Orthotopic heart transplantation represents the definitive, yet increasingly difficult to acquire, therapeutic option for end-stage heart failure. In 2008, a total of 2143 orthotopic heart transplantations were performed in the US, a 3% decline from the previous year. At the end of 2008, a total of 1684 patients were on a waiting list for orthotopic heart transplantation. The mortality for patients on the waiting list was reported as 170 per 1000 patient-years at risk, representing the highest risk in all solid organ transplantations. Additionally, a major shift has occurred over the previous decade in the United Network of Organ Sharing status at the time of transplantation, with the majority occurring in patients listed as status 1A or 1B (Table 1). This is likely reflective of the major advancements in mechanical circulatory support (MCS) over the latter portion of the previous decade. Indeed, the number of pump implants reported to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database in 2008 was far greater than the 18 months before that time, owing in large measure to enhanced use of continuous-flow ventricular assist systems (VASs) (Figure 1).
Development and Advancement of MCS Technology

MCS technology has improved greatly since implantation of the first paracorporeal left ventricular assist device (LVAD) by Michael DeBakey in 1966. Today, there are more than 20 VASs and total artificial hearts (TAHs) in development or clinical use worldwide (Table 2). Left ventricular assist systems (LVASs) may be categorized into 2 technological series: positive-displacement pulsatile pumps and continuous-flow rotary pumps. Positive-displacement pulsatile pumps, such as the Thoratec HeartMate XVE, are full support systems; however, they are not long-term solutions, as the XVE begins to break after approximately 1 year of use. Continuous-flow rotary pumps can be further divided into axial and centrifugal flow designs. The impeller of an axial-flow pump, such as the Thoratec HeartMate II, in an analogous mechanism to an Archimedes screw, imparts kinetic energy onto blood as it passes through the VAD housing. Centrifugal-flow pumps move blood using a water-wheel–like impeller design in an analogous fashion to an electricity turbine at the base of a dam.

LVASs today are smaller than ever; some are as light as 93 g, such as the Micromed Heart Assist, and may be contained entirely within the thoracic cavity, such as the HeartWare HVAD. As pumps have become smaller, so have the transcutaneous leads (driveline) used to deliver power and data to the LVAD apparatus; some allow for a retroauricular lead placement, such as the Jarvik 2000, which may lower the risk of infectious sequelae. The transdermal energy transfer system, which eliminates the transcutaneous lead and uses the skin as an electrical conductor, is the ideal driveline technology and has been used, albeit only marginally successfully, in the Arrow (Penn State) LionHeart VAD and the AbioCor Total Artificial Heart.

Until recently, TAH technology has only marginally advanced over the first device, the Liotta TAH implanted by Denton Cooley in 1969. The most widely used TAH, the Jarvik-7, now marketed as the CardioWest TAH-t, first implanted by William DeVries in 1982, represents an enhancement of the Liotta technology. The CardioWest TAH-t replaces both native ventricles and all 4 cardiac valves with 2 positive-displacement pulsatile ventricle housings. The AbioCor TAH, a fully implantable rigid dysynchronous positive-displacement pulsatile pump, resulted in early setbacks in patient survival due to thrombosis, bleeding, and infections, and is available in the US only under a humanitarian device exemption. A promising pseudo-pulsatile continuous-flow TAH is in development and is currently being implanted in nonhuman models.

The shift in LVAD technology away from pulsatile support began with the MicroMed DeBakey VAD, the first of its kind used in humans, which uses a continuous axial-flow rotary pump design. Following the MicroMed DeBakey VAD was the Jarvik 2000, which also uses an axial-flow design. Designed to be implanted via a subcostal left-thoracotomy surgical approach with the outflow cannula anastomosed to the descending aorta, the Jarvik 2000 offers surgical and size advantages over conventional pulsatile pumps. Preliminary experience gained through clinical use of both pumps assisted in the design and modification of the most widely used LVAS in clinical practice today, the Thoratec HeartMate II (Figure 2).

The HeartMate II LVAS uses a continuous axial-flow rotary pump design with a magnetically driven impeller that rotates on 2 ball-and-cup bearings held in place by the inlet and outlet stators. It has been evaluated in 2 pivotal trials, the bridge to transplantation (BTT) and destination

<table>
<thead>
<tr>
<th>Status</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>1. Mechanical circulatory support, 30 days of 1A time, or</td>
</tr>
<tr>
<td></td>
<td>2. Mechanical circulatory support-related complication, indefinitely, or</td>
</tr>
<tr>
<td></td>
<td>3. Intraaortic counterpulsation (balloon pump), or</td>
</tr>
<tr>
<td></td>
<td>4. Swan-Ganz catheter plus either 2 continuous infusion inotropes, or ( \geq 0.5 , \text{µg/kg/min} ) of milrinone, or ( \geq 7.5 , \text{µg/kg/min} ) of dobutamine alone.</td>
</tr>
<tr>
<td>1A(e)</td>
<td>1A may be acquired by exemption (e) for inpatients only if the above therapies are counterproductive, such as in end-stage restrictive cardiomyopathy.</td>
</tr>
<tr>
<td>1B</td>
<td>Must meet 1 of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>1. Mechanical circulatory support, indefinitely, or</td>
</tr>
<tr>
<td></td>
<td>2. 1 continuous infusion inotrope.</td>
</tr>
<tr>
<td></td>
<td>2 Actively listed patients who do not meet the above criteria.</td>
</tr>
<tr>
<td></td>
<td>7 Listed patients who are considered temporarily unsuitable for transplantation.</td>
</tr>
</tbody>
</table>

Figure 1. Proportion of continuous and pulsatile flow pump implants reported to the Interagency Registry for Mechanically Assisted Circulatory Support (July 2006-December 2009).
therapy (DT) studies, and was the first axial-flow pump to be approved by the Food and Drug Administration for both indications. The outcomes attributable to the HeartMate II are superior when compared with those of conventional pulsatile pumps and optimal medical therapy (Figure 3). Survival in the HeartMate II BTT trial was 75% at 6 months and 68% at 12 months. Survival in the HeartMate II DT trial was 68% at 12 months and 58% at 24 months. These results are in contrast to the survival outcomes achieved with the pulsatile HeartMate XVE (55% at 12 months and 24% at 24 months) and even more so when compared to medical management (<50% at 6 months, 25% at 12 months, and 8% at 24 months), as described in the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial (Figure 3).

The next generation of LVASs is the continuous centrifugal-flow rotary pumps. These pumps may offer advantages over axial-flow technology. The HeartWare HVAD impeller is leavened in place and spun using opposing magnetic charges, is lubricated with hydrodynamic thrust bearings, and uses a smaller driveline (diameter) than the HeartMate II. Theoretically, this pump has zero wear potential; as such, the MCS community is looking forward to publication of the device’s long-term durability statistics (see Addendum). There are 5 such pumps in development or clinical use today (Table 2).

