NewYork-Presbyterian
The University Hospital of Columbia and Cornell

ADVANCES IN ADULT AND PEDIATRIC CARDIOLOGY, INTERVENTIONAL CARDIOLOGY, AND CARDIOVASCULAR SURGERY

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College

INSIDE FALL 2013

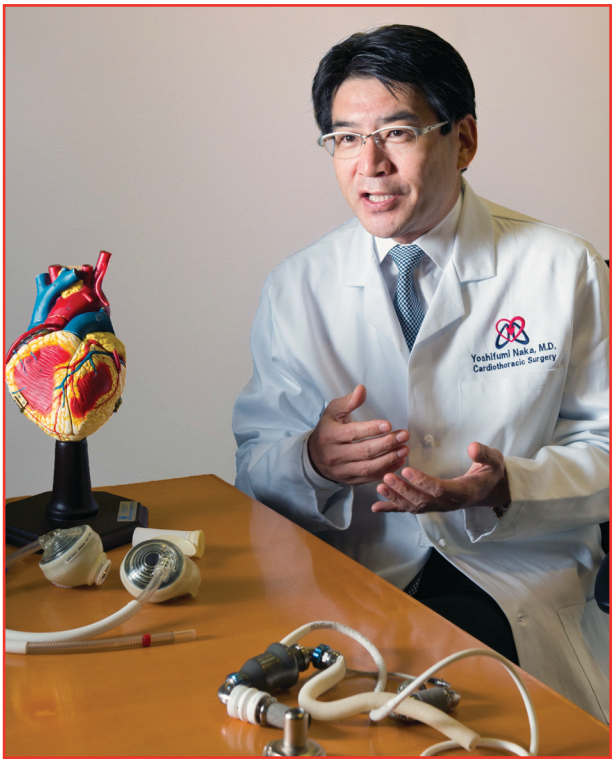
In the most recent edition of America's Best Hospitals published by *U.S.News & World Report*, the cardiovascular programs of NewYork-Presbyterian Hospital were ranked #1 in the New York City metropolitan area and #3 in the nation.

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL CARDIOLOGY & HEART SURGERY 2013-14

Ventricular Assist Devices as Destination Therapy: Why and When to Make This Decision

End-stage heart disease affects some six million Americans a year and is the principal diagnosis of patients discharged from hospitals. Despite many advances in medical therapies, it is estimated that over one million patients will progress to significant heart failure with high mortality rates. In recent years, left ventricular assist devices (LVADs) have transitioned in their role as a bridge-to-transplant to a destination therapy for patients with advanced heart failure. While these devices are highly effective in prolonging survival in patients refractory to medical management, they are not without their challenges. This article addresses some important questions about the decision-making process for recommending an LVAD as a permanent therapy and the associated risks and benefits to patients.

According to Yoshifumi Naka, MD, PhD, Director of the Mechanical Circulatory Support Program and Cardiac Transplantation Program at NewYork-Presbyterian, the Mechanical Circulatory Support Program at NewYork-Presbyterian/Columbia was initiated in 1990 to provide a bridge-to-transplantation to support patients until suitable donor hearts became available. In the two decades since, cardiologists and cardiothoracic surgeons at NewYork-Presbyterian/Columbia and NewYork-Presbyterian/Weill Cornell have reached across their subspecialties, pooling their expertise to find a viable therapy for end-stage heart failure when medical therapies have nothing left to offer and transplant is not an option.



Yoshifumi Naka, MD, PhD

VADs: The Early Years

The landmark REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial published in 2001 in *The New England Journal of Medicine* demonstrated that end-stage heart failure patients who received an LVAD device had a 52.1 percent chance of surviving one year, compared with a 24.7 percent survival rate for patients on medical management. But at two years, the likelihood of survival was only 22.9 percent for patients with the LVAD versus 8.1 percent for those on medical therapies. LVAD as a destination therapy was virtually abandoned and efforts to improve pump technology were stepped up. It would be nearly a decade before mechanical circulatory devices – although routinely used as a bridge-to-transplant – would be deemed suitable by the Food and Drug Administration as an alternative therapy for heart failure.

Interestingly, consideration of circulatory assist devices as a destination therapy has come full circle. "The initial mission of the NIH Heart, Lung and Blood Institute many years ago was not to use these mechanical assist devices as an adjunct therapy to transplant, but actually as the ultimate therapy for patients with heart failure," says Donna M. Mancini, MD, Medical Director, Center for Advanced Cardiac Care at NewYork-Presbyterian/ Columbia. "In the '70s and '80s when there were major problems with survival following heart transplant, heart transplant almost disappeared. It was during this period that the focus of research was on mechanical devices. With the advent of cyclosporine, the survival rate following transplants increased remarkably, transplants made a significant rebound, and the devices came into use as a complement to transplant."

