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ABSTRACT & COMMENTARY

Late Mortality With Paclitaxel-Coated Balloons and Stents in Peripheral Arterial Disease

By Jeffrey Zimmet, MD, PhD

Associate Professor of Medicine, University of California, San Francisco; Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center

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

SYNOPSIS: A newly published meta-analysis of randomized, controlled trials concerning paclitaxel-coated balloons and stents in femoral popliteal disease patients revealed a marked increase in all-cause death at two and five years.

SOURCE: Katsanos K, Spiliopoulos S, Kitrou P, et al. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: A systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2018;7:e011245.

Endovascular treatment of occlusive arterial disease of the leg has been increasing steadily over time. The femoral and popliteal arteries remain the most common sites of involvement. However, interventional treatment is marked by high rates of restenosis and target vessel failure. Drug-eluting stents (DES) and drug-coated balloons (DCB) have emerged as tools to improve patency outcomes in these vessels, with paclitaxel representing the most common anti-restenotic agent in this arena. Numerous randomized, controlled trials (RCTs) have demonstrated that devices delivering this drug effectively reduce restenosis and target lesion revascularization in the leg. Several paclitaxel DCB and DES devices have been approved for use in the United States and in Europe.

A new meta-analysis of paclitaxel-eluting devices for treatment of femoral popliteal disease revealed that while all-cause mortality was similar between paclitaxel and control groups at one year, follow-up data at two years and five years show striking increases in all-cause death. Prompted by hints of increased mortality in a

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small number of RCTs with longer-term follow-up and by a single below-the-knee study that demonstrated higher rates of major amputations in the paclitaxel arm compared with control, Katsanos et al sought to identify high-quality RCTs of paclitaxel devices in the treatment of the femoral and popliteal arteries. Ultimately, the authors analyzed a collection of 28 RCTs that included 4,663 patients. Of these studies, four used a paclitaxel DES. The remaining 24 RCTs used paclitaxel DCBs.

The authors of each included RCT reported all-cause death out to one year, with a nearly identical 2.3% crude risk of death in both the paclitaxel and the control arms among the included subjects. The authors of 12 of the 28 RCTs reported all-cause death out to two years, totaling 2,316 patients. Availability of five-year data was much more limited, with only three RCTs (n = 863 patients) comprising this part of the analysis. At two years, the crude risk of death was 7.2% and 3.8% in the paclitaxel and control arms, respectively (hazard ratio [HR], 1.68; 95% confidence interval [CI], 1.15-2.47). At five years, the risk was 14.7% and 8.1%, respectively (HR, 1.93; 95% CI, 1.27-2.93).

The two-year numbers correspond to a 68% relative risk increase in all-cause death with paclitaxel-coated devices compared with standard balloons, with a number-needed-to-harm of 29. At five years, the relative risk increase was 93%, with a number-needed-to-harm of just 14. Interestingly, higher dosages of paclitaxel appeared to correlate with a greater risk of mortality. In a meta-regression analysis of the absolute risk difference of all-cause death against exposure to paclitaxel expressed as the dose-time product, there was a highly significant association between paclitaxel and the absolute risk of death.

The authors concluded that their data demonstrated a credible and large relative increase in longer-term all-cause death after exposure to paclitaxel-eluting balloons and stents for treatment of arterial disease of the upper leg. They labeled their results "alarming" and postulated that late paclitaxel toxicity may be responsible for their findings, calling for more study with longer-term follow-up.

■ COMMENTARY

The finding of a late increase in mortality with this entire class of otherwise-promising therapeutic agents certainly is unexpected. To many in the field, the conclusions lack a mechanistic explanation and strain credibility. However, that is not the inference of the field as a whole. In response to this study, the creators of two ongoing investigations of paclitaxel-containing devices in peripheral artery disease (PAD) — the BASIL-3 and SWEDEPAD 1 and 2 trials — have elected to halt enrollment pending further information.

[The finding of a late increase in mortality with this entire class of otherwise-promising therapeutic agents certainly is unexpected.]

