Introduction:

Heart failure is among the leading causes of death in the developed countries. An estimated 6.6 million Americans have congestive heart failure (CHF) and, each year, there are an estimated 400,000 new cases diagnosed.\(^{(1-2)}\) Increasing prevalence, hospitalizations, and deaths have made CHF a major chronic condition in the United States. Almost 50% of patients diagnosed with CHF will be dead within 5 years.\(^{(1-2)}\)

In addition, CHF is the most common diagnosis in hospital patients age 65 years and older. In that age group, one fifth of all hospitalizations have a primary or secondary diagnosis of heart failure.\(^{(1)}\)

End-stage heart failure is associated with considerable morbidity and mortality. Patients classified as having end-stage heart failure are those with symptoms at rest despite maximal medical therapy (NYHA Class III/IV). In the United States, approximately 40,000 new patients present each year in end-stage heart failure.\(^{(3)}\) Medical treatment is focused on limiting disease progression, improving quality of life and prolonging the survival of these patients.

For patients whose symptoms continue to progress despite maximal medical therapy, surgical intervention is often the only remaining treatment option. Heart transplantation remains the definitive surgical treatment, with a reported 5 year survival rate of approximately 50%.\(^{(4)}\) However, there are a limited number of healthy donor hearts available each year for transplantation forcing many patients to potentially wait years for an available donor heart. It has been estimated that only 1 in 24 cardiac patients who need a donor heart receive one.\(^{(3)}\)

Fortunately, the development of mechanical circulatory support devices over the past 20-30 years has greatly increased the options in the surgical treatment of these patients. These devices, commonly referred to as ventricular assist devices (VADs) were originally developed as rescue devices, however, they have evolved as an accepted treatment for patients with end-stage heart failure. There are currently 3 common indications for the use of VADS:
1. **Bridge to recovery** – Short-term use, with length thought of as days to weeks.
2. **Bridge to transplantation (BTT)** – Instituted in individuals listed for cardiac transplantation and failing conventional medical therapy.
3. **Destination therapy** – Success with VADs as BTT therapy has led to the development and use of these devices as an alternative to transplant.

**First Generation Mechanical Circulatory Assist Devices:**

The first generation of left ventricular assist devices (LVADs) attempt to mimic physiologic blood circulation by providing pulsatile blood flow. The most common of these devices are **Abiomed BVS 5000/AB ventricle systems** (Abiomed Inc. Danvers, MA, USA), **Thoratec PVAD/ Implantable VAD (IVAD)** (Thoratec Corp. Pleasantville, CA, USA), **Thoratec Heartmate XVE** (Thoratec Corp. Pleasantville, CA, USA), and **Worldheart Novacor System (LVAS)** (Worldheart Corp. Oakland, CA, USA).

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial demonstrated meaningful survival advantage and improved quality of life for patients with end-stage heart failure (NYHA Class IV) treated with placement of a left ventricular assist device versus optimal medical management. Subsequent studies have demonstrated the effectiveness of the Heartmate XVE as long-term destination therapy with appropriate patient selection and timing of implantation.

Tremendous success has been achieved with these pulsatile flow devices, but they are associated with significant morbidity as well. The factors contributing to this morbidity are thought to include the size of the device, the need for extensive surgical dissection, and the large diameter percutaneous lead required for their power supply. In addition, the durability of these devices is limited due to the large number of mechanical parts and the repeated movements caused by the repeated opening and closing of the device chamber. The REMATCH trial, while establishing a meaningful survival benefit, also demonstrated the substantial risk of mechanical failure and device-related complications including infection and bleeding in patients undergoing placement of these mechanical assist devices. In patients surviving up to 2 years, almost 65% had to undergo device replacement in the trial. A subsequent study demonstrated the Heartmate XVE has a 2-year durability of less than 5% despite several design enhancements.

