PREVENT Trial Protocol Lowers Incidence of LVAD Thrombosis

Left ventricular assist devices (LVADs) provide lifesaving therapy to many patients with end-stage heart failure, whether they are used as a bridge to transplant or as destination therapy. Technical improvements in device and battery design have made this therapy feasible for many patients. Currently, almost half the patients waiting for transplant at Mayo Clinic’s campus in Rochester, Minnesota, are supported by an LVAD. Individuals receiving an LVAD as destination therapy tend to be older, have significant comorbidities, and are not transplant candidates, but many regain an excellent quality of life after LVAD implantation.

Device thrombosis has always been a vexing problem, because not all LVAD components are biocompatible. Patients who received early pulsatile-flow VADs were at a significant risk of embolic stroke from thrombus formation in these larger, bulky devices. Current-generation continuous-flow devices have a more compact design, predisposing them to thrombosis of the entire pump.

The risk of thrombosis is highest early after device implantation; prior studies have demonstrated early pump thrombosis rates of up to 8.4% in patients receiving the HeartMate II (Thoratec/St. Jude Medical) LVAD. Most device management protocols are institution specific and highly variable, especially regarding anticoagulation, making comparison difficult. The nonrandomized “Prevention of HeartMate II Pump Thrombosis Through Clinical Management” (PREVENT) trial evaluated the effect of treatment with a standardized management protocol on the incidence of pump thrombosis during the first 3 months after device implant (Box). This observational study involved 300 patients (83% male, mean age 57 years, 78% destination, 22% bridge to transplant) with no prior mechanical circulatory support at 24 transplant centers.

Suspected pump thrombosis was defined as having 2 of the following: abnormal pump parameters, worsening heart failure, and hemolysis. It also needed to be accompanied by intravenous anticoagulation treatment, pump explantation, urgent transplantation, stroke, or death. By the 3-month follow-up, there were 12 suspected thrombotic events in 11 patients. Confirmed pump thrombosis had the same criteria but also included documented, photographic evidence of a thrombosis. Of the 12 suspected events, 9 were confirmed (2.9%, less than half of historical rates). The outcomes for these confirmed events were 7 pump exchanges and 2 urgent transplantations. In the patients who had nonconfirmed pump-thrombosis events, 1 had a pump exchange and 1 died, but neither was found to have thrombus. The third patient remains under supervision.
The overall survival rate was 91% at 90 days post-implantation, and survival free of pump thrombosis was 88%. For adverse events, there was an 18% rate of GI bleeding at 3 months, 16% rate of right heart failure, 3% rate of ischemic stroke, and 2% rate of drive-line infection. When the adherence to the overall recommendations and its impact on outcomes were examined, the results showed no significant difference in confirmed pump thrombosis, but there was a trend toward more-adverse cases for those with partial adherence versus those with good adherence (4% versus 1.9%, respectively). In addition, combined endpoint of suspected thrombosis, hemolysis, or ischemic stroke was significantly greater with partial adherence (12.1% versus 5.1%, P < 0.05).

A study presented earlier at the International Society for Heart and Lung Transplantation (ISHLT) meeting showed that the new HeartMate 3 had 80% survival in 50 patients in Europe implanted with the LVAD and no incidence of pump thrombosis; however, this device is not yet approved for use in the U.S. and worldwide experience is extremely limited. “The HeartMate II LVAD will continue to be implanted in the U.S. for the foreseeable future,” said Simon Maltais, MD, PhD, a cardiovascular surgeon at Mayo Clinic in Rochester, Minnesota, and lead investigator of the study, during his presentation of trial results at the ISHLT 2016 Annual Meeting and Scientific Sessions. “Based on these results, we recommend adoption of the PREVENT recommendations for all patients with a HeartMate II LVAD to reduce pump thrombosis risk.”

**PREVENT Protocol**

**Implantation**
- Create an inferiorly deep and laterally positioned pump pocket.
- Make sure the inflow cannula is positioned parallel to the septum.
- Avoid right ventricular compression by carefully positioning the outflow graft.
- Place the pump below the diaphragm and anchor it.