Research continued on the devices as destination therapy, but it wasn't until January 2010 that the FDA approved the HeartMate II® LVAD as a long-term treatment for patients with end-stage heart failure. The second generation device was smaller, making it suitable for a wider range of candidates, and more than doubled the survival rate of its predecessor – the HeartMate® XVE – from 23 percent to 58 percent. Today, device therapy – in appropriately selected patients – offers a 60 percent likelihood of surviving two years. Survival with currently available medical therapy remains below 10 percent.

INTERMACS
HEART FAILURE CLINICAL PROFILES

Profile 1 (Sickest)	Critical cardiogenic shock
Profile 2	Progressive decline on inotropic support
Profile 3	Stable but inotropic dependent
Profile 4	Resting symptoms – home on oral therapy
Profile 5	Exertion intolerant
Profile 6	Exertion limited
Profile 7	Advanced NYHA Class III symptoms

As of August 2013, INTERMACS had more than 10,480 patients enrolled in its registry from more than 140 centers – including NewYork-Presbyterian – nationwide.

NEW YORK HEART ASSOCIATION
HEART FAILURE FUNCTIONAL CLASSIFICATION SYSTEM

Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

According to Dr. Yoshifumi Naka, patients meeting the characteristics of INTERMACS profile one and up to four or five are considered equivalent to New York Heart Association Class IV – the most severe disease symptoms.

The Right Time to VAD

About half of those who have heart failure die within five years of diagnosis. Heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood, reducing the ability of the heart to pump and maintain normal bodily function. Implantable mechanical pumps can assist circulation by the ventricles.

"When patients with heart failure – whether it is ischemic heart failure due to a history of heart attacks or any type of cardiomyopathy – reach a phase where medical therapy is limited and no longer offers them a good solution for either quality or longevity of life, that is the time to consider heart replacement therapy," says Ulrich P. Jorde, MD, Medical Director of the Mechanical Circulatory Support Program at NewYork-Presbyterian/ Columbia. "Traditionally, heart replacement therapy meant heart transplantation. However, a shortage of donor organs has greatly limited transplant as an option and there are now long waiting lists for donor organs. Additionally, many patients with end-stage heart failure do not meet the criteria for transplant for reasons that include age and the existence of

co-morbidities such as cancer or other organ disease."

"For patients with heart failure who have been hospitalized multiple times in the past year or who require intravenous inotropic agents intermittently or all the time, we need to make a brave decision and consider moving to a different lifestyle," says Nir Uriel, MD, a cardiologist with the Center for Advanced Cardiac Care at NewYork-Presbyterian/ Columbia. "That would be the VAD."

"The decision-making algorithm for choosing patients for destination mechanical assist devices is different than the decision-making tree for bridge-to-transplant because there is no rescue therapy," says Evelyn M. Horn, MD, Director of Advanced Heart Failure, Mechanical Assist and Pulmonary Hypertension Programs, Perkin Heart Failure Center at NewYork-Presbyterian/ Weill Cornell. "The use of LVAD can be 1,000 percent correct in the right patient and 1,000 percent incorrect in the wrong patient. One needs to be sure, first and foremost, that we will be improving the patient's quality of life and that the patient and family are comfortable in managing life with the device."

According to Dr. Horn, timing of VAD implantation is critical and should be considered earlier in the disease progression than it has in the past. Outcomes studies indicate that the healthier patients at the time of implant do better. "When in the course of the trajectory of heart failure should the patient be referred for destination therapy? That is the question," emphasizes Dr. Horn. "Every patient is different. VAD as a destination therapy is not for the almost dying patient. It needs to be offered in the right window – when the patient has failed therapy, has had repeated admissions for heart failure, is not tolerating medications because of kidney dysfunction or hypotension, or has stopped responding to resynchronization therapy, but before other organ dysfunction has begun to develop."

Evelyn M. Horn, MD, and Irina Sobol, MD

Two systems are available to help classify the stage and severity of heart failure: the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and the New York Heart Association (NYHA) functional classification system. INTERMACS, which was established in 2005 by the National Heart, Lung and Blood Institute, the Centers for Medicare and Medicaid Services, and the Food and Drug Administration to track patient outcomes, has defined seven clinical profile levels – with profile 1 representing the sickest patients. The NYHA system relates symptoms to everyday activities and the patient's quality of life.