The Abiomed BVS5000 is currently FDA approved for use a short-term, bridge-to-recovery device. For longer term, bridge-to-transplant use, the Thoratec PVAD/IVAD, the Thoratec Heartmate XVE are all FDA approved. The Worldheart Novacor LVAS is no longer currently available. In the United States currently, the Heartmate XVE is FDA approved as destination therapy. However, due to the demonstrated effectiveness and increased safety of the continuous flow assist devices, the Heartmate XVE is rarely used today.
Second generation Mechanical Circulatory Assist Devices:

Continuous-flow LVADs represent the second generation of mechanical circulatory assist devices. Their development was spurred on by several factors including the need for greater reliability and to reduce the size of the pump. Continuous flow LVADs can be further divided into two categories: centrifugal and axial flow pumps. Axial flow pumps have several advantages over centrifugal pumps. They are more compact and weigh less than centrifugal pumps and thus less invasive to implant. Axial flow pumps are able to generate higher flow rates at lower pressures than centrifugal pumps, and axial flow pumps consume power, allowing for more compact and lighter power supply components as well as potentially implantable batteries.

The first axial flow LVAD used, the Medtronic Hemopump, was developed by Dr. Richard Wampler and tested at the Utah Artificial Heart Institute. Its success demonstrated the feasibility of the clinical use of implantable continuous-flow VADs. This device is no longer available in the United States, but its use established the basis for all subsequent axial flow VADs in use today.

Several axial flow continuous flow LVADs are currently available for treatment of adult heart failure patients in the United States. These include:

1. **Thoratec Heartmate II** (Thoratec Corp. Pleasantville, CA, USA): The Heartmate II VAD consists of an internal blood pump with a percutaneous lead connecting the pump to an external power source. The pump’s only moving part is the impeller, which spins on bearings lubricated by blood and powered by an electromagnetic motor. The pump has an implant volume of 63 ml and can generate up to 10L/min of flow at a mean pressure of 100 mmHG. Several studies have been undertaken demonstrating improved outcomes. Frazier et al reported a series of 43 patients implanted with a Heartmate II for bridge-to-transplantation and destination therapy. They found an 80% 1-year survival rate as well as markedly improved functional status and quality of life. The Heartmate II Bridge-to-transplantation trial was a multicenter trial looking at 133 patients. They found a median duration of support of 126 days, a 75% survival rate at 6 months and 685 at 12 months along with significant functional status improvement at 3 months. In addition, John et al studied 32 patients who underwent Heartmate II implantation as a bridge-to-transplantation. They found a 30 day survival of 96.9% and 86.9% survival at 6 months (alive or transplanted). The Heartmate II DT Clinical Trial was subsequently undertaken and looked at 200 patient at 40 clinical sites randomized in a 2:1 fashion for Heartmate II vs. Heartmate XVE. The study found a one-year survival of 68% and two year survival of 58% and a lower rate of all major adverse events as compared to the Heartmate XVE. Currently, the Heartmate II is approved by the FDA for bridge-to-transplantation and destination therapy.

2. **Jarvik 2000** (Jarvik Heart, Inc. Manhattan, NY, USA): The Jarvik 2000 blood pump weighs 90 grams and is about the size of a C battery. It consists of a blood pump, a 16 mm outflow graft and a percutaneous power cable to connect to an
external power supply. This pump produces axial flow by means of a single rotating, vaned impeller driven by a direct-current motor contained within the housing. \(^{(4)}\) The optimal speed of the pump is determined by adjusting the pump settings under echocardiographic guidance, with the goal being to maximize the contribution of the native heart to the cardiac output. Several single and multi-center studies have shown the Jarvik 2000 to be safe and effective when used as both bridge-to-transplantation and destination therapy. \(^{(14-16)}\) These studies have suggested that this device works best when it is used to augment ventricular function rather than capturing the entire cardiac output. In addition, this device has been shown to be remarkably reliable, with one study showing zero component failures in more than 100 patients. \(^{(17)}\) The Jarvik 2000 Bridge-to-transplant study looking at 150 patients has been completed. Currently, the Jarvik 2000 is available in the United States as part of an FDA approved clinical trial (RELIVE Trial) as destination therapy. It is CE approved in Europe for both bridge-to-transplantation and for destination therapy.

