia, implantation of a pacemaker or ICD, or a catheter-ablation procedure was noted in 43% of the patients. Pacemakers were placed for bradycardia indications in 7.9% of the patients. ICDs were implanted in 10.4% of the patients, with 27 patients receiving them for primary prevention of sudden death and 19 patients receiving them after a sustained episode of ventricular tachycardia or ventricular fibrillation. Twelve of 27 patients who received an ICD for primary prevention later experienced one or more episodes of clinical ventricular arrhythmia that was treated by their ICD. Clinical, sustained ventricular tachycardia was documented in 79 patients (14.2%). In the multivariate analysis, the number of prior cardiac surgeries, the QRS duration, and the presence of left diastolic dysfunction were significant predictors of ventricular arrhythmias.

Atrial tachyarrhythmias were noted in 20.1% of the study group. Intra-atrial reentrant tachycardia was seen in 11.5%, atrial fibrillation in 7.4%, and other arrhythmias in 6.7%. Intra-atrial reentrant tachycardia was associated with the increased number of prior cardiac surgeries and the presence of either hypertension or right atrial enlargement. Atrial fibrillation was associated with age, prior cardiac surgery, left atrial enlargement, and decreased ejection fraction.

The authors conclude that the arrhythmia burden in adults with surgical repair tetralogy of Fallot is high, with a high prevalence of sustained atrial and ventricular arrhythmias and bradycardia. Both atrial and ventricular arrhythmias increase with age. Atrial fibrillation and ventricular arrhythmias were more common in patients with left ventricular dysfunction. The identification of diastolic dysfunction as a risk factor for ventricular arrhythmias is a new observation.

■ COMMENTARY

This study provides important data on the prevalence and natural history of atrial and ventricular arrhythmias after surgical correction of tetralogy of Fallot. The high prevalence of atrial and ventricular arrhythmias and bradycardia in these patients clearly indicates the need for careful long-term follow-up. It is difficult from these data to know if improved surgical techniques used in the last two decades will lower the incidence of late post-operative arrhythmias. The authors clearly document that the prevalence of arrhythmias seems to increase markedly 30-40 years after surgery. Therefore, the highest prevalence is seen in those who were operated on more than 25-30 years ago. Hopefully, the more recent tendencies for earlier complete repair will lower the future prevalence of arrhythmias in these patients. ■

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. ■

CME Questions

21. Which of the following is a new treatment for inappropriate sinus tachycardia?

a. Nebivolol
b. Ranolazine
c. Prasugrel
d. Ivabradine

22. Patients with repaired tetralogy of Fallot often have:

a. atrial tachyarrhythmias.
b. ventricular arrhythmias.
c. bradycardia.
d. All of the above

23. Control of which of the following is important for the medical therapy of type B aortic dissection?

a. Pain
b. Blood pressure
c. Heart rate
d. A and B

24. Transcatheter aortic valve replacement seems useful for which patients?

a. Asymptomatic patients with moderate aortic stenosis
b. Asymptomatic patients with severe AS
c. Patients with severe symptomatic AS, at high risk for surgery
d. Patients who refuse surgery

25. Myocardial biopsies from both ventricles results in:

a. increased complications.
b. increased diagnostic yield.
c. confirmation of MRI findings.
d. A and B

26. Unilateral pulmonary edema is almost always due to:

a. acute severe mitral regurgitation.
b. diastolic heart failure.
c. mitral stenosis.
d. hypertensive urgency.

Answers: 21. (d); 22. (d); 23. (d); 24. (c); 25. (b); 26. (a)

United States Postal Service
Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Clinical Cardiology Alert	0 7 4 1 - 4 2 1 8	10/1/10
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta,
Fulton County, GA 30305

Contact Person: Robin Salet
Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*
Robert Mate, President and CEO
AHC Media LLC, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

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	Atlanta, GA 30305

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Full Name	Complete Mailing Address
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13. Publication Name: Clinical Cardiology Alert
14. Issue Date for Circulation Data Below: September 2010

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			761	768
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	506	493
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c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			572	540
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h. Copies Not Distributed			156	193
i. Total *(Sum of 15g, and h.*			761	768
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			95%	94%

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2010 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: President and CEO — Date: 9/28/10

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Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

Volume 15, Number 11 Pages 21-22 November 2010

Can vitamins stop photoaging of the skin?

Source: Zussman J, et al. Vitamins and photoaging: Do scientific data support their uses? *J Am Acad Derm* 2010;63: 507-525.

UV light is responsible for some of the skin changes associated with aging, which is known as photoaging (PHA). Expenditures in the United States for so-called "cosmeceuticals" is anticipated to reach more than $6 billion this year, although only a few components of commonly applied topical agents have any clearly demonstrated benefit.