On the mechanistic side, Katsanos et al noted that paclitaxel devices designed for use in the periphery are fundamentally different from those previously deployed in the coronary bed. For example, on average, devices designed for use in the femoral popliteal arteries contain more than an order of magnitude higher level of paclitaxel compared with the coronary Taxus stent. The drug-coated balloon paradigm results in significantly greater levels of a crystalline form of the drug released into the systemic circulation.

For now, it is difficult to know what to do with these data in the context of devices that have made their way into mainstream use and that represent some of the most effective technologies for treatment of PAD of the leg. Most authorities have cautioned against an overreaction. In the short term, making patient-level data from the individual trials available may allow for a better understanding of the profile of patient deaths over time and provide a greater level of knowledge. Ultimate answers may not be achieved without further trials and longer-term prospective follow-up. In either case, we are certain to hear more about this issue in the coming year. ■

ABSTRACT & COMMENTARY

TAVR Beneficial for Patients With Severely Reduced Ejection Fraction

By Van Selby, MD

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

Dr. Selby reports he is a consultant for Alnylam Pharmaceuticals and Akcea Therapeutics.

SYNOPSIS: In patients with low-flow, low-gradient aortic stenosis and severe left ventricular dysfunction, transcatheter aortic valve replacement was associated with significant improvement in left ventricular ejection fraction and similar mortality compared to patients with milder left ventricular dysfunction.

SOURCE: Maes F, Lerakis S, Barbosa Ribeiro H, et al. Outcomes from transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis and left ventricular ejection fraction less than 30%: A substudy from the TOPAS-TAVI Registry. *JAMA Cardiol* 2018; Dec 19. doi: 10.1001/jamacardio.2018.4320. [Epub ahead of print].

Management of low-flow, low-gradient aortic stenosis (LFLG AS), typically defined as an aortic valve area < 1.0 cm^2 with a mean transvalvular gradient ≤ 40 mmHg and reduced stroke volume, can be challenging. When evaluating candidacy for aortic valve replacement, dobutamine stress echocardiography (DSE) is used often to distinguish true-severe from pseudo-severe AS and to assess contractile reserve. In patients with LFLG AS and severely reduced left ventricular ejection fraction (LVEF), data regarding outcomes after transcatheter aortic valve replacement (TAVR) and the utility of DSE for predicting post-TAVR outcomes are lacking.

Maes et al performed a substudy of the True or Pseudo-Severe Aortic Stenosis-TAVI (TOPAS-TAVI) registry of patients undergoing TAVR for LFLG AS, defined as a mean transvalvular gradient < 35 mmHg with effective orifice area < 1.0 cm^2 and LVEF ≤ 40%. Patients were divided into two groups: very low LVEF (< 30%) and low LVEF (30-40%). The primary outcomes were change in LVEF over time, periprocedural complications, and late mortality. Most patients with very low LVEF underwent DSE before TAVR. The association between presence of contractile reserve (defined as an increase in stroke volume of 20% or greater with dobutamine) and post-TAVR outcomes also was assessed.

Of 293 patients included in the analysis, 128 had very low LVEF and 165 low LVEF. The mean LVEF in the very low LVEF group was 22%. There was no difference in periprocedural complications or 30-day mortality (4.1% vs. 4.7%; $P = 0.65$) between patients with very low vs. low LVEF. Over a median follow-up of 23 months, there was no difference in long-term survival (hazard ratio, 0.96 for very low vs. low LVEF; $P = 0.88$). Patients with very low LVEF demonstrated a greater improvement in LVEF at one-year follow-up (11.9% vs. 3.6% in the low EF group; $P < 0.001$).

Of the 92 patients with very low LVEF who underwent pre-TAVR DSE, 49% did not demonstrate contractile reserve. Lack of contractile reserve was not related to survival or change in LVEF after TAVR. The authors concluded that in patients with LFLG AS and severe LV dysfunction, TAVR is associated with similar outcomes compared to patients with milder LV dysfunction. Further, they determined that assessment of contractile reserve is not useful for predicting survival or change in LVEF.