3. Percutaneous devices such as the **TandemHeart pVAD** (Cardiac Assist, Inc. Pittsburgh, PA, USA) and the **Impella Pump System** (Abiomed Inc. Danvers, MA, USA) are available for use in the United States as bridge-to-recovery devices. Multiple studies have been conducted demonstrating the clinical efficacy and relative safety of these devices in a variety of clinical settings including as support during high-risk percutaneous or surgical revascularization procedures, as temporary circulatory support in the setting of reversible, severe left ventricular failure and a bridge to a permanent assist device or transplantation in the setting of severe, end-stage heart failure. \(^{(21)}\)

4. In the pediatric population, the axial continuous flow LVAD, the **Micromed HeartAssist 5™ Pediatric VAD** (Micromed Cardiovascular, Inc. Houston, TX, USA), the modern version of the Micromed Debakey VAD is FDA approved. In addition, the **Berlin Heart™ Excor** pediatric ventricular assist device gained FDA approval in December 2011 for use as a BTT device in children.

**Third Generation Mechanical Circulatory Assist Devices:**

Currently, development of the 3\(^{rd}\) generation LVAD is underway. These devices are continuous-flow devices with an axial blood flow pattern, similar to the 2\(^{nd}\) generation VADs. The difference between the 2\(^{nd}\) and 3\(^{rd}\) generation devices lie in the distinguishing design element of “contact” vs. “noncontact” bearing design. \(^{(9)}\) The 2\(^{nd}\) generation devices have an internal rotor within the path of blood flow that is suspended by contact bearings. \(^{(9)}\) This design carries several potential concerns. First, the presence of contact bearings used in suspending the rotor represent a point of frictional wear that could result in device failure. In addition, the 2\(^{nd}\) generation VADs carries with them a risk of thrombus formation on the rotor and bearing contact points, resulting in a potential increased risk for embolic stroke. As a result, these devices require long-term antithrombotic therapy potentially increasing the risk of hemorrhagic complications. \(^{(9)}\)

In contrast, a 3\(^{rd}\) generation rotary pump utilizes either magnetic or hydrodynamic levitation of the impeller. Impeller rotation to augment blood flow through the device is
achieved through magnetic coupling to the pump motor.\(^{(9)}\) The absence of contact bearings has the potential to significantly improve durability as well as reduce the risk of thrombus formation within the pump and possibly reduce the need and intensity of long-term antithrombotic therapy.\(^{(9)}\) Currently, there are 4 devices in various stages of clinical trials in Europe and the United States. These include:

1. **VentrAssist** (Ventracor Inc. Foster City, CA, USA): Ventracor was dissolved and the intellectual property rights were sold to Thoratec, Corp.
2. **DuraHeart** (Terumo Heart Inc. Ann Arbor, MI, USA): Clinical trials have concluded in Europe and it has achieved CE approval. A clinical evaluation of the device in the United States began in January 2010.\(^{(9)}\) The first implantation occurred July 30, 2008.
3. **HVAD** (HeartWare Corp. Miami, FL, USA): The ADVANCE clinical trial evaluating the HVAD for bridge-to-transplantation was completed and published in June 2012. A total of 140 patients were implanted and the trial found the survival to transplantation or explantation comparable to existing, approved LVADs and improved functional status and quality-of-life at 6 months.\(^{(25)}\) The Heartware HVAD received FDA approval for bridge-to-transplantation indications in November 2012.
4. **Levacor** (World Heart Corp. Oakland, CA, USA): Clinical evaluation was halted in February 2011 and the program was closed in July 2011. World Heart Corp. is currently developing MiFlow and PediaFlow devices for use in the adult and pediatric populations.\(^{(26)}\)
5. **Incor** (Berlin Heart GmbH Berlin, Germany): CE approved for use in the European Union. Currently available for use on a case-by-case basis for humanitarian use. Clinical evaluation worldwide has been initiated in the United States.

The clinical experience with the “third generation” continuous flow LVADs has demonstrated good efficacy with regard to the hemodynamic support of end-stage heart failure patients. In addition, studies have demonstrated similar reliability and safety as compared to the well-studied 2\(^{nd}\) generation mechanical circulatory assist devices. Additional study is needed to determine if their novel design confers added long-term reliability as compared to the 1\(^{st}\) and 2\(^{nd}\) generation devices.

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**Bibliography:**