Preoperative Preparation

Patient characteristics at the time of VAS implantation predict postoperative morbidity and mortality. Globally, these characteristics are described by the 7 levels defined in the INTERMACS database (Table 3). As severity of illness increases, the risk of mortality after VAS implant also increases; accordingly, the highest risk is manifested in re-

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Table 2. Mechanical Circulatory Support Devices in Clinical Use or Development Worldwide

<table>
<thead>
<tr>
<th>Device</th>
<th>Flow Mechanism</th>
<th>Ventricular Support</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temporary support devices</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous extracorporeal membranous oxygenation</td>
<td>Continuous</td>
<td>BIVAD (bypass)</td>
<td>PC BTR</td>
</tr>
<tr>
<td>BVSS5000 (AbioMed; Danvers, MA)</td>
<td>Pulsatile (cylinder)</td>
<td>BIVAD or SVAD</td>
<td>PC BTR</td>
</tr>
<tr>
<td>Impella 2.5 and 5.0 (AbioMed)</td>
<td>Axial</td>
<td>LVAD</td>
<td>BTR</td>
</tr>
<tr>
<td>CentriMag (Levitronix; Zurich, Switzerland)</td>
<td>Centrifugal</td>
<td>BIVAD or SVAD</td>
<td>PC BTR</td>
</tr>
<tr>
<td>TandemHeart (CardiacAssist, Inc.; Pittsburgh, PA)</td>
<td>Centrifugal</td>
<td>BIVAD or SVAD</td>
<td>BTR</td>
</tr>
<tr>
<td><strong>Durable support devices</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive displacement pumps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB5000 (AbioMed)</td>
<td>Pulsatile sac-type (ventricle)</td>
<td>BIVAD or SVAD</td>
<td>PC BTR, BTT</td>
</tr>
<tr>
<td>Excor (Berlin Heart; Berlin, Germany)</td>
<td>Pulsatile sac-type</td>
<td>BIVAD or SVAD</td>
<td>BTT</td>
</tr>
<tr>
<td>MEDOS VAD (MEDOS Medizintechnik AG; Stolberg, Germany)</td>
<td>Pulsatile sac-type</td>
<td>BIVAD or SVAD</td>
<td>EU only</td>
</tr>
<tr>
<td>Thoratec PVAD/IVAD (Thoratec Corp.; Pleasanton, CA)</td>
<td>Pulsatile sac-type</td>
<td>BIVAD or SVAD</td>
<td>EU only</td>
</tr>
<tr>
<td>HeartMate XVE (Thoratec Corp.; Pleasanton, CA)</td>
<td>Electric pusher plate</td>
<td>LVAD</td>
<td>BTT, DT</td>
</tr>
<tr>
<td>AbioCor (AbioMed)</td>
<td>Pulsatile sac-type</td>
<td>TAH</td>
<td>DT (HDE)</td>
</tr>
<tr>
<td>CardioWest (SynCardia Systems, Inc.; Tucson, AZ)</td>
<td>Pulsatile sac-type</td>
<td>TAH-I</td>
<td>BTT</td>
</tr>
<tr>
<td><strong>Continuous-flow rotary pumps</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Assist 5 (Micromed Cardiovascular, Inc.; Houston, TX)</td>
<td>Axial</td>
<td>LVAD</td>
<td>BTT (IDE)</td>
</tr>
<tr>
<td>HeartMate II (Thoratec Corp.)</td>
<td>Axial</td>
<td>LVAD</td>
<td>BTT DT</td>
</tr>
<tr>
<td>Incor (Berlin Heart)</td>
<td>Axial</td>
<td>LVAD</td>
<td>EU only</td>
</tr>
<tr>
<td>Jarvik 2000 (Jarvik Heart, Inc.; New York, NY)</td>
<td>Axial</td>
<td>LVAD</td>
<td>BTT (IDE)</td>
</tr>
<tr>
<td>MVA (HeartWare, Inc.; Miami Lakes, FL)</td>
<td>Axial</td>
<td>LVAD</td>
<td>Nonhuman models</td>
</tr>
<tr>
<td>Synergy (CircuLife, Inc.; Saddle Brook, NJ)</td>
<td>Axial</td>
<td>LVAD</td>
<td>EU only (CEM)</td>
</tr>
<tr>
<td>CorAide (Cleveland Clinic; Cleveland, OH)</td>
<td>Centrifugal</td>
<td>LVAD</td>
<td>Nonhuman models</td>
</tr>
<tr>
<td>DuraHeart (Terumo Heart, Inc.; Grand Rapids, MI)</td>
<td>Centrifugal</td>
<td>LVAD</td>
<td>BTT (IDE)</td>
</tr>
<tr>
<td>EVAHEART (Evaheart Medical USA, Inc.; Pittsburgh, PA)</td>
<td>Centrifugal</td>
<td>LVAD</td>
<td>BTT (IDE)</td>
</tr>
<tr>
<td>HVAD (HeartWare, Inc.)</td>
<td>Centrifugal</td>
<td>LVAD</td>
<td>BTT (IDE)</td>
</tr>
<tr>
<td>LevaCor VAD (World Heart, Inc.; Salt Lake City, UT)</td>
<td>Centrifugal</td>
<td>LVAD</td>
<td>BTT (IDE)</td>
</tr>
<tr>
<td>CFATH (Cleveland Clinic)</td>
<td>Centrifugal, pseudo-pulsatile</td>
<td>TAH</td>
<td>Nonhuman models</td>
</tr>
</tbody>
</table>

BIVAD = biventricular assist device; BTR = bridge to recovery; BTT = bridge to transplantation; CEM = available only in the European Conformité Européenne Mark approval trial; DT = destination therapy; EU = Europe; HDE = available in the US only by humanitarian device exemption; IDE = available only in an investigational device exemption trial; LVAD = left ventricular assist device; PC = postcardiotomy; SVAD = single ventricular assist device; TAH = total artificial heart; TAH-I = temporary total artificial heart.
cipients characterized as INTERMACS level 1 (Figure 4).

Some preoperative factors are reversible in the weeks, days, and hours before surgery. Such variables include the nutritional, hemodynamics and volume, hepatic and renal, coagulation, and infectious disease status of the recipient.

**NUTRITIONAL STATUS**

The nutritional status of the recipient both pre- and postimplantation should be maximized to a serum prealbumin level >15 mg/dL, ideally through enteral means. A serum prealbumin level below this target 2 weeks after VAS implantation has been associated with an increased risk of in-hospital mortality.

Diets should be high-protein and high-calorie to maximize albumin and immunoglobulin production and maintain intravascular oncotic pressure. Efforts to induce postoperative weight loss in the intensive care unit (ICU) or within the first 2 weeks after VAS implantation, through fasting or underfeeding, should be avoided.

**HEMODYNAMICS AND VOLUME MANAGEMENT**

The effect of preimplant hemodynamic optimization is well characterized by the mortality risk of VAS recipients in INTERMACS level 3 at the time of implantation (Table 3, Figure 4) compared to levels 2 and 4. It may be that the added hemodynamic and vasodilatory properties of the inotropes milrinone and dobutamine affect postimplantation survival.

Optimization of ventricular stroke work, particularly of the right ventricle, to ≥600 mm Hg•mL/m² through use of pulmonary and systemic vasodilators, may decrease the incidence of right ventricular failure after VAS implantation. Such medications often require the use of continuous or intermittent filling pressure monitoring using a pulmonary artery catheter (Swan-Ganz) in the preoperative period and include nitroglycerin, sodium nitroprusside, nesiritide, hydralazine, sildenafil, milrinone, and dobutamine.

