PARTNER Investigators Announce Dramatic Trial Results

Aortic stenosis is becoming increasingly prevalent in the United States as the population ages. As many as 300,000 individuals in the United States currently have symptomatic aortic stenosis. Surgical valve replacement, either with tissue or mechanical valve prostheses, has been the gold standard for treatment of extensive valve stenosis for many years. Improvements in surgical technique, durable valve prostheses, and better anticoagulation regimens have resulted in excellent patient survival and functional status. Recently, aortic valve repair has been offered to select patients with good results. Nevertheless, approximately one-third of individuals with symptomatic aortic stenosis are not candidates for open surgical replacement or repair because of their advanced age, severe comorbid conditions, or both.

The PARTNER Trial (Placement of Aortic Transcatheter Valve Trial) is a multicenter, prospective randomized trial comparing in parallel a balloon-expandable, stented investigational valve prosthesis (Figure) placed via the transfemoral or transapical route vs standard surgical treatment (cohort A) and the same valve prosthesis vs best medical care (including balloon angioplasty) in patients ineligible for surgical treatment (cohort B). The trial is being conducted at 21 centers in the United States, Canada, and Germany, including the Mayo Clinic campus in Rochester, Minnesota. The results of this second cohort of 358 patients (cohort B) have been released; the surgical arm of the trial (cohort A) is ongoing and results are anticipated in 2011.

Although the 30-day rates of stroke and vascular complications were higher in the group treated with the investigational valve, survival at 1 year was dramatically higher in patients receiving the valve compared with those who received best medical therapy (69.3% vs 49.3%). Furthermore, patients who received the valve had fewer hospitalizations and better symptom relief than those receiving standard medical care.

“The survival of the group receiving best medical care, including balloon valvuloplasty, was essentially the historical survival rate of patients with severe aortic stenosis,” says Charanjit S. Rihal, MD, chair of the Division of Cardiovascular Diseases and a principal investigator of the study at Mayo Clinic in Rochester. “Medical therapy had no impact on survival.” He also notes that some patients are not candidates for the valve because of characteristics of the valve annulus or because they have severe peripheral vascular disease. “Valve design and improved delivery systems should enable
the deployment of percutaneous valves in more of these patients in the future, with a reduced risk of stroke, vascular damage, and major bleeding.”

Importantly, the results of this cohort should not be extrapolated to other patient groups. “The long-term durability of this investigational valve is as yet unknown,” observes Thoralf M. Sundt III, MD, a cardiovascular surgeon and also a principal investigator of the study at Mayo Clinic in Rochester. “In patients with low operative risk, the standard approach to aortic valve replacement and repair may still be the best option. Nevertheless, it will be gratifying to have another option to offer high-risk patients.” The results of the surgical cohort will provide further insight. Ultimately, trials in other patient subsets and long-term patient follow-up will determine the role of percutaneous valves in the treatment of valvular disease.

For further information regarding the PARTNER Trial at Mayo Clinic, please contact Dr Rihal (507-255-2440) or Dr Sundt (507-255-7064).

**IN THE NEWS**

**Mayo Investigators Demonstrate Superior Benefit of Primed Adult Stem Cells in Heart Failure**

The potential use of stem cells to promote tissue regeneration in diseased hearts is an area of keen interest and intense investigation. Unaltered adult stem cells have yielded limited benefit in early clinical trials; new studies by Mayo researchers have demonstrated that human adult mesenchymal stem cells, when guided to become procardiogenic, can produce superior tissue regeneration in the setting of chronic myocardial infarction.

The international multidisciplinary team was led by Andre Terzic, MD, PhD, Division of Cardiovascular Diseases, Mayo Clinic in Rochester, Minnesota. In this study, human mesenchymal stem cells from sternal bone marrow were retrieved from patients undergoing coronary artery bypass graft surgery. These stem cells were then guided to acquire regenerative potency through a cardiogenic priming process. Primed mesenchymal stem cells demonstrated considerable regenerative potential when injected into mice with chronic myocardial infarction. The ejection fraction and 1-year survival of these treated mice improved significantly compared with sham treatment or treatment with unaltered stem cells. Upregulated cardiac transcription factors were a molecular characteristic of mesenchymal stem cells associated with successful cardiopoiesis.

The use of adult stem cells in prior studies has yielded conflicting outcomes, limiting broad application. This study importantly provides an explanation for this disparity; that is, cells from different individuals have differing reparative capacity. Furthermore, molecular characteristics can be identified in harvested stem cells that predict reparative success and therapeutic efficacy. According to Dr Terzic, nonreparative stem cells can be converted into reparative counterparts through the innovative process of guided cardiopoiesis, an approach currently tested in an ongoing clinical trial in patients with chronic ischemic cardiomyopathy.