■ COMMENTARY

Among patients referred for surgical aortic valve replacement, presence of LFLG AS with left ventricular dysfunction is associated with higher perioperative risk and worse long-term survival. On the other hand, the authors of the TOPAS-TAVI registry previously reported that patients with LFLG AS and reduced LVEF experience acceptable outcomes after TAVR. In this substudy of TOPAS-TAVI, Maes et al demonstrated that even patients with LFLG AS and severely reduced LVEF demonstrate similar post-TAVR survival compared to those with milder reductions in LVEF. Furthermore, these patients experienced the largest improvement in systolic function after TAVR. As TAVR volumes increase and eligibility criteria continue to expand, studies evaluating challenging patient groups such as LFLG AS and severely reduced LVEF are crucial to guide appropriate patient selection.

DSE is a frequently used test to distinguish true-severe from pseudo-severe aortic stenosis. Contractile reserve, the ability to augment stroke volume in response to dobutamine, also is used to predict recovery of LV function after correction of aortic stenosis. The absence of contractile reserve has been associated with poor outcomes following surgical aortic valve replacement. The original TOPAS-TAVI registry revealed no association

between presence of contractile reserve and outcomes in patients with LFLG AS and LVEF < 40%. The authors of this substudy extended these findings to patients with severely reduced LVEF, showing that even patients with LVEF < 30% can recover LV systolic function following TAVR, regardless of contractile reserve. While DSE still plays a role for differentiating true-severe vs. pseudo-severe AS, the utility of assessing contractile reserve in these patients is less clear now. Although the authors demonstrated acceptable TAVR outcomes in LFLG AS with LV dysfunction, it is important to remember the mortality rate was approximately 40% in both LVEF groups during the median 23-month follow-up period. This highlights the overall poor prognosis associated with LFLG AS and may be helpful for patients trying to decide whether to pursue TAVR.

There were several important limitations to this registry study. Although the baseline clinical characteristics appeared similar between the very low and low LVEF groups, it is possible that selection bias (particularly among those with very low LVEF) led to unidentified differences between the groups. Approximately one-quarter of patients with very low LVEF did not undergo DSE prior to TAVR. The relatively small number of patients may have limited the ability to detect differences in outcomes. When taking these limitations into consideration, the authors' conclusion that "these results support the use of TAVR for LFLG AS, irrespective of the severity of left ventricular dysfunction and DSE results" may be a bit strong.

However, it is reasonable to say that LVEF < 30% and lack of contractile reserve should not be considered contraindications to TAVR in patients with LFLG AS. Hopefully, others will study this challenging patient population further to help refine patient selection for TAVR. ■

ABSTRACT & COMMENTARY

The Natural History of Tricuspid Regurgitation

By Michael H. Crawford, MD, Editor

SYNOPSIS: A retrospective analysis of patients with moderate or severe tricuspid valve regurgitation (TR) and who underwent an earlier echo with no or mild TR showed that progression of TR was independently associated with age, female sex, new device leads, and right ventricular or tricuspid annular dilation.

SOURCES: Prihadi EA, van der Bijl P, Gursoy E, et al. Development of significant tricuspid regurgitation over time and prognostic implications: New insights into natural history. *Eur Heart J* 2018;39:3574-3581.

Carabello BA. The progression of tricuspid regurgitation: It seems capricious, or are we just too ignorant to understand it? *Eur Heart J* 2018;39:3582-3583.

Once moderate to severe tricuspid regurgitation (TR) has developed, patients are difficult to manage medically and invasive options to correct TR are limited. Prihadi et al analyzed the echocardiographic database of the university hospital in Leiden, Netherlands, for patients with moderate to severe TR to assess the factors promoting TR and the prognosis of rapidly developing TR. Patients with prior tricuspid valve surgery, active endocarditis, age < 18 years, and known congenital tricuspid valve abnormalities were excluded. The first 1,000 consecutive patients with moderate to severe TR who underwent an echo between 1991 and 2005 that showed no or mild TR comprised the study population. Patients were divided into four groups based on the time between the older echo that showed no or mild TR and the more recent echo that showed moderate to severe TR: group 1 (fastest), group 2 (fast), group 3 (slow), group 4 (slowest). Clinical data on the patients were obtained retrospectively from the hospital information system for cardiology. Two investigators re-read all echoes and derived quantitative data. Tricuspid annulus diameter > 21mm/m^2 in the four-chamber view was considered significant dilatation. TR severity was derived from a multimeasurement approach. Trace TR was considered no TR for the analysis. TR was classified as primary or organic if the tricuspid valve leaflets were damaged and secondary or functional if there was annular or RV dilatation. Device lead-associated TR was considered organic if there was no left heart disease. Isolated TR associated with atrial fibrillation was classified as functional.

