



EDUCATIONAL OBJECTIVE: Readers will identify trends in the management of patients with advanced heart failure.

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Advanced heart failure: Transplantation, LVADs, and beyond

■ ABSTRACT

For patients with advanced heart failure, outcomes are good after heart transplantation, but not enough donor hearts are available. Fortunately, mechanical circulatory assist devices have become an excellent option and should be considered either as a bridge to transplantation or as “destination therapy.” Current mechanical circulatory assist devices improve quality of life in patients who are candidates.

■ KEY POINTS

After heart transplantation, survival rates are high and quality of life is excellent, although coronary artery disease, renal dysfunction, and the need for immunosuppressive drugs are ongoing challenges.

Changes in donor heart allocation made in 2006 more strongly favor the sickest patients and have reduced the rate of mortality on the waiting list.

Continuous-flow left-ventricular assist devices offer many advantages over the older pulsatile-flow devices, including improved outcomes, smaller size, less noise, and greater durability.

Inotropic therapy is purely palliative and should not be viewed as an alternative to heart transplantation or device implantation.

PATIENTS WITH ADVANCED HEART FAILURE far outnumber the hearts available for transplantation. Partly as a consequence of this shortage, left-ventricular assist devices (LVADs) are being used more widely.

This article is an update on options for managing severe, advanced heart failure, with special attention to new developments and continuing challenges in heart transplantation and LVADs.

■ THE PREVALENCE OF HEART FAILURE

About 2.6% of the US population age 20 and older have heart failure—some 5.8 million people. Of these, about half have systolic heart failure.¹ Patients with systolic heart failure can be classified by degree of severity under two systems:

The New York Heart Association (NYHA) classifies patients by their functional status, from I (no limitation in activities) to IV (symptoms at rest). NYHA class III (symptoms with minimal exertion) is sometimes further broken down into IIIa and IIIb, with the latter defined as having a recent history of dyspnea at rest.

The joint American College of Cardiology and American Heart Association (ACC/AHA) classification uses four stages, from A (high risk of developing heart failure, ie, having risk factors such as family history of heart disease, hypertension, or diabetes) to D (advanced heart disease despite treatment). Patients in stage D tend to be recurrently hospitalized despite cardiac resynchronization therapy and drug therapy, and they cannot be safely discharged without specialized interventions. The options for these patients are limited: either end-of-life care or extraordi-

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nary measures such as heart transplantation, long-term treatment with inotropic drugs, permanent mechanical circulatory support, or experimental therapies.²

The estimated number of people in ACC/AHA stage D or NYHA class IV is 15,600 to 156,000. The approximate number of heart transplants performed in the United States each year is 2,100.³

■ WHICH AMBULATORY PATIENTS ARE MOST AT RISK?

The range for the estimated number of patients with advanced heart failure (NYHA class IIIb or IV) is wide (see above) because these patients may be hard to recognize. The most debilitated patients are obvious: they tend to be in the intensive care unit with end-organ failure. However, it is a challenge to recognize patients at extremely high risk who are still ambulatory.

The **European Society of Cardiology**⁴ developed a definition of advanced chronic heart failure that can help identify patients who are candidates for the transplant list and for an LVAD. All the following features must be present despite optimal therapy that includes diuretics, inhibitors of the renin-angiotensin-aldosterone system, and beta-blockers, unless these are poorly tolerated or contraindicated, and cardiac resynchronization therapy if indicated:

- Severe symptoms, with dyspnea or fatigue at rest or with minimal exertion (NYHA class III or IV)
- Episodes of fluid retention (pulmonary or systemic congestion, peripheral edema) or of reduced cardiac output at rest (peripheral hypoperfusion)
- Objective evidence of severe cardiac dysfunction (at least one of the following): left ventricular ejection fraction less than 30%, pseudonormal or restrictive mitral inflow pattern on Doppler echocardiography, high left or right ventricular filling pressure (or both left and right filling pressures), and elevated B-type natriuretic peptides
- Severely impaired functional capacity demonstrated by one of the following: inability to exercise, 6-minute walk test dis-

tance less than 300 m (or less in women or patients who are age 75 and older), or peak oxygen intake less than 12 to 14 mL/kg/min

- One or more hospitalizations for heart failure in the past 6 months.