Vitamin A derivatives, particularly the prescription retinoids such as tretinoin cream and tazarotene, are FDA-approved for aging-related fine line wrinkles, skin roughness, and mottled hyperpigmentation. OTC vitamin A derivatives have less convincing evidence, but of these, retinol should be the preferred agent according to Zussman et al.

Amelioration of PHA has been seen in several topical vitamin C trials using L-ascorbic acid; chemically related compounds (e.g., ascorbyl palmitate, ascorbyl tetraiopalmitate) provide greater vitamin C stability, but do not have sufficient clinical trial outcomes data to advocate for them.

Topical formulations of vitamin E, although widely touted for antioxidant potential, do not have data to support their use in management of PHA. Limited data on topical niacin suggest promise.

The best method to address photoaging is overall good nutrition and an appropriate combination of sunscreen and sun avoidance. ■

Once weekly exenatide vs sitagliptin or pioglitazone for type 2 diabetes

Source: Bergenstal RM, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): A randomised trial. *Lancet* 2010;376:431-439.

The incretin class of medications (exenatide, liraglutide, sitagliptin, saxagliptin) all share the favorable quality of not being associated with weight gain. Recently published data support the efficacy, tolerability, and simplicity of once-weekly exenatide. Bergenstal et al compared exenatide once weekly (EXEN-W) with sitagliptin (STG) or pioglitazone (PIO) as add-on therapy for persons with type 2 diabetes (n = 491) who had not attained goal with metformin.

At the end of 26 weeks, several outcomes favored EXEN-W. A1c on EXEN-W was 0.6% lower than STG, and 0.3% lower than PIO. Weight loss was also greatest in the EXEN-W group. Adverse effect profiles with each treatment arm were consistent with prior trials, and the discontinuation rate was similar for each group.

EXEN-W reduced systolic BP more than sitagliptin, but similarly to pioglitazone. Favorable lipid effects were seen with each treatment arm: The greatest increase in HDL was seen with pioglitazone.

As clinicians make their therapeutic choices for diabetes management, the relevance of medication impact upon CV risk factors such as BP, weight, and lipids merits our consideration. ■

Tai chi for fibromyalgia

Source: Wang C, et al. A randomized trial of tai chi for fibromyalgia. *N Engl J Med* 2010;363:743-754.

FDA-approved pharmacologic treatments for fibromyalgia (FIB) include duloxetine, milnacipran, and pregabalin. Although each of these agents has shown both statistically significant and clinically relevant impact, few patients are relieved of all problematic symptoms. Hence, additional treatment paths for FIB are sought.

Exercise has long been recognized as having a favorable impact on FIB, although it has been uncertain which type of exercise should be preferred. For a variety of reasons, some patients will not readily embrace strenuous or aerobic exercise programs, leaving a therapeutic gap in activity programs that can be relied upon to improve FIB symptoms and functionality.

Wang et al enrolled FIB patients (n = 66) into a 12-week program comparing tai chi to a stretching + wellness education component. For the physical activities, both groups participated in two 60-minute sessions per week for 12 weeks. Fibromyalgia patients were diagnosed using the American College of Rheumatology criteria.

At the conclusion of the study, Fibromyalgia Impact Questionnaire and SF-36 physical component scores were superior in the tai chi group as compared to the stretching group. Discontinuation of medications used to treat FIB was seen in both active treatment groups, with a trend favoring tai chi.

Tai chi instruction was provided by a single tai chi master to all of the subjects in that group. Generalizability — whether clinicians can anticipate similar efficacy when tai chi is taught by others — remains to be confirmed. ■

Prevalence of hearing loss in U.S. adolescents

Source: Shargorodsky J, et al. Change in prevalence of hearing loss in U.S. adolescent. *JAMA* 2010;304:772-778.

My grandmother always claimed that listening to loud rock and roll music would be the demise of my hearing … but I still don't know if she was right. In those days we used to listen to something called a record player (younger clinicians interested to see such an archaic device can readily locate one on Google), and I have always wondered whether those cars bouncing up and down at the traffic light next to me, loaded with rap music, would be determined to be similarly ototoxic, or worse. Well, if the NHANES data are correct, we still don't know.

According to this analysis of data from NHANES, the prevalence of hearing loss has increased when one compares the 1988-1994 interval with 2005-2006. Indeed, the relative risk of any hearing loss (induced by any factor) has increased by more than 30%.

Hearing loss was associated with poverty and a history of > 3 ear infections, but not exposure to persistent (> 5 hrs/week) loud noise or firearm use. In support of grandma's point of view, a recent study from Australia noted hearing loss 70% more often in teens who had used personal stereo devices.

Overall, the prevalence of any hearing loss increased from 11.1% to 14.0% over the decade studied; further elucidation of modifiable risk factors would be helpful. ■

When to initiate dialysis? Early vs late GFR threshold

Source: Cooper BA, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010;363:609-619.

