Application of mechanical cardiac support now requires consideration of a wider range of goals beyond bridging to transplantation to include destination therapy and perhaps bridging to recovery. Responsible dissemination of the technology requires identification of patient populations from which to select candidates most likely to benefit. At this early stage, benefit is most apparent against a high background mortality from end-stage heart failure.

Populations of Advanced Heart Failure

Heart failure affects an estimated 5 million patients in the United States. Of those, ≈60% have heart failure with left ventricular dilation and reduced ejection fraction. Trials demonstrating benefit of therapies for heart failure have focused primarily on mild–moderate heart failure with reduced ejection fraction, generally with annual mortality in the range of 8% to 18%.

Advanced heart failure has been defined as symptoms limiting daily activity (New York Heart Association class III and IV) despite attempted therapy with angiotensin-converting enzyme inhibitors, β-blockers, digoxin, and diuretics, a description that applies to ≈300,000 to 800,000 patients in the United States. Although often labeled as “refractory,” many patients enjoy improved quality of life and decreased hospitalizations after referral to experienced heart failure centers, where aggressive medical strategies focus on relief of congestion. Surgical approaches include complex revascularization, valvular repair/replacement, or ventricular reconstruction. When technically successful, biventricular pacing can improve functional status for many of the 25% to 40% of patients with marked ventricular asynchrony. If early stabilization allows institution of β-adrenergic–blocking agents, prognosis is further improved. Dedicated heart failure management programs that facilitate patient education, compliance, and fluid balance have been integral to benefits observed with these therapies.

The highest-risk heart failure populations are best identified after optimization of current therapies. Low left ventricular ejection fraction is not sufficient description of either function or prognosis once heart failure has become advanced. Neither does development of class IV symptoms necessarily condemn patients to continued disability or imminent mortality. For those patients who can achieve and maintain freedom from congestion at 1 month, 2-year survival approaches 80%. Peak oxygen consumption integrates cardiac reserve, peripheral conditioning, and general status, predicting mortality when <10 to 12 mL · kg⁻¹ · min⁻¹ and survival when >16 to 18 mL · kg⁻¹ · min⁻¹, and may also improve within 3 to 6 months after referral. Cachexia is another integrated measure associated with poor outcome but has not been consistently defined. Laboratory indices of failing homeostasis, such as hyponatremia and worsening renal function, predict poor outcome in populations but are less useful in individuals. Within an experienced group with uniform strategies, ambulatory patients with persistent class IV symptoms can be further identified as high risk by the development of circulatory or renal limitations to angiotensin-
Potential Populations for Support

- Acute cardiogenic shock
- Chronic CHF into low output state with organ dysfunction
- CHF Class IV inotrope-dependent
- CHF IV ACEI-intolerant due to symptomatic hypotension or progressive renal dysfunction
- Class IV on ACEI therapy
  Plus additional risk factors, e.g.
  - Cachexia
  - Peak oxygen uptake < 10 mL/kg/min
  - Hypokalemia
  - Progressive renal dysfunction
- CHF IV on oral therapy including ACEI
- Class IV stabilized to Class III

Estimated 50% Mortality

<table>
<thead>
<tr>
<th>In imminent 1 month, without reversible factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 months</td>
</tr>
<tr>
<td>About 6 months</td>
</tr>
<tr>
<td>6-12 months</td>
</tr>
<tr>
<td>&gt; 12 months</td>
</tr>
<tr>
<td>&gt; 24 months</td>
</tr>
</tbody>
</table>

sin-converting enzyme inhibitors and inability to wean from inotropic infusions (Figure).

