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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Left Ventricular Assist Devices

A Rapidly Evolving Alternative to Transplant

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ABSTRACT

Left ventricular assist devices are becoming an increasingly prevalent therapy for patients with Stage D heart failure with reduced ejection fraction. Technological advances have improved the durability of these devices and have significantly lengthened survival in these patients. Quality of life is also improved, although adverse events related to device therapy remain common. Nevertheless, with the continuing organ donor shortage for cardiac transplantation, left ventricular assist devices are frequently serving as a substitute for transplant, particularly in the elderly patient. (J Am Coll Cardiol 2015;65:2542–55) © 2015 by the American College of Cardiology Foundation.

Heart failure (HF) incidence and prevalence is increasing at epidemic proportions. This rise in HF incidence is, in part, due to the success cardiologists have made in salvaging patients who have acute myocardial infarctions. Improved survival in patients with HF and the aging of the population has contributed to the increasing prevalence of HF (1–3). In the United States alone, 5.8 million Americans have HF. The incidence is estimated at 650,000 new cases annually, with over a million annual hospital admissions. More than 300,000 deaths/year are attributed to HF, and the annual cost to manage these patients is close to $40 billion. Approximately 50% of the HF population has heart failure with reduced ejection fraction (HFrEF). In this subset of patients, probably 10% have advanced symptoms (New York Heart Association [NYHA] functional class IIIB to IV), yielding an estimated cohort of approximately 200,000 to 250,000 patients (1–3) who will be the focus of our review.

THERAPEUTIC IMPROVEMENTS IN HFrEF

MEDICAL THERAPIES. Many advances have been made in the management of HFrEF, notably with the use of neurohormonal antagonists. These agents have prolonged survival and improved the quality of life in patients with HFrEF. However, since this therapy was developed in the 1980s and 1990s, newer pharmacological therapies have been few (4). Treatment with the Food and Drug Administration (FDA)-approved selective sinus-node inhibitor ivabradine reduces hospital admission for worsening HF (5). More recently, LCZ696, which combines angiotensin II inhibition with a neprilysin inhibitor, has been demonstrated to hold promise for HFrEF patients (6).

SURGICAL THERAPIES. The greatest advances in HFrEF therapy over the last decade have been surgical approaches (7–9). Biventricular pacing has resulted in improved survival, reverse remodeling, and improved quality of life (10). For patients with refractory HFrEF (i.e., Stage D), progress in cardiac replacement therapies has been substantial. However, palliation with continuous intravenous (IV) inotropes remains the only therapeutic option for many Stage D HFrEF patients, as cardiac replacement therapies with allografts or devices have been offered only to a small subset of these patients. A therapeutic algorithm for Stage D HFrEF is shown in the **Central Illustration**. In this algorithm, the initial screen is

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eligibility for cardiac transplantation, followed by assessment for destination mechanical support, and eventually, palliation. Indeed, in the 2013 International Society of Heart Lung Transplant guidelines for use of mechanical devices, the initial question asked is whether the patient is to be considered a transplant candidate (11). With the rapid advances in mechanical circulatory support, this algorithm may be revised in the near future such that the initial question is eligibility for destination therapy (DT), followed by heart transplantation candidacy and palliation (**Central Illustration**).

HEART TRANSPLANTATION VERSUS LEFT VENTRICULAR ASSIST DEVICE IN ADVANCED HFrEF

Stage D HFrEF patients are typically referred to cardiac transplant centers, where they undergo an extensive evaluation to determine their candidacy. Optimization of the medical regimen and consideration for revascularization or other standard therapies are assessed. Significant comorbidities that could be life-threatening at the time of transplant surgery or post-transplant are carefully excluded before patients are accepted as transplant candidates (12). The short- and long-term outcomes following cardiac transplantation have been exceptional, with a median survival of 10.7 years and survival conditional on surviving to 1 year after transplant of 13.6 years (13). Quality of life has greatly improved as immunosuppressive agents have become more targeted for the rejection process. This therapeutic success has resulted in a glut of patients awaiting this life-saving therapy.

THE CHRONIC LIMITATION OF ORGAN AVAILABILITY. In the United States, 3,990 patients are currently listed for heart transplant (14–16). The medical urgency of patients listed has steadily increased, with the majority of those now registered for cardiac transplant requiring inotropic or mechanical support. The major limitation to the growth of cardiac transplant has been the limited donor supply. Despite many campaigns to increase donor volume by local or federal agencies, the donor supply has remained flat and is limited to approximately 2,500 hearts annually in the United States. Currently, warm preservation devices, such as the Organ Care System (Transmedics, Amherst, Massachusetts), which provides a clinical platform for ex vivo human heart perfusion, offer hope for increased numbers of potential donor organs. This device may provide donors beyond the current geographic limit imposed with cold preservation techniques and/or identify viable donors with clinical characteristics that ordinarily would preclude transplant in the absence of a metabolic assessment (17). The recently completed PROCEED II (Randomized Study of Organ Care System Cardiac for Preservation of Donated Hearts for Eventual Transplantation) trial (17) demonstrated noninferiority of ex vivo preservation to cold ischemia in 130 transplant recipients undergoing transplant with standard donors. Three cases of heart transplant using organs from after cardiac death were reported in Australia using this organ preservation system (18). Nevertheless, despite the hope for more usable organs, the donor supply remains flat; clearly transplant is not the solution for the estimated 250,000 patients with advanced HFrEF who could benefit from cardiac replacement therapy. Fortunately, concomitant with the improvement in therapy for heart transplantation, mechanical assist devices to support patients with end-stage HFrEF have continued to evolve. More and more transplant candidates are requiring mechanical support as they wait for an acceptable organ. In 2000, the International Society for Heart Transplantation reported that 19.1% of transplant recipients were mechanically supported; this number increased to 41.0% in 2012 (13). Left ventricular assist device (LVAD) support is typically offered to transplant candidates who are developing end-organ damage despite maximal medical therapy, including inotropic support, or to those candidates who are inotrope-dependent with an anticipated long waitlist time (i.e., large size and/or blood type O recipients). These categories correspond to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) levels 1 to 3. The INTERMACS is a North American registry established in 2005 that collects clinical data for patients receiving mechanical circulatory support device therapy to treat advanced HF. The INTERMACS scale assigns patients with advanced HF into 7 levels according to hemodynamic profile and functional capacity (**Figure 1**). Ventricular support devices offer improved survival to transplant with excellent quality of life. However, implantation of the LVAD is another surgical procedure with associated risks, such as stroke, infection, bleeding, and sensitization, that may prolong the time to finding a suitable organ and, in some cases, may preclude transplant.

PATIENT SELECTION FOR HEART TRANSPLANT VERSUS LVAD. In patients with cardiogenic shock or post-cardiotomy syndrome, many short-term mechanical devices provide biventricular support. For chronic patients with Stage D HFrEF who are not transplant candidates, the only mechanical device

ABBREVIATIONS AND ACRONYMS

BTT = bridge to transplant

CF = continuous flow

DT = destination therapy

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LVAD = left ventricular assist device

MELD = Model for End-Stage Liver Disease

NYHA = New York Heart Association