Preimplant volume management is equally critical in the prevention of right ventricular failure, elimination of right ventricular assist device (RVAD) use, and minimization of bleeding due to hepatic congestion. In the HeartMate II BTT trial, independent predictors of right ventricular failure included a central venous pressure (CVP)/pulmonary capillary wedge pressure (PCWP) ratio >0.63 and a serum blood urea nitrogen (BUN) level >39 mg/dL. Additionally, preoperative uremia impacts the degree of postoperative bleeding due to platelet dysfunction. Continuous renal replacement therapy serves to acutely lower BUN and may mitigate the risk of uremic bleeding.

**ANTIMICROBIAL PROPHYLAXIS**

There are few data regarding the most appropriate perioperative antimicrobial prophylaxis regimen for VAS implantation. The RE-
Many centers have eliminated rifampin and use various β-lactams. A survey is ongoing to quantify the effectiveness of regimens used at HeartMate II centers in the US.

**Postoperative Management**

**HEMOSTASIS**

In the initial postoperative period, patients recovering from VAS implantation are treated similarly to those who underwent other cardiac surgical procedures. Following decannulation from cardiopulmonary bypass, complete heparin reversal with protamine is performed and bleeding becomes the primary concern. Perioperative blood loss is one of the most serious and common adverse events following VAS implantation, far outweighing the acute risk of systemic or pump thrombosis. Treatment of perioperative acute blood loss in patients with a VAS is similar to that of other patients who undergo cardiac surgery, including measures such as administration of antifibrinolytics, blood products, and rarely, recombinant factors; however, important differences do exist.

Management of critical bleeding with blood component therapy is adjusted based on patient-specific characteristics. Selection of blood products will differ depending on whether the goal of the VAS implant is DT or BTT. Allogeneic packed red blood cell (PRBC), platelet, fresh frozen plasma, and cryoglobulin transfusions may result in allosensitization (development of antibodies against donor human leukocyte antigens). Sensitized patients whose ultimate goal is transplantation have a limited donor pool, spend more time on the waiting list, and are at higher risk for antibody-mediated rejection following transplantation. Limiting the amount of allogeneic transfusions is important when treating blood loss in the BTT patient. Autologous PRBC transfusion, most often returned to the patient from the cell-saver intraoperative apparatus, does not induce antibody sensitization and is preferred for the BTT patient. Use of leukocyte-reduced PRBCs is an alternative to autologous PRBC transfusion. Leukofiltration reduces the number of white blood cells in a unit of blood product, thereby decreasing the risk of human leukocyte antigen immunization. Use of leukocyte-reduced and blood-type (ABO) matched platelets may also prevent allosensitization in patients who receive large amounts of blood products.

Off-label use of recombinant factor VIIa (rFVIIa) in cardiac surgery is widely reported. Administration of rFVIIa in cardiac surgery decreases PRBC transfusion and reoperation, but may increase the risk of serious thromboembolic events such as stroke, bypass-graft loss, and myocardial infarction. Use of rFVIIa after VAD implantation has been retrospectively reported. Despite reducing PRBC requirements, rFVIIa administration is associated with an increased risk of thromboembolism in patients supported by a VAD. In a recent retrospective report on 188 VAD implants over 2 years, 62 patients received rFVIIa for refractory bleeding during or immediately after VAD implantation. Thirty-two patients received a low dose (10-20 µg/kg) and 30 received a high dose (30-70 µg/kg). Compared with predose measurements, significant reductions were observed in prothrombin time (PT, low dose 15.3 vs 10.6 seconds, p = 0.002; high dose 14.6 vs 11.1 seconds, p = 0.009) as well as activated partial thromboplastin time (aPTT, low dose 52.7 vs 37.7 seconds, p = 0.001; high dose 67.3 vs 50.0 seconds, p = 0.02). Hemoglobin values rose significantly after administration in both groups (low dose 9.1 vs 10.5 g/dL, p = 0.0004; high-dose 9.8 vs 11.0 g/dL, p = 0.02). The number of PRBC units, platelets, and fresh frozen plasma transfused decreased significantly after rFVIIa administration, regardless of dose used. Similar to other studies of rFVIIa, the rate of thromboembolic events was higher in the high-dose (n = 11, 36.7%) versus the low-dose (n = 3, 9.4%) group (p < 0.001).

Based on available data, rFVIIa use should be avoided until all identifiable coagulation abnormalities have been corrected. If rFVIIa is necessary, it is important to find the minimum effective dose required to achieve hemostasis. Higher doses of rFVIIa increase the risk of thromboembolism and cost. Lower doses (10-20 µg/kg) are likely as effective as higher doses and confer a lower risk of adverse events.

**DEVICE HEMODYNAMICS**

VADs are preload-sensitive pumps. Positive displacement pulsatile pumps, such as the HeartMate XVE (auto mode), function optimally when the chamber fills during...
native ventricular systole; continuous-flow rotary pumps fill relatively evenly during both systole and diastole.\textsuperscript{49,50} There is some degree of enhanced filling of the continuous-flow rotary pumps during ventricular systole, which is measured by the difference in power requirements between systole and diastole to maintain the fixed speed of the impeller and is quantified as the pulsatility index (HeartMate II).\textsuperscript{7} The pulsatility index at isolated times is a crude marker of pump preload; however, it also varies by impeller speed and the degree of native ventricular function and recovery. The trend in pulsatility index values can provide a more meaningful measure of changes in pump preload. Pump flow is a direct measure on pulsatile pumps such as the HeartMate XVE; conversely, it is a calculated number on the HeartMate II and is predominantly reliant on impeller speed and power requirements for estimation. In HeartMate XVE support, a decline in pump flow likely reflects a decline in circulating blood volume, whereas a similar decline in the HeartMate II can be a result of multiple factors, making it a less-than-ideal marker on which to base volume assessment.\textsuperscript{7} The degree of preload sensitivity of the continuous axial-flow rotary pumps differs by pump design. In vitro, the Jarvik 2000 appears variable in its degree of preload sensitivity, whereas the HeartMate II is more predictable in the same model.\textsuperscript{51} Traditional measures, such as CVP, PCWP, and clinical examination, as well as the appearance of the ventricles on echocardiography, should be used to guide volume management. Pulsatile pumps are able to provide a greater degree of ventricular unloading than are continuous-flow rotary pumps, and patients supported with the latter often require chronic diuretic therapy to maintain euvolemia.

