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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

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ABSTRACT & COMMENTARY

Does Finding the Portal of Entry of Bacteria in Infective Endocarditis Matter?

By Michael Crawford, MD, Editor

SYNOPSIS: A comprehensive, systematic search for the portal of bacterial entry in infective endocarditis is frequently successful and affords an opportunity to prevent recurrent episodes.

SOURCES: Delahaye F, et al. Systematic search for present and potential portals of entry for infective endocarditis. *Am Coll Cardiol* 2016;67:151-158.

Chu VH. When the cat's out of the bag: Searching for portals of entry in infective endocarditis. *J Am Coll Cardiol* 2016;67:159-161.

It would seem that the portal of entry (POE) of the microorganisms responsible for infective endocarditis (IE) is important to prevent further episodes, which occur in up to 30% of patients with IE. However, little data on this topic exist. Thus, investigators from Lyon, France, prospectively and systematically sought the POE in all cases of IE admitted between 2005 and 2011. A dentist, an ENT physician, and a urologist examined all patients. A gynecologist also examined all female patients. If skin lesions were present, a dermatologist saw them. Patients also underwent dental, cerebral, and thoracic-abdominal-pelvic X-rays. If the organism identified originated in the gastrointestinal (GI) tract, if the patient was > 50 years of age, or if there was a family history of colon polyposis, patients received a colonoscopy. For each case, the most probable POE was inferred from the results of these tests and the natural habitat of the identified causative microorganism. Researchers performed treatment of the POE where feasible. From 444 IE admissions, 82 were excluded because they died in hospital and 44 were excluded for incomplete data, leaving 318 patients with 320 episodes of IE. In 74% of patients, researchers identified a POE; of these, 40% were cutaneous, 29% oral or dental, and 23% were GI. The majority of cutaneous sources were related to healthcare or IV drug use. Dental infections were the source for the majority with oral/dental POEs, rather than dental procedures (59% vs 12%). Half those with GI POEs had colonic polyps. The authors concluded that the search for a POE in patients with IE is frequently successful, and they advise a systematic oral examination in all and colonoscopy in selected patients with IE.

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Prevention of IE has revolved around antibiotic prophylaxis for procedures likely to result in significant bacteremia in individuals at high risk of IE. One of those high-risk features is previous IE. So efforts to identify the likely POE and treat or eliminate it would make sense. However, not only is there little literature on this topic, but physicians pay scant attention to it in patients with IE. This study is remarkable in its comprehensive approach to finding the POE. Researchers were able to identify a likely POE in about three-quarters of their patients. In about one-third, researchers discovered additional potential POEs for new episodes of IE. Although not assessed in this study, it is hard to argue that treating these POEs and potential POEs would not have a beneficial effect.

Based on the results of this study, a more streamlined and cost-effective approach to finding the POE emerged. Routine ENT or GU evaluations were low yield and should be reserved for those with evidence of infections in these areas. On the other hand, a comprehensive oral exam was high yield (53%). It constituted a dental exam and panoramic X-rays of the teeth. Of the oral POEs, 59% were tooth infections, some only detected by X-ray, and 28% were periodontal. Only 12% were related to dental procedures. Colonoscopy was also high yield (40%) in a high-risk subgroup, age > 50 years, or a family history of colonic polyposis. In addition, a dermatologist examined those with suspicious skin lesions. Healthcare-associated skin issues were identified in 41% and 34% had community-acquired lesions. The former included vascular access (44%), EP devices (28%), and operative wounds (28%). The latter included IV drug use (22%) and insect bites or cat scratches (3%). The rest had ulcers and other wounds.

The study's major weakness is that the role of organism identification (performed in all but 9 cases) in determining the POE is not spelled out clearly. Not all POEs were cultured and those that were did not undergo genetic analysis to see if they were the same organism identified in the blood cultures. However, the likely POE correlated well with the known body habitat of the organisms identified by blood culture. Also, in 25% with no POE discovered, the distribution of the organisms was similar to that found in those with a POE identified. In addition, the authors did not discuss the possibility of multiple POEs.

