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

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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.

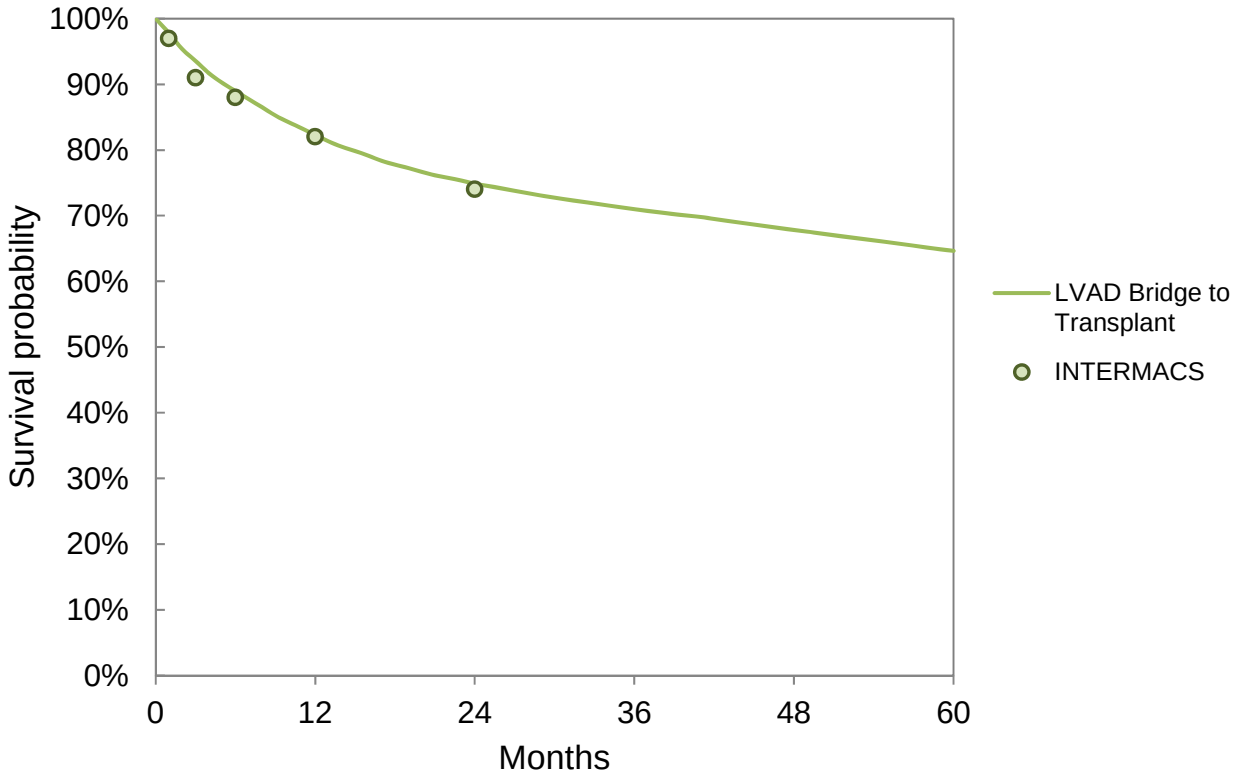

Figure A2. Model comparison with data for heart transplantation.