**RECOGNITION**

Samuel J. Asirvatham, MD
Peter A. Brady, MD
Sunil V. Mankad, MD
Rick A. Nishimura, MD
Brian D. Powell, MD

Samuel J. Asirvatham, MD, Peter A. Brady, MD, Sunil V. Mankad, MD, Rick A. Nishimura, MD, and Brian D. Powell, MD, received 2010 Outstanding Teacher of the Year Awards presented by the cardiovascular disease fellows.
Cardiac resynchronization therapy (CRT) has been used clinically to treat patients with congestive heart failure (CHF) for almost a decade. Many patients with CHF have electrical conduction delay, as evidenced electrocardiographically by a prolonged QRS duration. In certain patients, this electrical conduction delay results in dyscoordinate contraction of the ventricular septum and left ventricular free wall, leading to decreased ventricular systolic function. CRT pacemakers (and defibrillators) resynchronize the ventricles by simultaneously pacing the right and left ventricles via a pacing lead in the coronary sinus branches.

“The initial randomized clinical trials demonstrated improved left ventricular systolic function, fewer hospitalizations for heart failure, and improved survival in patients randomly assigned to CRT compared with those who received medical therapy alone,” says Brian D. Powell, MD, an electrophysiologist at Mayo Clinic in Rochester. Approximately 70% of patients experience improvement in heart failure symptoms with CRT. Enrollment in previous trials was limited to patients with New York Heart Association (NYHA) class III-IV heart failure symptoms, QRS wider than 120 milliseconds, and ejection fraction (EF) less than 35%, on optimal medical therapy. Until recently, it was unknown if CRT would benefit patients with NYHA class I-II heart failure symptoms.

Many patients with NYHA class I-II symptoms meet criteria for placement of an implantable cardioverter-defibrillator (ICD) as primary prevention to lower their risk of sudden death. Should these mildly symptomatic patients receive a CRT defibrillator (CRT-D) at the time of the primary prevention ICD placement if they have a wide QRS interval? Many of these patients eventually progress to NYHA III-IV symptoms over time. Should “upgrading” the device to a CRT-D be deferred until symptoms progress, or should the initial device be a CRT-D while their heart failure symptoms are mild? Two recently completed trials—MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) and REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction)—evaluated the effect of CRT on patients with minimal or mild CHF symptoms (NYHA class I-II). The larger MADIT-CRT trial randomized more than 1,800 patients with EF less than 30%, QRS wider than 130 milliseconds, and NYHA class I-II to CRT-D or to standard ICD alone. Patients in the CRT-D group had a significant reduction in the combined end point of death or heart failure hospitalization (25% for the ICD group vs 17% for the CRT-D group; \(P=0.001\)) (Figure 1). “The difference in the combined end point was primarily driven by fewer heart failure hospitalizations in the CRT-D group,” according to Margaret M. Redfield, MD, director of the Heart Failure Clinic at Mayo Clinic in Rochester.
The CRT-D group also had improved EF at follow-up compared with the ICD group. Subgroup analyses of both the MADIT-CRT and REVERSE trials suggested that patients with QRS wider than 150 milliseconds were more likely to benefit from CRT-D compared with an ICD alone (Figure 2).

Based on the results of these 2 trials, the US Food and Drug Administration approved a new indication for CRT-D for ischemic cardiomyopathy patients with NYHA class I or greater heart failure or for nonischemic cardiomyopathy with NYHA class II or greater, including all patients with EF less than 30%, QRS wider than 130 milliseconds, and left bundle branch block. The requirement of left bundle branch block was based on subgroup analysis. This new indication expands the use of CRT-D to patients with less symptomatic heart failure.

Do patients with CHF and narrow QRS benefit from CRT? Initial single-center, nonrandomized case series reported improvement in left ventricular function in patients with CHF and narrow QRS who received CRT. The theory was that the QRS duration on electrocardiography may not accurately detect electrical dyssynchrony that may benefit from CRT. This was primarily driven by the perception of ventricular dyssynchrony as measured by echocardiographic tissue velocity parameters. These parameters have since been found to be less reproducible and reliable than previously thought. Data from the PROSPECT (Predictors of Response to CRT) trial and the Mayo Clinic Cardiac Resynchronization Registry found that dyssynchrony as measured by echocardiography (tissue velocity, M-mode, pulsed wave Doppler) did not adequately correlate with patients’ clinical improvement or improvement in ventricular function. The RethinQ (Resynchronization Therapy in Normal QRS) trial randomized patients with NYHA class III symptoms, EF less than 35%, narrow QRS (<130 milliseconds), and echocardiographic evidence of dyssynchrony to receive an ICD alone or CRT-D. There was no significant difference in the primary end point of improvement in peak oxygen consumption at 6 months. At this time, there is no conclusive evidence to support the use of CRT in patients with a narrow QRS duration of less than 120 milliseconds.

