Title

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Journal

Circulation. Heart failure, 7(3)

ISSN

1941-3289

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Publication Date

2014-05-01

DOI

10.1161/circheartfailure.113.000807

Peer reviewed

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Circ Heart Fail. 2014;7:470-478; originally published online February 21, 2014;
doi: 10.1161/CIRCHEARTFAILURE.113.000807
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3289. Online ISSN: 1941-3297

Comparative Survival and Cost-Effectiveness of Advanced Therapies for End-Stage Heart Failure

Elisa F. Long, PhD; Gary W. Swain, MD, MBA; Abeel A. Mangi, MD

Background—Treatment options for end-stage heart failure include inotrope-dependent medical therapy, orthotopic heart transplantation (OHT), left ventricular assist device (LVAD) as destination therapy or bridge to transplant.

Methods and Results—We developed a state-transition model to simulate 4 treatment options and associated morbidity and mortality. Transition probabilities, costs, and utilities were estimated from published sources. Calculated outcomes included survival, quality-adjusted life-years, and incremental cost-effectiveness. Sensitivity analyses were performed on model parameters to test robustness. Average life expectancy for OHT-eligible patients is estimated at 1.1 years, with 39% surviving to 1 year. OHT with a median wait time of 5.6 months is estimated to increase life expectancy to 8.5 years, and costs <$100 000/quality-adjusted life-year gained, relative to inotrope-dependent medical therapy. Bridge to transplant-LVAD followed by OHT further is estimated to increase life expectancy to 12.3 years, for $226 000/quality-adjusted life-year gained versus OHT. Among OHT-ineligible patients, mean life expectancy with inotrope-dependent medical therapy is estimated at 9.4 months, with 26% surviving to 1 year. Patients who instead received destination therapy-LVAD are estimated to live 4.4 years on average from extrapolation of recent constant hazard rates beyond the first year. This strategy costs $202 000/quality-adjusted life-year gained, relative to inotrope-dependent medical therapy. Patient's age, time on wait list, and costs associated with care influence outcomes.

Conclusions—Under most scenarios, OHT prolongs life and is cost effective in eligible patients. Bridge to transplant-LVAD is estimated to offer >3.8 additional life-years for patients waiting ≥6 months, but does not meet conventional cost-effectiveness thresholds. Destination therapy-LVAD significantly improves life expectancy in OHT-ineligible patients. However, further reductions in adverse events or improved quality of life are needed for destination therapy-LVAD to be cost effective. **(*Circ Heart Fail*. 2014;7:470-478.)**

Key Words: cost-benefit analysis ■ transplantation

Heart failure afflicts >5 million Americans,[1] with 700 000 people newly diagnosed each year.[2] In 2013, heart failure cost our healthcare system >$32 billion and is expected to double by 2030.[2] A considerable proportion of hospitalized patients with heart failure have inotrope-dependent stage D heart failure[3–5] and experience a 1-year survival rate of only 25%.[6–8] The nationwide cost of index hospitalizations alone for orthotopic heart transplantation (OHT) and left ventricular assist device (LVAD) implantation approached $1 billion in 2009.[9]

Clinical Perspective on p 478

OHT is considered the definitive therapy for patients with inotrope-dependent stage D heart failure, with 1-year survival exceeding 85%.[10,11] Median survival for all OHT recipients is currently 10 years, increasing to 13 years conditional on surviving the first year.[10] More than 3500 people are currently listed for OHT, with a median wait-list time of 5 to 6 months,[12] although only 2200 OHT operations are performed annually in the United States, in part attributable to limited donor availability.[10,13]

Randomized clinical trials involving patients with stage D heart failure have demonstrated improvements in survival among transplant-ineligible patients undergoing LVAD implantation as destination therapy (DT). The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial showed a 48% reduction in risk of death in LVAD patients when compared with patients receiving inotrope-dependent medical therapy (IDMT).[6] Heartmate-II investigators subsequently showed that patients implanted with continuous-flow LVADs achieved a 54% reduction in risk of death when compared with patients implanted with earlier LVADs used in the REMATCH trial.[14] Further analysis has shown a 1-year survival approaching 80% among patients receiving DT-LVAD.[15] Patients who undergo LVAD implantation as a bridge to transplant (BTT) obtain 1-year survival rates nearly as high as OHT.[16] The presence

Received July 9, 2013; accepted February 14, 2014.

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The Data Supplement is available at http://circheartfailure.ahajournals.org/lookup/suppl/doi:10.1161/CIRCHEARTFAILURE.113.000807/-/DC1.

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of an LVAD does not seem to impact survival after OHT, although this is currently under debate.[17,18]

Although ≈1800 LVADs were implanted in the United States in 2012—more than double the number implanted in 2008. Although these predictions are challenging to establish, it has been estimated that far more patients might be eligible for LVAD or OHT in the United States alone.[15,19] Given the substantial costs of both procedures,[9] the economic impact of such strategies deserves consideration. In this analysis, we evaluated the health benefits, survival, costs, and comparative cost-effectiveness of treatment strategies for patients with inotrope-dependent stage D heart failure.

Methods

Study Design

We developed a novel decision-analytic model (Figure 1) to estimate survival and costs among patients with inotrope-dependent stage D heart failure under different treatment strategies. Among transplant-ineligible patients, we compared IDMT with DT-LVAD. For transplant-eligible patients, we evaluated IDMT, OHT, BTT-LVAD, and DT-LVAD. Although these patients would likely receive a heart transplant once a suitable organ becomes available, we included DT-LVAD as a hypothetical scenario to assess whether conditions exist where it may be preferable to receive DT-LVAD in lieu of BTT or OHT. In addition, the DT-LVAD strategy characterizes patients who start as BTT-LVAD but become ineligible for OHT and thereby convert to a DT-LVAD platform by default. Sensitivity analyses on parameters were performed to test model assumptions. Additional details are provided in the Appendix in the Data Supplement. The study was approved by the Human Investigations Committee of the Human Research Protection Program at Yale University.

A health state-transition model with 1-month cycle lengths was created to simulate a cohort of 20 000 hypothetical patients. Each month, patients transition between health states based on the risk of developing condition-specific complications or dying, with transition probabilities were derived from survival rates reported in the literature (Appendix Table I in the Data Supplement). Probability values were modeled as time varying, where appropriate, to more accurately reflect clinical course. Age-related mortality rates were estimated from Centers for Disease Control life tables,[20] with a base-case initial patient age of 50 years (Appendix Table II in the Data Supplement). All analyses were conducted using a lifetime horizon. The model was implemented in TreeAge Pro 2013 Software.