In summary, patients with high-risk cardiac conditions for IE, such as prosthetic valves or other material, EP devices, and certain types of congenital heart disease, not only need antibiotic prophylaxis for IE, but should have any infections treated expeditiously. Those with IE should have reasonable efforts to find the POE and treat it if feasible. The type of exams performed could be guided by the organisms found: a careful skin exam in those with Staph species, an oral exam and X-rays in those with oral Strep species, and colonoscopy in those with GI organisms detected. ■

ABSTRACT & COMMENTARY

Nitrate Therapy Shows Possible Harm in Heart Failure with Preserved Ejection Fraction

By Van Selby, MD

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

SYNOPSIS: In heart failure with preserved ejection fraction, the use of isosorbide mononitrate was associated with a nonsignificant decrease in physical activity level, and no improvement in symptoms or quality of life.

SOURCE: Redfield MM, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med* 2015;373:2314-2324.

No pharmacologic therapy has been proven to improve survival in heart failure with preserved ejection fraction (HFpEF). Long-acting nitrates are used frequently to improve symptoms, but the effectiveness of this practice has not been studied in a clinical trial.

The Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) trial tested the hypothesis that isosorbide mononitrate would increase patient activity level in HFpEF. One hundred and ten patients were randomized to isosorbide mononitrate vs placebo, using a crossover design. Inclusion criteria included age ≥ 50 years, New York Heart Association (NYHA) functional class II-IV symptoms, and at least one of the following criteria: history of heart failure (HF) hospitalization, elevated B-type natriuretic peptide (BNP) level, elevated pulmonary artery wedge pressure, or evidence of diastolic dysfunction on echocardiography. Additionally, all patients reported dyspnea, chest pain, or fatigue as the cause of their exercise limitation. Researchers administered isosorbide mononitrate at 30 mg and doubled the dose every week to a target dose of 120 mg daily. The primary outcome was daily activity level, measured using a patient-worn accelerometer.

Compared to patients receiving placebo, those taking isosorbide mononitrate 120 mg daily showed a nonsignificant trend toward lower daily activity (difference of -381 accelerometer units, 95% confidence interval [CI], -780 to 31; $P = 0.06$), with a significant decrease in the total hours of activity per day ($P = 0.02$). Activity levels decreased with increasing doses of isosorbide mononitrate in a stepwise manner. There were no statistically significant differences in 6-minute-walk distance, BNP, or quality of life scores.

Both adverse events and discontinuation of study drug were more common among the isosorbide mononitrate group. The authors concluded that in HFpEF, treatment with isosorbide mononitrate as compared to placebo is associated with decreased daily activity levels and no significant improvement in submaximal exercise capacity or quality of life.

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Nitrates have been shown to improve symptoms in both heart failure with reduced ejection fraction (HFrEF) and ischemic heart disease. Based on these studies and our hemodynamic understanding of HF, long-acting nitrates are used frequently in the management of HFpEF as well. However, this strategy has never been evaluated rigorously in HFpEF. The authors of NEAT-HFpEF demonstrated that empiric use of long-acting nitrates is not beneficial and may actually be detrimental in this population.

These findings are somewhat surprising, and the authors offered several potential explanations. The pathophysiology of HFpEF is different from that of HFrEF or ischemic heart disease. Patients with HFpEF have more comorbidities as well as autonomic dysfunction, chronotropic incompetence, and vascular stiffness. All these comorbidities contribute to symptoms in HFpEF. Additionally, nitrates do not improve these conditions.

The observed difference in reported side effects between isosorbide mononitrate and placebo was insufficient to explain the decline in physical activity, but nitrates may cause subtle, unreported side effects that led patients to be less active. The dose of isosorbide increased at a faster rate than what is common in clinical practice. Patients may have better tolerated a slower dose escalation.

Another possible explanation is patient selection. As has been seen in other clinical trials, identifying patients who truly have HFpEF rather than dyspnea due to other etiologies can be challenging. Nitrates are particularly effective for relieving elevated left-sided filling pressures. Perhaps if the trial had been limited to patients with documented elevation in left-sided pressures, or at least symptoms of elevated pressure such as orthopnea, the authors could have identified a subset of HFpEF patients more likely to benefit from nitrate therapy. Alternatively, it is also possible the increased vascular stiffness in HFpEF makes the left-sided pressures less responsive to the hemodynamic effects of nitrates.