Populations for Cardiac Transplantation

For the individual patient, further intervention is considered by comparing expected outcomes with and without the intervention. Most experience with advanced heart failure has derived from evaluation for transplantation. Without a controlled trial, this therapy was established after a rigorous observational study federally funded at expert centers, where patients were deemed to have had “less than 6 months to live.” Subsequent improvements in both transplantation and medical therapy led to a downward shift of population risk, such that patients now have better outcomes than initially, both with and without transplantation. Although earlier risk analyses encompassed both sudden and hemodynamic deaths, the decreasing prevalence of unexpected sudden death now allows focus on symptoms and death related to hemodynamic deterioration. Absolute indications for transplantation include refractory cardiogenic shock, dependence on intravenous inotropic support (both Status I), or persistent class IV symptoms with peak oxygen consumption < 10 mL · kg⁻¹ · min⁻¹. Anticipated benefit for transplantation in this group is the difference between 1-year survival of <50% without transplantation and 83% after transplantation, with almost 50% alive at 10 years. Most patients awaiting transplantation are ambulatory on oral therapy (Status II), fulfilling relative indications of major daily limitation with peak oxygen consumption 11 to 14. Their anticipated benefits are less dramatic but still highly favorable. Although of major importance for the individual recipient, cardiac transplantation is epidemiologically trivial inasmuch as donor heart supply is limited to 2200 yearly in the United States, where an estimated 100 000 patients might meet criteria without major contraindications.

Populations for Destination Left Ventricular Assist Device

Patients With Proven Benefit

Permanent therapy with mechanical cardiac output was originally envisioned for patients with end-stage heart failure for whom donor hearts were not available. In the recent Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, inclusion criteria resembled those for transplantation: class IV heart failure, left ventricular ejection fraction < 25%, and either peak oxygen consumption < 12 to 14 mL · kg⁻¹ · min⁻¹ or dependence on intravenous inotropic infusion. Extrapolation from transplant evaluation led to underestimation of disease severity in patients signing up for randomization to mechanical cardiac support, who were considered ineligible for transplantation. The enrolled patients represented the most severe profile randomized in a heart failure trial, both in terms of the robust factors of blood pressure, sodium, and creatinine and in terms of the mortality (Table 1). The population was intermediate in severity between Status I (urgent) and Status II transplantation candidates, but significantly older.

Although REMATCH randomized patients to left ventricular assist device (LVAD) versus “optimal medical management,” most patients randomized were already beyond current medical therapy. Hypotension and progressive renal dysfunction had led to discontinuation of renin–angiotensin system inhibitors in 32% of patients. Development of circulatory-renal limitation preventing angiotensin-converting enzyme inhibitor use has been associated elsewhere with 6-month mortality over 50%. Few of these patients could be considered for β-adrenergic–blocking agents, presenting a worse profile than the recent Carvedilol ProspEctive RaNdomIzed CUmulative Survival (COPERNICUS) trial, where 6-month control mortality was 10%, compared with 48% in REMATCH. For 71% of patients, continuous intravenous inotropic agents were given at enroll-
ment, consistent with the indication for palliation of refractory heart failure in recent American College of Cardiology/American Heart Association guidelines. Mortality for patients on multiple experiences of chronic inotropic infusions has been close to 50% at 6 months.

In this uniquely compromised study population of 129 patients, assist devices decreased mortality by 48% over 2 years. The improvement in survival was greatest for patients receiving intravenous inotropic therapy at randomization, in whom 1-year mortality was reduced by the LVAD from 76% to 51%. It is sobering that the benefit of the device would not have been appreciated without the control arm, which had a mortality rate twice that projected.

In trials of patients likely to survive anyway, calculation of relative decreases in mortality emphasizes the positive impact of interventions (Table 2). Relative mortality reduction with the LVAD was similar to that for spironolactone and carvedilol in moderate-to-severe heart failure. When the natural history predicts mortality during the trial, however, it may be more relevant to calculate the increase in survival (Table 2). For patients on intravenous inotropic therapy at the time of randomization, implantation of the LVAD increased 1-year survival by 104%.