Survival Rates

We calibrated the model to published survival rates for ≤4 years follow-up in LVAD patients and 7 years for transplant patients

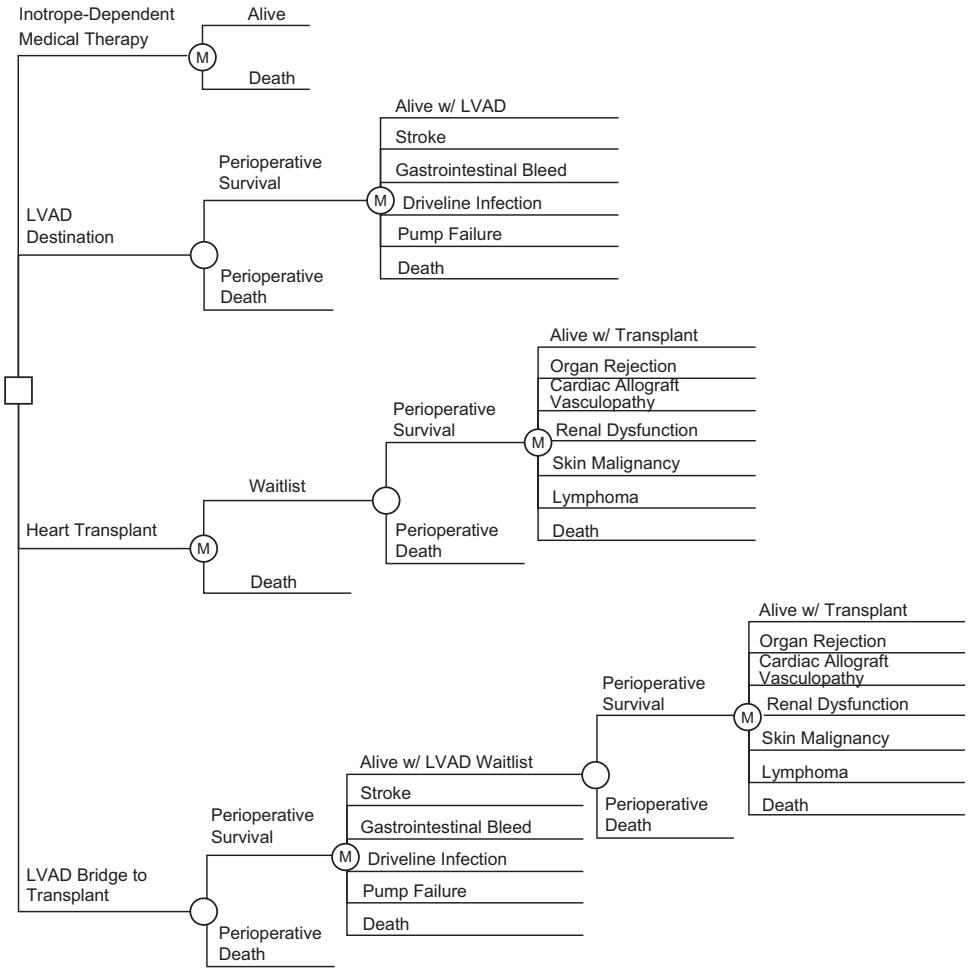

Figure 1. Decision-analytic model diagram for treatment of end-stage heart failure. The initial square node represents a decision point where a treatment regimen is chosen. The open circle nodes represent chance events, and the M circle nodes represent the health states. Patients can transition among health states according to specified transition probabilities. Patients may die from any health state based on the associated mortality rate or from age-related mortality. The model assigns costs and quality-of-life values to each health state. The simulation then calculates the average lifetime costs and quality-adjusted life-years of each treatment regimen, based on a cohort of 20 000 patients. LVAD indicates left ventricular assist device.

Table 1. Survival, Complication Rates, Costs, and Quality-of-Life Inputs to Model

Survival Probability		Freedom From Complications		Costs (2012 $)		Quality-of-Life Factor	
IDMT, OHT eligible[21]		Stroke[15]		Monthly IDMT care[7,22]		IDMT[7,23]	0.53
6 mo	0.63	1 mo	0.97	12 mo before death	9072	LVAD month 1[23]	0.51
1 y	0.40	3 mo	0.95	12–24 mo before death	4404	LVAD months 2+[15]	0.72
2 y	0.16	1 y	0.89	24+ mo before death	2039	Heart transplant[23]	0.76
IDMT, OHT ineligible[6,7]		2 y	0.83	LVAD index hospitalization[9,24]	239 160	Stroke[25]	0.68
6 mo	0.51	3 y	0.81	Monthly post-LVAD care[26–28]		Gastrointestinal bleed*	0.60
1 y	0.26	Driveline infection[15]		Months 1–12	10 984	Driveline infection*	0.60
2 y	0.08	6 mo	0.93	Months 12+	3121	Transplant rejection*	0.76
LVAD, OHT eligible[15,29]		1 y	0.85	OHT index hospitalization[9]	195 208	CAV*	0.76
6 mo	0.88	2 y	0.72	Monthly post-OHT care[26,27]		Renal dysfunction[30]	0.57
1 y	0.82	Gastrointestinal bleed[31–33]		Months 1–12	10 363	Skin malignancy[34]	0.65
2 y	0.74	6 mo	0.94	Months 12+	2326	Lymphoma/other malignancies[34,35]	0.55
LVAD, OHT ineligible[15,29]		1 y	0.88	End-of-life care[7]	49 838		
6 mo	0.85	2 y	0.77	Acute stroke[36]	20 155		
1 y	0.77	Pump failure[15]		Monthly poststroke care[36]	3076		
2 y	0.62	6 mo	0.98	Gastrointestinal bleed[37]	12 165		
Post–heart transplant[10,11,22]		1 y	0.96	Driveline infection[24]	41 504		
6 mo	0.92	2 y	0.92	CAV*	10 674		
1 y	0.86	Transplant rejection[10]		Monthly post-CAV care*	1067		
2 y	0.82	1 y	0.78	Renal dysfunction initial care[38]	10 674		
3 y	0.79	2 y	0.68	Monthly renal dysfunction care[38]	6674		
7 y	0.66	4 y	0.60	Skin malignancy[39]	3963		
		Malignancy[10]		Monthly post–skin malignancy care[39]	132		
		1 y	0.97	Lymphoma/other malignancies[39]			
		5 y	0.86	Months 1–24	1651		
		10 y	0.71	Months 24+	528		
		CAV[10]					
		1 y	0.92				
		3 y	0.82				
		7 y	0.63				
		Renal dysfunction[10]					
		1 y	0.94				
		3 y	0.89				
		7 y	0.80				

CAV indicates cardiac allograft vasculopathy; IDMT, inotrope-dependent medical therapy; LVAD, left ventricular assist device; and OHT, orthotopic heart transplant.
*Value determined by expert opinion and Yale-New Haven Hospital data.

(Table 1). Beyond these time horizons, we extrapolated the appropriate mortality rates to project future survival; however, the model may be updated to reflect newer estimates as data become available.

Contemporary survival rates for LVAD patients were obtained from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), which enrolled 6885 LVAD patients between 2006 and 2012.[15] LVAD survival at 6, 12, and 24 months was 88%, 82%, and 74%, respectively. We assumed a higher mortality rate in the first month postimplantation and increased rates of serious complications which contribute to higher mortality for the first 12 months postimplantation. Beyond 12 months, we assumed a constant monthly mortality hazard rate based on a similar observation in INTERMACS from 12 to 48 months.[15] Our model closely matches INTERMACS data for patients with continuous-flow LVADs in the current era (Appendix Figure I in the Data Supplement).[15,29] We also assumed 5% lower survival at 1 year for DT patients ineligible for OHT.[15]

OHT survival was obtained from the International Society of Heart and Lung Transplantation (ISHLT), where post-transplant survival rates for years 1 through 7 were 86%, 82%, 79%, 76%, 73%, 69%, and 66%, respectively.[10] We calibrated transition probabilities to closely match ISHLT data (Appendix Figure II in the Data Supplement); we assumed a higher mortality rate for the first 12 months post-transplantation, but then a constant monthly mortality rate thereafter. Similar post-transplant mortality rates were used for patients who received IDMT or LVAD pretransplantation.[11,16–18] The median wait-list time to receive a heart in the United States was 5.6 months based on the Scientific Registry of Transplant Recipients (SRTR).[12] In our model, we randomly generated a different wait-list time for each patient, such that the median wait time is 5.6 months. Under a constant hazard rate of an organ becoming available, this implies that 77% of patients receive a heart within 1 year.