In summary, patients with EF less than 35%, QRS wider than 120 milliseconds, and NYHA III-IV CHF symptoms on optimal medical therapy should be considered for CRT. Recent randomized studies support expanding the use of CRT for patients with NYHA class I-II symptoms, EF less than 30%, and QRS wider than 130 milliseconds.
Hybrid Approach to Coronary Artery Disease

The options for revascularization in patients with coronary artery disease (CAD) increasingly appear to be in direct competition with each other. The long-established role of coronary artery bypass graft (CABG) surgery is being challenged by the outcomes achieved with percutaneous coronary intervention (PCI) deploying drug-eluting stents (DESs). The ongoing SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) Trial comparing CABG to PCI with DES for patients with multivessel CAD or left main CAD has shown, in early follow-up, similar early survival in both treatment groups. The trial does recognize the limitations of PCI in patients with complex anatomy in the coronary lesions (calcification, sequential lesions, bifurcation lesions, etc) and suggests more limited durability of PCI.

There may be a better way to approach this evolving field. From the patient’s perspective, it is not a question of one technique (provided by one type of specialist) “winning out” over another technique (provided by another type of specialist). Rather, patients expect the best treatment approach based on their coronary disease, anatomy, and comorbid conditions with the goals of a good outcome while minimizing risk and allowing early return to their normal activities. “A hybrid approach that would combine the advantages of CABG and the advantages of PCI might be the optimal approach available for treating CAD today,” according to Richard C. Daly, MD, a cardiovascular surgeon at Mayo Clinic in Rochester.

Advantages of PCI

PCI has the obvious advantage of being minimally invasive with minimal patient discomfort and allowing early return to normal activity. The approach may also minimize risk for some potential complications. The results of the SYNTAX Trial have suggested that the risk of stroke with PCI is less than that with CABG, although the 2 treatment groups received different antiplatelet medical therapy. There has been concern in the past that the durability of PCI may be less than that with CABG, with increased need for later interventions. Although DESs have not been compared directly with saphenous vein graft (SVG) conduits, current stents may provide durability that is at least as good as SVG conduits. Indeed, the 1-year patency rate of SVG conduits is probably about 85% to 90%, while that for DESs may be slightly better than 90%. Data on follow-up with actual angiography are limited, so this conclusion is inferred from data on the need for reintervention, but would seem to be reasonably accurate. Finally, new technology and evolving skills of interventional cardiologists have allowed a percutaneous approach to multivessel disease, left main disease, and more complex coronary lesions.

Advantages of CABG

The clear advantage and most important aspect of CABG are the use of the left internal mammary artery (LIMA) bypass graft to the left anterior descending coronary artery (LAD). The LIMA-to-LAD graft has been shown to be crucial for optimal long-term survival. If patent early, the LIMA graft is probably patent indefinitely, and 10- and 20-year patency rates exceed 90%. Bypass grafts treat the culprit lesions but also provide prophylaxis against future proximal lesions and protect the entire zone of vulnerable myocardium in diffusely unstable coronary endothelium. The complexity of the coronary lesions is not a factor as it is in PCI because bypass grafts can be placed around any type of proximal lesion. CABG can be performed off-pump, and LIMA-to-LAD anastomosis lends itself to an off-pump approach because the heart position does not need to be manipulated excessively. Although it is controversial, an off-pump approach to CABG probably does reduce risk of renal insufficiency, pulmonary injury, and bleeding. Many studies have also shown a reduced length of hospital stay with off-pump CABG. Single LIMA-to-LAD grafting performed off-pump does not require any manipulation of the aorta, and thus the risk of stroke is minimized.

Single bypass graft of the LIMA to the LAD can be performed in a minimally invasive manner and off-pump. The approach is called a minimally invasive...
direct coronary artery bypass (MIDCAB) and involves mobilization of the LIMA with a thoracoscopic or robotic technique and direct anastomosis of the LIMA to the LAD through a minimally invasive, 4- to 5-cm left anterior thoracotomy. Following this procedure, patients can return to work early, the result is cosmetically acceptable, and length of hospital stay is usually short.