On the first echo, 71% showed signs of mild TR and 29% no TR. After the second echo, 81% showed signs of moderate TR and 19% showed signs of severe TR. Only 5.8% of patients on the second echo showed signs of organic TR, most of which was device lead-related. Less than 1% of patients exhibited a primary leaflet abnormality. Group 1 developed significant TR in < 1.2 years, group 2 in 1.3-4.7 years, group 3 in 4.8-8.9 years,

and group 4 in nine years. Group 1 patients were older, more likely female, and had more comorbidities.

Progression of TR was independently associated with age, device leads, mild or no TR, decreased right ventricular function, and increased tricuspid annulus diameter. Also, any left heart valve surgery between echoes was associated with fast TR progression. Survival rates were significantly lower in group 1 vs. the other groups and were independent of age and left and right ventricular systolic function. The authors concluded that perhaps by the identification of patients likely to develop moderate to severe TR by echo surveillance, earlier therapy application could reduce mortality rates.

■ COMMENTARY

For years, we believed that TR almost always was secondary to left heart disease or pulmonary hypertension and that effective treatment of these conditions would alleviate TR. Long-term follow-up of left heart valve surgery patients has shown that in some patients, TR did not improve; in others, such surgery improved TR initially, only to worsen later for inexplicable reasons. Also, we now see significant TR associated with device lead placement and chronic atrial fibrillation alone. These two causes represented 5.4% of the study population in this report. Thus, secondary TR still dominates. Until recently, there was little to do for these patients beyond treating the underlying pulmonary or left heart disease. Even after the underlying causes were treated, many patients still are quite symptomatic from their TR, and diuretic management of their venous congestion is challenging. Surgical tricuspid valve replacement is not attractive due to high reported mortality. Now that percutaneous devices designed to reduce or eliminate TR are in development (stented valves for the valve or cavae, valve clips), there is more interest in the earlier treatment of TR.

Prihadi et al addressed the issue of identifying patients who may benefit from earlier correction or abrogation of TR. Their retrospective analysis of factors that predicted rapid progression to moderate to severe TR showed that older age, female sex, a dilated tricuspid annulus (> 35mm), reduced right ventricular function, and subsequent left heart valve surgery independently predicted rapid development of significant TR. Also, the rapid development of significant TR was associated with all-cause mortality independent of age, right ventricular systolic pressure, and right or left ventricular function.

These data support the guideline recommendation to perform tricuspid valve annuloplasty during left heart valve surgery if moderate or more TR is present or the tricuspid annulus is enlarged. However, these data do not necessarily support interventions to abrogate TR in those likely to progress rapidly. This would have to be tested in a prospective trial. We do not know whether TR causes increased mortality directly or is just the canary in the mine. Until studies with the new devices for TR are conducted, we can follow patients with TR more closely, try to manage the likely underlying causes better, and treat any systemic venous congestion more aggressively. ■

ABSTRACT & COMMENTARY

In-Ambulance Troponin Measurements

By Michael H. Crawford, MD, Editor

SYNOPSIS: A study of triaging suspected non-ST-elevation acute coronary syndrome patients by employing in-ambulance troponin measurements augmented the predictive value for 45-day major adverse cardiac events. This could help identify very high-risk patients who would benefit from urgent coronary angiography.

SOURCE: van Dongen DN, Fokkert MJ, Tolsman RT, et al. Value of prehospital troponin assessment in suspected non-ST-elevation acute coronary syndrome. *Am J Cardiol* 2018;122:1610-1616.