Estimates of survival among patients receiving IDMT vary widely, in part because of differences in baseline patient characteristics. The REMATCH trial demonstrated survival rates of 23% at 1 year and 8% at 2 years among OHT-ineligible patients, which formed the basis for our survival assumptions in this population.[6,7] Survival estimates for OHT-eligible patients on IDMT were based on an analysis of United Network for Organ Sharing status 1A and 1B patients who did not receive an LVAD while awaiting OHT. Survival rates of 63%, 40%, and 16% at 6 months, 1 year, and 2 years, respectively, were assumed in our analysis of OHT-eligible IDMT patients.[21]

In addition to estimating survival curves based on our simulation, we calculated the mean life expectancy associated with each treatment modality. We simulated each patient's health state transitions according to the mortality and complication rates until death. We then averaged across all patients to compute the mean life expectancy.

Complication Rates

Our model captured the development of specific clinical complications (Figure 1) and accounted for the associated costs and quality-of-life decrements. After LVAD implantation, common complications include stroke, gastrointestinal bleeding, driveline infection, or pump failure requiring device replacement.[40] Among heart transplant recipients, organ rejection, cardiac allograft vasculopathy, renal dysfunction, and malignancy are possible complications. BTT-LVAD patients may experience complications resulting from either LVAD or OHT. All complication rates were validated against published estimates (Appendix Table III in the Data Supplement).

Quality of Life and Costs

Outcomes estimated for each strategy were average life expectancy, quality-adjusted life-years (QALYs), lifetime costs, and incremental cost-effectiveness ratios (ICERs) relative to the next-best strategy in terms of cost per life-year gained or QALY gained. We adhered to recommendations for cost-effectiveness studies by using a societal perspective and discounting both costs and QALYs at a 3% annual rate.[41]

Quality-of-life estimates were obtained from literature review (Table 1). Each health state was associated with a quality-of-life value ranging from 0 to 1, where 0 represents death and 1 represents ideal health. QALYs were computed by aggregating the total time spent in each health state and applying the appropriate utility weight.

The costs of each treatment intervention, associated complications, and follow-up health care were estimated (Table 1). All costs were updated to 2012 US dollars using the medical care component of the consumer price index.[42] Direct medical costs associated with the index hospitalization for LVAD implantation and OHT were based on the Heartmate-II DT trial[24] and the Nationwide Inpatient Sample.[9] Professional fees were derived from a prior analysis of Medicare claims for patients undergoing LVAD implantation in 2008.[7] Direct costs for repeat hospitalizations and outpatient care were derived from 3674 patient-months from June 2011 to May 2013 at Yale-New Haven Hospital, which included 30 LVAD, 32 OHT, and 32 IDMT patients. These costs were reconciled with costs of post-LVAD implant, post-OHT care, and IDMT from previous reports.[7,22,26–28]

Results

Base-Case Analysis

Based on a simulation of 20 000 patients with inotrope-dependent stage D heart failure aged 50 years (Figure 2), average life expectancy for OHT-eligible patients on IDMT was 1.1 years, with a 1-year survival rate of 40%, consistent with published estimates.[43] Similar patients who immediately receive OHT live for an additional 13.8 years on average, with a 5-year survival rate of 74%. Our model results are similar to post-transplantation survival estimates reported by ISHLT.[10,22] However, because patients typically face a waiting period before a heart becomes available, we calculated life expectancy while accounting for this wait-list time. Given a median OHT wait-list time of 5.6 months, life expectancy is 8.5 years, with a 5-year survival rate of 44%, assuming patients received IDMT while awaiting OHT. Patients with similar transplant wait-list times who instead receive BTT-LVAD live an additional 12.3 years on average, slightly less than patients who are immediately transplanted (13.8 years) because of LVAD-associated complications and surgical mortality risk (Table 2).

Among patients who are OHT ineligible, the average life expectancy with IDMT was 9.4 months with a 1-year survival of 26%, consistent with prior reports.[6] Alternatively, from extrapolation of recent constant hazard rates beyond the first year, DT-LVAD quintuples life expectancy to 4.4 years in OHT-ineligible patients, generating 1-year and 2-year survival rates of 78% and 62%, respectively, consistent with reports in the literature.[29]

Cost-Effectiveness Analysis

Under the base-case scenario, OHT costs ≈$97 000 per QALY gained or $54 000 per life-year gained relative to IDMT in OHT-eligible patients (Figure 3). If a patient from this cohort receives BTT-LVAD, the ICER exceeds $226 000 per QALY gained relative to OHT, primarily attributable to the substantial inpatient hospital costs associated with both

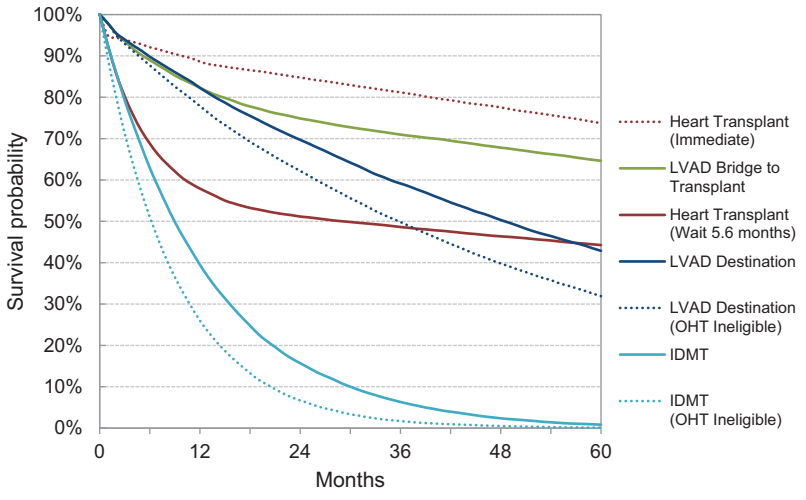

Figure 2. Model-projected survival during 5 years. Each line corresponds to the fraction of a cohort surviving over time. Immediate heart transplantation (dashed) and transplantation following a median wait time of 5.6 months (solid) are both shown. Bridge to transplant-left ventricular assist device (LVAD) assumes a median wait of 5.6 months following LVAD implantation. Inotrope-dependent medical therapy (IDMT) or destination therapy-LVAD among patients who are transplant eligible (solid) or ineligible (dashed) are also shown. OHT indicates orthotopic heart transplant.