Unlike their pulsatile counterparts, which reliably deliver a set stroke volume with each ejection irrespective of changes in systemic vascular resistance, the continuous-flow rotary pumps are relatively afterload sensitive. Analogous to increased water pump strain and poor forward flow through a kinked garden hose, the continuous-flow rotary pump does not perform optimally in the setting of high systemic vascular resistance. Medical management of VAD-associated hypertension is similar to traditional medical therapies used in heart failure such as angiotensin converting enzyme (ACE) inhibitors and $\beta$-blockers.\textsuperscript{7,52,53} Ventricular unloading lowers renin and aldosterone but upregulates the production of cardiac angiotensin stimulating sympathetic tone; thus, ACE inhibitors may provide a mechanistic advantage over other afterload-reducing therapies.\textsuperscript{53} Afterload-reducing therapies should be used to maintain mean arterial pressure between 70 and 80 mm Hg.\textsuperscript{7,54}

Due to continuous ventricular unloading by axial or centrifugal pumps, pulse pressure variation narrows and blood flow becomes laminar as impeller speed is increased. Diastolic pressure rises in this scenario, necessitating the use of mean arterial pressure as the preferred measure of blood pressure.\textsuperscript{54} Automated blood pressure cuffs and traditional auscultation with a sphygmomanometer may fail to find systolic and diastolic pressures. Use of an audio Doppler with a sphygmomanometer is often the only way to determine mean arterial pressure in the absence of arterial cannulation.\textsuperscript{7}

**THROMBOSIS PROPHYLAXIS**

**Thromboelastography**

Thromboelastography (TEG) evaluates the contributions of clotting factors, fibrinolysis, platelets, anticoagulants, and other blood elements to the dynamics of the viscoelastic (clot-strengthening) properties of whole blood under low shear conditions from the beginning of coagulation through fibrinolysis.\textsuperscript{55} Thromboelastography is unlike conventional clot-based assays such as aPTT and PT, which use citrated plasma activated with calcium and a surface activator such as kaolin or thromboplatin for the aPTT and PT, respectively, to measure the contributions of selected clotting factors in thrombus formation.\textsuperscript{56} Neither the aPTT nor PT provide information related to clot strength or stability, the effects of fibrinolysis, or the varied contributions of circulating cells to clot formation and stability.\textsuperscript{57}

Thromboelastography uses whole blood as its analyte. The blood sample is most commonly collected in tubes containing sodium citrate, which allows for a short delay of up to 30 minutes following venipuncture before the blood sample is processed. An aliquot of the blood sample is used for the analysis. The test involves the addition of calcium, which activates coagulation, and the mixture is then observed over time as it undergoes fibrin clot formation. The raw data from the TEG test are then transformed into a fibrin clot formation curve, which is used to derive various indices that reflect the clotting and fibrinolytic properties of the blood sample.

**Figure 4.** Proportion of VAS implantation by Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) patient profile and associated mortality risk (June 2006-March 2009). Percent mortality of the INTERMACS levels 4-7 are calculated in aggregate.\textsuperscript{4}
sample is then placed into the TEG analyzer and is recalcified to initiate clotting. Some laboratories used a factor XII activator such as kaolin or a factor VII activator such as tissue factor to accelerate clot formation.\textsuperscript{58-60}

There are several standard parameters from the TEG tracing with which the clinician should become familiar (Figure 5). Reaction time represents initial fibrin clot formation and can be prolonged by anticoagulants, clotting factor deficiencies, or endogenous clotting inhibitors.\textsuperscript{55,61} The firming time represents attainment of a prespecified level of clot strength that results from interaction of clotting factors with platelets.\textsuperscript{55,61} Thus, firming time reflects the rate of clot strengthening. Several factors, including anticoagulants, clotting factors (fibrinogen), platelet count and function, and hematocrit, influence firming time. The angle is the slope formed from reaction time tangential to the diverging TEG tracing and is similar to firming time in that $\alpha$ represents the rate of clot formation.\textsuperscript{55,61} The angle may be modified by clotting factor concentrations, platelet function, and, to a lesser extent, by anticoagulants. Maximum amplitude is measured as the maximal vertical distance between the divergence of the TEG tracing and represents the maximal strength of the clot.\textsuperscript{55,61} It is largely a marker of platelet and fibrinogen functionality. The coagulation index is a global assessment of coagulation status.\textsuperscript{55,61} The coagulation index is calculated from a multiple regression equation that uses the measured TEG parameters R, firming time, angle, and maximum amplitude. TEG is widely used in TAH support and is gaining use in the postoperative management of patients who have undergone VAD implantation.\textsuperscript{62-65} However,
each institution must determine its reference ranges for each TEG parameter based on the practices of the individual coagulation laboratory. Limitations of TEG are minor and include availability of the analyzer and the technical expertise required to run the test.

**Prophylaxis Regimen**

After VAS implantation, a hypercoagulable state is expressed that is dependent on pump design and patient characteristics. This hypercoagulable state consists of a complex interaction of inflammation; contact- and tissue-factor–initiated coagulation; hyperfibrinogenemia; platelet activation, which is frequently accompanied by thrombocytosis; endothelial cell activation; either hyper- or hypofibrinolysis; and hemolysis. Counterbalancing this multifactorial hypercoagulable condition frequently requires an individualized thromboprophylaxis regimen consisting of anticoagulants in combination with antiplatelet agents (Tables 4 and 5).

Based on experience, we believe that in pumps requiring anticoagulants, dosing should be guided by TEG results (Figure 5). The non–kaolin-activated TEG is more sensitive to heparin’s anticoagulant effects compared to

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### Table 4. Selected Thromboprophylaxis Regimens by Device Type

<table>
<thead>
<tr>
<th>Device Type</th>
<th>HeartMate XVE</th>
<th>HeartMate II</th>
<th>Jarvik 2000</th>
<th>HeartWare HVAD</th>
<th>CardioWest</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVAS</td>
<td>Pulsatile</td>
<td>Axial-flow</td>
<td>Axial-flow</td>
<td>Centrifugal-flow</td>
<td>Pulsatile</td>
</tr>
<tr>
<td>Heparin</td>
<td>–</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Warfarin</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aspirin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>R</td>
<td>R</td>
<td>±</td>
<td>R</td>
<td>±</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>–</td>
<td>–</td>
<td>R</td>
<td>–</td>
<td>±</td>
</tr>
</tbody>
</table>

LVAS = left ventricular assist system; R = rarely used by some centers in individualized situations; TAH = total artificial heart; – = not routinely used; ± = used by some centers in individualized situations; + = used in nearly all situations.

May substitute argatroban or bivalirudin for patients with suspected or known heparin-induced thrombocytopenia.

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### Table 5. Example Thromboprophylaxis Regimens and Dosing