**Anticoagulation**
- Start titrated heparin within 48 hours post-implantation.
- Initiate warfarin within 48 hours and target an INR of 2.0 to 2.5.

**Antiplatelet Management**
- Two to 5 days post-implantation, start aspirin therapy at 81 to 325 mg/day.

**Pump Management**
- Make sure the pump runs at a speed >8600 rpm and preferably >9000 rpm.
- Mean arterial pressure should be maintained at <90 mm Hg.

**RECOGNITION**

**New Medical Director of the Mayo Clinic Institutional Review Board**

R Scott Wright, MD, a cardiologist in the Department of Cardiovascular Diseases at Mayo Clinic in Rochester, Minnesota, has been selected as the next medical director of the Mayo Clinic Institutional Review Board (IRB) effective January 1, 2017. In his new role, Dr Wright will oversee the quality, resources, effectiveness, and accreditation of the Mayo Clinic Human Research Protection Program. Dr Wright will chair the Human Subject Protection Program Oversight Group, as well as the IRB Administrative and Executive committees. In addition, he will liaise as a member of the Conflict of Interest Committee and Stem Cell Research Oversight Subcommittee.
Pediatric and adult structural interventional cardiologists have teamed up at Mayo Clinic in Rochester, Minnesota, to provide advanced levels of care for patients with bioprosthetic systemic AV valve dysfunction. Congenital and transcatheter valve implantation expertise, in combination with a team approach, has led to significant advances in and contributions to this field. Utilizing techniques learned from percutaneous valve implantation procedures, Mayo Clinic physicians have been instrumental in advancing the treatment of patients who have previously undergone surgery to replace the mitral or tricuspid valve with a tissue bioprosthesis, and have published some of the earliest reports and publications on this type of approach. Existing dysfunctional bioprosthetic valves can be “replaced” with transcatheter valves.

Tricuspid Valve
Mayo Clinic has a large referral population of patients with tricuspid valve abnormalities, such as Ebstein anomaly. Tricuspid valve surgical replacement is often necessary as part of treatment. “Bioprosthetic tissue valves implanted surgically will eventually become dysfunctional with regurgitation, stenosis, or combined dysfunction,” according to Nathaniel W. Taggart, MD, a pediatric cardiologist at Mayo Clinic in Rochester, Minnesota. “If a patient can be treated with transcatheter valve-in-valve (VIV) therapy, that approach is preferred over open-heart surgery and an additional median sternotomy.” Two types of transcatheter valves are being used in an off-label fashion, either a Melody (Medtronic Inc, St. Paul, Minnesota) percutaneous valve or a Sapien (Edwards Lifesciences, Irvine, California) valve. The type of valve used will depend on the size of the existing bioprosthesis (inner diameter) and nature of the valve dysfunction (Figure 1). Allison Cabalka, MD, a pediatric interventional cardiologist at Mayo Clinic in Rochester, Minnesota, and Charanjit S. Rihal, MD, an interventional cardiologist and chair of the Department of Cardiovascular Diseases in the Center for Cardiovascular Sciences at Mayo Clinic in Rochester, Minnesota, are lead collaborators in a multicenter international registry. They have recently published results of transcatheter tricuspid valve implantation for treatment of dysfunctional surgical bioprosthetic valves (Circ. 2016;133[16]:1582-1593).

“Currently, over 40 patients have had tricuspid valve-in-valve implantation at Mayo Clinic with excellent results. Transvenous implantation is carried out via a femoral or an internal jugular approach; valve type and size are determined by the specifications of the existing bioprosthesis. Typically, the Melody valve is used for smaller diameter or tightly stenotic bioprosthetic valves, while the Sapien (S3, diameter up to 29 mm) is used for larger diameter bioprostheses,” says Dr. Cabalka. For the initial registry publication, data were collected on 156 patients with bioprosthetic TV dysfunction who underwent catheterization with planned tricuspid VIV. Patient median age in the registry cohort was 40 years with 71% of patients falling into NYHA class III or IV. After TVIV, both
the tricuspid valve inflow gradient (stenosis) and
degree of tricuspid regurgitation improved signifi-
cantly. The median post-catheterization hospital
stay was 2 days. At follow-up, approximately 75%
of patients were in NYHA class I or II (p<0.001
vs pre-tricuspid VIV). Implant procedures were
associated with a very low risk of complica-
tions, including paravalvular leak. Medium-term
follow-up has been completed and longer-term
follow-up is in progress. Most patients continue
to be treated with aspirin in addition to warfarin
for anticoagulation to prevent valve thrombosis.