Table 2. Model Results and Cost-Effectiveness Analysis

Strategy	Lifetime Costs, ($)*	5-Year Survival, %†	Life Expectancy, y	QALYs*	Incremental Cost-Effectiveness Ratio,‡ $/life-year	Incremental Cost-Effectiveness Ratio,‡ $/QALY
Heart transplant ineligible						
Inotrope-dependent medical therapy	112 600	0	0.78	0.41	…	…
LVAD destination therapy	593 000	32	4.42	2.79	131 800	201 600
Heart transplant eligible						
Inotrope-dependent medical therapy	130 300	1	1.13	0.58	…	…
Heart transplant						
Immediate	802 200	74	13.76	7.67	53 200	94 800
Wait-list 5.6 mo	529 000	44	8.48	4.70	54 300	96 900
Wait-list 12 mo	405 700	31	6.18	3.41	54 500	97 300
LVAD bridge to transplant						
Immediate	1 025 500	71	13.12	7.32	Dominated	Dominated
Wait-list 5.6 mo	1 011 900	65	12.29	6.83	126 700	226 300
Wait-list 12 mo	978 000	59	11.41	6.40	109 400	191 400

LVAD indicates left ventricular assist device; and QALY, quality-adjusted life-year.
*Lifetime costs and QALYs are discounted at a 3% annual rate.
†Results are based on a simulation of 20 000 hypothetical patients aged 50 years.
‡Incremental cost-effectiveness ratios for LVAD destination therapy and heart transplant are relative to inotrope-dependent medical therapy, and LVAD bridge to transplant is relative to heart transplant.

procedures. In the hypothetical scenario where an OHT-eligible patient underwent LVAD implantation with the intention of later undergoing OHT, but for whatever reason converted to DT-LVAD, this strategy would cost $175 000 per QALY gained but would confer fewer QALYs than OHT or BTT-LVAD. In OHT-ineligible patients, DT-LVAD carries an ICER of $202 000 per QALY gained or $132 000 per life-year gained, compared with medical therapy.

Sensitivity Analyses

Age

Our base-case simulation considered 50-year-old patients. As patients age, all cohorts experience a decrease in life expectancy driven by age-related mortality (Figure 4), resulting in worsening cost-effectiveness. We projected 75-year-old LVAD patients' survival rates of 78% (1 year), 65% (2 years), and 52% (3 years). INTERMACS reports survival rates of 75%, 63%, and 54% for patients aged ≥70 years.[44] Among 75-year-old heart transplant recipients, we projected post-transplant survival rates of 86%, 80%, 73%, 67%, and 60% at years 1 through 5, respectively, compared with 80%, 76%, 72%, 67%, and 66% reported by ISHLT for patients aged ≥70 years.[10] Modest survival rate differences may arise because both INTERMACS and ISHLT pool survival data for all patients aged >70 years.

In OHT-eligible patients, OHT costs <$100 000 per QALY gained relative to IDMT in patients aged <63 years, whereas BTT-LVAD exceeds $200 000 per QALY gained relative to OHT across all ages, assuming a median wait-list time of 5.6 months.

Among OHT-ineligible patients, DT-LVAD exceeds $150 000 per QALY gained relative to IDMT even for patients in their 40s. Some debate exists about whether DT-LVAD

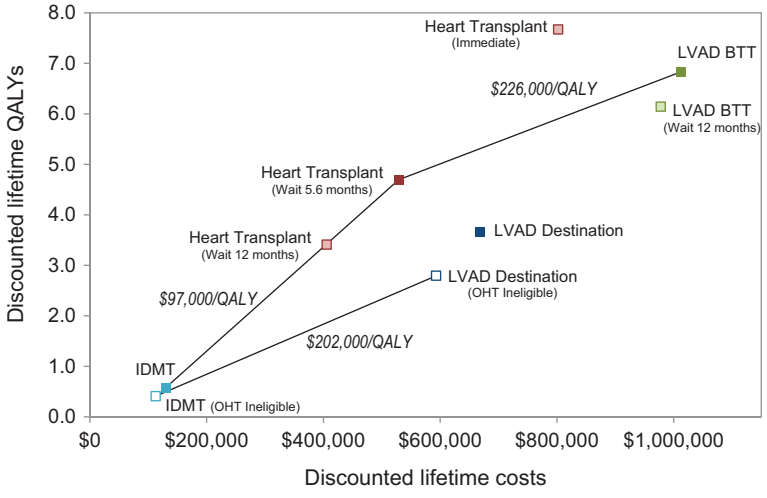

Figure 3. Cost-effectiveness of end-stage heart failure therapy options. Discounted lifetime costs and quality-adjusted life-years (QALYs) are shown for each treatment regimen. The cost-effectiveness frontier (black line) represents those strategies that are most economically efficient. Among orthotopic heart transplant (OHT)–ineligible patients (open squares), destination therapy-left ventricular assist device (LVAD) is compared with inotrope-dependent medical therapy (IDMT). All other points (closed squares) correspond to OHT-eligible patients. The cost-effectiveness of OHT is relative to IDMT, and bridge to transplant (BTT)-LVAD is relative to OHT.