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Drug</th>
<th>Dose</th>
<th>Initiation Parameters</th>
<th>Goal</th>
<th>Monitoring Parameters</th>
<th>TEG Effect</th>
<th>LTA Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation</td>
<td>Heparin</td>
<td>Start: 2-5 units/kg/h</td>
<td>Start: day +1 when chest tube drainage &lt;30 mL/h for 4 h</td>
<td>Normocoagulability by Cl on TEG</td>
<td>TEG (R, K), fibrinogen, CBC, renal function, blood stasis, bleeding</td>
<td>↑ R, K</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Bivalirudin</td>
<td>Start: 0.005 mg/kg/h</td>
<td>Start: day +1 when chest tube drainage &lt;30 mL/h for 4 h</td>
<td>Above</td>
<td>Above plus: genomics, INR, drug interactions, hepatic function, albumin, prealbumin, vitamin K intake</td>
<td>↑ R, K</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Start: 2-5 mg/day</td>
<td>Start: day +2-5 after recovery of hepatic function and with stable nutrition</td>
<td>Above</td>
<td>Above plus: genomics, INR, drug interactions, hepatic function, albumin, prealbumin, vitamin K intake</td>
<td>↑ R, K</td>
<td>None</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>Aspirin</td>
<td>Start: 81 mg/day</td>
<td>Start: return to ICU chest tube drainage &lt;30 mL/h for 4 h and if platelets ≥50,000 x 10^6/L</td>
<td>Suppressed LTA platelet function: AA: 20-40%</td>
<td>↓ α, MA</td>
<td>↓ α, MA</td>
<td>↓ AA, ADP, EPI</td>
</tr>
<tr>
<td></td>
<td>Dipyridamol</td>
<td>Start: 50 mg every 8 hours</td>
<td>Start: day +1-5 if platelets ≥50,000 x 10^6/L</td>
<td>Normocoagulability by Cl on TEG</td>
<td>TEG (α, MA), LTA, CBC, ↓ α, MA, ADP, hepatic function, bleeding</td>
<td>↓ α, MA</td>
<td>↓ ADP, EPI</td>
</tr>
<tr>
<td>Viscosity reduction</td>
<td>Pentoxifylline</td>
<td>Start: 200 mg every 8 hours</td>
<td>Start: only if FBG &gt;350 mg/dL</td>
<td>Normocoagulability by Cl on TEG</td>
<td>TEG, FBG</td>
<td>↓ Cl</td>
<td>None</td>
</tr>
</tbody>
</table>

α = angle; AA = arachidonic acid; ADP = adenosine diphosphate; CBC = complete blood cell count; CI = coagulation index; EPI = epinephrine; FBG = fibrinogen; ICU = intensive care unit; INR = international normalized ratio; K = firming time; LTA = light transmittance aggregometry; MA = maximum amplitude; R = reaction time; TEG = thromboelastography.

*Expected.
aPTT, thereby avoiding over-anticoagulation and increased risk for bleeding. In addition, reliance on arbitrarily selected aPTT results may result either in greater incidence of early hemorrhagic complications or hypercoagulability. The aliquot of the TEG blood sample to which heparin is added permits evaluation of both the underlying, nonheparinized coagulation status as well as the anticoagulant effects of concurrent warfarin therapy. Given the early postimplant end-organ dysfunction and hemorrhagic diathesis, initial heparin infusion rates should be low, in the range of 2-5 units/kg/h, and titrated according to daily TEG results targeting a goal of normocoagulability as determined by the coagulation index. The direct thrombin inhibitors argatroban and bivalirudin have been used in lieu of heparin, especially in patients with a history of heparin-induced thrombocytopenia. However, in vitro studies suggest that currently available direct thrombin inhibitors, although prolonging clot initiation similarly to heparin, are not as effective as heparin in attenuating clot propagation and clot strength.

Warfarin is most frequently used for long-term anticoagulation. It is generally recommended to overlap initiation of warfarin with ongoing parenteral anticoagulant therapy. However, emerging evidence with the HeartMate II suggests that withholding postoperative heparin and starting de novo warfarin between the second and fifth postoperative day does not increase the risk of pump-related thrombosis and decreases the risk of bleeding.

Initial dosing of warfarin in patients supported by a VAS generally ranges from 2 to 5 mg/day, but should be altered if necessary based on the patient’s hepatic and renal function, age, weight, and nutritional status; concomitant use of potential interacting drugs; and the presence of infection. The international normalized ratio (INR) target for warfarin varies among devices. Recent recommendations for the HeartMate II propose an INR range of between 1.5 and 2.5. We suggest that the INR range should be individualized based on results of TEG-guided monitoring with the target INR range resulting in normocoagulability.

Given the persistent platelet activation induced by a VAS, antiplatelet therapy is typically required. Aspirin is recommended as first-line therapy; however, concomitant therapy with dipyridamole may be needed in select cases. Postimplant aspirin hyporesponsiveness is not infrequent but usually resolves with an increase in dose. Nonetheless, aspirin hyporesponsiveness can recur, in part, as a result of concurrent elevations both in platelet count and fibrinogen. Dipyridamole, in a dose-related fashion when combined with aspirin, decreases both platelet aggregation and platelet adhesiveness more than aspirin alone. The clinical use of titrated doses of dipyridamole, in combination with aspirin, has resulted in a low incidence of embolic neurologic events in patients who undergo implantation with the CardioWest TAH.

As with anticoagulants, we believe that antiplatelet therapy should be individualized using TEG in conjunction with platelet count and fibrinogen. Careful monitoring of the patient’s overall clinical condition and concurrent drug therapy is strongly recommended since conditions such as acquired von Willebrand factor deficiency, anemia, and uremia, as well as several nonantiplatelet drugs, may produce important measurable antiplatelet effects or thrombocytopenia. Light transmittance aggregometry, using platelet-rich plasma, has been used to assess antiplatelet responsiveness in patients supported with the CardioWest TAH. Multiple platelet agonists such as adenosine diphosphate, epinephrine, collagen, and arachidonic acid can be used during the testing procedure. Doses of aspirin and dipyridamole are adjusted as needed with a goal of suppressing adenosine diphosphate– and arachidonic acid–induced platelet aggregation and preserving the response to collagen. Hyporesponsiveness to collagen-induced platelet aggregation has been reported as a significant risk factor for bleeding.

Complications

While VAS devices have greatly advanced the management of end-stage heart failure, they also pose the risk of multiple complications that may adversely affect morbidity and mortality. A single-center, retrospective analysis of patients receiving MCS devices found a cumulative adverse event rate of 89.2% 60 days following implantation. Patients in the device group of the REMATCH trial were more than twice as likely as patients in the medical therapy group to have a serious adverse event. Adverse events experienced following VAD implantation cover a wide spectrum and are dependent on pump design; the most commonly reported include right ventricular failure, arrhythmias, anemias, bleeding, neurologic events, and infections. Thrombosis has become an increasingly uncommon adverse effect. Understanding the mechanisms behind VAS-associated complications may help to prevent their occurrence, and prompt identification and management might minimize their effects.

RIGHT VENTRICULAR FAILURE

Assessment of right ventricular function is critical in evaluation of possible VAD candidates, as postoperative right ventricular failure, defined as the need for inotropic agents for >7 postoperative days or the addition of an RVAD, is associated with poor outcomes. Patients with postimplant right ventricular failure requiring biventricular support have prolonged ICU stays, increased transfusion requirements, a higher incidence of renal failure, and a higher mortality rate than patients requiring single ventricular support. Commonly, patients with left sided heart
failure have a component of right ventricular dysfunction related to increased left ventricular filling pressures and rightward septal shift. Right ventricular function will often improve following the unloading of the left ventricle during LVAD support, and no further intervention is required. Other etiologies of right ventricular failure, such as pulmonary arterial hypertension, must be ruled out prior to placement of the device, as these are not alleviated by LVAD support.

Despite meticulous screening, right ventricular failure occurs following 13–30% of LVAD implants, depending on device.31,89,90 There are a number of preoperative risk factors for right ventricular failure after LVAD implantation; the most common is preoperative right ventricular dysfunction.89,91-93 Additional risk factors that have been identified are low cardiac index, low right ventricular stroke work, high serum creatinine level, previous cardiac surgery, and low systolic blood pressure.89 Notably, few analyses were performed with continuous-flow devices, and preliminary data showed a similar incidence but decreased severity of right ventricular dysfunction after continuous-flow device implant.84 In a post hoc analysis of the HeartMate II BTT trial, 13% of patients experienced right heart failure defined as the need for an RVAD or extended inotrope support.31 Risk factors for right heart failure in this population were high central venous pressure, preoperative ventilator support, and high BUN.