Treadmill exercise time is an easily performed test. Hsich et al⁵ found that the longer patients can walk, the lower their risk of death, and that this variable is about as predictive of survival in patients with systolic left ventricular dysfunction as peak oxygen consumption, which is much more cumbersome to measure.

The **Seattle Heart Failure Model** gives an estimate of prognosis for ambulatory patients with advanced heart failure. Available at <http://depts.washington.edu/shfm/>, it is based on age, sex, NYHA class, weight, ejection fraction, blood pressure, medications, a few laboratory values, and other clinical information. The model has been validated in numerous cohorts,⁶ but it may underestimate risk and is currently being tested in clinical trials (REVIVE-IT and ROADMAP; see at www.clinicaltrials.gov).

Recurrent hospitalization is a simple predictor of risk. A study of about 7,000 patients worldwide found that after hospitalization with acute decompensated heart failure, the strongest predictor of death within 6 months was readmission for any reason within 30 days of the index hospitalization (Starling RC, unpublished observation, 2011). Any patient with heart failure who is repeatedly hospitalized should have a consultation with a heart failure specialist.

■ INOTROPIC THERAPY FOR BRIDGING

Inotropic drugs, which include intravenous dobutamine (Dobutrex) and milrinone (Primacor), are used to help maintain end-organ function until a patient can obtain a heart transplant or LVAD.

Inotropic therapy should not be viewed as an alternative to heart transplantation or device implantation. We inform patients that inotropic therapy is purely palliative and may actually increase the risk of death, which is about 50% at 6 months and nearly 100% at 1 year. A patient on inotropic therapy who

Ambulatory heart failure patients at high risk may be hard to recognize

is not a candidate for a transplant or for an assist device should be referred to a hospice program.⁷

■ CARDIAC TRANSPLANTATION: SUCCESSES, CHALLENGES

Survival rates after heart transplantation are now excellent. The 1-year survival rate is about 90%, the 5-year rate is about 70%, but only about 20% survive 20 years or longer.^{8,9} The prognosis is not as good as for combined heart-lung transplantation patients.

Age is an important factor and is a contentious issue: some medical centers will not offer transplantation to patients over age 65. Others regard age as just another risk factor, like renal dysfunction or diabetes.

Quality of life after heart transplantation is excellent: patients are usually able to return to work, regardless of their profession.

The leading cause of death after heart transplantation is malignancy, followed by coronary artery vasculopathy, then by graft failure. Some patients develop left ventricular dysfunction and heart failure of unknown cause. Others develop antibody-mediated rejection; in recent years this has been more promptly recognized, but treatment remains a challenge.

Acute rejection, which used to be one of the main causes of death, now has an extremely low incidence because of modern drug therapies. In a US observational study currently being conducted in about 200 patients receiving a heart transplant (details on CTOT-05 at www.clinicaltrials.gov), the incidence of moderate rejection during the first year is less than 10% (Starling RC, unpublished observation). But several concerns remain.

Adverse effects of immunosuppressive drugs continue to be problematic. These include infection, malignancy, osteoporosis, chronic kidney toxicity, hypertension, and neuropathy.

Renal dysfunction is one of the largest issues. About 10% of heart transplant recipients develop stage 4 kidney disease (with a glomerular filtration rate < 30 mL/min) and need kidney transplantation or renal replacement therapy because of the use of calcineurin inhibitors for immunosuppression.¹⁰

Coronary artery vasculopathy was the larg-

est problem when heart transplantation began and continues to be a major concern and focus of research.^{11,12} Case 1 (below) is an example of the problem.

Case 1:

Poor outcome despite an ideal scenario

A 57-year-old businessman had dilated cardiomyopathy and progressive heart failure for 10 years. He was listed for transplantation in 2008 and was given an LVAD (HeartMate II, Thoratec Corp, Pleasanton, CA) as a bridge until a donor heart became available.