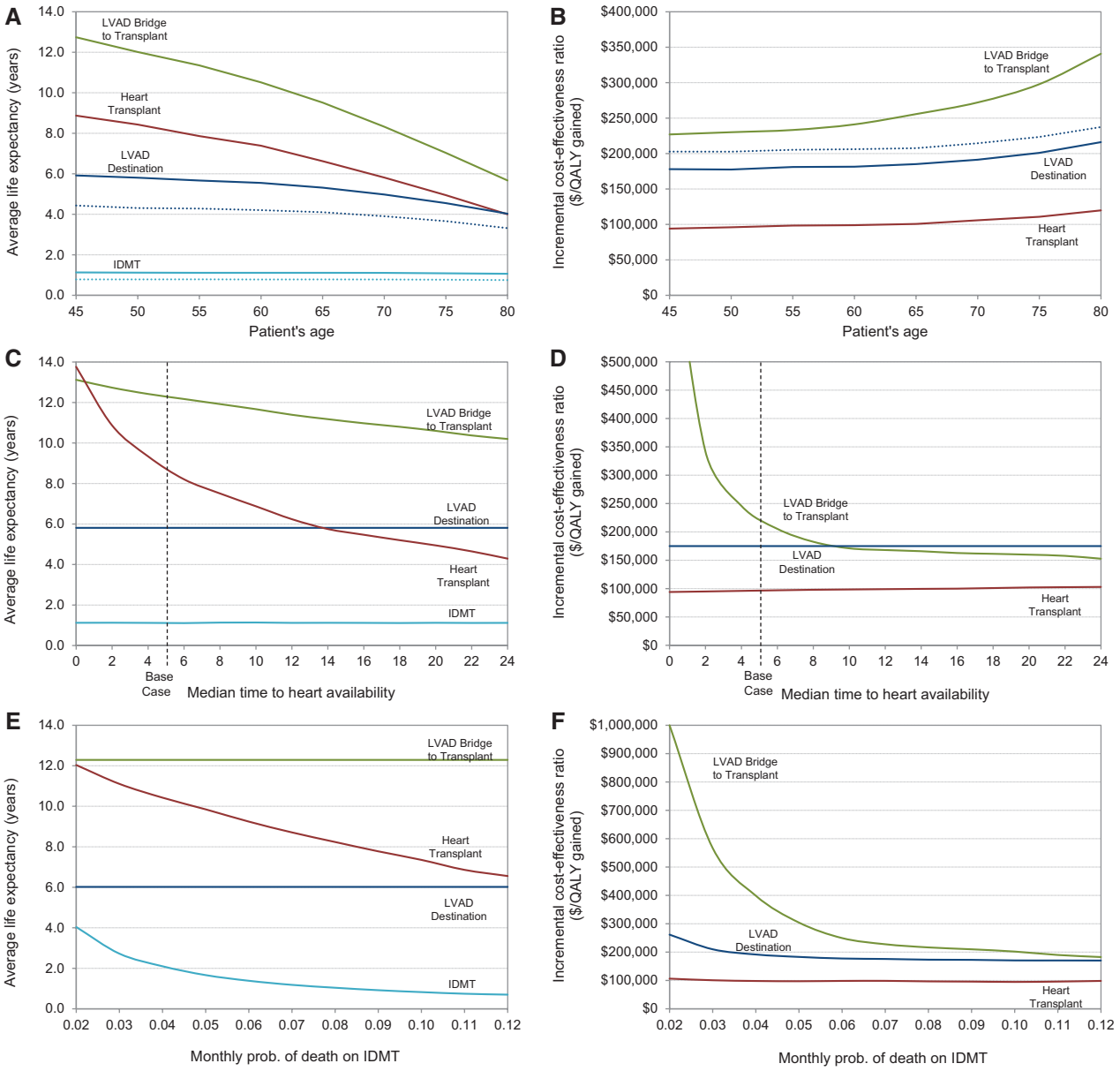

Figure 4. Sensitivity analysis of key model parameters. Sensitivity analysis graphs illustrate the impact on life expectancy and cost-effectiveness ($ per quality-adjusted life-year [QALY] gained) given variations in key model parameters: patient's age (**A** and **B**), median wait time for heart transplantation (**C** and **D**), and the monthly probability of death with inotrope-dependent medical therapy (IDMT; **E** and **F**). Patients are categorized as orthotopic heart transplant (OHT) eligible (solid lines) or OHT ineligible (dashed lines). LVAD indicates left ventricular assist device.

should be offered to patients aged >70 years.[7,15] In this analysis, DT-LVAD confers an average life expectancy of 3.6 years among patients aged >70 years (compared with 4.4 years for 50-year-old patients) with an ICER of $225 000 per QALY gained relative to OHT.

Transplant Wait Time

Median wait time for heart transplant is 5.6 months, with significant variability depending on region and patient characteristics including blood type, size, and allo-antibody sensitization. To assess the sensitivity of transplant wait-list time, we varied the median wait time from 0 to 24 months (Figure 4). A projected life expectancy of 13.8 years conferred by immediate OHT decreases to 4.3 years given a median wait-list time of 24 months. The cost-effectiveness of OHT remains relatively constant because both life expectancy and lifetime costs decrease proportionately with longer waits. If the expected wait for OHT is <1 month, IDMT is preferred to BTT-LVAD while awaiting OHT. For any wait >1 month, BTT-LVAD generates the longest life expectancy. The cost-effectiveness of BTT-LVAD (relative to OHT only) improves as the wait-list time increases because the comparator strategy of IDMT followed by OHT worsens. For example, with a median transplant wait-list time of 24 months, BTT-LVAD costs $150 000 per QALY gained.

Medical Therapy Mortality

We examined how varying survival of patients on IDMT might influence health outcomes (Figure 4). In our base-case

analysis, the monthly probability of death for OHT-eligible IDMT patients was 0.074. Decreasing this probability by half increases the life expectancy with OHT from 8.5 to 10.8 years. As one might expect, the cost-effectiveness of OHT or LVAD implantation worsens as IDMT survival improves, because the baseline strategy of IDMT seems more favorable. With an average life expectancy on IDMT of 2.5 years—sufficient time for most patients to receive OHT—the ICER for BTT-LVAD exceeded $500 000 per QALY gained.

Complication Rates

Our state-transition model incorporated clinically relevant postprocedural complications for the life of the patient. Hypothetically, if LVAD-specific and OHT-specific complications were eliminated completely, cost-effectiveness would improve substantially. OHT in patients with a 5.6-month median wait-list time would cost only $56 000 per QALY gained, BTT-LVAD would cost $128 000 per QALY gained, and DT-LVAD would cost ≈$100 000 per QALY gained. This suggests that that future improvements in LVAD implantation and management of complications could make DT-LVAD a viable alternative to heart transplantation.

Discussion

Our analysis adds to the growing body of evidence comparing clinical outcomes and costs of treatment for end-stage heart failure. Our projected survival rates and freedom from complications closely match values reported by INTERMACS for LVADs through 4 years postimplantation and by ISHLT for heart transplants through 7 years postsurgery. Because many clinical trials and observational studies track patients for a limited time, a comprehensive model such as the one we have developed can offer insights about long-term survival and health benefits of different therapies.

Our results suggest that OHT significantly improves life expectancy and costs <$100 000 per QALY gained, a threshold often considered cost effective for the United States.[43] Although the wait-list time influences survival and lifetime costs, OHT remains more cost effective than DT-LVAD in transplant-eligible patients, across a wide range of assumptions. We recognize, however, that certain OHT-eligible patients may experience precipitous decline in clinical condition and may require BTT-LVAD. Although this strategy does not meet conventional cost-effectiveness thresholds under our base-case assumptions, it offers a substantial gain in life expectancy compared with IDMT while awaiting OHT. With a longer transplant wait-list time, decreased index hospitalization costs, or reduced LVAD complication rates, the cost-effectiveness of BTT-LVAD falls <$150 000 per QALY gained.

The impact of DT-LVAD as a life-prolonging modality in critically ill patients who have no other option should be emphasized. The cost-effectiveness of this therapy has improved dramatically since a 2004 analysis based on the REMATCH trial data reported an ICER of $802 700.[45] We expect that as survival and quality of life continue to improve and as adverse events, lengths of stay, device costs, and need for readmission decrease, that cost-effectiveness of this strategy will continue to improve. Although a patient's age impacts overall life expectancy with an LVAD or OHT, increasing age alone does not impact the relative ranking of each strategy in terms of cost-effectiveness.

One challenge in studying a population with end-stage heart failure is its inherent heterogeneity. Prior studies have demonstrated that cost-effectiveness is not an inherent property of any particular therapy but depends on the patient population in which the therapy is used.[46] Accordingly, it is important to identify subgroups that will derive benefit based on appropriate, evidence-based selection of patients. To obtain appropriate survival estimates, we separated patients with stage D heart failure based on transplant eligibility. Patients who were OHT ineligible could only receive DT-LVAD as clinical guidelines dictate. In contrast, survival estimates for OHT-eligible patients were in accordance with status 1A or 1B patients who did not receive an LVAD.[45] These are clearly different subgroups with projected life expectancies that differ by 30% to 50%. In addition, OHT-eligible patients may need to move to DT-LVAD as occasionally occurs in clinical practice. The cost-effectiveness of LVAD as DT or BTT may worsen as survival on medical therapy alone improves.

Our cost-effectiveness estimates of DT-LVAD differ slightly from those reported by Rogers et al,[7] in part because we accounted for the decrement in utility from complications, stratified patients based on OHT-eligibility, and applied more recent INTERMACS data in which LVAD survival is improved. We found LVAD as BTT to be more cost effective than reported by Moreno et al[28] primarily because we assumed a lower survival rate in OHT-eligible IDMT patients by excluding from the analysis IDMT patients who subsequently underwent LVAD implantation.

Our analysis builds on prior studies through our inclusion of commonly tracked medical complications after LVAD implantation and OHT and their associated costs. If such costs were ignored, the cost-effectiveness of both strategies improved by ≈40%, highlighting the importance of including medical complications when evaluating relative cost-effectiveness. It also suggests that as the field continues to mature and outcomes improve, that cost-effectiveness should also improve.

A limitation of our study stems from the paucity of cost data associated with different health states in our model. Although our cost assumptions were based on published estimates, the exact patient population may differ, resulting in over- or underestimates. We estimated quality-of-life factors for each complication state based on published estimates that may include other patient populations. Future studies should examine the costs and utilities associated with each complication state. Mortality rates were extrapolated beyond available registry data for LVAD and transplant patients, which could be revised as additional data become available. Finally, our state-transition model included the most common tracked complications associated with LVADs or OHT, but the model simplified the complex progression of stage D heart failure.