There are 3 primary etiologies for right ventricular failure following LVAD implantation. First, right ventricular myocardial damage may be preexisting or may develop intraoperatively due to inadequate cardioplegia or an intraoperative myocardial infarction. Second, sudden unloading of an overloaded left ventricle causes the intraventricular septum to shift leftward, impacting right ventricular geometry and performance. Right ventricular failure due to leftward septal shift is often due to excessively high LVAD impeller speed or the use of a pulsatile device. Lastly, patients may have preexisting pulmonary hypertension from chronic heart failure, valvular disease, or unknown etiologies. Pulmonary hypertension may be unmasked when filling pressures to the left ventricle are decreased, but pulmonary pressures remain elevated.

Perioperative use of vasopressor agents such as phenylephrine, norepinephrine, and epinephrine may result in a rise in pulmonary pressures, thereby increasing the workload on the right side of the heart. Preferential use of vasopressin in this patient population may be warranted due to postcardiomyopathy vasopressin deficiency and the lack of effects on the pulmonary vasculature.95-97 Because optimal flow to the newly implanted LVAD is dictated by right ventricular function, immediate and effective treatment for right heart dysfunction is paramount in the postoperative period. While RVAD support may be indicated in some patients, medical therapy with inotropes and pulmonary vasodilators is often the first intervention. Most patients supported with a VAD will require early inotropic support postoperatively, with a preference for agents that cause pulmonary vasodilation in the case of right ventricular failure (Table 6).98,99

Chronic heart failure–related elevations in left atrial pressure, pulmonary venous congestion, and alterations in sympathetic tone lead to increases in pulmonary pressures. The L-arginine/nitric oxide (NO) pathway plays an important role in the regulation of pulmonary vascular tone.100 Cyclic guanosine monophosphate (cGMP) is the second messenger that mediates the pulmonary vasodilatory effects of NO, which is inactivated by the phosphodiesterase (PDE) family of enzymes. In the lung, phosphodiesterase type-5 (PDE-5) is the primary PDE enzyme responsible for metabolizing cGMP, but PDE-3 also contributes to vasodilation.89 This system can be therapeutically manipulated by providing inhaled NO, inhibiting the degradation of NO by the PDE enzymes, or both, which results in increased NO concentrations at the level of the pulmonary arteries, producing vasodilation.

Use of inhaled NO in cardiac surgery is well described.101 In addition to any preexisting pulmonary hypertension, cardiopulmonary bypass causes an increase in pulmonary vascular tone. Inhaled NO causes a local vasodilation, decreasing pulmonary vascular resistance while improving oxygenation. For patients with right ventricular failure, the decrease in pulmonary vascular resistance improves right ventricular output. Unlike other pulmonary vasodilators given systemically (milrinone, epoprostenol), NO does not cause a decrease in systemic vascular resistance. NO is inactivated by binding to hemoglobin, resulting in methemoglobin. Methemoglobin does not carry oxygen, resulting in a leftward shift of the oxygen-hemoglobin dissociation curve, impairing the release of oxygen from hemoglobin. Methemoglobin concentrations should be monitored closely during inhaled NO therapy.

The use of NO following pulsatile LVAD implantation has been retrospectively evaluated.102-105 At doses of 10–40 ppm, NO has been shown to decrease pulmonary artery pressure as well as increase LVAD output. Initiating NO

| Table 6. Inotropes Used After VAS Implantation98,99 |

<table>
<thead>
<tr>
<th>Agent</th>
<th>Contractility</th>
<th>Chronotropy</th>
<th>SVR</th>
<th>PVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>+++</td>
<td>++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dopamine</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>+++</td>
<td>+++++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Milrinone</td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; VAS = ventricular assist system; + = increase; – = decrease.

*Vasodilatory actions of isoproterenol are offset by increases in right ventricular output and an increase in pulmonary artery pressure is seen.
While weaning patients from cardiopulmonary bypass may alleviate the need for RVAD placement, there have been no reports of NO use following a continuous-flow LVAD insertion, but similar outcomes should be expected.

Due to the cost and toxicity of NO, alternative inhalation agents for pulmonary hypertension following cardiac surgery have been evaluated. Prostacyclin (epoprostenol) is a potent pulmonary and systemic vasodilator when given intravenously. However, when nebulized and given via inhalation, prostacyclin’s effects are limited to the pulmonary vasculature. Prostacyclin exhibits a linear dose-response curve, with maximal effect achieved at approximately 50 ng/kg/min. Prostacyclin decreases pulmonary artery pressures and increases cardiac output following cardiothoracic surgery, including LVAD implantation. The efficacy of inhaled prostacyclin, combined with its ease of administration, low cost, and excellent safety profile, make it an attractive option for the treatment of right heart dysfunction following LVAD implantation.

Sildenafil causes pulmonary vasodilation via PDE-5 inhibition in the pulmonary vasculature. In addition to this decrease in right ventricular afterload, sildenafil has been found to have inotropic effects in a hypertrophied right ventricle. This dual mechanism makes sildenafil an attractive option for treatment of right ventricular failure after LVAD implantation. In the largest evaluation, sildenafil was studied in an open-label clinical trial of 58 patients with an LVAD. All patients had improved PCWP (11.8 ± 2.0 mm Hg from baseline value of 23.2 ± 6.2 mm Hg, p = NS) after LVAD implantation but unchanged PVR (5.65 ± 3.00 to 5.39 ± 1.78 Wood units, p = NS). Sildenafil was initiated in 26 patients and titrated to an average dosage of 51.9 mg 3 times daily. A decrease in mean pulmonary artery pressure from 36.5 ± 8.6 to 24.3 ± 3.6 mm Hg (p < 0.0001) was seen in sildenafil-treated patients, which corresponded to a decrease in PVR from 5.87 ± 1.93 to 2.96 ± 0.92 (p < 0.001) Wood units. There were no significant changes in either variable from baseline in control patients. Additionally, systolic and diastolic function improved in the sildenafil group, with no serious adverse effects. Based on available data, sildenafil is an appropriate chronic treatment for patients with LVAD and right ventricular dysfunction or high pulmonary artery pressures that compromise left ventricular filling. A starting dose of 20 mg 3 times daily is appropriate, titrated to adequate pulmonary artery pressures via the continuous or intermittent use of a pulmonary artery catheter.

**VENTRICULAR ARHYTHMIAS**

Excessive unloading of the left or right ventricle may exacerbate underlying electrical dysfunction of a myopathic heart. Ventricular suck-down (suction) events, the complete unloading of the ventricle resulting in intracardiac tissue (typically the ventricular septum or valve leaflets) temporarily occluding the inflow cannula, in the setting of continuous-flow rotary pump support, have been reported to transiently increase the risk and induce episodes of monomorphic ventricular tachycardia. Since most ventricular arrhythmias tend to be monomorphic ventricular tachycardia, pharmacotherapy includes electrolyte optimization (potassium 4.5-5 mEq/L; magnesium >2 mg/dL), β-blockade, amiodarone, and the sodium channel blockers procainamide, lidocaine, and mexilitine. Moreover, the nonuse of β-blockers has been strongly associated with ventricular arrhythmias in the setting of VAD support (OR 7.04, p = 0.001). 