**The Hybrid Approach to Coronary Revascularization**

A hybrid approach to coronary revascularization would combine the advantages of both CABG and PCI. The hybrid approach involves a MIDCAB, which provides the patient with the benefits of LIMA-to-LAD bypass graft, performed in a minimally invasive manner using thoracoscopic or robotic mobilization of the LIMA and a small left anterior thoracotomy for the LIMA-to-LAD anastomosis. This procedure is either preceded by or follows PCI of the non-LAD coronary lesions with DES. The patient avoids the need for sternotomy and cardiopulmonary bypass and has complete revascularization in a minimally invasive manner, maintaining the advantage of the LIMA-to-LAD graft.

The hybrid technique may be either a 2-stage approach with the MIDCAB preceding or following PCI by days or weeks or a single-stage procedure in which all steps are performed during a single surgical session. A single-stage approach would require a specialized operating room containing all the fluoroscopic equipment necessary for PCI. The single-stage approach would have better patient satisfaction and would potentially have a reduced length of hospital stay. Nevertheless, the 2-stage approach does have specific advantages. With a 2-stage approach, the antiplatelet therapy could be timed to reduce bleeding at MIDCAB and allow adequate antiplatelet therapy dosing for PCI. A functioning LIMA-to-LAD graft would allow subsequent PCI to be performed safely for ostial circumflex lesions, complex left main lesions, and perhaps other lesions. A 2-stage approach would eliminate the need for a costly specialized operating room and also would allow the PCI to be performed in a catheterization laboratory with full available functionality.

**Patient Selection**

Patients with multivessel CAD, including LAD disease, a graftable LAD, and non-LAD lesions amenable to PCI, could be considered for a hybrid approach. Candidates could include patients who normally might not be considered for PCI, including those with complex or distal left main disease, ostial LAD or circumflex disease, and complex or multiple LAD lesions. Other patients who might benefit are those who have minimal conduits available for CABG. This approach may also pose reduced risk in patients with more advanced age, frailty, renal insufficiency, diabetes, and aortic calcification or atherosclerosis.

A hybrid approach would be contraindicated in patients who are not good candidates for MIDCAB, including those with a nongraftable or a deep intramyocardial LAD. Also, patients who have had previous left thoracotomy or left subclavian artery stenosis or who are unable to tolerate single lung ventilation should not have MIDCAB. Patients with severe obesity are not good candidates for this approach because of the difficulty identifying the LAD and mobilizing it with a thoracoscopic or robotic approach. A hybrid approach is also contraindicated in patients who are not candidates for PCI, possibly including those with chronic total coronary artery occlusions, calcified or complex lesions in the non-LAD vessels, and limited vascular access for PCI.

**Outcomes of a Hybrid Approach to Coronary Vascularization**

A few groups have reported outcomes with a limited number of patients using a hybrid approach. The group from Emory University has reported on a hybrid approach in 106 patients, with no mortalities or strokes.

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**RECOGNITION**

**Timothy J. Nelson, MD, PhD**

Cardiovascular fellow at Mayo Clinic in Rochester, is the 2010 recipient of the American Heart Association Melvin L. Marcus Young Investigator Award in Basic Cardiovascular Sciences for his work on stem cell regenerative platforms and heart repair. The award is presented annually to a young investigator to encourage continued research careers in cardiovascular or circulatory physiology.

**George A. Beller, MD** (right), former chair of the division of cardiovascular disease at the University of Virginia, presented the 16th annual Robert L. Frye, MD, lecture. Dr Frye is on the left.
One patient had a perioperative myocardial infarction. All LIMA grafts were patent. All reports are small and nonrandomized but have shown safety and efficacy. Long-term outcomes are unknown.

Conclusions

The hybrid approach to revascularization of CAD is promising. For low-risk patients, it allows the benefit of a minimally invasive approach along with the long-term benefit of the LIMA-to-LAD bypass. Potential early return to work and reduced need for further intervention may contribute to cost-effectiveness in this group over time, but those advantages are speculative. Select high-risk patients may benefit from a minimally invasive approach. Complex LAD lesions are readily bypassed but may be difficult to treat with PCI. A functioning LIMA-to-LAD graft allows a percutaneous approach to complex left main and ostial circumflex lesions with more safety. DESs in non-LAD lesions are likely at least as durable as SVG, at least in the medium term. A 2-stage approach does not require a specialized operating room with fluoroscopic capabilities.

The approach does require collaboration between surgery and cardiology and willingness on the part of surgeons to continue to adapt to less invasive techniques. Although clinical data on outcomes are very limited at this stage, improvements in technology and the changing population with CAD will increasingly make the hybrid approach to treatment the optimal choice for many patients.
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