In 2009, he received a heart transplant under ideal conditions: the donor was a large 30-year-old man who died of a gunshot wound to the head in the same city in which the patient and transplant hospital were located. Cardiopulmonary resuscitation was not performed, and the cold ischemic time was just a little more than 3 hours. Immune indicators were ideal with a negative prospective cross-match.

Laboratory results after transplantation included creatinine 1.7 mg/dL (normal 0.6–1.2 mg/dL), low-density lipoprotein cholesterol 75 mg/dL, high-density lipoprotein cholesterol 64 mg/dL, and triglycerides 90 mg/dL.

The patient was given immunosuppressive therapy with cyclosporine (Neoral), mycophenolate (CellCept), and prednisone. Because his creatinine level was high, he was also perioperatively given basiliximab (Simulect), a monoclonal antibody to the alpha chain (CD25) of the interleukin-2 receptor. (In a patient who has poor renal function, basilixumab may help by enabling us to delay the use of calcineurin inhibitors.) He also received simvastatin (Zocor) 10 mg.

Per Cleveland Clinic protocol, he underwent 13 biopsy procedures during his first year, and each was normal (grade 0 or 1R). Evaluation by cardiac catheterization at 1 year showed some irregularities in the left anterior descending artery, but a stent was not deemed necessary. Also, per protocol, he underwent intravascular ultrasonography, which revealed abnormal thickness in the intima and media, indicating that coronary artery disease was developing, although it was nonobstructive.

Two months after this checkup, the patient collapsed and suddenly died while shop-

A simple predictor of risk is whether a patient is recurrently hospitalized

ping. At autopsy, his left anterior descending artery was found to be severely obstructed.

Coronary artery vasculopathy is still a major problem

This case shows that coronary artery vasculopathy may develop despite an ideal transplantation scenario. It remains a large concern and a focus of research.

Coronary vasculopathy develops in 30% to 40% of heart transplant recipients within 5 years, and the incidence has not been reduced by much over the years. However, probably fewer than 5% of these patients die or even need bypass surgery or stenting, and the problem is managed the same as native atherosclerosis. We perform routine annual cardiac catheterizations or stress tests, or both, and place stents in severely blocked arteries.

THE DONOR SHORTAGE: CHANGING HOW HEARTS ARE ALLOCATED

The number of patients receiving a heart transplant in the United States—about 2,000 per year—has not increased in the past decade. The European Union also has great difficulty obtaining hearts for people in need, and almost every transplant candidate there gets mechanical support for some time. The gap between those listed for transplant and the number transplanted each year continues to widen in both the United States and Europe.

All transplant candidates are assigned a status by the United Network of Organ Sharing (UNOS) based on their medical condition. The highest status, 1A, goes to patients who are seriously ill, in the hospital, on high doses of inotropic drugs (specific dosages are defined) and mechanical circulatory support such as an LVAD, and expected to live less than 1 month without a transplant. Status 1B patients are stable on lower-dose inotropic therapy or on mechanical support, and can be in the hospital or at home. Status 2 patients are stable and ambulatory and are not on inotropic drugs.

In July 2006, UNOS changed the rules on how patients are prioritized for obtaining an organ. The new rules are based both on severity of illness (see above) and geographic proximity to the donor heart—local, within 500

miles (“zone A”) or within 500 to 1,000 miles (“zone B”). The order of priority for donor hearts is:

- Local, status 1A
- Local, status 1B
- Zone A, status 1A
- Zone A, status 1B
- Local, status 2
- Zone B, status 1A
- Zone B, status 1B
- Zone A, status 2.

As a result of the change, donor hearts that become available in a particular hospital do not necessarily go to a patient in that state. Another result is that status 2 patients, who were previously the most common transplant recipients, now have much less access because all status 1 patients within 500 miles are given higher priority. Since the change, only 8% of hearts nationwide go to status 2 patients, which is 67% fewer than before. At the same time, organs allocated to status 1A patients have increased by 26%, and their death rates have fallen.³

The new allocation system is a positive change for the sickest patients, providing quicker access and a reduction in waiting-list mortality.¹³ The drawback is that status 2 patients who are less ill are less likely to ever receive an organ until their condition worsens.

