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Critical analysis of the latest clinical research in cardiovascular medicine

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ABSTRACT & COMMENTARY

Revascularization for Isolated Proximal LAD Disease: PCI is Easiest, but is it Best?

By Jeffrey Zimmet, MD, PhD

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

SOURCE: Hannan EL, et al. Coronary artery bypass graft surgery versus drug-eluting stents for patients with isolated proximal left anterior descending disease. *J Am Coll Cardiol* 2014;64:2717-2726.

Among patients with obstructive coronary disease requiring revascularization, guidelines would suggest a clear preference for coronary artery bypass grafting (CABG) over percutaneous coronary intervention (PCI) only in certain defined subsets, including those with left main disease and in diabetics with multi-vessel disease. Patients with isolated proximal LAD disease represent a unique high-risk subset of those with single-vessel disease, in that the size of the affected territory and associated ischemic risk makes CABG a viable option. In fact, U.S. guidelines currently assign a slight advantage to CABG with a left internal mammary graft to the left anterior descending (LAD) for such patients, rating this as a IIa indication vs a IIb recommendation for PCI. This is despite a relative paucity of data on this subset of patients, at least using contemporary treatments. In fact, of the nine randomized, controlled trials forming the basis for 17 published studies examining this question, most are quite small, and all but one were performed using bare-metal stents; the single small RCT incorporating drug-eluting stents (DES) used first-generation devices that are no longer part of the treatment landscape.

Hannan and colleagues contribute to this important topic with an observational study based on New York state registry data. For the period from the beginning of 2008 and the end of 2010, all patients who received CABG or PCI with

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DES for isolated proximal LAD disease were identified. Of the 6064 patients in this set, 5340 received PCI with DES and 724 underwent CABG. Based on available data, 715 CABG patients were propensity matched to 715 PCI patients, after which the characteristics of the matched patients were found to be similar. To maximize chances that downstream events would be captured in the database, only New York state residents were included. Three-year outcomes for the matched sets were reported.

Prior to propensity matching, unadjusted mortality and the combined endpoint of mortality, MI, and/or stroke were lower in the overall slightly healthier PCI group (4.3% vs 5.9%, $P < 0.04$ and 6.1% vs 8.3%, $P < 0.03$, respectively), but repeat revascularization was significantly higher among DES patients (12.2% vs 6.5%, $P < 0.0001$). Among the propensity-matched pairs, there were no significant differences in 3-year mortality rates or mortality, myocardial infarction (MI), and/or stroke rates. However, the rates for repeat revascularization remained significantly lower for CABG patients (adjusted hazard ratio, 0.54; 95% confidence interval, 0.36-0.81).

The study concludes that the majority (88%) of patients with isolated proximal LAD disease undergo PCI. While there were no differences between CABG and DES in mortality or the combined outcome of mortality, MI, and stroke, repeat revascularization rates were significantly higher among PCI patients. The authors suggest that the preference for CABG in U.S. guidelines is discordant with their data, although they note that randomized trials involving large cohorts are needed to fully answer this question.

■ COMMENTARY

It should come as no surprise that PCI procedures greatly outnumber CABG for patients with isolated disease of the proximal LAD. The majority of such patients are diagnosed in the cardiac catheterization laboratory, where PCI may be performed in an ad hoc fashion without the involvement of the cardiac surgical team. Patients and cardiologists alike will most often elect the less-invasive revascularization option when given a choice. In this light, the current study gives support and reassurance that real-world patients are not being harmed with respect to the all-important hard outcomes of death, MI, and stroke.

On the other hand, the repeat revascularization data from this study are relatively compelling. The investigators found an absolute difference of nearly 5% between the two revascularization strategies, favoring CABG, which agrees with older studies. This advantage held up even when examining unadjusted data from the entire dataset, in which PCI patients had lower rates of important comorbidities, including prior MI, cerebrovascular and peripheral vascular disease, chronic obstructive pulmonary disease, and congestive heart failure. The accompanying editorial by cardiac surgeon Friedrich-Wilhelm Mohr of Leipzig University touts this benefit (*Left Internal Mammary to LAD Artery Still Rules the Roost*), and further points out that additional advantage may be gained through use of novel surgical techniques such as minimally invasive direct coronary artery bypass surgery. Such minimally invasive procedures are not done well or even offered at every heart center; however, knowledge of the local landscape must figure into practical decision-making.