**ANEMIA**

The reported incidence of anemia ranges widely due to variability in patient population, device implanted, and definition of anemia. A single-center, retrospective review of patients with LVAD found that anemia, defined as hemoglobin <12.0 g/dL, was an independent predictor of adverse outcomes including mortality. The underlying mechanism of VAD-associated anemia has long been presumed to be related to device-induced hemolysis. Hemolytic anemia is typically transient and responds well to decreases in revolutions per minute of the continuous-flow pumps.

Additional research suggests that chronic systemic inflammation from device implantation may result in anemia of chronic disease. Inflammatory cytokines, released in response to blood contact with VAD surfaces, inhibit erythropoietin-stimulated erythrocyte maturation. Given the inhibition of erythrocyte maturation, interest in the use of erythropoietin-stimulating agents has risen.

**GASTROINTESTINAL BLEEDING**

As with anemia, the incidence of gastrointestinal (GI) bleeding appears to depend on the type of device implanted. Rates of GI bleeding were 22–40% in recipients of continuous-flow devices as compared with 0–6.5% in those with pulsatile devices. Several theories seeking to explain this discrepancy have been proposed, including arteriovenous malformations and acquired von Willebrand disease. Narrow pulse pressures produced by nonpulsatile flow may promote development of arteriovenous malformations. While arteriovenous malformations can remain asymptomatic, it has been hypothesized that platelet dysfunction from antithrombotic therapy and acquired von Willebrand disease increase vulnerability to GI bleeding. von Willebrand factor promotes platelet adhesion and aggregation at the site of vascular injury. Increased shear stress and flow acceleration following VAD implantation result in loss of high-molecular weight von Willebrand factor multimers and impaired von Willebrand factor function, consistent with acquired von...
Willebrand disease. Proposed pharmacologic strategies in continuous-flow LVAD patients with GI bleeding include localized sclerotherapy, antifibrinolytics such as tranexamic acid, and recombinant human factor VIII/von Willebrand factor complexes (Humate-P, CSL Behring, King of Prussia, PA). Transient interruption of anticoagulation and reduction in pump speed to allow more pulsatile flow have also been proposed.

NEUROLOGIC EVENTS

In addition to increased risk of bleeding, VAD recipients are at risk for strokes and transient ischemic attacks. As with other VAD complications, the reported incidence of stroke varies, with estimates ranging from 3% to 47%. Strokes appear to occur most frequently soon after device implantation, although overall risk increases with longer duration of VAD support. These events may affect device outcomes, including heart transplantation and mortality. A single case report exists describing the successful use of intraarterial thrombolysis for acute ischemic stroke in a patient supported by a Novacor LVAD. Thrombolysis cannot be widely recommended in this patient population due to a paucity of data regarding intracranial hemorrhage and systemic bleeding risk. Additionally, patients who experience an ischemic stroke should not receive aggressive anticoagulation due to the risk of hemorrhagic transformation.

With limited treatment options and a potentially significant impact on patient outcomes, prevention of thrombotic events in patients supported by a VAD is essential. Compliance with the antithrombotic regimens mentioned previously, especially in the early period following device implantation, can greatly reduce the risk of thromboembolic events.

INFECTIONS

VAS support may also be complicated by infection, with occurrence rates ranging from 25% to 50%. Infection is a major source of postimplantation morbidity and mortality and is associated with prolonged hospitalization, VAS malfunction, heart transplantation delay, need for surgical revision, and removal or exchange of the infected device. Data from the REMATCH trial indicated that the mortality rate of HeartMate XVE recipients experiencing sepsis may be 50% higher than in those without sepsis. Risk factors for infection in the VAS recipient population include concomitant conditions that impair immune function (e.g., renal dysfunction, diabetes), malnutrition, urinary and intravascular catheters, mechanical ventilation, and advanced age. Device-specific factors, including delayed wound healing, larger VAS size, driveline exit-site trauma, and extended duration of support, also play a role. One such device-specific factor is the induction of an aberrant state of T-cell activation that leads to programmed cell death among CD4-bearing T-cells during HeartMate XVE support. This is thought to be related to the textured fibril coating on blood-contacting surfaces inside the XVE chamber and may predispose the acquisition of fungal VAS infections.

Infections occurring during VAS support may be systemic, such as bloodstream infections (BSIs), or localized to the device itself. Several VAS components are susceptible to infection, including the percutaneous driveline exit site, the driveline tract, the device and its surrounding pocket, and the internal (blood-containing) components (Figure 6). Pathogens may be introduced by direct contamination during surgical implantation, via the driveline or driveline exit site, or by hematogenous dissemination from distant sources. The most common pathogens associated with VAS infection include staphylococci, Enterococcus spp., gram-negative bacilli such as Pseudomonas aeruginosa, and Candida spp.

BSIs without evidence of device involvement may be treated as routine bacteremia. Empiric therapy should include antimicrobials effective against common pathogens associated with VAD support, including multidrug-resistant gram-negative rods, in accordance with local resistance patterns. Delineation of the origin of a BSI as arising from a device versus a nondevice source is very difficult; thus,
clinical symptoms must also guide duration in addition to traditional pump evaluations. Device-related BSIs may be definitively established only through explant VAD cultures. Device-related BSIs should be suspected in the presence of septic emboli, new incompetence of pump inflow or outflow valves (pulsatile pumps), or in patients with recurrent or persistent BSIs. Device-related BSIs are optimally treated with device explantation and/or changeout and long-term (longer than 6 weeks) parenteral antimicrobial therapy. As pump replacement in patients with device-related BSIs may be technically challenging, United Network of Organ Sharing grants 1A status for heart transplantation in transplant-eligible patients (Table 1). If device salvage is attempted, prolonged antimicrobial therapy (until device changeout or transplantation) may be necessary.

Infections localized to the driveline or driveline exit site can often be treated with antimicrobial therapy, immobilization of the driveline, and local wound care. Optimal duration of antimicrobial therapy is undefined and is dependent on the depth and degree of tissue involvement. Typically, driveline infections require prolonged treatment (4–6 weeks) with parenteral antimicrobials and may necessitate chronic suppression. If, however, the infection tracks deeply along the driveline or involves the area of device implantation (pump pocket), excisional debridement and temporary placement of drains are often required. Pump pocket infections are difficult to treat and frequently recur despite extensive debridement and protracted antimicrobial treatment longer than 6–12 weeks). Pump pockets are typically hypo-vascularized, which may result in subtherapeutic antimicrobial deposition via the parenteral route. As a result, pocket debridement, followed by localized administration of continuous antimicrobial irrigation via inflow and outflow drains in the pump pocket, has been advocated. Insertion of poly-methylmethacrylate antimicrobial-impregnated beads has also been described in a few case reports. Ultimately, pump pocket infections may necessitate VAS changeout.