Heart transplant outcomes are publicly reported

The Scientific Registry of Transplant Recipients publicly reports heart transplant outcomes (www.srtr.org). For any transplant center, the public can learn the number of patients waiting for a transplant, the death rate on the waiting list, the number of transplants performed in the previous 12 months, the waiting time in months, and observed and risk-adjusted expected survival rates. A center that deviates from the expected survival rates by 10% or more may be audited and could lose its certification.

Also listed on the Web site is the percentage of patients who receive a support device before receiving a transplant. This can vary widely between institutions and may reflect the organ availability at the transplant center (waiting times) or the preferences and expertise of the transplantation team. We believe

Coronary vasculopathy develops in about 30% to 40% of heart transplant recipients within 5 years

that the mortality rate on the waiting list will be reduced with appropriate use of LVADs as a bridge to transplantation when indicated. We have now transitioned to the use of the improved continuous-flow LVADs and rarely maintain patients on continuous inotropic therapy at home to await a donor organ.

■ MECHANICAL CIRCULATORY SUPPORT: BRIDGE OR DESTINATION?

Mechanical circulatory support devices are increasingly being used to sustain patients with advanced heart failure. Currently at Cleveland Clinic, more LVADs are implanted than hearts are transplanted.

Mechanical circulatory support is indicated for patients who are listed for transplant to keep them functioning as well as possible while they are waiting (bridge to transplant). For others it is “destination therapy”: they are not candidates for a transplant, but a device may improve and prolong the rest of their life.

Case 2:

A good outcome despite a poor prognosis

A 71-year-old man was rejected for transplantation by his local hospital because of his age and also because he had pulmonary artery hypertension (78/42 mm Hg; reference range 15–30/5–15 mm Hg) and creatinine elevation (3.0 mg/dL; reference range 0.6–1.5 mg/dL). Nevertheless, he did well on a mechanical device and was accepted for transplantation by Cleveland Clinic. He received a transplant and is still alive and active 14 years later.

Comment. Determining that a patient is not a good transplantation candidate is often impossible. Putting the patient on mechanical support for a period of time can often help clarify whether transplantation is advisable. Probably most patients who receive mechanical support do so as a bridge to decision: most are acutely ill and many have organ dysfunction, pulmonary hypertension, and renal insufficiency. After a period of support, they can be assessed for suitability for transplantation.

LVADs continue to improve

Many devices are available for mechanical circulatory support.¹⁴ In addition to LVADs, there are right-ventricular assist devices (RVADs),

and devices that simultaneously support both ventricles (BiVADs). Total artificial hearts are also available, as are acute temporary percutaneous devices. These temporary devices—TandemHeart (CardiacAssist, Pittsburgh, PA) and Impella (Abiomed, Danvers, MD)—can be used before a long-term mechanical device can be surgically implanted.

LVADs are of three types:

- Pulsatile volume-displacement pumps, which mimic the pumping action of the natural heart. These early devices were large and placed in the abdomen.
- Continuous axial-flow pumps, which do not have a “heartbeat.” These are quieter and lighter than the early pumps, and use a turbine that spins at 8,000 to 10,000 rpm.
- Continuous centrifugal-flow pumps. These have a rotor spinning at 2,000 to 3,000 rpm, and most of them are magnetically powered and suspended.

The superiority of LVADs over medical therapy was clearly shown even in early studies that used pulsatile LVADs.¹⁵ The results of such studies and the increased durability of the devices have led to their rapidly expanded use.

The newer continuous-flow pumps offer significant improvements over the old pulsatile-flow pumps, being smaller, lighter, quieter, and more durable (TABLE 1). A 2007 study of 133 patients on a continuous axial-flow LVAD (HeartMate II) found that 76% were still alive after 6 months, and patients had significant improvement in functional status and quality of life.¹⁶ In a postapproval study based on registry data, HeartMate II was found superior to pulsatile pumps in terms of survival up to 12 months, percentage of patients reaching transplant, and cardiac recovery. Adverse event rates were similar or lower for HeartMate II.¹⁷

Another study compared a continuous-flow with a pulsatile-flow LVAD for patients who were ineligible for transplantation. Survival at 2 years was 58% with the continuous-flow device vs 24% with the pulsatile-flow device ($P = .008$).¹⁸ Since then, postmarket data of patients who received an LVAD showed that 85% are still alive at 1 year.¹⁹ This study can be viewed as supporting the use of LVADs as destination therapy.