Many patients rate the quality of survival to be of equal or greater importance than the duration. The initial heart failure symptom score of 75 indicates more severe limitation than any previous trial. Improvement to below 50 confirms a major symptomatic improvement, to a level expected for NYHA class III. These results are apparent despite a high complication rate, with median 88 hospital days after LVAD compared with 24 days on continued medical therapy. The LVAD patients experienced 340 days alive out of the hospital, compared with 106 for patients on medical therapy.

The majority of the morbidity and mortality resulted from device infections and failures. The REMATCH surgical experience strongly suggests that infectious morbidity could be markedly reduced by meticulous attention to driveline immobilization by specifically designed garments, use of more pliable materials in driveline fabrication, and vigorous nutritional supplementation in cachectic patients. Modifications of the device inflow valve, device controller software, and motor design are also likely to afford improved future durability.

Preliminary cost data from the investigation reflects early experience in this population and the investigational protocol. Of the average cost of $202,000 (range $76,000 to $732,000, median $141,000), one third was for the device itself and one quarter was for intensive care unit days. It is anticipated that the initial cost of this new technology application will decline with wider acceptance and experience but is comparable to more expensive medical therapies.

### TABLE 2. What Is Meaningful Benefit in End-Stage Disease?

<table>
<thead>
<tr>
<th>Study (Therapy)</th>
<th>Control vs Therapy, % of patients</th>
<th>Relative Benefit, %</th>
<th>Absolute Benefit (Year 1 = No. Patients/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLVD (ACE inhibitor)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at 1 y</td>
<td>14 vs 11</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Survival at 1 y</td>
<td>86 vs 89</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CONSENSUS (ACE inhibitor)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at 1 y</td>
<td>62 vs 45</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>Survival at 1 y</td>
<td>38 vs 55</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>COPERNICUS (β-blocker)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at 1 y</td>
<td>18.5 vs 11</td>
<td>41</td>
<td>7.5</td>
</tr>
<tr>
<td>Survival at 1 y</td>
<td>81.5 vs 89</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>RALES (spironolactone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at 1 y</td>
<td>25 vs 17</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>Survival at 1 y</td>
<td>75 vs 83</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>REMATCH-inotropic (LVAD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at 1 y</td>
<td>76 vs 51</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>Survival at 1 y</td>
<td>24 vs 49</td>
<td>104</td>
<td></td>
</tr>
</tbody>
</table>

SOLVD indicates Studies Of Left Ventricular Dysfunction. Other abbreviations as in Table 1.
cardiac transplantation and lower than liver transplantation. The current target population for this device is estimated at 5000 to 10,000 but is likely to increase as the outcomes improve. Preparing for equitable access to this technology presents multiple societal challenges different from those created by the limited organ supply for transplantation.

Bridge and Recovery

Bridge

LVADs have been used in over 3500 patients as a bridge to transplantation, with over 50% of recent implantable device recipients discharged home. As transplantation offers good-quality survival of almost 50% at 10 years, patients requiring transplantation if eligible. However, increasing time on the waiting list has allowed progressively longer experiences with these devices. As some candidates choose to defer transplantation while enjoying device support, the distinction between bridging and destination is blurring, although transplantation candidates still present a more favorable comorbidity profile than primary “destination” LVAD patients.