In conclusion, our study demonstrates that heart transplantation results in improved survival and is a cost-effective strategy for most transplant-eligible patients with inotrope-dependent stage D heart failure, compared with medical therapy alone. However, if the anticipated wait-list time exceeds 1 month, BTT-LVAD results in greater life expectancy for patients awaiting OHT than medical therapy alone.

Given national average transplant wait times for status 1A and 1B patients, the cost-effectiveness of BTT-LVAD exceeds $225 000 per QALY gained, but improves substantially with longer expected transplant wait times. In patients ineligible for transplantation, DT-LVAD substantially improves survival compared with medical therapy, although advances in medical complication rates or implantation costs must improve to render it as cost effective as other medical technologies.

Disclosures

Dr Mangi has received speaking fees and consulting fees from Thoratec Corporation.

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CLINICAL PERSPECTIVE

Congestive heart failure exerts a significant epidemiological burden on our society. Therapies for advanced heart failure have evolved rapidly during the last decade with significant improvements in survival and outcomes, resulting in robust diffusion of these therapies to the heart failure population. In a social, political, and economic climate where discussions on healthcare expenditures dominate the conversation, we wished to gain greater clarity into the real-world contemporary outcomes and costs of left ventricular assist device (LVAD) implantation and cardiac transplantation as compared with inotropic medical therapy. We developed a novel decision-analytic model, which not only accounts for survival, but also is the first to account for condition-specific complications for patients receiving inotropes, those undergoing LVAD for destination therapy, LVAD as bridge to transplant, and cardiac transplantation. Cost estimates were obtained from a major academic hospital and other published sources. Our results suggest that contemporary cardiac transplantation and LVAD implantation exert significant beneficial influence on survival rates, longevity, and quality of life. Costs for cardiac transplantation have continued to decrease, and it now approaches the threshold for cost-effectiveness in the United States. LVAD therapy is still expensive but costs significantly less than it did a decade ago and offers dramatic improvements in survival and quality of life which continue to make it an attractive therapeutic option. We can expect that careful attention to patient selection, thoughtful and more efficient use of transplant wait lists, and continued control of complications requiring hospital readmission will render all therapies more cost effective in the future.

Comparative Survival and Cost Effectiveness of Advanced Therapies for End-stage Heart Failure

Elisa F. Long, PhD; Gary W. Swain, MD; Abeel A. Mangi, MD

TECHNICAL APPENDIX

We developed a customized health state transition model to simulate the projected survival, quality-adjusted life expectancy, costs, and cost-effectiveness of different strategies for treating inotrope-dependent stage D heart failure. We summarize additional model assumptions and parameter values in the following sections.

Model Structure

The decision-analytic model (main text, Figure 1) was developed to compare the costs and health benefits of four different therapies for end-stage heart failure: inotrope-dependent medical therapy (IDMT), left-ventricular assist device as destination therapy (DT-LVAD), left-ventricular assist device as bridge to transplant (BTT-LVAD), and orthotopic heart transplant (OHT). Patients are classified as either *OHT-eligible* or *OHT-ineligible*, with the latter group only eligible to receive IDMT or DT-LVAD. The model was used to simulate a hypothetical cohort of 20,000 patients through one of the possible therapy regimens and the associated natural history of disease, until death. Health and cost outcomes were computed over each patient's lifetime, and average values were computed. Additional cohort-level statistics were summarized, such as the proportion alive after 5 years.

After choosing one of the relevant strategies, depending on OHT-eligibility, a patient begins in a particular health state. Each month, he/she can transition to another health state or

death, according to defined transition probabilities (Table A1). We assumed that patients can make only a single transition during each monthly cycle. In pure Markov models, transition probabilities are independent of past events (known as the *memoryless* property) and depend only on the proximate state. We relax this assumption, however, to capture time-dependence in mortality and complication rates, to more accurately model clinical experience. For example, the mortality rate following LVAD implantation is higher for the first month post-surgery than for later months.

The state-transition model simulates a disease pathway for each hypothetical patient, including operative survival, complication rates, time on waitlist for transplant, and eventual death. Each patient will experience different clinical manifestations, and therefore each model run is stochastic and generates different results due to randomness.

Patient Population

Our base-case population is patients aged 50 years with inotrope-dependent stage D heart failure, who would be classified as UNOS status 1A or 1B, and require one of the four therapy regimens. We considered wide variations in initial patient age in detailed sensitivity analysis. For all patients, we estimated the age-adjusted baseline risk of death from CDC life tables (Table A2), and we converted annual mortality rates into monthly probabilities. In the model, we allowed this baseline risk of death to change as surviving patients become older.

We also stratified the population based on eligibility for heart transplant. No prior study has directly compared the cost-effectiveness of LVAD as destination therapy in these two populations. Prior clinical trials (e.g., REMATCH) that compared LVAD with medical therapy typically included patients who were ineligible for OHT, which can lead to biased estimates of

IDMT-related survival. Other UNOS registry studies gave medical therapy status at the time a patient joined the transplant waitlist, and thus included patients who later received an LVAD prior to transplantation. Because a clinical trial comparing the latest IDMT regimens with continuous flow LVADs is unlikely to happen due to ethical concerns, a model-based analysis such as the one we have developed can offer insights about the potential survival for patients on IDMT under varying assumptions.

Therapy Strategies

Inotrope-dependent medical therapy (IDMT)

We assumed that all patients in the IDMT strategy stay in this branch until death (i.e., we do not consider the possibility of switching strategies). Patients who are eligible for OHT but receive IDMT have a monthly probability of death of 0.074, which was calibrated to survival data. Similarly, we considered a population of OHT-ineligible patients, who have a monthly probability of dying of 0.1058.

We applied a quality-of-life factor for all patients on IDMT, and used this to compute quality-adjusted survival. We calculated the total cost of IDMT by estimating the monthly cost of care in the final 12 months of life, final 13-24 months, and with more than 24 months before death. Monthly cost of IDMT was estimated to be $9,072 during the 12 months preceding death, $4,404 during the 12-24 months before death, and $2,039 if more than 24 months before death. An additional one-time cost of $49,838 was assumed for end of life care for all patients.

Left-ventricular assist device as destination therapy (DT-LVAD)

Patients who receive an LVAD as destination therapy begin the first model cycle in the LVAD surgery state, where they may experience an operative death. Given survival, patients then enter a recurrent "Alive with LVAD" state, from which they may develop an LVAD-related complication or die. Otherwise, patients remain in this state and incur a baseline post-LVAD cost of care, and associated quality-of-life. We assumed that patients can only develop a single complication in each cycle, which is a reasonable assumption for relatively rare events. Following a complication, patients then transition back to a complication-free state.

Patients may experience a stroke with higher probability in the first month post-surgery and at a lower rate in subsequent months. If a stroke occurs, we assumed a decrement in quality-of-life during the initial month, using a multiplicative factor. We also accounted for the initial cost of stroke care, as well as monthly follow-up care in subsequent months for all stroke patients. We also assigned a high probability of death (0.40) due to stroke.

Other complications following LVAD implantation include driveline infection, gastrointestinal (GI) bleed, and pump failure. We assumed that the risk of driveline infection is higher in the first year following implantation. For driveline infections, we assumed that the risk of immediate death increases, and we accounted for the associated costs of treatment and decrement in quality-of-life. We treated GI bleeds in a similar manner, but assumed a lower chance of death. In the rare event of a pump failure, we assumed that patients immediately undergo an LVAD replacement surgery with similar cost to the original procedure, with no additional mortality risk (other than operative death) or change in quality-of-life.