Quality of life for patients receiving an LVAD has been excellent. When biventricu-

Currently at Cleveland Clinic, more LVADs are implanted than hearts are transplanted

TABLE 1

Pulsatile vs continuous-flow left ventricular assist devices

	PULSATILE DEVICES	CONTINUOUS-FLOW DEVICES
Weight (g)	1,250	390
Volume (mL)	450	63
Noise	Audible	Silent
Moving parts	Many	One (rotor)
Maximal flow (L/min)*	10	10
Clinical durability (years)	1.5	> 5 (estimated)

*At a mean pressure of 100 mm Hg

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Many patients receive LVADs as a 'bridge' before transplantation

lar pacemakers for resynchronization therapy first became available, distances on the 6-minute walk test improved by 39 m, which was deemed a big improvement. LVAD devices have increased the 6-minute walk distance by 156 m.²⁰

Adverse events with LVADs have improved, but continue to be of concern

Infections can arise in the blood stream, in the device pocket, or especially where the driveline exits the skin. As devices have become smaller, driveline diameters have become smaller as well, allowing for a better seal at the skin and making this less of a problem. Some centers report the incidence of driveline infections as less than 20%, but they continue to be a focus of concern.¹⁸

Stroke rates continue to improve, although patients still require intensive lifelong anticoagulation. The target international normalized ratio varies by device manufacturer, ranging from 1.7 to 2.5.

Bleeding. Acquired von Willebrand syndrome can develop in patients who have an LVAD, with the gastrointestinal system being the most frequent site of bleeding.²¹

Device thrombosis occurs very rarely (2%–3%) but is very serious and may require pump exchange.

Mechanical malfunction. As duration of therapy lengthens, problems are arising with

aging devices, such as broken wires or short circuits. New-generation pumps have markedly improved durability and reliability.

Good data are kept on device outcomes

The Interagency for Mechanically Assisted Circulatory Support (INTERMACS) maintains a national registry of patients with a mechanical circulatory support device to treat advanced heart failure. It was jointly established in 2006 by the National Heart, Lung, and Blood Institute, Centers for Medicare and Medicaid Services (CMS), the US Food and Drug Administration, and others. Reporting to INTERMACS is required for CMS reimbursement.

The INTERMACS database now has about 4,500 patients at 126 medical centers and is yielding useful information that is published in annual reports.²² The 2011 report focused on the experience with mechanical circulatory support as destination therapy and showed that patients who receive continuous-flow pumps have significantly better survival rates than those with pulsatile-flow pumps.²³ An earlier report showed that the level of illness at the time of implantation predicts survival²⁴; this information now drives cardiologists to try to improve patient status with a temporary support device or intra-aortic balloon pump before implanting a durable device. The sickest patients (INTERMACS

level 1) have the poorest outcomes, and centers now do fewer implantations in patients in this category. We have learned this important lesson from the INTERMACS registry.

The new devices have received a lot of media attention, and patient accrual has increased steadily as the devices have been approved.

On November 20, 2012, the US Food and Drug Administration approved the HeartWare Ventricular Assist System (HeartWare, Framingham, MA) for heart failure patients awaiting a transplant.

■ FUTURE DIRECTIONS

PROCEED II is an ongoing global clinical trial comparing the outcomes with donor hearts transported in standard cold storage to those transported in an experimental transport de-

vice that pumps the heart under physiologic conditions. If proven effective, this device could allow long-distance transport of donor hearts and expand the donor population.