As VAS-associated infections are often difficult to treat, implementation of strategies to prevent infection is vital. These strategies include screening and treatment of nasal *Staphylococcus aureus* colonization, aseptic surgical technique, optimization of host defenses through maintenance of normoglycemia and nutritional support, perioperative antimicrobial prophylaxis, and avoidance of trauma and microbial contamination at the driveline exit site. Technical advances in VAS design, such as the development of fully implantable devices, will further minimize infectious complications.

OTHER COMPLICATIONS

Additional VAS-associated complications include, but are not limited to, renal and hepatic dysfunction and psychiatric disorders. As these complications are associated with increased morbidity and mortality, prevention, when possible, and optimal management are important aspects of patient care. Knowledge of VAS-associated complications and their underlying mechanisms may help to prevent their occurrence. With the increasing use of VAS therapy for end-stage heart failure, further research characterizing complications and their management will help optimize patient outcomes.

Role of the Clinical Pharmacist

The role of the clinical pharmacist in the care of subspecialty populations has been described in various forums. Use of MCS devices is a subspecialty of advanced heart failure and cardiac transplantation. The HeartMate II clinical investigators called for the involvement of a pharmacist in assessment and optimization of care for patients on MCS. In an analogous fashion to solid organ transplantation, MCS patients are closely followed by a team of care coordinators and specialist physicians, including cardiac surgeons and heart failure cardiologists. The clinical pharmacist is an integral part of these teams at our institutions. Indeed, many of the larger MCS centers in the US employ a clinical pharmacist in their cardiac surgical ICU; however, if the MCS implantation goes smoothly, the patient may spend less than 48 hours in the ICU. As such, 2 of our institutions employ a longitudinal clinical specialist model with involvement in all intensities of the care of the MCS patient.

The clinical pharmacist can have a great impact on all of the topics discussed in this review through direct patient care, protocol development, research activities, and patient and provider education. In particular, the clinical pharmacist should be actively involved in preoperative optimization and postoperative blood product minimization to achieve surgical hemostasis. Pharmacist involvement in this activity is critical to minimize allosensitization in the BTT patient. Conversely, the clinical pharmacist should be actively involved in the antithrombotic therapy of the patient to minimize bleeding risk and prevent thrombosis. An intimate understanding of the impact of pharmacotherapeutic options for hemodynamic support is critical for pump optimization. Likewise, antiarrhythmic drug therapy may be tailored based on the underlying electrical characteristics of the VAS, using the expertise of the clinical pharmacist. Perioperative antimicrobial prophylaxis, infection treatment, and chronic suppression are areas of stewardship for pharmacists. Similar to care of patients with heart failure, involvement in the educational process of the MCS patient may enhance adherence to afterload reduction and the complicated thromboprophylaxis regimen and perhaps extend time between readmissions to the hospital, although this has not been evaluated in the VAS population.

The International Society for Heart and Lung Transplantation (ISHLT) focuses on the basic and clinical sciences for the failing heart and lungs. The ISHLT is developing
consensus documents regarding definitions of disease and treatment in the field of mechanical circulatory support. There is an ongoing effort by pharmacist members of the ISHLT to develop a clinical pharmacy and pharmacology council. Pharmacists seeking involvement and collaboration in this field should consider membership in the ISHLT.

Summary

Orthotopic heart transplantation alone cannot sustain the increasing demand for advanced therapies for end-stage heart failure. MCS devices, such as VAS and TAH, provide enhanced BTT success and extend the quality of life for these patients. Pharmacotherapy is necessary both before and after implantation of an MCS device. Likewise, pharmacologic management of the adverse effects of MCS devices may minimize the morbidity associated with these pumps. The clinical pharmacist can contribute significantly to management of MCS through direct patient care, protocol development, research activities, and education of patients and providers.

Addendum

Preliminary results of the ADVANCE BTT trial of the HeartWare HVAD were presented at the 2010 American Heart Association scientific sessions. The results were encouraging; at 6 months, 92% of patients (per protocol) were alive with their original device or had received a transplant. Moreover, at 1 year, 90.6% of all patients (intent-to-treat) who had received an implant or transplant were alive.198

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References


Selección del estudio y método de extracción de la información: Se evaluaron para su inclusión todos los estudios originales relevantes, meta-análisis, estudios sistemáticos, directrices, y recapitulaciones. Se examinaron las referencias de los artículos relevantes para buscar material adicional que no se hubiera encontrado en la búsqueda inicial.

Síntesis de los datos: La asistencia circulatoria mecánica (ACM) ha avanzado de forma significativa desde que se implantó el primer dispositivo de asistencia ventricular izquierda en 1966. Los avances adicionales en la tecnología de ACM que tuvieron lugar en la última década están cambiando el tratamiento global de la insuficiencia cardíaca terminal y del transplante cardíaco. Estas bombas mejoran las tasas de puente para transplante, incrementan las tasas de supervivencia y mejoran la calidad de vida del paciente. La farmacoterapia asociada a los dispositivos de ACM puede servir para optimizar el rendimiento de las bombas y mejorar la respuesta del paciente, así como minimizar la morbilidad asociada a sus efectos adversos. Este estudio destaca el conocimiento necesario para proporcionar los servicios de farmacia clínica adecuados a pacientes con dispositivos de ACM.

Conclusiones: Los pacientes con dispositivos de ACM representan una subespecialidad dentro de la insuficiencia cardíaca avanzada y el transplante cardíaco. Los investigadores clínicos del dispositivo HeartMate II pidieron la implicación de un farmacéutico en la valoración y optimización de pacientes con dispositivos ACM, en un reciente estudio global. El manejo farmacoterapéutico de pacientes con dispositivos ACM es muy especial y requiere una individualización según las características de la bomba y del receptor.

Traducido por Violeta Lopez Sanchez

Revue de la Pharmacothérapie Pour le Support de la Circulation Mécanique
CR Ensor, CA Paciullo, WD Cahoon Jr, et PE Nolan Jr
Ann Pharmacother 2011;45:60-77.

Résumé:

Objectifs: Présenter une revue de la pharmacothérapie utilisée dans le support de la circulation mécanique chez les patients souffrant d’insuffisance cardiaque terminale et présenter des recommandations aux pharmaciens vis-à-vis la sélection, l’évaluation et l’optimisation des médicaments pour ces patients.

Synthèse des données: Le support de la circulation mécanique (SCM) a évolué de façon dramatique depuis l’implantation du premier dispositif dans un ventricule en 1966. Les avancements durant la dernière décennie ont changé la prise en charge de l’insuffisance cardiaque terminale et de la transplantation cardiaque. Les pompes ont permis d’allonger le temps possible avant la transplantation, la survie, de même que la qualité de vie. La pharmacothérapie impliquée dans le SCM peut servir à améliorer la performance des pompes et améliorer les résultats de santé. Cette revue met en évidence les connaissances requises afin de pouvoir offrir les services de pharmacie clinique aux patients ayant des dispositifs de circulation mécanique.

Conclusions: Les patients nécessitant un SCM représentent une sous-spécialité dans le traitement de l’insuffisance et transplantation cardiaque. De plus, les chercheurs de l’étude HeartMate II ont réclamé l’implication des pharmaciens dans la prise en charge de ces patients. La gestion de la pharmacothérapie des patients nécessitant du SCM est unique et requiert un traitement individualisé selon les caractéristiques du patient et du dispositif utilisé.