Recovery

Some patients have demonstrated sufficient recovery of ventricular function to allow successful device weaning. This is most apparent for acute-onset fulminating myocarditis, with which spontaneous recovery is common if circulation is maintained acutely. Patients presenting less dramatically with ≤6 months of cardiomyopathy have almost 50% chance of major spontaneous improvement, rarely requiring mechanical support. Major recovery after a year of symptomatic heart failure has been less often observed, although a degree of improvement is common. Left ventricular size contracts, fetal gene expression diminishes, fibrosis regresses, and myocyte architecture often improves after a month of support. Although the experience has been variable, fewer than 10% of patients have demonstrated sufficient recovery of left ventricular function within 3 to 6 months to undergo device explantation. Recovery is most often seen in dilated cardiomyopathy and may be influenced by multiple factors, including the degree of unloading, neurohormonal inhibition, and the underlying myocardial injury. Early use of neurohormonal antagonists and timed therapy with clenbuterol may prove equal or superior. A new generation of smaller, more efficient, nonpulsatile devices may offer a less surgically traumatic approach, though hemodynamic effectiveness and durability remain unproven in large patient populations. Early experience with the Abiocor total artificial heart confirms hemodynamic effectiveness for this more complex class of devices, which may be particularly well suited for severe biventricular failure. Substantial morbidity and concerns about the quality of life for patients in recent trials mandate continued caution. Hindsight will likely reveal the current era to be an early stage in the evolution of device therapy for heart failure. As the technology improves, use of devices for end-stage heart failure will likely increasingly mirror the use of hemodialysis for end-stage renal failure.

Next Destinations

New Devices

Although REMATCH proved the survival and quality-of-life benefit of the Thoratec HeartMate device for patients with end-stage heart failure not considered appropriate for transplantation, similar pulsatile implantable devices (eg, World- heart Novacor, Arrow Lionheart) and newer modifications may prove equal or superior. A new generation of smaller, more efficient, nonpulsatile devices may offer a less surgically traumatic approach, though hemodynamic effectiveness and durability remain unproven in large patient populations. Early experience with the Abiocor total artificial heart confirms hemodynamic effectiveness for this more complex class of devices, which may be particularly well suited for severe biventricular failure. Substantial morbidity and concerns about the quality of life for patients in recent trials mandate continued caution. Hindsight will likely reveal the current era to be an early stage in the evolution of device therapy for heart failure. As the technology improves, use of devices for end-stage heart failure will likely increasingly mirror the use of hemodialysis for end-stage renal failure.

New Populations

Who will form the new populations for clinical evaluation of devices? End-stage disease and immediate impact of current devices defy precedents set by pharmacological trials. At this time, it does not seem ethical to randomize a population similar to REMATCH to a medical therapy arm unless physical constraints prevent implantation of currently available devices. Subsequent trials will likely include provision for compassionate device placement in patients reaching preestablished criteria for imminent mortality. Comparison of 2 active device interventions can be done when the newer device offers potential advantage for either quality of life or survival. The international mechanical cardiac support device registry currently being implemented will be vital to provide benchmarks of performance as the experience with destination therapy expands beyond the 68 device patients from REMATCH.

As devices and the techniques for infection prophylaxis continue to improve, the benefits for both survival and function will be easier to identify. New trials may then include patients with lesser immediate compromise and risk of death (Figure). As device reliability improves, trials will likely focus more on composite end points of quality of life and survival and may eventually be designed to demonstrate decreased disease progression. The complexity of resources required restricts the trial population to a fraction of that required to demonstrate small absolute benefits in pharmaceutical trials. To streamline identification of target populations before device approval and refine their definition afterward, a high priority for further progress in this field is the development of independent registries of patients with advanced heart failure. Implantable circulatory support devices represent one of several expensive technologies, such as
coated stents and implantable defibrillators, that warrant close surveillance to maximize benefit within the context of the total resources available for health care.

Summary

We are entering an era in which long-term mechanical circulatory support will likely play an increasing role in the approach to end-stage heart disease. The extension of mechanical circulatory support devices into destination therapy has revealed the limitations of our understanding of these populations. Current candidates for benefit from these devices demonstrate progression of disease beyond the scope of current medical therapy as provided in experienced centers, with estimated 50% mortality at 6 months. The recent REMATCH trial doubled 1-year survival to that of ambulatory class IV patients on oral therapy, providing a benchmark for future progress. Trials of devices for end-stage disease require innovative design. As devices and techniques continue to improve, benefit for both survival and function may be demonstrated in patients with decreasing severity of disease. Acceptance of devices presents societal challenges for equitable health resource allocation.

References

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Lynne Warner Stevenson and Eric A. Rose

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