It is now feasible to measure troponin levels in the ambulance. Troponin is a key component of the HEART score (history, ECG, age, risk factors, troponin), which has shown prognostic value in patients with suspected non-ST-elevation acute coronary syndrome (NSTE-ACS).

Van Dongen et al sought to determine whether prehospital troponin measurements added value to the prehospital HEAR score (a risk score without the troponin component of the HEART score) for predicting major adverse coronary events (MACE) within 45 days in patients triaged for suspected NSTE-ACS in two hospitals and 33 ambulances. MACE was defined as cardiac ischemia, all-cause mortality, or coronary revascularization. Patients with coma, cognitive impairment, shock, sustained ventricular tachycardia, and end-stage renal disease were excluded. Cardiac troponin T (TnT) was performed in the ambulance using the Roche device, which provides a value in about 10 minutes. TnT < 40ng/L (limit of detection) was scored 0 on the HEART scale and > 40 ng/L was scored 2.

Of 823 eligible patients, 700 had complete data and were included in the analysis. The median duration of symptom onset until TnT measurement was 150 minutes (range, 65-435 minutes). Using the HEAR score, 26% of patients were classified as low risk (< 3 points). Using the HEART score, 25% of patients were classified as low risk. No patient classified as low risk under either scoring system died within 45 days. MACE within 45 days occurred in 17% of patients (six patients died). Using the HEAR scale, 7% of low-risk patients experienced a MACE. Using the HEART scale, 3% of low-risk patients experienced a MACE ($P < 0.001$). The area under the curve (AUC) for predicting MACE using the HEAR score was 0.65 (confidence interval [CI], 0.6-0.71). The AUC using the HEART score was 0.74 (CI, 0.69-0.79; $P < 0.001$). The AUC for prehospital TnT alone was 0.67 (CI, 0.60-0.73). The authors concluded that the prehospital TnT component of the HEART score added predictive value for 45-day MACE in patients with suspected NSTE-ACS.

■ COMMENTARY

The HEART score is a useful and well-validated tool for stratifying patients with suspected NSTE-ACS into high, low, and intermediate risk for MACE. Low-risk patients often are discharged from the ED, high-risk patients are admitted to the hospital, and intermediate patients typically are held in a chest pain unit for further noninvasive testing. Traditionally, the HEART score was determined in the ED, but pressure to triage the higher-risk patients more quickly moved the "HAR" part of the score to the ambulance, with higher-risk patients undergoing an ECG within 10 minutes of ED arrival. As ECG technology moved to the field, a "HEAR" score could be calculated in the ambulance or even pretransport. Point of care troponin has been available for some time but has not achieved widespread use in the United States outside of EDs. While moving it to prehospital could increase the efficiency of triaging chest pain patients rather than waiting for someone to run troponin in the ED or laboratory, would it really make a difference?

Van Dongen sought to compare the triage accuracy of the HEAR score vs. the complete HEART score in the field or ambulance. The hazard ratio for MACE with a HEAR score > 3 was 3.57 compared to 8.89 for a HEART score > 3. Not surprisingly, adding the TnT in the field added considerable predictive value. In studies of the HEART score in the hospital, the AUC for MACE was higher (0.83) than that reported in this study for prehospital use (0.74). One explanation for this finding may be that the added value of troponin is related to the time from symptom onset until when the test is performed. Obviously, this time would be less in the field than at the ED. In this study, 73 patients who experienced MACE tested negative on TnT in the field, and prehospital TnT alone had an AUC less than the full HEART score (0.67 vs. 0.74, respectively). Thus, prehospital HEART is better for identifying high-risk patients rather than low-risk patients.

The strength of this study is that the authors used one urban and one rural hospital. Also, there was a 99.6% follow-up rate. But there also were weaknesses. TnT could not be obtained in 157 eligible patients because of various technical problems. While the authors stated that the assay needs improvement, they used the fourth-generation assay, not the new high-sensitivity troponin assay. Finally, the ambulance system only employed critical care-trained bachelor's degree nurses who have used the HEART score since 2012. This level of expertise and experience may be hard to duplicate in other countries.