One particularly interesting aspect of this study is the use of patient-worn accelerometers for measuring the primary outcome. This provides continuous assessment of physical activity in a real-world setting, and may be a better measure of functional status than traditional measures such as NYHA class or 6-minute-walk distance. It would not be surprising to see increased use of mobile technology in future HF clinical trials.

Based on the findings of NEAT-HFpEF, nitrate therapy should not be used indiscriminately in HFpEF. That said, selected patients may still benefit, and a brief trial of long-acting nitrates in patients with clear evidence of elevated left-sided filling pressures, either by catheterization or symptoms, still seems reasonable. Patients with HFpEF and co-existing coronary artery disease may also benefit.

Given the lack of mortality benefit and potential for harm, it would be reasonable to discontinue nitrate therapy in those who do not experience clear symptomatic improvement. ■

ABSTRACT & COMMENTARY

One Procedure or Two? Study Examines Staging for Multi-vessel PCI in NSTEMI

By Jeffrey Zimmet, MD, PhD

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

SYNOPSIS: Patients with non-ST elevation myocardial infarction and multi-vessel disease were randomized to percutaneous coronary intervention (PCI) of all significant lesions during the index procedure, or to staged PCI. Those undergoing single-stage PCI had lower rates of major adverse cardiovascular and cerebrovascular events at 1 year, driven by lower rates of target-lesion revascularization.

SOURCE: Sardella G, et al. Single-staged compared with multi-staged PCI in multivessel NSTEMI patients: The SMILE Trial. *J Am Coll Cardiol* 2016;67:264-272.

In patients presenting with non-ST elevation myocardial infarction (NSTEMI) and multi-vessel disease for whom a percutaneous coronary intervention (PCI) is a treatment strategy, multiple questions remain about the extent and timing of treatment. This is a common scenario. Some reports have estimated that as many as 50% of NSTEMI patients present with multi-vessel disease. Although full revascularization is clearly the standard when patients undergo coronary artery bypass surgery, the landscape is more murky for PCI-treated patients. When pursuing a complete revascularization approach, how should one accomplish it? Should one approach only the "culprit" lesion during the index procedure? Should one undertake treatment of the non-culprit vessels during the same session?

The SMILE trial, performed at two centers in Italy, addresses the latter question. SMILE was an unblinded investigation of 548 consecutive NSTEMI patients, randomized in a 1:1 fashion to single- or multi-stage PCI. Those assigned to multi-stage revascularization had PCI of only the culprit lesion at the initial procedure and subsequently underwent a second procedure between 3 and 7 days later during the index hospitalization. Researchers used transradial access in > 80% of cases, although that number dropped to approximately 65% during the second procedure in the multi-stage group. Researchers employed fractional flow reserve (FFR) in approximately 25% of patients. The baseline characteristics of each group were similar, as were the use of drug-eluting stents, completeness of revascularization, and medical regimens at time of hospital discharge.

At 1 year, the rate of major adverse cardiovascular and cerebrovascular events (MACCE) was significantly lower in the single-stage group (13.63% vs 23.19%; hazard ratio [HR], 0.549; 95% confidence interval [CI], 0.363-0.828; P = 0.004). This difference was driven primarily by a higher rate of target vessel revascularization (TVR) in the multi-stage group (n = 40 [15.20%] vs n = 22 [8.33%]; 95% CI, 0.310-0.878; P = 0.01). Cardiac and overall death, myocardial infarction (MI), stroke, and hospitalization for unstable angina were not different between groups. The Bleeding Academic Research Consortium (BARC) type 1 bleeding (minor bleeding that is "not actionable" and does not generally cause the patient to seek treatment) was higher in the multi-stage group, although the more clinically-meaningful BARC types 2, 3, 4, and 5 were not significantly different between groups.

The authors concluded that in patients with NSTEMI and multi-vessel disease, single-stage PCI during the initial procedure is superior to multiple procedures in terms of MACCE and minor bleeding at 1 year.

■ COMMENTARY

One of the most surprising things about SMILE is that the study was designed with the assumption that multi-stage revascularization would be superior to single. As the study reached the opposite conclusion, we are left asking what happened and whether we should believe the results.

The first thing we should realize is that this study does nothing to address what is likely the more interesting question regarding multi-vessel disease: the issue of whether complete revascularization itself is superior to more-selective revascularization. SMILE used complete revascularization as the default approach and only examined the timing of PCI.