The most notable factors that are routinely left out of analyses such as these are lesion and vessel characteristics that concretely affect the choice of revascularization. Features such as lesion length, vessel tortuosity and calcification, and involvement of significant sidebranches all increase PCI complexity, while the quality of the downstream anastomotic target and the distal coronary tree affect the projected success of bypass. In day-to-day practice, PCI is performed immediately for proximal LAD lesions that are anatomically suitable. Cardiologists would do well to think beyond the immediate procedure and to involve the Heart Team for optimal decision-making when appropriate. ■

ABSTRACT & COMMENTARY

Spironolactone Shows Potential Benefit in HFPEF Patients

By Van Selby, MD

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

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

SOURCE: Pfeffer M, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015;131:34-42.

To date, no treatment has been shown to improve outcomes in heart failure with preserved ejection fraction (HFPEF). The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial randomized patients with symptomatic heart failure, LV ejection fraction ≥ 45%, and either a heart failure-related hospitalization in the previous 12 months or an elevated serum brain natriuretic peptide to spironolactone or placebo. Spironolactone failed to demonstrate a significant impact on the primary outcome of cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure. Post-hoc analyses found substantial differences between the groups enrolled from Russia/Georgia and those enrolled from the Americas (United States, Argentina, Brazil, and Canada). To better understand these differences, Pfeffer and colleagues compared the baseline characteristics, prognosis, and response to spironolactone between the two regions.

The authors found significant regional differences in nearly every important baseline variable. Patients from the Americas represented a higher-risk cohort, with a primary event rate of 12.6 events per 100 patient years in the Americas compared to an event rate of 2.3 per 100 patient years in Russia/Georgia ($P < 0.01$). The primary event rate among patients from the Americas was similar to what has been previously reported in trials of patients with HFPEF, while the event rate in patients from Russia/Georgia was multifold lower. Patients from the Americas who were randomized to spironolactone also had significantly greater risk of hyperkalemia, rise in serum creatinine, and decrease in blood pressure compared to those from Russia/Georgia.

Along with baseline differences, there was marked regional variation in the effect of spironolactone. In the Americas, spironolactone was associated with a significant reduction in the primary endpoint (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69-0.98), whereas subjects from Russia/Georgia saw no difference (HR, 1.10; 95% CI, 0.79-1.51). In the Americas, spironolactone was also associated with significant reductions in both cardiovascular death and hospitalization for heart failure. The authors acknowledge the general limitations of post-hoc analyses, but conclude that in the absence of stronger data, these findings may be informative to clinicians treating HFPEF in North America.

■ COMMENTARY

Large clinical trials have identified multiple therapies with clear, meaningful benefit for patients with heart failure and reduced ejection fraction, with an associated improvement in prognosis. For the half of heart failure patients with preserved ejection fraction, finding effective therapies has proven much more elusive, and current guidelines for the treatment of HFPEF are sparse. The reasons for this are multifactorial. Diagnostic uncertainty is one reason, and probably explains much of the observed variation in baseline characteristics identified in this analysis. Other reasons include substantial heterogeneity in both the phenotype and pathophysiology of HFPEF.

Renin angiotensin aldosterone system (RAAS) inhibition, a fundamental component of therapy for heart failure with reduced ejection fraction, has now been evaluated in three trials of patients with HFPEF (CHARM-Preserved, I-PRESERVE, and TOPCAT). None demonstrated clear benefit. The findings of Pfeffer and colleagues challenge these negative findings, and renew hope for RAAS inhibition in the treatment of HFPEF. Furthermore, this study provides crucial guidance for the design of future trials in patients with HFPEF, and emphasizes the challenge and importance of identifying patients with true HFPEF as opposed to those with dyspnea due to other causes.

Secondary analyses must be interpreted with caution. TOPCAT was a negative trial, and the regional comparison was one of 15 prespecified subgroups. Subgroup testing increases the risk of chance findings, and results are generally considered hypothesis-generating rather than conclusive. That said, this analysis deserves further consideration for several reasons, and may influence the clinical management of patients with HFPEF in the Americas. First, the authors found a clear mechanism to explain the observed difference in benefit from spironolactone. The observed characteristics and event rates in Russia/Georgia suggest that many of the enrolled patients may not have had HFPEF as it is generally defined in the Americas. Subjects in the Americas also had a markedly different physiologic response to spironolactone, with greater effect on blood pressure, serum potassium, and creatinine. Taken together, it is easy to argue the observed differences were due to more than just chance.