> *One needs to be sure, first and foremost, that we will be improving the patient's quality of life and that the patient and family are comfortable in managing life with the device.*
>
> *— Evelyn M. Horn, MD*

"INTERMACS profile guidelines run from one to seven. One is the sickest; seven is the least sick," explains Dr. Naka. "Once patients become dependent on an inotrope, they are considered INTERMACS three as long as they are not in the hospital or they've just been ambulated. Many INTERMACS four patients are reclassified as INTERMACS three once we monitor their hemodynamics. At Columbia, 95 percent of our patients who receive a VAD are between INTERMACS one and three."

The Hospital's cardiovascular specialists agree that there are two main questions to consider when recommending an LVAD as a destination therapy. First, how long is the patient expected to survive if continued on medical therapy only? Secondly, what will the patient's quality of life be on medical therapy as compared to life with an LVAD?

"There are many reasons why a patient may not qualify for placement of a left ventricular assist device," says Dr. Mancini. "These include the presence of any other significant medical condition that would not be treated by the correction of their heart failure, such as metastatic cancer, end stage pulmonary disease, renal or liver failure, prior strokes…it's a long list. The patient must also have a good support network in the event that the device fails or has a problem."

"The majority of our patients are recommended to receive a VAD once they become dependent on inotropic agents or they become sicker but cannot receive inotropic infusions because they may cause more problems," says Dr. Naka. "Most studies show that once you are dependent on inotropic treatment, one-year survival is about 25 percent; two-year survival is

Arash Salemi, MD

less than 10 percent. Once you've become inotropically dependent, you definitely need the surgery – either for a heart transplant or a device."

"Nobody wants the pump, but nobody wants to die either," says Dr. Jorde. "At the end of the day the dilemma is whether the patient will be willing to live with a VAD or let the disease take its natural course."

Exciting Progress, Continuing Challenges: Weighing Risk Versus Benefit

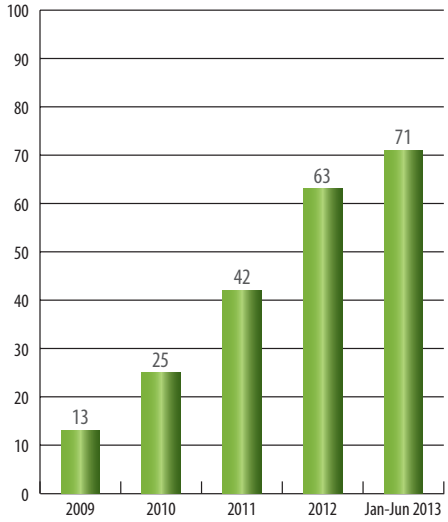
"Over the course of the past 20 years, with multiple device iterations, we have reached a point now where the ventricular assist devices that are currently in use and on the market are well-tolerated by patients," says Arash Salemi, MD, cardiothoracic surgeon, NewYork-Presbyterian/Weill Cornell. "The general goal of the assist device is to assume the pumping function of a severely weakened heart. The devices do just that by taking the blood as it enters the ventricular chamber and redirecting it through a pump to the aorta, supplying oxygenated blood to the rest of the body."

"Improvements after VAD implantation in both survival and quality of life for advanced heart failure patients are compelling," says Dr. Naka. "But decisions must be based on the risk-benefit of this particular therapy. The benefit, as I've experienced, is that a two-year survival is much better than what medical therapy can offer at this point in time. Device therapy is associated with VAD-specific complications, which can include infection, major bleeding episodes, strokes and other thromboembolic events, and device malfunction or failure. These complications are not insignificant. The other challenging issue is the condition of the patient at the time of surgery. These patients are very sick."

"One particular consequence of LVAD implantation could be the development of right ventricular failure," says Irina Sobol, MD, a cardiologist with the Perkin Heart Failure Center at NewYork-Presbyterian/Weill Cornell. "Because of our interest in pulmonary hypertension, we are acutely aware and uniquely suited for the management of this complication."

"VAD therapy, in fact, brings out incipient right heart failure that may not have existed before," adds Dr. Horn. "As physicians who treat pulmonary hypertension and right heart failure, we may provide additional expertise in understanding the complexities of managing the unloaded left ventricle with an LVAD and the stressed right ventricle, which may now appear more similar to the displaced septum of a pulmonary hypertensive right ventricle."