SMILE tells us that BARC type 1 bleeding was significantly less common in patients undergoing a single procedure compared with those who received two. This is a plausible and understandable difference — patients in the multi-stage group were exposed to arterial access and to procedural anticoagulation twice, as opposed to once, and a higher rate of transfemoral access was used in the staged procedures.

This is where easy explanations end. The paper stated that single-stage revascularization is superior to multi-stage in terms of 1-year MACCE, "mainly due to an unexplained higher incidence of TVR." A closer look at TVR shows the curves don't separate until about 6 months from randomization. For two groups who achieved similar levels of complete revascularization and left the hospital on similar medications, it is difficult to fathom how this difference could be explained. The authors related this to a higher rate of stress testing at 6 months in the multi-stage group, but again failed to explain why this should make sense. The accompanying editorial, by Drs. Henriques and Claessen, noted that the TVR rate in the multi-stage group (15.4% at 12 months) was considerably higher than what is generally observed in contemporary trials ("when interpreting SMILE, one may find a reason to frown," according to the editorial). This TVR rate was even higher than in the SYNTAX trial, which enrolled patients with significantly higher burden of disease and used now-obsolete first-generation drug-eluting stents.

How, then, might this study change practice? Although the superiority of single-stage revascularization may not be a fully believable result, it is important to note that these patients clearly did not have a detriment in terms of important outcomes including death, MI, and contrast-induced nephropathy. The original hypothesis, after all, was that longer procedure times, higher contrast volumes, and higher likelihood of periprocedural MI and other complications would doom single-stage PCI to a second-place finish. In the end, we are left with the opportunity to tailor therapy to our patients and their particular circumstances. SMILE assures us that we are not harming patients by undertaking single-stage procedures for patients without major comorbidities and with modest lesion complexity. Patients with chronic kidney disease and those with higher degrees of technical difficulty, among other issues, will still benefit from a staged approach. ■

ABSTRACT & COMMENTARY

Permanent Pacemaker After TAVR: Is This a Modifiable Risk?

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 study of the latest-generation balloon-expandable valves demonstrates a higher rate of new conduction abnormalities and pacemaker implants than previous models, and identifies patient- and procedure-related variables that affect these outcomes.

SOURCE: Husser O, et al. Predictors of permanent pacemaker implantations and new-onset conduction abnormalities with the SAPIEN 3 balloon-expandable transcatheter heart valve. *JACC Cardiovasc Interv* 2016;9:244-254.

New conduction abnormalities requiring permanent pacemaker implantation are generally considered to be more common following transcatheter aortic valve replacement (TAVR) than after surgical aortic valve replacement, and are an important limitation of this mode of therapy. Historical numbers suggest a wide range of pacemaker rates across studies, with clear differences among valve platforms. A recent meta-analysis of 41 studies involving 11,210 TAVR patients reported median pacemaker rates of 28% for the self-expanding Medtronic Corevalve system, and 6% for the balloon-expandable Edwards Sapien valve.

The recently approved Edwards Sapien 3 valve includes several major improvements over previous generations, including smaller introducer size, greater control of deployment, and an outer sealing skirt to reduce paravalvular leak. Along with these enhancements, however, come reports of significantly higher pacemaker rates for this device.

Husser et al examined the determinants of new conduction system abnormalities and pacemaker implantation in a series of 244 consecutive patients receiving the Sapien 3 valve at their institution in Munich. Patients with existing pacemakers, bicuspid valves, or valve-in-valve procedures were excluded,

leaving a study group of 208 patients. The resulting group was a relatively typical TAVR population, with a mean age of 81 years and a logistic EuroSCORE of 16%. The 23-, 26-, and 29-mm valve sizes were used in 44%, 38%, and 18% of cases, respectively. Thirty-nine percent of cases were performed with conscious sedation, and 98% of cases achieved device success.

Sixteen percent of patients required pacemaker implantation prior to hospital discharge. New-onset or worsened conduction abnormalities occurred in 17% of patients — left bundle branch block in 16% (25 of 184 without pre-existing conduction disease) and right bundle branch block (RBBB) in 1% (2 of 184). As in prior publications, multivariate analysis showed that baseline electrocardiographic abnormalities were predictive of new pacemaker requirement, including RBBB, atrial fibrillation, and bradycardia.