Full HEART score determination in the field probably is most useful if the patient has symptoms for > 120 minutes. Also, in-the-field troponin measurements are likely to increase the sensitivity for detecting ACS but decrease the positive predictive value. This increase in false-positives may create extra work for the hospital. On the other hand, in-the-field troponin measurements may augment the identification of the very high-risk non-NSTE-ACS patient who may need urgent coronary angiography. ■

ABSTRACT & COMMENTARY

Are Frequent PVCs Causing Left Ventricular Dysfunction?

By Joshua Moss, MD

Associate Professor of Clinical Medicine, Cardiac Electrophysiology, Division of Cardiology, University of California, San Francisco

Dr. Moss reports he is a consultant for Abbott, Boston Scientific, and Medtronic.

SYNOPSIS: Premature ventricular contraction-induced cardiomyopathy was phenotypically different than a tachycardia-mediated cardiomyopathy in a swine model. Paced ventricular bigeminy led to left ventricular (LV) dyssynchrony, a decline in LV ejection fraction associated with biventricular myocardial fibrosis, and a widening of the sinus QRS.

SOURCE: Walters TE, Rahmutula D, Szilagyi J, et al. Left ventricular dyssynchrony predicts the cardiomyopathy associated with premature ventricular contractions. *J Am Coll Cardiol* 2018;72:2870-2882.

Frequent premature ventricular contractions (PVCs) can lead to the development of a cardiomyopathy in some patients. Elimination of PVCs can facilitate recovery of left ventricular (LV) function. The pathophysiology of this finding remains unclear. Additionally, in asymptomatic patients with frequent PVCs, it is difficult to predict who is likely to develop a cardiomyopathy and who should be considered for prophylactic PVC elimination.

Walters et al sought to create a swine model to explore PVC-mediated cardiomyopathy and prospectively evaluate the association between LV dyssynchrony during ectopic beats with development of cardiomyopathy. Phase 1 of the study was aimed at assessing the effects of ventricular pacing on the development of cardiomyopathy by exposing animals to 14 weeks of paced bigeminy from the RV apex (n = 10 swine), continuous pacing at 140 beats/minute from the RV apex (n = 5), or sham pacing (n = 5). In Phase 2, the ventricles were paced from various locations to determine the association of resultant degrees of LV dyssynchrony with development of cardiomyopathy. Paced bigeminal PVCs were delivered from the RV free wall (n = 5) or LV epicardial free wall (n = 5). In five additional animals, paced atrial bigeminy was delivered as a control. Biweekly transthoracic echocardiograms were performed on all animals, followed by a hemodynamic study (Phase 2 only) to further assess LV dyssynchrony prior to histological and molecular analysis.

During Phase 1, there was a significant decline in mean LVEF after 14 weeks in both paced groups compared to sham pacing. The irregular pacing of the bigeminal PVC group was associated with a greater decline in LVEF than continuous tachycardia pacing (68% to 45% vs. 70% to 55%). A molecular analysis showed significant differences in levels of various cellular calcium-handling proteins in the paced PVC group compared with control animals. These protein levels did not differ significantly between control animals and the tachycardia group.

After Phase 2, with pacing from various ventricular sites, there was a significantly greater reduction in LVEF after 12 weeks of paced PVCs from the LV epicardial free wall (65% to 40%) compared with paced PVCs from the RV free wall (66% to 49%). Similar patterns were observed for between-group divergence in the LV chamber dimensions, calculated fractional shortening, and sinus QRS duration. A histological analysis showed significant myocardial fibrosis in both paced PVC groups compared to control animals, with the highest extent of fibrosis in the LV epicardial free wall PVC group. There were no statistically significant differences in measured calcium-handling protein levels between the two paced groups. A univariate analysis showed that longer ectopic beat QRS duration and greater ectopic beat dyssynchrony were significantly associated with larger declines in LVEF over the 12-week study period. The authors concluded that in a swine model, PVC-induced cardiomyopathy is phenotypically distinct from a tachycardia-induced cardiomyopathy and is strongly related to the extent of LV dyssynchrony.