NEWYORK-PRESBYTERIAN HOSPITAL DESTINATION THERAPY ACTIVE PATIENT VOLUME 2009 – 2013



NewYork-Presbyterian Hospital's heart failure programs include cardiac surgeons, cardiologists, and numerous medical and ancillary professionals dedicated to the care of these patients. "There is a critical need for very close follow-up by a heart failure team pre- and post-implantation and post-discharge to home," says Dr. Salemi. "The patient and their family need to be well-versed in the use of the assist device so they are able to respond appropriately to the different bells and whistles that may manifest themselves following hospitalization."

(continued on page 5)

NEWYORK-PRESBYTERIAN HOSPITAL 2012 DESTINATION THERAPY OUTCOMES

30-Day Readmission	39%
Survival – One Year	82% (through June 2013)
Mortality – One Year	18%
Functional Capacity – Six Months (300 m or >)	70%

(continued from page 4)

"I have seen the evolution of the left ventricular assist device program at Weill Cornell blossom into a very complex program that provides comprehensive care for patients with all forms of congestive heart failure," says Dr. Sobol. "We have a multidisciplinary approach to management that includes anesthesia, surgery, nurse practitioners, and social work. Our weekly LVAD rounds are also attended by psychiatrists and the nephrology team with involvement of gastroenterology and infectious disease specialists. This approach allows us to significantly improve both the quality and continuity of care our patients receive."

NewYork-Presbyterian cardiothoracic surgeons and cardiologists have played a key role in bringing LVAD devices into common use as a destination therapy, now implanting some 80 to 100 devices a year with several patients who are five to seven years out. "Today we are talking about a 60 to 70 percent survival benefit, which is a major breakthrough," says Dr. Jorde. "This could save the lives of thousands of Americans a year. Not only saving lives, but also returning patients to full, active lives."

Nir Uriel, MD, and Ulrich P. Jorde, MD

The Next Generation

Dating back to the REMATCH trial, led by Eric A. Rose, MD, former Surgeon-in Chief, NewYork-Presbyterian/Columbia has a 20-year history of testing, refining, and implanting LVADs as a bridge-to-transplant and, more recently, as a destination therapy. Researchers here have developed programs in physiology, immunology, vascular biology, hematology, and cellular and molecular biology looking at the effects and outcomes of long-term implantable devices.

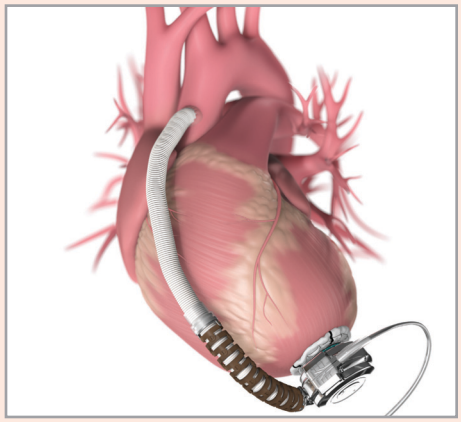
"There are still some quality-of-life issues with LVADs," says Dr. Yoshifumi Naka. "Patients are tethered to the device since it is not yet fully implantable. You also need to change the batteries. And you can't take a bath or go swimming since current devices require a dry line going through the abdominal skin. Otherwise an infection can develop.

"So we are now investigating devices that are smaller, quieter, and more portable, as well as fully implantable, or capable of providing biventricular support," continues Dr. Naka. "We are one of the first centers in the United States evaluating new third generation circulatory devices – the HeartMate® III and HeartWare® VAD – available only in clinical trials as destination therapies. These less invasive procedures may lead to decreased procedural time, reduced bleeding and infection, and shorter length of hospitalization."

"The earliest LVADs were cumbersome and difficult to manage," says Dr. Arash Salemi. "The newer generations are enabling us to make these devices available to a huge population of patients who, otherwise, for one reason or another, would be excluded from a transplant listing. The destination therapy indication has really transformed treatment for advanced heart failure."

Image reprinted with the permission of Thoratec Corporation

Soon to be available in clinical trials as a destination therapy, HeartMate® III features a small pump with proven magnetic levitation technology and a hemo-compatible profile designed to further advance clinical outcomes with low rates of bleeding and thrombosis.



Images courtesy of HeartWare

The HVAD® pump is a miniaturized device designed to be implanted in the pericardial space. It sits inside the patient's chest and connects directly to the heart, avoiding the need for abdominal surgery.

NewYork-Presbyterian Heart

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