Implantation depth, measured at the nonseptal side and expressed as percent of the frame height below the aortic annulus, was found to be an independent predictor of new or worsened conduction abnormalities or pacemaker. The degree of oversizing was calculated in standard fashion using data from multislice CT scans and the nominal expanded size of each bioprosthetic valve. The median percentage oversizing was 7% by area and 2% by perimeter measurements. No significant association was found between the overall degree of oversizing and need for permanent pacemaker. However, among the 19 cases that were oversized beyond the manufacturer's recommendations, so-called out-of-range oversizing, the rate of new or worsened conduction abnormality or pacemaker was a very high 58% vs 28% for the remainder of the population ($P = 0.007$).

The authors concluded that in this large single-center TAVR study, the need for permanent pacemaker or the occurrence of new or worsened conduction system disease occurred in one-third of patients receiving the Sapien 3 valve. Additionally, the authors noted a clear relationship between implantation depth and extreme valve oversizing. They suggested that careful attention to implantation depth and valve sizing may have the potential to reduce pacemaker rates and should be the subject of future study.

■ COMMENTARY

It is noteworthy that advances in TAVR technology that afford benefits in one area (sealing of paravalvular leak, in this case) may be associated with greater risks in another. The one in three risk of conduction abnormalities observed in this study is higher than what has been reported with prior iterations of the Edwards balloon-expandable TAVR valve.

The patient-level variables associated with new pacemaker requirement in this study, most notably RBBB, atrial fibrillation, and baseline bradycardia, are obviously not modifiable for particular patients, but may affect patient selection and counseling. Both TAVR centers and referring providers should be aware of these variables. The suggestion that implanters may affect pacemaker rates through attention to implant depth is intriguing. It is notable that this study's expression of implant depth as a percentage of frame height below the annular frame is a non-standard measure that will be unfamiliar to most. Communicating depth in terms of millimeters below the annular plane would be both more intuitive and more directly useful to practitioners.

New conduction system disease, most prominently that requiring permanent pacemaker implantation, is a major limitation of the TAVR procedure. Nearly every study to date has demonstrated pacemaker rates following TAVR that are significantly (and sometimes strikingly) higher than those expected after surgical AVR. This issue has had an effect on the care of TAVR patients since the inception of this procedure, but has scarcely affected choice of therapy for those patients at prohibitive surgical risk. Recently, the FDA granted approval for the PARTNER III trial, which will study the Sapien 3 valve in patients with low predicted risk of mortality from surgery (STS score < 4). As TAVR is applied to intermediate and even low-risk patients, and in particular to younger patients, the pacemaker issue will loom larger in the risk/benefit calculation surrounding this procedure. ■

ABSTRACT & COMMENTARY

Gender Equality in Primary Prevention ICD Benefit

By Cara Pellegrini, MD

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

SYNOPSIS: In a propensity-matched study, women who received a primary prevention implantable cardioverter defibrillator had a significant survival advantage, which was similar to that observed among men.

SOURCE: Zeitler EP, et al. Comparative effectiveness of implantable cardioverter defibrillators for primary prevention in women. *Circ Heart Fail* 2016;9:e002630.

The benefit of primary prevention implantable cardioverter defibrillators (ICDs) in women is controversial. As women constituted only 10-30% of enrolled subjects in the randomized, controlled trials that established efficacy of primary prevention devices, these trials were underpowered to show benefit in this subgroup. Subsequently, two meta-analyses have examined this issue with conflicting results, and other post-hoc and observational analyses of primary prevention ICDs in women have had similarly mixed results. National guidelines are sex neutral in their recommendations, yet the actual use of primary prevention ICDs is lower in women than men, possibly reflecting residual concern regarding the paucity of current data.

To address this void, Zeitler et al used data from the Get With The Guidelines for Heart Failure (GWTG-HF) registry, linked with data from the Centers for Medicare and Medicaid Services, to compare outcomes in women who were hospitalized for heart failure and who did or did not receive an ICD. They collected patient demographic and medical history variables, medication and laboratory data, and hospital characteristics. As the population was not randomized to determine receipt of the intervention, the collected variables were used to create a propensity model for ICD implantation to make the groups more comparable — that is, to minimize confounding. Researchers repeated a similar process for men. All-cause mortality was the primary outcome.