Mitral Valve
Repeat operation in the first 10 years following
mitral valve replacement is required in as many as
35% of patients. Repeat mitral valve replacement
carries significant risk, making transcatheter
treatment options appealing. Mitral VIV has been
pioneered and performed successfully by Mayo
Clinic physicians for over 5 years. “At Mayo Clinic,
a total percutaneous approach is used via an an-
tegrade transvenous transseptal delivery (Figure
2), in contrast to many centers where a predomi-
nantly transapical approach has been used. The
total percutaneous approach allows for rapid pa-
tient recovery and relatively short hospital stays
(median length of stay 2 days) in our most recent
experience,” says Mackram F. Eleid, MD, inter-
ventional cardiologist at Mayo Clinic in Roches-
ter, Minnesota. A recently published multicenter
collaboration led by Mayo Clinic cardiologists has
shown success rates >90% with the transvenous
transseptal mitral VIV procedure (JACC Cardio-

Similar to tricuspid valve-in-valve, the Sapien
valve is most commonly used and size is selected
based on the internal dimensions of the dysfunc-
tional bioprosthesis and detailed perioperative
imaging. Similar to tricuspid VIV, all patients are
treated with aspirin and warfarin anticoagulation
to prevent valve thrombosis. One-year follow-up
data has been promising, but more long-term
data is needed to understand the role of this ex-
citing treatment option.

In summary, the goal with the structural heart
team approach is to be able to provide compre-
hensive care to patients with complex valvular
abnormalities (both congenital and acquired),
with VIV therapy being an important part of com-
prehensive care in order to extend the life of sur-
gically placed bioprosthetic valves.

**Figure 1.** Tricuspid valve-in-valve implantation in a teenage patient with severe Ebstein anomaly and a 25-mm tissue bioprosthesis utilizing a Melody valve implanted on a 22-mm diameter delivery system. This patient has normal Melody valve function nearly 4 years after the procedure. A, Right ventricular angiogram demonstrating severe transvalvular regurgitation with brisk appearance of contrast in the right atrium. B, Static balloon sizing of the existing bioprosthesis is performed to determine implant valve type and size. C, Positioning of the Melody valve within the bioprosthesis from transfemoral approach with guidewire positioned in distal pulmonary artery branch. D, Right ventricular angiogram following successful valve implantation demonstrating complete resolution of tricuspid valve regurgitation.
Figure 2. Transvenous transseptal mitral valve-in-valve procedure. A, Balloon atrial septostomy is performed to allow Sapien valve (Edwards Lifesciences, Irvine, California) delivery. B, Sapien valve is carefully positioned within the prosthesis over a left ventricular anchor wire. C, Balloon-expandable Sapien valve is deployed within the surgical valve. D, Equipment is removed.
Mayo Clinic Launches Cardiovascular Genomics Clinic

The implementation of genomic medicine promises to individualize care for cardiovascular patients. A cardiovascular genomics task force has been established to facilitate practice of state-of-the-art genomic medicine in the Department of Cardiovascular Diseases, in collaboration with the Department of Laboratory Medicine and Pathology and the Center for Individualized Medicine at Mayo Clinic in Rochester, Minnesota.

The task force will work toward providing advanced genomic testing in the context of multidisciplinary clinical care, develop infrastructure for conduct of exploratory translational projects involving next-generation sequencing, and conduct clinical trials in cardiovascular genomic medicine. In addition, annual educational symposia will be held to improve the awareness of genomic medicine among front-line cardiovascular providers, including indications for genetic testing and interpretation of results.