The second reason Pfeffer's findings may influence management is the complete absence of alternative therapies to treat HFPEF. Despite the caveats of secondary analyses, physicians may see spironolactone as preferable to doing nothing for these high-risk patients. At the American Heart Association annual scientific sessions in November, many heart failure experts commented that they plan to use spironolactone in the management of HFPEF, and it will be interesting to see how these findings are addressed in future guidelines. In deciding to treat HFPEF with spironolactone, it is important to make sure the patient has an anticipated risk profile similar to those enrolled from the Americas. ■

ABSTRACT & COMMENTARY

Coronary Stents and Noncardiac Surgery

By Jeffrey Zimmet, MD, PhD

SOURCE: Holcomb CN, et al. The incremental risk of noncardiac surgery on adverse cardiac events following coronary stenting. *J Am Coll Cardiol* 2014;64:2730-2739.

Contemporary data suggest that approximately one in five patients will require non-cardiac surgery within 2 years of coronary stent implantation. The most feared complication here is stent thrombosis, which is more common in this setting due to the combination of stopping antiplatelet drugs and the systemic pro-thrombotic and pro-inflammatory effects of the surgery itself. While stent thrombosis is virtually always a serious event, it is especially morbid in the postoperative setting due to the need for antithrombotic medications and the consequent risk of bleeding at the surgical site. As an academic interventional cardiologist, I find that a significant proportion of my clinic consultations center around this topic: How soon can my stented patient undergo surgery? Can the antiplatelet agents be held for surgery? What is the risk of adverse cardiac outcomes if my patient with stents goes to surgery now?

One of the major issues with studying this question involves identifying large enough patient numbers to come to firm conclusions. Holcomb and colleagues mined the Veterans Affairs database to identify all patients receiving bare metal stents (BMS) or drug-eluting stents (DES) between October 1, 1999 and September 30, 2009. They then compared all patients who had noncardiac surgery within 24 months of coronary stent implantation to those with stents who did not undergo subsequent surgery. Each patient undergoing surgery was matched to two patients who did not have surgery. Importantly, the authors tracked events by time from stenting in both the surgical and nonsurgical cohorts, as cardiac events in post-stent patients are most frequent in the early weeks to months. The incremental risk of cardiac events following noncardiac surgery was then expressed as a risk difference.

As would be expected, the incremental risk was highest in the early weeks post stenting, and fell off with time. The risk difference for adverse cardiac events with noncardiac surgery, adjusted for surgical characteristics, was 2.8% during the first 6 weeks, 2.0% between 6 weeks and 6 months, and then decreased to just under 1% after 6 months, where it remained stable out to 24 months. These differences were driven primarily by disparities in death and MI. When surgery was performed more than 6 months after stenting,

the incremental risk of surgery was decreased significantly, primarily for patients having more complex inpatient procedures and for patients who were defined as high risk by the revised cardiac risk index. Minor outpatient procedures were not associated with a significant incremental risk. Therefore, the authors suggest that waiting until at least 6 months post stent is important, primarily for higher-risk patients and procedures.

When looking at patients by stent type, the study found that event rates were higher in bare metal stent (BMS) patients whether or not they underwent surgery. Within the first 6 months post-stent, the incremental risk of surgery was similar regardless of stent type. The incremental risk dropped significantly after 6 months only in patients with DES, but not in those with BMS.

■ COMMENTARY

This study addresses multiple important issues in the care of this common and challenging set of patients. Firstly, it supports the notion that the initial 6 weeks post-stent is the highest-risk time period during which nearly 10% of patients in this study experienced an adverse cardiac event. Surgery should be avoided during this period if at all possible. Conversely, patients with a recognized need for noncardiac surgery within 6 weeks should avoid coronary stenting, with consideration given to CABG when appropriate, to balloon angioplasty alone when feasible, or to medical therapy without revascularization. Patients with stents who must go to surgery within 6 weeks should continue dual antiplatelet therapy if possible, although there are no data to suggest that this improves safety.