In this group of older women with heart failure and reduced left ventricular ejection fraction (LVEF), implantation of an ICD (or prescription for implantation shortly after discharge) was associated with improved survival over a median follow-up of about 3 years (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.66-0.92; $P = 0.003$). The benefit was similar to that observed in men (HR, 0.76; 95% CI, 0.67-0.87; $P < 0.001$). There was no significant sex-based interaction. Notably, the benefit in the ICD group was immediately apparent, with early separation of the survival curves. The authors concluded that among patients with heart failure with a reduced LVEF, a primary prevention ICD was associated with a significant survival advantage among both women and men, supporting guideline-directed use of primary prevention ICDs.

■ COMMENTARY

The observed mortality benefit in both sexes in this registry study was similar to the observed mortality benefit of ICD vs placebo in SCD-HeFT, the landmark randomized clinical trial of primary prevention ICDs with the most similar population (HR, 0.77). By controlling for hospital characteristics, this study goes beyond previous observational studies in addressing likely sources of confounding. Notably, aside from age and LVEF, the biggest discrepancies between the groups who did and did not receive an ICD were site-related factors. Patients admitted to teaching hospitals in the Northeast with a large number of beds and a capacity for on-site cardiac procedures were far more likely to receive an ICD.

Yet, there are a number of limitations to this study. First and foremost, it is not a randomized, controlled trial, and residual confounding can still be present, despite the authors' great efforts to account for it with propensity matching. All practicing clinicians can appreciate that nothing can substitute for examining a patient to determine appropriateness for an elective procedure, or lack thereof. It is hard to fully capture with a collection of variables all that goes into judgment of likely outcomes. Indeed, neither New York Heart Association class nor a characterization of functional status, two factors that clearly would enter into a clinical thought process, could be included in this analysis. The very act of performing a propensity match by its nature excludes the sickest patients with a high burden of disease who are too dissimilar to find a match. Conversely, generalization to heart failure patients who are healthy enough to avoid hospitalization, or simply younger than this population, could be specious.

Nonetheless, this study is critical. A clear signal of benefit is particularly warranted in women, who suffer disproportionately from procedural complications related to primary prevention ICD implantation. Should a study firmly establish benefit, a greater push for correction of the current underutilization of primary prevention ICDs by women will be needed. Even among institutions that have chosen to participate in GWTG-HF, a voluntary quality improvement program, only 11% of eligible women and 16% of eligible men received an ICD or prescription for one at time of heart failure hospitalization discharge. Finally, despite the current study's limitations, the data likely provide the most definitive answer we will receive, given that there is no longer sufficient equipoise to allow for a specific randomized, controlled trial of primary prevention ICD use in women. ■

QUESTIONS & COMMENTS:
Contact Jonathan Springston, Associate Managing Editor, at (404) 262-5416 or email at jonathan.springston@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

CME/CE QUESTIONS

1. **Identifying the point of bacterial entry in cases of infective endocarditis is important because:**
   a. it helps pick the appropriate antibiotics.
   b. it will contribute to the decision for surgery.
   c. it could be the site for future episodes.
   d. All of the above

2. **In patients with heart failure symptoms with preserved left ventricular ejection fraction, isosorbide mononitrate:**
   a. improved quality of life.
   b. increased 6-minute walk distance.
   c. reduced total daily activity time.
   d. reduced B-type natriuretic peptide levels.

3. **A new percutaneous aortic valve replacement designed to reduce paravalvular leaks has shown:**
   a. lower peri-procedural mortality.
   b. increased incidence of new conduction abnormalities.
   c. increased need for permanent pacemaker implant.
   d. Both b and c
   e. All of the above

4. **A study in non-ST elevation myocardial infarction patients comparing initial complete revascularization by percutaneous coronary intervention (PCI) vs culprit lesion PCI, followed at another time by complete revascularization by PCI showed initial complete PCI:**
   a. reduced target vessel revascularization.
   b. reduced mortality.
   c. increased stroke.
   d. increased bleeding.

5. **Primary prevention implantable cardioverter defibrillator placement in women vs men with systolic heart failure resulted in:**
   a. lower mortality.
   b. higher mortality.
   c. equivalent survival.
   d. a delayed benefit in survival.

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