The number of individuals requiring renal replacement therapy (dialysis) continues to grow. Because dialysis is an expensive, time-intensive, and intrusive intervention, it is wise to try to refine an optimum threshold for initiation of dialysis. Intuition might suggest that earlier is better than later, but few data to support this notion are in evidence.

Cooper et al performed a study of adults (n = 828) who qualified for dialysis. Study subjects were randomized to either early (GFR = 10-15 mL/min/1.73 m^2) or late (GFR = 5-7 mL/min/1.73 m^2) dialysis. The primary outcome of the trial was all-cause mortality.

Over an 8-year interval, 828 diabetic subjects with Stage V CKD (GFR < 15 mL/min/1.73 m^2) were randomized to initiate dialysis at either the early or late GFR threshold. The mean time to dialysis initiation in the early group was 1.8 months vs 7.4 months in the late group, but this difference might be expanded further, since more than 75% of the late start group actually initiated dialysis because of symptoms before reaching a GFR of 7.

Overall mortality during 3.6 years of follow-up was not significantly different between the two groups. There does not appear to be any mortality detriment associated with delaying dialysis until GFR is 7 mL/min/1.73 m^2 or less, although many patients may require earlier dialysis due to symptoms. ■

Postoperative abdominal wall hernias: Best repair methodology

Source: Itani KM, et al. What to advise patients about hernias. *Arch Surg* 2010;145:322-328.

The literature indicates that almost one-fourth of persons who undergo abdominal surgery will subsequently incur an abdominal wall hernia. The optimum method for repairing such hernias has not been established. Itani et al performed a randomized trial of laparoscopic vs open repair of ventral incisional hernias at four Veterans Affairs hospitals (n = 162).

There was a substantial risk reduction for complications in the laparoscopic group vs the open repair group (absolute incidence = 31.5% vs 47.9%). In particular, surgical wound site infection was almost 4-fold less in the laparoscopic group. Pain scores at 1 year were less in the laparoscopic group, and return to work was quicker. The only major advantage of open surgical treatment was the incidence of major complications, primarily bowel injury (4.4% in the laparoscopic group vs 1.4% in the open surgery group). One additional advantage of open surgical repair was a trend toward lower recurrence in this group (8.2% vs 12.5%; *P* = NS).

In general, asymptomatic incisional ventral hernias do not require repair, but once they are symptomatic, laparoscopic surgery shows distinct advantages. The surgeons in this trial had not performed a high volume of laparoscopic procedures; hence, clinicians might anticipate even better outcomes as experience accrues. ■

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

Executive Editor: Coles McKagen. **Editor:** Stephen Brunton, MD. **Senior Managing Editor:** Paula Cousins. This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

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Dabigatran Leading Race to Replace Warfarin

In this issue: FDA Advisory Committee recommends approval of dabigatran, safety of proton pump inhibitors, effectiveness of glucosamine and chondroitin, FDA Actions.

Advisory Committee recommends approval of dabigatran

In the race to find a drug to replace warfarin, Boehringer Ingelheim may have a leg up with the impending approval of dabigatran. The Cardiovascular and Renal Drugs Advisory Committee of the FDA unanimously recommended approval of the drug in September for the prevention of stroke and systemic clots in patients with atrial fibrillation. Dabigatran is a direct thrombin inhibitor that is given in a fixed dose twice a day and does not require monitoring. It is speculated that dabigatran will replace warfarin as the preferred anticoagulant in many settings, including many patients with atrial fibrillation. The approval was based on the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, which was published last December. The study of more than 18,000 patients with atrial fibrillation showed that dabigatran given at a dose of 110 mg was similar in effectiveness to warfarin in prevention of strokes and systemic embolism, but had a significantly lower rate of major hemorrhage. A higher dose of 150 mg was associated with lower rates of stroke and systemic embolism compared to warfarin and similar rates of hemorrhage (*N Engl J Med* 2009;361:1139-1151). The FDA panel recommended approval of the higher dose, but was split on recommending the 110 mg dose. There was a slightly higher rate of heart attacks with dabigatran compared to warfarin, although the reviewers did not think this was serious enough to warrant holding the drug back. Dabigatran, once approved, will be marketed as Pradaxa®. Several companies are working on their own products to fill the same niche in what has been estimated to be a $10-20 billion market. Drugs in development include Bristol-Myers Squibb's apixaban and rivaroxaban, which is being jointly developed by Bayer Healthcare and Johnson & Johnson. Both drugs are direct inhibitors of Factor Xa. ■