Orthotopic heart transplant (OHT)

In our base-case analysis, we assumed that patients in this branch enter a “Waitlist” state, during which they receive IDMT. The costs, quality-of-life, and mortality rates are the same as IDMT patients who are OHT-eligible. During each cycle, a patient may die or continue to wait until a heart becomes available. We assumed that the wait time is exponentially distributed with a median wait of 5.6 months based on U.S. registry data, but we varied this length in sensitivity analysis. Once a heart becomes available, the patient transitions to a “Transplant Surgery” state, during which he/she may die or transition to a post-transplant state.

Several serious complications can afflict heart transplant survivors and increase the chance of dying. Patient bodies may reject the organ, in which case they may die, recover, or be re-transplanted. We assumed that the probability of rejection is highest during the first year post-transplant. Patients could also develop cardiac allograft vasculopathy (CAV) or renal dysfunction, both of which are also more likely in the first year post-transplant. Both CAV and renal dysfunction generate a reduction in quality-of-life, as well as a one-time initial cost and a recurrent monthly cost, reflecting continual clinical care. Finally, we accounted for the risk of developing skin malignancy or lymphoma/other malignancy, where the risk of dying is substantially higher with lymphoma/other malignancy. As with CAV and renal dysfunction, we applied both a one-time cost of diagnosis/treatment for each type of malignancy, and a recurring cost of continual screening or treatment following the initial month of diagnosis. By relaxing the memoryless property required of Markov models, we could more realistically capture the immediate and ongoing costs associated with serious cardiac-associated complications.

Left-ventricular assist device as bridge to transplant (BTT-LVAD)

Patients in this branch receive an LVAD in the first month as with DT-LVAD patients, but enter a "Post-LVAD on Waitlist" state, during which they also wait for a median time of 5.6 months for heart transplant. During this time, they may develop an LVAD-associated complication as discussed above. Once a heart becomes available, patients transition to a second surgery state, and have an associated risk of operative death. Surviving patients are essentially identical to the OHT patients described previously, with no additional decrement to quality-of-life or mortality due to a previously implanted LVAD.

Model Outcomes

In each simulation run of 20,000 hypothetical patients, the TreeAge software produces an entire sequence of state transitions for each patient, until death. The software calculated life expectancy (*LE*) for each patient as the sum of time spent alive in any health state:

$$LE = \sum_{t=0}^{T} I_t$$

where I_t is 1 if the patient is alive in month *t*, and *T* refers to the number of periods. We assumed that *T* = 600 months (50 years) to ensure that the model tracks all patients until death. Of note, we did not discount life expectancy because we want a basis of comparison for other clinical studies that report undiscounted survival.

We then calculated the lifetime costs and quality-adjusted life years (QALYs) for each hypothetical patient:

$$COST = \sum_{t=0}^{T} \frac{C_t}{(1+r)^t}$$

$$QALY = \sum_{t=0}^{T} \frac{Q_t}{(1+r)^t}$$

where C_t corresponds to the monthly cost of the care for patients in the associated health state at time t, Q_t corresponds to the monthly quality-of-life adjustment for the associated health state, and r is the monthly discount rate. We assumed a monthly discount rate of $r = 0.03/12$.

We then calculated average costs, $\overline{COST}$, and quality-adjusted life years, $\overline{QALY}$, across all simulated patients receiving each therapy regimen. The incremental cost-effectiveness ratio (ICER) of each therapy option, relative to the next-best strategy, was calculated as:

$$ICER = \frac{\overline{COST}_{Therapy\ A} - \overline{COST}_{Therapy\ B}}{\overline{QALY}_{Therapy\ A} - \overline{QALY}_{Therapy\ B}}$$

Model Validation

To compute each transition probability, we reviewed the literature to determine survival probabilities with each therapy regimen at different time points. We assumed that events (death, development of complications) follow a constant hazard rate, resulting in an exponentially distributed length of time between events. We allowed some rates to vary over time, to more accurately reflect the clinical course of therapy.

We fit each hazard rate to data using ordinary-least squares. For example, given a mortality rate, λ, the probability of dying by time t is:

$$p = 1 - e^{-\lambda t}$$

Given multiple data points on survival at different time points, we selected the λ that provided the best overall fit. For some parameters, such as risk of death following LVAD implantation, we fit multiple hazard rates (λ_1, λ_2, etc.) to capture differences in mortality immediately following LVAD implantation or heart transplantation. Because most survival data are available for short follow-up periods, a constant hazard rate was assumed to extrapolate survival for the remaining

lifetime of the model. We estimated transition probabilities for developing complications in a similar manner.

Finally, we validated our model against published estimates of various complication rates (Table A3). In general, we found that the model very closely matches data on post-LVAD and post-transplant related complications. In Figure A1, we show a comparison of our model projected survival with BTT-LVAD with data for up to 24 months from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry. Our modeled survival curve included mortality resulting from operative death, post-LVAD death, or death from stroke, GI bleed, driveline infection, or re-implantation due to pump failure. In Figure A2, we compare our model-projected survival following heart transplantation (assuming no time on the waitlist) with the International Society for Heart and Lung Transplantation (ISHLT) database. In this case, our projected survival accounts for mortality due to operative death, post-transplant death, organ rejection, CAV, renal dysfunction, skin malignancy, or lymphoma/other malignancy. In general, our model's survival estimates fit closely with published survival estimates. We did not calibrate the model to differential LVAD-related or transplant-related mortality based on age, although we accounted for baseline age-related mortality.

Table A1. Monthly transition probabilities used in model

Strategy	Starting State	Jump to State	Value
Inotrope Dependent Medical Therapy (IDMT)	Alive on IDT (if OHT-eligible)	Death	0.074
	Alive on IDT (if OHT-ineligible)	Death	0.1058
LVAD (DT or BTT)	LVAD Surgery	Death	0.020
	Alive with LVAD (month 1)	Stroke	0.045
		Gastrointestinal Bleed	0.011
		Driveline Infection	0.019
		Pump Failure	0.004
		Death	0.020
	Alive with LVAD (months 2-12)	Stroke	0.004
		Gastrointestinal Bleed	0.011
		Driveline Infection	0.019
		Pump Failure	0.004
		Death (if OHT-eligible)	0.009
		Death (if OHT-ineligible)	0.014
	Alive with LVAD (months 12+)	Stroke	0.004
		Gastrointestinal Bleed	0.011
		Driveline Infection	0.010
		Pump Failure	0.004
		Death (if OHT-eligible)	0.009
		Death (if OHT-ineligible)	0.014
	Stroke	Death	0.400
	Gastrointestinal Bleed	Death	0.01
	Driveline Infection	Death	0.230
Heart Transplant	Transplant Waitlist on IDT	Transplant Surgery	0.116
		Death	0.074
	Transplant Surgery	Death	0.050
	Alive Post-Transplant (months 1-12)	Organ Rejection	0.025
		Cardiac Allograft Vasculopathy	0.0078
		Renal Dysfunction	0.0065
		Skin Malignancy	0.00156
		Lymphoma/Other Malignancy	0.00104
		Death	0.005

	Alive Post-Transplant (months 13-24)	Organ Rejection	0.009
		Cardiac Allograft Vasculopathy	0.005
		Renal Dysfunction	0.0025
		Skin Malignancy	0.00156
		Lymphoma/Other Malignancy	0.00104
		Death	0.0009
	Alive Post-Transplant (months 24+)	Organ Rejection	0.003
		Cardiac Allograft Vasculopathy	0.005
		Renal Dysfunction	0.0025
		Skin Malignancy	0.00156
		Lymphoma/Other Malignancy	0.00104
		Death	0.0009
	Organ Rejection	Death	0.002
	Cardiac Allograft Vasculopathy	Death	0.050
	Renal Dysfunction	Death	0.005
	Skin Malignancy	Death	0.005
	Lymphoma/Other Malignancy	Death	0.050

Starting state = starting health state of each monthly cycle.
Jump to state = ending health state of each monthly cycle.
Individuals remain in the initial state with probability =1-(sum of other transition probabilities).
The model begins with individuals in one of three initial states: IDMT, LVAD surgery, or transplant waitlist.