The incremental risk of surgery remains elevated between 6 weeks and 6 months, but then appears to plateau and remains relatively stable out to 2 years and most likely longer. Although current ACC/AHA guidelines recommend delaying surgery for at least 12 months after DES implantation, this study would suggest that a time cutoff of 6 months would provide similar outcomes. This is in line with several other recent studies, and is in agreement with the shorter 6-month duration currently recommended by the European Society of Cardiology. But while the peri-operative risk drops after 6 months, it levels off and remains significant even at 24 months. For all patients with prior coronary stents, serious consideration should be given to continuing aspirin peri-operatively regardless of time since implantation, and to performing complex and higher-risk surgeries at centers with full cardiac interventional capabilities.

Although it appears counterintuitive, the observation that patients with BMS have higher post-surgical event rates than those with DES is clearly demonstrated here. The evidence supports the idea that this increased risk is more likely due to the patient comorbidities that led to the preference for BMS, rather than to an interaction with stent type and surgery. It also calls into question the strategy of implanting BMS in patients requiring early surgery. More studies will be required to define the optimal solution for such patients. ■

ABSTRACT & COMMENTARY

Impact of Late Tricuspid Regurgitation After Left Heart Valve Surgery

By Michael H. Crawford, MD, Editor

SOURCES: Kaminerlauder AA, et al. Right ventricular dysfunction, but not tricuspid regurgitation, is associated with outcomes late after left heart valve procedure. *J Amer Coll Cardiol* 2014;64:2633-2642.

Due to the success of left heart valve disease surgical corrections, patients may experience late tricuspid regurgitation (TR). This prospective, long-term observational study sought to assess the clinical impact of significant (moderate or severe) TR late after left heart valve procedures. Over a 2-year period between 2007-2008, 571 consecutive patients with previous left heart valve surgery at least 6 months prior were recruited for this long-term follow-up study. A right ventricular electrical catheter through the tricuspid valve excluded 32 patients, for a total population of 539. The average interval between enrollment and surgery was 50 months, and the majority

of the procedures were aortic valve replacement (65%). The frequency of significant late TR was highest in those with concomitant tricuspid valve surgery (43%), followed by combined aortic and mitral valve surgery (25%), mitral alone (17%), and aortic alone (14%). Baseline characteristics showed that those with late TR were most often female and more often presented with atrial fibrillation. Baseline echocardiographic data showed that the late TR patients had larger left and right ventricles and atria and worse RV systolic function. During the mean follow-up duration of 53 months, 117 (22%) patients died, usually of a cardiovascular cause. Only two patients had tricuspid valve repair during follow-up, and one died perioperatively. Overall survival was significantly worse in those with significant late TR. By multivariate analysis age, left atrial size, right ventricular function, and prior coronary bypass surgery were highly predictive of mortality. The authors concluded that right ventricular systolic function, but not late TR, was predictive of mortality late after left heart valve surgery.

■ COMMENTARY

This prospective, observational study supports the concept that late TR following left heart valve surgery is best treated medically. Their average 53-month follow up of such patients shows that significant TR is not an independent predictor of survival, but right ventricular function is. So unless repairing or replacing the tricuspid valve is likely to improve right ventricular function, it doesn't make sense to operate. If the TR is most likely related to post-capillary pulmonary hypertension due to residual left heart disease, then tricuspid valve surgery makes even less sense. The authors claim this is frequently the case, as in their study, elevated pulmonary pressures were more common in the late TR patients.

In my experience, medical therapy is challenging and directed at symptom relief, since there is no known medical therapy for TR per se. Diuretics are the mainstay of treatment and do reduce or even eliminate symptoms, but it requires considerable diligence on the part of the patient to watch their diet, weigh themselves daily, and adjust their diuretic dose. Patients who are not able to manage this may be candidates for surgery. If pulmonary hypertension is present, therapies to reduce pulmonary pressures could be successful in reducing TR, but there are little data on this approach. If non-pulmonary hypertension right ventricular dysfunction is the cause of the TR, treatment to improve right ventricular function, such as revascularization, could help, but again, there are scant data on this approach as well.

Although I believe this study is a significant advance in our knowledge in this area, there are several weaknesses of the study. It is basically a mortality study. There are no data on other outcomes such as hospitalization for heart failure. Also, the authors speculate in the mechanisms of late TR, but there are little collaborating data in this regard. For example, left ventricular volumes and diastolic dysfunction were not assessed. In addition, there are considerable technical issues with measuring right ventricular function by echocardiography, and the authors never quite explain their method of assessment. Interestingly, right ventricular fractional area change was lower in those with significant TR, but tricuspid annulus plane systolic excursion was not different. Finally, the whole concept of what is abnormal right ventricular function in someone with marked TR is debatable due to systolic unloading into the low pressure right atrium.