Safety of proton pump inhibitors

Recent studies have suggested that proton pump inhibitors (PPIs) may negate some of the benefit of clopidogrel (Plavix®) in patients with cardiovascular (CV) disease. A new study refutes these findings, and at the same time raises more questions about the safety of PPIs. In a nationwide cohort study from Denmark, all patients discharged after first-time myocardial infarction (MI) were reviewed during 2000-2006. Of the more than 56,000 patients, 16% were rehospitalized for MI or stroke or experienced CV death. Nearly 25,000 patients were discharged on clopidogrel, of which nearly 30% received a concomitant PPI. Patients who were discharged on the combination of a PPI with clopidogrel or on a PPI alone had elevated but similar rates of death or rehospitalization for MI at 30 days (hazard ratio [HR], 1.29 for the combination [95% CI, 1.17-1.42]; HR, 1.29 for PPI alone [CI, 1.21-1.37]), indicating that

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the risk of a PPI with clopidogrel was no higher than a PPI alone. The authors conclude that there seems to be no significant interaction between PPIs and clopidogrel; however, PPIs may be associated with an increased risk for adverse CV outcomes after discharge. The authors postulate that the increased CV risk from PPIs is likely caused by unmeasured confounders (*Ann Intern Med* 2010;153:378-386). As pointed out in an accompanying editorial, this study may be very confusing for clinicians who have recently received warnings regarding the combination of clopidogrel with a PPI. It further highlights the potential risks of PPIs in patients with questionable or inappropriate indications for the drugs and the need for further studies into their risks and benefits (*Ann Intern Med* 2010;153:413-415). ■

Glucosamine and chondroitin

Millions of patients take glucosamine and chondroitin on a daily basis, hoping it is a safe alternative treatment for osteoarthritis. A new study suggests that the combination is ineffective but harmless. In a meta-analysis of 10 trials and more than 3800 patients, glucosamine, chondroitin, or the combination was compared to placebo with regard to pain scores and X-ray appearance of the hip and knee joint. None of the endpoints crossed the boundary of the minimal clinical important difference (95% credible intervals). The authors conclude that compared with placebo, glucosamine, chondroitin, and the combination do not reduce joint pain or have an impact on narrowing of joint space of the hip or knee. They further state that insurers should not cover the cost of these preparations, but since there is little harm, patients may wish to continue buying and taking it (*BMJ* 2010;341:c4675). ■

FDA Actions

The FDA has announced that it will significantly restrict the use of rosiglitazone (Avandia®) to patients with type 2 diabetes who cannot control the disease on other medications. The FDA had the option of removing the drug from the market, a move that was recently taken by the European Medicines Agency; however, the agency decided to limit access at least for now. Rosiglitazone has been associated with an elevated risk of cardiovascular events.

The FDA has approved fingolimod (Gilenya®), the first oral drug to reduce relapses and delay disability progression in patients with relapsing-remitting multiple sclerosis. The drug is the first of a new class called sphingosine 1 phosphate receptor modulators. Patients need to be closely monitored for symptomatic bradycardia. Fingolimod will be marketed by Novartis Pharmaceuticals.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA has voted against recommending approval of lorcaserin hydrochloride for the treatment of obesity (see September *Pharmacology Watch*). Although the drug was shown to be effective, resulting in at least a 5% body weight loss for half of patients taking the drug over 1 year, there were concerns over valvular heart disease. Arena Pharmaceuticals argued that valvulopathy was not a significant issue and that they met the FDA's predefined goals for safety. The FDA is not required to follow subcommittee recommendations, however it usually does.

The same subcommittee also recently reviewed the weight-loss drug sibutramine (Meridia-Abbott Laboratories) and delivered a **split vote on whether sibutramine should stay on the market.** Sibutramine has been the subject of controversy since last November when initial data from the Sibutramine Cardiovascular Outcomes trial revealed a higher rate of cardiovascular disease associated with the drug. The full study was published in September and showed that cardiovascular events were observed significantly more frequently in the sibutramine group than in the placebo group (11.4% vs 10.0%; $P = 0.02$). The rate of cardiovascular death or death from any cause, however, was no different in the two groups (*N Engl J Med* 2010;363:905-917). The FDA subcommittee voted 8-8, with 8 members voting to remove the drug from the market and the other 8 voting to allow the drug to remain on the market with tougher warnings and a restricted distribution pattern. The FDA vote is expected later this fall.

The **FDA has approved pegloticase for the treatment of refractory gout in patients who have not responded to or can't tolerate conventional therapy.** The drug is administered intravenously every 2 weeks. It appears to work by metabolizing uric acid to allantoin, which is then cleared through the kidneys. The approval was based on two 6-month trials in more than 200 patients that showed the drug reduces uric acid levels and reduces uric acid deposits in joints and soft tissue. About one in four patients will experience severe allergic reactions to the infusion, so patients should be given an antihistamine and a corticosteroid prior to administration. The drug was not studied in patients with congestive heart failure and should not be used in this population. Savient Pharmaceuticals will market pegloticase as Krystexxa™. ■