■ COMMENTARY

This study revealed numerous important findings. In a swine model, cardiomyopathy induced with paced ectopic beats is phenotypically different from that induced with paced ventricular tachycardia, specifically regarding changes in cellular proteins associated with calcium handling. Additionally, the severity of the induced cardiomyopathy was strongly associated with the degree of ventricular dyssynchrony during ectopic beats, as demonstrated by comparing animals with ectopic beats delivered from different ventricular sites. The molecular calcium-handling changes observed in the paced PVC-cardiomyopathy animals were similar to those seen in other cardiomyopathy disease states.

While it is well recognized clinically that frequent PVCs may lead to LV dysfunction, many questions remain regarding the mechanisms of this process and which patients are at highest risk. Retrospective data have suggested that cardiomyopathy is more likely to develop when ectopic beats account for more than 10-14% of all heartbeats, but many patients with an even higher PVC burden maintain normal LV function indefinitely. Therefore, exposing asymptomatic patients to the treatment risks for PVCs before the development of any LV dysfunction generally is not advised. Furthermore, elimination of PVCs in some patients with suspected PVC-mediated cardiomyopathy does not always result in improvement or normalization of LV function. The results of this study add valuable knowledge about the potential mechanisms of PVC-mediated cardiomyopathy, forming the basis of additional investigation that could help clinicians predict LV dysfunction in advance and provide therapeutic targets to interrupt the process.

The authors noted that the majority of decline in LVEF in the paced PVC group occurred within the first six to eight weeks of pacing, followed by a subsequent lengthening of the sinus QRS complex. This observation suggests that changes mediated by LV dyssynchrony result in development of myocardial fibrosis and subsequent QRS widening, as opposed to QRS widening causing LV dyssynchrony. Irreversible myocardial fibrosis may contribute to the lack of LVEF recovery following PVC suppression in some patients. The primary limitation of this study was its generalizability, given the swine

model with a 50% paced ectopic beat burden (bigeminy) from the RV apex, RV free wall, or LV epicardium. Somewhat different molecular changes were noted in a previously published canine model of PVC-cardiomyopathy with shorter PVC coupling intervals. Mechanisms could be different still in humans with less frequent PVCs originating from other more common anatomic sites (such as the ventricular outflow tracts and papillary muscles). Nevertheless, a prospective evaluation of ectopic beat dyssynchrony and likelihood of cardiomyopathy development is warranted, as this may provide clinicians with a tool to help risk-stratify and treat patients with frequent PVCs. ■

CME/CE QUESTIONS

1. Which of the following is most correct concerning TAVR for low-flow, low-gradient aortic stenosis with reduced ejection fraction patients?

a. TAVR can be accomplished safely.

b. TAVR is contraindicated.

c. TAVR is contraindicated if ejection fraction is < 30%.

d. TAVR is contraindicated if stroke volume fails to increase with dobutamine.

2. Progression from mild to moderate or severe tricuspid regurgitation is related to:

a. device lead placement through the tricuspid valve.

b. a dilated or dysfunctional right ventricle.

c. intervening left heart valve surgery.

d. All of the above

3. In a swine model of pacing-induced cardiomyopathies, which dysrhythmia showed the greatest decline in left ventricular ejection fraction?

a. Continuous pacing at 140 beats/minute from the right ventricular apex

b. Paced bigeminy from the left ventricular epicardial free wall

c. Paced bigeminy from the right ventricular apex

d. Paced bigeminy from the right ventricular free wall

4. Adding in-ambulance troponin measurements in suspected non-ST-elevation acute coronary syndrome patients triaged by the HEART score showed:

a. zero deaths in low-risk patients.

b. enhanced prediction of 45-day major adverse coronary events.

c. that a longer time from symptom onset enhanced predictive accuracy.

d. All of the above

5. A new meta-analysis of long-term randomized trial results using paclitaxel-coated balloons and stents vs. other devices used in peripheral arterial disease has shown:

a. identical one-year mortality rates.

b. increased mortality at two and five years with paclitaxel devices.

c. a dose response relationship with paclitaxel and mortality.

d. All of the above

CME/CE 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.