These limitations notwithstanding, perhaps we should consider late significant TR after left heart valve surgery a medical problem and approach it with the vigor we do in heart failure patients in general. Surgery may be an option in highly selected patients with the realization that reported operative mortality (30 days) is in the 15-20% range. ■

ABSTRACT & COMMENTARY

Risk of Stroke with Intracardiac Devices and Patent Foramen Ovale

By Edward P. Gerstenfeld, MD

Professor of Medicine, Chief, Cardiac Electrophysiology, University of California, San Francisco

Dr. Gerstenfeld does research for Biosense Webster, Medtronic, and Rhythmia Medical.

SOURCE: Poddar KL, et al. Risk of cerebrovascular events in patients with patent foramen ovale and intracardiac devices. *JACC Cardiovasc Interv* 2014;7:1221-1226.

After some case reports of stroke due to electrophysiology (EP) device thrombosis in patients with a patent foramen ovale (PFO), concern has been raised about the risk of stroke with intracardiac devices in patients with known PFO. Thus, these investigators from the Cleveland Clinic did a retrospective database study of 2921 echocardiography-detected PFO patients and categorized them as having an EP device (231) or not. Patients with a stroke prior to detection of the PFO, or who had closure of the PFO during the follow-up period were excluded. The primary endpoint was ischemic stroke. Propensity scoring was used to match device patients to those without devices, which resulted in two groups with 231 patients each for the comparison.

Ischemic stroke occurred in 2.6% (n = 6) in both propensity-matched groups over an 11-year total follow up (minimum 4 years). A subgroup analysis of atrial fibrillation patients revealed a 7% stroke risk in both groups. The authors concluded that the risk of stroke among patients with an intracardiac EP device is the same whether they have a PFO or not.

■ COMMENTARY

As the use of EP devices has increased, concern has risen about the risk of stroke in patients with PFO who develop device lead thrombosis. This study allays those fears since the PFO-plus device group had the same stroke risk as those with a PFO alone. This is a retrospective database study that suffers from selection biases and unadjusted covariates. However, unlike other such studies, the investigators did propensity matching to minimize selection biases. Factors such as medication use (statins, oral anti-coagulants) and atrial fibrillation were matched between the groups. Also, patients with prior stroke were excluded because they have a higher incidence of another stroke. In addition, patients who had their PFO closed during the follow-up period were excluded. The major limitation of the study was the low event rate, but this, in itself, is reassuring.

The fact that atrial fibrillation was present in almost all of the stroke patients reminds us that there are several other causes of stroke in device patients that are more important than PFOs, whose relationship to stroke is controversial. Others include proximal aortic atheroma and left ventricular dysfunction or aneurysms.

The results are a relief since closing PFOs before placing an EP device or anticoagulating everyone with a device and a PFO would be challenging and of unknown value given the lack of data. Our efforts are better spent determining if other treatable conditions that raise the risk of stroke, such as atrial fibrillation, are present. ■

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.

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CME QUESTIONS

1. **Late tricuspid regurgitation following left heart valve surgery is usually due to?**
   a. Right ventricular dysfunction
   b. Unrecognized tricuspid valve disease
   c. Right atrial injury
   d. Infective endocarditis

2. **Coronary bypass surgery vs percutaneous coronary intervention for isolated proximal left anterior descending disease results in?**
   a. Reduced mortality rates
   b. Reduced MI rates
   c. Reduced stroke rates
   d. Reduced repeat revascularization rates

3. **A recent study suggests that which of the following may benefit diastolic heart failure patients (HFpEF)?**
   a. Candesartan
   b. Irebesartan
   c. Spironolactone
   d. Ramapril

4. **If possible elective non-cardiac surgery should be delayed for a minimum of how long after coronary stent placement?**
   a. 6 weeks
   b. 3 months
   c. 6 months
   d. 12 months

5. **The risk of stroke in electrophysiology device patients with a patent foramen ovale over 0-4 years is about?**
   a. 1%
   b. 3%
   c. 5%
   d. 7%