An early, important initiative was to establish a Cardiovascular Genomics Clinic (CVGC) in the Department of Cardiovascular Diseases. This clinic provides consultation for patients with inherited lipid disorders, particularly familial hypercholesterolemia; individualized cardiovascular pharmacogenetics; and consultation for patients with dilated cardiomyopathy. Additionally, evaluations are provided for individuals with rare inherited cardiovascular disorders and panel-negative inherited cardiovascular diseases who need to be considered for whole-exome sequencing (Table).

Familial hypercholesterolemia (FH) is a heritable disorder of low-density lipoprotein cholesterol (LDL-C) metabolism associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). FH should be suspected in the setting of:

- A high LDL-C level (≥190 mg/dL without medication, ≥130 mg/dL on treatment)
- Cutaneous lesions suspected to be xanthomas or arcus senilis
- An LDL-C of >160 mg/dL in the setting of personal or family history of premature ASCVD
- Family history of FH

Patients with familial combined hyperlipidemia and familial hypertriglyceridemia also are evaluated in the CVGC. Resources include a genetic counselor to establish family pedigree, genetic testing to confirm genetic etiology, and screening of family members. While family screening can be accomplished by serum lipid levels, it’s felt by many expert bodies that genetic testing is more efficient and cost-effective, as LDL-C levels may fluctuate.

Genetic testing through the CVGC is now available to identify abnormal genes that may be inherited and lead to FH. A reflex genetic testing approach for FH used at Mayo Clinic includes (i) sequencing of LDLR supplemented by large deletion/duplication analysis, and (ii) APOB R3500Q and R3500W genotyping.

Familial dilated cardiomyopathy should be suspected when an individual who has been diagnosed with idiopathic dilated cardiomyopathy (DCM) has at least one relative diagnosed with idiopathic DCM or one first-degree relative with...
an unexplained sudden death under the age of 35 years.

Approximately 30% to 50% of patients with so-called idiopathic DCM are thought to have a genetic basis. Although familial forms are most often inherited in an autosomal-dominant fashion, recessive and sex-linked patterns have also been reported. Children born to individuals who have an autosomal dominant form of DCM could have a 50% chance of inheriting the genetic variant that causes familial DCM. It is important to understand that inheriting such a genetic variant that is associated with DCM does not necessarily translate to that individual developing the disease. However, absence of that genetic variant on a screening of a child of the affected individual could provide reassurance that the child is unlikely to develop the inherited form of DCM. Therefore, identifying the genetic variant associated with familial DCM could have important implications in counseling the affected family. Such counseling and screening of family members, including recommendations for ongoing monitoring and appropriate genetic testing for family members and patients with familial DCM, are provided in a multidisciplinary manner.

Rare Inherited Disorders, Cardiovascular Diagnostic Odysseys

The CVGC evaluates patients with syndromic disorders with cardiovascular involvement, early-onset myocardial infarction/atherosclerotic vascular disease, and rare arteriopathies, including dissection/aneurysm syndromes. Patients are evaluated by a cardiologist, medical geneticist, and genetic counselor. Whole-exome sequencing is sometimes utilized to establish diagnosis. The use of whole-exome sequencing and diagnostic odysseys has been reported to be around 25%.

Panel-Negative Hereditary Cardiovascular Diseases

Patients with hereditary cardiovascular diseases such as familial aortopathies are frequently assessed by sequencing of a candidate panel of genes. However, these panels identify an underlying genetic mutation in only 15% to 20% of the cases. Individuals that test negative for these panels can be referred to the CVGC for further evaluation, including consideration of whole-exome sequencing.

CV Pharmacogenomics (PGx)

The CVGC also provides consultation for:

- Specific questions related to beta-blockers, antiarrhythmic drugs, statin, clopidogrel or warfarin pharmacogenomics
- Statin-related myopathy
- Clopidogrel resistance
- Personalized pharmacogenetics consultation, including either single-gene or panel pharmacogenetics testing, to determine how medications can be prescribed in an individualized manner to the patient. This facilitates the provision of the right drug to the right patient to enhance clinical efficacy and minimize adverse events.