A prospective, randomized study is now enrolling patients to evaluate induction therapy with rituximab (Rituxan) plus conventional immunosuppression (tacrolimus [Prograf], mycophenolate, steroid taper) vs placebo induction plus conventional immunosuppression. The study will enroll 400 patients (200 to each treatment arm) at 25 sites and will have a 36-month accrual period with 12-month follow-up (see <http://clinicaltrials.gov/show/NCT01278745>). The study is based on data in primates that found that eliminating B cells with an anti-CD20 drug before transplantation markedly reduced the incidence of coronary artery vasculopathy. ■

■ REFERENCES

- Lloyd-Jones D, Adams RJ, Brown TM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 2010; 1221:e46–e215.
- Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; 119:1977–2016.
- 2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999–2008. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD.
- Metra M, Ponikowski P, Dickstein K, et al; Heart Failure Association of the European Society of Cardiology. Advanced chronic heart failure: a position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2007; 9:684–694.
- Hsieh E, Gorodeski EZ, Starling RC, Blackstone EH, Ishwaran H, Lauer MS. Importance of treadmill exercise time as an initial prognostic screening tool in patients with systolic left ventricular dysfunction. *Circulation* 2009; 119:3189–3197.
- Gorodeski EZ, Chu EC, Chow CH, Levy WC, Hsieh E, Starling RC. Application of the Seattle Heart Failure Model in ambulatory patients presented to an advanced heart failure therapeutics committee. *Circ Heart Fail* 2010; 3:706–714.
- Gorodeski EZ, Chu EC, Reese JR, Shishehbor MH, Hsieh E, Starling RC. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. *Circ Heart Fail* 2009; 2:320–324.
- Taylor DO, Stehlik J, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth official adult heart transplant report—2009. *J Heart Lung Transplant* 2009; 28:1007–1022.
- Stehlik J, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult heart transplant report—2010. *J Heart Lung Transplant* 2010; 29:1089–1103.
- Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; 349:931–940.
- Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med* 1999; 340:272–277. Erratum in: *N Engl J Med* 1999; 340:976.
- Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003; 349:847–858.
- Singh TP, Almond CS, Taylor DO, Graham DA. Decline in heart transplant wait list mortality in the United States following broader regional sharing of donor hearts. *Circ Heart Fail* 2012; 5:249–258.
- Baughman KL, Jarcho JA. Bridge to life—cardiac mechanical support. *N Engl J Med* 2007; 357:846–849.
- Rose EA, Gelijns AC, Moskowitz AJ, et al; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001; 345:1435–1443.
- Miller LW, Pagani FD, Russell SD, et al; HeartMate II Clinical Investigators. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007; 357:885–896.
- Starling RC, Naka Y, Boyle AJ, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol* 2011; 57:1890–1898.
- Slaughter MS, Rogers JG, Milano CA, et al; HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009; 361:2241–2251.
- John R, Naka Y, Smedira NG, et al. Continuous flow left

- ventricular assist device outcomes in commercial use compared with the prior clinical trial. *Ann Thorac Surg* 2011; 92:1406–1413.
20. **Starling RC.** Improved quantity and quality of life: a winning combination to treat advanced heart failure. *J Am Coll Cardiol* 2010; 55:1835–1836.
 21. **Uriel N, Pak SW, Jorde UP, et al.** Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. *J Am Coll Cardiol* 2010; 56:1207–1213.
 22. **Kirklin JK, Naftel DC, Kormos RL, et al.** The fourth INTERMACS annual report: 4,000 implants and counting. *J Heart Lung Transplant* 2012; 31:117–126.
 23. **Kirklin JK, Naftel DC, Kormos RL, et al.** Third INTERMACS Annual Report: the evolution of destination therapy in the United States. *J Heart Lung Transplant* 2011; 30:115–123.
 24. **Kirklin JK, Naftel DC, Kormos RL, et al.** Second INTERMACS annual report: more than 1,000 primary left ventricular assist device implants. *J Heart Lung Transplant* 2010; 29:1–10.

■ SUGGESTED READING

- Costanzo MR, Dipchand A, Starling R, et al; International Society of Heart and Lung Transplantation Guidelines.** The International Society of Heart and Lung Transplantation guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010; 29:914–956.
- Mehra MR, Kobashigawa J, Starling R, et al.** Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates–2006. *J Heart Lung Transplant* 2006; 25:1024–1042.
- Slaughter MS, Pagani FD, Rogers JG, et al; HeartMate II Clinical Investigators.** Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. *J Heart Lung Transplant* 2010; 29(4 suppl):S1–S39.

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