Table A2. U.S. CDC mortality table, 2008.

Age (years)	Annual Mortality Prob.	Age (years)	Annual Mortality Prob.	Age (years)	Annual Mortality Prob.	Age (years)	Annual Mortality Prob.
0-1	0.006614	25-26	0.000974	50-51	0.004340	75-76	0.033092
1-2	0.000461	26-27	0.000967	51-52	0.004714	76-77	0.036258
2-3	0.000281	27-28	0.000965	52-53	0.005093	77-78	0.039855
3-4	0.000219	28-29	0.000974	53-54	0.005470	78-79	0.044057
4-5	0.000172	29-30	0.000994	54-55	0.005854	70-80	0.048832
5-6	0.000155	30-31	0.001021	55-56	0.006264	80-81	0.053944
6-7	0.000139	31-32	0.001053	56-57	0.006719	81-82	0.059417
7-8	0.000126	32-33	0.001089	57-58	0.007226	82-83	0.065677
8-9	0.000110	33-34	0.001135	58-59	0.007798	83-84	0.073177
9-10	0.000093	34-35	0.001184	59-60	0.008433	84-85	0.081481
10-11	0.000081	35-36	0.001243	60-61	0.009136	85-86	0.090859
11-12	0.000087	36-37	0.001315	61-62	0.009899	86-87	0.101806
12-13	0.000123	37-38	0.001401	62-63	0.010716	87-88	0.114105
13-14	0.000196	38-39	0.001508	63-64	0.011591	88-89	0.127686
14-15	0.000293	39-40	0.001636	64-65	0.012548	89-90	0.142634
15-16	0.000395	40-41	0.001779	65-66	0.013649	90-91	0.159027
16-17	0.000490	41-42	0.001939	66-67	0.014902	91-92	0.176936
17-18	0.000581	42-43	0.002130	67-68	0.016259	92-93	0.196416
18-19	0.000666	43-44	0.002351	68-69	0.017681	93-94	0.217508
19-20	0.000746	44-45	0.002592	69-70	0.019200	94-95	0.240235
20-21	0.000832	45-46	0.002837	70-71	0.020829	95-96	0.264593
21-22	0.000915	46-47	0.003087	71-72	0.022726	96-97	0.290553
22-23	0.000972	47-48	0.003356	72-73	0.024967	97-98	0.318057
23-24	0.000993	48-49	0.003654	73-74	0.027482	98-99	0.347015

Table A3. Freedom from complications model validation.

Freedom from complications	**Data**	**Model**
Stroke		
1 month	0.97	0.96
3 months	0.95	0.95
1 year	0.89	0.91
2 years	0.83	0.88
3 years	0.81	0.85
Driveline infection		
6 months	0.93	0.93
1 year	0.85	0.85
2 years	0.72	0.75
GI bleed		
6 months	0.94	0.96
1 year	0.88	0.91
2 years	0.77	0.82
Pump failure		
6 months	0.98	0.99
1 year	0.96	0.97
2 years	0.92	0.93
Transplant rejection		
1 year	0.78	0.79
2 years	0.68	0.71
4 years	0.60	0.66
Malignancy		
1 year	0.97	0.98
5 years	0.86	0.88
10 years	0.71	0.78
CAV		
1 year	0.92	0.93
3 years	0.82	0.84
7 years	0.63	0.70
Renal dysfunction		
1 year	0.94	0.94
3 years	0.89	0.89
7 years	0.80	0.81

Figure A1. Model comparison with data for LVAD as bridge to transplant.

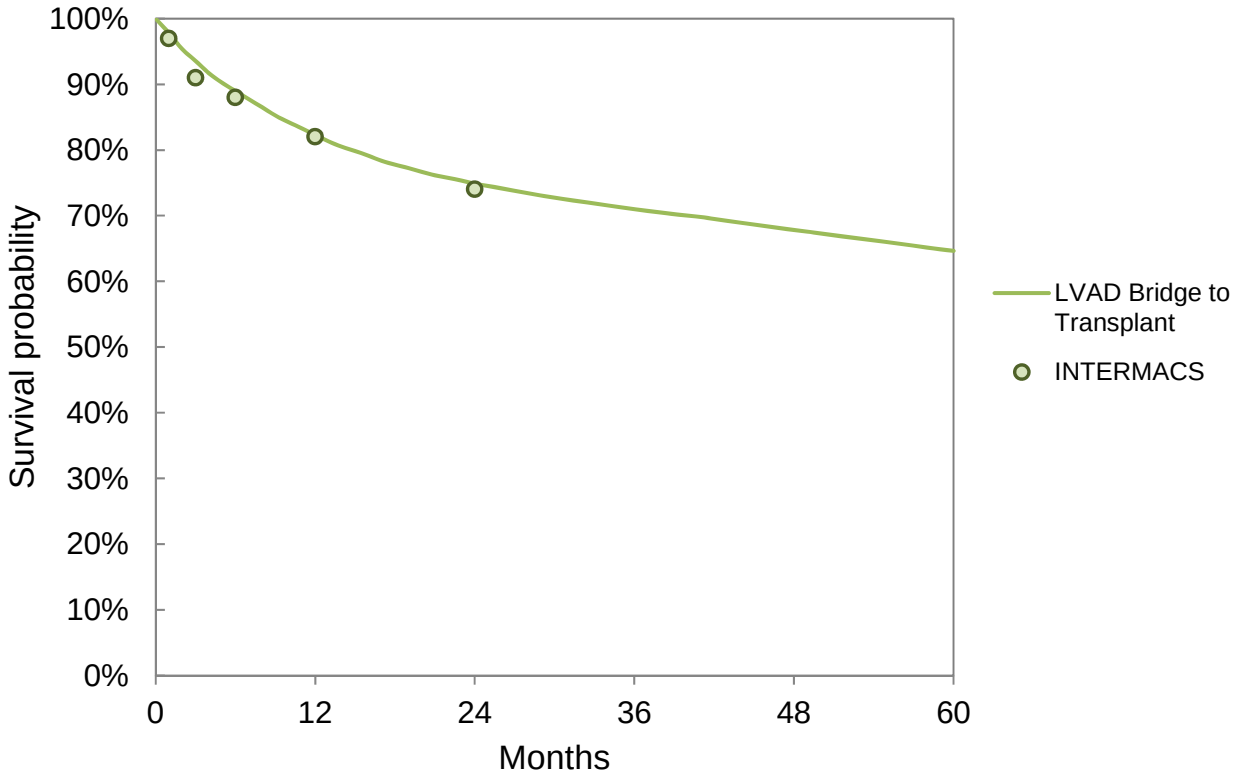

Figure A2. Model comparison with data for heart transplantation.