Genetic testing through the CVGC is now available to identify abnormal genes that may be inherited and alter the patient’s response to commonly used cardiovascular drugs. For additional information or to schedule an appointment, please call 507-538-8124.

Indications for Referral to Cardiovascular Genomics Clinic

- Inherited lipid disorders
- Dilated cardiomyopathy
- Cardiovascular pharmacogenetics
- Rare inherited disorders, cardiovascular diagnostic odysseys
- Panel-negative hereditary cardiovascular diseases

RECOGNITION

Sunil V. Mankad, MD, a cardiologist at Mayo Clinic in Rochester, Minnesota, is the recipient of the 2016 Richard Popp Excellence in Teaching Award presented by the American Society of Echocardiography (ASE). This award was named in honor of Richard Popp, MD, and it recognizes an outstanding teacher nominated by his or her students and peers. Recipients epitomize the ideal qualities of a mentor and role model, and because of these attributes, have made a major impact on practitioners in the field of cardiovascular ultrasound. The award was presented at the annual ASE gala on June 11, 2016, in Seattle, Washington. Dr. Mankad (right) is pictured at the award ceremony with Susan Wiegers, MD, (left), president of the American Society of Echocardiography.
Cardiology Update 2016: The Heart of the Matter
August 4-7, 2016
Sedona, AZ

13th Annual Mayo Clinic Electrophysiology Board Review Course
August 12-15, 2016
Rochester, MN

Pediatric and Adult Congenital Cardiology Review Course 2016
August 21-26, 2016
Dana Point, CA

21st Annual Mayo Clinic Cardiovascular Board Review and Recertification Course
August 27-31, 2016
Rochester, MN

Optional Echo Focus Pre-Course Session
August 26-31, 2016
Rochester, MN

Challenges in Clinical Cardiology: A Case-Based Update
September 9-11, 2016
Chicago, IL

September 10-13, 2016
Chicago, IL

13th Annual Mayo Clinic Interventional Cardiology Board Review
September 16-18, 2016
Rochester, MN

Echo in the City of Rivers 2016: Practical Review of Valvular Heart Disease
September 23-25, 2016
Pittsburgh, PA

Innovations in Atrial Fibrillation and Impact on the Brain: Impacting Quality of Life and Stroke Risk
September 24-25, 2016
Seattle, WA

Internal Medicine Review for Nurse Practitioners, Physician Assistants, and Primary Care Physicians NPPA 2016
September 28-30, 2016
Rochester, MN

Heart Disease in Women: A New Era of Understanding, Recognition, Prevention, Diagnosis and Treatment 2016
October 8-9, 2016
Rochester, MN

26th Annual Cases in Echocardiography, Cardiac CT, and MRI
October 19-22, 2016
Napa, CA

Cardiovascular Medicine 2016: Updates for Practitioners
October 21-22, 2016
Boston, MA

7th Annual Cardiology Conference for Healthcare Professionals
October 22-23, 2016
Wisconsin Dells, WI

The Genetics of Heart & Vascular Disease
October 28-29, 2016
Amelia Island, FL

Echocardiography in Pediatric and Adult Congenital Heart Disease Case Studies
November 3-6, 2016
Phoenix, AZ

AHA Symposium—The Heart Brain Clinic: A Collaborative Approach to Optimize Patient Care
November 13, 2016
New Orleans, LA

Mayo Clinic Update in Echocardiography: Role of Echo from Prevention to Intervention 2016
November 17-20, 2016
Scottsdale, AZ

Coronary Artery Disease: Case-Based Learning
November 18-20, 2016
Las Vegas, NV

5th Annual Heart Rhythm & EGG Course: A Case-Based Approach 2016
November 30-December 4, 2016
Scottsdale, AZ

Echo on Marco Island: Case-Based Approach
December 1-4, 2016
Marco Island, FL

The Heart Beat of Cardiology: Practical Application of Echocardiography
December 8-10, 2016
Chicago, IL

CARDIOVASCULAR SELF-STUDY
https://cardiovascular.education-registration.com/selfstudy
www.celinks.mayo.edu/cme/cvselfstudy